TITLE PAGE

Protocol Title: A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects.

Protocol Number: 205184

Short Title: GSK2982772 high dose safety and PK study in healthy volunteers.

Compound Number: GSK2982772

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

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1. PROTOCOL SYNOPSIS FOR STUDY 205184

Protocol Title: A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects.

Short Title: GSK2982772 high dose safety and PK study in healthy volunteers.

Rationale: The purpose of this study is to evaluate the safety, tolerability and pharmacokinetics (PK) of repeat oral doses of GSK2982772 (TID and BID, if required) in healthy subjects. TID dosing will be administered as a 7hr, 7hr, 10hr dosing interval and BID as a 12hr dosing interval.

Objectives and Endpoints:

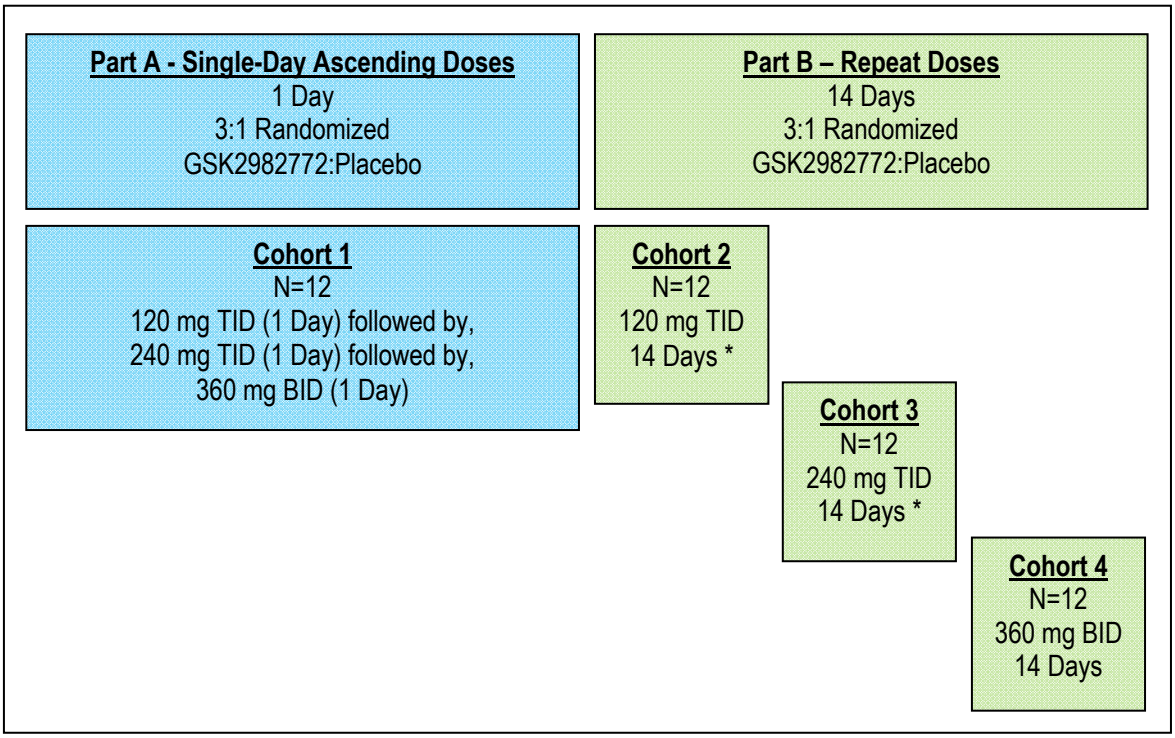
Objective	Endpoint
Primary	
• To investigate the safety and tolerability of repeat doses of GSK2982772 in healthy subjects.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature). • Physical examinations. • 12-Lead ECG monitoring.
Secondary	
• To characterise the PK profile of repeat doses of GSK2982772 in healthy subjects.	• A 24 hr profile to be collected on Day 1 of Part A and Day 14 of Part B. On Day 1 of Part B, the PK profile will be evaluated following the first dose only. Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr ($AUC_{(0-24)}$) and AUC over each dose interval (i.e. $AUC_{(0-7)}$, $AUC_{(7-14)}$ and $AUC_{(14-24)}$ for TID and $AUC_{(0-12)}$ and $AUC_{(12-24)}$ for BID). Maximum observed plasma drug concentration (C_{max}) following each dose, time to maximum observed plasma drug concentration (T_{max}) following each dose, observed trough plasma drug concentrations (C_0, C_7, C_{14} and C_{24} for TID dosing and C_0, C_{12} and C_{24} for BID dosing).
• To assess the impact of food on the PK of repeat doses of GSK2982772 in healthy subjects at steady state	• Derived PK parameters for GSK2982772, including $AUC_{(0-7)}$, $AUC_{(7-14)}$, C_{max}, after 1st dose of day and T_{max} after 1st dose of day.

Objective	Endpoint
• To assess potential effect of repeat doses of GSK2982772 on CYP3A4 enzyme activity.	• Plasma 4β-hydroxycholesterol to cholesterol ratio pre-treatment and following 14 days of repeat dosing of GSK2982772.
Exploratory	
• To investigate the levels of circulating glucuronide metabolite (M8; GSK3562183) and desmethyl metabolite (M9; GSK2997852) in healthy subjects after repeat dosing of GSK2982772.	• Quantify M8 (GSK3562183) and M9 (GSK2997852) in select plasma PK samples at pre-dose and 2 hr following Day 14 of repeat dosing of GSK2982772.

Overall Design:

This is a single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772, in repeat oral doses in healthy subjects. The study design schematic is depicted in the Figure below:

Study Design



*With Food Effect Treatment

Type and Number of Participants:

Healthy volunteer subjects will be enrolled, such that up to approximately 12 subjects (9 active, 3 placebo) in each Cohort (up to approximately 48 in total) complete dosing and critical assessments. A subject is defined to have completed the study when he/she has attended all study visits.

Sentinel dosing will be employed within each Cohort for both Part A and Part B of the study. The doses in the single-ascending dose portion of the study (Part A) will be staggered such that for each of the three treatment periods, on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and adverse events) through approximately 24 hours after their last dose on Day 1, the remaining subjects may be randomized to dosing in that period. The doses in the repeat dose portion of the study (Part B) will be staggered such that for each treatment period on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo) and dosed for at least 7 days before the rest of the cohort is randomized. Assuming 2 subjects are dosed on Day 1 to 7 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and adverse events) through approximately Day 7, the remaining subjects may be randomized to dosing.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence (Cohort 1) or treatment (Cohorts 2-4) and start from the period to be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator.

Treatment Groups and Duration:

The study duration, including screening and follow-up, is not expected to exceed 13 weeks for Part A and 8 weeks for Part B of the study.

Study Duration – Cohort 1

Screening	Approximately 28 days.
Number of Subjects	One Cohort of 12 subjects (N=12).
Treatment Period	Cohort 1 will comprise of three treatment periods, investigating three dosing regimens. Each dose regimen consists of 1 day treatment duration, with subjects in house for 4 nights (through at least 48 hours post-last dose). Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight, and will be released following completion of the assessments on Day 4 of each treatment period, provided there are no safety concerns.
Washout Period	Will be at least 7 days between dose regimens for an individual subject.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

Study Duration – Cohorts 2-4

Screening	Approximately 28 days.
Number of Subjects	Three Cohorts of 12 subjects each (N=36).
Treatment Period	The treatment duration will be 14 days. Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight and will be released following completion of the assessments on Day 17, provided there are no safety concerns.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities (SoA) tables (Section 2.1 and Section 2.2), are essential and required for study conduct.

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA tables (Section 2.1 and Section 2.2).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, or other assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File, which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- The Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

2.1. Time and Events Table – Part A (Cohort 1)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Outpatient Visit	X						X	
Admission to Clinical Unit		X						
Inpatient Stay at Clinical Unit			←==X==→					
Discharge from Clinical Unit						X		*Following completion of all assessments.*
Informed Consent	X							
Inclusion and Exclusion Criteria	X							
Demography	X							
Full Physical Examination	X							*Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination		X		X		X		
Height	X							
Weight	X							
Drug/Alcohol/Cotinine Screen	X	X						*Tests include alcohol breath test, cotinine breath test and urine drug screen.*
Medical/Medication/Drug/Alcohol History	X							
HIV, Hepatitis B and C Screening	X							
Tuberculosis Test	X							*Conducted at the standard practice of the site.*
Serum Pregnancy Test (WOCBP only)	X						X	
Urine Pregnancy Test (WOCBP only)		X				X		
Meals		X	X[a]	X	X	X		[a] *On Day 1, subjects will fast 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1.* ***TID dosing****: On Day 1, lunch and dinner will be served between 2 to 3hr prior to doses 2 and 3, respectively.* ***BID dosing:*** *On Day 1, lunch will be served approximately 4 to 5hr after dose 1. Dinner will be served between 2 to 3hr prior to dose 2. A snack may be consumed approximately 2 to 3hr after dose 2. Water is permitted with dosing and at all times. Subjects will receive standardized meals scheduled at the same time in each period.*
Haem/Chem/Urinalysis Test (Include Liver Chemistries)	X	X	X	X		X	X	*Non-fasted samples can be collected on Day -1.*

Procedure	Screening	Study Period (Days)					Follow-Up	Notes
PK Blood Sampling			X	X				***TID Dosing:*** *PK samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr, 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr, 14hr, 14hr 20min, 14hr 40 min, 15hr, 15hr 30min, 16hr, 19hr, 22hr, 24hr.* ***BID Dosing:*** *PK samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr, 12hr 20min, 12hr 40min, 13hr, 13hr 30min, 14hr, 15hr, 16hr, 19hr, 22hr, 24hr.*
Neuro. Examination		←X→		X	←X→			***TID Dosing:*** *Neurological examinations to be conducted either on Day -1 or pre-dose Day 1 and then at the subsequent time points post first-dose on Day 1: 2hr, 9hr, 16hr, 24hr and 48hr. Then 24 and 48hr after the last dose administered on Day 1.* ***BID Dosing:*** *Neurological examinations to be conducted either on Day -1 or pre-dose Day 1 and then at the subsequent time points post first-dose: 2hr, 14hr, 24hr and 48hr. Then 24 and 48 hr after the last dose administered on Day 1.*
Telemetry			←X→					*Continuous at least 24hr post-evening dose. Initiate at least 15 min. prior to dosing.*
12-Lead ECG	X	X	T	X	←X→			*Vital signs to include HR, BP, temperature and respiration rate.* ***TID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day 1 and then at the subsequent time points post first-dose: 40min, 2hr, 4hr, 7hr (pre-2nd dose), 9hr, 14hr (pre-3rd dose), 16hr, 24hr and 48hr. Then 24 and 48hr after the last dose administered on Day 1.* ***BID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day 1 and then at the subsequent time points post first-dose: 40 min, 2hr, 4hr, pre-2nd dose, 12hr 20 min, 14hr, 24hr and 48 hr. Then 24 and 48hr after the last dose administered on Day 1.* *T = Triplicate.*
Vital Signs	X	X	T	X	←X→		X	
Randomization		X						
Study Treatment			X[b]					[b] ***TID dosing:*** *GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval.* ***BID dosing:*** *GSK2982772 or placebo will be administered using a 12hr dosing interval.*
AE Review		←========X=======→					X	
SAE Review		←========X=======→					X	
Concomitant Medication Review	X	←========X=======→					X	

2.2. Time and Events Table – Part B (Cohorts 2-4)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
Outpatient Visit	X																			X	
Admission to Clinical Unit		X																			
Inpatient Stay at Clinical Unit			←==========X==========→																		
Discharge from Clinical Unit																			X		*Following completion of all assessments.*
Informed Consent	X																				
Inclusion and Exclusion Criteria	X																				
Demography	X																				
Full Physical Examination	X																		X		
Brief Physical Examination		X		X		X			X			X					X			X	*Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Height	X																				
Weight	X								X										X		
Drug/Alcohol/Cotinine Screen	X	X																			*Tests include alcohol breath test, cotinine breath test and urine drug screen.*
Medical/Medication/Drug/Alcohol History	X																				
HIV, Hepatitis B and C Screening	X																				
Tuberculosis Test	X																				
Anti-Nuclear Antibody	X								X										X		
Serum Pregnancy Test (WOCBP only)	X																			X	
Urine Pregnancy Test (WOCBP only)		X																	X		
C-SSRS	X	←X→							X										X	X[c]	*May be completed on either Day -1 or Day 1, but no later than 1hr prior to dosing. To be completed pre-dose on Day 7.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
																				[c] *C-SSRS to be conducted on follow-up only in the instance that a subject withdraws from the study.*
Meals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	***TID Dosing:*** *On Day 1 through 14 subjects will fast 8hr overnight. Breakfast will be served approximately 2hr after dosing on Days 1-8, 10, 12 and 13 and 2hr after dosing on Day 14. A "standard" and a "high fat" breakfast will be served approximately 30 minutes prior to dosing on Day 9 and Day 11, respectively. On all study days, lunch and dinner will be served between 2 to 3hr prior to dose 2 and dose 3, respectively.* ***BID Dosing:*** *On Day 1, subjects will fast 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Lunch will be served approximately 4-5hr after dose 1. Dinner will be served between 2-3hr prior to dose 2. A snack may be consumed approximately 2-3hr after dose 2. Water is permitted with dosing and at all times. Subjects will receive standardized meals scheduled at the same time in each period.*
Haem/Chem/Urinalysis Test (Include Liver Chemistries and fasting lipid panel)	X	X	X	X		X			X			X					X			X	*May be completed on either Day -1 or Day 1, but no later than 1hr prior to dosing. To be drawn pre-dose on Days 2, 4, 7 and 10.*
Telemetry			X		X											X				*Continuous at least 24 hr post-evening dose. Initiate at least 15 min. prior to dosing.*
PK blood sampling			X[d,g]	X[e]	X[e]	X[e]	X[e]		X[e]		X[f]		X[f]			X[g]				[d] *On Day 1, PK samples will be collected pre-dose and at the following time points post first-dose: 20min, 40min, 1hr, 1hr*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
																				30min, 2hr, 3hr, 5hr and 7hr. *[e] On Days 2,3 4, 5 and 7 pre-dose samples only .* *[f] Days 9, and 11: Cohort 2 and Cohort 3 PK sampling at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr (prior to 2nd dose) 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr. Cohort 4 is currently not planned to have PK assessment but may be included depending on outcome of food effect in Cohorts 2 and 3.* *[g] Day 14 sampling for Cohorts 2, 3 and 4 will be over 24hr according to the following schedules:* *For **TID Dosing:** PK samples to be taken pre-dose and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr (pre-2nd dose) 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr, 14hr (pre 3rd dose), 14hr 20min, 14hr 40 min, 15hr, 15hr 30min, 16hr, 19hr, 22hr, 24hr.* *For **BID Dosing:** PK samples to be taken pre-dose on Day 1 and then at the subsequent time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr (pre 2nd dose), 12hr 20min, 12hr 40min, 13hr, 13hr 30min, 14hr, 15hr, 16hr, 19hr, 22hr, 24hr.*
Metabolite sampling																X[h]				*[h] Metabolite sampling will be conducted pre-dose and 2hr post first dose on Day 14 only.*
4β-hydroxycholesterol sampling		X[i]															X[i]			*[i] Sample to be taken pre-dose on either Day-1 or Day 1.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
																				[j] *Sample to be taken at 24hr post first dose on Day 14.*
Neuro. examination			X		X		X			X									X		***TID Dosing:*** *Neurological examinations to be conducted either on Day-1 or pre-dose Day 1 and then at the subsequent time points post first dose: 2hr, 9hr, 16hr, 24hr and 48hr. To be completed pre-dose on Day 7 and then 48 hr post-last dose on Day 14.* ***BID Dosing:*** *Neurological examinations to be conducted pre-dose either on Day-1 or Day 1 and then at the subsequent time points post first dose: 2hr, 14hr, 24hr and 48hr. To be completed pre-dose on Day 7 and then 48hr post-last dose on Day 14.*
12-Lead ECG	X	X	T	X		X			X							X				X	*Vital signs to include HR, BP, temperature and respiration rate.* *On Day 1:* ***TID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day-1 and pre-dose Day 1 and then at the subsequent time points post first-dose: 40min, 2hr, 4hr, 7hr (pre-2nd dose), 9hr, 14hr (pre-3rd dose), 16hr, 24hr, 48hr. Then 24 and 48hr after the first dose and last dose administered on Day 14.* ***BID Dosing:*** *12-Lead ECG and Vital Signs to be conducted pre-dose either on Day-1 or Day 1 and then at the subsequent time points post first-dose: 40 min, 2hr, 4hr, 12hr (pre-2nd dose), 14hr, 24hr, 48hr. Then 24 and 48hr after the first and last dose administered on Day 14.* *On Days 3 to 14, pre-dose samples only.* *T = Triplicate.*
Vital signs	X	X	T	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Randomization		X																		
Study Treatment			X	X	X	X	X	X	X	X	X	X	X	X	X	X				***TID dosing:*** *GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval.* ***BID dosing:*** *GSK2982772 or placebo will be administered using a 12hr dosing interval.*
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

- The timing and number of planned study assessments, including safety, pharmacokinetic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

3. INTRODUCTION

3.1. Study Rationale

The current study is being conducted to support administration of higher dose levels than initially studied in the First Time in Human (FTiH) study - 200975. The dose in the FTiH study was capped at 120 mg BID based on exposure margins with the no observable adverse effect limit (NOAEL) in the 28-day monkey toxicology study (10 mg/kg/day). Subsequently, a 13-week toxicity study in monkeys has completed which increased the NOAEL to 30 mg/kg/day which will allow for an approximate 4-fold increase in the safety margins, in terms of systemic exposure to GSK2982772. The current study is being conducted to explore administration of higher dose levels than achieved in the FTiH study to support subsequent Phase 2a Proof of Concept (PoC) studies and Phase 2b dose range studies in subjects with psoriasis (PsO), rheumatoid arthritis (RA) and ulcerative colitis (UC).

3.2. Background

GSK2982772 is a first-in-class, highly selective, small molecule inhibitor of receptor-interacting serine/threonine protein-1 (RIP1) kinase. 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 regulates inflammatory signalling in response to stimuli such as tumour necrosis factor (TNF) and ligands of the Toll-like receptor family in both kinase-dependent and -independent manners [Ofengeim, 2013]. Upon binding to its receptor, tumour necrosis factor receptor-1 (TNFR1), TNFα triggers one of three distinct cellular fates; NFκB activation, apoptosis, or the more recently identified programmed necrosis [Ofengeim, 2013]. In addition, recent studies have shown that the programmed necrosis signalling complex also regulates the induction of certain cytokines. Although RIP1 serves as a key decision checkpoint for all three of these pathways, its kinase activity is only requisite for the initiation of programmed necrosis and pro-inflammatory cytokine production [Berger, 2014]. The discovery of this newly defined inflammatory, programmed necrotic pathway calls into question the major contributor to human disease downstream of the TNFR1. As such, a RIP1 kinase inhibitor represents a novel, selective mechanism for the treatment of inflammatory conditions such as Crohn's Disease, Plaque Psoriasis, and Rheumatoid Arthritis through multiple mechanisms, including the blockade of cell death, danger associated molecular pattern (DAMP)-driven inflammation and pro-inflammatory cytokine production.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the Investigator's Brochure (IB). The following section outlines the risk assessment and mitigation strategy for this protocol:

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 GLP toxicology study, CNS findings were observed in 2/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance and decreased activity. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical Data:** A FTiH study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date (see IB [GlaxoSmithKline Document Number 2014N204126_02]). No drug-associated CNS adverse events (AEs) were identified and no Serious AEs (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.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids. **Clinical Data:** In the FTiH study, no SAEs were reported. One subject experienced an Adverse Event (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded investigator determined this to be potentially drug-related.	**Subject Selection:** Subjects with recurrent, chronic or active infections will be excluded from the study. Subjects will be screened for TB, HIV, Hepatitis B and C, and excluded from the study if positive. Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. **Subject Monitoring:** Subjects will be monitored for signs of infection. See Individual Safety Stopping Criteria for atypical or opportunistic infections (Section 8.1.5).
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.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit: risk (e.g., risk of theoretical decreased responsiveness). Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
Respiratory	**Non-clinical data:** In the single-dose Safety Cardiovascular and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (MV) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02].	**Subject Monitoring:** Subjects should be monitored for standard respiratory-related 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 up to 120 mg BID were administered x 14 days in 48 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related AEs were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based on 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 Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. Baseline and treatment emergent assessment of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		suicidality will be conducted by trained site personnel using the C-SSRS in all subjects.
Reproductive Toxicity	**Non-Clinical Data:** In the rat embryofetal development study, there were no maternal or developmental toxicity at doses ≤200 mg/kg/day. In the rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection:** Male and female subjects of childbearing potential will be included in this study only if they agree to use highly effective methods of contraception and avoid conception for defined periods of time before first administration of study drug until 30 days (females) and 90 days (males) after the last administration of study drug. Females of childbearing potential will undergo serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria:** If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		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 and P-glycoprotein (Pgp) inhibitors 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 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 GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].	**Subject Selection:** Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. **Subject Monitoring:** Subjects' concomitant medication usage will be reviewed prior to inclusion and monitored throughout the study. Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.

3.3.2. Benefit Assessment

The proposed study with GSK2982772 will be conducted in healthy volunteers; no medical benefit will be derived by volunteers' participation. Subjects will indirectly gain through their contribution to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

The known risks associated with GSK2982772 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential subjects is considered low. Routine safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, cardiac rhythm monitoring, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff.

The study will be conducted in a hospital-based unit or unit with immediate access to hospital facilities for the treatment of medical emergencies. The in-house periods as detailed in the SoA (Section 2) will allow for continuous medical monitoring for all subjects following the first dose in each treatment group. Subjects will only be discharged from the unit 48 hours post-dose if the Investigator deems it safe to do so.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

4. OBJECTIVES AND ENDPOINTS

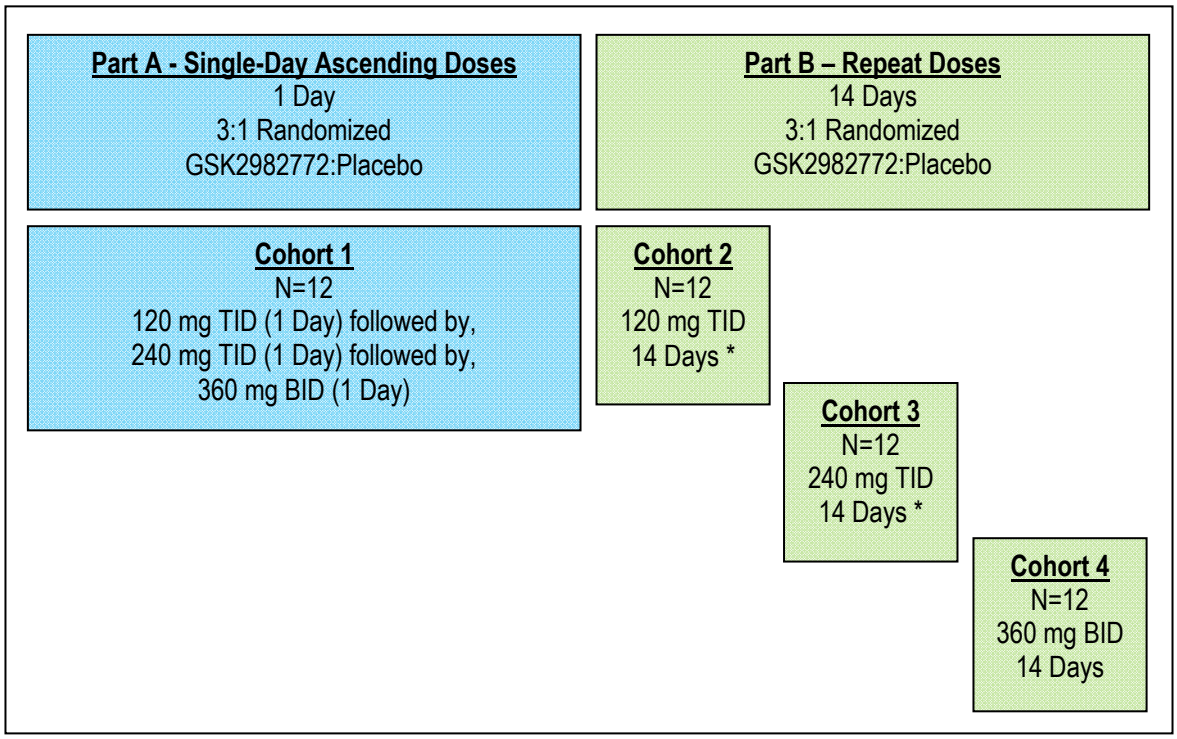
Objective	Endpoint
Primary	
• To investigate the safety and tolerability of repeat doses of GSK2982772 in healthy subjects.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature). • Physical examinations. • 12-Lead ECG monitoring.
Secondary	
• To characterise the pharmacokinetic (PK) profile of repeat doses of GSK2982772 in healthy subjects.	• A 24 hr profile to be collected on Day 1 of Part A and Day 14 of Part B. On Day 1 of Part B, the PK profile will be evaluated following the first dose only. Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr ($AUC_{(0-24)}$) and AUC over each dose interval (i.e. $AUC_{(0-7)}$, $AUC_{(7-14)}$ and $AUC_{(14-24)}$ for TID and $AUC_{(0-12)}$ and $AUC_{(12-24)}$ for BID). Maximum observed plasma drug concentration (C_{max}) following each dose, time to maximum observed plasma drug concentration (T_{max}) following each dose, observed trough plasma drug concentrations (C_0, C_7, C_{14} and C_{24} for TID dosing and C_0, C_{12} and C_{24} for BID dosing).
• To assess the impact of food on the PK of repeat doses of GSK2982772 in healthy subjects at steady state	• Derived PK parameters for GSK2982772, including $AUC_{(0-7)}$, $AUC_{(7-14)}$, C_{max}, after 1st dose of day and T_{max} after 1st dose of day.
• To assess potential effect of repeat doses of GSK2982772 on CYP3A4 enzyme activity.	• Plasma 4β-hydroxycholesterol to cholesterol ratio pre-treatment and following 14 days of repeat dosing of GSK2982772.
Exploratory	
• To investigate the levels of circulating glucuronide metabolite (M8; GSK3562183) and desmethyl metabolite (M9; GSK2997852) in healthy subjects after repeat dosing of GSK2982772.	• Quantify M8 (GSK3562183) and M9 (GSK2997852) in select plasma PK samples at pre-dose and 2 hr following Day 14 of repeat dosing of GSK2982772.

5. STUDY DESIGN

5.1. Overall Design

This is a single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772, in repeat oral doses in healthy subjects. The study design schematic is depicted in Figure 1.

Figure 1 Study Design



*With Food Effect Treatment

This study is planned to include approximately 48 subjects and consists of 2 parts:

- Part A (Cohort 1) – single ascending dose, randomized, placebo-controlled, 3-way crossover.
- Part B (Cohorts 2, 3 and 4) – repeat dose, randomized, placebo-controlled, sequential-group.

For TID dosing, GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval. For BID dosing, GSK2982772 or placebo will be administered using a 12hr dosing interval.

The impact of food on the PK of GSK2982772 will be investigated during the 14 Day repeat dose phase of the study (Part B) in Cohorts 2 and 3. On Days 1 to 14, subjects will fast for 8hr overnight. Breakfast will be served 2hr after dosing on Days 1 through 8, 10,

12 and 14. A standard breakfast will be served 30 minutes prior to dosing on Day 9, and a high fat breakfast will be served 30 minutes prior to dosing on Day 11.

All of the Cohorts in this study will be double-blind with respect to the subjects, investigator and site staff (with the exception of the site pharmacist). The Sponsor, the GSK study team, will be unblinded throughout.

5.2. Number of Participants

Sufficient number of healthy subjects will be enrolled, such that approximately 12 subjects in each Cohort complete dosing and critical assessments. If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Subjects that participate in Part A of the study cannot participate in Part B.

5.3. Sentinel Dosing

Sentinel dosing will be employed within each dosing period in Part A of the study. The doses in the single-ascending dose portion of the study (Part A) will be staggered such that for each of the three treatment periods, on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and AEs) through approximately 24 hours after their last dose on Day 1, the remaining subjects may be randomized to dosing in that period. The doses in the repeat dose portion of the study (Part B) will be staggered such that for each treatment period on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo) and dosed for at least 7 days before the rest of the cohort is randomized. If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence, at the discretion of the Sponsor in consultation with the investigator.

5.4. Dose Escalation Decisions

The decision to proceed to the next dose level of GSK2982772 within the study will be made by a Dose Escalation Committee (DEC) consisting of Principal Investigator, or delegate, and other relevant GSK clinical staff (See Section 10.5).

5.5. 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 (Section 2).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5.6. Scientific Rationale for Study Design

In Part A, each cohort will initially evaluate the safety, tolerability and PK of GSK2982772 administered for 1 day as a TID or BID dosing regimen (Cohort 1).

In Part B, the 14-day TID or BID repeat dosing (Cohort 2, 3 and 4) was chosen since it will provide sufficient safety and tolerability data to bridge to longer duration studies with the recently achieved safety margins from the 13-week toxicology study in monkeys. In the previous FTiH study (200975), GSK2982772 was administered up to 120 mg BID for 14 days and was well tolerated with no safety concerns identified. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

Cohort 4, 360 mg BID dosing regimen, may only be evaluated if the results of a modified release (MR) formulation study (205017) being conducted in parallel with the current study indicate that a MR formulation is not feasible for GSK2982772. In which case a BID regimen using the current immediate release formulation may be taken forward in to Phase 2a PoC studies. Additionally, Cohort 4 dose may be modified to include the repetition of a previous or lower TID or BID dose based on the results of the safety and tolerability review or if further characterization of the safety profile at a previously tested dose is required.

In the previous FTiH (Study 200975), the impact of a high-fat meal on the absorption of GSK2982772 was investigated following single dose administration of GSK2982772 at a dose of 40 mg. The rate and extent of absorption was similar in the fed state as compared to the fasted state, although there was evidence of a time lag in the absorption in the fed state, probably as a result of delayed gastric emptying. It is likely that higher doses to be used in this study will have a similar food effect to that observed at 40 mg. Therefore, this study plans to evaluate the impact of food during the repeat dose phase in Cohorts 2 and 3 rather than conducting a standalone single dose food effect PK study.

5.7. Dose Justification

An adaptive dose-escalation approach, guided by the observed safety, tolerability and plasma PK exposure will be taken to allow an efficient evaluation of a range of doses above the 120 mg BID dose that was evaluated in the FTiH study.

The initial starting dose planned is 120 mg TID and the maximum daily dose is anticipated to be approximately 720 mg administered as 240 mg TID and 360 mg BID.

For doses of up to 120 mg BID, the pharmacokinetics of GSK2982772 are approximately linear. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. After attainment of C_{max}, at approximately 2 hours post-dose, GSK2982772 concentrations decline rapidly until about 12 hours post-dose, with a $t_{1/2}$ of approximately 2 to 3 hours. The majority of the systemic exposure to GSK2982772 is observed within the first 12 hours after administration. Following repeat dosing of GSK2982772, there is no evidence of drug accumulation for either a QD or BID dosing regimen. The major circulating metabolite is an N-glucuronide which accounts for approximately 70% of drug related material in plasma. Since glucuronidation is a high

capacity clearance mechanism it is unlikely that the kinetics of GSK2982772 will become saturable with more frequent dosing nor at the higher doses planned in the current study.

Due to the short half-life of GSK2982772 (~2-3 hr), it is expected that steady-state will be achieved by Day 2 of dosing and that negligible accumulation will be observed. Therefore, the PK safety margins described for Day 1 and for Day 14 of dosing will be similar.

The predicted mean $AUC_{(0-24)}$ for the highest planned doses of 240 mg TID and 360 mg BID (40.2 µg*h/mL) approximates parity with the mean $AUC_{(0-24)}$ observed at the NOAEL (30 mg/kg/day) in the 13-week monkey toxicology study (48.4 µg*h/ml). Mean C_{max} values for the 240 mg TID (3.21 µg/mL) and 360 mg BID (4.31 µg/mL) doses are predicted to be $1/4^{th}$ and $1/3^{rd}$ respectively, of the C_{max} observed at the NOAEL (12.3 µg/mL). The doses for Cohorts 2 and 3 may be adjusted based on PK/safety data from previous treatment periods. It is planned that the 95^{th} percentile for the predicted $AUC_{(0-24)}$ values will not exceed the maximum $AUC_{(0-24)}$ value observed at the NOAEL and for C_{max} the 95^{th} percentile will not exceed the mean C_{max} and the NOAEL. The current predicted 5^{th} -95^{th} percentiles for $AUC_{(0-24)}$ and C_{max} values using repeat dose PK data from FTiH study and mean/individual $AUC_{(0-24)}$ and C_{max} values from the 13-week Monkey Study at 30 mg/kg/day (NOAEL) and 100 mg/kg/day are shown in Figure 2 and Figure 3, respectively.

Figure 2 Mean and 95% Prediction Interval for Human AUC(0-24) Values versus Mean and Individual Monkey C_{max} Values at Week 13

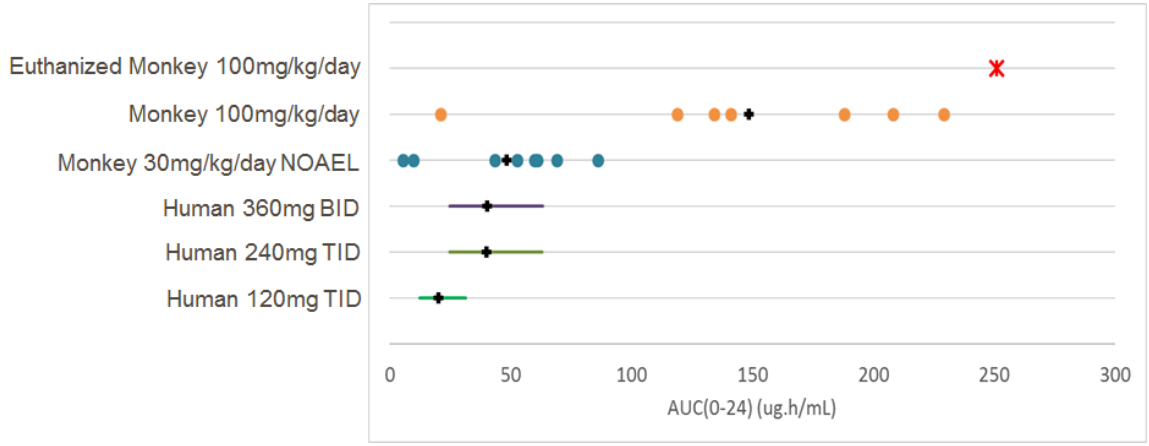
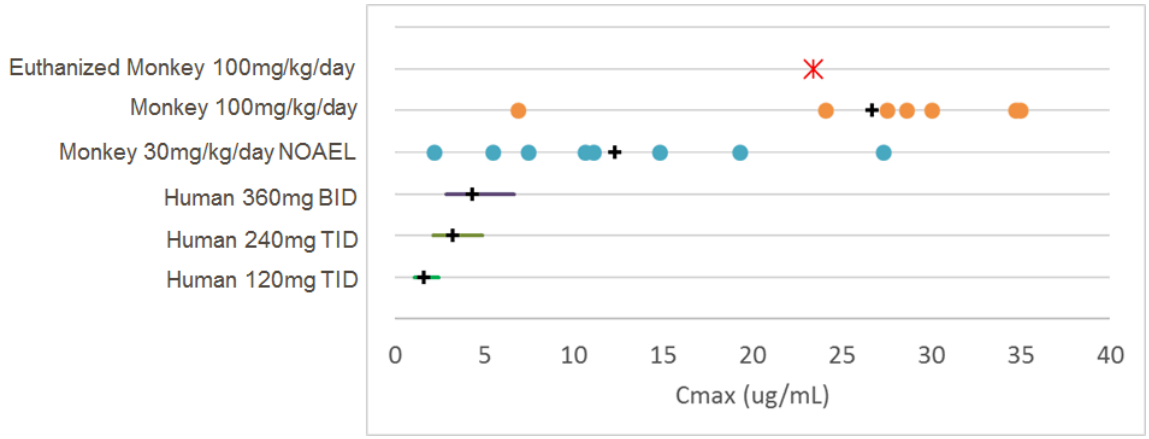


Figure 3 Mean and 95% Prediction Interval for Human Cmax values Versus Mean and Individual Monkey Cmax values at Week 13



6. STUDY POPULATION

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

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. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. Note: Screened subjects with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigator.

WEIGHT
3. Body weight ≥50 kg and body mass index (BMI) within the range 19 - 30 kg/m^2 (inclusive).

SEX
4. Male and/or Female Subjects **a. Male participants:** A male participant must agree to use contraception as detailed in Appendix 5 of this clinical study proposal 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 corresponding to time needed to eliminate study treatment 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 or presence of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, 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. History of herpes zoster (shingles) reactivation.
3. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration <5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) QuantiFERON-TB Gold test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.
4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)
7. QTc >450 msec NOTES: • The QTc is the QT interval corrected for heart rate according to Bazett's

formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.

- The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
- For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

8. History of serious or recurrent infections or has had an active infection within 14 days of receiving study medication.
9. History of diagnosis of obstructive sleep apnoea or significant respiratory disorder. Childhood asthma that has fully resolved is permitted.
10. Part A: History of active SIB within the past 6 months or any history of attempted suicide in a participant's lifetime.
11. History of current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.

PRIOR/CONCOMITANT THERAPY

12. Past or intended use of over-the-counter or prescription medication, including herbal medications, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is the longest) prior to dosing. Specific medications listed in Section 7.6 may be allowed.
13. Subject received a vaccine (either live attenuated or now-live) within 30 days prior to randomisation, or plans to receive a live attenuated vaccine within 30 days + 5 half-lives (32 days) of the last dose of study medication.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56-day period.
15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.

DIAGNOSTIC ASSESSMENTS
16. Presence of Hepatitis B surface antigen (HBsAg) at screening Positive Hepatitis C antibody test result at screening. 17. Positive pre-study drug/alcohol screen. 18. Positive human immunodeficiency virus (HIV1 and 2) antibody test. 19. Regular use of known drugs of abuse. 20. Subjects with impaired renal function defined as Chronic Kidney Disease Epidemiology Collaboration (CKS-EPI) Creatinine > 1.6mg/dL with an age appropriate GFR ≤60 (mL/min/1.73 m^2) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Snyder, 2009 and Levey, 2010]. 21. An elevated C-reactive protein (CRP) outside of the normal reference range.
OTHER EXCLUSIONS
22. Regular alcohol consumption within 6 months prior to the study defined as: • For UK - an average weekly intake of >14 units for males and 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. 23. Cotinine levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening. 24. 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 25. Unwilling or unable to swallow multiple size 00 capsules as part of study participation.

PART B SPECIFIC CRITERIA
26. History of SIB as measured using the C-SSRS or a history of attempted suicide. 27. A positive anti-nuclear antibody (ANA) outside of the normal reference range. 28. Total cholesterol ≥300 mg/dL or triglycerides ≥250 mg/dL.

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 7 days prior to each first dose of study treatment in Part A up until discharge from the unit. In Part B, subjects must refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the first dose of study treatment until after the final dose.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- During each dosing period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 6 months prior to screening until after the final follow-up visit.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Participants will abstain from travelling to regions of high endemic infection, as determined by the investigator, for the duration of the study.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 only on approval of the GSK Medical Monitor. Rescreened participants should be assigned the same participation number as for the initial screening.

7. TREATMENTS

The term study treatment is used throughout the protocol and 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

	Study Treatment	
Product name:	GSK2982772	Placebo
Formulation description	API filled capsule	Placebo blend filled capsule
Dosage form:	HPMC capsule	HPMC capsule
Unite dose strength(s)/Dosage level(s):	120 mg maximum fill per capsule	NA
Route of administration:	For oral use only	For oral use only
Dosing instructions:	Dose with water	Dose with water
Physical description:	Size 00, white, opaque capsule containing white to almost white solid	Size 00, white, opaque capsule containing white to almost white solid
Source of procurement	Study medication is supplied by GlaxoSmithKline	Study medication is supplied by GlaxoSmithKline
Method for individualizing dosage:	Site to assemble	Site to assemble

7.2. Method of Treatment Assignment

On Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to either GSK2982772 or placebo, according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software.

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to the site.

Study treatment will be dispensed at the study visits summarized in SoA. Each participant will be dispensed blinded study treatment, labelled with his/her unique randomization number, throughout the study. Returned study treatment should not be re-dispensed to the participants

In all four cohorts, subjects will be randomized in a 3:1 ratio to either GSK2982772 or placebo. In Cohort 1, the subjects will be randomized to one of three sequences (ABP, APC, PBC), where the treatments are:
A 120 mg TID
B 240 mg TID

C 360 mg BID
P Placebo

The planned dose levels are defined in Section 5.1.

The randomisation will reflect the fact that at least 2 of the 12 subjects (one subject will receive GSK2928772 and one subject will receive matched-placebo) will be dosed first (on Day 1) in each part to enable dose staggering.

Once a treatment allocation number has been assigned to a subject, it cannot be reassigned to any other subject.

7.3. Blinding

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

- The Investigator or treating physician will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will endeavour to ensure that there are no differences in time taken to dispense following randomization
- This 3rd party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator
- Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.
- The IVRS/IWRS will be programmed with blind-breaking instructions.
- In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination.
- If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.
- If a participant's treatment assignment is unblinded, GSK must be notified within 24 hours after breaking the blind.
- The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

- A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

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

7.4. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.5. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- 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.

7.6. 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 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 non-prescription 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 at doses of ≤2 grams/day, is permitted for use any time 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.

7.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK, or with GSK2982772, after completion of the study because only healthy volunteers are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Dose Modification/Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum total daily dose will not intentionally exceed the 13-week NOAEL exposure in monkeys. Currently, the highest planned dose is 720 mg/day of GSK2982772.

The decision to proceed to the next dose level of GSK2982772 in each part of this study will be made by the DEC, including the Medical Monitor and the Investigator and relevant clinical site staff (see Section 10.5) based on safety, tolerability, and preliminary PK data obtained in at least 6 subjects (through at least 24 hours post-dose) with at least 6 subjects having received active treatment (GSK2982772) at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed the PK criteria defined in Section 8.1.2. Planned doses may also be repeated.

The Principal Investigator and the GSK Medical Monitor will review the following and dosing **will be** halted and progression to the next higher dose level stopped if:

- One (1) or more subjects experience a SAE which has a reasonable possibility of relation to study drug.
- Two (2) or more subjects experience a severe or clinically significant non-serious AE (based upon investigator judgment) which has a reasonable possibility of relation to study drug.
- Two (2) or more subjects in a Part A cohort or 3 or more subjects in a Part B cohort experience the same AE of moderate severity which has a reasonable possibility of relation to study drug.
- Consistent Common Terminology Criteria for Adverse Events (CTCAE) Nervous System AEs of any grade occur across subjects that have a reasonable possibility of relation to study drug.

If dosing is halted and if deemed acceptable by GSK internal safety review to proceed with or modify dose escalation to further characterize the safety profile, a formal request with appropriate data and substantial amendment will be submitted to MHRA (Medicines and Healthcare Products Regulatory Agency) for approval.

8.1.2. Pharmacokinetic Dose Modification or Stopping Criteria

The 240 mg TID dose and/or the 360 mg BID dose in Cohorts 1, 3 and 4 may be adjusted up or down based on PK data from previous treatment periods. It is planned that the 95th

percentile for the predicted $AUC_{(0-24)}$ values will not exceed the maximum $AUC_{(0-24)}$ value observed at the NOAEL and for C_{max} the 95th percentile will not exceed the mean C_{max} and the NOAEL.

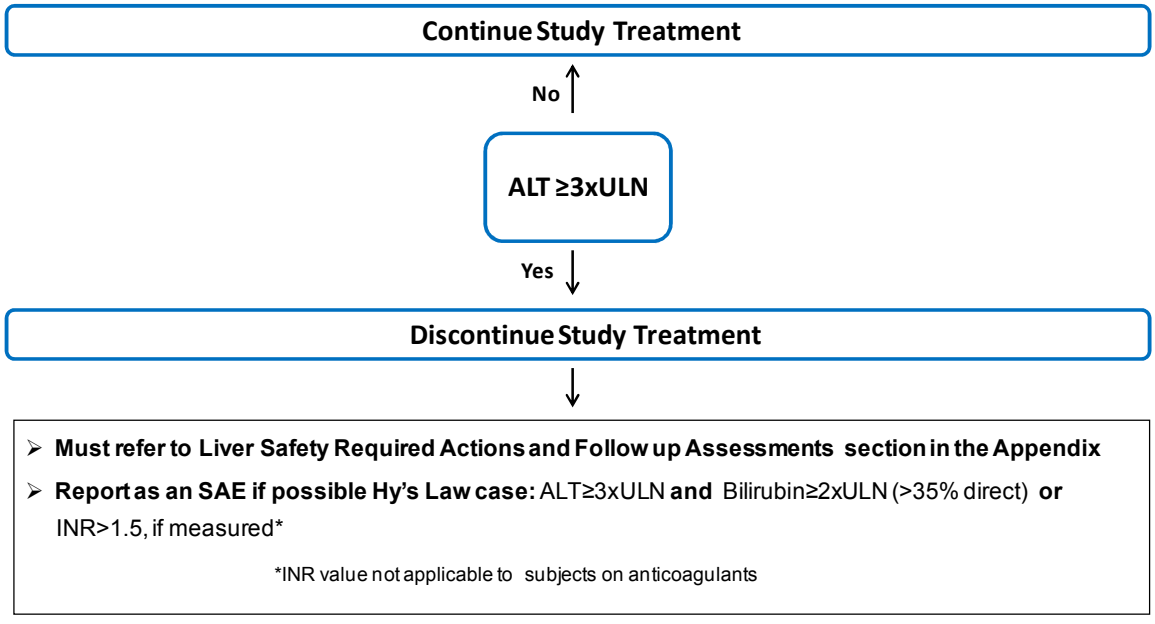
8.1.3. Liver Chemistry Stopping Criteria

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:

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes 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.

8.1.4. QTc Stopping Criteria

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

- QTcF > 500 msec,
- Change from baseline: QTc > 60 msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study (i.e., QTcF in this 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 QTcF, then QTcF 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 single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

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.

8.1.5. 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 (See Section 8.1.3) or QTc stopping criteria (see Section 8.1.4) are met.
- The participant experiences any signs of suicidal ideation or behaviour (See Section 9.3.6).

8.1.6. Group Safety Stopping Criteria

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

8.1.7. Nervous System Stopping Criteria

The CNS observations in the 4-week GLP toxicology study in monkeys were found to be random, diverse, and unpredictable in monkeys (see Section 3.3.1). There were no similar findings observed in the 13-week GLP toxicology study in monkeys. The CTCAE Nervous System is a monitoring tool which provides the Principal Investigator

the appropriate guidance for grading of a neurological event. The significance of any neurological event experienced by a subject will be determined based on clinical judgment, characteristics of the event and/or based upon changes from a baseline assessment.

The Principal Investigator and the GSK Medical Monitor will review all neurological events utilizing the CTCAE Nervous System criteria and dosing may be halted if and progression to the next higher dose level stopped as per Section 8.1.1.

A subject will be withdrawn from the study if:

- A Grade 3 or greater CTCAE Nervous System finding is observed or a significant neurologic change from a subject's baseline physical examination is observed.
- Any adverse event included in the CTCAE for Nervous System, which is also considered to be clinically significant by the Principal Investigator, will be reviewed for potential subject withdrawal.

Note: Appendix 7 (Section 12.7) provides Guidance for Grading Adverse Events that is taken from the CTCAE Version 4.03.

8.1.8. Rechallenge

8.1.8.1. 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. The reason for withdrawal should be documented in the 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- 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.

If a subject chooses to withdraw from the study after dosing, then the Investigator must make every effort to complete the follow-up assessments detailed in the SoA (Section 2).

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 medical record.
- 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.

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 (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 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. 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).

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

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- 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 immediately and under no circumstance should this exceed 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.

9.1.2. 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.

9.1.3. 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, and non-serious AEs of special interest (as defined in Section 3.3.1), 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.

9.1.4. 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, IRB/ IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the

sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat an overdose as and when they are made aware of this.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days for 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.

9.3. Safety Assessments

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

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) 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.

9.3.2. Neurological Exams

Neurological examination will include, at a minimum, assessment of: mental status, gait, balance, coordination, cranial nerves, motor power, reflexes, and sensory system (light touch and pain). Assessments will be standardized across all scheduled time points (see SoA). Significant changes from the baseline or any clinically significant changes will be noted as part of further scheduled examinations or unscheduled examinations (if needed).

Clinically significant abnormalities or changes in status from baseline will be:

- entered as an adverse event,
- may trigger increased monitoring of the subject(s),
- may result in withdrawal of the subject (see Section 8.2),
- may result in referral to a specialist.

9.3.3. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine or semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine or semi-supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- In Part A and B on Day 1, vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure measurements pre-dose on Day 1 (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

9.3.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession with at least 2 minutes but no more than 10 minutes apart.
- Continuous cardiac telemetry will be performed at time points indicated in the SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

9.3.5. 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.
- 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 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 SRM and the SoA.

9.3.6. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There is some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some subjects. 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 and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

Families and caregivers of participants 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) in Part B only, the Baseline/Screening assessment of suicidal ideation and behaviour and treatment emergent suicidal ideation and behaviour will be monitored during study 205184 using C-SSRS. At Days 7 and 17 of the study, the ‘Since Last Visit C-SSRS’ will be completed. Refer to Section 2, SoA, for more information.

Subjects who answer ‘Yes’ to any suicidal behaviour or ‘Yes’ to suicidal ideation Questions 4 or 5 will be referred to their General Practitioner (GP) or appropriate

psychiatric care. The medical monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 9.1). 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.

9.4. Pharmacokinetics

9.4.1. Blood Sample Collection

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of GSK2982772 at the time points indicated in Section 2, SoA Tables. The actual date and time (24-hour clock time) of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of M8 (GSK3562183) and M9 (GSK2997852). This will be collected at the time points indicated in Section 2, SoA Tables. The actual date and time of each blood sample collection will be recorded.

Blood will be collected into EDTA tubes and processed to plasma for 4β-hydroxycholesterol and cholesterol. This will be collected at the time points indicated in Section 2, SoA Tables. The actual date and time of each blood sample collection will be recorded.

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

9.4.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of GSK2982772 will be determined in plasma samples, and concentrations of M8 (GSK3562183) and M9 (GSK2997852) will be determined in select plasma samples, using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma sample has been analysed for GSK2982772 (or M8 [GSK3562183] and M9 [GSK2997852] as indicated above), any remaining plasma sample may be analysed for other compound-related material and the results may be reported under a separate PTS-IVIVT, GlaxoSmithKline protocol.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.4.3. Plasma Sample for CYP3A4 Enzyme Activity

Plasma derived from select PK blood samples in Part B (as in the SoA Table), will be analyzed for 4β-hydroxycholesterol and cholesterol as a potential *in vivo* marker of CYP3A4 enzyme activity. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential marker.

Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SRM.

Baseline and Day 14, post-treatment plasma samples will be analyzed using a validated, specific, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method to determine concentrations of 4β-hydroxycholesterol and total cholesterol. A comparison will be made between the ratio of 4β-hydroxycholesterol : cholesterol at baseline and on Day 14 to assess potential changes in CYP3A4 enzyme activity following GSK2982772 treatment.

Analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of PTS-IVIVT and Third Party Resource, GlaxoSmithKline.

9.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6. Pharmacological Biomarkers

Pharmacological biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

The objectives of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK2982772. No formal hypotheses will be tested.

An estimation approach will be used to describe PK of GSK2982772, where point estimates and corresponding 90% confidence intervals will be constructed.

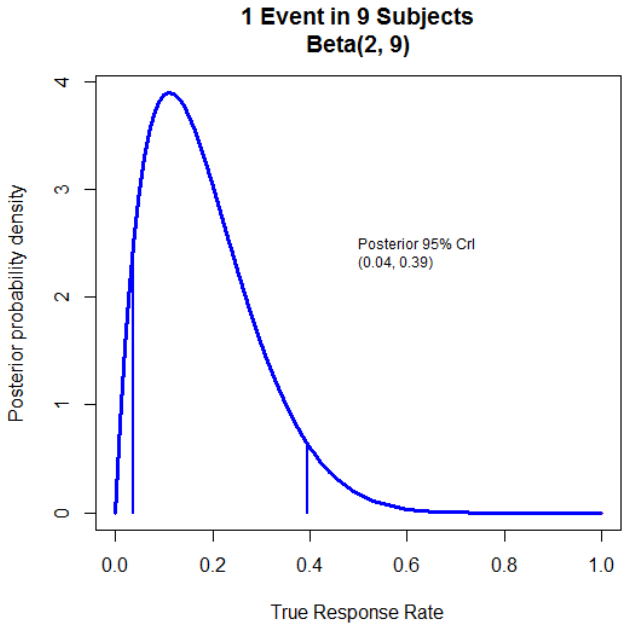
10.1. Sample Size Determination

No statistical techniques were used to calculate the sample size, and sample size is based on feasibility.

The primary objective of the study is safety, where the number of safety events are of interest. A maximum of 9 subjects will receive each active dose and; therefore, if 0/9 of a particular safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 33.6% could not be ruled out. Whereas if 1/9 of the same safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 48.2% could not be ruled out.

Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe one safety event in 9 then the posterior distribution would be Beta (2, 9), as outlined below:

Bayesian Approach to Determine Confidence in a Safety Event.



Thus, we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.39.

Pharmacokinetic Parameters

To date the pharmacokinetics of GSK2982772 have been studied up to 120 mg BID. The maximum between-subject coefficient of variation (CVb) for $AUC_{(0-\tau)}$ and C_{max} observed in study 200975 was 27.1 and 36.1 respectively.

Based on these estimates of variability, slightly more conservative for a cross-over study and a sample size of 9 completers in Cohort 2, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of AUC and C_{max} will be within approximately 17.9% and 24.2% of the point estimate, respectively.

10.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of subjects who completed each active dose, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 10.1 Sample Size Determination) would change. These changes are outlined in Table 1:

Table 1 Safety Events - Sample Size Sensitivity

N Completing Cohort	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95%CI indicating that a true incidence rate of x% could not be ruled out
9	2	60.0%
	3	70.0%
	4	78.8%
8	0	36.9%
	1	52.7%
	2	65.1%
	3	75.5%
7	0	41.0%
	1	57.8%
	2	70.9%
	3	81.6%

Pharmacokinetic Parameters

A sample size sensitivity analysis has also been conducted on the PK parameters to investigate the effect of fewer number of subjects, or 10% difference in the between-subject coefficient of variation on the precision of the point estimate. These changes are outlined in Table 2:

Table 2 Pharmacokinetic Parameters – Sample Size Sensitivity

	Number of Subjects	CVb	Precision (%)
Cmax	6	26.1%	29.8
	6	28.8%	33.4
	6	31.5%	37.0
	9	19.6%	21.7
	9	21.7%	24.2
	9	23.7%	26.7
AUC(0-tau)	6	19.7%	21.8
	6	21.9%	24.5
	6	24.0%	27.1
	9	14.9%	16.1
	9	16.5%	17.9
	9	18.1%	19.8

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	The 'PK Population' is defined as subjects in the 'Safety' population for whom a PK sample was obtained and analyzed.

10.4. Statistical Analyses

10.4.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

All safety analyses will be performed on the Safety Population.

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

10.4.2. PK Analyses

Endpoint	Statistical Analysis Methods
Secondary	PK analyses will be described in the RAP. The PK of TID and BID dosing on Day 1 in Part A will be evaluated. In Part B the comparisons of interest will be: The PK profile following the 1st dose of the day following administration in the fed state (standard meal on Day 9 and high fat meal on Day 11) or in the fasted state (Day 14). The pharmacokinetic profile following the 1st dose on Day 14 (fasted) and the 1st dose on Day 1 (fasted); Pharmacokinetic data will be listed and presented in graphical form and will be summarized descriptively. Statistical summaries of the PK parameter data will be the responsibility of

	Clinical Statistics, GlaxoSmithKline. Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters by treatment. In addition, for loge-transformed variables geometric mean, 95% confidence interval and %CVb (100 * √ (exp(SD_2) -1)) will be provided, where the SD is the standard deviation of log-transformed data.

10.4.3. Other Analyses

Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum) of circulating glucuronide metabolite (M8; GSK3562183) and des-methyl metabolite will be investigated in healthy subjects after single and repeat dosing of GSK2982772.

10.4.4. Interim Analyses

An interim analysis may be performed during the study on completed cohorts in Part A and Part B of the study to aid internal decision making only. There will be no changes to the study design or planned number of subjects in future cohorts as a result of the interim analysis.

For Parts A and B of the study, interim PK analyses will be performed on plasma GSK2982772 concentration-time data generated during the conduct of this study.

The decision to proceed to higher dose strengths will be made by the DEC based on assessment of safety, tolerability and pharmacokinetic data at the preceding dose. The exception to this will be in Part A where only a safety assessment (not PK) for the 120 mg TID dose will be performed. To date, the PK of GSK2982772 has been well-characterised up to 120 mg BID in the FTiH study and the 120 mg TID for Part A represents a 50% increase in dose where PK simulations are predictable. This analysis can include review of individual subject data, summaries, graphical presentations and/or statistical analysis.

The RAP will describe the planned interim analyses in greater detail.

10.5. Dose Escalation Committee

The decision to proceed to the next dose level of GSK2982772 in each Cohort will be made by a DEC consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Clinical Investigational lead and/or Study Team Leader, GSK Pharmacokineticist, a GSK GCSP representative and GSK Statistician. All GSK personnel including the GSK Statistician and the GSK Pharmacokineticist will remain unblinded throughout the course of the study.

For Part A, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will

consist at a minimum of: listings of all AEs, clinical laboratory results, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and PK results derived from 24-hour plasma profiles.

The decision and selection of dose to proceed to Part B, will be made by the DEC based on safety, tolerability, and PK data from the same dose levels evaluated in Part A.

For Part B, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: listings of all AEs, clinical laboratory results, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry) and ECG findings through Day 16 of the previous cohorts(s) in Part B. Also included will be any PK results derived through at least Day 7 of the previous cohort(s).

11. REFERENCES

Berger SB, Kasparcova V, Hoffman S, Swift B, Dare L, Schaeffer M, et al. Cutting edge: RIP1 kinase activity is dispensable for normal development but is a key regulator of inflammation in SHARPIN-deficient mice. J Immunol. 2014; 192(12):5476-80.

GlaxoSmithKline Document Number 2014N204126_02. GSK2982772 Investigator's Brochure, Version 3. Effective Date: 27-January-2017.

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

Levey AS and Stevens LA. Estimating GFR Using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation: More Accurate GFR Estimates, Lower CKD Prevalence Estimates and Better Risk Predictions. Am J Kidney Dis. 2010; 55:622-627.

Ofengeim D and Yuan J. Regulation of RIP1 kinase signalling at the crossroads of inflammation and cell death. Nat Rev Mol Cell Biol. 2013; 14(11):727-736.

Snyder JJ, Foley RN, and Collins AJ. Prevalence of CKD in the United States: A Sensitivity Analysis Using the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2009; 53(2):218-228.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ANA	Anti-nuclear Antibody
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-7)}$	Area under the concentration-time curve from time zero to 7 hours post first dose (TID dosing)
$AUC_{(7-14)}$	Area under the concentration-time curve from 7 to 14 hours post first dose (TID dosing)
$AUC_{(14-24)}$	Area under the concentration-time curve from 14 to 24 hours post first dose (TID dosing)
$AUC_{(0-12)}$	Area under the concentration-time curve from 0 to 12 hours post first dose (BID dosing)
$AUC_{(12-24)}$	Area under the concentration-time curve from 12 to 24 hours post first dose (BID dosing)
$AUC_{(0-24)}$	Area under the concentration-time curve from time zero to 24 hours post first dose
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
$AUC_{(0-\tau)}$	AUC from 0 hours to the time of next dosing.
BID	Twice a day
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CVb	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4

DEC	Dose Escalation Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FSH	Follicle stimulating hormone
FTiH	First Time in Human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HPMC	Hydroxypropylmethyl cellulose
HR	Heart Rate
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IgG	Immunoglobulin G
IP	Investigational Product
IRB/IEC	The Institutional Review Board/ Independent Ethics Committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kg	Kilogram
LDH	Lactate dehydrogenase
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
mg	Milligram
mL	Millilitre
MR	Modified Release
MS	Multiple Sclerosis
MSDS	Material Safety Data Sheet
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	No observable adverse effect limit
NTI	Narrow Therapeutic Index
Pgp	P-glycoprotein
PK	Pharmacokinetics
PoC	Proof of Concept
PsO	Psoriasis
PSRAE	Possible Suicidality Related Adverse Event
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula
QTcF	Electrocardiogram QT interval corrected for heart rate using

	Fridericia's formula
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RIP1	Receptor-interacting protein-1
SAE	Serious Adverse Event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SIB	Suicidal Ideation Behaviour
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse events
TB	Tuberculosis
TID	Three times a day
T_{max}	Time taken to maximum observed plasma drug concentration
TNF	Tumour Necrosis Factor
TNFR1	Tumour Necrosis Factor Receptor-1
UC	Ulcerative Colitis
µg	Microgram
UK	United Kingdom
ULN	Upper Limit of Normal
WOCBP	Woman of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Quantiferon

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the Doctor's Laboratory.
- 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.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red Blood Cell (RBC) Indices: Mean Corpuscular Volume (MCV) Mean corpuscular haemoglobin (MCH) %Reticulocytes	White Blood Cell (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
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (Fasted)[2]	Calcium	Alkaline phosphatase	Albumin
			Anti-nuclear antibody [(ANA), Part B only]	C-reactive protein (CRP)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Alcohol breath test and urine drug screen (to include at minimum:			

Laboratory Assessments	Parameters
	amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Breath cotinine • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential). To be done at screening and Day 17 of Part B. • Urine hCG pregnancy test (as needed for women of child bearing potential)[3] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Tuberculosis test • Total Cholesterol, Low-density lipoprotein, triglycerides (Part B only) • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula. 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 (excluding studies of hepatic impairment or cirrhosis).
2. Non-fasted samples can be collected on Day -1.
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Laboratory that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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 medical record 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 or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with Standard Operating Procedure (SOP)-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

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 multicenter 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

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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 (e.g., 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.

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

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 assessmentse.g.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 (i.e., 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 (e.g., 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 (e.g., 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 (e.g., 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.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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.
- 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 Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit

this information to the medical monitor or the SAE coordinator.

- 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 Study Reference Manual.

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
- Documented tubal ligation

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 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 4 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
- In addition, male participants must refrain from donating sperm for duration of study and for 90 days after study completion or from last dose

Female participants

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 4.

Table 4 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[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • 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.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 7 days after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing 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.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the test kit approved by the sponsor and in accordance with instructions provided in its package insert.

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

Any female participant who becomes pregnant while participating will discontinue study treatment.

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 hr
• 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 24 hours 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 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:

• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hr** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	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. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
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.

12.7. Appendix 7: Nervous System Adverse Events (CTCAE Criteria)

Taken from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

The purpose of this Appendix is to provide guidance and is to be used in conjunction with the Investigator's judgment.

Table 5 Guidance For Grading Adverse Events

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-	A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-	A disorder characterized by systematic and extensive loss of memory.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Aphonia	-	-	Voicelessness; unable to speak	-	-	A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-	A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-	A disorder characterized by a conspicuous change in cognitive function.
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-	A disorder characterized by a deterioration in the ability to concentrate.
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death	A disorder characterized by a decrease in ability to perceive and respond.
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-	A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-	A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-	A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-	A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated		A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a pathologic process involving the brain.
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by a reduction in the strength of the facial muscles.
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the facial nerve (seventh cranial nerve).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-	A disorder characterized by characterized by excessive sleepiness during the daytime.
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by bleeding from the cranium.
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-	A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum ± mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum ± moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death	A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-	A disorder characterized by a deterioration in memory function.
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by uncontrolled and purposeless movements.
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by intense painful sensation along a nerve or group of nerves.
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involuntary movements of the eyeballs.
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the olfactory nerve (first cranial nerve).
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral motor nerves.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.
Presyncope	-	Present (e.g., near fainting)	-	-	-	A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by paralysis of the recurrent laryngeal nerve.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by characterized by excessive sleepiness and drowsiness.
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death	A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.
Syncope	-	-	Fainting; orthostatic collapse	-	-	A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-	A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	-

TITLE PAGE

Protocol Title: A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects.

Protocol Number: 205184/ Amendment 01

Short Title: GSK2982772 high dose safety and PK study in healthy volunteers.

Compound Number: GSK2982772

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
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Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): EudraCT 2017-002662-45

Approval Date: 07-DEC-2017

SPONSOR SIGNATORY:

PPD

Dec 7th 2017

Ramiro Castro-Santamaria, MD, MBA
Head Unit Physician
Immuno-Inflammation Therapy Area

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 01	07-DEC-2017
Original Protocol	31-JUL-2017

Amendment 01 07-Dec-2017

Overall Rationale for the Amendment:

Clarification of the allowed contraception methods for female participants of child bearing potential and male participants with female partners of child bearing potential. Pharmacogenetic sampling has been incorporated into the protocol and glucuronide levels will be assessed in Part A of the study, as well as Part B. In addition, further administrative clarifications have been made.

Section # and Name	Description of Change	Brief Rationale
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 3.3.1. Risk Assessment 6.1. Inclusion Criteria 12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	An additional line for 'Highly effective contraceptive method (WOCBP only)' and 'Contraception with male condoms (WOCBP using hormonal contraceptive method and male subjects with female partners of childbearing potential only)' has been added to the SoA tables in Section 2.1. and Section 2.2. Updated wording for the subject selection for the risk of Reproductive Toxicity. Updated wording for Inclusion Criteria 4 for Male and Female subjects. Update of the contraception guidance wording for women of child bearing potential and male subjects with female partners of child bearing potential.	Female subjects of child-bearing potential who use hormonal contraception are required to have their sexual partners use a male condom from the first dose of study drug until the follow-up visit to avoid conception until at least 30 days after the last administration of drug. This is being added as a precautionary measure for all WOCBP because an AE of "breakthrough bleeding" was reported in Cohort 1 TP2 of this study in a female subject who is on a combination oral contraceptive pill. In the FTiH Study 200975, there was no increase detected in an in vivo marker for CYP3A4 enzyme activity following repeat dose administration up to 120 mg BID. Measurement of 4β-hydroxycholesterol is being evaluated in this study to determine CYP3A4 enzyme activity in repeat dose administration up to 720 mg/day. Until data are available the added contraception is being required.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 9.6. Genetics 12.6. Appendix 6: Genetics	A line for Pharmacogenetic Sampling has been added to both Part A and Part B of the study. A Genetics section has been added to the protocol (9.6) and appendix (6)	To take a pharmacogenetic sample from consenting subjects. One subject in Cohort 1 (not the subject with break through bleeding), had consistently high exposure to GSK2982772 compared to the other subjects (~2-fold higher C_{max}) for the 120 mg and 240 mg TID dose levels. This may be due to a UGT1A9 genetic polymorphism, which is responsible for the conversion to the glucuronide metabolite of GSK2982772.
2.1. Time and Events Table – Part A	Addition of a note in PK blood sampling row to state "Remaining PK plasma samples from Part A may be analysed for metabolite	To include the assessment of metabolite concentrations in Part A of the study (currently Part B only).

Section # and Name	Description of Change	Brief Rationale
(Cohort 1) Synopsis-Objectives and Endpoints Section 4. Objectives and Endpoints 9.4.2. Sample Analysis	sampling." Metabolite sampling will be assessed after single-day of dosing, as well as repeat dosing. Updated wording to in this section to state "any remaining plasma sample may be analysed for any compound-related material and the results may be reported as part of this study or under a separate PTS-IVIVT, GlaxoSmithKline protocol."	
2.2. Time and Events Table – Part B (Cohorts 2-4)	A pre-dose PK sampling time point has been added to the Note 'f' for Cohort 2 and Cohort 3.	No pre-dose sample was written into the original protocol on Days 9 and 11 of Cohorts 2 and 3.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4)	Addition of a PK sampling timepoint at 17hr post-first dose in the TID Dosing regimens in Cohort 1. Addition of a PK sampling timepoint at 17 hr post-first dose in the TID Dosing regimen of Cohorts 2 and 3.	An additional PK sampling time point at 3hr post-last dose has been added to better characterize the PK profile and to ensure the C_{max} is not missed.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 6.2. Exclusion Criteria 12.2.	'Cotinine Screen' has been changed to 'Smoking Screen' and 'Cotinine Breath Test' has been changed to 'Smoking Breath Test' in Section 2.1. and Section 2.2. Carbon monoxide levels have been included in Exclusion Criteria 24. In the 'Other Screening Tests' section, 'Cotinine Breath Test' has	The 'Cotinine Breath Test' either includes urine cotinine and/or smoking breath test. The study will determine evidence of current smoking using a non-invasive breath carbon monoxide (CO) test device, which will provide CO levels to determine evidence of smoking.

Section # and Name	Description of Change	Brief Rationale
Appendix 2: Clinical Laboratory Tests	been changed to 'Smoking Breath Test'.	
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 12.2. Appendix 2: Clinical Laboratory Tests	In Part A of the study, Haem/Chem/Urinalysis assessments can be non-fasted for Day -1 and the Follow-Up Visit. In Part B of the study Haem/Chem/Urinalysis assessments can be non-fasted for Day -1 only. Additional wording included to Note 2 in Table 3 - Non-fasted samples can be collected on Day -1 (All Parts) and at the Follow-Up visit (Part A Only).	The fasting lipid panel in Part B was separated out in the SoA since it was noted to be performed on Day -1 or Day 1. This was moved to Day 1 only since subjects will not be fasted on Day -1. The 4β-hydroxycholesterol will be checked on Day 1, as a fasted sample. It is recommended that all other lab time points being performed (inclusive of the follow-up visit) are to be performed under fasted conditions since this is essential to assess lipid profiles.
6.2. Exclusion Criteria	An additional Exclusion Criteria (16) has been added. "The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). All subsequent exclusion criteria numbers have increased by 1.	To define the minimum length of time since a subject was last exposed to a new chemical entity.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 7.2. Method of Treatment	Updated wording in the 'Notes' section under the procedure "Randomization" in Section 2.1. and Section 2.2 to state: "Randomization can occur on either Day -1 or Day 1 in both Parts A and B of the study." Updated wording to include that randomization can take place on Day -1 or Day 1 in Section 7.2.	There was a discrepancy in the SoA under the procedure "Randomization" in both Part A and B on Day -1 and Section 7.2. Randomization can take place on either Day -1 or Day 1.

Section # and Name	Description of Change	Brief Rationale
Assignment		
9.3.3. Vital Signs	The semi-supine position has been removed from this section.	To remove any ambiguity with this assessment, the supine position will be the only position used to assess vital signs.
2.2. Time and Events Table – Part B (Cohorts 2-4)	A comment has been added to the Meals row to state that "Meals will be served as per the site schedule on Days -1, 16 and 17."	Clarification of the wording for the meal schedule on non-dosing and non PK sampling days.
2.2. Time and Events Table – Part B (Cohorts 2-4)	Superscript 'g' has been removed from the PK blood sampling on Day 1.	Superscript 'g' refers to study assessments on Day 14 of the protocol and not Day 1. This is a correction of a typographical error.
6.2. Exclusion Criteria	Update of the wording in Exclusion Criteria 3 to change the definition of what constitutes a positive tuberculin skin test from <5 mm skin induration at 48 to 72 hours to >5 mm skin induration at 48 to 72 hours.	Correction of a typographical error. An induration of >5 mm skin induration at 48 to 72 hours is considered a positive TB test.
7.2. Method of Treatment Assignment	The Method of Treatment Assignment has been updated to note that subjects in Cohort 1 will be randomized to 1 of 4 treatment sequences rather than 1 of 3. The additional treatment sequence (ABC) has been added.	Correction of a typographical error. There is no change to the randomization ratio, which is 3:1.
2.1. Time and Events Table – Part A (Cohort 1)	Removal of the 10hr time interval post-last dose in note 'b' for TID dosing. This now reads "**TID dosing:** GSK2982772 or placebo will be administered using a 7hr, 7hr dosing interval."	Correction of a typographical error. Since Part A is a single-day of dosing, this 10hr interval has been removed.
2.2. Time and Events Table – Part B (Cohorts 2-4)	The Neurological Examination originally on Day 4 has been moved to Day 3.	Correction of a typographical error. 48hr post-first dose assessment would be on Day 3.
6.2. Exclusion Criteria	Exclusion Criteria 29 has been updated to state "Fasting total cholesterol" rather than "Total fasting cholesterol".	Correction of typographical error.

Section # and Name	Description of Change	Brief Rationale
5.7. Dose Justification	The title in Figure 2 has been changed from "Monkey C_{max}" to "Monkey AUC(0-24)".	Correction of the PK parameter stated in the Figure 2 title.
12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating and Follow-Up Assessments	In the 'Reporting of SAE to GSK' section, facsimile transmission of the SAE paper CRF has been changed to email transmission.	Notification of an SAE via email is the preferred method of transmission to the Medical Monitor and SAE Coordinator.

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1. PROTOCOL SYNOPSIS FOR STUDY 205184

Protocol Title: A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects.

Short Title: GSK2982772 high dose safety and PK study in healthy volunteers.

Rationale: The purpose of this study is to evaluate the safety, tolerability and pharmacokinetics (PK) of repeat oral doses of GSK2982772 (TID and BID, if required) in healthy subjects. TID dosing will be administered as a 7hr, 7hr, 10hr dosing interval and BID as a 12hr dosing interval.

Objectives and Endpoints:

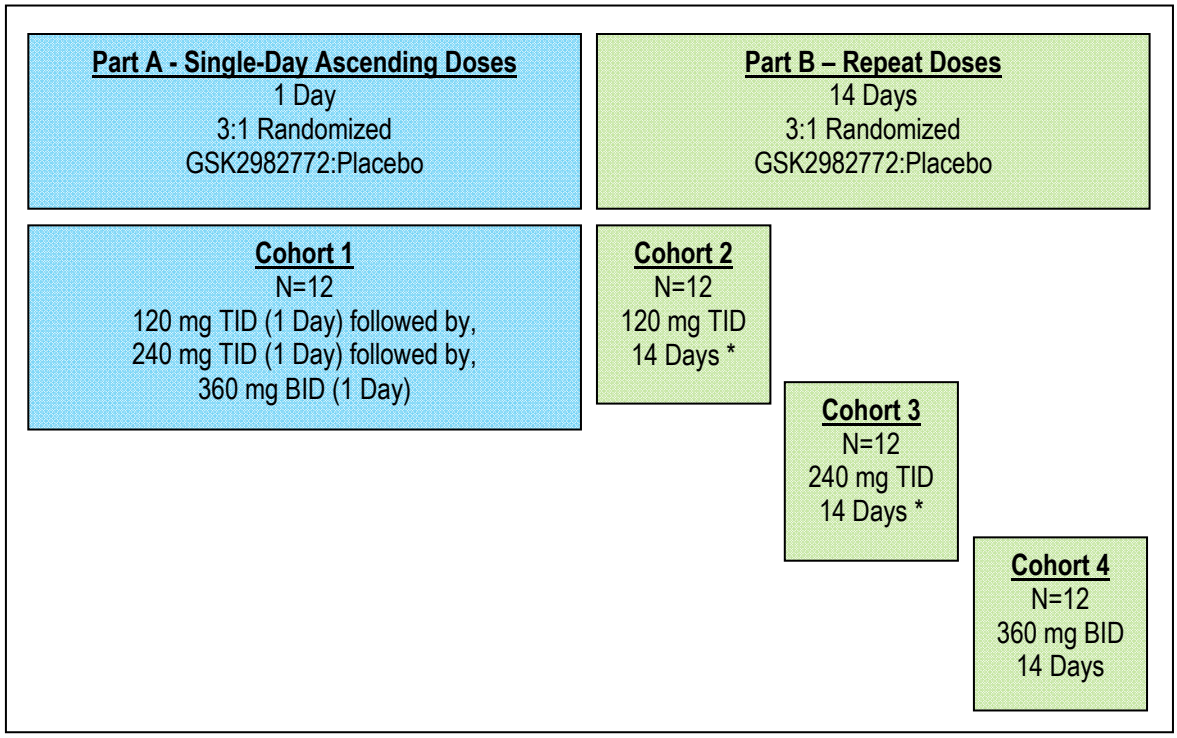
Objective	Endpoint
Primary	
• To investigate the safety and tolerability of repeat doses of GSK2982772 in healthy subjects.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature). • Physical examinations. • 12-Lead ECG monitoring.
Secondary	
• To characterise the PK profile of repeat doses of GSK2982772 in healthy subjects.	• A 24 hr profile to be collected on Day 1 of Part A and Day 14 of Part B. On Day 1 of Part B, the PK profile will be evaluated following the first dose only. Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr ($AUC_{(0-24)}$) and AUC over each dose interval (i.e. $AUC_{(0-7)}$, $AUC_{(7-14)}$ and $AUC_{(14-24)}$ for TID and $AUC_{(0-12)}$ and $AUC_{(12-24)}$ for BID). Maximum observed plasma drug concentration (C_{max}) following each dose, time to maximum observed plasma drug concentration (T_{max}) following each dose, observed trough plasma drug concentrations (C_0, C_7, C_{14} and C_{24} for TID dosing and C_0, C_{12} and C_{24} for BID dosing).
• To assess the impact of food on the PK of repeat doses of GSK2982772 in healthy subjects at steady state	• Derived PK parameters for GSK2982772, including $AUC_{(0-7)}$, $AUC_{(7-14)}$, C_{max}, after 1st dose of day and T_{max} after 1st dose of day.

Objective	Endpoint
• To assess potential effect of repeat doses of GSK2982772 on CYP3A4 enzyme activity.	• Plasma 4β-hydroxycholesterol to cholesterol ratio pre-treatment and following 14 days of repeat dosing of GSK2982772.
Exploratory	
• To investigate the levels of circulating glucuronide metabolite (M8; GSK3562183) and desmethyl metabolite (M9; GSK2997852) in healthy subjects after single-day and repeat dosing of GSK2982772.	• Quantify M8 (GSK3562183) and M9 (GSK2997852) in select plasma PK samples after single-day dosing and at pre-dose and 2 hr following Day 14 of repeat dosing of GSK2982772.

Overall Design:

This is a single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772, in repeat oral doses in healthy subjects. The study design schematic is depicted in the Figure below:

Study Design



*With Food Effect Treatment

Type and Number of Participants:

Healthy volunteer subjects will be enrolled, such that up to approximately 12 subjects (9 active, 3 placebo) in each Cohort (up to approximately 48 in total) complete dosing and critical assessments. A subject is defined to have completed the study when he/she has attended all study visits.

Sentinel dosing will be employed within each Cohort for both Part A and Part B of the study. The doses in the single-ascending dose portion of the study (Part A) will be staggered such that for each of the three treatment periods, on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and adverse events) through approximately 24 hours after their last dose on Day 1, the remaining subjects may be randomized to dosing in that period. The doses in the repeat dose portion of the study (Part B) will be staggered such that for each treatment period on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo) and dosed for at least 7 days before the rest of the cohort is randomized. Assuming 2 subjects are dosed on Day 1 to 7 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and adverse events) through approximately Day 7, the remaining subjects may be randomized to dosing.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence (Cohort 1) or treatment (Cohorts 2-4) and start from the period to be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator.

Treatment Groups and Duration:

The study duration, including screening and follow-up, is not expected to exceed 13 weeks for Part A and 8 weeks for Part B of the study.

Study Duration – Cohort 1

Screening	Approximately 28 days.
Number of Subjects	One Cohort of 12 subjects (N=12).
Treatment Period	Cohort 1 will comprise of three treatment periods, investigating three dosing regimens. Each dose regimen consists of 1 day treatment duration, with subjects in house for 4 nights (through at least 48 hours post-last dose). Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight, and will be released following completion of the assessments on Day 4 of each treatment period, provided there are no safety concerns.
Washout Period	Will be at least 7 days between dose regimens for an individual subject.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

Study Duration – Cohorts 2-4

Screening	Approximately 28 days.
Number of Subjects	Three Cohorts of 12 subjects each (N=36).
Treatment Period	The treatment duration will be 14 days. Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight and will be released following completion of the assessments on Day 17, provided there are no safety concerns.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities (SoA) tables (Section 2.1 and Section 2.2), are essential and required for study conduct.

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA tables (Section 2.1 and Section 2.2).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, or other assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File, which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- The Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

2.1. Time and Events Table – Part A (Cohort 1)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Outpatient Visit	X						X	
Admission to Clinical Unit		X						
Inpatient Stay at Clinical Unit			←==X==→					
Discharge from Clinical Unit						X		*Following completion of all assessments.*
Informed Consent	X							
Inclusion and Exclusion Criteria	X							
Demography	X							
Full Physical Examination	X							*Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination		X		X		X		
Height	X							
Weight	X							
Drug/Alcohol/Smoking Screen	X	X						*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/Drug/Alcohol History	X							
HIV, Hepatitis B and C Screening	X							
Tuberculosis Test	X							*Conducted at the standard practice of the site.*
Serum Pregnancy Test (WOCBP only)	X						X	
Urine Pregnancy Test (WOCBP only)		X				X		
Highly effective contraceptive method (WOCBP only)	X	X	X	X	X	X	X	*Must use method for a minimum of 28 days prior to first dose of study medication until the follow-up visit*
Contraception with male condoms (WOCBP using hormonal contraceptive method and male subjects with female partners of childbearing potential only)		X	X	X	X	X	X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Meals		X	X[a]	X	X	X		[a] *On Day 1, subjects will fast 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1.* ***TID dosing****: On Day 1, lunch and dinner will be served between 2 to 3hr prior to doses 2 and 3, respectively.* ***BID dosing:*** *On Day 1, lunch will be served approximately 4 to 5hr after dose 1. Dinner will be served between 2 to 3hr prior to dose 2. A snack may be consumed approximately 2 to 3hr after dose 2.* *Water is permitted with dosing and at all times. Subjects will receive standardized meals scheduled at the same time in each period.*
Haem/Chem/Urinalysis Test (Include Liver Chemistries)	X	X	X	X		X	X	*Non-fasted samples can be collected on Day -1 and Follow-Up Visit.*
PK Blood Sampling			X	X				***TID Dosing:*** *PK samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr, 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr, 14hr, 14hr 20min, 14hr 40 min, 15hr, 15hr 30min, 16hr, 17hr, 19hr, 22hr, 24hr.* ***BID Dosing:*** *PK samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr, 12hr 20min, 12hr 40min, 13hr, 13hr 30min, 14hr, 15hr, 16hr, 19hr, 22hr, 24hr.* *Remaining PK plasma samples from Part A may be analysed for metabolite sampling.*
Neuro. Examination		←X→		X	←X→			***TID Dosing:*** *Neurological examinations to be conducted either on Day -1 or pre-dose Day 1 and then at the subsequent time points post first-dose on Day 1: 2hr, 9hr, 16hr, 24hr and 48hr. Then 24 and 48hr after the last dose administered on Day 1.* ***BID Dosing:*** *Neurological examinations to be conducted either on Day -1 or pre-dose Day 1 and then at the subsequent time points post first-dose: 2hr, 14hr, 24hr and 48hr. Then 24 and 48 hr after the last dose administered on Day 1.*
Telemetry			←X→					*Continuous at least 24hr post-evening dose. Initiate at least 15 min. prior to dosing.*
12-Lead ECG	X	X	T	X	←X→			*Vital signs to include HR, BP, temperature and respiration rate.* ***TID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Vital Signs	X	X	T	X	←X→		X	*1 and then at the subsequent time points post first-dose: 40min, 2hr, 4hr, 7hr (pre-2nd dose), 9hr, 14hr (pre-3rd dose), 16hr, 24hr and 48hr. Then 24 and 48hr after the last dose administered on Day 1.* ***BID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day 1 and then at the subsequent time points post first-dose: 40 min, 2hr, 4hr, pre-2nd dose, 12hr 20 min, 14hr, 24hr and 48 hr. Then 24 and 48hr after the last dose administered on Day 1. T = Triplicate.*
Randomization		X						*Randomization can occur on either Day -1 or Day 1.*
Study Treatment			X[b]					[b] ***TID dosing:*** *GSK2982772 or placebo will be administered using a 7hr, 7hr dosing interval.* ***BID dosing:*** *GSK2982772 or placebo will be administered using a 12hr dosing interval.*
Pharmacogenetic Sample (PGx)			X					*A PGx blood sample is collected at the Day 1 visit, after the subject has been randomized and provided informed consent for genetic research. If the sample is not collected at the Day 1 visit, it can be collected at any time during the study after randomization.*
AE Review		←=======X======→					X	
SAE Review		←=======X======→					X	
Concomitant Medication Review	X	←=======X======→					X	

2.2. Time and Events Table – Part B (Cohorts 2-4)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Outpatient Visit	X																			X	
Admission to Clinical Unit		X																			
Inpatient Stay at Clinical Unit			←==========X==========→																		
Discharge from Clinical Unit																			X		*Following completion of all assessments.*
Informed Consent	X																				
Inclusion and Exclusion Criteria	X																				
Demography	X																				
Full Physical Examination	X																		X		*Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination		X		X		X			X			X					X			X	
Height	X																				
Weight	X								X										X		
Drug/Alcohol/Smoking Screen	X	X																			*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/ Drug/Alcohol History	X																				
HIV, Hepatitis B and	X																				

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
C Screening																				
Tuberculosis Test	X																			
Anti-Nuclear Antibody	X								X										X	
Serum Pregnancy Test (WOCBP only)	X																			X	
Urine Pregnancy Test (WOCBP only)		X																	X	
Highly effective contraceptive method (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*Must use method for a minimum of 28 days prior to first dose of study medication until the follow-up visit.*
Contraception with male condoms (WOCBP using hormonal contraceptive method and male subjects with female partners of childbearing potential only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	←X→							X										X	X[c]	*May be completed on either Day -1 or Day 1, but no later than 1hr prior to dosing. To be completed pre-dose on Day 7.* [c] *C-SSRS to be conducted on follow-up <u>only</u> in the instance that a subject withdraws from the study.*
Meals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		***<u>TID Dosing:</u>*** *On Day 1 through 14 subjects will fast 8hr overnight. Breakfast will be served approximately*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					2hr after dosing on Days 1-8, 10, 12 and 13 and 2hr after dosing on Day 14. A "standard" and a "high fat" breakfast will be served approximately 30 minutes prior to dosing on Day 9 and Day 11, respectively. On all study days, lunch and dinner will be served between 2 to 3hr prior to dose 2 and dose 3, respectively. ***BID Dosing:*** *On Day 1 through 14, subjects will fast 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Lunch will be served approximately 4-5hr after dose 1. Dinner will be served between 2-3hr prior to dose 2. A snack may be consumed approximately 2-3hr after dose 2. Water is permitted with dosing and at all times. Subjects will receive standardized meals scheduled at the same time in each period. Meals will be served as per the site schedule on Days -1, 16 and 17.*
Haem/Chem/ Urinalysis Test (Include Liver Chemistries)	X	X	X	X		X			X			X					X			X	*Collection on Day 1 no later than 1hr prior to dosing. To be drawn pre-dose on Days 2, 4, 7 and 10.*
Fasting lipid panel	X		X	X		X			X			X					X			X	*Collection on Day 1 no later than 1hr*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					prior to dosing. To be drawn pre-dose on Days 2, 4, 7 and 10.
Telemetry			X		X											X					*Continuous at least 24 hr post-evening dose. Initiate at least 15 min. prior to dosing.*
PK blood sampling			X[d]	X[e]	X[e]	X[e]	X[e]		X[e]		X[f]		X[f]			X[g]					[d] *On Day 1, PK samples will be collected pre-dose and at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr and 7hr.* [e] *On Days 2,3 4, 5 and 7 pre-dose samples only.* [f] *Days 9, and 11: Cohort 2 and Cohort 3 PK sampling will be collected pre-dose and at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr (prior to 2nd dose) 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr. Cohort 4 is currently not planned to have PK assessment but may be included depending on outcome of food effect in Cohorts 2 and 3.* [g] *Day 14 sampling for Cohorts 2, 3 and 4 will be over 24hr according to the following schedules:* *For **TID Dosing:** PK samples to be taken pre-dose and then at the following time points post first-dose:*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr (pre-2nd dose) 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr, 14hr (pre 3rd dose), 14hr 20min, 14hr 40 min, 15hr, 15hr 30min, 16hr, 17hr, 19hr, 22hr, 24hr. *For **BID Dosing:** PK samples to be taken pre-dose on Day 1 and then at the subsequent time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr (pre 2nd dose), 12hr 20min, 12hr 40min, 13hr, 13hr 30min, 14hr, 15hr, 16hr, 19hr, 22hr, 24hr.*
Metabolite sampling																X[h]					[h] *Metabolite sampling will be conducted pre-dose and 2hr post first dose on Day 14 only.*
4β-hydroxycholesterol sampling			X[i]														X[j]				[i] *Sample to be taken pre-dose on Day 1 in a fasted state.* [j] *Sample to be taken at 24hr post first dose on Day 14. Sample should be in a fasted state.*
Neuro. examination		X		X	X				X									X			***TID Dosing:** Neurological examinations to be conducted either on Day-1 or pre-dose Day 1 and then at the subsequent time points post first dose: 2hr, 9hr, 16hr, 24hr and 48hr. To be completed pre-dose on Day 7 and then 48 hr post-last dose on Day 14.*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
																				BID Dosing: *Neurological examinations to be conducted pre-dose either on Day-1 or Day 1 and then at the subsequent time points post first dose: 2hr, 14hr, 24hr and 48hr. To be completed pre-dose on Day 7 and then 48hr post-last dose on Day 14.*
12-Lead ECG	X	X	T	X		X			X							X				X	*Vital signs to include HR, BP, temperature and respiration rate.* *On Day 1:* ***TID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day-1 and pre-dose Day 1 and then at the subsequent time points post first-dose: 40min, 2hr, 4hr, 7hr (pre-2nd dose), 9hr, 14hr (pre-3rd dose), 16hr, 24hr, 48hr. Then 24 and 48hr after the first dose and last dose administered on Day 14.* ***BID Dosing:*** *12-Lead ECG and Vital Signs to be conducted pre-dose either on Day-1 or Day 1 and then at the subsequent time points post first-dose: 40 min, 2hr, 4hr, 12hr (pre-2nd dose), 14hr, 24hr, 48hr. Then 24 and 48hr after the first and last dose administered on Day 14.* *On Days 3 to 14, pre-dose samples only.* *T = Triplicate.*
Vital signs	X	X	T	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
Randomization		X																			*Randomization can occur on either Day -1 or Day 1.*
Study Treatment			X	X	X	X	X	X	X	X	X	X	X	X	X	X					***TID dosing:*** *GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval.* ***BID dosing:*** *GSK2982772 or placebo will be administered using a 12hr dosing interval.*
Pharmacogenetic Sample (PGx)			X																		*A PGx blood sample is collected at the Day 1 visit, after the subject has been randomized and provided informed consent for genetic research. If the sample is not collected on Day 1, it can be collected at any time during the study after randomization.*
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

- The timing and number of planned study assessments, including safety, pharmacokinetic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

3. INTRODUCTION

3.1. Study Rationale

The current study is being conducted to support administration of higher dose levels than initially studied in the First Time in Human (FTiH) study - 200975. The dose in the FTiH study was capped at 120 mg BID based on exposure margins with the no observable adverse effect limit (NOAEL) in the 28-day monkey toxicology study (10 mg/kg/day). Subsequently, a 13-week toxicity study in monkeys has completed which increased the NOAEL to 30 mg/kg/day which will allow for an approximate 4-fold increase in the safety margins, in terms of systemic exposure to GSK2982772. The current study is being conducted to explore administration of higher dose levels than achieved in the FTiH study to support subsequent Phase 2a Proof of Concept (PoC) studies and Phase 2b dose range studies in subjects with psoriasis (PsO), rheumatoid arthritis (RA) and ulcerative colitis (UC).

3.2. Background

GSK2982772 is a first-in-class, highly selective, small molecule inhibitor of receptor-interacting serine/threonine protein-1 (RIP1) kinase. 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 regulates inflammatory signalling in response to stimuli such as tumour necrosis factor (TNF) and ligands of the Toll-like receptor family in both kinase-dependent and -independent manners [Ofengeim, 2013]. Upon binding to its receptor, tumour necrosis factor receptor-1 (TNFR1), TNFα triggers one of three distinct cellular fates; NFκB activation, apoptosis, or the more recently identified programmed necrosis [Ofengeim, 2013]. In addition, recent studies have shown that the programmed necrosis signalling complex also regulates the induction of certain cytokines. Although RIP1 serves as a key decision checkpoint for all three of these pathways, its kinase activity is only requisite for the initiation of programmed necrosis and pro-inflammatory cytokine production [Berger, 2014]. The discovery of this newly defined inflammatory, programmed necrotic pathway calls into question the major contributor to human disease downstream of the TNFR1. As such, a RIP1 kinase inhibitor represents a novel, selective mechanism for the treatment of inflammatory conditions such as Crohn's Disease, Plaque Psoriasis, and Rheumatoid Arthritis through multiple mechanisms, including the blockade of cell death, danger associated molecular pattern (DAMP)-driven inflammation and pro-inflammatory cytokine production.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the Investigator's Brochure (IB). The following section outlines the risk assessment and mitigation strategy for this protocol:

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 GLP toxicology study, CNS findings were observed in 2/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance and decreased activity. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical Data:** A FTiH study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date (see IB [GlaxoSmithKline Document Number 2014N204126_02]). No drug-associated CNS adverse events (AEs) were identified and no Serious AEs (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.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids. **Clinical Data:** In the FTiH study, no SAEs were reported. One subject experienced an Adverse Event (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded investigator determined this to be potentially drug-related.	**Subject Selection:** Subjects with recurrent, chronic or active infections will be excluded from the study. Subjects will be screened for TB, HIV, Hepatitis B and C, and excluded from the study if positive. Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. **Subject Monitoring:** Subjects will be monitored for signs of infection. See Individual Safety Stopping Criteria for atypical or opportunistic infections (Section 8.1.5).
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.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
		If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit: risk (e.g., risk of theoretical decreased responsiveness). Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
Respiratory	**Non-clinical data:** In the single-dose Safety Cardiovascular and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (MV) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02].	**Subject Monitoring:** Subjects should be monitored for standard respiratory-related 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 up to 120 mg BID were administered x 14 days in 48 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related AEs were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based on 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 Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. Baseline and treatment emergent assessment of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		suicidality will be conducted by trained site personnel using the C-SSRS in all subjects.
Reproductive Toxicity	**Non-Clinical Data:** In the rat embryofetal development study, there were no maternal or developmental toxicity at doses ≤200 mg/kg/day. In the rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection:** Female subjects of childbearing potential will be included in this study only if they agree to use one of the highly effective methods of contraception beginning at least 28 days prior to first dose of study drug until 30 days after the last administration of study drug. Women using a hormonal contraceptive method will also be required to have partners use a male condom from the first dose of study drug and until the follow-up visit to avoid conception until at least 30 days after the last administration of study drug. Male subjects with female partners of childbearing potential must agree to use male condoms to avoid conception for defined periods of time before first administration of study drug until 90 days after the last administration of study drug. It is also recommended that a male subject with a female partner of childbearing potential employ a highly effective contraceptive method throughout this same period of time. Females of childbearing potential will undergo

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria:** If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-Clinical Data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (Pgp) inhibitors 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 an	**Subject Selection:** Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. **Subject Monitoring:** Subjects' concomitant medication usage will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].	reviewed prior to inclusion and monitored throughout the study. Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.

3.3.2. Benefit Assessment

The proposed study with GSK2982772 will be conducted in healthy volunteers; no medical benefit will be derived by volunteers' participation. Subjects will indirectly gain through their contribution to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

The known risks associated with GSK2982772 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential subjects is considered low. Routine safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, cardiac rhythm monitoring, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff.

The study will be conducted in a hospital-based unit or unit with immediate access to hospital facilities for the treatment of medical emergencies. The in-house periods as detailed in the SoA (Section 2) will allow for continuous medical monitoring for all subjects following the first dose in each treatment group. Subjects will only be discharged from the unit 48 hours post-dose if the Investigator deems it safe to do so.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

4. OBJECTIVES AND ENDPOINTS

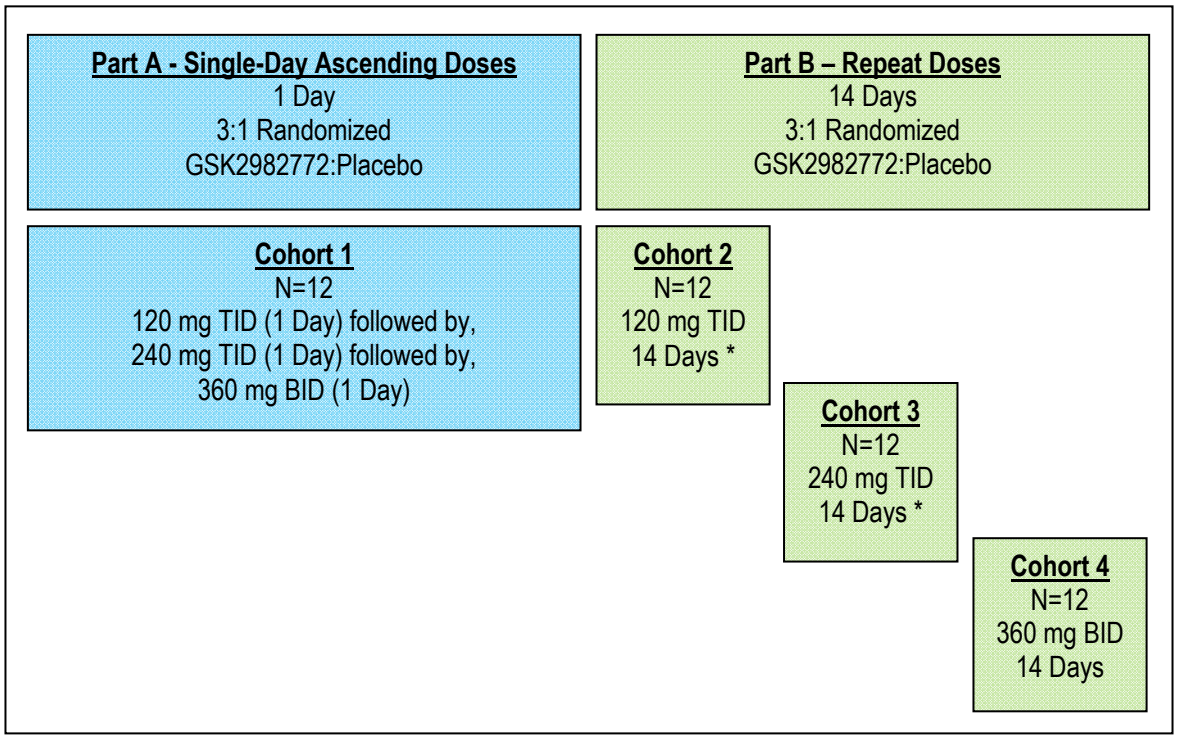
Objective	Endpoint
Primary	
• To investigate the safety and tolerability of repeat doses of GSK2982772 in healthy subjects.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature). • Physical examinations. • 12-Lead ECG monitoring.
Secondary	
• To characterise the pharmacokinetic (PK) profile of repeat doses of GSK2982772 in healthy subjects.	• A 24 hr profile to be collected on Day 1 of Part A and Day 14 of Part B. On Day 1 of Part B, the PK profile will be evaluated following the first dose only. Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr ($AUC_{(0-24)}$) and AUC over each dose interval (i.e. $AUC_{(0-7)}$, $AUC_{(7-14)}$ and $AUC_{(14-24)}$ for TID and $AUC_{(0-12)}$ and $AUC_{(12-24)}$ for BID). Maximum observed plasma drug concentration (C_{max}) following each dose, time to maximum observed plasma drug concentration (T_{max}) following each dose, observed trough plasma drug concentrations (C_0, C_7, C_{14} and C_{24} for TID dosing and C_0, C_{12} and C_{24} for BID dosing).
• To assess the impact of food on the PK of repeat doses of GSK2982772 in healthy subjects at steady state	• Derived PK parameters for GSK2982772, including $AUC_{(0-7)}$, $AUC_{(7-14)}$, C_{max}, after 1st dose of day and T_{max} after 1st dose of day.
• To assess potential effect of repeat doses of GSK2982772 on CYP3A4 enzyme activity.	• Plasma 4β-hydroxycholesterol to cholesterol ratio pre-treatment and following 14 days of repeat dosing of GSK2982772.
Exploratory	
• To investigate the levels of circulating glucuronide metabolite (M8; GSK3562183) and desmethyl metabolite (M9; GSK2997852) in healthy subjects after single-day and repeat dosing of GSK2982772.	• Quantify M8 (GSK3562183) and M9 (GSK2997852) in select plasma PK samples after single-day dosing and at pre-dose and 2 hr following Day 14 of repeat dosing of GSK2982772.

5. STUDY DESIGN

5.1. Overall Design

This is a single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772, in repeat oral doses in healthy subjects. The study design schematic is depicted in Figure 1.

Figure 1 Study Design



*With Food Effect Treatment

This study is planned to include approximately 48 subjects and consists of 2 parts:

- Part A (Cohort 1) – single ascending dose, randomized, placebo-controlled, 3-way crossover.
- Part B (Cohorts 2, 3 and 4) – repeat dose, randomized, placebo-controlled, sequential-group.

For TID dosing, GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval. For BID dosing, GSK2982772 or placebo will be administered using a 12hr dosing interval.

The impact of food on the PK of GSK2982772 will be investigated during the 14 Day repeat dose phase of the study (Part B) in Cohorts 2 and 3. On Days 1 to 14, subjects will fast for 8hr overnight. Breakfast will be served 2hr after dosing on Days 1 through 8, 10,

12 and 14. A standard breakfast will be served 30 minutes prior to dosing on Day 9, and a high fat breakfast will be served 30 minutes prior to dosing on Day 11.

All of the Cohorts in this study will be double-blind with respect to the subjects, investigator and site staff (with the exception of the site pharmacist). The Sponsor, the GSK study team, will be unblinded throughout.

5.2. Number of Participants

Sufficient number of healthy subjects will be enrolled, such that approximately 12 subjects in each Cohort complete dosing and critical assessments. If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Subjects that participate in Part A of the study cannot participate in Part B.

5.3. Sentinel Dosing

Sentinel dosing will be employed within each dosing period in Part A of the study. The doses in the single-ascending dose portion of the study (Part A) will be staggered such that for each of the three treatment periods, on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and AEs) through approximately 24 hours after their last dose on Day 1, the remaining subjects may be randomized to dosing in that period. The doses in the repeat dose portion of the study (Part B) will be staggered such that for each treatment period on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo) and dosed for at least 7 days before the rest of the cohort is randomized. If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence, at the discretion of the Sponsor in consultation with the investigator.

5.4. Dose Escalation Decisions

The decision to proceed to the next dose level of GSK2982772 within the study will be made by a Dose Escalation Committee (DEC) consisting of Principal Investigator, or delegate, and other relevant GSK clinical staff (See Section 10.5).

5.5. 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 (Section 2).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5.6. Scientific Rationale for Study Design

In Part A, each cohort will initially evaluate the safety, tolerability and PK of GSK2982772 administered for 1 day as a TID or BID dosing regimen (Cohort 1).

In Part B, the 14-day TID or BID repeat dosing (Cohort 2, 3 and 4) was chosen since it will provide sufficient safety and tolerability data to bridge to longer duration studies with the recently achieved safety margins from the 13-week toxicology study in monkeys. In the previous FTiH study (200975), GSK2982772 was administered up to 120 mg BID for 14 days and was well tolerated with no safety concerns identified. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

Cohort 4, 360 mg BID dosing regimen, may only be evaluated if the results of a modified release (MR) formulation study (205017) being conducted in parallel with the current study indicate that a MR formulation is not feasible for GSK2982772. In which case a BID regimen using the current immediate release formulation may be taken forward in to Phase 2a PoC studies. Additionally, Cohort 4 dose may be modified to include the repetition of a previous or lower TID or BID dose based on the results of the safety and tolerability review or if further characterization of the safety profile at a previously tested dose is required.

In the previous FTiH (Study 200975), the impact of a high-fat meal on the absorption of GSK2982772 was investigated following single dose administration of GSK2982772 at a dose of 40 mg. The rate and extent of absorption was similar in the fed state as compared to the fasted state, although there was evidence of a time lag in the absorption in the fed state, probably as a result of delayed gastric emptying. It is likely that higher doses to be used in this study will have a similar food effect to that observed at 40 mg. Therefore, this study plans to evaluate the impact of food during the repeat dose phase in Cohorts 2 and 3 rather than conducting a standalone single dose food effect PK study.

5.7. Dose Justification

An adaptive dose-escalation approach, guided by the observed safety, tolerability and plasma PK exposure will be taken to allow an efficient evaluation of a range of doses above the 120 mg BID dose that was evaluated in the FTiH study.

The initial starting dose planned is 120 mg TID and the maximum daily dose is anticipated to be approximately 720 mg administered as 240 mg TID and 360 mg BID.

For doses of up to 120 mg BID, the pharmacokinetics of GSK2982772 are approximately linear. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. After attainment of C_{max}, at approximately 2 hours post-dose, GSK2982772 concentrations decline rapidly until about 12 hours post-dose, with a $t_{1/2}$ of approximately 2 to 3 hours. The majority of the systemic exposure to GSK2982772 is observed within the first 12 hours after administration. Following repeat dosing of GSK2982772, there is no evidence of drug accumulation for either a QD or BID dosing regimen. The major circulating metabolite is an N-glucuronide which accounts for approximately 70% of drug related material in plasma. Since glucuronidation is a high

capacity clearance mechanism it is unlikely that the kinetics of GSK2982772 will become saturable with more frequent dosing nor at the higher doses planned in the current study.

Due to the short half-life of GSK2982772 (~2-3 hr), it is expected that steady-state will be achieved by Day 2 of dosing and that negligible accumulation will be observed. Therefore, the PK safety margins described for Day 1 and for Day 14 of dosing will be similar.

The predicted mean $AUC_{(0-24)}$ for the highest planned doses of 240 mg TID and 360 mg BID (40.2 µg*h/mL) approximates parity with the mean $AUC_{(0-24)}$ observed at the NOAEL (30 mg/kg/day) in the 13-week monkey toxicology study (48.4 µg*h/ml). Mean C_{max} values for the 240 mg TID (3.21 µg/mL) and 360 mg BID (4.31 µg/mL) doses are predicted to be $1/4^{th}$ and $1/3^{rd}$ respectively, of the C_{max} observed at the NOAEL (12.3 µg/mL). The doses for Cohorts 2 and 3 may be adjusted based on PK/safety data from previous treatment periods. It is planned that the 95^{th} percentile for the predicted $AUC_{(0-24)}$ values will not exceed the maximum $AUC_{(0-24)}$ value observed at the NOAEL and for C_{max} the 95^{th} percentile will not exceed the mean C_{max} and the NOAEL. The current predicted 5^{th} -95^{th} percentiles for $AUC_{(0-24)}$ and C_{max} values using repeat dose PK data from FTiH study and mean/individual $AUC_{(0-24)}$ and C_{max} values from the 13-week Monkey Study at 30 mg/kg/day (NOAEL) and 100 mg/kg/day are shown in Figure 2 and Figure 3, respectively.

Figure 2 Mean and 95% Prediction Interval for Human AUC(0-24) Values versus Mean and Individual Monkey AUC(0-24) Values at Week 13

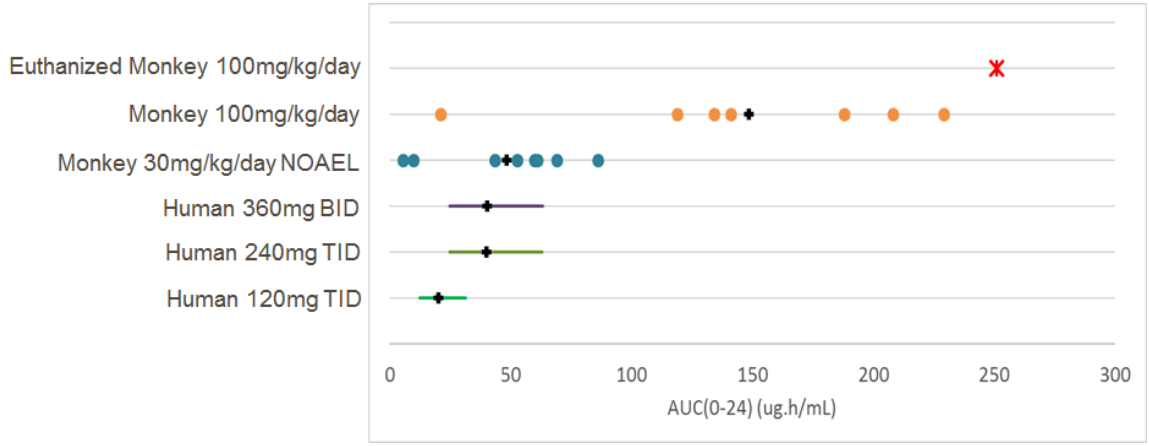
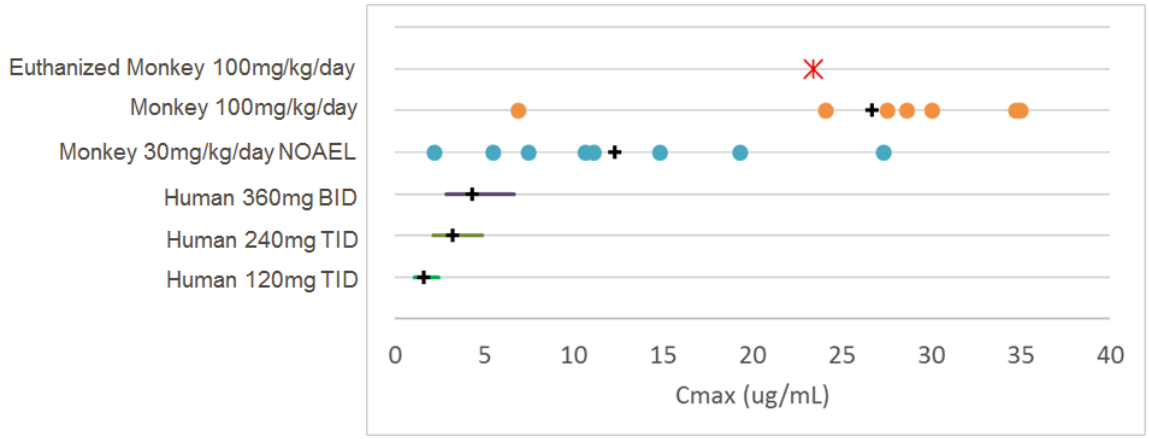


Figure 3 Mean and 95% Prediction Interval for Human Cmax values Versus Mean and Individual Monkey Cmax values at Week 13



6. STUDY POPULATION

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

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. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. Note: Screened subjects with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigator.

WEIGHT
3. Body weight ≥50 kg and body mass index (BMI) within the range 19 - 30 kg/m^2 (inclusive).

SEX
4. Male and/or Female Subjects **a. Male participants:** A male participant with a female partner of reproductive potential must agree to use contraception as detailed in Appendix 5 of this clinical study proposal 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 for a minimum of 28 days days prior to the treatment period and for at least 30 days after the last administration of study drug. A WOCBP using a hormonal method of highly effective contraception must also agree to partner use of a male condom during the treatment period and for at least 30 days after the last administration of study drug.

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 or presence of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, 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. History of herpes zoster (shingles) reactivation.
3. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) QuantiFERON-TB Gold test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression.
4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones)

7. QTc >450 msec

   NOTES:

   - The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read.
   - The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial.
   - For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

8. History of serious or recurrent infections or has had an active infection within 14 days of receiving study medication.
9. History of diagnosis of obstructive sleep apnoea or significant respiratory disorder. Childhood asthma that has fully resolved is permitted.
10. Part A: History of active SIB within the past 6 months or any history of attempted suicide in a participant's lifetime.
11. History of current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.

PRIOR/CONCOMITANT THERAPY

12. Past or intended use of over-the-counter or prescription medication, including herbal medications, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is the longest) prior to dosing. Specific medications listed in Section 7.6 may be allowed.
13. Subject received a vaccine (either live attenuated or now-live) within 30 days prior to randomisation, or plans to receive a live attenuated vaccine within 30 days + 5 half-lives (32 days) of the last dose of study medication.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE

14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56-day period.
15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
16. The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

DIAGNOSTIC ASSESSMENTS
17. Presence of Hepatitis B surface antigen (HBsAg) at screening Positive Hepatitis C antibody test result at screening. 18. Positive pre-study drug/alcohol screen. 19. Positive human immunodeficiency virus (HIV1 and 2) antibody test. 20. Regular use of known drugs of abuse. 21. Subjects with impaired renal function defined as Chronic Kidney Disease Epidemiology Collaboration (CKS-EPI) Creatinine > 1.6mg/dL with an age appropriate GFR ≤60 (mL/min/1.73 m^2) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Snyder, 2009 and Levey, 2010]. 22. An elevated C-reactive protein (CRP) outside of the normal reference range.
OTHER EXCLUSIONS
23. Regular alcohol consumption within 6 months prior to the study defined as: • For UK - an average weekly intake of >14 units for males and 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. 24. Cotinine or carbon monoxide levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening. 25. 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 26. Unwilling or unable to swallow multiple size 00 capsules as part of study participation.

PART B SPECIFIC CRITERIA
27. History of SIB as measured using the C-SSRS or a history of attempted suicide. 28. A positive anti-nuclear antibody (ANA) outside of the normal reference range. 29. Fasting total cholesterol ≥300 mg/dL or triglycerides ≥250 mg/dL.

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 7 days prior to each first dose of study treatment in Part A up until discharge from the unit. In Part B, subjects must refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the first dose of study treatment until after the final dose.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- During each dosing period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 6 months prior to screening until after the final follow-up visit.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Participants will abstain from travelling to regions of high endemic infection, as determined by the investigator, for the duration of the study.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 only on approval of the GSK Medical Monitor. Rescreened participants should be assigned the same participation number as for the initial screening.

7. TREATMENTS

The term study treatment is used throughout the protocol and 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

	Study Treatment	
Product name:	GSK2982772	Placebo
Formulation description	API filled capsule	Placebo blend filled capsule
Dosage form:	HPMC capsule	HPMC capsule
Unite dose strength(s)/Dosage level(s):	120 mg maximum fill per capsule	NA
Route of administration:	For oral use only	For oral use only
Dosing instructions:	Dose with water	Dose with water
Physical description:	Size 00, white, opaque capsule containing white to almost white solid	Size 00, white, opaque capsule containing white to almost white solid
Source of procurement	Study medication is supplied by GlaxoSmithKline	Study medication is supplied by GlaxoSmithKline
Method for individualizing dosage:	Site to assemble	Site to assemble

7.2. Method of Treatment Assignment

On Day -1 or Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to either GSK2982772 or placebo, according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software.

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to the site.

Study treatment will be dispensed at the study visits summarized in SoA. Each participant will be dispensed blinded study treatment, labelled with his/her unique randomization number, throughout the study. Returned study treatment should not be re-dispensed to the participants

In all four cohorts, subjects will be randomized in a 3:1 ratio to either GSK2982772 or placebo. In Cohort 1, the subjects will be randomized to one of four sequences (ABC, ABP, APC, PBC), where the treatments are:

A 120 mg TID
B 240 mg TID

C 360 mg BID
P Placebo

The planned dose levels are defined in Section 5.1.

The randomisation will reflect the fact that at least 2 of the 12 subjects (one subject will receive GSK2928772 and one subject will receive matched-placebo) will be dosed first (on Day 1) in each part to enable dose staggering.

Once a treatment allocation number has been assigned to a subject, it cannot be reassigned to any other subject.

7.3. Blinding

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

- The Investigator or treating physician will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will endeavour to ensure that there are no differences in time taken to dispense following randomization
- This 3rd party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator
- Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.
- The IVRS/IWRS will be programmed with blind-breaking instructions.
- In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination.
- If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.
- If a participant's treatment assignment is unblinded, GSK must be notified within 24 hours after breaking the blind.
- The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

- A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

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

7.4. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.5. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- 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.

7.6. 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 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 non-prescription 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 at doses of ≤2 grams/day, is permitted for use any time 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.

7.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK, or with GSK2982772, after completion of the study because only healthy volunteers are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Dose Modification/Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum total daily dose will not intentionally exceed the 13-week NOAEL exposure in monkeys. Currently, the highest planned dose is 720 mg/day of GSK2982772.

The decision to proceed to the next dose level of GSK2982772 in each part of this study will be made by the DEC, including the Medical Monitor and the Investigator and relevant clinical site staff (see Section 10.5) based on safety, tolerability, and preliminary PK data obtained in at least 6 subjects (through at least 24 hours post-dose) with at least 6 subjects having received active treatment (GSK2982772) at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed the PK criteria defined in Section 8.1.2. Planned doses may also be repeated.

The Principal Investigator and the GSK Medical Monitor will review the following and dosing **will be** halted and progression to the next higher dose level stopped if:

- One (1) or more subjects experience a SAE which has a reasonable possibility of relation to study drug.
- Two (2) or more subjects experience a severe or clinically significant non-serious AE (based upon investigator judgment) which has a reasonable possibility of relation to study drug.
- Two (2) or more subjects in a Part A cohort or 3 or more subjects in a Part B cohort experience the same AE of moderate severity which has a reasonable possibility of relation to study drug.
- Consistent Common Terminology Criteria for Adverse Events (CTCAE) Nervous System AEs of any grade occur across subjects that have a reasonable possibility of relation to study drug.

If dosing is halted and if deemed acceptable by GSK internal safety review to proceed with or modify dose escalation to further characterize the safety profile, a formal request with appropriate data and substantial amendment will be submitted to MHRA (Medicines and Healthcare Products Regulatory Agency) for approval.

8.1.2. Pharmacokinetic Dose Modification or Stopping Criteria

The 240 mg TID dose and/or the 360 mg BID dose in Cohorts 1, 3 and 4 may be adjusted up or down based on PK data from previous treatment periods. It is planned that the 95th percentile for the predicted $AUC_{(0-24)}$ values will not exceed the maximum $AUC_{(0-24)}$ value observed at the NOAEL and for C_{max} the 95th percentile will not exceed the mean C_{max} at the NOAEL.

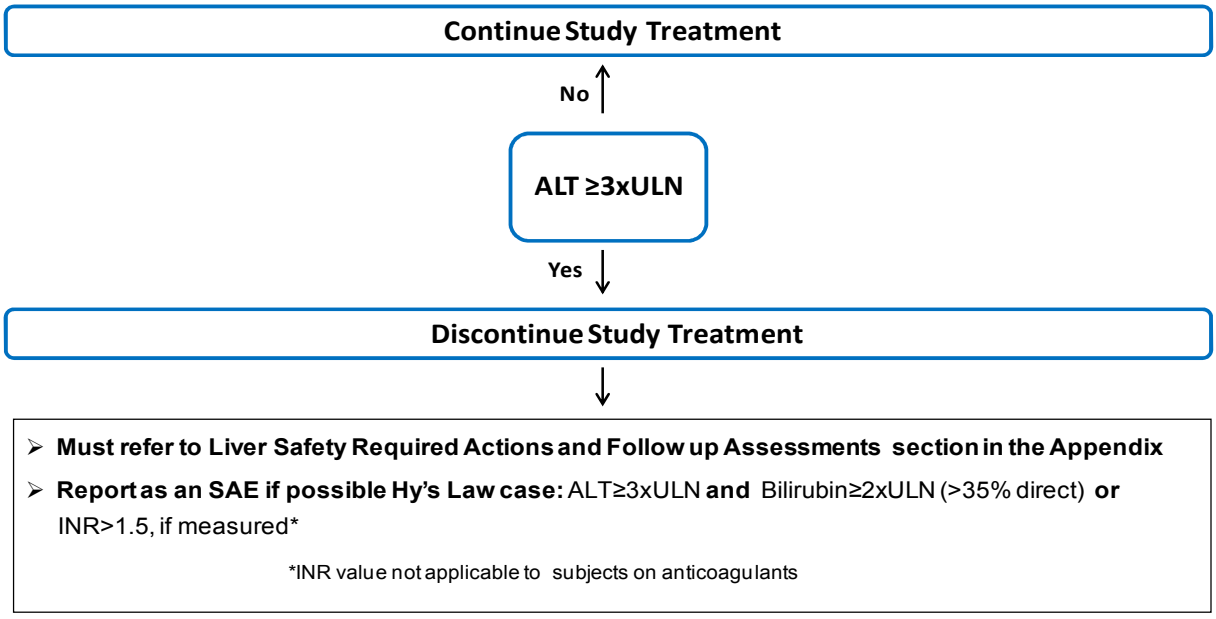
8.1.3. Liver Chemistry Stopping Criteria

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:

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes 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.

8.1.4. QTc Stopping Criteria

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

- QTcF > 500 msec,
- Change from baseline: QTc > 60 msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study (i.e., QTcF in this 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 QTcF, then QTcF 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 single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

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.

8.1.5. 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 (See Section 8.1.3) or QTc stopping criteria (see Section 8.1.4) are met.
- The participant experiences any signs of suicidal ideation or behaviour (See Section 9.3.6).

8.1.6. Group Safety Stopping Criteria

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

8.1.7. Nervous System Stopping Criteria

The CNS observations in the 4-week GLP toxicology study in monkeys were found to be random, diverse, and unpredictable in monkeys (see Section 3.3.1). There were no similar findings observed in the 13-week GLP toxicology study in monkeys. The CTCAE Nervous System is a monitoring tool which provides the Principal Investigator the appropriate guidance for grading of a neurological event. The significance of any neurological event experienced by a subject will be determined based on clinical judgment, characteristics of the event and/or based upon changes from a baseline assessment.

The Principal Investigator and the GSK Medical Monitor will review all neurological events utilizing the CTCAE Nervous System criteria and dosing may be halted if and progression to the next higher dose level stopped as per Section 8.1.1.

A subject will be withdrawn from the study if:

- A Grade 3 or greater CTCAE Nervous System finding is observed or a significant neurologic change from a subject's baseline physical examination is observed.
- Any adverse event included in the CTCAE for Nervous System, which is also considered to be clinically significant by the Principal Investigator, will be reviewed for potential subject withdrawal.

Note: Appendix 8 (Section 12.8) provides Guidance for Grading Adverse Events that is taken from the CTCAE Version 4.03.

8.1.8. Rechallenge

8.1.8.1. 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. The reason for withdrawal should be documented in the 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- 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.

If a subject chooses to withdraw from the study after dosing, then the Investigator must make every effort to complete the follow-up assessments detailed in the SoA (Section 2).

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 medical record.
- 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.

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 (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 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. 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).

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

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- 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 immediately and under no circumstance should this exceed 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.

9.1.2. 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.

9.1.3. 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, and non-serious AEs of special interest (as defined in Section 3.3.1), 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.

9.1.4. 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, IRB/ IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the

sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat an overdose as and when they are made aware of this.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days for 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.

9.3. Safety Assessments

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

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) 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.

9.3.2. Neurological Exams

Neurological examination will include, at a minimum, assessment of: mental status, gait, balance, coordination, cranial nerves, motor power, reflexes, and sensory system (light touch and pain). Assessments will be standardized across all scheduled time points (see SoA). Significant changes from the baseline or any clinically significant changes will be noted as part of further scheduled examinations or unscheduled examinations (if needed).

Clinically significant abnormalities or changes in status from baseline will be:

- entered as an adverse event,
- may trigger increased monitoring of the subject(s),
- may result in withdrawal of the subject (see Section 8.2),
- may result in referral to a specialist.

9.3.3. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- In Part A and B on Day 1, vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure measurements pre-dose on Day 1 (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

9.3.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession with at least 2 minutes but no more than 10 minutes apart.
- Continuous cardiac telemetry will be performed at time points indicated in the SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

9.3.5. 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.
- 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 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 SRM and the SoA.

9.3.6. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There is some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some subjects. 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 and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

Families and caregivers of participants 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) in Part B only, the Baseline/Screening assessment of suicidal ideation and behaviour and treatment emergent suicidal ideation and behaviour will be monitored during study 205184 using C-SSRS. At Days 7 and 17 of the study, the ‘Since Last Visit C-SSRS’ will be completed. Refer to Section 2, SoA, for more information.

Subjects who answer ‘Yes’ to any suicidal behaviour or ‘Yes’ to suicidal ideation Questions 4 or 5 will be referred to their General Practitioner (GP) or appropriate

psychiatric care. The medical monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 9.1). 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.

9.4. Pharmacokinetics

9.4.1. Blood Sample Collection

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of GSK2982772 at the time points indicated in Section 2, SoA Tables. The actual date and time (24-hour clock time) of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of M8 (GSK3562183) and M9 (GSK2997852). This will be collected at the time points indicated in Section 2, SoA Tables. The actual date and time of each blood sample collection will be recorded.

Blood will be collected into EDTA tubes and processed to plasma for 4β-hydroxycholesterol and cholesterol. This will be collected at the time points indicated in Section 2, SoA Tables. The actual date and time of each blood sample collection will be recorded.

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

9.4.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of GSK2982772 will be determined in plasma samples, and concentrations of M8 (GSK3562183) and M9 (GSK2997852) will be determined in select plasma samples, using the currently approved bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma sample has been analysed for GSK2982772 (or M8 [GSK3562183] and M9 [GSK2997852] as indicated above), any remaining plasma sample may be analysed for any compound-related material and the results may be reported as part of this study or under a separate PTS-IVIVT, GlaxoSmithKline protocol.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.4.3. Plasma Sample for CYP3A4 Enzyme Activity

Plasma derived from select PK blood samples in Part B (as in the SoA Table), will be analyzed for 4β-hydroxycholesterol and cholesterol as a potential *in vivo* marker of CYP3A4 enzyme activity. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential marker.

Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SRM.

Baseline and Day 14, post-treatment plasma samples will be analyzed using a validated, specific, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method to determine concentrations of 4β-hydroxycholesterol and total cholesterol. A comparison will be made between the ratio of 4β-hydroxycholesterol : cholesterol at baseline and on Day 14 to assess potential changes in CYP3A4 enzyme activity following GSK2982772 treatment.

Analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of PTS-IVIVT and Third Party Resource, GlaxoSmithKline.

9.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study Reference Manual.

9.7. Pharmacological Biomarkers

Pharmacological biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

The objectives of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK2982772. No formal hypotheses will be tested.

An estimation approach will be used to describe PK of GSK2982772, where point estimates and corresponding 90% confidence intervals will be constructed.

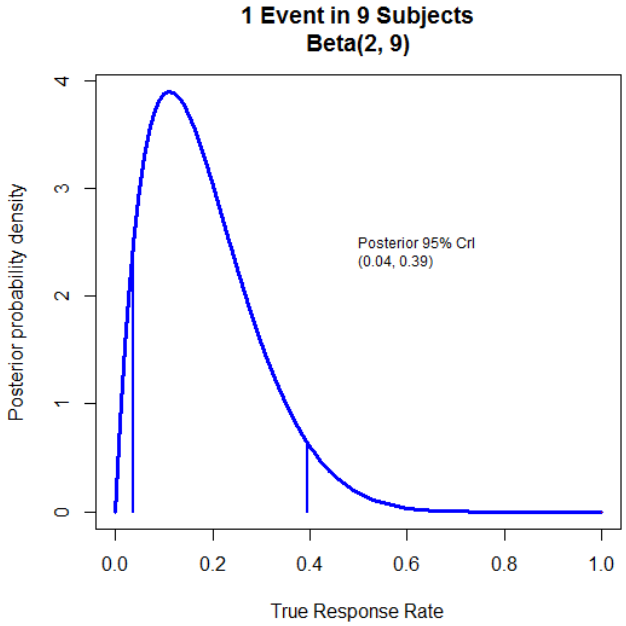
10.1. Sample Size Determination

No statistical techniques were used to calculate the sample size, and sample size is based on feasibility.

The primary objective of the study is safety, where the number of safety events are of interest. A maximum of 9 subjects will receive each active dose and; therefore, if 0/9 of a particular safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 33.6% could not be ruled out. Whereas if 1/9 of the same safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 48.2% could not be ruled out.

Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe one safety event in 9 then the posterior distribution would be Beta (2, 9), as outlined below:

Bayesian Approach to Determine Confidence in a Safety Event.



Thus, we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.39.

Pharmacokinetic Parameters

To date the pharmacokinetics of GSK2982772 have been studied up to 120 mg BID. The maximum between-subject coefficient of variation (CVb) for $AUC_{(0-\tau)}$ and C_{max} observed in study 200975 was 27.1 and 36.1 respectively.

Based on these estimates of variability, slightly more conservative for a cross-over study and a sample size of 9 completers in Cohort 2, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of AUC and C_{max} will be within approximately 17.9% and 24.2% of the point estimate, respectively.

10.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of subjects who completed each active dose, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 10.1 Sample Size Determination) would change. These changes are outlined in Table 1:

Table 1 Safety Events - Sample Size Sensitivity

N Completing Cohort	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95%CI indicating that a true incidence rate of x% could not be ruled out
9	2	60.0%
	3	70.0%
	4	78.8%
8	0	36.9%
	1	52.7%
	2	65.1%
	3	75.5%
7	0	41.0%
	1	57.8%
	2	70.9%
	3	81.6%

Pharmacokinetic Parameters

A sample size sensitivity analysis has also been conducted on the PK parameters to investigate the effect of fewer number of subjects, or 10% difference in the between-subject coefficient of variation on the precision of the point estimate. These changes are outlined in Table 2:

Table 2 Pharmacokinetic Parameters – Sample Size Sensitivity

	Number of Subjects	CVb	Precision (%)
Cmax	6	26.1%	29.8
	6	28.8%	33.4
	6	31.5%	37.0
	9	19.6%	21.7
	9	21.7%	24.2
	9	23.7%	26.7
AUC(0-tau)	6	19.7%	21.8
	6	21.9%	24.5
	6	24.0%	27.1
	9	14.9%	16.1
	9	16.5%	17.9
	9	18.1%	19.8

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	The 'PK Population' is defined as subjects in the 'Safety' population for whom a PK sample was obtained and analyzed.

10.4. Statistical Analyses

10.4.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

All safety analyses will be performed on the Safety Population.

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

10.4.2. PK Analyses

Endpoint	Statistical Analysis Methods
Secondary	PK analyses will be described in the RAP. The PK of TID and BID dosing on Day 1 in Part A will be evaluated. In Part B the comparisons of interest will be: The PK profile following the 1st dose of the day following administration in the fed state (standard meal on Day 9 and high fat meal on Day 11) or in the fasted state (Day 14). The pharmacokinetic profile following the 1st dose on Day 14 (fasted) and the 1st dose on Day 1 (fasted); Pharmacokinetic data will be listed and presented in graphical form and will be summarized descriptively. Statistical summaries of the PK parameter data will be the responsibility of

Endpoint	Statistical Analysis Methods
	Clinical Statistics, GlaxoSmithKline. Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters by treatment. In addition, for loge-transformed variables geometric mean, 95% confidence interval and %CVb (100 * √ (exp(SD_2) -1)) will be provided, where the SD is the standard deviation of log-transformed data.

10.4.3. Other Analyses

Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum) of circulating glucuronide metabolite (M8; GSK3562183) and des-methyl metabolite will be investigated in healthy subjects after single-day and repeat dosing of GSK2982772.

10.4.4. Interim Analyses

An interim analysis may be performed during the study on completed cohorts in Part A and Part B of the study to aid internal decision making only. There will be no changes to the study design or planned number of subjects in future cohorts as a result of the interim analysis.

For Parts A and B of the study, interim PK analyses will be performed on plasma GSK2982772 concentration-time data generated during the conduct of this study.

The decision to proceed to higher dose strengths will be made by the DEC based on assessment of safety, tolerability and pharmacokinetic data at the preceding dose. The exception to this will be in Part A where only a safety assessment (not PK) for the 120 mg TID dose will be performed. To date, the PK of GSK2982772 has been well-characterised up to 120 mg BID in the FTiH study and the 120 mg TID for Part A represents a 50% increase in dose where PK simulations are predictable. This analysis can include review of individual subject data, summaries, graphical presentations and/or statistical analysis.

The RAP will describe the planned interim analyses in greater detail.

10.5. Dose Escalation Committee

The decision to proceed to the next dose level of GSK2982772 in each Cohort will be made by a DEC consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Clinical Investigational lead and/or Study Team Leader, GSK Pharmacokineticist, a GSK GCSP representative and GSK Statistician. All GSK personnel including the GSK Statistician and the GSK Pharmacokineticist will remain unblinded throughout the course of the study.

For Part A, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: listings of all AEs, clinical laboratory results, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and PK results derived from 24-hour plasma profiles.

The decision and selection of dose to proceed to Part B, will be made by the DEC based on safety, tolerability, and PK data from the same dose levels evaluated in Part A.

For Part B, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: listings of all AEs, clinical laboratory results, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry) and ECG findings through Day 16 of the previous cohorts(s) in Part B. Also included will be any PK results derived through at least Day 7 of the previous cohort(s).

11. REFERENCES

Berger SB, Kasparcova V, Hoffman S, Swift B, Dare L, Schaeffer M, et al. Cutting edge: RIP1 kinase activity is dispensable for normal development but is a key regulator of inflammation in SHARPIN-deficient mice. J Immunol. 2014; 192(12):5476-80.

GlaxoSmithKline Document Number 2014N204126_02. GSK2982772 Investigator's Brochure, Version 3. Effective Date: 27-January-2017.

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

Levey AS and Stevens LA. Estimating GFR Using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation: More Accurate GFR Estimates, Lower CKD Prevalence Estimates and Better Risk Predictions. Am J Kidney Dis. 2010; 55:622-627.

Ofengeim D and Yuan J. Regulation of RIP1 kinase signalling at the crossroads of inflammation and cell death. Nat Rev Mol Cell Biol. 2013; 14(11):727-736.

Snyder JJ, Foley RN, and Collins AJ. Prevalence of CKD in the United States: A Sensitivity Analysis Using the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2009; 53(2):218-228.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ANA	Anti-nuclear Antibody
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-7)}$	Area under the concentration-time curve from time zero to 7 hours post first dose (TID dosing)
$AUC_{(7-14)}$	Area under the concentration-time curve from 7 to 14 hours post first dose (TID dosing)
$AUC_{(14-24)}$	Area under the concentration-time curve from 14 to 24 hours post first dose (TID dosing)
$AUC_{(0-12)}$	Area under the concentration-time curve from 0 to 12 hours post first dose (BID dosing)
$AUC_{(12-24)}$	Area under the concentration-time curve from 12 to 24 hours post first dose (BID dosing)
$AUC_{(0-24)}$	Area under the concentration-time curve from time zero to 24 hours post first dose
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
$AUC_{(0-\tau)}$	AUC from 0 hours to the time of next dosing.
BID	Twice a day
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CVb	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4

DEC	Dose Escalation Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FSH	Follicle stimulating hormone
FTiH	First Time in Human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HPMC	Hydroxypropylmethyl cellulose
HR	Heart Rate
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IgG	Immunoglobulin G
IP	Investigational Product
IRB/IEC	The Institutional Review Board/ Independent Ethics Committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kg	Kilogram
LDH	Lactate dehydrogenase
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
mg	Milligram
mL	Millilitre
MR	Modified Release
MS	Multiple Sclerosis
MSDS	Material Safety Data Sheet
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	No observable adverse effect limit
NTI	Narrow Therapeutic Index
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
PoC	Proof of Concept
PsO	Psoriasis
PSRAE	Possible Suicidality Related Adverse Event
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula

QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RIP1	Receptor-interacting protein-1
SAE	Serious Adverse Event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SIB	Suicidal Ideation Behaviour
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse events
TB	Tuberculosis
TID	Three times a day
T_{max}	Time taken to maximum observed plasma drug concentration
TNF	Tumour Necrosis Factor
TNFR1	Tumour Necrosis Factor Receptor-1
UC	Ulcerative Colitis
UDP	Uridine diphosphate
µg	Microgram
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	Upper Limit of Normal
WOCBP	Woman of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Quantiferon

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the Doctor's Laboratory.
- 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.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red Blood Cell (RBC) Indices: Mean Corpuscular Volume (MCV) Mean corpuscular haemoglobin (MCH) %Reticulocytes	White Blood Cell (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
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (Fasted)[2]	Calcium	Alkaline phosphatase	Albumin
			Anti-nuclear antibody [(ANA), Part B only]	C-reactive protein (CRP)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Alcohol breath test and urine drug screen (to include at minimum:			

Laboratory Assessments	Parameters
	amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Smoking Breath Test • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential). To be done at screening and Day 17 of Part B. • Urine hCG pregnancy test (as needed for women of child bearing potential)[3] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Tuberculosis test • Total Cholesterol, Low-density lipoprotein, triglycerides (Part B only) • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula. 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 (excluding studies of hepatic impairment or cirrhosis).
2. Non-fasted samples can be collected on Day -1 (All Parts) and at the Follow-Up visit (Part A Only).
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Laboratory that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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 medical record 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 or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with Standard Operating Procedure (SOP)-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

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 multicenter 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

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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 (e.g., 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.

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

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 assessmentse.g.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 (i.e., 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 (e.g., 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 (e.g., 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 (e.g., 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.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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.
- 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 Paper CRF
• Email transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of email 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 Study Reference Manual.

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 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 treatment phase and until at least 90 days after the last administration of study drug:
    - 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 and recommend subject or partner use of an additional method of contraception with a failure rate of <1% per year as

described in Table 4 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
- In addition, male participants must refrain from donating sperm for duration of study and for 90 days after study completion or from last dose

Female participants

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 4 for a minimum of 28 days prior to the first dose of study drug and until at least 30 days after the last administration of study drug. For female particpants using a hormonal method of contraception, partner use of male condoms is also required during the treatment period and until at least 28 days after the last administration of study drug.

Table 4 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[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • 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.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case the use of a male condom should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing 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.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the test kit approved by the sponsor and in accordance with instructions provided in its package insert.

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

Any female participant who becomes pregnant while participating will discontinue study treatment.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

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

12.7. Appendix 7: 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 hr
• 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 24 hours 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 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:

• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hr** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	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. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
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.

12.8. Appendix 8: Nervous System Adverse Events (CTCAE Criteria)

Taken from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

The purpose of this Appendix is to provide guidance and is to be used in conjunction with the Investigator's judgment.

Table 5 Guidance For Grading Adverse Events

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-	A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-	A disorder characterized by systematic and extensive loss of memory.
Aphonia	-	-	Voicelessness; unable to speak	-	-	A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-	A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-	A disorder characterized by a conspicuous change in cognitive function.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-	A disorder characterized by a deterioration in the ability to concentrate.
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death	A disorder characterized by a decrease in ability to perceive and respond.
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-	A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-	A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-	A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-	A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated		A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a pathologic process involving the brain.
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by a reduction in the strength of the facial muscles.
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the facial nerve (seventh cranial nerve).
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-	A disorder characterized by characterized by excessive sleepiness during the daytime.
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by bleeding from the cranium.
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-	A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum ± mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum ± moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death	A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-	A disorder characterized by a deterioration in memory function.
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by uncontrolled and purposeless movements.
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by intense painful sensation along a nerve or group of nerves.
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involuntary movements of the eyeballs.
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the olfactory nerve (first cranial nerve).
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral motor nerves.
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Presyncope	-	Present (e.g., near fainting)	-	-	-	A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by paralysis of the recurrent laryngeal nerve.
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by characterized by excessive sleepiness and drowsiness.
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death	A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.
Syncope	-	-	Fainting; orthostatic collapse	-	-	A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-	A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	-

12.9. Appendix 9: Protocol Amendment History

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

TITLE PAGE

Protocol Title: A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects.

Protocol Number: 205184/ Amendment 02

Short Title: GSK2982772 high dose safety and PK study in healthy volunteers.

Compound Number: GSK2982772

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): EudraCT 2017-002662-45

Approval Date: 26-Feb-2018

SPONSOR SIGNATORY:

PPD

26th Feb 2018

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Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 02 Republishing	26-Feb-2018
Amendment 02	15-FEB-2018
Amendment 01	07-DEC-2017
Original Protocol	31-JUL-2017

Amendment 02 Republishing 26-Feb-2018

Overall Rationale for the Amendment:

Due to a number of asymptomatic, non-serious and self-limiting cardiac arrhythmias observed in Cohorts 1 and 2 prompting a temporary dosing hold, the 120 mg TID for 14 days will be repeated in Cohort 3. The randomization ratio has been changed to 9:5 (Active:Placebo) in the remaining Cohorts of Part B (Cohorts 3, 4 and 5) to provide a more balanced comparison between subjects on active and placebo. Furthermore, 24 hour Holter monitoring will now be conducted at the screening visit to better understand the background telemetry patterns of each subject prior to the start of dosing.

Two additional PK timepoints will be collected on Day 1 in Cohorts 3 and 4 to enable the C_{max} to be determined following the second dose of the day.

In addition, further administrative clarifications have been made.

Section # and Name	Description of Change	Brief Rationale
1. Protocol Synopsis for Study 205184	The Study Design schematic has been updated to add Cohort 3 and adjust the randomization ratio from 3:1 to 9:5 in Cohorts 3, 4 and 5. The Type and Number of Participants has been raised to 14 subjects in each Cohort 3, 4 and 5, which has been reflected in the Treatment Groups Table.	Except for the two sentinel subjects in Cohort 2, dosing was not completed in this Cohort because of the temporary halt, therefore this dose level will be repeated under the new Cohort designation of Cohort 3. Cohort 3 will not require sentinel dosing since this was completed in the original dose level (Cohort 2).
5.1. Overall Design	Figure 1 Study Design has been updated to add an additional Cohort and adjust the randomization ratio from 3:1 to 9:5 in Cohorts 3, 4 and 5.	The randomization ratio for Cohorts 3, 4 and 5 has changed from 3:1 to 9:5, with the overall number of subjects participating in each of these Cohorts increasing from 12 to 14. This will provide a more balanced review with the number of subjects on active and placebo.
5.2. Number of Participants	The text has been edited to state that there will be 12 subjects in each Cohort 1 and Cohort 2 and 14 subjects in each of Cohorts 3, 4 and 5.	
5.3. Sentinel Dosing	The wording has been updated such that sentinel dosing will take place in all Cohorts, except Cohort 3.	
5.6. Scientific Rationale for Study Design	The additional Cohort (3) has been included in the rationale for Part B of the study.	
7.2. Method of Treatment Assignment	The randomization ratio has been changed from 3:1 to 9:5 in Cohorts 3, 4 and 5. No sentinel dosing will take place in Cohort 3.	
10.2. Sample Size Sensitivity	The title for Table 1 has been updated to Safety Events - Sample Size Sensitivity on Active Dose.	
2.2. Time and Events Table – Part B (Cohorts 2-5)	An additional row has been added to the SoA to include 24-hour Holter monitoring at screening.	24-hour Holter monitoring has been included in the screening visit for Cohorts 3, 4 and 5 to better understand the background telemetry patterns of each subject prior to the start of study drug.
9.3.7. Holter	A section has been added to include 24-hour Holter monitoring	

Section # and Name	Description of Change	Brief Rationale
Monitoring	at screening.	
2.2. Time and Events Table – Part B (Cohorts 2-5)	2 additional PK timepoints have been added on Day 1 of the TID dose Cohorts, at 9hr and 11hr post-first dose of the day.	To ensure the C_{max} has been analysed after the second-dose of Day 1 in the TID Cohorts.
12.9. Appendix 9: Protocol Amendment History	The summary of changes from Protocol Amendment 01 have been moved from the Protocol Amendment Summary of Changes Table to Appendix 9.	Update for Protocol Amendment 02.

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1. PROTOCOL SYNOPSIS FOR STUDY 205184

Protocol Title: A single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772 in repeat oral doses in healthy subjects.

Short Title: GSK2982772 high dose safety and PK study in healthy volunteers.

Rationale: The purpose of this study is to evaluate the safety, tolerability and pharmacokinetics (PK) of repeat oral doses of GSK2982772 (TID and BID, if required) in healthy subjects. TID dosing will be administered as a 7hr, 7hr, 10hr dosing interval and BID as a 12hr dosing interval.

Objectives and Endpoints:

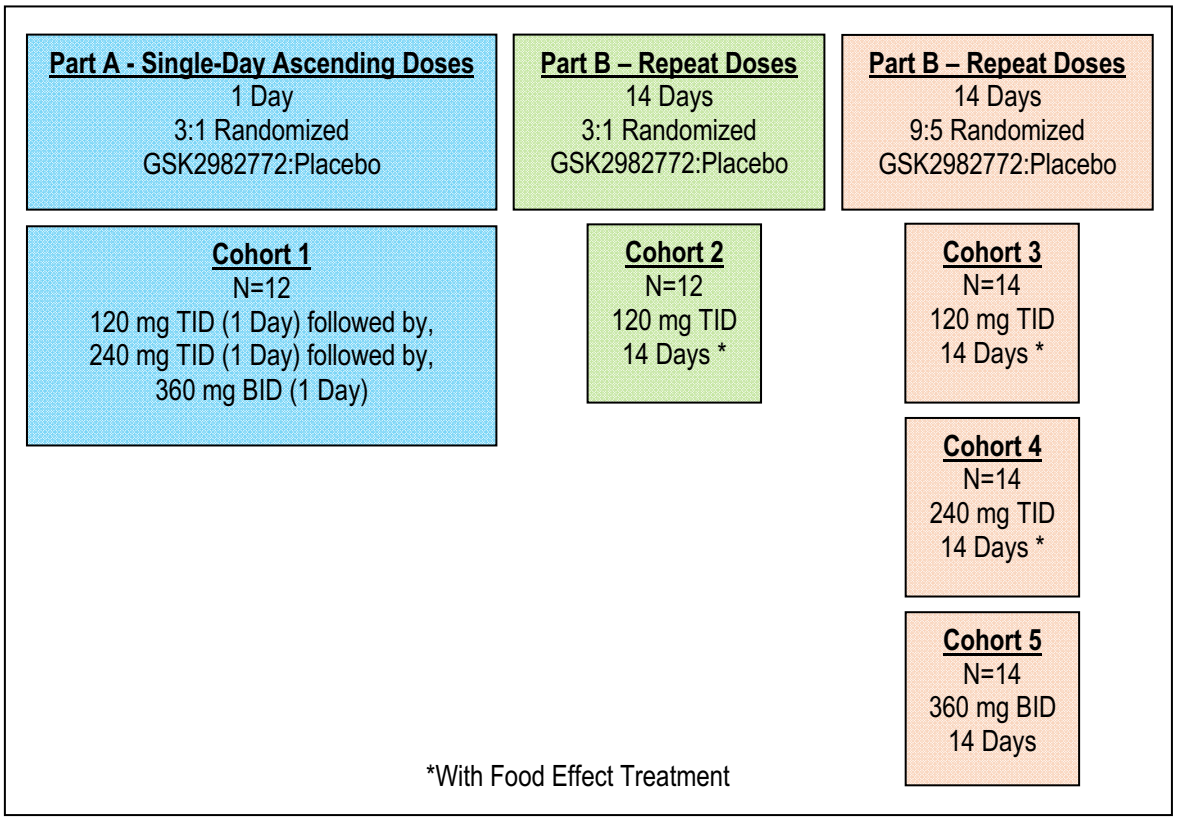
Objective	Endpoint
Primary	
• To investigate the safety and tolerability of repeat doses of GSK2982772 in healthy subjects.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature). • Physical examinations. • 12-Lead ECG monitoring.
Secondary	
• To characterise the PK profile of repeat doses of GSK2982772 in healthy subjects.	• A 24 hr profile to be collected on Day 1 of Part A and Day 14 of Part B. On Day 1 of Part B, the PK profile will be evaluated following the first dose only. Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr ($AUC_{(0-24)}$) and AUC over each dose interval (i.e. $AUC_{(0-7)}$, $AUC_{(7-14)}$ and $AUC_{(14-24)}$ for TID and $AUC_{(0-12)}$ and $AUC_{(12-24)}$ for BID). Maximum observed plasma drug concentration (C_{max}) following each dose, time to maximum observed plasma drug concentration (T_{max}) following each dose, observed trough plasma drug concentrations (C_0, C_7, C_{14} and C_{24} for TID dosing and C_0, C_{12} and C_{24} for BID dosing).
• To assess the impact of food on the PK of repeat doses of GSK2982772 in healthy subjects at steady state	• Derived PK parameters for GSK2982772, including $AUC_{(0-7)}$, $AUC_{(7-14)}$, C_{max}, after 1st dose of day and T_{max} after 1st dose of day.

Objective	Endpoint
• To assess potential effect of repeat doses of GSK2982772 on CYP3A4 enzyme activity.	• Plasma 4β-hydroxycholesterol to cholesterol ratio pre-treatment and following 14 days of repeat dosing of GSK2982772.
Exploratory	
• To investigate the levels of circulating glucuronide metabolite (M8; GSK3562183) and desmethyl metabolite (M9; GSK2997852) in healthy subjects after single-day and repeat dosing of GSK2982772.	• Quantify M8 (GSK3562183) and M9 (GSK2997852) in select plasma PK samples after single-day dosing and at pre-dose and 2 hr following Day 14 of repeat dosing of GSK2982772.

Overall Design:

This is a single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772, in repeat oral doses in healthy subjects. The study design schematic is depicted in the Figure below:

Study Design



Type and Number of Participants:

Healthy volunteer subjects will be enrolled, such that up to approximately 12 subjects (9 active, 3 placebo) in Cohorts 1 and 2 (up to approximately 24 in total) and 14 subjects (9 active, 5 placebo) in Cohorts 3, 4 and 5 (up to approximately 42 in total) complete dosing and critical assessments. A subject is defined to have completed the study when he/she has attended all study visits.

Sentinel dosing will be employed within each Cohort for both Part A and Part B of the study, except Cohort 3 since this was completed in the original dose level (Cohort 2). The doses in the single-ascending dose portion of the study (Part A) will be staggered such that for each of the three treatment periods, on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and adverse events) through approximately 24 hours after their last dose on Day 1, the remaining subjects may be randomized to dosing in that period. The doses in the repeat dose portion of the study (Part B) will be staggered such that for each treatment period on Day 1, two of the 12 subjects in Cohort 2 and two of the 14 subjects in Cohorts 4 and 5 will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo) and dosed for at least 7 days before the rest of the cohort is randomized. Assuming 2 subjects are dosed on Day 1 to 7 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and adverse events) through approximately Day 7, the remaining subjects may be randomized to dosing.

If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Replacement subjects will be assigned to the same treatment sequence (Cohort 1) or treatment (Cohorts 2-4) and start from the period to be replaced at the discretion of the Sponsor and in consultation with the Principal Investigator.

Treatment Groups and Duration:

The study duration, including screening and follow-up, is not expected to exceed 13 weeks for Part A and 8 weeks for Part B of the study.

Study Duration – Cohort 1

Screening	Approximately 28 days.
Number of Subjects	One Cohort of 12 subjects (N=12).
Treatment Period	Cohort 1 will comprise of three treatment periods, investigating three dosing regimens. Each dose regimen consists of 1 day treatment duration, with subjects in house for 4 nights (through at least 48 hours post-last dose). Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight, and will be released following completion of the assessments on Day 4 of each treatment period, provided there are no safety concerns.
Washout Period	Will be at least 7 days between dose regimens for an individual subject.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

Study Duration – Cohort 2

Screening	Approximately 28 days.
Number of Subjects	One Cohort of 12 subjects (N=12).
Treatment Period	The treatment duration will be 14 days. Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight and will be released following completion of the assessments on Day 17, provided there are no safety concerns.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

Study Duration – Cohorts 3, 4 and 5

Screening	Approximately 28 days.
Number of Subjects	Three Cohorts of 14 subjects each (N=42).
Treatment Period	The treatment duration will be 14 days. Subjects will be admitted to the unit the day before dosing, will remain in the unit overnight and will be released following completion of the assessments on Day 17, provided there are no safety concerns.
Follow-up	At least 7 days and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Schedule of Activities (SoA) tables (Section 2.1 and Section 2.2), are essential and required for study conduct.

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA tables (Section 2.1 and Section 2.2).

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:

    1. 12-Lead ECG
    2. Vital Signs
    3. Blood Draws

Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

- The timing and number of planned study assessments, including safety, pharmacokinetic, or other assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File, which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.
- The Institutional Review Board/Independent Ethics Committee (IRB/IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.

A table defining the allowed variance in timings of assessments without being considered a protocol deviation will be included in the SRM.

2.1. Time and Events Table – Part A (Cohort 1)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Outpatient Visit	X						X	
Admission to Clinical Unit		X						
Inpatient Stay at Clinical Unit			←==X==→					
Discharge from Clinical Unit						X		*Following completion of all assessments.*
Informed Consent	X							
Inclusion and Exclusion Criteria	X							
Demography	X							
Full Physical Examination	X							*Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination		X		X		X		
Height	X							
Weight	X							
Drug/Alcohol/Smoking Screen	X	X						*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/Drug/Alcohol History	X							
HIV, Hepatitis B and C Screening	X							
Tuberculosis Test	X							*Conducted at the standard practice of the site.*
Serum Pregnancy Test (WOCBP only)	X						X	
Urine Pregnancy Test (WOCBP only)		X				X		
Highly effective contraceptive method (WOCBP only)	X	X	X	X	X	X	X	*Must use method for a minimum of 28 days prior to first dose of study medication until the follow-up visit*
Contraception with male condoms (WOCBP using hormonal contraceptive method and male subjects with female partners of childbearing potential only)		X	X	X	X	X	X	

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Meals		X	X[a]	X	X	X		[a] *On Day 1, subjects will fast 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1.* ***TID dosing**: On Day 1, lunch and dinner will be served between 2 to 3hr prior to doses 2 and 3, respectively.* ***BID dosing:** On Day 1, lunch will be served approximately 4 to 5hr after dose 1. Dinner will be served between 2 to 3hr prior to dose 2. A snack may be consumed approximately 2 to 3hr after dose 2.* *Water is permitted with dosing and at all times. Subjects will receive standardized meals scheduled at the same time in each period.*
Haem/Chem/Urinalysis Test (Include Liver Chemistries)	X	X	X	X		X	X	*Non-fasted samples can be collected on Day -1 and Follow-Up Visit.*
PK Blood Sampling			X	X				***TID Dosing:** PK samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr, 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr, 14hr, 14hr 20min, 14hr 40 min, 15hr, 15hr 30min, 16hr, 17hr, 19hr, 22hr, 24hr.* ***BID Dosing:** PK samples to be taken pre-dose on Day 1 and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr, 12hr 20min, 12hr 40min, 13hr, 13hr 30min, 14hr, 15hr, 16hr, 19hr, 22hr, 24hr.* *Remaining PK plasma samples from Part A may be analysed for metabolite sampling.*
Neuro. Examination		←X→		X	←X→			***TID Dosing:** Neurological examinations to be conducted either on Day -1 or pre-dose Day 1 and then at the subsequent time points post first-dose on Day 1: 2hr, 9hr, 16hr, 24hr and 48hr. Then 24 and 48hr after the last dose administered on Day 1.* ***BID Dosing:** Neurological examinations to be conducted either on Day -1 or pre-dose Day 1 and then at the subsequent time points post first-dose: 2hr, 14hr, 24hr and 48hr. Then 24 and 48 hr after the last dose administered on Day 1.*
Telemetry			←X→					*Continuous at least 24hr post-evening dose. Initiate at least 15 min. prior to dosing.*
12-Lead ECG	X	X	T	X	←X→			*Vital signs to include HR, BP, temperature and respiration rate.* ***TID Dosing:** 12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)					**Follow-Up** (No more than 14 days post last dose)	**Notes**
		-1	1	2	3	4		
Vital Signs	X	X	T	X	←X→		X	*1 and then at the subsequent time points post first-dose: 40min, 2hr, 4hr, 7hr (pre-2nd dose), 9hr, 14hr (pre-3rd dose), 16hr, 24hr and 48hr. Then 24 and 48hr after the last dose administered on Day 1.* ***BID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day -1 and pre-dose on Day 1 and then at the subsequent time points post first-dose: 40 min, 2hr, 4hr, pre-2nd dose, 12hr 20 min, 14hr, 24hr and 48 hr. Then 24 and 48hr after the last dose administered on Day 1. T = Triplicate.*
Randomization		X						*Randomization can occur on either Day -1 or Day 1.*
Study Treatment			X[b]					[b] ***TID dosing:*** *GSK2982772 or placebo will be administered using a 7hr, 7hr dosing interval.* ***BID dosing:*** *GSK2982772 or placebo will be administered using a 12hr dosing interval.*
Pharmacogenetic Sample (PGx)			X					*A PGx blood sample is collected at the Day 1 visit, after the subject has been randomized and provided informed consent for genetic research. If the sample is not collected at the Day 1 visit, it can be collected at any time during the study after randomization.*
AE Review		←=======X======→					X	
SAE Review		←=======X======→					X	
Concomitant Medication Review	X	←=======X======→					X	

2.2. Time and Events Table – Part B (Cohorts 2-5)

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
Outpatient Visit	X																			X	
Admission to Clinical Unit		X																			
Inpatient Stay at Clinical Unit			←==========X==========→																		
Discharge from Clinical Unit																			X		*Following completion of all assessments.*
Informed Consent	X																				
Inclusion and Exclusion Criteria	X																				
Demography	X																				
Full Physical Examination	X																		X		*Additional exams/screens may be performed, or brief exams made full exams, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate). Tests will be conducted within site specified standards.*
Brief Physical Examination		X		X		X			X			X					X			X	
Height	X																				
Weight	X								X										X		
Drug/Alcohol/Smoking Screen	X	X																			*Tests include alcohol breath test, smoking breath test and urine drug screen.*
Medical/Medication/ Drug/Alcohol History	X																				
HIV, Hepatitis B and	X																				

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
C Screening																				
Tuberculosis Test	X																			
Anti-Nuclear Antibody	X								X										X	
Serum Pregnancy Test (WOCBP only)	X																			X	
Urine Pregnancy Test (WOCBP only)		X																	X	
Highly effective contraceptive method (WOCBP only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*Must use method for a minimum of 28 days prior to first dose of study medication until the follow-up visit.*
Contraception with male condoms (WOCBP using hormonal contraceptive method and male subjects with female partners of childbearing potential only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C-SSRS	X	←X→							X										X	X[c]	*May be completed on either Day -1 or Day 1, but no later than 1hr prior to dosing. To be completed pre-dose on Day 7.* *[c] C-SSRS to be conducted on follow-up only in the instance that a subject withdraws from the study.*
Meals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		***TID Dosing:*** *On Day 1 through 14 subjects will fast 8hr overnight. Breakfast will be served approximately*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					2hr after dosing on Days 1-8, 10, 12 and 13 and 2hr after dosing on Day 14. A "standard" and a "high fat" breakfast will be served approximately 30 minutes prior to dosing on Day 9 and Day 11, respectively. On all study days, lunch and dinner will be served between 2 to 3hr prior to dose 2 and dose 3, respectively. ***BID Dosing:*** *On Day 1 through 14, subjects will fast 8hr overnight prior to dose 1. A breakfast will be served approximately 2hr after dose 1. Lunch will be served approximately 4-5hr after dose 1. Dinner will be served between 2-3hr prior to dose 2. A snack may be consumed approximately 2-3hr after dose 2. Water is permitted with dosing and at all times. Subjects will receive standardized meals scheduled at the same time in each period. Meals will be served as per the site schedule on Days -1, 16 and 17.*
Haem/Chem/ Urinalysis Test (Include Liver Chemistries)	X	X	X	X		X			X			X					X			X	*Collection on Day 1 no later than 1hr prior to dosing. To be drawn pre-dose on Days 2, 4, 7 and 10.*
Fasting lipid panel	X		X	X		X			X			X					X			X	*Collection on Day 1 no later than 1hr*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					prior to dosing. To be drawn pre-dose on Days 2, 4, 7 and 10.
Holter Monitoring (24-hour)	X																				
Telemetry			X		X											X					*Continuous at least 24 hr post-evening dose. Initiate at least 15 min. prior to dosing.*
PK blood sampling			X[d]	X[e]	X[e]	X[e]	X[e]		X[e]		X[f]		X[f]			X[g]					[d] *On Day 1, PK samples will be collected pre-dose and at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr, 9hr and 11hr.* [e] *On Days 2,3 4, 5 and 7 pre-dose samples only.* [f] *Days 9, and 11: Cohort 2, 3 and Cohort 4 PK sampling will be collected pre-dose and at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr (prior to 2nd dose) 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr. Cohort 5 is currently not planned to have PK assessment but may be included depending on outcome of food effect in Cohorts 2, 3 and 4.* [g] *Day 14 sampling for Cohorts 2, 3, 4 and 5 will be over 24hr according to the following schedules:* *For **TID Dosing:** PK samples to be*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					taken pre-dose and then at the following time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 5hr, 7hr (pre-2nd dose) 7hr 20min, 7hr 40 min, 8hr, 8hr 30min, 9hr, 10hr, 12hr, 14hr (pre 3rd dose), 14hr 20min, 14hr 40 min, 15hr, 15hr 30min, 16hr, 17hr, 19hr, 22hr, 24hr. *For **BID Dosing:** PK samples to be taken pre-dose on Day 1 and then at the subsequent time points post first-dose: 20min, 40min, 1hr, 1hr 30min, 2hr, 3hr, 4hr, 6hr, 8hr, 10hr, 12hr (pre 2nd dose), 12hr 20min, 12hr 40min, 13hr, 13hr 30min, 14hr, 15hr, 16hr, 19hr, 22hr, 24hr.*
Metabolite sampling																X[h]					[h] *Metabolite sampling will be conducted pre-dose and 2hr post first dose on Day 14 only.*
4β-hydroxycholesterol sampling			X[i]														X[j]				[i] *Sample to be taken pre-dose on Day 1 in a fasted state.* [j] *Sample to be taken at 24hr post first dose on Day 14. Sample should be in a fasted state.*
Neuro. examination		X		X	X				X									X			***TID Dosing:** Neurological examinations to be conducted either on Day-1 or pre-dose Day 1 and then at the subsequent time points post first dose: 2hr, 9hr, 16hr, 24hr and 48hr. To*

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																	**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	
																				be completed pre-dose on Day 7 and then 48 hr post-last dose on Day 14. ***BID Dosing:*** *Neurological examinations to be conducted pre-dose either on Day-1 or Day 1 and then at the subsequent time points post first dose: 2hr, 14hr, 24hr and 48hr. To be completed pre-dose on Day 7 and then 48hr post-last dose on Day 14.*
12-Lead ECG	X	X	T	X		X			X							X				X	*Vital signs to include HR, BP, temperature and respiration rate.* *On Day 1:* ***TID Dosing:*** *12-Lead ECG and Vital Signs to be conducted on Day-1 and pre-dose Day 1 and then at the subsequent time points post first-dose: 40min, 2hr, 4hr, 7hr (pre-2nd dose), 9hr, 14hr (pre-3rd dose), 16hr, 24hr, 48hr. Then 24 and 48hr after the first dose and last dose administered on Day 14.* ***BID Dosing:*** *12-Lead ECG and Vital Signs to be conducted pre-dose either on Day-1 or Day 1 and then at the subsequent time points post first-dose: 40 min, 2hr, 4hr, 12hr (pre-2nd dose), 14hr, 24hr, 48hr. Then 24 and 48hr after the first and last dose administered on Day 14.* *On Days 3 to 14, pre-dose samples*
Vital signs	X	X	T	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Procedure	**Screening** (Up to 28 days before Day 1)	**Study Period** (Days)																		**Follow-up** (No more than 14 days post last dose)	**Notes**
		-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**		
																					only. *T = Triplicate.*
Randomization		X																			*Randomization can occur on either Day -1 or Day 1.*
Study Treatment			X	X	X	X	X	X	X	X	X	X	X	X	X	X					***TID dosing:*** *GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval.* ***BID dosing:*** *GSK2982772 or placebo will be administered using a 12hr dosing interval.*
Pharmacogenetic Sample (PGx)			X																		*A PGx blood sample is collected at the Day 1 visit, after the subject has been randomized and provided informed consent for genetic research. If the sample is not collected on Day 1, it can be collected at any time during the study after randomization.*
AE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

- The timing and number of planned study assessments, including safety, pharmacokinetic or other assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

- 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 IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

3. INTRODUCTION

3.1. Study Rationale

The current study is being conducted to support administration of higher dose levels than initially studied in the First Time in Human (FTiH) study - 200975. The dose in the FTiH study was capped at 120 mg BID based on exposure margins with the no observable adverse effect limit (NOAEL) in the 28-day monkey toxicology study (10 mg/kg/day). Subsequently, a 13-week toxicity study in monkeys has completed which increased the NOAEL to 30 mg/kg/day which will allow for an approximate 4-fold increase in the safety margins, in terms of systemic exposure to GSK2982772. The current study is being conducted to explore administration of higher dose levels than achieved in the FTiH study to support subsequent Phase 2a Proof of Concept (PoC) studies and Phase 2b dose range studies in subjects with psoriasis (PsO), rheumatoid arthritis (RA) and ulcerative colitis (UC).

3.2. Background

GSK2982772 is a first-in-class, highly selective, small molecule inhibitor of receptor-interacting serine/threonine protein-1 (RIP1) kinase. 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 regulates inflammatory signalling in response to stimuli such as tumour necrosis factor (TNF) and ligands of the Toll-like receptor family in both kinase-dependent and -independent manners [Ofengeim, 2013]. Upon binding to its receptor, tumour necrosis factor receptor-1 (TNFR1), TNFα triggers one of three distinct cellular fates; NFκB activation, apoptosis, or the more recently identified programmed necrosis [Ofengeim, 2013]. In addition, recent studies have shown that the programmed necrosis signalling complex also regulates the induction of certain cytokines. Although RIP1 serves as a key decision checkpoint for all three of these pathways, its kinase activity is only requisite for the initiation of programmed necrosis and pro-inflammatory cytokine production [Berger, 2014]. The discovery of this newly defined inflammatory, programmed necrotic pathway calls into question the major contributor to human disease downstream of the TNFR1. As such, a RIP1 kinase inhibitor represents a novel, selective mechanism for the treatment of inflammatory conditions such as Crohn's Disease, Plaque Psoriasis, and Rheumatoid Arthritis through multiple mechanisms, including the blockade of cell death, danger associated molecular pattern (DAMP)-driven inflammation and pro-inflammatory cytokine production.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK2982772 can be found in the Investigator's Brochure (IB). The following section outlines the risk assessment and mitigation strategy for this protocol:

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 GLP toxicology study, CNS findings were observed in 2/12 monkeys which were administered 100 or 300 mg/kg/day. CNS findings included uncoordination, irregular gait, trembling, hunched appearance and decreased activity. The NOAEL for this study was determined at 10 mg/kg/day. In the 13-week GLP toxicology study, there were no CNS findings observed in monkeys administered 10, 30 or 100 mg/kg/day. The NOAEL for this study was determined at 30 mg/kg/day. **Clinical Data:** A FTiH study with single ascending and multiple ascending dose study has been performed in 67 healthy male volunteers to date (see IB [GlaxoSmithKline Document Number 2014N204126_02]). No drug-associated CNS adverse events (AEs) were identified and no Serious AEs (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.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
Immunosuppression	The possibility of immunosuppression, including an increase in the frequency and/or severity of infection, may result from the intended pharmacologic effect of GSK2982772. This may be enhanced in subjects taking other immunomodulating drugs or corticosteroids. **Clinical Data:** In the FTiH study, no SAEs were reported. One subject experienced an Adverse Event (AE) herpes zoster approximately 27 days after receiving his last dose with GSK2982772 or placebo. The blinded investigator determined this to be potentially drug-related.	**Subject Selection:** Subjects with recurrent, chronic or active infections will be excluded from the study. Subjects will be screened for TB, HIV, Hepatitis B and C, and excluded from the study if positive. Investigators are expected to follow local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus. **Subject Monitoring:** Subjects will be monitored for signs of infection. See Individual Safety Stopping Criteria for atypical or opportunistic infections (Section 8.1.5).
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.

Potential Risk of Clinical Significance	**Summary of Data/Rationale for Risk**	**Mitigation Strategy**
		If indicated, non-live vaccines (e.g. inactivated influenza vaccines) may be administered while receiving GSK2982772 based on a treating physician assessment of the benefit: risk (e.g., risk of theoretical decreased responsiveness). Investigators will be expected to have followed local and/or national guidelines with respect to vaccinations, including against influenza and pneumococcus.
Respiratory	**Non-clinical data:** In the single-dose Safety Cardiovascular and Respiratory Study in monkeys, a decrease in minute volume (MV) and respiratory rate was observed at all doses (10, 100, and 300 mg/kg). These findings were noted to be reversible and mild in severity. In a 14-day repeat dose Safety Respiratory Study in monkeys, no respiratory effects on total pulmonary ventilation (MV) or respiratory rate were observed at doses of 1 or 10 mg/kg/day. See IB for GSK2982772 [GlaxoSmithKline Document Number 2014N204126_02].	**Subject Monitoring:** Subjects should be monitored for standard respiratory-related 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 up to 120 mg BID were administered x 14 days in 48 healthy male volunteers. Extensive respiratory monitoring with end-tidal CO2 (ETCO2), oxygen saturation (SpO2) and nocturnal respiratory rate monitoring was performed. No SAEs occurred, and no drug-associated respiratory-related AEs were identified.	
Suicidality	GSK2982772 is considered to be a CNS-active drug based on 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 Behaviour (SIB) as measured using the Columbia Suicide Severity Rating Scale (C-SSRS) or a history of attempted suicide will be excluded from the study. **Subject Monitoring:** Subjects should be monitored appropriately and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. Baseline and treatment emergent assessment of

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		suicidality will be conducted by trained site personnel using the C-SSRS in all subjects.
Reproductive Toxicity	**Non-Clinical Data:** In the rat embryofetal development study, there were no maternal or developmental toxicity at doses ≤200 mg/kg/day. In the rabbit embryofetal development study, GSK2982772 was administered at doses of 0, 10, 100, 300 or 600 mg/kg/day on gestation day 7 to 19. No developmental toxicity was evident at doses up to 300 mg/kg/day.	**Subject Selection:** Female subjects of childbearing potential will be included in this study only if they agree to use one of the highly effective methods of contraception beginning at least 28 days prior to first dose of study drug until 30 days after the last administration of study drug. Women using a hormonal contraceptive method will also be required to have partners use a male condom from the first dose of study drug and until the follow-up visit to avoid conception until at least 30 days after the last administration of study drug. Male subjects with female partners of childbearing potential must agree to use male condoms to avoid conception for defined periods of time before first administration of study drug until 90 days after the last administration of study drug. It is also recommended that a male subject with a female partner of childbearing potential employ a highly effective contraceptive method throughout this same period of time. Females of childbearing potential will undergo

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		serum pregnancy test at screening and then urine pregnancy testing at regular intervals during the study. Pregnant and lactating females are not eligible for inclusion in the study. **Withdrawal Criteria:** If a female subject should become pregnant during the study, study medication should be discontinued. The subject will be followed to determine the outcome of the pregnancy. Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
Drug Interaction	**Non-Clinical Data:** In vitro studies with GSK2982772 assessing potential drug-drug interactions with Cytochrome P450 3A4 (CYP3A4) substrates and P-glycoprotein (Pgp) inhibitors 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 an	**Subject Selection:** Subjects who are taking concomitant medications known to inhibit Pgp or are CYP3A4 narrow therapeutic index (NTI) substrates will be excluded from the study. **Subject Monitoring:** Subjects' concomitant medication usage will be

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].	reviewed prior to inclusion and monitored throughout the study. Subjects should be monitored throughout the study for potential effects of interaction between GSK2982772 and other concomitant medications.

3.3.2. Benefit Assessment

The proposed study with GSK2982772 will be conducted in healthy volunteers; no medical benefit will be derived by volunteers' participation. Subjects will indirectly gain through their contribution to the process of developing new therapies in an area of unmet need.

3.3.3. Overall Benefit:Risk Conclusion

The known risks associated with GSK2982772 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential subjects is considered low. Routine safety and tolerability will be evaluated from reported AEs, scheduled physical examinations, vital sign measurements, cardiac rhythm monitoring, 12-lead ECGs, and clinical laboratory test results as well as continued observation by clinical staff.

The study will be conducted in a hospital-based unit or unit with immediate access to hospital facilities for the treatment of medical emergencies. The in-house periods as detailed in the SoA (Section 2) will allow for continuous medical monitoring for all subjects following the first dose in each treatment group. Subjects will only be discharged from the unit 48 hours post-dose if the Investigator deems it safe to do so.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with GSK2982772 are justified by the anticipated benefits that may be afforded by the future development of a new therapy in an area of unmet need.

4. OBJECTIVES AND ENDPOINTS

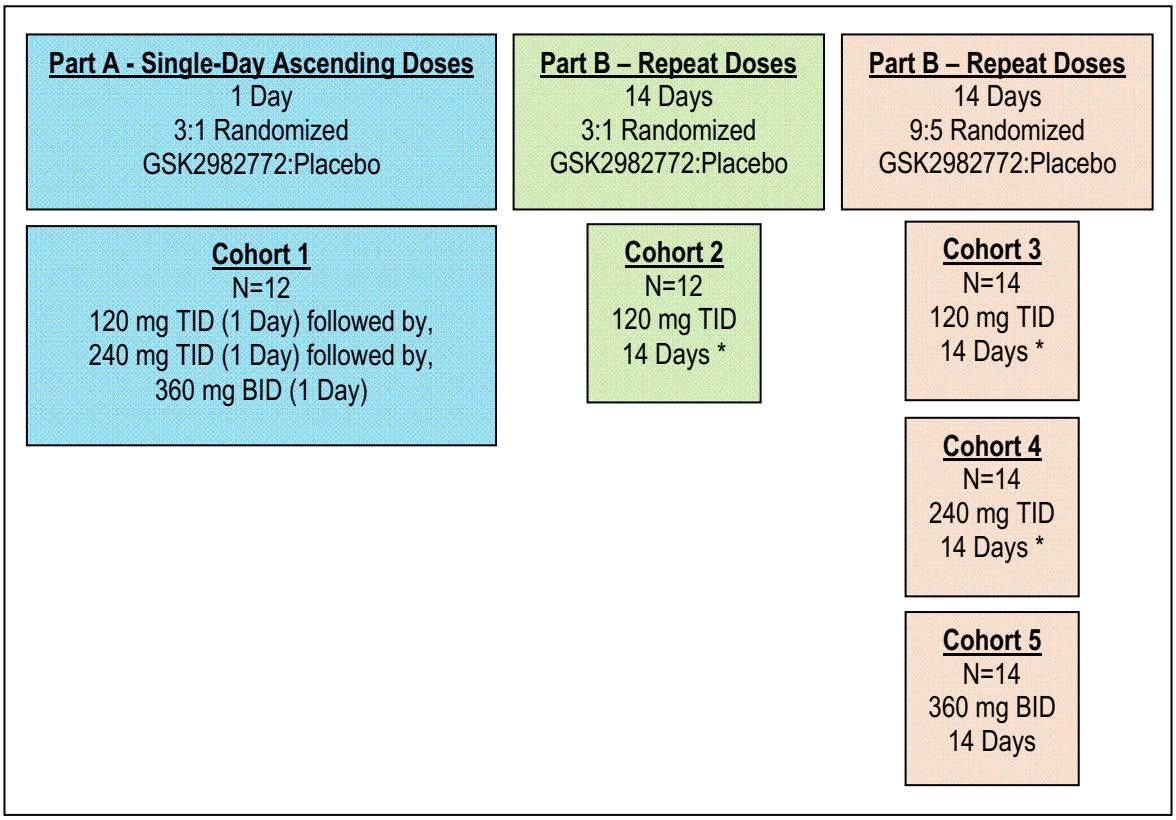
Objective	Endpoint
Primary	
• To investigate the safety and tolerability of repeat doses of GSK2982772 in healthy subjects.	• Adverse events. • Clinical laboratory values (clinical chemistry, haematology and urinalysis). • Vital sign measurements (blood pressure, heart rate, respiratory rate and body temperature). • Physical examinations. • 12-Lead ECG monitoring.
Secondary	
• To characterise the pharmacokinetic (PK) profile of repeat doses of GSK2982772 in healthy subjects.	• A 24 hr profile to be collected on Day 1 of Part A and Day 14 of Part B. On Day 1 of Part B, the PK profile will be evaluated following the first dose only. Derived PK parameters for GSK2982772, including area under the plasma drug concentration versus time curve over 24 hr ($AUC_{(0-24)}$) and AUC over each dose interval (i.e. $AUC_{(0-7)}$, $AUC_{(7-14)}$ and $AUC_{(14-24)}$ for TID and $AUC_{(0-12)}$ and $AUC_{(12-24)}$ for BID). Maximum observed plasma drug concentration (C_{max}) following each dose, time to maximum observed plasma drug concentration (T_{max}) following each dose, observed trough plasma drug concentrations (C_0, C_7, C_{14} and C_{24} for TID dosing and C_0, C_{12} and C_{24} for BID dosing).
• To assess the impact of food on the PK of repeat doses of GSK2982772 in healthy subjects at steady state	• Derived PK parameters for GSK2982772, including $AUC_{(0-7)}$, $AUC_{(7-14)}$, C_{max}, after 1st dose of day and T_{max} after 1st dose of day.
• To assess potential effect of repeat doses of GSK2982772 on CYP3A4 enzyme activity.	• Plasma 4β-hydroxycholesterol to cholesterol ratio pre-treatment and following 14 days of repeat dosing of GSK2982772.
Exploratory	
• To investigate the levels of circulating glucuronide metabolite (M8; GSK3562183) and desmethyl metabolite (M9; GSK2997852) in healthy subjects after single-day and repeat dosing of GSK2982772.	• Quantify M8 (GSK3562183) and M9 (GSK2997852) in select plasma PK samples after single-day dosing and at pre-dose and 2 hr following Day 14 of repeat dosing of GSK2982772.

5. STUDY DESIGN

5.1. Overall Design

This is a single-centre, randomized, double-blind (sponsor-unblinded), placebo-controlled study to evaluate the safety, tolerability and pharmacokinetics of GSK2982772, in repeat oral doses in healthy subjects. The study design schematic is depicted in Figure 1.

Figure 1 Study Design



*With Food Effect Treatment

This study is planned to include approximately 66 subjects and consists of 2 parts:

- Part A (Cohort 1) – single ascending dose, randomized, placebo-controlled, 3-way crossover.
- Part B (Cohorts 2, 3, 4 and 5) – repeat dose, randomized, placebo-controlled, sequential-group.

For TID dosing, GSK2982772 or placebo will be administered using a 7hr, 7hr and 10hr dosing interval. For BID dosing, GSK2982772 or placebo will be administered using a 12hr dosing interval.

The impact of food on the PK of GSK2982772 will be investigated during the 14 Day repeat dose phase of the study (Part B) in Cohorts 2, 3 and 4. On Days 1 to 14, subjects

will fast for 8hr overnight. Breakfast will be served 2hr after dosing on Days 1 through 8, 10, 12 and 14. A standard breakfast will be served 30 minutes prior to dosing on Day 9, and a high fat breakfast will be served 30 minutes prior to dosing on Day 11.

All of the Cohorts in this study will be double-blind with respect to the subjects, investigator and site staff (with the exception of the site pharmacist). The Sponsor, the GSK study team, will be unblinded throughout.

5.2. Number of Participants

Sufficient number of healthy subjects will be enrolled, such that approximately 12 subjects in Cohorts 1 and 2 and 14 subjects in Cohorts 3, 4 and 5 complete dosing and critical assessments. If subjects prematurely discontinue the study, additional replacement subjects may be randomized in order to guarantee that sufficient subjects are treated with GSK2982772 at any given dose before escalating to the following dose. Subjects that participate in Part A of the study cannot participate in Part B.

5.3. Sentinel Dosing

Sentinel dosing will be employed within each dosing period in Part A of the study. The doses in the single-ascending dose portion of the study (Part A) will be staggered such that for each of the three treatment periods, on Day 1, two of the 12 subjects will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo). Assuming 2 subjects are dosed on Day 1 and assuming adequate safety in the judgment of the Principal Investigator (e.g., vital signs, ECGs, and AEs) through approximately 24 hours after their last dose on Day 1, the remaining subjects may be randomized to dosing in that period. The doses in the repeat dose portion of the study (Part B) will be staggered such that for each treatment period on Day 1, two subjects in each Cohort, except Cohort 3 since this was completed in the original dose level (Cohort 2), will be randomized to treatment (one subject will receive GSK2982772 and one subject will receive matched-placebo) and dosed for at least 7 days before the rest of the cohort is randomized. If participants prematurely discontinue the study, additional replacement participants may be recruited and assigned to the same treatment sequence, at the discretion of the Sponsor in consultation with the investigator.

5.4. Dose Escalation Decisions

The decision to proceed to the next dose level of GSK2982772 within the study will be made by a Dose Escalation Committee (DEC) consisting of Principal Investigator, or delegate, and other relevant GSK clinical staff (See Section 10.5).

5.5. 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 (Section 2).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5.6. Scientific Rationale for Study Design

In Part A, each cohort will initially evaluate the safety, tolerability and PK of GSK2982772 administered for 1 day as a TID or BID dosing regimen (Cohort 1).

In Part B, the 14-day TID or BID repeat dosing (Cohort 2, 3, 4 and 5) was chosen since it will provide sufficient safety and tolerability data to bridge to longer duration studies with the recently achieved safety margins from the 13-week toxicology study in monkeys. In the previous FTiH study (200975), GSK2982772 was administered up to 120 mg BID for 14 days and was well tolerated with no safety concerns identified. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02].

Cohort 5, 360 mg BID dosing regimen, may only be evaluated if the results of a modified release (MR) formulation study (205017) being conducted in parallel with the current study indicate that a MR formulation is not feasible for GSK2982772. In which case a BID regimen using the current immediate release formulation may be taken forward in to Phase 2a PoC studies. Additionally, Cohort 5 dose may be modified to include the repetition of a previous or lower TID or BID dose based on the results of the safety and tolerability review or if further characterization of the safety profile at a previously tested dose is required.

In the previous FTiH (Study 200975), the impact of a high-fat meal on the absorption of GSK2982772 was investigated following single dose administration of GSK2982772 at a dose of 40 mg. The rate and extent of absorption was similar in the fed state as compared to the fasted state, although there was evidence of a time lag in the absorption in the fed state, probably as a result of delayed gastric emptying. It is likely that higher doses to be used in this study will have a similar food effect to that observed at 40 mg. Therefore, this study plans to evaluate the impact of food during the repeat dose phase in Cohorts 2, 3 and 4 rather than conducting a standalone single dose food effect PK study.

5.7. Dose Justification

An adaptive dose-escalation approach, guided by the observed safety, tolerability and plasma PK exposure will be taken to allow an efficient evaluation of a range of doses above the 120 mg BID dose that was evaluated in the FTiH study.

The initial starting dose planned is 120 mg TID and the maximum daily dose is anticipated to be approximately 720 mg administered as 240 mg TID and 360 mg BID.

For doses of up to 120 mg BID, the pharmacokinetics of GSK2982772 are approximately linear. Please see GSK2982772 IB [GlaxoSmithKline Document Number 2014N204126_02]. After attainment of C_{max}, at approximately 2 hours post-dose, GSK2982772 concentrations decline rapidly until about 12 hours post-dose, with a $t_{1/2}$ of approximately 2 to 3 hours. The majority of the systemic exposure to GSK2982772 is observed within the first 12 hours after administration. Following repeat dosing of GSK2982772, there is no evidence of drug accumulation for either a QD or BID dosing regimen. The major circulating metabolite is an N-glucuronide which accounts for approximately 70% of drug related material in plasma. Since glucuronidation is a high

capacity clearance mechanism it is unlikely that the kinetics of GSK2982772 will become saturable with more frequent dosing nor at the higher doses planned in the current study.

Due to the short half-life of GSK2982772 (~2-3 hr), it is expected that steady-state will be achieved by Day 2 of dosing and that negligible accumulation will be observed. Therefore, the PK safety margins described for Day 1 and for Day 14 of dosing will be similar.

The predicted mean $AUC_{(0-24)}$ for the highest planned doses of 240 mg TID and 360 mg BID (40.2 µg*h/mL) approximates parity with the mean $AUC_{(0-24)}$ observed at the NOAEL (30 mg/kg/day) in the 13-week monkey toxicology study (48.4 µg*h/ml). Mean C_{max} values for the 240 mg TID (3.21 µg/mL) and 360 mg BID (4.31 µg/mL) doses are predicted to be $1/4^{th}$ and $1/3^{rd}$ respectively, of the C_{max} observed at the NOAEL (12.3 µg/mL). The doses for Cohorts 2, 3, 4 and 5 may be adjusted based on PK/safety data from previous treatment periods. It is planned that the 95^{th} percentile for the predicted $AUC_{(0-24)}$ values will not exceed the maximum $AUC_{(0-24)}$ value observed at the NOAEL and for C_{max} the 95^{th} percentile will not exceed the mean C_{max} and the NOAEL. The current predicted 5^{th} -95^{th} percentiles for $AUC_{(0-24)}$ and C_{max} values using repeat dose PK data from FTiH study and mean/individual $AUC_{(0-24)}$ and C_{max} values from the 13-week Monkey Study at 30 mg/kg/day (NOAEL) and 100 mg/kg/day are shown in Figure 2 and Figure 3, respectively.

Figure 2 Mean and 95% Prediction Interval for Human AUC(0-24) Values versus Mean and Individual Monkey AUC(0-24) Values at Week 13

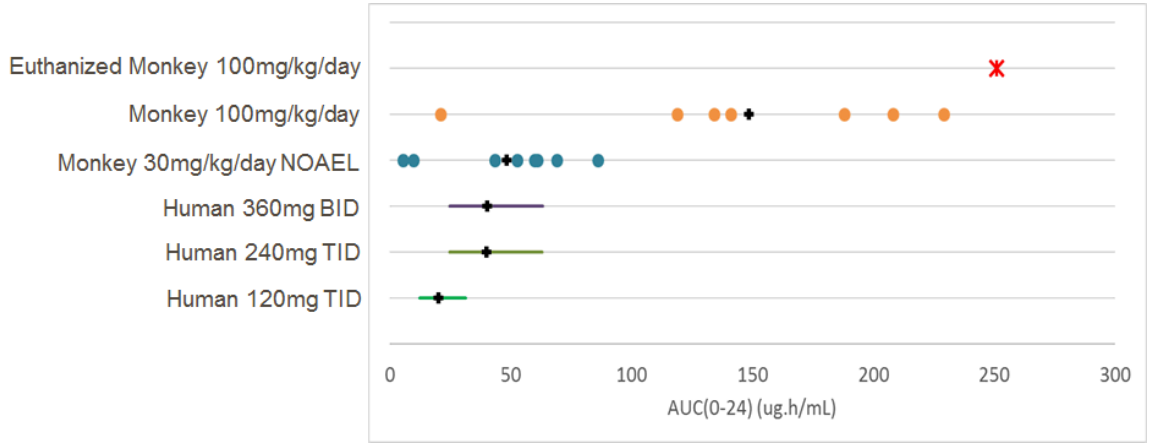
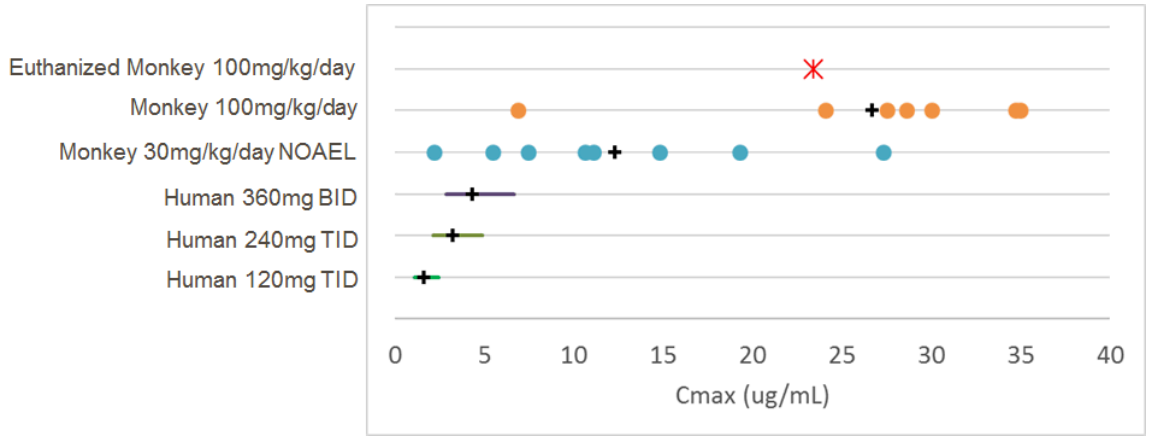


Figure 3 Mean and 95% Prediction Interval for Human Cmax values Versus Mean and Individual Monkey Cmax values at Week 13



6. STUDY POPULATION

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

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. Healthy as determined by the Investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, neurological examination, laboratory tests and cardiac monitoring. A subject with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the Investigator in consultation with the Medical Monitor (if required) agree and document that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures. Note: Screened subjects with laboratory values outside of the normal range may be repeated once for inclusion into the study at the discretion of the Investigator.

WEIGHT
3. Body weight ≥50 kg and body mass index (BMI) within the range 19 - 30 kg/m^2 (inclusive).

SEX
4. Male and/or Female Subjects **a. Male participants:** A male participant with a female partner of reproductive potential must agree to use contraception as detailed in Appendix 5 of this clinical study 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),

SEX
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 for a minimum of 28 days days prior to the treatment period and for at least 30 days after the last administration of study drug. A WOCBP using a hormonal method of highly effective contraception must also agree to partner use of a male condom during the treatment period and for at least 30 days after the last administration of study drug.

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 or presence of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematological, 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. History of herpes zoster (shingles) reactivation. 3. Evidence of active or latent tuberculosis (TB) as documented by medical history and examination, chest x-rays (posterior anterior and lateral), and TB testing: either a positive tuberculin skin test (TST; defined as a skin induration >5 mm at 48 to 72 hours, regardless of Bacillus Calmette-Guerin (BCG) or other vaccination history) or a positive (not indeterminate) QuantiFERON-TB Gold test. NOTE: The choice to perform a TST or a QuantiFERON-TB Gold test will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatment(s). This test may not be suitable if previous treatment(s) produced significant immunosuppression. 4. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN). 5. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).

MEDICAL CONDITIONS
6. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones) 7. QTc >450 msec NOTES: • The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method, machine-read or manually over-read. • The specific formula that will be used to determine eligibility and discontinuation for an individual subject should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual subject and then the lowest QTc value used to include or discontinue the subject from the trial. • For purposes of data analysis, QTcB, QTcF, another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP). 8. History of serious or recurrent infections or has had an active infection within 14 days of receiving study medication. 9. History of diagnosis of obstructive sleep apnoea or significant respiratory disorder. Childhood asthma that has fully resolved is permitted. 10. Part A: History of active SIB within the past 6 months or any history of attempted suicide in a participant's lifetime. 11. History of current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.

PRIOR/CONCOMITANT THERAPY
12. Past or intended use of over-the-counter or prescription medication, including herbal medications, within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is the longest) prior to dosing. Specific medications listed in Section 7.6 may be allowed. 13. Subject received a vaccine (either live attenuated or now-live) within 30 days prior to randomization, or plans to receive a live attenuated vaccine within 30 days + 5 half-lives (32 days) of the last dose of study medication.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
14. Participation in the study would result in loss of blood or blood products in excess of 500 mL within a 56-day period. 15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day. 16. The subject has participated in a clinical trial and has received an investigational

product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

DIAGNOSTIC ASSESSMENTS
17. Presence of Hepatitis B surface antigen (HBsAg) at screening Positive Hepatitis C antibody test result at screening. 18. Positive pre-study drug/alcohol screen. 19. Positive human immunodeficiency virus (HIV1 and 2) antibody test. 20. Regular use of known drugs of abuse. 21. Subjects with impaired renal function defined as Chronic Kidney Disease Epidemiology Collaboration (CKS-EPI) Creatinine > 1.6mg/dL with an age appropriate GFR ≤60 (mL/min/1.73 m^2) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [Snyder, 2009 and Levey, 2010]. 22. An elevated C-reactive protein (CRP) outside of the normal reference range.
OTHER EXCLUSIONS
23. Regular alcohol consumption within 6 months prior to the study defined as: • For UK - an average weekly intake of >14 units for males and 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. 24. Cotinine or carbon monoxide levels indicative of smoking or history or regular use of tobacco- or nicotine-containing products within 6 months prior to screening. 25. 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 26. Unwilling or unable to swallow multiple size 00 capsules as part of study participation.

PART B SPECIFIC CRITERIA
27. History of SIB as measured using the C-SSRS or a history of attempted suicide. 28. A positive anti-nuclear antibody (ANA) outside of the normal reference range. 29. Fasting total cholesterol ≥300 mg/dL or triglycerides ≥250 mg/dL.

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 7 days prior to each first dose of study treatment in Part A up until discharge from the unit. In Part B, subjects must refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days prior to the first dose of study treatment until after the final dose.

6.3.2. Caffeine, Alcohol, and Tobacco

- During each dosing period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing until after collection of the final PK sample.
- During each dosing period, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Use of tobacco products will not be allowed from 6 months prior to screening until after the final follow-up visit.

6.3.3. Activity

- Participants will abstain from strenuous exercise for 48 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (e.g., watching television, reading).
- Participants will abstain from travelling to regions of high endemic infection, as determined by the investigator, for the duration of the study.

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized. 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 only on approval of the GSK Medical Monitor. Rescreened participants should be assigned the same participation number as for the initial screening.

7. TREATMENTS

The term study treatment is used throughout the protocol and 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

	Study Treatment	
Product name:	GSK2982772	Placebo
Formulation description	API filled capsule	Placebo blend filled capsule
Dosage form:	HPMC capsule	HPMC capsule
Unite dose strength(s)/Dosage level(s):	120 mg maximum fill per capsule	NA
Route of administration:	For oral use only	For oral use only
Dosing instructions:	Dose with water	Dose with water
Physical description:	Size 00, white, opaque capsule containing white to almost white solid	Size 00, white, opaque capsule containing white to almost white solid
Source of procurement	Study medication is supplied by GlaxoSmithKline	Study medication is supplied by GlaxoSmithKline
Method for individualizing dosage:	Site to assemble	Site to assemble

7.2. Method of Treatment Assignment

On Day -1 or Day 1 participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to either GSK2982772 or placebo, according to the randomization schedule generated prior to the study by the Statistics Department at GSK, using validated internal software.

All participants will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information & directions for the IWRS will be provided to the site.

Study treatment will be dispensed at the study visits summarized in SoA. Each participant will be dispensed blinded study treatment, labelled with his/her unique randomization number, throughout the study. Returned study treatment should not be re-dispensed to the participants

In Cohorts 1 and 2, subjects will be randomized in a 3:1 ratio to either GSK2982772 or placebo. In Cohorts 3, 4 and 5, subjects will be randomized in a 9:5 ratio to either GSK2982772 or placebo. In Cohort 1, the subjects will be randomized to one of four sequences (ABC, ABP, APC, PBC), where the treatments are:

A 120 mg TID
B 240 mg TID
C 360 mg BID
P Placebo

The planned dose levels are defined in Section 5.1.

The randomization will reflect the fact that at least 2 of the 12 subjects in Cohorts 1 and 2 and at least 2 of the 14 subjects in Cohort 4 and 5 (one subject will receive GSK2928772 and one subject will receive matched-placebo) will be dosed first (on Day 1) in each part to enable dose staggering.

Once a treatment allocation number has been assigned to a subject, it cannot be reassigned to any other subject.

7.3. Blinding

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

- The Investigator or treating physician will remain blinded to each participant's assigned study treatment throughout the course of the study. In order to maintain this blind, an otherwise uninvolved 3rd party will be responsible for the reconstitution and dispensation of all study treatment and will endeavour to ensure that there are no differences in time taken to dispense following randomization
- This 3rd party will instruct the participant to avoid discussing the taste, dosing frequency, or packaging of the study treatment with the investigator
- Unblinded monitors and in the event of a Quality Assurance audit, the auditor(s) will be allowed access to un-blinded study treatment records at the site(s) to verify that randomization/dispensing has been done accurately.
- The IVRS/IWRS will be programmed with blind-breaking instructions.
- In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination.
- If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant.
- If a participant's treatment assignment is unblinded, GSK must be notified within 24 hours after breaking the blind.
- The date and reason that the blind was broken must be recorded in the source documentation and Case Report Form (CRF), as applicable.

- A subject will be withdrawn if the subject's treatment code is unblinded by the investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

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

7.4. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Only 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.5. Treatment Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- 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.

7.6. 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 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 non-prescription 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 at doses of ≤2 grams/day, is permitted for use any time 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.

7.7. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK, or with GSK2982772, after completion of the study because only healthy volunteers are eligible for study participation.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Dose Modification/Stopping Criteria

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum total daily dose will not intentionally exceed the 13-week NOAEL exposure in monkeys. Currently, the highest planned dose is 720 mg/day of GSK2982772.

The decision to proceed to the next dose level of GSK2982772 in each part of this study will be made by the DEC, including the Medical Monitor and the Investigator and relevant clinical site staff (see Section 10.5) based on safety, tolerability, and preliminary PK data obtained in at least 6 subjects (through at least 24 hours post-dose) with at least 6 subjects having received active treatment (GSK2982772) at the prior dose level. The actual doses to be administered may be adjusted based on safety, tolerability and preliminary PK data at previous dose levels; these dose adjustments may involve either an increase or a decrease in the planned dose, but will not exceed the PK criteria defined in Section 8.1.2. Planned doses may also be repeated.

The Principal Investigator and the GSK Medical Monitor will review the following and dosing **will be** halted and progression to the next higher dose level stopped if:

- One (1) or more subjects experience a SAE which has a reasonable possibility of relation to study drug.
- Two (2) or more subjects experience a severe or clinically significant non-serious AE (based upon investigator judgment) which has a reasonable possibility of relation to study drug.
- Two (2) or more subjects in a Part A cohort or 3 or more subjects in a Part B cohort experience the same AE of moderate severity which has a reasonable possibility of relation to study drug.
- Consistent Common Terminology Criteria for Adverse Events (CTCAE) Nervous System AEs of any grade occur across subjects that have a reasonable possibility of relation to study drug.

If dosing is halted and if deemed acceptable by GSK internal safety review to proceed with or modify dose escalation to further characterize the safety profile, a formal request with appropriate data and substantial amendment will be submitted to MHRA (Medicines and Healthcare Products Regulatory Agency) for approval.

8.1.2. Pharmacokinetic Dose Modification or Stopping Criteria

The 240 mg TID dose and/or the 360 mg BID dose in Cohorts 1, 4 and 5 may be adjusted up or down based on PK data from previous treatment periods. It is planned that the 95th percentile for the predicted $AUC_{(0-24)}$ values will not exceed the maximum $AUC_{(0-24)}$ value observed at the NOAEL and for C_{max} the 95th percentile will not exceed the mean C_{max} at the NOAEL.

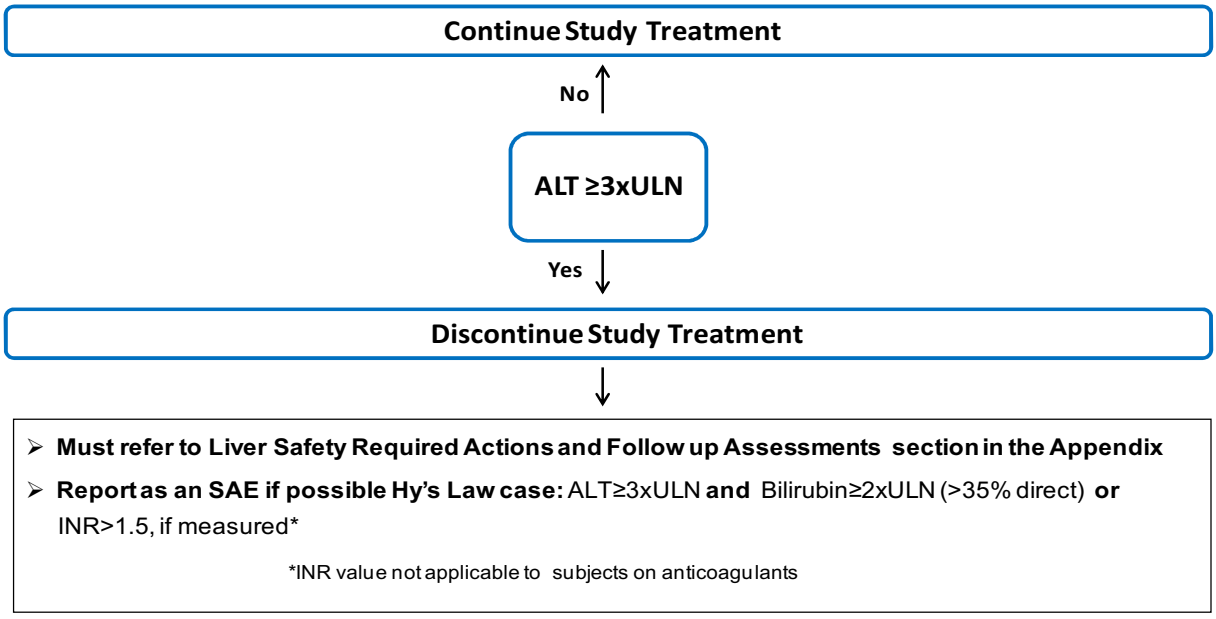
8.1.3. Liver Chemistry Stopping Criteria

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:

- when in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules, the investigator believes study treatment discontinuation is in the best interest of the participant.

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



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

8.1.4. QTc Stopping Criteria

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

- QTcF > 500 msec,
- Change from baseline: QTc > 60 msec

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study (i.e., QTcF in this 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 QTcF, then QTcF 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 single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. If an ECG demonstrates a prolonged QTc, obtain 2 more ECGs over a brief period (5-10 minutes), and then use the averaged QTc values of the 3 ECGs to determine whether the subject should be discontinued from the study.

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.

8.1.5. 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 (See Section 8.1.3) or QTc stopping criteria (see Section 8.1.4) are met.
- The participant experiences any signs of suicidal ideation or behaviour (See Section 9.3.6).

8.1.6. Group Safety Stopping Criteria

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

8.1.7. Nervous System Stopping Criteria

The CNS observations in the 4-week GLP toxicology study in monkeys were found to be random, diverse, and unpredictable in monkeys (see Section 3.3.1). There were no similar findings observed in the 13-week GLP toxicology study in monkeys. The CTCAE Nervous System is a monitoring tool which provides the Principal Investigator the appropriate guidance for grading of a neurological event. The significance of any neurological event experienced by a subject will be determined based on clinical judgment, characteristics of the event and/or based upon changes from a baseline assessment.

The Principal Investigator and the GSK Medical Monitor will review all neurological events utilizing the CTCAE Nervous System criteria and dosing may be halted if and progression to the next higher dose level stopped as per Section 8.1.1.

A subject will be withdrawn from the study if:

- A Grade 3 or greater CTCAE Nervous System finding is observed or a significant neurologic change from a subject's baseline physical examination is observed.
- Any adverse event included in the CTCAE for Nervous System, which is also considered to be clinically significant by the Principal Investigator, will be reviewed for potential subject withdrawal.

Note: Appendix 8 (Section 12.8) provides Guidance for Grading Adverse Events that is taken from the CTCAE Version 4.03.

8.1.8. Rechallenge

8.1.8.1. 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. The reason for withdrawal should be documented in the 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.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- 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.

If a subject chooses to withdraw from the study after dosing, then the Investigator must make every effort to complete the follow-up assessments detailed in the SoA (Section 2).

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 medical record.
- 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.

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 (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 500 mL.
    - Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. 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).

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

- All SAEs will be collected from the start of treatment until the follow-up visit at the time points specified in the SoA (Section 2). However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study.
- 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 immediately and under no circumstance should this exceed 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.

9.1.2. 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.

9.1.3. 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, and non-serious AEs of special interest (as defined in Section 3.3.1), 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.

9.1.4. 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, IRB/ IEC, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the

sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.1.5. Pregnancy

- Details of all pregnancies in female participants and, if indicated, 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 (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.2. Treatment of Overdose

GSK does not recommend specific treatment for an overdose. The investigator will use clinical judgement to treat an overdose as and when they are made aware of this.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2982772 can no longer be detected systemically (at least 2 days for 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.

9.3. Safety Assessments

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

9.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Skin, Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height (screening only) 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.

9.3.2. Neurological Exams

Neurological examination will include, at a minimum, assessment of: mental status, gait, balance, coordination, cranial nerves, motor power, reflexes, and sensory system (light touch and pain). Assessments will be standardized across all scheduled time points (see SoA). Significant changes from the baseline or any clinically significant changes will be noted as part of further scheduled examinations or unscheduled examinations (if needed).

Clinically significant abnormalities or changes in status from baseline will be:

- entered as an adverse event,
- may trigger increased monitoring of the subject(s),
- may result in withdrawal of the subject (see Section 8.2),
- may result in referral to a specialist.

9.3.3. Vital Signs

- Temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a supine position after 5 minutes' rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- In Part A and B on Day 1, vital signs (to be taken before blood collection for laboratory tests) will consist of 3 pulse and 3 blood pressure measurements pre-dose on Day 1 (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the CRF.

9.3.4. Electrocardiograms

- Triplicate 12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1.4 for QTc withdrawal criteria and additional QTc readings that may be necessary.
- At each time point at which triplicate ECG are required, 3 individual ECG tracings should be obtained as closely as possible in succession with at least 2 minutes but no more than 10 minutes apart.
- Continuous cardiac telemetry will be performed at time points indicated in the SoA (Section 2). Full disclosures will be reviewed in detail and the review maintained as part of the subject's source documents.

9.3.5. 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.
- 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 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 SRM and the SoA.

9.3.6. Suicidal Risk Monitoring

GSK2982772 is considered to be a CNS-active drug. There is some concern that some CNS-active drugs may be associated with an increased risk of suicidal thinking or behaviour when given to some subjects. 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 and observed closely for suicidal ideation and behaviour or any other unusual changes in behaviour. All subjects who experience signs of suicidal ideation or behaviour must immediately be discontinued from study medication.

Families and caregivers of participants 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) in Part B only, the Baseline/Screening assessment of suicidal ideation and behaviour and treatment emergent suicidal ideation and behaviour will be monitored during study 205184 using C-SSRS. At Days 7 and 17 of the study, the ‘Since Last Visit C-SSRS’ will be completed. Refer to Section 2, SoA, for more information.

Subjects who answer ‘Yes’ to any suicidal behaviour or ‘Yes’ to suicidal ideation Questions 4 or 5 will be referred to their General Practitioner (GP) or appropriate

psychiatric care. The medical monitor will be notified. If appropriate, an AE or SAE should be reported (see Section 9.1). 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.

9.3.7. Holter Monitoring

Holter monitoring will be performed at screening only. This 24-hour Holter ECG will be performed to eliminate subjects with clinically significant cardiac arrhythmias and to inform whether possible cardiac rhythm abnormalities potentially observed during continuous cardiac telemetry monitoring or 12-lead ECG are different from baseline. If necessary, additional or extended monitoring (e.g., telemetry or Holter) may be performed at the investigator or sponsor's discretion to further characterize any emerging safety signals.

9.4. Pharmacokinetics

9.4.1. Blood Sample Collection

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of GSK2982772 at the time points indicated in Section 2, SoA Tables. The actual date and time (24-hour clock time) of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Blood will be collected into EDTA tubes and processed to plasma for PK analysis of M8 (GSK3562183) and M9 (GSK2997852). This will be collected at the time points indicated in Section 2, SoA Tables. The actual date and time of each blood sample collection will be recorded.

Blood will be collected into EDTA tubes and processed to plasma for 4β-hydroxycholesterol and cholesterol. This will be collected at the time points indicated in Section 2, SoA Tables. The actual date and time of each blood sample collection will be recorded.

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

9.4.2. Sample Analysis

Plasma analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of Platform Technology and Science In Vitro/In Vivo Translation (PTS IVIVT) and Third Party Resource, GlaxoSmithKline. Concentrations of GSK2982772 will be determined in plasma samples, and concentrations of M8 (GSK3562183) and M9 (GSK2997852) will be determined in select plasma samples, using the currently approved

bioanalytical methodology. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Once the plasma sample has been analysed for GSK2982772 (or M8 [GSK3562183] and M9 [GSK2997852] as indicated above), any remaining plasma sample may be analysed for any compound-related material and the results may be reported as part of this study or under a separate PTS-IVIVT, GlaxoSmithKline protocol.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

9.4.3. Plasma Sample for CYP3A4 Enzyme Activity

Plasma derived from select PK blood samples in Part B (as in the SoA Table), will be analyzed for 4β-hydroxycholesterol and cholesterol as a potential *in vivo* marker of CYP3A4 enzyme activity. Samples collected pre-treatment and at steady-state will be compared to evaluate this potential marker.

Details on CYP3A4 enzyme activity marker plasma sample collection, processing, storage and shipping procedures are provided in the SRM.

Baseline and Day 14, post-treatment plasma samples will be analyzed using a validated, specific, and sensitive liquid chromatography–mass spectrometry (LC-MS/MS) method to determine concentrations of 4β-hydroxycholesterol and total cholesterol. A comparison will be made between the ratio of 4β-hydroxycholesterol : cholesterol at baseline and on Day 14 to assess potential changes in CYP3A4 enzyme activity following GSK2982772 treatment.

Analysis will be performed at a bioanalytical site (to be detailed in the SRM) under the control of PTS-IVIVT and Third Party Resource, GlaxoSmithKline.

9.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.6. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the Study Reference Manual.

9.7. Pharmacological Biomarkers

Pharmacological biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

The objectives of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK2982772. No formal hypotheses will be tested.

An estimation approach will be used to describe PK of GSK2982772, where point estimates and corresponding 90% confidence intervals will be constructed.

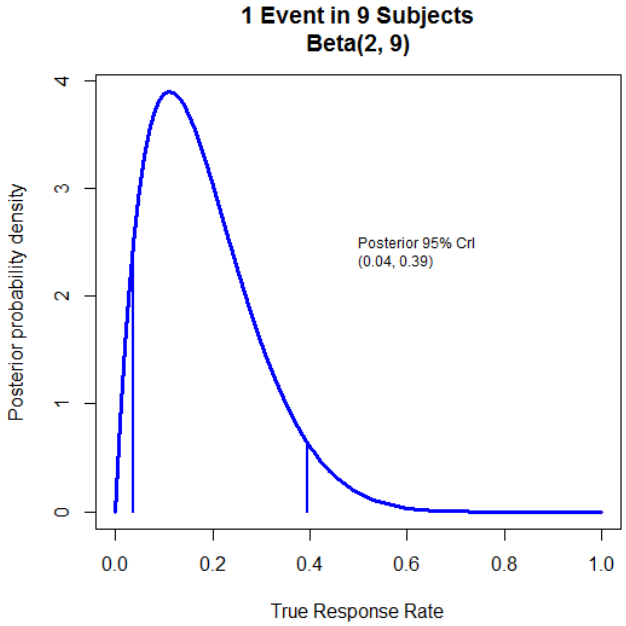
10.1. Sample Size Determination

No statistical techniques were used to calculate the sample size, and sample size is based on feasibility.

The primary objective of the study is safety, where the number of safety events are of interest. A maximum of 9 subjects will receive each active dose and; therefore, if 0/9 of a particular safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 33.6% could not be ruled out. Whereas if 1/9 of the same safety event in the GSK2982772 group is observed, the upper limit of the exact 95% CI indicates that a true incidence rate of 48.2% could not be ruled out.

Using a Bayesian approach to determine the confidence interval around an observed safety event, we would assume a flat Beta (1,1) prior, and if we were to observe one safety event in 9 then the posterior distribution would be Beta (2, 9), as outlined below:

Bayesian Approach to Determine Confidence in a Safety Event.



Thus, we can be 95% certain that the true probability of the safety event lies between 0.04 and 0.39.

Pharmacokinetic Parameters

To date the pharmacokinetics of GSK2982772 have been studied up to 120 mg BID. The maximum between-subject coefficient of variation (CVb) for $AUC_{(0-\tau)}$ and C_{max} observed in study 200975 was 27.1 and 36.1 respectively.

Based on these estimates of variability, slightly more conservative for a cross-over study and a sample size of 9 completers in Cohort 2, it is estimated that the lower and upper bounds of the 90% confidence interval for the means of AUC and C_{max} will be within approximately 17.9% and 24.2% of the point estimate, respectively.

10.2. Sample Size Sensitivity

A sample size sensitivity analysis has been conducted on the primary endpoint, to investigate different safety event rates. If the number of subjects who completed each active dose changes, then the true incidence rates of safety events that could not be ruled out (as outlined in Section 10.1 Sample Size Determination) would change. These changes are outlined in Table 1:

Table 1 Safety Events - Sample Size Sensitivity on Active Dose

N Completing Cohort	Number of a particular safety event observed with GSK2982772	Upper limit of exact 95%CI indicating that a true incidence rate of x% could not be ruled out
9	2	60.0%
	3	70.0%
	4	78.8%
8	0	36.9%
	1	52.7%
	2	65.1%
	3	75.5%
7	0	41.0%
	1	57.8%
	2	70.9%
	3	81.6%

Pharmacokinetic Parameters

A sample size sensitivity analysis has also been conducted on the PK parameters to investigate the effect of fewer number of subjects, or 10% difference in the between-subject coefficient of variation on the precision of the point estimate. These changes are outlined in Table 2:

Table 2 Pharmacokinetic Parameters – Sample Size Sensitivity

	Number of Subjects	CVb	Precision (%)
Cmax	6	26.1%	29.8
	6	28.8%	33.4
	6	31.5%	37.0
	9	19.6%	21.7
	9	21.7%	24.2
	9	23.7%	26.7
AUC(0-tau)	6	19.7%	21.8
	6	21.9%	24.5
	6	24.0%	27.1
	9	14.9%	16.1
	9	16.5%	17.9
	9	18.1%	19.8

10.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who sign the ICF
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received.
PK	The 'PK Population' is defined as subjects in the 'Safety' population for whom a PK sample was obtained and analyzed.

10.4. Statistical Analyses

10.4.1. Safety Analyses

Safety data will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

All safety analyses will be performed on the Safety Population.

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

10.4.2. PK Analyses

Endpoint	Statistical Analysis Methods
Secondary	PK analyses will be described in the RAP. The PK of TID and BID dosing on Day 1 in Part A will be evaluated. In Part B the comparisons of interest will be: The PK profile following the 1st dose of the day following administration in the fed state (standard meal on Day 9 and high fat meal on Day 11) or in the fasted state (Day 14). The pharmacokinetic profile following the 1st dose on Day 14 (fasted) and the 1st dose on Day 1 (fasted); Pharmacokinetic data will be listed and presented in graphical form and will be summarized descriptively. Statistical summaries of the PK parameter data will be the responsibility of

Endpoint	Statistical Analysis Methods
	Clinical Statistics, GlaxoSmithKline. Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum,) will be calculated for all pharmacokinetic parameters by treatment. In addition, for loge-transformed variables geometric mean, 95% confidence interval and %CVb (100 * √ (exp(SD_2) -1)) will be provided, where the SD is the standard deviation of log-transformed data.

10.4.3. Other Analyses

Descriptive statistics (n, arithmetic mean, standard deviation, 95% CI, minimum, median and maximum) of circulating glucuronide metabolite (M8; GSK3562183) and des-methyl metabolite will be investigated in healthy subjects after single-day and repeat dosing of GSK2982772.

10.4.4. Interim Analyses

An interim analysis may be performed during the study on completed cohorts in Part A and Part B of the study to aid internal decision making only. There will be no changes to the study design or planned number of subjects in future cohorts as a result of the interim analysis.

For Parts A and B of the study, interim PK analyses will be performed on plasma GSK2982772 concentration-time data generated during the conduct of this study.

The decision to proceed to higher dose strengths will be made by the DEC based on assessment of safety, tolerability and pharmacokinetic data at the preceding dose. The exception to this will be in Part A where only a safety assessment (not PK) for the 120 mg TID dose will be performed. To date, the PK of GSK2982772 has been well-characterised up to 120 mg BID in the FTiH study and the 120 mg TID for Part A represents a 50% increase in dose where PK simulations are predictable. This analysis can include review of individual subject data, summaries, graphical presentations and/or statistical analysis.

The RAP will describe the planned interim analyses in greater detail.

10.5. Dose Escalation Committee

The decision to proceed to the next dose level of GSK2982772 in each Cohort will be made by a DEC consisting of the Principal Investigator (or appropriate designee), Medical Monitor, GSK Clinical Investigational lead and/or Study Team Leader, GSK Pharmacokineticist, a GSK GCSP representative and GSK Statistician. All GSK personnel including the GSK Statistician and the GSK Pharmacokineticist will remain unblinded throughout the course of the study.

For Part A, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: listings of all AEs, clinical laboratory results, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry), ECG and PK results derived from 24-hour plasma profiles.

The decision and selection of dose to proceed to Part B, will be made by the DEC based on safety, tolerability, and PK data from the same dose levels evaluated in Part A.

For Part B, dose escalation decisions will be based on data obtained from 6 or more subjects receiving GSK2982772 at the prior dose level. The review of the data set will consist at a minimum of: listings of all AEs, clinical laboratory results, flagged vital signs, flagged findings during continuous cardiac monitoring (telemetry) and ECG findings through Day 16 of the previous cohorts(s) in Part B. Also included will be any PK results derived through at least Day 7 of the previous cohort(s).

11. REFERENCES

Berger SB, Kasparcova V, Hoffman S, Swift B, Dare L, Schaeffer M, et al. Cutting edge: RIP1 kinase activity is dispensable for normal development but is a key regulator of inflammation in SHARPIN-deficient mice. J Immunol. 2014; 192(12):5476-80.

GlaxoSmithKline Document Number 2014N204126_02. GSK2982772 Investigator's Brochure, Version 3. Effective Date: 27-January-2017.

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

Levey AS and Stevens LA. Estimating GFR Using the CKD Epidemiology Collaboration (CKD-EPI) Creatinine Equation: More Accurate GFR Estimates, Lower CKD Prevalence Estimates and Better Risk Predictions. Am J Kidney Dis. 2010; 55:622-627.

Ofengeim D and Yuan J. Regulation of RIP1 kinase signalling at the crossroads of inflammation and cell death. Nat Rev Mol Cell Biol. 2013; 14(11):727-736.

Snyder JJ, Foley RN, and Collins AJ. Prevalence of CKD in the United States: A Sensitivity Analysis Using the National Health and Nutrition Examination Survey (NHANES) 1999-2004. Am J Kidney Dis. 2009; 53(2):218-228.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALS	Amyotrophic lateral sclerosis
ALT	Alanine aminotransferase
ANA	Anti-nuclear Antibody
API	Active Pharmaceutical Ingredient
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{(0-7)}$	Area under the concentration-time curve from time zero to 7 hours post first dose (TID dosing)
$AUC_{(7-14)}$	Area under the concentration-time curve from 7 to 14 hours post first dose (TID dosing)
$AUC_{(14-24)}$	Area under the concentration-time curve from 14 to 24 hours post first dose (TID dosing)
$AUC_{(0-12)}$	Area under the concentration-time curve from 0 to 12 hours post first dose (BID dosing)
$AUC_{(12-24)}$	Area under the concentration-time curve from 12 to 24 hours post first dose (BID dosing)
$AUC_{(0-24)}$	Area under the concentration-time curve from time zero to 24 hours post first dose
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments
$AUC_{(0-\tau)}$	AUC from 0 hours to the time of next dosing.
BID	Twice a day
BMI	Body Mass Index
BP	Blood Pressure
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	Maximum observed concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine phosphokinase
CRF	Case Report Form
CRP	C-Reactive Protein
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CVb	Coefficient of Variation
CYP3A4	Cytochrome P450 3A4

DEC	Dose Escalation Committee
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
FSH	Follicle stimulating hormone
FTiH	First Time in Human
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
HBsAg	Hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HPMC	Hydroxypropylmethyl cellulose
HR	Heart Rate
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IgG	Immunoglobulin G
IP	Investigational Product
IRB/IEC	The Institutional Review Board/ Independent Ethics Committee
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
kg	Kilogram
LDH	Lactate dehydrogenase
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
mg	Milligram
mL	Millilitre
MR	Modified Release
MS	Multiple Sclerosis
MSDS	Material Safety Data Sheet
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NOAEL	No observable adverse effect limit
NTI	Narrow Therapeutic Index
Pgp	P-glycoprotein
PGx	Pharmacogenetics
PK	Pharmacokinetics
PoC	Proof of Concept
PsO	Psoriasis
PSRAE	Possible Suicidality Related Adverse Event
QTc	Electrocardiogram QT interval corrected for heart rate
QTcB	Electrocardiogram QT interval corrected for heart rate using Bazett's formula

QTcF	Electrocardiogram QT interval corrected for heart rate using Fridericia's formula
RA	Rheumatoid Arthritis
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RIP1	Receptor-interacting protein-1
SAE	Serious Adverse Event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SIB	Suicidal Ideation Behaviour
SoA	Schedule of Activities
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SRT	Safety Review Team
SUSAR	Suspected unexpected serious adverse events
TB	Tuberculosis
TID	Three times a day
T_{max}	Time taken to maximum observed plasma drug concentration
TNF	Tumour Necrosis Factor
TNFR1	Tumour Necrosis Factor Receptor-1
UC	Ulcerative Colitis
UDP	Uridine diphosphate
µg	Microgram
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UK	United Kingdom
ULN	Upper Limit of Normal
WOCBP	Woman of Child Bearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NONE

Trademarks not owned by the GlaxoSmithKline group of companies
Quantiferon

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 3 will be performed by the Doctor's Laboratory.
- 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.

Table 3 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	Red Blood Cell (RBC) Indices: Mean Corpuscular Volume (MCV) Mean corpuscular haemoglobin (MCH) %Reticulocytes	White Blood Cell (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
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (Fasted)[2]	Calcium	Alkaline phosphatase	Albumin
			Anti-nuclear antibody [(ANA), Part B only]	C-reactive protein (CRP)
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Alcohol breath test and urine drug screen (to include at minimum:			

Laboratory Assessments	Parameters
	amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)] • Smoking Breath Test • Serum human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential). To be done at screening and Day 17 of Part B. • Urine hCG pregnancy test (as needed for women of child bearing potential)[3] • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Tuberculosis test • Total Cholesterol, Low-density lipoprotein, triglycerides (Part B only)[2] • Estimated glomerular filtration rate (eGFR) will be calculated using the CKD-EPI formula. 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 8.1.3 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Non-fasted samples can be collected on Day -1 (All Parts) and at the Follow-Up visit (Part A Only).
3. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Laboratory that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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 Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

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

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative 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 medical record 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 or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with Standard Operating Procedure (SOP)-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

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 multicenter 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

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.
- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

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 (e.g., 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.

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

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 assessmentse.g.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 (i.e., 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 (e.g., 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 (e.g., 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 (e.g., 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.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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.
- 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 Paper CRF
• Email transmission of the SAE paper CRF is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • In rare circumstances and in the absence of email 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 Study Reference Manual.

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 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 treatment phase and until at least 90 days after the last administration of study drug:
    - 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 and recommend subject or partner use of an additional method of contraception with a failure rate of <1% per year as

described in Table 4 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
- In addition, male participants must refrain from donating sperm for duration of study and for 90 days after study completion or from last dose

Female participants

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 4 for a minimum of 28 days prior to the first dose of study drug and until at least 30 days after the last administration of study drug. For female particpants using a hormonal method of contraception, partner use of male condoms is also required during the treatment period and until at least 28 days after the last administration of study drug.

Table 4 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[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • 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.

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case the use of a male condom should be utilized during the treatment period and for at least 30 days after the last dose of study treatment.

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test
- Additional pregnancy testing 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.
- Pregnancy testing, with a sensitivity of 25 mIU/mL will be performed using the test kit approved by the sponsor and in accordance with instructions provided in its package insert.

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

Any female participant who becomes pregnant while participating will discontinue study treatment.

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

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

12.7. Appendix 7: 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 hr
• 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 24 hours 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 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:

• Anti-nuclear antibody, anti-smooth muscle</td></tr>
</table>

Liver Chemistry Stopping Criteria	
liver event follow up assessments within **24-72 hr** • Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline	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. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
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.

12.8. Appendix 8: Nervous System Adverse Events (CTCAE Criteria)

Taken from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

The purpose of this Appendix is to provide guidance and is to be used in conjunction with the Investigator's judgment.

Table 5 Guidance For Grading Adverse Events

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-	A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-	A disorder characterized by systematic and extensive loss of memory.
Aphonia	-	-	Voicelessness; unable to speak	-	-	A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-	A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-	A disorder characterized by a conspicuous change in cognitive function.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-	A disorder characterized by a deterioration in the ability to concentrate.
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death	A disorder characterized by a decrease in ability to perceive and respond.
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-	A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-	A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-	A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-	A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated		A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a pathologic process involving the brain.
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by a reduction in the strength of the facial muscles.
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the facial nerve (seventh cranial nerve).
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-	A disorder characterized by characterized by excessive sleepiness during the daytime.
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by bleeding from the cranium.
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-	A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-	A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum ± mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum ± moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum ± moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death	A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-	A disorder characterized by a deterioration in memory function.
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by uncontrolled and purposeless movements.
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by intense painful sensation along a nerve or group of nerves.
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involuntary movements of the eyeballs.
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the olfactory nerve (first cranial nerve).
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral motor nerves.
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Presyncope	-	Present (e.g., near fainting)	-	-	-	A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by paralysis of the recurrent laryngeal nerve.
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death	A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by characterized by excessive sleepiness and drowsiness.
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death	A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.
Syncope	-	-	Fainting; orthostatic collapse	-	-	A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-	A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-	A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).

CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death	-

12.9. Appendix 9: Protocol Amendment History

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

Amendment 01 (07-Dec-2017)

Overall Rationale for the Amendment: Clarification of the allowed contraception methods for female participants of child bearing potential and male participants with female partners of child bearing potential. Pharmacogenetic sampling has been incorporated into the protocol and glucuronide levels will be assessed in Part A of the study, as well as Part B. In addition, further administrative clarifications have been made.

Section # and Name	Description of Change	Brief Rationale
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 3.3.1. Risk Assessment 6.1. Inclusion Criteria 12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	An additional line for 'Highly effective contraceptive method (WOCBP only)' and 'Contraception with male condoms (WOCBP using hormonal contraceptive method and male subjects with female partners of childbearing potential only)' has been added to the SoA tables in Section 2.1. and Section 2.2. Updated wording for the subject selection for the risk of Reproductive Toxicity. Updated wording for Inclusion Criteria 4 for Male and Female subjects. Update of the contraception guidance wording for women of child bearing potential and male subjects with female partners of child bearing potential.	Female subjects of child-bearing potential who use hormonal contraception are required to have their sexual partners use a male condom from the first dose of study drug until the follow-up visit to avoid conception until at least 30 days after the last administration of drug. This is being added as a precautionary measure for all WOCBP because an AE of "breakthrough bleeding" was reported in Cohort 1 TP2 of this study in a female subject who is on a combination oral contraceptive pill. In the FTiH Study 200975, there was no increase detected in an in vivo marker for CYP3A4 enzyme activity following repeat dose administration up to 120 mg BID. Measurement of 4β-hydroxycholesterol is being evaluated in this study to determine CYP3A4 enzyme activity in repeat dose administration up to 720 mg/day. Until data are available the added contraception is being required.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 9.6. Genetics 12.6. Appendix 6: Genetics	A line for Pharmacogenetic Sampling has been added to both Part A and Part B of the study. A Genetics section has been added to the protocol (9.6) and appendix (6)	To take a pharmacogenetic sample from consenting subjects. One subject in Cohort 1 (not the subject with break through bleeding), had consistently high exposure to GSK2982772 compared to the other subjects (~2-fold higher C_{max}) for the 120 mg and 240 mg TID dose levels. This may be due to a UGT1A9 genetic polymorphism, which is responsible for the conversion to the glucuronide metabolite of GSK2982772.
2.1. Time and Events Table – Part A	Addition of a note in PK blood sampling row to state "Remaining PK plasma samples from Part A may be analysed for metabolite	To include the assessment of metabolite concentrations in Part A of the study (currently Part B only).

Section # and Name	Description of Change	Brief Rationale
(Cohort 1) Synopsis-Objectives and Endpoints Section 4. Objectives and Endpoints 9.4.2. Sample Analysis	sampling." Metabolite sampling will be assessed after single-day of dosing, as well as repeat dosing. Updated wording to in this section to state "any remaining plasma sample may be analysed for any compound-related material and the results may be reported as part of this study or under a separate PTS-IVIVT, GlaxoSmithKline protocol."	
2.2. Time and Events Table – Part B (Cohorts 2-4)	A pre-dose PK sampling time point has been added to the Note 'f' for Cohort 2 and Cohort 3.	No pre-dose sample was written into the original protocol on Days 9 and 11 of Cohorts 2 and 3.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4)	Addition of a PK sampling timepoint at 17hr post-first dose in the TID Dosing regimens in Cohort 1. Addition of a PK sampling timepoint at 17 hr post-first dose in the TID Dosing regimen of Cohorts 2 and 3.	An additional PK sampling time point at 3hr post-last dose has been added to better characterize the PK profile and to ensure the C_{max} is not missed.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 6.2. Exclusion Criteria 12.2.	'Cotinine Screen' has been changed to 'Smoking Screen' and 'Cotinine Breath Test' has been changed to 'Smoking Breath Test' in Section 2.1. and Section 2.2. Carbon monoxide levels have been included in Exclusion Criteria 24. In the 'Other Screening Tests' section, 'Cotinine Breath Test' has	The 'Cotinine Breath Test' either includes urine cotinine and/or smoking breath test. The study will determine evidence of current smoking using a non-invasive breath carbon monoxide (CO) test device, which will provide CO levels to determine evidence of smoking.

Section # and Name	Description of Change	Brief Rationale
Appendix 2: Clinical Laboratory Tests	been changed to 'Smoking Breath Test'.	
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 12.2. Appendix 2: Clinical Laboratory Tests	In Part A of the study, Haem/Chem/Urinalysis assessments can be non-fasted for Day -1 and the Follow-Up Visit. In Part B of the study Haem/Chem/Urinalysis assessments can be non-fasted for Day -1 only. Additional wording included to Note 2 in Table 3 - Non-fasted samples can be collected on Day -1 (All Parts) and at the Follow-Up visit (Part A Only).	The fasting lipid panel in Part B was separated out in the SoA since it was noted to be performed on Day -1 or Day 1. This was moved to Day 1 only since subjects will not be fasted on Day -1. The 4β-hydroxycholesterol will be checked on Day 1, as a fasted sample. It is recommended that all other lab time points being performed (inclusive of the follow-up visit) are to be performed under fasted conditions since this is essential to assess lipid profiles.
6.2. Exclusion Criteria	An additional Exclusion Criteria (16) has been added. "The subject has participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer). All subsequent exclusion criteria numbers have increased by 1.	To define the minimum length of time since a subject was last exposed to a new chemical entity.
2.1. Time and Events Table – Part A (Cohort 1) 2.2. Time and Events Table – Part B (Cohorts 2-4) 7.2. Method of Treatment	Updated wording in the 'Notes' section under the procedure "Randomization" in Section 2.1. and Section 2.2 to state: "Randomization can occur on either Day -1 or Day 1 in both Parts A and B of the study." Updated wording to include that randomization can take place on Day -1 or Day 1 in Section 7.2.	There was a discrepancy in the SoA under the procedure "Randomization" in both Part A and B on Day -1 and Section 7.2. Randomization can take place on either Day -1 or Day 1.

Section # and Name	Description of Change	Brief Rationale
Assignment		
9.3.3. Vital Signs	The semi-supine position has been removed from this section.	To remove any ambiguity with this assessment, the supine position will be the only position used to assess vital signs.
2.2. Time and Events Table – Part B (Cohorts 2-4)	A comment has been added to the Meals row to state that "Meals will be served as per the site schedule on Days -1, 16 and 17."	Clarification of the wording for the meal schedule on non-dosing and non PK sampling days.
2.2. Time and Events Table – Part B (Cohorts 2-4)	Superscript 'g' has been removed from the PK blood sampling on Day 1.	Superscript 'g' refers to study assessments on Day 14 of the protocol and not Day 1. This is a correction of a typographical error.
6.2. Exclusion Criteria	Update of the wording in Exclusion Criteria 3 to change the definition of what constitutes a positive tuberculin skin test from <5 mm skin induration at 48 to 72 hours to >5 mm skin induration at 48 to 72 hours.	Correction of a typographical error. An induration of >5 mm skin induration at 48 to 72 hours is considered a positive TB test.
7.2. Method of Treatment Assignment	The Method of Treatment Assignment has been updated to note that subjects in Cohort 1 will be randomized to 1 of 4 treatment sequences rather than 1 of 3. The additional treatment sequence (ABC) has been added.	Correction of a typographical error. There is no change to the randomization ratio, which is 3:1.
2.1. Time and Events Table – Part A (Cohort 1)	Removal of the 10hr time interval post-last dose in note 'b' for TID dosing. This now reads "**TID dosing:** GSK2982772 or placebo will be administered using a 7hr, 7hr dosing interval."	Correction of a typographical error. Since Part A is a single-day of dosing, this 10hr interval has been removed.
2.2. Time and Events Table – Part B (Cohorts 2-4)	The Neurological Examination originally on Day 4 has been moved to Day 3.	Correction of a typographical error. 48hr post-first dose assessment would be on Day 3.
6.2. Exclusion Criteria	Exclusion Criteria 29 has been updated to state "Fasting total cholesterol" rather than "Total fasting cholesterol".	Correction of typographical error.

Section # and Name	Description of Change	Brief Rationale
5.7. Dose Justification	The title in Figure 2 has been changed from "Monkey C_{max}" to "Monkey AUC(0-24)".	Correction of the PK parameter stated in the Figure 2 title.
12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating and Follow-Up Assessments	In the 'Reporting of SAE to GSK' section, facsimile transmission of the SAE paper CRF has been changed to email transmission.	Notification of an SAE via email is the preferred method of transmission to the Medical Monitor and SAE Coordinator.