TITLE PAGE

Protocol Title: A single-centre, randomized, double-blind (sponsor open), placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK2983559, in single (in both fed and fasted states) and repeat oral doses in healthy participants

Protocol Number: 205021/ Amendment 01

Short Title: GSK2983559 First time in human study

Compound Number: GSK2983559

Sponsor Name and Legal Registered Address:

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SPONSOR SIGNATORY:

PPD

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Immunoinflammation Therapy Area

24th July 2018.
Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 01	24-JUL-2018
Original Protocol Republishing	17-OCT-2017
Original Protocol	06-OCT-2017

Amendment 01 24-JUL-2018

Overall Rationale for the Amendment:

As described in Section 5.5.5 and Section 8.2 of this protocol, plasma concentrations of the mutagenic substance 5-ABT and its metabolite NAc-5-ABT are being monitored throughout the study to ensure that participants remain below the threshold of toxicological concern (TTC) of <120 µg/day (for up to one month of dosing) as defined by the ICH M7 guidance. Following administration of a single dose of 100 mg GSK2983559 in Cohort 1 of Part A, quantifiable concentrations of 5-ABT were observed in 4 of the 8 subjects dosed with GSK2983559. The maximum observed 5-ABT concentration of 1.25 ng/mL was below the stopping criteria of 3 ng/mL. The presence of quantifiable concentrations of 5-ABT in plasma is believed to be due to hydrolysis of the drug substance to form 5-ABT in the acidic conditions of the stomach. It is also known that the drug product contains 5-ABT; however, this is being controlled to < 10 ppm in the current synthetic route and extraction procedure.

This amendment will change the formulation from a standard capsule (HPMC) to an enteric capsule (HPMCAS) to determine if an enteric formulation minimises the gastric conversion of drug substance to 5-ABT. The disintergration of an enteric capsule is pH dependent and is expected to avoid hydrolysis in the stomach and release active pharmaceutical ingredient (API) in the higher pH environment in the proximal small intestine. The 5-ABT stopping criteria are unchanged and continue with progression in to Cohort 2 and if controlled will carry through Cohort 6.

PK parameters AUC and C_{max} for GSK2983559 and GSK2668176 increase approximately linearly with increasing doses. Draft preliminary review of blinded safety data indicate that there are no clinical significant safety concerns. No SAEs or deaths have been reported. Cohort 2 is planned to start with a 200 mg dose and escalate to the top predicted dose which values **will not** exceed the mean GSK2668176 $AUC_{(0-24)}$ and C_{max} values observed at one third of the No Observable Effect Limit (NOAEL) in minipig. The sample size for Cohort 2 will be increased from 8 to 12 subjects to monitor for 5-ABT concentrations in more subjects and to ensure at least 8 active subjects progress to the food effect dosing in this cohort.

Section # and Name	**Description of Change**	**Brief Rationale**
Section1. Protocol Synopsis Section 5.1. Overall Design Section 5.2. Number of Participants	The Number of Participants has been raised to 12 in Cohort 2, which has been reflected in the Treatment Groups Table. Figure 1 Study Design has been updated to change the number of subjects in Cohort 2 from 8 to 12. Table 6 updated with number of participants for Cohort 2. The text has been edited to state that there will be 12 subjects in Cohort 2 and this cohort will switch to the enteric capsule. Table 6 Treatment Sequences for Part A – Cohort 2 updated from 8 to 12 subjects and DL9 in treatment period 4 updated to remove OL and become an optional dose if required.	Cohort 2 increase in sample size is needed to monitor for 5-ABT concentrations and ensure at least 8 active subjects progress to the food effect in this cohort using the enteric capsule.
Section 5.5.3 Anticipated efficacious dose	Updated section to reflect predicted pharmacological dose. Removed Table 7.	PK and PD data are now available from Cohort 1 to determine predicted pharmacological dose.
Section 5.5.4 Top dose selection for Part A and B	Updated section and Table 8 with observed and predicted fold cover to NOAEL.	
Section 5.5.5 Assessment and control of 5-ABT Section 7 Treatments	Removed Table (previously numbered Table 9) Predicted amount of 5-ABT. Provide rationale for enteric (HPMCAS) capsule for remaining cohorts. Section 7.1 updated with HPMCAS capsule information.	Table not applicable since quantifiable concentrations of 5-ABT have been observed below TTC in 4 out of 8 subjects treated with 100 mg in Cohort 1.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 7.3 Method of Treatment Assignment	Cohort 2 and Treatment codes updated.	To include up to 4 dosing sequences in 1:1:1:1 ratios. Original planned treatment description updated to what has been administered in Cohort 1 and what is planned for Cohort 2.
Section 11.1 Sample Size Determiniation	Maximum number of participants updated in Part A or B.	Probability of an observed safety event changes with an increase in sample size.

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1. SYNOPSIS

Protocol Title: A single-centre, randomized, double-blind (sponsor open), placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of GSK2983559, in single (in both fed and fasted states) and repeat oral doses in healthy participants

Short Title: GSK2983559 First time in human study

Rationale: This study is the first administration of GSK2983559, a selective receptor interacting protein 2 (RIP2) kinase inhibitor, to humans. The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and exploratory pharmacodynamics (PD) of single (fed and fasted) and repeat oral doses of up to 14 days with GSK2983559 in healthy participants. The intention of this study is to provide sufficient confidence in the safety of the molecule to inform progression to further repeat dose proof of concept studies.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of single (fed and fasted) and repeat doses of GSK2983559 in healthy participants.	• Safety and tolerability of GSK2983559 as assessed by clinical monitoring and reporting of adverse events and serious adverse events, change in laboratory values, electrocardiogram (ECG), vital signs, physical examinations.
Secondary	
• To characterise the PK profile of single (fasted) doses of GSK2983559 and its active moiety GSK2668176 in healthy participants.	• Derived PK parameters for GSK2983559 and GSK2668176 including area under the plasma drug concentration versus time curve (area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration [$AUC_{(0-t)}$], area Under the Concentration-time curve from time zero to infinity [$AUC_{(0-\infty)}$]), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fasted) doses, where data allow.
• To characterise the PK profile of repeat doses of GSK2983559 and its active moiety GSK2668176 in healthy participants.	• Derived PK parameters for GSK2983559 and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\tau)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single and repeat doses, and estimation of an accumulation ratio where data allow.

Objectives	Endpoints
• To assess the effect of food on the pharmacokinetics of GSK2983559 and its active moiety GSK2668176 in fasted and fed state in healthy participants.	• Derived PK parameters for GSK2983559, and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fed and fasted) dose, where data allow.

Overall Design:

This study will be a randomised, double-blind (sponsor open), placebo-controlled, two-part study of oral administration of GSK2983559 in healthy participants. Part A will be a single ascending dose crossover design in two separate cohorts of participants (Cohorts 1 and 2). In addition to the crossover treatment periods, subjects in Cohort 2 will participate in an additional treatment period and receive open-label GSK2983559 under fed conditions. Part B will be a repeat dose design in up to 4 cohorts of participants (Cohorts 3-6). This study is planned to include approximately 62 participants.

Parts A and B of this study will be double-blind with respect to participants, investigator and site staff (except for the site pharmacist). Sponsor open refers only to members of the Dose Escalation Committee (DEC) at defined meetings. Members and requirements are provided in a Dose Escalation Charter.

- **Part A** – single ascending doses, randomized, placebo controlled, crossover.

Part A plans to explore up to 9 single ascending dose levels. This will be 2 cohorts, Cohort 1 (standard capsule) and Cohort 2 (enteric capsule), of 10 and 12 healthy participants, respectively. The total duration of Part A of the study for each participant, including screening and follow-up, is approximately 11 weeks.

- **Part B** – repeat ascending dose, randomized, placebo controlled, sequential-group.

Part B will consist of up to four cohorts of 10 healthy participants. The total duration of Part B of the study for each participant, including screening and follow-up, is approximately 15 weeks. The treatment period will be 14 days.

In all cases the decision to proceed to the next dose level will be made at a DEC meeting (see Study Governance Considerations).

2. SCHEDULE OF ACTIVITIES (SOA)

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

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

Any changes in the timing or addition of time points for any planned study assessments as a result of emerging pharmacokinetic data must be documented and approved by the relevant study team members and then archived in the sponsor and site study files. The competent authority (CA) and ethics committee (EC) will be informed of any safety issues that constitute a substantial amendment and require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF). The changes will be approved by the CA and the EC before implementation.

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

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

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

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

Table 1 Screening and Follow Up SOA

Procedure	Screening	Follow-up Visit	Notes
	(up to 28 days prior to Day 1)		
Outpatient Visit	X	X	Follow-up Visit to occur approximately 7 days or 5 half lives (as determined from Part A PK data), whichever is longer, and no greater than 14 days after last study drug administration.
Informed Consent	X		
Inclusion and Exclusion Criteria	X		
Medical/medication/drug/alcohol history	X		
Demographics	X		
Full Physical Examination	X		Additional examinations may be performed, or brief examinations made full examinations, by the Investigator, as deemed necessary (e.g. where safety or laboratory findings indicate).
Brief Physical Examination		X	
Drug/alc./cotinine screen	X		Tests include alcohol breath test, urine cotinine and drug screen.
HIV, Hep B and Hep C screen	X		
Tuberculosis Test	X		Conducted as standard practice of the site.
Serum Pregnancy Test (all females)	X		
FSH and estradiol (all females)	X		
Hema/Chem/Urinalysis tests	X	X	
Coagulation Panel	X		
Lipid panel (Part B only)	X		
Height and weight	X		
Holter Monitoring (24-hour)	X		
12-lead ECG	T	X	T= Triplicate
Vital signs	X	X	Vital signs to include heart rate, blood pressure, respiration rate and temperature.
Concomitant Medication Review	X	X	
AE and SAE Review		X	

Table 2 Part A SOA

Procedure	Study Day (each dosing session)																		Notes
	Day -1	Day 1 (time relative to dose) See Study Reference Manual for assessment time windows																Day 2	Day 3	*Participants to be admitted to the unit the day before dosing (Day -1), and remain in house until discharge after 48-hour post-dose assessments (Day 3) are completed.*
		Pre dose	0 h	15min	30min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	3.5hr	4hr	5hr	6hr	8 hr	10 hr	12 hr	24 hr	48 hr	
Pregnancy test (all females)	X																			
Brief Physical Examination	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).*
Drug/alc./cotinine screen	X																			*Additional assessments may be performed at the discretion of the Investigator. Tests will be conducted within site specified standards.*
Heam/Chem/Coags/Urinalysis	X	X													X			X	X	*Non-fasted samples will be collected on Day -1 and at 8 hours on Day 1. Non-fasted chemistry only will be collected at 8 hour time point.*
Neuro. examination	X							X										X	X	
Telemetry		<----------																		*Continuous at least 8 hours post-dose. Initiate at least 15 min. prior to dosing*
Vital signs	X	T			X		X	X	X	X		X	X		X		X	X	X	*Vital signs to include HR, BP, respiration rate and temperature. T = Triplicate (HR and BP only) single respiration rate and temperature. Timings will be reviewed as cohorts progress and may be adjusted to ensure appropriate measurements relative to peak concentrations for subsequent cohorts.*
12-lead ECG	T	T					X	X	X	X		X	X		X		X	X	X	
Meals **All**	D											Per site Schedule								*Prior to dosing, participants will fast for 8 hrs overnight; no food is allowed for at least 4 hrs post-dose. Water is permitted with dosing and at all times except 1 hour pre-dose through 2-hours post-dose. Participants will receive standardized meals scheduled at the same time in each period.*
Cohort 2, fed period	D	B																		
Study Treatment dosing			X																	*A minimum interval of 30 minutes will be observed between the dosing of the first 2 participants at each dose level. A minimum interval of 15 minutes will be observed between the dosing of the remaining 6 participants.*
PK Blood Sample		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	*The number and sampling times may be adjusted once the human PK data are available.*
Urine Collection for Metabolites		X	<----------0-24 hours---------->																	*Participants will void bladder prior to dosing, a sample will be kept as control. 0-24-hr urine samples will be collected.*
PD Blood Sample		X						X					X		X			X	X	*Two samples will be drawn at pre-dose. The PD sampling time points may be updated based on emerging PK data. PD samples will not be collected in the food efect part of the study.*
TE Blood Sample		X						X					X		X			X	X	*TE samples will not be collected in the food effect part of the study*
Adverse Event Review		<----------X---------->																		*See section 10.1.1 for pre-dose SAE requirements*
Concomitant Med.	<----------X---------->																			
For ECG and vital signs T=Triplicate, For Meals B=Breakfast, D=Dinner																				

Table 3 Part B SOA

Procedure	Study Day(s)																Notes
	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	*Participants to be discharged after the 48-hour post-dose assessments are completed on Day 16.*
Pregnancy test (all females)	X																	
Brief Physical Examination	X	Please see separate SOA for D1 assessments	X		X			X			X				Please see separate SOA for D14 assessments	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.*
Full Physical Examination																	X	
Drug/alc./cotinine screen	X																	
Weight	X							X									X	
Telemetry			X															*Continuous initiating 15 min. pre-dose through at least 8 hrs post-dose*
12-lead ECG	T		X	X	X			X			X					X 24h post D14 dose		*Day 2 – Day 13 readings to be performed pre-dose. Vital signs include HR, BP, respiration rate and temperature. T=Triplicate; Vitals signs Triplicate (HR and BP only) single respiration rate and temperature.*
Vital signs	T		X	X	X	X	X	X	X	X	X	X	X	X		X 24h post D14 dose		
Hem/Chem/Coag/Urinalysis	X		X		X			X			X					X		*On Days 2, 4, 7 and 10 to be drawn at pre-dose.*
Neuro. Examination	X		X					X								X		
Fasting lipid panel		X														X		*Fasting from at least 12:01 am.*
Meals Served	X	Please see separate SOA for D1 assessments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Study Treatment Dosing			X	X	X	X	X	X	X	X	X	X	X	X	Please see separate SOA for D14 assessments			*Dosing frequency (qd or bid) to be determined based on Part A data.*
PK Blood Sample			X 24h post D1 dose	X	X	X	X	X			X		X			X 24h post D14 dose	X 48h post D14 dose	*Pre-dose PK samples collected on Days 3 through 7, Day 10 and Day 12.*
PD Blood Sample			X 24h post D1 dose													X 24h post D14 dose	X 48h post D14 dose	
TE Blood Sample			X 24h post D1 dose													X 24h post D14 dose	X 48h post D14 dose	
AE Assessment		<----------x---------->																*See section 10.1.1 for pre-dose SAE requirements*
Concomitant Med. Review	<----------x---------->																	

Table 4 Part B Day 1 and Day 14 SOA

Procedure	Study Days Days 1 and 14 (time relative to dose) See Study Reference Manual for assessment time windows																						Notes
	Pre dose	0	15 min	30 min	1 hr	1.5 hr	2 hr	2.5 hr	3 hr	3.5	4hr	5hr	6hr	8 hr	10 hr	12 hr	12.5 h	13 h	13.5 h	14 h	14.5 h	15.5	16 h	
Hema/Chem/Coag/Urinalysis	X													X										*Pre-dose for Day 1 may be drawn on either Day 1 or Day -1 and does not include pre-dose on Day 14. Non-fasted Chemistry only at 8-hour time point on Day 1.*
Neuro. Examination							X																	*No examinations to be performed on Day 14.*
12-lead ECG and vital signs	T			X		X	X	X	X		X	X		X		X								*Vital signs to include HR, BP, respiration rate and temperature. T = Triplicate (HR and BP only) single respiration rate and temperature. Time points may be added or subtracted after review of Part A data.*
Telemetry	<----------X---------->																							*Continuous at least 8 hours post-dose. Initiate at least 15 min. prior to dosing*
PK Blood Sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	*The number and sampling times may be adjusted once the human PK data are available.*
Metabolite Blood Sample	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	X BID dosing only	*The number and sampling times may be adjusted once the human PK data are available.*
Urine Collection for Metabolites	X	<----------0-24 hours----------> or for BID dosing <----------0-12 hours---------->																						*Participants will void bladder prior to dosing, a sample will be kept as a control. 0-24-hr urine samples (or 0-12hr samples for BID dosing) will be collected.*
PD Blood Sample	X						X					X		X										*Two samples will be drawn at pre-dose. The PD sampling time points may be updated based on emerging PK data. PD samples will not be collected in the food efect part of the study.*
TE Blood Sample	X						X					X		X										*The TE sampling time points may be updated based on emerging PK data. TE samples will not be collected in the food effect part of the study*
Study Treatment Dosing		X														X BID dosing only								*Dosing frequency (qd or bid) to be determined based on Part A data.*
Meals Served											Per site schedule													*On Days 1 and 14 - participants will fast 8 hrs overnight; no food is allowed for at least 4 hrs post-dose. Water permitted with dosing and at all times except 1 hour pre-dose through 2-hours post-dose. Participants will receive standardized meals scheduled at the same time in each period.*

3. INTRODUCTION

3.1. Study Rationale

This study is the first administration of GSK2983559, a selective RIP2 kinase inhibitor, to humans. The purpose of this study is to evaluate the safety, tolerability, pharmacokinetics (PK), and exploratory pharmacodynamics (PD) of single (fed and fasted) and repeat oral doses of up to 14 days with GSK2983559 in healthy participants. The intention of this study is to provide sufficient confidence in the safety of the molecule to inform progression to further repeat dose proof of concept studies.

3.2. Background

GSK2983559 is a novel oral first-in-class inhibitor of Receptor Interacting Protein Kinase-2 (RIPK2). GSK2983559 is a phosphate ester pro-drug, which breaks down rapidly into GSK2668176 providing an increase in solubility and exposure. GSK2668176 is a potent, reversible, and highly-selective inhibitor of RIP2 kinase (RIPK2).

RIPK2 is a serine/threonine kinase, comprised of an N-terminal kinase domain, an intermediate domain, and C-terminal caspase-activation-and-recruitment (CARD) domain. The nucleotide-binding oligomerization domain 1 (NOD1)/RIP2 and NOD2/RIP2 pathways are widely expressed in both immune and non-immune cells. Upon activation RIP2 undergoes post-translational modifications (ubiquitination and autophosphorylation), which facilitate NF-κB and mitogen-activated protein kinase (MAPK) activation, and lead to release of multiple proinflammatory cytokines (e.g., tumour necrosis factor [TNF], interleukin [IL]-1, -6, -8, etc.). Properly regulated, these pathways play an important role in maintaining innate immune homeostasis and host defense.

Dysregulation of these pathways has been linked to multiple inflammatory diseases. Mutations in the Leucine-rich repeat (LRR) domain of NOD2 have been linked to increased susceptibility to Crohn's disease (CD). In both CD and ulcerative colitis (UC) a breakdown in intestinal immune homeostasis is associated with disruption of epithelial barrier integrity, leading to inappropriate interaction between commensal bacteria and mucosal immune cells, aberrant activation of pattern recognition receptors (PRRs), and RIPK2-dependent inflammation. Activating mutations in the nucleotide binding domain of NOD2 have been linked to Blau Syndrome, a rare, monogenic, autoinflammatory disease characterized by granulomatous inflammation affecting multiple organs, often presenting with the clinical trial of arthritis, uveitis, and dermatitis. RIP2-dependent signaling has also been implicated in additional inflammatory diseases, including rheumatoid arthritis, psoriasis, vasculitis, type 2 diabetes, and multiple sclerosis.

3.3. Benefit/Risk Assessment

To date, GSK2983559 has not been administered to human participants; therefore, no clinical data are available. This is the first single and repeat dose study proposed in human participants with GSK2983559. GlaxoSmithKline is not aware of any compound targeting this pathway having previously been administered in humans.

The risk assessment of GSK2983559 is based on the pre-clinical studies conducted to date. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2983559 can be found in the GSK2983559 Investigator's Brochure [GlaxoSmithKline Document Number 2016N308990_00]. Details of these risks and the proposed strategy to mitigate/monitor these risks are detailed in Section 3.1 below. The proposed risk assessment and management plan for the study has been developed in accordance with the tenets of European Medicines Agency (EMA) guideline on strategies to identify and mitigate risks for first time in human (FTiH) clinical trials with investigational medicinal products [European Medicines Evaluation Agency (EMEA)/ Committee for Medicinal Products for Human Use (CHMP)/SWP/28367/07]. GlaxoSmithKline (GSK) has assessed this study for any risks that may be posed to participants taking part. Only healthy male and female participants of non-child bearing potential (NCBP) will participate in this study.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK2983559]		
Neurobehavioral effects	**Non-clinical data**: Non-reproducible neurobehavioural observations in an acute study in rats at doses ≥15mg/kg/day (vocalisation, increased touch response, grip strength and body tone). No central nervous system (CNS)-related clinical signs were seen in any other acute or repeat dose study in rats, dogs or minipigs.	**Participant Selection**: • Participants with known history of significant neurological or psychiatric disorders or suicidal ideation behaviour will be excluded from GSK2983559 clinical studies. • Participants with potentially increased susceptibility for neurologic or psychiatric effects will be excluded based on medical history at screening. **Participant Monitoring**: • Targeted physical examinations with comprehensive neurological assessments will be conducted at appropriate intervals throughout the study. • Participants will be monitored for standard CNS-related adverse events (AEs). Common terminology criteria for adverse events (CTCAE) Nervous System Stopping Criteria are included in the protocol.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Immunosuppression	There is a theoretical risk of immunosuppression, including an increase in the frequency and/or severity of infection, resulting from the intended pharmacologic effect of GSK2983559.	**Participant Selection**: • Participants with recurrent, chronic or active infections will be excluded from GSK2983559 clinical studies. • Participants will be screened for tuberculosis (TB), human immunodeficiency virus (HIV), and Hepatitis B and C, and excluded from this study. **Participant Monitoring**: • Participants will be monitored for signs of infection.
Vaccinations	There is a theoretical risk that GSK2983559 could decrease a participant's immune response to vaccines or allow symptoms to develop following vaccination with a live vaccine when administered on therapy. Currently, there are no preclinical or clinical data with respect to this potential risk.	**Participant Selection**: • Routine or planned attenuated or live vaccines should not be administered to participants for 30 days prior to the first dose of GSK2983559, during study participation, and for 5 half-lives plus 30 days after receiving GSK2983559. • Non-live vaccines (e.g., inactivated influenza vaccines) may be administered while receiving GSK2983559.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Hepatotoxicity	**Non-clinical data**: Increased mean serum glutamate dehydrogenase (GLDH) and alanine aminotransferase (ALT) concentrations correlated with mixed inflammatory cell infiltrates present around the bile duct regions in the liver in female rats given 240 mg/kg/day (6-week study). These changes were not observed in male rats at any dose. Additional liver findings, including hepatocellular necrosis, have been observed in rats and minipigs at non-tolerated doses.	**Participant Monitoring**: • Clinical hematologic and chemistry laboratory tests are readily measurable in the clinic and will be monitored periodically throughout the study (see SoA in Section 2). • Liver Chemistry Stopping Criteria are included in the clinical protocol.
Phototoxicity	**Non-clinical data**: There is a potential risk that GSK2983559 can lead to photosensitivity responses in some people. In a ultraviolet/visible light (UV/VIS) spectrum for GSK2983559 (max abs [absorbance] 340 nm) and GSK2668176 (max abs 339 nm) in acetonitrile (ACN)/water showed an absorbance between 290-700 nm demonstrated a risk for potential phototoxicity effects.	**Participant Selection**: • Participants must agree to avoid prolonged UV exposure to natural sunlight or tanning beds for the duration of the study. • Participants should be advised to wear protective clothing (e.g., sun hat, long sleeves) covering exposed areas and use a broad spectrum ultraviolet A/ultraviolet B (UVA/UVB) sunscreen and lip balm (SPF ≥30) on exposed areas when outdoors for a minimum of 5 half-lives after receiving GSK2983559. Participants should also wear sunglasses which filter UVA and UVB rays for a minimum of 5 half-lives after receiving GSK2983559. **Participant Monitoring**: • Participants should be monitored for adverse effects potentially related to phototoxicity.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Mutagenicity/ Genotoxicity	**Non-clinical data**: 5-amino-benzothiazole (5-ABT), an impurity and acid degradant, is mutagenic in an in vitro Ames assay. It is unknown if GSK2983559 itself presents a genotoxic hazard to humans.	**Participant Monitoring**: • Plasma samples from FTIH will be analysed for 5ABT and N-acetyl 5ABT at each dose level. Dose escalation will be halted if in any individual the C_{max} of combined concentration of 5-ABT and n-acetyl-5-amino benzothiazole (NAc-5-ABT) (in ng/mL equivalents 5-ABT) is > 3 ng/mL in either the standard or enteric capsule.
Reproductive toxicity	**Non-clinical data:** Animal reproductive studies have not been conducted with GSK2983559. Therefore, the compound must not be administered to pregnant women, nursing mothers or women of childbearing potential.	**Subject Selection:** • Male and female participants of non-childbearing potential (WONCBP) may be included in this study. • Male participants must agree to use highly effective methods of contraception during the treatment period and for at least 5 half-lives plus an additional 90 days after the last dose of study treatment and refrain from donating sperm during this period (Appendix 5).

3.3.2. Benefit Assessment

The proposed study with GSK2983559 will be conducted in healthy participants. No medical benefit will be derived by participants' participation. Participants 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 GSK2983559 can be appropriately mitigated by the careful selection of study participants and the proposed safety monitoring procedures. As such, the risk to potential participants is considered low. Routine safety and tolerability will be evaluated from reported adverse events (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 will allow for continuous medical monitoring for all participants following the first dose in each treatment group. Participants will only be discharged from the unit 48 hours after their last dose of GSK2983559 if the Investigator deems it safe to do so.

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with GSK2983559 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

Objectives	Endpoints
Primary	
• To assess the safety and tolerability of single (fed and fasted) and repeat doses of GSK2983559 in healthy participants.	• Safety and tolerability of GSK2983559 as assessed by clinical monitoring and reporting of adverse events and serious adverse events, change in laboratory values, ECG, vital signs, physical examinations.
Secondary	
• To characterise the PK profile of single (fasted) doses of GSK2983559 and its active moiety GSK2668176 in healthy participants.	• Derived PK parameters for GSK2983559 and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fasted) doses, where data allow.
• To characterise the PK profile of repeat doses of GSK2983559 and its active moiety GSK2668176 in healthy participants.	• Derived PK parameters for GSK2983559 and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\tau)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single and repeat doses, and estimation of an accumulation ratio where data allow.
• To assess the effect of food on the pharmacokinetics of GSK2983559 and its active moiety GSK2668176 in fasted and fed state in healthy participants.	• Derived PK parameters for GSK2983559, and GSK2668176 including area under the plasma drug concentration versus time curve ($AUC_{(0-t)}$, $AUC_{(0-\infty)}$), maximum observed plasma drug concentration (C_{max}), time to maximum observed plasma drug concentration (t_{max}), and terminal half-life ($t_{1/2}$) following single (fed and fasted) dose, where data allow.
Exploratory	
• To determine the PD effect of single and repeat doses of GSK2983559 in healthy participants.	• PD/biomarker endpoints may include, but not be limited to, assessments of pharmacologic effects through measurements of target engagement and pathway activation. These may include measurements of RIP-2 receptor occupancy, and levels of MIP1α, MIP1β and TNF proteins, following stimulation of whole blood, as data permit.
• To investigate the metabolic profile of GSK2983559 following single and/or repeat doses in healthy participants in blood and urine	• Identification and quantitative estimates of GSK2983559 and its active moiety GSK2668176 and potential metabolites following single and repeat doses in plasma and urine.
• To characterize exposure to 5-ABT and NAc-5-ABT after single and repeated doses of GSK2983559 in healthy participants.	• Concentration of 5-ABT and NAc-5-ABT (adjusted to 5-ABT concentration based on MW) and derive C_{max} for the combined concentration curve of 5-ABT and MW adjusted NAc-5-ABT

5. STUDY DESIGN

5.1. Overall Design

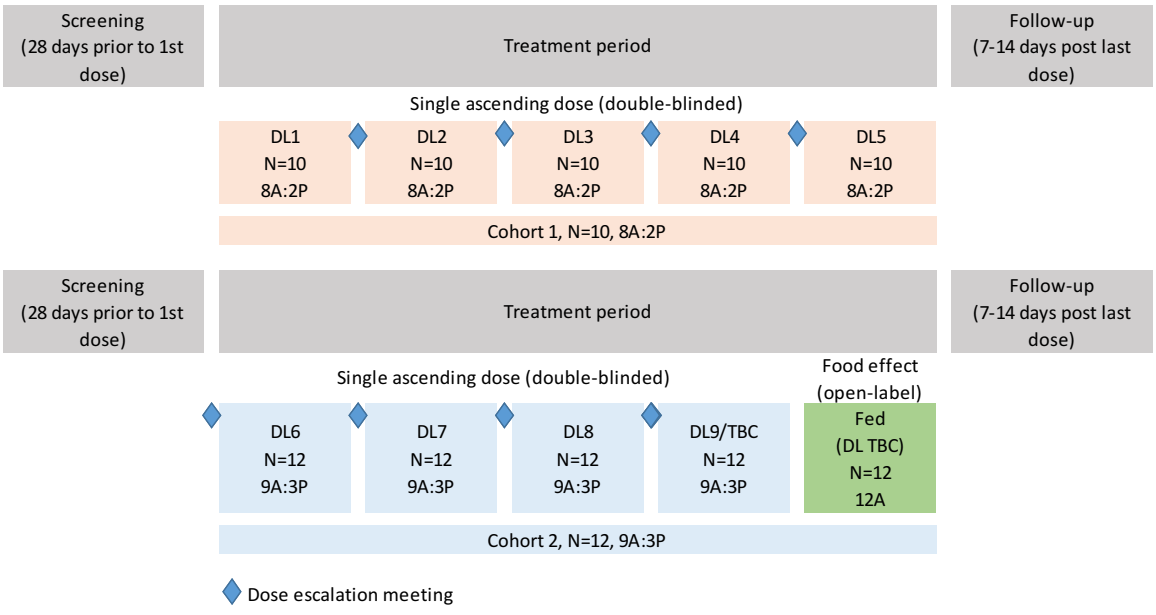
This study will be a randomised, double-blind (sponsor open), placebo-controlled, two-part study of oral administration of GSK2983559 in healthy participants. Part A will be a single ascending dose crossover design in two separate cohorts of participants (Cohorts 1 and 2). In addition to the crossover treatment periods, subjects in Cohort 2 will participate in an additional treatment period and receive open-label GSK2983559 under fed conditions. Part B will be a repeat dose design in up to 4 cohorts of participants (Cohorts 3-6). This study is planned to include approximately 62 participants.

Parts A and B of this study will be double-blind with respect to participants, investigator and site staff (with the exception of the site pharmacist). Sponsor open refers only to members of the Dose Escalation Committee (DEC) at defined meetings. Members and requirements are provided in a Dose Escalation Charter.

- **Part A** – single ascending doses, randomized, placebo controlled, crossover.

Part A plans to explore up to 9 single ascending dose levels. This will be 2 cohorts, Cohort 1 (standard capsule) and Cohort 2 (enteric capsule), of 10 and 12 healthy participants, respectively. The total duration of Part A of the study for each participant, including screening and follow-up, is approximately 11 weeks.

Figure 1 Study design – Part A



Separate participants will be enrolled into both cohorts of Part A.

The design for the 2 cohorts is as follows:

- Cohort 1: 5-way crossover design with the standard capsule. Each participant will receive single ascending oral doses of either GSK2983559 or placebo in a 4:1 ratio according to the randomisation schedule, in study periods 1 to 5, in a blinded manner.
- Cohort 2: 4-way crossover design with the enteric capsule for single ascending dose, including an additional period for assessing GSK2983559 under fed conditions (period 5 – open-label).
  During the blinded part, each participant will receive single ascending oral doses of either GSK2983559 or placebo in a 3:1 ratio according to the randomisation schedule, in study periods 1 to 4, in a blinded manner.
  If dose levels 6-9 are not investigated, Cohort 2 will only be used for evaluating the effect of food. It will be an open-label 2-way crossover design.
- Cohorts 1 and 2 will be dosed sequentially, incorporating sentinel participants: Cohort 1 will complete all 5 dosing periods before Cohort 2 begins.
- Following completion of Cohort 1 and before starting Cohort 2, a GSK internal safety board (independent of DEC) will be reviewing the data.
- Based on emerging PK data, all doses may not be investigated.
- There will be a at least 48-hour washout period between each dose escalation step but the washout period may be extended depending on emerging data.

Treatment period

- Cohort 1 (single dose) will be comprised of up to 5 study periods, each at least 4 days in duration with participants in-house for 3 nights (through 48 hours post-dose). During each treatment period, participants will be admitted to the unit the day before dosing and will be discharged after completion of the 48-hour post-dose assessments.
- Cohort 2 (single dose) will be comprised of up to 4 study periods, each at least 4 days in duration with participants in-house for 3 nights (through 48 hours post-dose). During each treatment period, participants will be admitted to the unit the day before dosing and will be discharged after completion of the 48-hour post-dose assessments.
- Participants in Cohort 2 (food effect) will participate in up to 2 additional treatment periods and receive a single oral dose of GSK2983559 under fasted (Period 4) and/or fed (Period 5) conditions, dose to be determined by DEC.
  If the dose level chosen for the food effect assessment was administered in:
    - Cohort 1: participants will receive the dose of open-label GSK2983559 under fasted (Period 4) and fed (Period 5).
    - Cohort 2: participants will only receive the dose of open-label GSK2983559 under fed (Period 5) conditions.
- All participants will participate in no more than 5 Treatment Periods (see Table 5 and Table 6).
- Participants will have a follow-up visit at least 7 days or 5 half-lives whichever is longer, and no greater than 14 days after last dose of GSK2983559. If warranted, additional follow-up visits may be scheduled.

Dosing

- Participants will be randomized on Day 1 followed by a single oral dose of GSK2983559.

- Sentinel dosing will be employed within each ascending dose cohort and treatment period (except for when investigating the food effect). On Day 1, one participant will receive GSK2983559 and one participant will receive matched-placebo, to evaluate tolerability and safety for at least 24 hours post-dose. Dosing in the remaining 8 and 10 participants in Cohorts 1 and 2, and treatment period will occur at least 24 hours later after review of safety results from the initial 2 participants in a 7:1 and 4:1 ratios (GSK2983559: placebo) for Cohorts 1 and 2, respectively

The decision to proceed to the next single dose level will be made at a DEC meeting (see Appendix 3: Study Governance Considerations).

Treatment sequences for Part A:

The treatment sequences for Part A are outlined below and the planned dose levels (DLs) are defined in Section 5.5. The dose of GSK2983559 administered with a high-fat meal will be a dose level already evaluated in the dose escalation part of the study and will be determined by DEC and based on attainment of adequate exposure and safety.

Table 5 Treatment sequences for Part A – Cohort 1

Cohort 1:	5-way crossover design with standard capsule					
Sequence	Number of participants (N=10)	Period 1	Period 2	Period 3	Period 4	Period 5
1	2	Placebo	DL2	DL3	DL4	DL5
2	2	DL1	Placebo	DL3	DL4	DL5
3	2	DL1	DL2	Placebo	DL4	DL5
4	2	DL1	DL2	DL3	Placebo	DL5
5	2	DL1	DL2	DL3	DL4	Placebo

Table 6 Treatment sequences for Part A – Cohort 2

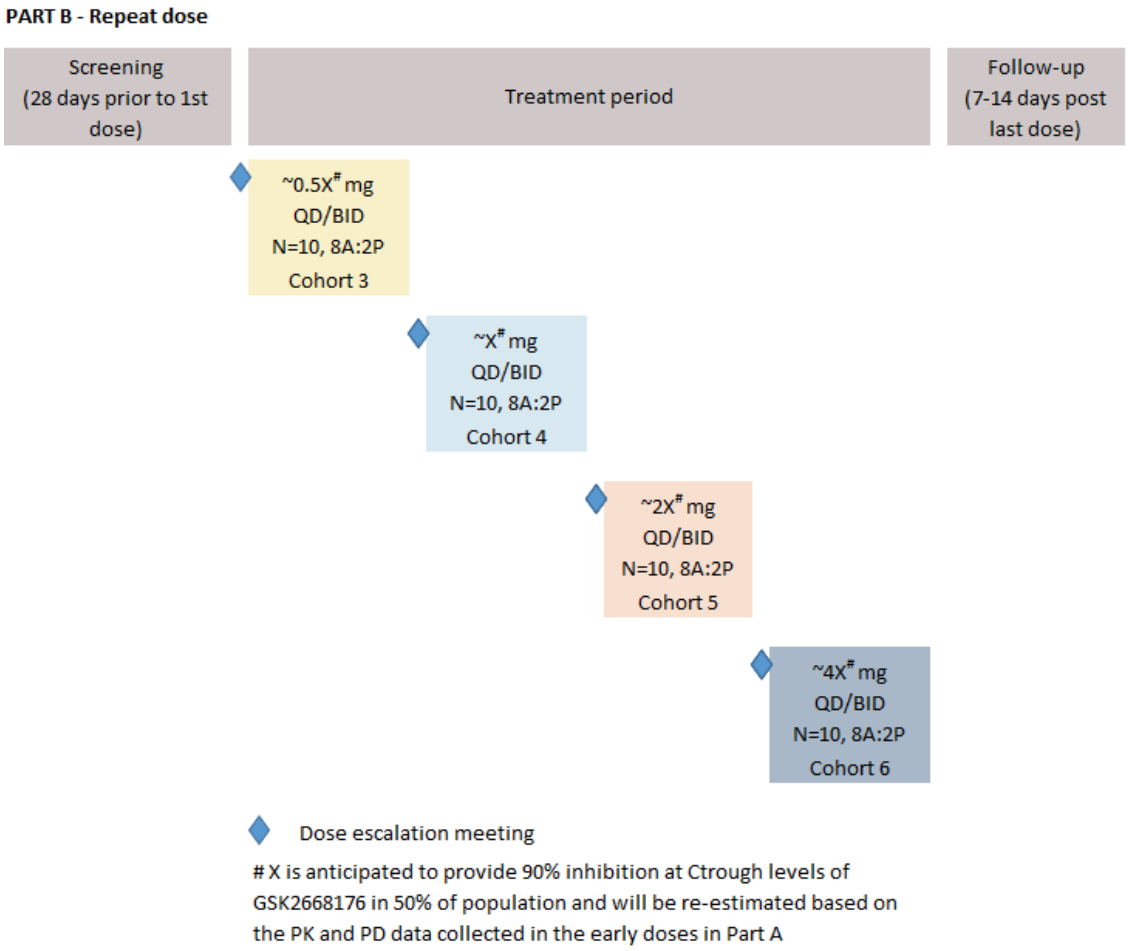
Cohort 2:	4-way crossover design + open-label period for food effect with enteric capsule					
Sequence	Number of participants (N= 12)	Period 1	Period 2	Period 3	Period 4*	Period 5 (w/food)
1	3	Placebo	DL7	DL8	DL9	TBC
2	3	DL6	Placebo	DL8	DL9	TBC
3	3	DL6	DL7	Placebo	DL9	TBC
4	3	DL6	DL7	DL8	Placebo	TBC

* If exposure levels are lower than expected, doses higher than Period 3 (DL9), may be evaluated. If the dose level chosen for the food effect period was already evaluated in Cohort 2 (i.e., DL6-8), participants will only receive the dose of GSK2983559 under fed (period 5) conditions.
Abbreviations: DL: dose level; BL: blinded; TBC: to be confirmed

- **Part B** – repeat ascending dose, randomized, placebo controlled, sequential-group with enteric capsule.

Part B will consist of up to four cohorts of 10 healthy participants. The total duration of Part B of the study for each participant, including screening and follow-up, is approximately 15 weeks. The treatment period will be 14 days.

Figure 2 Study design – Part B



See Section 5.5.5 for dose justification in Part B.

Separate cohorts of participants will be enrolled into Parts A and B.

Cohorts 3-6 will be dosed sequentially (i.e., Cohort 4 starts after dosing in Cohort 3 is completed).

The participants in each cohort will be randomised in a 4:1 ratio to receive either GSK2983559 or placebo (enteric capsule), according to the randomisation schedule.

Treatment period

- The treatment period will be 14 days.
- Participants will be admitted to the unit the day before dosing, will remain in the unit overnight, and will be discharged following completion of the assessments on Day 16, provided there are no safety concerns.
- Participants will have a follow-up visit at least 7 days or 5 half-lives (as determined from Part A PK data) whichever is longer, and no greater than 14 days after last study drug administration. If warranted, additional follow-up visits may be scheduled.

Dosing

- Once-daily (QD) dosing is planned in Part B, but twice-daily dosing (BID) may be considered based upon the PK profile as well as the safety and tolerability observed in Part A.
- Sentinel dosing will be employed within each cohort. On Day 1, one participant will receive GSK2983559 and one participant will receive matched-placebo, both participants will be dosed to steady state (approximately Day 2 minimum based on PK predictions from Part A). Dosing in the remaining 8 participants in each cohort will occur after review of safety results from the initial 2 participants in a 7:1 ratio (GSK2983559: placebo).

The decision on the dose level of GSK2983559 to be administered in Cohort 3 will be made at a DEC meeting based on all safety, tolerability, and PK data accumulated from Part A of the study. The decision to proceed to the next single dose level will be made at a DEC meeting (see Appendix 3: Study Governance Considerations).

5.2. Number of Participants

Participants will be screened to ensure that a minimum of 62 are eligible to be randomised (10 participants into Cohort 1, 12 participants into Cohort 2, and 10 participants into each of Cohorts 3-6), so that a minimum of evaluable participants are achieved in each of cohorts as described in the table below:

		Randomised	Evaluable
Part A	Cohort 1 (single dose)	10	4 out of 8 on active
	Cohort 2 (single dose)	12	4 out of 9 on active
	Cohort 2 (food effect)	up to 12	4 out of at least 8 on active
Part B	Cohorts 3-6 (repeat dose)	10	4 out of 8 on active
	Total	62	

Participants are considered as evaluable if the following are completed:

- Part A - Cohort 1 (single dose): screening and all 5 treatment periods.
- Part A - Cohort 2 (single dose): screening and all 3 or 4 treatment periods.
- Part A - Cohort 2 (food effect): screening and all 2 treatment periods (fed and fasted).
- Part B - Cohort 3-6 (repeat dose): screening and the 14-day treatment period.

Additional participants/cohorts may be enrolled to allow for evaluation of additional dose levels. No more than 10 additional participants will be allowed in a cohort either in Part A and/or B. The schedule of assessments will be as for these parts and the number of dosing periods will not exceed those in the current cohorts.

If a participant withdraws prematurely from Part A of the study, additional participants may be recruited and assigned to the same treatment sequence, starting from the current dosing period of the early withdrawal at the discretion of the sponsor in consultation with the investigator.

If a participant withdraws prematurely from Part B of the study, additional participants may be recruited and assigned to the same repeat dose level, starting from baseline at the discretion of the sponsor in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed:

- Part A (cohort 1) of the study if he/she has completed all the periods of Part A – cohort 1, including the follow-up visit.
- Part A (cohort 2 – single dose) of the study if he/she has completed all the periods of Part A – cohort 2 – single dose, including the follow-up visit.
- Part A (cohort 2 – food effect) of the study if he/she has completed the 2 periods of Part A – cohort 2 – food effect, including the follow-up visit.
- Part B of the study if he/she has completed all visits including the follow-up visit.

The end of the study is defined as the date of the last visit (including follow-up) of the last participant in the study (Part A and Part B).

5.4. Scientific Rationale for Study Design

The current study described herein has been designed to address regulatory guidance for FTIH studies and in particular General Considerations for Clinical Trials [The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E8/ Committee For Proprietary Medicinal Products (CPMP)/ICH/291/95] and Guideline on Strategies to Identify and Mitigate Risk for First-in-Human Clinical Trials with Investigational Medical Products [EMEA/CHMP/SWP/28367/07] as well as pre-clinical findings for GSK2983559, contributing to the frequency, type and duration of safety assessment and monitoring during treatment periods during each cohort.

The sequential design of the single dose components (Part A) and estimated 5-hour half-life ($t_{1/2}$) will allow for dose escalation to occur after less than 6 days of washout. The predicted time for GSK2668176 plasma concentrations to reach the lower limit of quantification (LLOQ, 0.20 ng/ml) after dosing for the highest selected dose (see Section 5.5 below) was 3 days. This will allow any adjustment needed based on emerging safety, tolerability, and PK information. The randomised crossover design was chosen to allow for treatment comparison between and within participants. Further, a food-effect evaluation is planned to support progression into patient studies.

In Part B, the 14-day dosing will provide exposure to PK steady state and will also be informative of the likely safety and tolerability in future longer studies.

5.5. Dose Justification

5.5.1. Human PK prediction

GSK2983559 is a phosphate ester pro-drug which is converted into GSK2668176 (active moiety) primarily by the alkaline phosphatase present in the intestinal lumen. The systemic exposure of the prodrug GSK2983559 is predicted to be <2% in humans and is considered to have a negligible contribution to clinical effect and is not considered relevant for human dose determination.

The human pharmacokinetic (PK) profiles as well as parameters of parent drug GSK2668176 following oral dosing of prodrug GSK2983559 were predicted using in vitro to in vivo extrapolation and allometric scaling. The predicted human mean absorption rate constant (0.85 1/h), clearance (0.426 L/h/Kg), volume of distribution (2.8 L/Kg), half-life (4.6 hours) and bioavailability (70%) were used to determine the blood PK profiles for GSK2668176 following oral administration of GSK2983559.

As the exposures observed in preclinical species were in plasma, the predicted human PK estimates in blood were multiplied by a factor of 0.83 (blood/plasma ratio=1.2 for GSK2668176) to give the corresponding human PK estimates in plasma for calculating the safety fold coverage to the no observable adverse effect limit (NOAEL).

5.5.2. Starting dose selection for Part A

The predicted human PK parameters along with the human whole blood (HWB) ex vivo assay data (HWB: muramyl dipepide (MDP)/TNFα Inhibitory concentration (IC)90=86.67 ng/mL) were used for human PK/PD predictions at various human dose levels. The 'Minimal Anticipated Biological Effect Level' (MABEL) approach was used as the basis to define the starting dose for GSK2983559 monotherapy in the single ascending dose phase of the study. A starting dose of 2 mg was chosen, as maximum and minimum PD inhibition are predicted to be approximately 30% and 3% at the predicted mean C_{max} and mimimum observed concentration (C_{min}) (24 h) values, respectively. Mean C_{max} and $AUC_{(0-\infty)}$ values of GSK2668176 in human plasma are projected to be 0.004 µg/mL and 0.038 µg.h/mL, respectively, for the starting dose of 2 mg GSK2983559; these human predicted exposures are 753- and 708-fold lower than plasma C_{max} and area under the concentration-time curve from time zero to 24 hours post first dose [AUC(0-24)] values at the NOAEL(60 mg/kg/day) in the six-week female rat preclinical toxicological study and 1870 and 1338-fold lower at the NOAEL (120mg/kg/day) in the six-week minipig preclinical toxicology study. In addition, the predicted mean C_{max} at the 2 mg/day human dose is 106-fold lower compared to C_{max} at the no observable effect limit (NOEL) (1 mg/kg) in the rat Irwin studies (neurobehavioural studies in male rats). Thus, a starting dose of 2 mg in human provides sufficient safety margins against the preclinical toxicological findings to ensure the safety of study participants.

5.5.3. Anticipated efficacious dose

The level of inhibition of *ex-vivo* cytokine response required for efficacy is not known. An efficacious dose may be anticipated with 90% inhibition of cytokine response at trough concentration measured at the end of a dosing interval at steady state (C_{trough}) (HWB:MDP/TNFα IC90=86.67 ng/mL). A dose of 800 mg QD was originally predicted to provide a mean inhibition of 90% at C_{trough} for 24 hours. A similar level of inhibition was predicted to be achieved with 100 mg BID dosing (total dose 200 mg/day). Accounting for between subject variability in PK and PD (assuming 30% between-subject variability on apparent total clearance of the drug from plasma after oral administration (CL/F)], V/F, absorption rate constant (K_a) and IC_{50} for simulations), a dose of 400 mg BID (total daily dose of 800 mg) was predicted to be required for 90% inhibition at C_{trough} in approximately 90% of population. Based on emerging GSK2668176 pharmacokinetic data from the current study, a dose of 400 mg QD is predicted to provide a mean inhibition of 90% at C_{trough} for 24 hours. Accounting for between subject variability in PK, a dose of 200 mg BID (total daily dose of 400 mg) is predicted to be required for 90% inhibition at C_{trough} in approximately 90% of population.

5.5.4. Top dose selection for Part A

The expected exposure from the anticipated efficacious dose of 200 mg BID would have to be tested in the single ascending dose part, thus, requiring the need for evaluating 400 mg. Since the level of inhibition of *ex-vivo* cytokine response required for efficacy is not known, doses that produce higher than 90% cytokine inhibition should be evaluated in the future efficacy dose ranging study. With the highest planned single dose of 600 mg, predicted plasma C_{max} (1.84 µg/mL) and $AUC_{(0-\infty)}$ (17.3 µg.h/mL) values are expected to provide >1.6-fold and >1.6-fold safety margin over the female rat NOAEL in the 6-week study for C_{max} and area under the concentation-time curve (AUC), respectively and 4.1-fold for C_{max} and 2.94-fold for AUC in minipigs. If exposure levels are lower than expected, doses higher than 600 mg may be evaluated. The progression from one dose level to another will be made based on the assessment of the available data from previous dose levels by the Dose Escalation Committee (See Appendix 3: Study Governance Considerations). Table 7 lists the predicted NOAEL cover for GSK2668176 at various planned GSK2983559 doses in the FTIH study.

Table 7 Average GSK2668176 AUC and C_{max} following single oral doses of GSK2983559, with Fold Cover to NOAEL

Dose (mg)	Projected human plasma $AUC_{(024)}$ (µg.h/mL)	Fold cover to NOAEL Minipig[1]	Fold cover to NOAEL male Rat[2]	Fold cover to NOAEL female Rat[3]	Projected human plasma C_{max} (µg/mL)	Fold cover to NOAEL Minipig[1]	Fold cover to NOAEL male Rat[2]	Fold cover to NOAEL female Rat[3]	Mean % PD inhibition coverage at C_{trough}
2*	0.095	535	815	283	0.0105	714	706	288	9
4*	0.230	221	337	117	0.026	288	285	116	21
10*	0.347	147	223	77.5	0.038	197	195	79.5	29
30*	0.812	62.6	95.3	33.1	0.094	79.8	78.8	32.1	45
100*	2.476	20.5	31.3	10.9	0.306	24.5	24.2	9.87	73
200#	4.952	10.3	15.6	5.43	0.612	12.3	12.1	4.93	84
400#	9.904	5.13	7.82	2.72	1.224	6.13	6.05	2.47	92
600#	14.86	3.42	5.21	1.81	1.836	4.08	4.04	1.64	94

Key:
1= 6 week Minipig NOAEL is 120 mg/kg/day GSK2983559: Gender-averaged Day 42 mean plasma AUC_{0-t} of 50.85 µg.h/mL GSK2668176 and C_{max} of 7.5 µg/mL GSK2668176.
2= 6-week Rat NOAEL in males is 240 mg/kg/day GSK2983559: Day 42 plasma AUC_{0-t} of 77.4 µg.h/mL GSK2668176 and plasma C_{max} of 7.41 µg/mL GSK2668176.
3= 6-week Rat NOAEL in females is 60 mg/kg/day GSK2983559: Day 42 plasma AUC_{0-t} of 26.9 µg.h/mL GSK2668176 and plasma C_{max} of 3.02 µg/mL GSK2668176.
*. Observed $AUC_{(0-24)}$ and C_{max}.
Predicted $AUC_{(0-24)}$ and C_{max} based on 100 mg values and assuming linear.

Dose selection for Food Effect

An assessment of the effect of food on the exposure to GSK2983559/ GSK2668176 will be incorporated into the single dose part of the study (Part A). The food effect was predicted to be non-significant up to 300 mg dose using GastroPlus (physiologically based pharmacokinetic modelling (PBPK) modeling platform). Fed State Simulated Intestinal Fluid / Fasted State Simulated Intestinal Fluid (FeSSIF / FaSSIF) ratio for GSK2983559 is 1.5; therefore, a 50% increase in exposure could be anticipated relative to fasting state exposure. The dose to be administered with food will be selected such that, if there were a 50% increase in exposure it would be predicted to be within the safety margins.

Dose selection for Part B

Part B (repeat dose) of the study will be initiated after completion of Part A. Dose selection will be based upon consideration of available safety, tolerability and PK data from Part A and/or preceding repeat dose cohorts in Part B. Based on the observed half-life of approximately 8 h GSK2668176 in humans, minimum accumulation is anticipated after BID dosing. The dose of GSK2983559, noted as X, is anticipated to provide 90% inhibition at C_{trough} levels of GSK2668176 in 50% of the population and will be re-estimated based on the PK and PD data collected in the early doses in Part A. The initial

dose in Part B (Cohort 3, repeat dose) will be approximately half X. Dose escalation in the repeat dose part of the study will not exceed 2-fold between cohorts and will be driven by safety and PK stopping criteria (see Section 8). In addition, a dose will not be assessed as a repeat dose until the anticipated steady-state exposure (C_{max} and $AUC_{(0-\tau)}$ on Day 14) for that dose have been evaluated and shown not to have met safety stopping criteria in the single dose portion of the study (Part A). Based on current PK predictions a dose of 200 mg BID dosing regimen is predicted to provide 90% inhibition in approximately 90% of subjects. Dose levels higher than this may be explored in order to evaluate dose response in future phase 2 dose ranging study provided that exposure levels for that dose has been previously evaluated in Part A of the study.

5.5.5. Assessment and control of 5-ABT

5-amino-benzothiazole (5-ABT), an impurity in the GSK2983559 drug substance (3-6 parts per million (ppm) [m.2.1.S.3.2 Impurities in chemistry, manufacturing and controls (CMC) investigational medicinal product dossier (IMPD)], was found to be mutagenic in an in vitro Ames assay. In addition, 5-ABT was formed from GSK2668176 in bio relevant media (pH 6.5 and pH 8 in FaSSIF and FeSSIF conditions), suggesting that a theoretical risk exists for its formation at physiological pH. According to ICH M7 guidance for the assessment and control of deoxyribonucleic acid (DNA) reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk, 5-ABT is classified as a Class 2 hazard (i.e. known mutagen with unknown carcinogenic potential) and must be controlled at or below the Threshold of Toxicological Concern (TTC) of 120 µg/day considering the duration of treatment of ≤ 1 month..

5-ABT is not predicted to be a metabolite, and has not been observed as a metabolite in in vitro hepatocyte or S9 incubations. Real time analysis of plasma samples from FTIH for 5-ABT and its metabolite N-acetyl 5-ABT will be performed to monitor exposure to 5-ABT in healthy volunteers.

Quantifiable concentrations of 5-ABT were observed below the stopping criteria (combined C_{max} of 5-ABT and NAc-5-ABT of 3 ng/mL) in 4 out of 8 subjects treated with GSK2983559 in Cohort 1 at the 100-mg dose level. The maximum observed 5-ABT concentration was 1.25 ng/mL. An enteric capsule [Hydroxypropylmethyl Cellulose Acetate Succinate (HPMCAS)] will be used starting in Cohort 2 and carry through to Cohort 6 to determine if this formulation will minimize the gastric conversion of drug substance to 5-ABT. The disintergration of an enteric capsule is pH dependent and is expected to avoid hydrolysis of the active pharmaceutical ingredient (API) to 5-ABT in the acidic environment of the stomach and release API in a higher pH environment in the proximal small intestine.

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

AGE
1. Male and female participants between 18 and 65 years of age inclusive, at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. Volunteers who are overtly healthy as determined by medical evaluation including medical and psychiatric history, physical examination, neurological examination, clinical laboratory tests and cardiac monitoring.
WEIGHT
3. Body weight ≥ 50 kg and body mass index (BMI) within the range 19-32 kg/m2 (inclusive).
SEX

4. Male and female participants:
 	
a. Male participants:
 	
A male participant must agree to use a highly effective contraception (see below) during the treatment period and for at least 5 half-lives plus an additional 90 days after the last dose of study treatment and refrain from donating sperm during this period.
 	
• 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 above:
 	
  • 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 Appendix 5 when having penile-vaginal intercourse with a woman of childbearing potential
 	
• Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.
 	
• Refrain from donating sperm for duration of study and for 90 days from the last dose.
 	
b. Female participants:
 	
A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and is not a woman of childbearing potential (WOCBP) as defined in Appendix 5.

INFORMED CONSENT
5. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this

protocol.

6. Participants must agree to avoid prolonged UV exposure to natural sunlight without required UVA/UVB protection or tanning beds for the duration of the study.

6.2. Exclusion Criteria

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

MEDICAL CONDITIONS

1. History or presence of/significant history 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 or current evidence of febrile seizures, epilepsy, convulsions, significant head injury, or other significant neurologic conditions.
3. History of clinically significant psychiatric disorders as judged by the investigator.
4. Any history of suicidal behavior within the past 6 months or any history of attempted suicide in a participant's lifetime.
5. Alanine transaminase (ALT) >1.5x upper limit of normal (ULN).
6. Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
7. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
8. History of GI surgery (with exception of appendectomy).
9. Average QTc > 450 msec

   NOTES:

   a. 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.
   b. The specific formula that will be used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study. In other words, several different formulae cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant 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).

PRIOR/CONCOMITANT THERAPY
10. Intended use of over-the-counter or prescription medication including herbal medications within 7 days prior to dosing [Specific medications listed in the protocol may be allowed]
11. Live or attenuated vaccine(s) within 30 days of randomisation, or plans to receive such vaccines during the study or plans to receive a vaccine within 30 days + 5 half-lives of the last dose of study medication.
12. Regular alcohol consumption within 6 months prior to the study defined as:
13. An average weekly intake of >21 units for males or >14 units for females. One unit is equivalent to 8 g of alcohol: a half-pint (~240 ml) of beer, 1 glass (125 ml) of wine or 1 (25 ml) measure of spirits.
14. Current use or history of regular tobacco- or nicotine-containing products within 6 months prior to screening. Subject must have urinary cotinine levels indicative of non-smoking status at screening visit.

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE
15. Exposure to more than 4 new chemical entities within 12 months prior to the first dosing day.
16. Current enrollment or past participation within the last 30 days before signing of consent in this or any other clinical study involving an investigational study treatment or any other type of medical research.

DIAGNOSTIC ASSESSMENTS
17. Participants with impaired renal function defined as Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) calculation ≤ 60 (mL/min/1.73m^2) estimated by the CKD-EPI equation [Snyder, 2009 and Levey, 2010].
18. An elevated C-reactive protein (CRP) outside of the normal reference range.
19. Presence of hepatitis B surface antigen (HBsAg), positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment. As potential for and magnitude of immunosuppression with this compound is unknown, participants with presence of hepatitis B core antibody (HBcAb) should also be excluded. Participants positive for HBsAg and/or positive for anti-HBc antibody (regardless of anti-HBs antibody status) are excluded.
20. A positive pre-study drug/alcohol screen.
21. A positive test for HIV antibody.
22. A positive diagnostic TB test at screening defined as a positive QuantiFERON-TB Gold test or T-spot test. In cases where the QuantiFERON or T-spot test is indeterminate, the participant may have the test repeated once, but they will not be eligible for the study unless the second test is negative. In cases where the QuantiFERON or T-spot test is positive, but a locally-read follow up chest x-ray,

shows no evidence of current or previous pulmonary tuberculosis, the participant may be eligible for the study at the discretion of the Investigator and GSK Medical Monitor.

OTHER EXCLUSIONS
23. Sensitivity to any of the study treatments, or components thereof, or drug or other allergy that, in the opinion of the Investigator or GSK Medical Monitor, contraindicates participation in the study.
24. Where participation in the study would result in donation of blood or blood products in excess of 500 mL within a 56-day period.
25. Part A (Food Effect) Cohort: Participant must have no dietary restrictions (e.g., lactose intolerance) or inability to eat a high fat meal.

6.3. Lifestyle Restrictions

6.3.1. UV exposure

- Participants should be advised to wear protective clothing (e.g., sun hat, long sleeves) covering exposed areas and use a broad spectrum UVA/UVB sunscreen and lip balm (SPF $\geq$ 30) on exposed areas when outdoors for a minimum of 5 half-lives after receiving GSK2983559. Participants should also wear sunglasses which filter UVA and UVB rays for a minimum of 5 half-lives after receiving GSK2983559.

6.3.2. 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, subject 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.

6.3.3. Fasted Conditions

6.3.3.1. Part A

During Part A (fasted treatment periods) participants will fast overnight from Day -1 to Day 1:

- Water is permitted with dosing and at all times except 1 hour pre-dose through 2-hours post-dose.
- Participants must fast from all food and drink (except water) for 8 hours pre-dose and prior to any clinical laboratory evaluations (except repeat evaluations).
- No food is allowed for at least 4 hours post-dose.

6.3.3.2. Part B

If once daily (QD) dosing is investigated, the following fasting conditions will be followed:

- Water is permitted with dosing and at all times except 1 hour pre-dose through 2-hours post-dose.
- Participants must fast every night from all food and drink (except water) for 8 hours pre-dose and prior to any clinical laboratory evaluations (except repeat evaluations).
- A schedule of meals in relation to dosing will be provided in the study reference manual (SRM).

If BID dosing is required, the fasted conditions will be determined on the basis of the data emerging from the food effect seen in Part A and will be detailed in the SRM.

6.3.3.3. Fed Conditions

With the exception of those outlined in Section 6.3.3.1, participants will receive standardized meals scheduled at the same time in each period.

In the final treatment period of Cohort 2 in Part A, participants will fast from approximately midnight on the day prior to dosing and will receive a standard high-fat meal 30 minutes prior to dosing. The breakfast will be consumed steadily over 25 minutes. Dose administration must occur within 5 minutes of completing breakfast. Participants will not receive any further food until 4 hours post-dose. Water will not be allowed from 1 hour before until 4 hours after dosing.

According to the European Medicines Agency – Guidelines on the Investigation of Drug Interaction, the high fat meal should contain 800-1000 kcal with 500-600 kcal from fat and 240 kcal from carbohydrates. A typical standard high-fat meal should consist of:

- Two eggs fried in butter
- Two strips of bacon
- Two slices of toast with butter
- 120 grams of hash brown potatoes cooked in butter
- 240 mL of whole milk

6.3.4. Caffeine, Alcohol, and Tobacco

- During each dosing session, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 24 hours before the start of dosing untildischarge from the clinic.

- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK and/or pharmacodynamic sample.
- Use of tobacco or nicotine-containing products will not be allowed from 6 months prior to screening until after the final follow-up visit.

6.3.5. 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 traveling 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 serious adverse events (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 participant number as for the initial screening.

7. TREATMENTS

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

7.1. Treatments Administered

Product name:	**GSK2983559**	**Placebo**	**GSK2983559**	**Placebo**
Formulation description:	API filled capsule	Avicel filled capsule	API filled capsule	Avicel filled capsule
Dosage form:	HPMC Capsule	HPMC Capsule	HPMC Capsule	HPMC Capsule
Unit dose strength(s)/Dosage level(s):	2-45 mg	NA	100, 114 mg	NA
Route/ Administration/ Duration:	Oral	Oral	Oral	Oral
Dosing instructions:	Dose with water	Dose with water	Dose with water	Dose with water
Physical description:	Size 0 Swedish Orange capsule containing white to almost white solid	Size 0 Swedish Orange capsule containing white to almost white solid	Size 00 White Opaque capsule containing white to almost white solid	Size 00 White Opaque capsule containing white to almost white solid
Manufacturer/ source of procurement:	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline	GlaxoSmithKline
Method for individualizing dosage:	Site to assemble	Site to assemble	Site to assemble	Site to assemble

HPMC – Hydroxypropylmethyl Cellulose

Product name:	**GSK2983559**	**Placebo**
Formulation description:	API filled capsule	Avicel filled capsule
Dosage form:	HPMCAS Capsule	HPMCAS Capsule
Unit dose strength(s)/Dosage level(s):	50-100 mg	NA
Route/ Administration/ Duration:	Oral	Oral
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
Manufacturer/ source of procurement:	GlaxoSmithKline	GlaxoSmithKline
Method for individualizing dosage:	Site to assemble	Site to assemble

HPMCAS – Hydroxypropylmethyl Cellulose Acetate Succinate

7.2. Dose Modification

This protocol allows some alteration from the currently outlined dosing schedule, but the maximum total daily dose will not intentionally exceed the PK stopping criteria defined in Section 8. Currently, the highest planned dose is 600 mg/day of GSK2983559.

7.3. Method of Treatment Assignment

At screening a unique number (case report form [CRF] number) will be assigned to any participant who has at least one Screening procedure performed, other than signed informed consent. The unique number will be used to identify individual participants during the course of the study.

Participants who meet the screening eligibility criteria will be randomised to a treatment group through an Interactive Response Technology (IRT). The IRT will confirm the participants CRF number and provide the randomisation number, where:

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

The randomisation is centrally controlled by the IRT.

Part A

Within Cohort 1, participants will be assigned to one of 5 dosing sequences in a 1:1:1:1:1 ratio.

Within Cohort 2, participants will be assigned to one of up to 4 dosing sequences in a 1:1:1:1 ratio.

Participants will be randomised to:

	Cohort 1	**Cohort 2**
Sequence	PBCDE APCDE ABPDE ABCPE ABCDP	PGHIJ FPHIJ FGPIJ FGHPJ

Where the treatment codes are as follows:

Treatment code	**Original Planned Treatment Description**	**Cohort 1 Actual Treatment & Cohort 2 Planned Treatment Description**
A	2 mg GSK2983559	
B	10 mg GSK2983559	4 mg GSK2983559
C	30 mg GSK2983559	10 mg GSK2983559
D	75 mg GSK2983559	30 mg GSK2983559
E	150 mg GSK2983559	100 mg GSK2983599
F	300 mg GSK2983559	200 mg GSK2983599
G	600 mg GSK2983559	400 mg GSK2983559
H	800 mg GSK2983559	600 mg GSK2983559
I	Dose TBC GSK2983559	Dose TBC GSK2983559
J	GSK2983559 Fed	GSK2983559 Fed
P	Placebo	

Part B

Within each cohort participants will be assigned to either GSK2983559 or placebo in a 4:1 ratio. The treatments will be determined following the completion of Part A, where the treatment codes will be:

Treatment code	Treatment Description
K	Dose 1 GSK2983559
L	Dose 2 GSK2983559
M	Dose 3 GSK2983559
N	Dose 4 GSK2983559
P	Placebo

7.4. Blinding

This will be a double blind (sponsor open) study with respect to allocation of GSK2983559 or placebo to participants. The food effect part of the study will be open-label.

The following will apply:

- The investigator or treating physician may unblind a participant's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the participant as judged by the investigator.
- Investigators have direct access to the participant's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF.
- A participant will be withdrawn if the participant'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 participant 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 participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.
- Sponsor open refers only to the DEC members involved in the review of the unblinded safety data on an as required basis and at the dose escalation meetings,

where no-one outside of this committee will be unblinded to the study data. Further details of how this will be managed are included in Appendix 3.

7.5. 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 Study Reference Manual.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.6. Treatment Compliance

- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.

7.7. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment 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 nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study treatment until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol, 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.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK, or with GSK2983559, after the completion of the study because only healthy participants are eligible for study participation.

8. DOSE ESCALATION CRITERIA

8.1. PK criteria for GSK2668176

Due to the non-tolerated high dose of 420 mg/kg/day GSK2983559 in minipigs, the PK stopping criteria are based on $AUC_{(0-24)}$ and C_{max} values at $1/3^{rd}$ of the NOAEL of 120 mg/kg/day GSK2983559 (GSK2668176 $AUC_{(0-24)}$ 50.9 µg*h/mL, C_{max} 7.5 µg/mL).

The decision to proceed to the next dose level of GSK2983559 in each part of this study will be made by the DEC, based on safety, tolerability, and preliminary PK data obtained (through at least 24 hours post dose) with at least 4 participants having received active treatment (GSK2983559) at the current 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 PK criteria. Planned doses may also be repeated.

It is planned that the predicted human mean GSK2668176 $AUC_{(0\ 24)}$ or C_{max} values **will not** exceed the mean GSK2668176 $AUC_{(0-24)}$ and C_{max} values observed at one third of the NOAEL in minipig (16.94 µg*h/mL and 2.5 µg/mL, respectively). In addition, the predicted human maximum $AUC_{(0\ 24)}$ or C_{max} values **will not** exceed the maximum observed $AUC_{(0\ 24)}$ and C_{max} values at one third NOAEL (21.6 µg*h/mL and 3.25 µg/mL).

8.2. PK criteria for 5-ABT and NAc-5-ABT

The drug product contains an impurity (5-ABT) known to be mutagenic (with unknown carcinogenic potential) that is controlled in drug production to assure its level is below a Threshold of Toxicological Concern (TTC) per the ICH M7 guideline. However, because of a possibility for 5-ABT to be formed in the body, monitoring for 5-ABT (and its metabolite, NAc-5-ABT) in blood plasma will be undertaken with application of the

same TTC (120 μg), which translates to a plasma concentration of 3 ng/mL under the assumption that the mutagenic impurity distributes into a volume equal to total body water of 42L. Based on this information, if in any individual the Cmax of combined concentration of 5-ABT and NAc-5-ABT (in ng/mL equivalents 5-ABT/mL) is > 3 ng/mL, it will suggest the TTC level of 120 μg has been reached and further dose-escalation will be stopped. During dose escalation, progression to the next dose level will be guided by the criteria where the maximum predicted 5-ABT amount for the next dose will not exceed the TTC of 120 μg.

8.3. Safety criteria

The Principal Investigator and the GSK Medical Monitor will review the following and study dosing **will be** stopped if any of these criteria is met:

- One (1) or more participants experience a serious adverse event (SAE) which has a reasonable possibility of relation to study drug.
- Two (2) or more participants experience a severe or clinically significant non-serious adverse event (based upon investigator judgment) which has a reasonable possibility of relation to study drug.
- Two (2) or more participants in a Part A cohort or 3 or more participants in a Part B cohort experience the same adverse event of moderate severity which has a reasonable possibility of relation to study drug.
- Consistent Common Terminology Criteria for Adverse Events (CTCAE) Nervous System adverse events of any grade occur across participants 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 Medicines and Healthcare Products Regulatory Agency (MHRA) for approval.

9. DISCONTINUATION CRITERIA

9.1. 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 initiates treatment with any prohibited medications.
- The participant develops a serious opportunistic or atypical infection.
- If any of the liver chemistry stopping criteria or QTc stopping criteria are met.
- The participant experiences any signs of suicidal ideation or behaviour.

9.2. Neurological/psychiatric Stopping Criteria

The CNS observations in the first good laboratory practice (GLP) acute neurobehavioural study in rats were found to be present at all single doses. The same findings were not observed in a second study with overlapping doses. 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 participant 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

A participant **will be** withdrawn from the study if any of these criteria is met:

- A Grade 3 or greater CTCAE Nervous System finding (see SRM) is observed or a significant neurologic change from a participant'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 participant withdrawal.

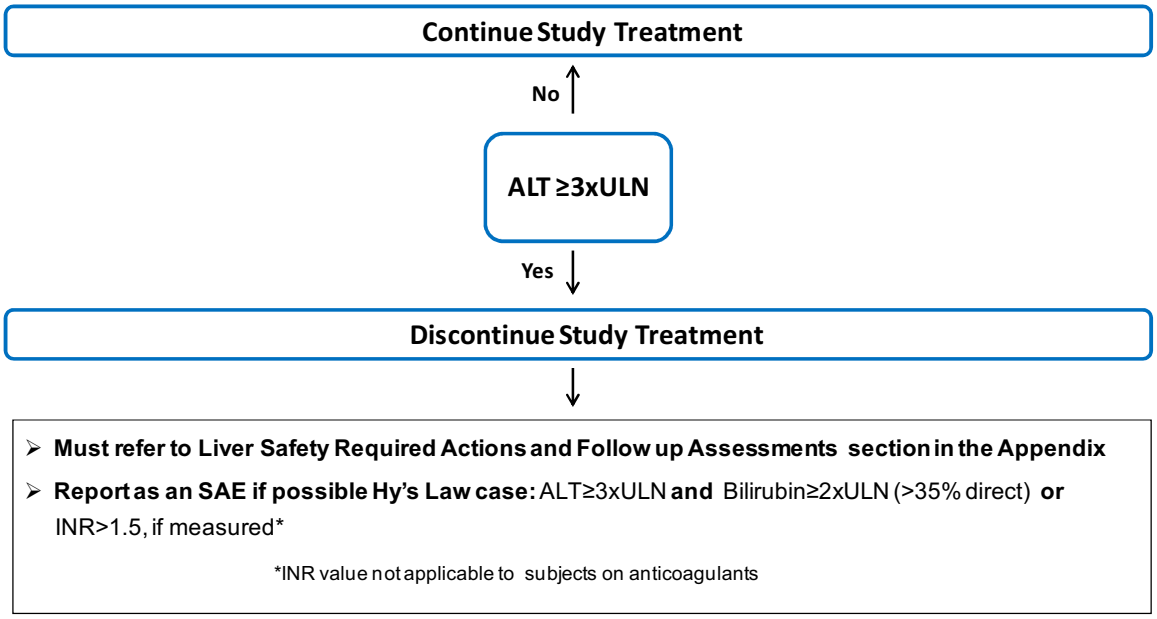
9.3. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the food and drug administration [FDA] premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Study treatment will be discontinued **for a participant** if liver chemistry stopping criteria are met:

Phase I Liver Chemistry Stopping Criteria – Liver Stopping Event Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Section 13.6

9.3.1. Study Treatment Restart or Rechallenge

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

9.4. QTc Stopping Criteria

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
    - For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
    - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

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

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

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.

9.5. 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, behavioral, compliance or administrative reasons.
- 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.

9.6. 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.

10. 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 (eg, 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.

10.1. 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 (see Section 9).

10.1.1. 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 case report form (CRF) not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours after becoming aware of the event, 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.

10.1.2. 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.

10.1.3. 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, will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 9.6). Further information on follow-up procedures is given in Appendix 4.

10.1.4. 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, Institutional Review Boards (IRB)/Independent Ethics Committees (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 institutional review board/independent ethics committee (IRB/IEC), if appropriate according to local requirements.

10.1.5. Pregnancy

- Details of all pregnancies in 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 Section 13.5.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

10.2. 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 should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until GSK2983559 can no longer be detected systemically (at least 48hours).
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.

10.3. Safety Assessments

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

10.3.1. Physical Examinations

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

10.3.2. 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 9.2),
- may result in referral to a specialist.

10.3.3. Vital Signs

- Vital signs will be measured in a semi-supine position after 5 minutes rest in a quiet setting without distractions (e.g., television, cell phones) and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- In Part A and Part B on Day 1 vital signs (to be taken before blood collection for laboratory tests) will consist of triplicate pulse and blood pressure measurements only (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). All 3 readings will be recorded on the CRF.

10.3.4. Electrocardiograms

- Triplicate OR Single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 9.4 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, but no more than 2 minutes apart. The full set of triplicates should be completed in less than 4 minutes.
- 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.
- Holter monitoring will be performed at screening only. This 24-hour Holter will be performed to eliminate participants with non-clinically overt cardiac arrhythmias.

10.3.5. 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 laboratory manual and the SoA.

10.4. Pharmacokinetics

10.4.1. Blood Sample Collection

Blood will be collected into ethylenediaminetetraacetic acid (EDTA) tubes and processed to plasma for PK analysis of GSK2983559, GSK2668176, 5ABT and NAc-5ABT 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.

In Part B on Day 1 and Day 14, at each sampling time point an additional blood sample will be collected for metabolite profiling.

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

10.4.2. Plasma 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 GSK2983559, GSK2668176, 5ABT and NAc-5ABT in plasma samples will be determined 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 GSK2983559, GSK2668176, 5ABT and NAc-5ABT, any remaining plasma sample may be analysed for other compound-related material and the results may be reported under a separate PTS-Global Spectroscopy, 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.

10.4.3. Urine sample collection and analysis

Urine samples for analysis of GSK2983559 and GSK2669176 as well as any metabolites will be collected at the time points listed in Section 2, SoA Table.

Prior to dosing on Day 1, each subject will be instructed to void their bladder and no more than 40 mL of this urine sample will be retained as a control. Urine collection time points listed in the SoA table will begin immediately following dose administration (0 to 24 hours). The time will be recorded for each urine sample collected as well as the 24-hour volume of urine for each subject. In Part A only, urine obtained at the highest dose reached will be shipped to GSK. Results will be reported under a separate PTS-Global Spectroscopy, GlaxoSmithKline protocol. Processing, storage and shipping procedures are provided in the Study Reference Manual (SRM).

10.5. Exploratory Pharmacodynamics and Target Engagement

Blood samples will also be collected at the time points indicated in Section 2 SOA. The actual date and time of these collections will be recorded. All procedures will be performed at the site.

10.6. Pharmacodynamic Samples

For this assay 1 mL of blood will be drawn into TruCulture tubes containing a standardized amount of the NOD2 agonist, MDP. Following a 6 hr incubation at 37°C, plasma cytokines (macrophage inflammatory protein 1 alpha [MIP1α], MIP1β, and TNF) will be quantified using the MesoScale Discovery platform. Two pre-dose baseline samples will be drawn to measure the maximum intrasubject inhibition via treatment with a tool compound with a similar chemical structure to GSK2983559. Details of the collection, processing, and storage of these PD samples are provided in the SRM.

10.7. Target Engagement (TE) Samples

Two sets of samples will be used to evaluate target engagement. (1) For ex-vivo evaluation of TE, blood will be drawn into 2 mL sodium heparin or K2 EDTA tubes. (2) For post-challenge evaluation of TE, an aliquot of the residual cells will be collected from the Truculture PD samples (described above). Cellular lysates will be prepared form both sets of samples and TE will be assessed using a novel competitive binding assay. Details of the collection, processing and storage of these TE samples are provided in the SRM.

11. STATISTICAL CONSIDERATIONS

The objectives of this study are to assess the safety and tolerability of single and repeat ascending doses of GSK2983559 in healthy volunteers. No formal hypotheses will be tested.

11.1. Sample Size Determination

A minimum number of 18 participants (10 in cohort 1 and 8 in cohort 2) will be recruited into Part A, and up to 40 participants (10 in each of 4 cohorts) will be recruited into Part B. An additional cohort may be added to Part A of the study to allow for evaluation of additional dose levels or repeat an existing dose level.

The sample size is based on feasibility considerations and no statistical techniques were used to calculate it.

Safety is the primary objective of Parts A and B, where numbers of safety events are of interest.

A maximum of 9 participants will receive each of the active doses in Part A or B. If 0 out of 9 participants with a particular safety event is observed, there is 95% certainty that the probability of observing a participant on active with a particular safety event will lie between 0.04 and 0.39.

There is no sample size re-estimation planned.

11.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	• All participants who were screened for eligibility
Randomized	• All participants who were randomly assigned to treatment in the study. • This population will be based on the treatment the participant was randomized to.
Safety	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant actually received. Note: Participants who were not randomized but received at least one dose of study treatment should be listed.
PK	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values). • This population will be based on the treatment the participant actually received.

11.3. Statistical Analyses

11.3.1. Safety Analyses

All safety analyses will be performed on the Safety Population.

Endpoint	Statistical Analysis Methods
Primary	Will be presented in tabular and/or graphical format and summarised descriptively according to GSK's Integrated Data Standards Library standards.

11.3.2. PK Analyses

All pharmacokinetic analyses will be performed on the Pharmacokinetic Population.

For the secondary pharmacokinetic (PK) endpoints in this study, no formal hypotheses will be tested.

Endpoint	Statistical Analysis Methods
Secondary	Plasma GSK2983559 and GSK2668176, concentration-time data will be analysed by non-compartmental methods. Calculations will be based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters will be determined, as data permit: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve [$AUC_{(0-24)}$, $AUC_{(0-t)}$ and $AUC_{(0-\infty)}$], and apparent terminal phase half-life ($t_{1/2}$). **Part A (single dose):** Dose proportionality will be assessed by visual inspection of dose normalised AUC(0 ∞) [or if not available AUC(0-t)] and C_{max} values versus dose. Analysis of these $\log_e$-transformed parameters may be carried out, using the power model. **Part A (food effect):** The ratio of fed state to fasted state may be assessed for the $\log_e$-transformed parameters $AUC_{(0-\infty)}$ [or if not available $AUC_{(0-t)}$] and $C_{max.}$ The effect of food will be assessed utilising a mixed effects model, with fed state (fasted or fed) as a fixed effect and participant as a random effect. **Part B:** The extent of accumulation after repeat dosing, the observed accumulation ratio (Ro), may be determined. The plasma steady state ratio (Rs) and an assessment of plasma steady state across the trough concentrations may also be made. Dose proportionality may be assessed using similar methods to the single dose Part A. For combined 5-ABT and NAc-5-ABT (corrected to 5-ABT), observed C_{max} and T_{max} will be determined using non-compartmental methods and will be summarised descriptively. Further details will be included in the RAP.

11.3.3. Other Analyses

Pharmacodynamic, and biomarker exploratory analyses will be described in the reporting and analysis plan. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

11.3.4. Interim Analyses

Dose escalation meetings will occur after each period in Part A and after the completion of 14 days dosing of each cohort in Part B. The decision to proceed to the next cohort and next dose strength to be studied, will be made by DEC based on assessment of safety (e.g., AEs, clinical laboratory results, vital signs and ECG) and plasma GSK2983559 pharmacokinetic and 5-ABT concentrations obtained in all participants at the prior dose level. Individual safety data (adverse events, laboratory safety tests, ECGs and vital

signs) will be reviewed. This study is double blind (sponsor open), where the participant, investigator and site staff will remain blinded to the treatment allocation. Sponsor open refers only to those members of the DEC.

Following completion of Cohort 1 (Part A) and before starting Cohort 2 (Part A), a GSK internal safety board (independent of DEC) will be reviewing the data.

A formal interim analysis may be performed during the study on completed cohorts in Part A of the study to aid internal decision making only. Only the DEC members will be unblinded. There will be no changes to the study design or planned number of participants in future cohorts as a result of this interim analysis. This analysis may include review of individual participant data, summaries, graphical presentations and/or statistical analysis.

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

12. REFERENCES

GlaxoSmithKline Document Number 2016N308990_00. Investigator Brochure for GSK2983559. Report Date 22-AUG-2017

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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.

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.

13. APPENDICES

13.1. Appendix 1: Abbreviations and Trademarks

5-ABT	5-amino-benzothiazole
Abs.	Absorbance
ACN	Acetonitrile
AE	Adverse Event
ALT	Alanine Aminotransferase
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-time curve
$AUC_{(0-24)}$	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.
$AUC_{(0-\infty)}$	Area Under the Concentration-time curve from time zero to infinity
BID	Twice a Day
BMI	Body Mass Index
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CARD	C-terminal Caspase-activation-and-recruitment
CD	Crohn's Disease
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	Apparent total clearance of the drug from plasma after oral administration
C_{max}	Maximum Observed Concentration
CMC	Chemistry, Manufacturing and Controls
C_{min}	Minimum Observed Concentration
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
CPK	Creatine Phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRP	C-Reactive Protein

CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough concentration measured at the end of a dosing interval at steady state
DEC	Dose Escalation Committee
DLs	Dose Levels
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EMA	European Medicines Agency
EMEA	Europe, the Middle East and Africa
FaSSIF	Fasted State Simulated Intestinal Fluid
FDA	Food and Drug Administration
FeSSIF	Fed State Simulated Intestinal Fluid
FSH	Follicle Stimulating Hormone
FTiH	First Time in Human
g	Gram
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GFR	Glomerular Filtration Rate
GI	Gastrointestinal Tract
GLDH	Glutamate Dehydrogenase
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
Haem.	Haematology
HBcAb	Hepatitis B Core Antibody
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
HPMCAS	Hydroxypropylmethyl Cellulose Acetate Succinate
HR	Heart Rate
Hr/hrs/h	Hours
HRT	Hormonal replacement therapy
HWB	Human Whole Blood
IB	Investigator's Brochure
IC	Inhibitory Concentration

ICF	Informed Consent Form
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-	Interleukin
IMPD	Investigational Medicinal Product Dossier
INR	International Normalized Ratio
IP	Investigational Product
IRB/IEC	The Institutional Review Board/ Independent Ethics Committee
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
Ka	Absorption Rate Constant
kcal	Kilocalorie
kg	Kilogram
L	Litre
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
LRR	Leucine-rich Repeat
m^2	Metre Squared
MABEL	Minimal Anticipated Biological Effect Level
MAPK	Mitogen-activated Protein Kinase
MDP	Muramyl Dipeptide
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
Min/mins	Minute
MIP1α	Macrophage Inflammatory Protein 1 Alpha
MIP1β	Macrophage Inflammatory Protein 1 Beta
mL	Millilitre
MSDS	Material Safety Data Sheet
msec.	Millisecond
NAc-5-ABT	n-acetyl-5-amino benzothiazole
NCBP	Non-Child Bearing Potential
ng	Nanogram
nm	Nanometre
NOAEL	No Observable Adverse Effect Limit
NOD1	Nucleotide-binding Oligomerization Domain 1
NOD2	Nucleotide-binding Oligomerization Domain 2
NOEL	No Observable Effect Limit

NQ	Non-quantifiable
PBPK	Physiologically Based Pharmacokinetic Modelling
PD	Pharmacodynamic
PK	Pharmacokinetics
ppm	Parts Per Million
PR	Pulse Rate
PRRs	Pattern Recognition Receptors
QD	Once Daily
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
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RIP2	Receptor Interacting Protein 2
RIPK2	Receptor-interacting Serine/Threonine Protein Kinase 2
RNA	Ribonucleic Acid
Ro	Accumulation Ratio
Rs	Steady State Ratio
SAE	Serious Adverse Event
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SoA	Schedule of Activities
SPF	Sun Protection Factor
SRM	Study Reference Manual
SUSAR	Suspected Unexpected Serious Adverse Events
$T_{1/2}$	Half Life
TB	Tuberculosis
TE	Target Engagement
TK	Toxicokinetic
T_{max}	Time taken to maximum observed plasma drug concentration
TNF	Tumour Necrosis Factor
TNFα	Tumour Necrosis Factor Alpha
TTC	Threshold of Toxicological Concern
UC	Ulcerative Colitis
µg	Microgram
µg.h	Microgam per hour
UK	United Kingdom
ULN	Upper Limit of Normal
UVA/UVB	Ultraviolet A/Ultraviolet B

UV/VIS	Ultraviolet/Visible light
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
GastroPlus
MesoScale
TruCulture

13.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 8 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.5.5 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 8 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count Red Clood Cell (RBC) Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine Gamma-Glutamyl transferase (GGT)	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein Albumin
	Glucose (fasted)[2]	Calcium	Alkaline phosphatase	C-reactive protein (CRP)
	Total cholesterol[2,3]	Low-density lipoprotein (LDL)[2,3]	Triglycerides[2,3]	
Coagulation Panel	Prothrombin Time (PT)	International normalized ratio (INR)	Partial thromboplastin time (PTT)	

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and 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: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines) • Urine Cotinine test • Serum human chorionic gonadotropin (hCG) pregnancy test for all women • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) • Tuberculosis test • 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 Section 13.6 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. Fasted with exception of Day -1 which can be non-fasted samples.
3. Lipid panel to be performed in Part B only.

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

13.3. 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 center.
- 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.

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.

Committees Structure

Dose Escalation Committee

The Dose Escalation Committee (DEC) will make the decision to proceed to the next dose level of GSK2983559 at the end of each single dose and repeat dose cohort; along with making the decision to move into Part B of the study.

The decision will be based on:

- All available safety and tolerability data from a minimum of 4 participants who have received a dose of GSK2983559 at the current dose level and have been followed for at least 48 hours post dose.
- All available safety and tolerability data accumulated from preceding dose levels.

- All available PK data (including levels of 5-ABT and NAc-5-ABT) from the current dose level for at least 4 participants who have been followed for at least 24 hours, and from preceding doses levels.

PK and safety stopping criteria will be strictly applied. Details of these criteria in Section 8.

There will be an open and closed part to the dose escalation meeting. At the beginning of the meeting blinded data will be discussed in an open forum with the investigator in attendance. If required, the data will then be reviewed in an unblinded fashion by the unblinded members of the DEC. Members and requirements are provided in a separate Dose Escalation Charter.

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

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants

are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the electronic case report form (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

13.4. 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 assessments (e.g., 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 fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in 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, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may

not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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**. • 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.

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

Definitions

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 enrollment.

Contraception Guidance

Male participants

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

- Refrain from donating sperm for duration of study and for 90 days after study completion or from last dose.

Table 9 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[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 90 after the last dose of study treatment

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.

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

Phase I liver chemistry stopping criteria and required follow up assessments

<table>
<tr><td colspan="2">Liver Chemistry Stopping Criteria</td></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><td colspan="2">Required Actions and Follow up Assessments</td></tr>
<tr><td>Actions</td><td>Follow Up Assessments</td></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF, and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the subject until liver chemistries resolve, stabilise, or return to within baseline (see MONITORING below)
MONITORING:
If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs
• Monitor subjects twice weekly until liver chemistries resolve, stabilise or return to within baseline
• A specialist or hepatology consultation is recommended
If ALT≥3xULN AND bilirubin < 2xULN and INR ≤1.5:
• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform</td><td>• Viral hepatitis serology[3]
• Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend
• Obtain blood sample for pharmacokinetic (PK) analysis, obtained within 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 hrs** • 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, immunoglobulin M (IgM) antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody; Hepatitis C ribonucleic acid (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.

13.7. Appendix 7: Protocol Amendment History

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