TITLE PAGE

Protocol Title: An open-label study in healthy male subjects, to determine the excretion balance and pharmacokinetics of [14C]-GSK2269557, administered as a single intravenous microtracer (concomitant with an inhaled non-radiolabelled dose) and a single oral dose.

Protocol Number: 206764 Amendment 01

Short Title: Absorption & elimination of radiolabelled GSK2269557

Compound Number: GSK2269557

Sponsor Name and Legal Registered Address:

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

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

Regulatory Agency Identifying Number(s): EudraCT 2017-002347-16

Approval Date: 30-OCT-2017

SPONSOR SIGNATORY:

PPD

30th October 2017

Dr Anthony Cahn
Head Respiratory TAU & Flexible Discovery Unit

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	Date
Amendment1	*30-Oct-2017*
Original Protocol	*09-Aug-2017*

Amendment 1 30-OCT-2017

Overall Rationale for the Amendment:

Protocol Amendment 1 was put in place to:

- Respond to comments from the Regulatory Authority: Medicines and Healthcare Products Regulatory Authoring.
- Reflect an update to the Investigator's Brochure (IB) published since approval of the original protocol.

A description of changes and rationale are provided in the table below. The previous protocol version text is shown with ~~strikethrough~~ revision marks denoting removed text; **bold** text denotes new text that has been added in this amendment.

Section # and Name	Description of Change	Brief Rationale
6.2. Exclusion Criteria	*Addition of exclusion criteria 26:* **Known sensitivity to any of the study treatments, or components thereof (including lactose and magnesium stearate [MgSt]), or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.**	MHRA request
8.1.3. Other study stopping criteria	A participant will be discontinued from the study if they experience **a serious adverse event and/or** unacceptable adverse events, as determined by the investigator and/or medical monitor. **Every effort should be made to complete safety follow-up procedures after a participant is discontinued from study drug.**	MHRA request
5.5.1. GSK2269557 Dose	For more detailed information on the clinical pharmacokinetics, see the GSK2269557 IB [GlaxoSmithKline Document Number ~~2012N141231_06~~ **2012-N141231_07**]. ~~and the Supplement to GSK2269557 IB [GlaxoSmithKline Document Number 2017N324691_00].~~ *(References to Investigator's Brochure also updated in Section 3).*	New Investigator's Brochure (version 8) published on 22 Sep 2017.
9.4.2. Vital Signs	For time points where vital signs are collected in triplicate**, only systolic and diastolic blood pressure, and pulse rate should be repeated.** There should be at least a 2 minute interval between readings.	Clarification of vital sign parameters required to be measured in triplicate.

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: An open-label study in healthy male subjects, to determine the excretion balance and pharmacokinetics of [14C]-GSK2269557, administered as a single intravenous microtracer (concomitant with an inhaled non-radiolabelled dose) and a single oral dose.

Short Title: Absorption & elimination of radiolabelled GSK2269557

Rationale: GSK2269557 is a potent and highly selective PI3K-delta inhibitor, being developed as an anti-inflammatory agent for the treatment of COPD and other inflammatory lung diseases. The pharmacokinetics, absorption, distribution and metabolism of GSK2269557 have been studied in animals, *in vitro*, and in previous clinical studies; however, the elimination routes, intravenous pharmacokinetics and metabolic pathways of GSK2269557 have not been fully elucidated in humans. This open-label study in 6 healthy male participants will assess the excretion balance of the treatment, intravenous clearance and volume of distribution, and estimate its inhaled and oral bioavailability. Participants will receive [^{14}C] radiolabelled GSK2269557, administered as a single microtracer by IV infusion (concomitant with an inhaled non-radiolabelled dose of GSK2269557), and a single dose of [^{14}C]-GSK2269557, administered as an oral solution. Samples from this study will also be used to characterise and where possible quantify the metabolites of GSK2269557 in plasma, urine, faeces and duodenal bile.

Objectives and Endpoints:

Objective	Endpoint
Primary	
• To determine total radioactivity (drug related material) in plasma following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled GSK2269557 dose) and a single oral dose of [^{14}C]-GSK2269557.	• AUC (0-inf), AUC (0–t), Cmax, tmax, t1/2 of total drug-related material (radioactivity) in plasma.
• To determine the rate and extent of excretion of total radioactivity in urine and faeces and the total recovery of radioactivity following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled dose) and a single oral dose of [^{14}C]-GSK2269557.	• Urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time.

Objective	Endpoint
Secondary	
• To determine parent GSK2269557 concentration in plasma following a single IV microtracer of [^{14}C]-GSK2269557 concomitant with an inhaled non-radiolabelled GSK2269557 dose and a single oral dose of [^{14}C]-GSK2269557.	• AUC(0-inf), AUC(0–t), Cmax, tmax, and t1/2 of parent GSK2269557 and [^{14}C]-GSK2269557[1] in plasma. • Volume and clearance of parent [^{14}C]-GSK2269557[1] after IV dose only.
• To estimate the absolute bioavailability of GSK2269557 following inhaled and oral administration.	• Oral and inhaled F (absolute bioavailability).
• To evaluate the safety and tolerability of GSK2269557 after single IV, oral and inhaled doses in healthy participants.	• Incidence of adverse events. • Laboratory safety, electrocardiogram (ECG) and vital signs parameters.
Exploratory	
• To generate samples that will be used to characterise the metabolic profile of GSK2269557 in plasma, urine, faeces, and duodenal bile (following IV dose only), following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled dose) and a single oral dose of [^{14}C]-GSK2269557 (these analytical investigations will be conducted and the results reported under a separate Platform Technology Services (PTS) In vitro/In vivo Translation (IVIVT), GlaxoSmithKline protocol).	• Characterisation and quantification of metabolites in plasma, urine, faeces, and duodenal bile (these analytical investigations will be conducted and the results reported in a separate GSK PTS IVIVT protocol).

[1] For measured concentrations of GSK2269557 in blood plasma, the nomenclature [^{14}C]-GSK2269557 describes the parent GSK2269557 concentration derived via analysis by liquid chromatography (LC) + Accelerator Mass Spectrometry (AMS), whereas GSK2269557 describes the parent GSK2269557 concentration derived via liquid chromatography-tandem mass spectrometry (LC/MS).

Overall Design: This is an open-label, single centre, non-randomised, 2-period single-sequence crossover, mass balance study to investigate the recovery, excretion, and pharmacokinetics (PK) of [^{14}C]-GSK2269557 administered as a single IV dose (concomitant with an inhaled non-radiolabelled dose) and a single oral dose, in healthy male participants.

Number of Participants: 6 healthy male participants.

Treatment Groups and Duration: Each participant will participate in the study for up to 11 weeks, and will have a screening visit, 2 treatment periods, and a follow-up visit. In each treatment period, participants will be resident in the unit from the morning before Day 1 (Day –1).

On Day 1 of treatment period 1, after an overnight fast of at least 8 h, each participant will take 1000 µg non-radiolabelled GSK2269557 by inhalation. Within 5 min after the inhalation, participants will receive 10 µg [^{14}C]-GSK2269557 (approximately 22.2 kBq; 0.6 µCi) by IV infusion over 15 min. Following dosing, blood, duodenal bile, urine and faecal samples will be collected up to 168 h after dosing (Day 8). Participants will be discharged on Day 8 after completion of the 168-h post-IV dosing sample collection. There will be a washout of at least 14 days after inhaled and IV dosing before participants take the oral dose of [^{14}C]-GSK2269557 in treatment period 2.

On Day 1 of treatment period 2, after an overnight fast of at least 8 h, each participant will take 800 µg [^{14}C] -GSK2269557 (approximately 1850 kBq; 50 µCi) as an oral solution. Following dosing, blood, urine and faecal samples will be collected for a minimum of 168 h (up to Day 8), but could be up to 336 h (Day 15) or longer after dosing, depending on the amount of radioactivity excreted by each participant. Liquid scintillation counting (LSC) will be performed daily on 24-h urine collections and 24-h faecal homogenates after Day 6 (at 144 h and 168 h from dosing).

- If less than 1% of the dose is excreted in each 24-h period on Day 6 (120-144 h) and Day 7 (144-168 h) for a given participant, that participant may be discharged as early as Day 8 (after the LSC results are available), and no further samples will be collected.
- If excretion is higher than 1%, or if the results are inconclusive, in each 24-h period on Day 6 (120-144 h) and Day 7 (144-168 h) for a given participant, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals, for up to 7 days (until the morning of Day 15). If less than 1% of the dose is excreted in any of the 24-h periods between Day 7 and Day 15, that participant will be discharged. All remaining participants will be discharged from the unit on Day 15.
- In the unlikely event that excretion is still higher than 1% upon discharge on Day 15, the participants will continue to collect faecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2–3 days for analysis.

Bile samples will be collected after the IV microtracer only, using Entero-Test string sampling of duodenal bile (subject to commercial availability).

Plasma samples will be prepared (from collected blood samples) to measure parent drug (GSK2269557, [^{14}C]-GSK2269557) and total radiolabelled drug-related material. Urine and faecal samples will be collected to measure total radiolabelled drug-related material. Samples of plasma, urine, bile and faeces will also be transferred to a separate study to characterise and, where possible, quantify metabolites in those matrices.

Safety data will include AE reporting, 12-lead ECG, vital signs, and laboratory safety tests.

2. SCHEDULE OF ACTIVITIES (SOA)

Schedule of activities for Treatment Period 1

Procedure	Screening	Treatment Period 1 (IV and inhaled dosing)									
	Day										
	–30 to –1	–1	1		2	3	4	5	6	7	8
			Pre-dose	Post- dose 0–16 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h
Admission to Unit		X									
Informed Consent	X										
Discharge from Unit											X
Demographics	X										
Full Physical Exam	X										
Brief Physical Exam		X									X
Inhaler training[1]		X									
Medical/medication/drug/alcohol history	X										
HIV, Hep B and Hep C screen	X										
Alcohol and cotinine tests, and urine drugs of abuse[2]	X	X									
Laboratory safety tests	X	X	X		X						X
12-lead ECG[3]	X	X	X	X	X						X
Vital signs (HR and BP)[3]	X	X	X	X	X						X
Inhaled dose				X							
IV infusion				X[4]							
Local tolerability assessment[5]				X	X	X					
Blood samples for background radiation, total radioactivity, [^{14}C]-GSK2269557 analysis and cold GSK2269557 analysis[6]	X[7]	X[7]	X[7,8]	X	X	X	X	X			X

Procedure	Screening	Treatment Period 1 (IV and inhaled dosing)								
	Day									
	–30 to –1	–1	1		2	3	4	5	6	7	8
			Pre-dose	Post- dose 0–16 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h
Blood samples for metabolite profiling			X[8]	X[9]							
Urine collection[10,11]			X	X	X	X	X	X	X	X	X
Faecal collection[12,13]			X[13]	X	X	X	X	X	X	X	X
Entero-Test[14]			←	→							
Meals[15]				X							
AE/concomitant medication review[16]		←									→

1. Training conducted by reviewing the Patient Information Leaflet with the participant. Additional training may be conducted at the discretion of the investigator.
2. Breath test will be performed to check alcohol consumption. Both CO breath tests and urine cotinine tests will be performed to check smoking state.
3. Triplicate measurements will be taken at screening and pre-dose on Day 1; single measurements will be taken at 6 h post-dose on Day 1 and at all other time points. Mean of triplicate measurements to be used as baseline.
4. IV infusion to begin as soon as possible (but within 5 min) after the start of the inhaled dose.
5. Local tolerability assessment for injection site reactions will be performed immediately after the end of dosing on Day 1 at 6 and 12 h, and on Days 2 and 3.
6. Sampling times relative to the start of the IV infusion. Blood samples for total radioactivity, [^{14}C]-GSK2269557 analysis and cold GSK2269557 analysis will be taken: pre-dose and at 0h (post inhalation and pre-IV infusion), at the end of infusion and at 0.33, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72, 96 and 168 h after the start of infusion.
7. Background radiation sample taken at screening, Day –1 and pre-dose only.
8. An additional pre-dose blood sample may be taken from 1 participant for preparation of a plasma shipment control (details provided in the SRM).
9. Blood samples for plasma metabolite profiling will be collected at 0.5 h and 4 h after the start of the IV infusion.
10. An aliquot from each urine collection will be taken for metabolic profiling (separate study).
11. Sampling times relative to the start of the IV infusion. Urine will be collected at pre-dose, 0-6 h, 6-24 h then over 24 h collection periods as follows: 24-48 h, 48-72 h, 72-96 h, 96-120 h, 120-144 h, 144-168 h.
12. An aliquot from each homogenised faecal collection will be taken for metabolic profiling (separate study).
13. Sampling times relative to the start of IV infusion. The pre-dose faecal collection sample can be collected up to 24 h pre-dose. Afterward faeces will be collected over 24 h collection periods as follows: 0-24 h, 24-48 h, 48-72 h, 72-96 h, 96-120 h, 120-144 h, 144-168h.
14. Entero-Test string device will be swallowed at approximately 3.5 h pre-dose (start of inhaled dose) while participants are in a fasted state and the string removed at about 2.5 h post-dose on Day 1. At about 0.5 h post-dose (i.e. 2 hours before string withdrawal) a food cue will be used to stimulate gall bladder emptying).

15. Meal times are 30 min, 4 h and 10 h post dose on Day 1. On all other days, meals will be served at the standard times for the unit.
16. AEs and SAEs will be collected from the signing of the ICF until the follow-up visit. However, any SAEs related to study participation or a GSK concomitant medication will be recorded from the time a participant consents to participate in the study and until the final follow-up visit contact.

Schedule of activities for treatment period 2

Procedure	Treatment Period 2 (Oral dosing)										Follow-up (7-14 days post-last dose)[2,3]
	Day										
	-1	1[1]		2	3	4	5	6	7	8	
		Pre-dose	Post-dose 0-16 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h	
Admission to Unit	X										
Discharge from Unit[2,3]										X	
Drugs of abuse	X										
Alcohol and cotinine tests[4]	X										
Brief Physical Exam		X									X
Laboratory safety tests	X	X		X						X	X
12-lead ECG	X	X	X[5]	X						X	X
Vital signs (HR and BP)	X	X	X[5]	X						X	X
Oral dose			X								
Blood samples for total radioactivity, [^{14}C]-GSK2269557 analysis and cold GSK2269557 analysis		X[6]	X	X	X	X	X			X	
Blood samples for metabolite profiling		X	X[7]	X							
Urine collection[8,9]		X	X	X	X	X	X	X	X	X	
Faecal collection[10,11]		X[11]	X	X	X	X	X	X	X	X	X[12]
Meals[13]			X								

Procedure	Treatment Period 2 (Oral dosing)									Follow-up (7-14 days post-last dose)[2,3]
	Day									
	-1	1[1]		2	3	4	5	6	7	8	
		Pre-dose	Post-dose 0-16 h	24 h	48 h	72 h	96 h	120 h	144 h	168 h	
AE/concomitant medication review[14]	←										→

1. There will be a washout of at least 14 days between dosing in treatment period 1 and 2.
2. If less than 1% of the dose is excreted in each 24 h period on Day 6 (120-144 h) and Day 7 (144-168 h) for a given participant, the participant may be discharged as early as Day 8 (after the LSC results are available), and no further samples (apart from for laboratory safety tests) will be collected. Follow-up procedures may be done at discharge and procedures scheduled for Day 8 and follow up will only be done once.
3. If excretion is higher than 1%, or if the results are inconclusive in each 24-h period on Day 6 (120-144 h) and Day 7 (144-168 h) for a given participant, that participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals, for up to 7 days (until the morning of Day 15), until excretion is less than 1%. All remaining participants will be discharged from the unit on Day 15. Follow-up procedures may be done at discharge. In the unlikely event that excretion is still higher than 1% upon discharge on Day 15, participants will continue to collect faecal samples only, at home, at 24-h intervals. Samples collected at home will be returned to the clinic every 2-3 days.
4. Breath test will be performed to check alcohol consumption. Both CO breath tests and urine cotinine tests will be performed to check smoking state.
5. Vital signs and ECG will be taken 6 h post dose.
6. Sampling times relative to the oral dose. Blood samples for total radioactivity, [^{14}C]-GSK2269557 analysis and cold GSK2269557 analysis will be taken: pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 96 and 168 h post-dose.
7. Blood samples for plasma metabolite profiling will be collected at 2 h and 6 h post-[^{14}C]-GSK2269557oral dose.
8. An aliquot from each urine collection will be taken for metabolic profiling (separate study).
9. Urine will be collected at pre-dose, at 0-6 h, 6-24 h then over 24 h collection periods as follows: 24-48 h, 48-72 h, 72-96 h, 96-120 h, 120-144 h, 144-168 h.
10. An aliquot from each faecal collection will be taken for metabolic profiling (separate study).
11. The pre-dose faecal sample can be collected up to 24 h pre-dose. Afterward faeces will be collected over 24 h collection periods as follows: 0-24 h, 24-48 h, 48-72 h, 72-96 h, 96-120 h, 120-144 h, 144-168 h.
12. If dose excretion is still higher than 1% after day 15 the participants will continue to collect faecal samples only, at home, at 24-h intervals until excretion is less than 1%.
13. Meal times are 4h and 10h post dose on Day 1. On all other days, meals will be served at the standard times for the unit.
14. AEs and SAEs will be collected from the signing of the ICF until the follow-up visit. However, any SAEs related to study participation or a GSK concomitant medication will be recorded from the time a participant consents to participate in the study and until the final follow-up visit contact.

3. INTRODUCTION

3.1. Study Rationale

This open-label study in 6 healthy male participants will assess the excretion balance of GSK2269557 in humans, using [^{14}C]-radiolabelled drug substance administered orally and as an intravenous (IV) infusion. [^{14}C]-GSK2269557 administered by IV infusion will be a microtracer; therefore, it will be administered concomitantly to an inhaled non-radiolabelled dose. This will be done in order to ensure that the pharmacokinetics represent a clinically relevant dose. The study will also provide an assessment of the bioavailability of GSK2269557 following oral and inhaled administration.

The pharmacokinetics, absorption, distribution and metabolism of GSK2269557 have been investigated through a series of IV, oral, intratracheal or inhaled studies in animals, and in *in vitro* studies using unlabelled GSK2269557. Only preliminary data are available so far for in human pharmacokinetics. GSK2269557 has been administered to humans in several clinical trials all via the inhalation route across a range of doses up to 3200 mcg twice daily for 7 Days in healthy volunteers and up to 1000 mcg once daily for 84 Days to exacerbating chronic obstructive pulmonary disease (COPD) patients. Definitive absorption, distribution, metabolism and excretion (ADME) characteristics derived from this study will provide important understanding of GSK2269557 in human including routes of elimination and metabolic pathways.

This study will use the Entero-Test (Entero-Test: HDC Corp., Mountain View, CA; or alternative source subject to commercial availability) for sampling of duodenal bile to conduct qualitative assessment of drug metabolites in this matrix in order to characterise biliary elimination pathways.

Samples from this study will also be used to characterise, where possible, and quantify the metabolites of GSK2269557 in plasma, urine, faeces and duodenal bile.

3.2. Background

GSK2269557 is a potent and highly selective inhaled phosphoinositide 3-kinase (PI3K)-delta (δ) inhibitor, being developed as an anti-inflammatory agent for the treatment of COPD and other inflammatory lung disease such as asthma. PI3Kδ is a member of the Class IA family of PI3Ks, that converts the membrane phospholipid phosphatidylinositol 4,5-biphosphate (PIP2) into phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 is a second messenger in many cellular processes including cell growth, differentiation and migration.
PI3Kδ has specific roles in mediating antigen receptor and cytokine signalling in T-cells, mast cells and B-cells PI3Kδ is thought to play an important part in various epithelial responses relevant for the development of COPD and asthma.

COPD is an umbrella term for the two disease processes: chronic bronchitis and emphysema. COPD invariably has a degree of both, though one phenotype/process may predominate in any individual. Inflammation has been linked to the pathogenesis of COPD. Tobacco smoke or other irritants activate epithelial cells and macrophages to

release inflammatory mediators, such as chemokines, that attract neutrophils and T-cells to the lungs. Both neutrophil and T-cell are targets of PI3Kδ inhibitors.

Chronic inflammation in the lung is also linked to the pathogenesis of asthma. Inflammation in asthma is associated with a T-cell response to allergens in the lung, with Th2 cytokines driving the differentiation, survival and function of the major effector cells involved in the allergic cascade. Th2 cells also play an essential role in the increased production of allergen-specific Immunoglobulin E (IgE) by B-cells. IgE mediates type I hypersensitivity allergic responses and the orchestration of local chronic allergic inflammation. Therefore, suppression of the Th2 drive in the lung has the potential to be disease modifying in asthma patients. GSK2269557 has been shown *in vivo* to potentially block T-cell activation in the lung, via reducing the production of pro-inflammatory Th2 cytokines interleukin (IL)-13, IL4 and IL-5, thus preventing recruitment of inflammatory cells to the lung.

As a PI3Kδ inhibitor, GSK2269557 has the potential to inhibit the major cell types responsible for the inflammation associated with both COPD and asthma. GSK2269557 has already been administered as a nebulised solution and dry powder formulation in single and repeated doses to humans and has been well tolerated across the range of doses used. A detailed description of the chemistry, pharmacology, efficacy, and safety of GSK2269557 is provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2012N141231_07].

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2269557 may be found in the Investigator's Brochure[GlaxoSmithKline Document Number 2012N141231_07]. Section 3.3.1 outlines the risk assessment and mitigation strategy for this protocol:

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product [e.g. GSK2269557]		
Radioactivity exposure risk ([^{14}C]-GSK2269557)	The total effective dose associated with IV and oral administrations of [^{14}C]-GSK2269557 is 0.75 mSv. That effective dose is within the lower end of WHO recommendation (0.5 to 5 mSv) for Category II projects, which is considered to be within dose limits for members of the public. The total effective dose is also below the GlaxoSmithKline Global Safety Board level of radiation which would require specific additional justification and exemption (10 mSv).	Participants will be monitored for recovery of radioactivity throughout the study.
Bronchospasm	Can potentially occur with any inhaled treatment.	All doses of study treatment will be administered in the clinical pharmacology unit in the presence of trained clinical staff. Treatment with a short-acting inhaled bronchodilator will be available. GSK2269557 should be discontinued immediately, the participant assessed and, if necessary, an alternative therapy instituted as deemed appropriate by the investigator or the attending physician. Participants will be withdrawn from the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Mucosal irritancy	Detected in 13 week toxicology study in the dog.	Participants will be regularly monitored for AEs. No evidence of mucosal irritancy has been seen so far in clinical studies.
Exposure to GSK2269557	The total systemic exposure of GSK2269557 from the combined IV microtracer (10 µg) and inhaled dose (1000 µg) is predicted to be below the systemic exposure from the highest dose of GSK2269557 tested in previous human studies (a single inhaled nebulised dose of 6400 µg). The oral dose to be tested is 800 µg. Overall GSK2269557 has been well tolerated in previous clinical studies and has an acceptable safety profile. The most commonly observed AEs have been cough and headache.	In addition to taking samples for pharmacokinetic analysis of GSK2269557, pharmacodynamic markers of GSK2269557 will be monitored: HR and QTc measurements will be taken, haematology and clinical chemistry will be monitored as part of the panel of laboratory safety tests.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Intravenous Dosing – Pain at the injection site	GSK2269557 has not previously been administered by IV infusion in humans. Doses of 12 µg/kg, 360 µg/kg and 1200 µg/kg of GSK2269557, dissolved in a 5% dextrose in water solution, were given as a 1 hour IV infusion (5 mL/kg/hr dosing volume) to male rats, in a rat cardiovascular study. No irritancy at site of injection has been reported for the study.	• Participants will be monitored for signs of pain at the injection site. Paracetamol or Acetaminophen, at doses of ≤ 2 g/day can be taken if required.
Entero-Test for bile collection risk	The use of the Entero-Test has been approved by the European regulatory authorities (ISO 9001 and CE Mark Certification; European Union Medical Devices Directive (MDD)). • Streaks of blood on the string due to local irritation have been infrequently noted. • Rarely, a patient will be unable to swallow the capsule because of gagging or will vomit after doing so. • Gagging upon retrieval of the string can occur. • On a few occasions, an entire string has been swallowed without ill effects and passes out from the body in the faeces.	• The string will be securely taped in place (to the cheek of each individual) during the collection time to minimise risk of swallowing the entire string. • Any participant incapable of swallowing the string will be allowed to participate in the study without duodenal bile collection.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Population		
Post-inhalation cough immediately following inhalation of study treatment (GSK2269557)	Treatment-related, mild and moderate cough (preferred term) were reported as adverse events (AEs), immediately after dosing, in previous studies of GSK2269557 conducted in both healthy participants and exacerbating COPD patients. Additional details are provided in the Investigator's Brochure [GlaxoSmithKline Document Number 2012N141231_07].	In this study, healthy participants will receive a single inhaled dose during treatment period 1. Participants will be in the presence of clinical staff during their 7-day post-dose residence at the clinical pharmacology unit and will be regularly monitored for AEs.
Inclusion of volunteers >30 years and <55 years (inclusive)	Justification of the use of healthy volunteers below the age of 50 years is required in accordance with the guidelines of the Administration of Radioactive Substances Advisory Committee and the Association of the British Pharmaceutical Industry, as well as GSK internal policies. In this study, healthy male volunteers between 30 and 55 years will be enrolled. This is acceptable, because the total effective dose of this study is considered to be within variations in natural background radiation with a minimal risk.	Not applicable.

3.3.2. Benefit Assessment

Healthy participants in this study will receive no direct medical benefit. However, they may benefit from the knowledge that they are contributing to the process of developing a new treatment in an area of unmet need. They might also benefit from the thorough medical assessments they receive during the course of the study.

3.3.3. Overall Benefit:Risk Conclusion

It is considered acceptable to conduct this study in healthy participants, because whilst they will receive no direct medical benefit, the risks from the study treatment and procedures are minimal. The study will be conducted in a fully equipped clinical pharmacology unit with access to hospital emergency facilities.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine total radioactivity (drug related material) in plasma following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled GSK2269557 dose) and a single oral dose of [^{14}C]-GSK2269557.	• AUC(0-inf), AUC(0–t), Cmax, tmax, t1/2 of total drug-related material (radioactivity) in plasma.
• To determine the rate and extent of excretion of total radioactivity in urine and faeces and the total recovery of radioactivity following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled dose) and a single oral dose of [^{14}C]-GSK2269557.	• Urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time.
Secondary	
• To determine parent GSK2269557 concentration in plasma following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled GSK2269557 dose) and a single oral dose of [^{14}C]-GSK2269557.	• AUC(0-inf), AUC(0–t), Cmax, tmax, and t1/2 of parent GSK2269557 and [^{14}C]-GSK2269557[1] in plasma. • Volume and clearance of parent [^{14}C]-GSK2269557 [1] after IV dose only.
• To estimate the absolute bioavailability of GSK2269557 following inhaled and oral administration.	• Oral and inhaled F (absolute bioavailability).

Objectives	Endpoints
• To evaluate the safety and tolerability of GSK2269557 after single IV, oral and inhaled doses in healthy participants.	• Incidence of adverse events • Laboratory safety, electrocardiogram (ECG) and vital signs parameters.
Exploratory	
• To generate samples that will be used to characterise the metabolic profile of GSK2269557 in plasma, urine, faeces, and duodenal bile (following IV dose only), following a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled dose) and a single oral dose of [^{14}C]-GSK2269557 (these analytical investigations will be conducted and the results reported under a separate Platform Technology Services (PTS) In vitro/In vivo Translation (IVIVT), GlaxoSmithKline protocol).	• Characterisation and quantification of metabolites in plasma, urine, faeces, and duodenal bile (these analytical investigations will be conducted and the results reported in a separate GSK PTS IVIVT protocol).

[1] For measured concentrations of GSK2269557 in blood plasma, the nomenclature [^{14}C]-GSK2269557 describes the parent GSK2269557 concentration derived via analysis by LC+AMS, whereas GSK2269557 describes the parent GSK2269557 concentration derived via LC/MS.

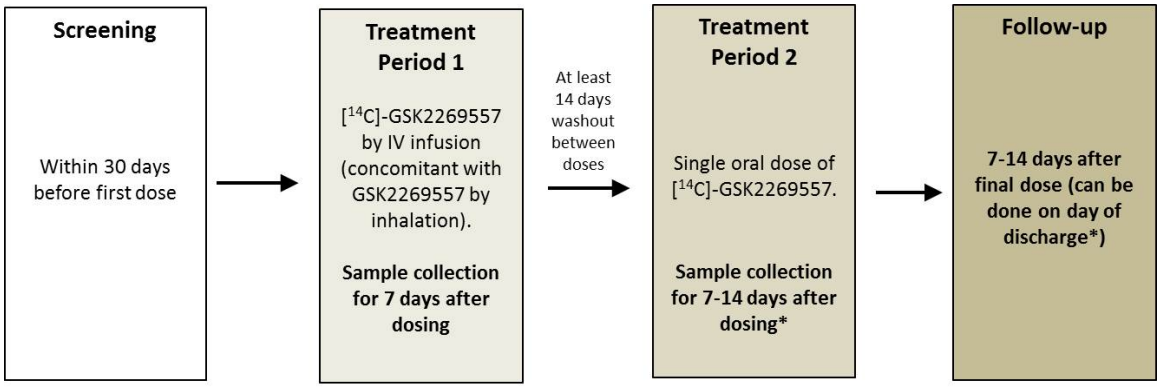
5. STUDY DESIGN

5.1. Overall Design

This is an open-label, single centre, non-randomised, 2-period, single-sequence crossover, mass balance study to investigate the recovery, excretion, and pharmacokinetics of [^{14}C]-GSK2269557 administered as a single IV dose (concomitant with an inhaled non-radiolabelled dose) and a single oral dose, in healthy male participants.

Each participant will participate in the study for up to 11 weeks, and will have a screening visit, 2 treatment periods, and a follow up visit (see Figure 1). If excretion is higher than 1%, or if the results are inconclusive, upon discharge on Day 15 (if participants haven't been discharged before then), participants will continue to collect faecal samples only, at home, at 24-h intervals which will be returned to the clinic every 2-3 days.

Figure 1 Study design schematic.



*If radioactivity excretion is higher than 1% upon discharge, faecal samples will be collected by participants at home after Day 15 (day of discharge/follow-up).

5.1.1. Screening Period

Participants must be screened within 30 days before the first dose, and must meet all eligibility criteria.

5.1.2. Study Periods

The study will be divided into treatment periods 1 (concomitant IV and inhaled dosing) and 2 (oral dosing). In each treatment period, participants will be resident in the unit from the afternoon before Day 1 (Day –1).

On Day 1 of treatment period 1, after an overnight fast of at least 8 h, each participant will take 1000 µg non-radiolabelled GSK2269557 by inhalation. Within 5 min after the inhalation, participants will receive 10 µg [^{14}C]-GSK2269557 (approximately 22.2 kBq; 0.6 µCi) by IV infusion over 15 min. Following dosing, blood, duodenal bile, urine and faecal samples will be collected up to 168 h after dosing (Day 8).

Participants will be discharged on Day 8 after completion of the 168-h post-IV dosing sample collection. There will be a washout of at least 14 days after inhaled and IV dosing before participants take the oral dose of GSK2269557 in treatment period 2.

On Day 1 of treatment period 2, after an overnight fast of at least 8 h, each participant will take 800 µg [^{14}C]-GSK2269557 (50 µCi or 1850 kBq) as an oral solution. Following dosing, blood, urine and faecal samples will be collected for a minimum of 168 h (up to Day 8), but could be up to 336 h (Day 15) or longer after dosing, depending on the amount of radioactivity excreted by each participant. Liquid scintillation counting (LSC) will be performed daily on 24 h urine collections and 24 h faecal homogenates after Day 6 (at 144 h and 168 h from dosing).

- If less than 1% of the dose is excreted in each 24-h period on Day 6 (120–144 h) and Day 7 (144–168 h) for a given participant, that participant may be discharged as early as Day 8 (after the LSC results are available), and no further samples will be collected.
- If excretion is higher than 1%, or if the results are inconclusive in each 24-h period on Day 6 (120-144h) and Day 7 (144-168h) for a given participant, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals, for up to 7 days (until the morning of Day 15). If less than 1% of the dose is excreted in any of the 24-h periods between Day 7 and Day 15, that participant will be discharged. All remaining participants will be discharged from the unit on Day 15.
- In the unlikely event that excretion is still higher than 1% upon discharge on Day 15, the participants will continue to collect faecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2–3 days for analysis.

The Entero-Test to measure duodenal bile will be used (subject to commercial availability) only for Treatment 1 (IV dosing). The Entero-Test will be inserted about 3.5 h before the start of the IV infusion while participants are in a fasted state, and it will be removed about 2.5 h after the end of the IV infusion. About 0.5 h after the end of the IV infusion (2 h before string withdrawal) a food cue will be used to stimulate gall bladder emptying.

Plasma samples will be prepared (from collected blood samples) to measure parent drug (GSK2269557, [^{14}C]-GSK2269557) and total radiolabelled drug-related material. Urine and faecal samples will be collected to measure total radiolabelled drug-related material. Samples of plasma, urine, bile and faeces will also be transferred to a separate study to characterise and, where possible, quantify metabolites in those matrices.

Safety data will include AE reporting, 12-lead ECG, vital signs, and laboratory safety tests.

5.1.3. Follow-up

Follow-up procedures will be done 7–14 days after the last dose, and can be done on the day of discharge or at a separate visit.

The follow-up period may be extended if:

(i) radioactivity excretion is still higher than 1%
(ii) a participant has an unresolved AE at the follow-up visit, which, in the opinion of the investigator, merits further follow-up;
(iii) new information becomes available that supports an extended follow-up period.

The investigator will decide on the nature of the extended follow-up. For example, participants may have a telephone follow-up at which they are asked about AEs, or participants may be asked to attend extra outpatient visits for additional monitoring of blood levels or, and for extra safety tests. The extra safety tests might include tests that are not described in this protocol. The investigator reserves the right, during or after the study, to repeat safety tests or to do any extra safety tests that are in the best interest of the participants. Those extra tests may or may not be described in this protocol.

5.2. Number of Participants

Six healthy male participants will be enrolled. Refer to Section 10.1 for details on sample size determination.

If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the sponsor and in consultation with the investigator.

5.3. Participant and Study Completion

A participant is considered to have completed the study if he has completed all phases of the study including the last visit.

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

5.4. Scientific Rationale for Study Design

In this study, a single IV microtracer of [^{14}C]-GSK2269557 (concomitant with an inhaled non-radiolabelled dose) and a single oral dose of [^{14}C]-GSK2269557, will be administered.

It is not technically possible to administer a radiolabelled inhaled dose of GSK2269557; therefore oral and IV doses will be used as surrogates. Oral administration is a surrogate for the swallowed portion of an inhaled dose. IV administration is a surrogate for the exposure resulting from the portion of the inhaled dose being absorbed into the systemic circulation. As an IV microtracer is being used, it will be administered concomitant to an inhaled non-radiolabelled dose, to ensure that the pharmacokinetics represent a clinically relevant dose.

Metabolic elimination pathways will be characterised after the IV dose to include the planned collection of duodenal bile. Complexities in human faecal sample analysis such as extraction, stability in the gastrointestinal (GI) tract, and endogenous contamination are minimised through assessment of the metabolic profile in duodenal bile.

5.5. Dose Justification

5.5.1. GSK2269557 Dose

This study will test single doses of GSK2269557, administered via different routes to healthy volunteers, in order to characterise the ADME properties of GSK2269557 in human. GSK2269557 is being developed for inhaled delivery and has been administered via inhalation at higher doses (6400 µg via nebulisation) than those proposed in this study (1000 µg). GSK2269557 has also been administered via inhalation, using the Diskus device, as a repeated dose of 1000 µg for 84 days to patients experiencing an exacerbation of COPD (study 116678). The inhaled dose of 1000 µg proposed in this study has been chosen to match the clinical material (device and formulation) for phase 2b and beyond, and to give a sufficient single dose to aid quantification of analytes.

The intravenous and oral dose routes have not previously been tested in humans, although testing has been conducted in pre-clinical studies. One of the purposes of the intravenous data is to define plasma pharmacokinetics and, in particular, central clearance rate from plasma. The proposed intravenous dose of 10 µg (given over a 15 minute infusion) represents less than 0.2% of the highest dose tested in humans (6400 µg) and is therefore expected to be well within the exposures generated previously. This includes the concomitant cold inhaled dose at 1000 µg. Due to absorption or first passes clearance effects; the oral dose of 800 µg is not expected to achieve systemic exposures close to those of an equivalent inhaled dose. However, based on previous data generated in humans using charcoal block (study 201544), exposure via this route is expected. In this study, approximately 23% of the systemic exposure of an inhaled 200 µg dose was attributable to the orally absorbed drug.

Table 1 shows the approximate estimates for exposures to participants following both treatment periods 1 and 2 using pharmacokinetic information obtained to date using a range of assumptions as detailed in the table. Systemic exposure multiples have been calculated based on both pre-clinical data and clinical experience with GSK2269557.

Table 1 Approximate estimates for exposures to participants

Period/Regimen	Parameter[1]	Exposure Margin	
		Pre-clinical[2]	**Clinical**[3]
1 = 1000 µg Inhaled + 10 µg IV	C_{max} (ng/mL)	13	2
	AUC_{0-24h} (ng.h/mL)	19	6
2 = 800 µg Oral	C_{max} (ng/mL)	94	11
	AUC_{0-24h} (ng.h/mL)	78	23

1. Using the geometric mean measured exposed individual based on study 201544 (200 µg top dose Day 1) to generate (linear extrapolation including an increase of 1.71 fold for Cmax and 1.54-fold on AUC due to formulation differences) the exposure for a 1000 µg Inhaled dose concomitant with a 10 mcg intravenous dose (15 min infusion) (intravenous dose exposures assume 1% of inhaled exposure as worst case) based on a single dose period 1 and following a single oral dose of 800 µg in period 2 (assuming 60:40 lung to oral deposition using study data from 201544 and charcoal block and linear extrapolation). Cmax and AUC0-24h of 3.5 ng/mL and 14.7 ng.h/mL for Period 1 and a Cmax and AUC0-24h of 0.47 ng/mL and 3.7 ng.h/mL for Period 2 respectively.
2. Based on the no observed adverse event level (NOAEL) derived from the rat 3 month toxicology study R29876 with a Cmax and AUC of 43.7 ng/mL and 286 ng.h/mL respectively.
3. Based on the highest achieved geometric mean value derived from reported trials to date of 5.3 ng/mL and 85 ng.h/mL based on exposure on Day 7 following repeat daily single doses (study PII115117).

For more detailed information on the clinical pharmacokinetics, see the GSK2269557 IB [GlaxoSmithKline Document Number 2012N141231_07].

5.5.2. Radiolabel Dose

The effective dose of radiolabelled drug administered in human mass balance studies is calculated from data on the distribution and elimination of the radioactive drug in *in vivo* experiments. The calculations have taken into account the nature of the isotope, the concentration of radioactivity in individual tissues/organs and the residence or elimination half-life of the radioactivity from those tissues/organs. Following oral administration of [^{14}C]-GSK2269557 the effective radioactive dose was calculated as 4 x 10^{-10} Sv/Bq which corresponds to 0.4 mSv/MBq (0.0148 mSv/μCi).

In this study each participant will be administered 1850 kBq (50 μCi) of radioactivity by the oral route. Each participant will also receive a small amount of radioactivity as a microtracer intravenous dose administered concomitantly with an inhaled administration: 22.2 kBq (0.6 μCi) – approximately 1/80th the oral radioactive dose.

By summing the radioactive doses (~1873 kBq) and, conservatively, using the effective radioactive dose calculated following oral administration (0.4 mSv/MBq), each participant will be exposed to an effective radioactive dose of 0.75 mSv. On this basis, the effective radioactive dose would be at the lower end of WHO category II (0.5 - 5 mSv – within dose limits for members of the public) and within International Commission on Radiological Protection (ICRP) category IIa (0.1 - 1 mSv – minor risk).

6. STUDY POPULATION

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

6.1. Inclusion Criteria

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

Age

1. Participant must be 30 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are overtly healthy as determined by the investigator or medically qualified designee based on a medical evaluation including medical history, physical examination, vital signs, laboratory tests, and cardiac monitoring. A participant with a clinical abnormality or laboratory parameter(s) which is/are not specifically listed in the inclusion or exclusion criteria, outside the reference range for the population being studied may be included only if the investigator agrees and documents that the finding is unlikely to introduce additional risk factors and will not interfere with the study procedures.
3. A history of regular bowel movements (averaging one or more bowel movements per day).

Weight

4. Body weight ≥ 50 kg and body mass index (BMI) within the range 19.0–31.0 kg/m^2 (inclusive).

Sex

5. Male.
6. Participants with female partners of child bearing potential must agree to use contraception as detailed in Appendix 2 of this protocol during the treatment period, from the time of first dose of study medication until follow-up, and refrain from donating sperm during this period.

Informed Consent

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

6.2. Exclusion Criteria

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

Medical Conditions

1. Alanine aminotransferase (ALT) > 1.5xULN.
2. Bilirubin > 1.5xULN (isolated bilirubin > 1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%).
3. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
4. Mean QT_CF > 450 msec.
5. Any clinically relevant abnormality identified at the screening medical assessment (physical examination/medical history), clinical laboratory tests, or 12-lead ECG.
6. A pre-existing condition(s) interfering with normal GI anatomy or motility, including constipation, malabsorption or other GI dysfunction which may interfere with the absorption, distribution, metabolism or elimination of the study drug. Participants with a history of cholecystectomy must be excluded.
7. At screening, a supine or semi-supine blood pressure (BP) that is persistently higher (triplicate measurements at least 2 min apart) than 140/90 millimetres of mercury (mmHg).
8. At screening, a supine or semi-supine mean HR outside the range 40–90 beats per minute (BPM).
9. Participant is mentally or legally incapacitated.
10. A history of respiratory disease (e.g. history of asthma) in the last 10 years.

Prior/Concomitant Therapy

11. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John's Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the first dose of study medication, unless in the opinion of the investigator and GSK Medical Monitor the medication will not interfere with the study procedures or compromise participant safety.

12. Need of Paracetamol or Acetaminophen, at doses of > 2 g/day. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

Prior/Concurrent Clinical Study Experience

13. The participant has participated in a clinical trial and has received an investigational product (IP) within 3 months before their first dose in the current study.
14. Participation in a clinical trial involving administration of ^{14}C-labelled compound(s) within the last 12 months. A participants' previous effective dose will be reviewed by the medical investigator to ensure there is no risk of contamination/carryover into the current study.

Diagnostic assessments

15. Presence of hepatitis B surface antigen (HBsAg), or positive hepatitis C antibody test result at screening.

    NOTE: Subjects with positive Hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative Hepatitis C ribonucleic acid (RNA) test is obtained.

16. Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study treatment.

    NOTE: Test is optional and subjects with negative Hepatitis C antibody test are not required to also undergo Hepatitis C RNA testing.

17. A positive test for Human Immunodeficiency Virus (HIV) antibody
18. A positive pre-study drug/alcohol screen.
19. Exposure to more than four new chemical entities within 12 months before the participant's first dose.
20. Participants have received a total body radiation dose of greater than 5.0 mSv (upper limit of WHO category II) or exposure to significant radiation (e.g. serial x-ray or computed tomography [CT] scans, barium meal etc) in the 12 months before this study.
21. An occupation which requires monitoring for radiation exposure, nuclear medicine procedures or excessive x-rays within the past 12 months.
22. Participation in the study would result in donation of blood or blood products in excess of 500 mL within a 90 day period.

23. Unwillingness or known inability to follow the procedures outlined in the protocol, including the use of the Enterotest capsule.

Other Exclusions

24. History of regular alcohol consumption within 6 months of the study, defined as an average weekly intake of >21 units. 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.
25. Urinary cotinine levels indicative of smoking; current smoker; or ex-smokers who (a) gave up less than 6 months ago or (b) who have a history of more than 10 pack-years.

$$\text{Pack-years} = \frac{\text{cigarettes per day x number of years smoked.}}{20}$$

26. Known sensitivity to any of the study treatments, or components thereof (including lactose and magnesium stearate [MgSt]), or drug or other allergy that, in the opinion of the investigator or medical monitor, contraindicates participation in the study.

6.3. Lifestyle Restrictions

6.3.1. Meals and Dietary Restrictions

- Participants will not be allowed to consume red wine, Seville oranges, grapefruit or grapefruit juice, pummelos, exotic citrus fruits, grapefruit hybrids or fruit juices from 7 days before the first dose of study medication until after their final visit.
- Adequate hydration should be encouraged to help facilitate stool sample production. If needed, participants may consume prunes or prune juice to facilitate stool samples.
- Participants should fast (no food or drink, except water) for at least 5 h before laboratory safety tests.
- Participants should fast (no food or drink, except water) for at least 8 h before dosing and for about 4 h after dosing (with the exception of a food stimulus given to stimulate gall bladder emptying for bile collection at 0.5 h after the start of the IV infusion – Treatment 1). Standard meals will be given at all other times.

6.3.2. Caffeine, Alcohol, and Tobacco

- Participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks and chocolate) for 24 hours before the start of dosing until collection of the final pharmacokinetic sample during each session.
- During each dosing session, participants will abstain from alcohol for 24 hours (7 days for red wine, see Section 6.3.1) before the start of dosing until collection of the final pharmacokinetic sample during each session. At all other times during the study (i.e. between screening and the post-study follow-up contact), participants will drink no more than 3 units of alcohol daily.
- Only non-smokers will be enrolled into the study.

6.3.3. Activity

- Participants will abstain from strenuous exercise from screening and until their final follow-up visit. Participants may participate in light recreational activities during studies (eg, watching television, reading).

6.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal set of screen failure information is required including demography, screen failure details, eligibility criteria, protocol deviations and any serious adverse events (SAEs) (as detailed in Section 9.2).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once. Rescreened participants should be assigned a new 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

Study treatment			
Study Treatment Name:	**[^{14}C]-GSK2269557 solution for IV infusion**	**GSK2269557 Ellipta DPI**	**[^{14}C]-GSK2269557 oral solution**
Dosage formulation:	[^{14}C]-GSK2269557 hemisuccinate salt (GSK2269557T) in normal saline	GSK2269557 hemisuccinate salt (GSK2269557H) blended with lactose and magnesium stearate[1]packed in foil blisters	[^{14}C]-GSK2269557 hemisuccinate salt (GSK2269557T) in water
Unit dose strength(s)/ Dosage level(s):	10 µg [^{14}C]-GSK2269557 (<0.5 µCi) in 10 mL	500 µg GSK2269557 per inhalation / 1000 µg dose	800 µg [^{14}C]-GSK2269557 (approximately 50 µCi) in 10 mL
Route of Administration:	IV infusion	Oral Inhalation	Oral
Dosing instructions:	Non-sterile powder is to be dissolved aseptically in 0.9% sodium chloride v/w to a concentration of 1 µg/mL free base equivalent. IV solution is prepared by sterile filtration. 20 mL will be withdrawn into Individual labelled participant specific 60 mL syringes. Only 10 mL of IV solution, equivalent to 10 µg GSK2269557 is then administered intravenously as a single dose over 15 minutes, as soon as possible (within 5 minutes) after the start of the inhaled dose	Inhale TWICE from this Inhaler, as directed.	Non-sterile powder is to be dissolved in sterile water to a concentration of 80 µg/mL. 10 mL of the solution, equivalent to 800 µg, is then administered as a single oral dose. Participants can have up to 250 mL water to wash the dose down
Packaging and Labelling .	Labelled drug substance will be provided in High Density Polyethylene (HDPE) containers with polypropylene closure to the site pharmacy.	Study Treatment will be provided in a foil overwrap. Each foil overwrap will be labelled as required per country requirement.	Labelled drug substance will be provided in HDPE containers with polypropylene closure to the site pharmacy.
Manufacturer	GSK	GSK	GSK
Device:		ELLIPTA™ inhaler	

1. Magnesium stearate 0.4% w/w of total drug product

For more information on the preparation of the oral and IV dosing solutions, please refer to the Study Reference Manual (SRM).

7.2. Dose Modification

Not applicable

7.3. Method of Treatment Assignment

This is an open-label study and all the participants will be assigned to each of the following treatments in a non-randomized manner. All participants will receive Treatment 1 (IV infusion [concomitant with an inhaled dose]) first, and Treatment 2 (oral dose) second.

7.4. Blinding

This will be an open-label study.

7.5. Preparation/Handling/Storage/Accountability

1. A description of the methods and materials required for preparation of [^{14}C]-GSK2269557 solution for IV infusion and oral administration is provided in the SRM and will be accompanied by a Quality Agreement.

A description of the storage and handling requirements for GSK2269557 inhalers is provided in the SRM.

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. Precaution will be taken to avoid direct contact with the study treatment. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the investigator. In the case of unintentional occupational exposure, notify the monitor, Medical Monitor and/or GSK study contact.

7.6. Treatment Compliance

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

- When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. For the oral dose, study site personnel will examine each participant's mouth to ensure that the study treatment was ingested.
- [^{14}C]-GSK2269557 will be intravenously administered to participants at the site. Administration will be documented in the source documents and reported in the case report form (CRF).

7.7. Concomitant Therapy

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

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

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

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

All inhibitors and inducers of the Cytochrome P450 pathway are prohibited (please refer to the SRM).

All inhibitors of P-glycoprotein are prohibited (please refer to the SRM).

Paracetamol or Acetaminophen, at doses of $\leq$ 2 g/day is permitted. Other concomitant medication may be considered on a case by case basis by the GSK Medical Monitor.

7.8. Treatment after the End of the Study

Participants will not receive any additional treatment from GSK after completion of the study because only healthy volunteers are eligible for study participation.

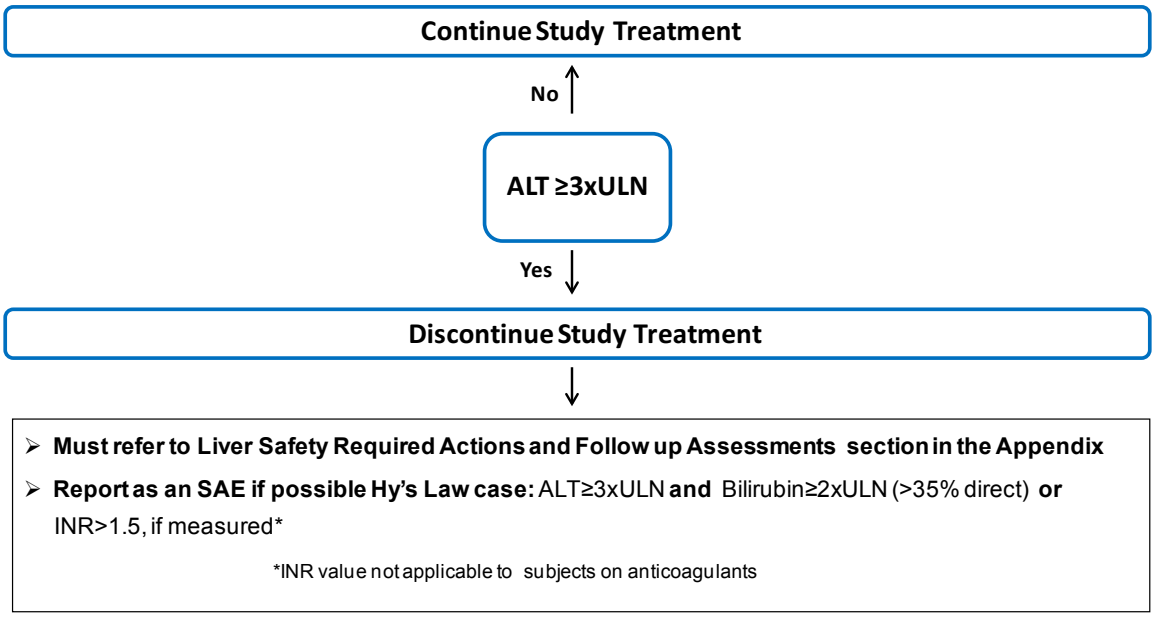
8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

8.1.1. Liver Chemistry Stopping Criteria

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 Appendix 4.

8.1.2. QTc Stopping Criteria

- The QTcF should be based on single or averaged QTcF values of triplicate electrocardiograms obtained over a brief recording period (less than 4 minutes). If an ECG demonstrates a prolonged QT interval, obtain 2 more ECGs over a brief period (e.g. 5 to 10 minutes), then use the averaged QT_CF value of the 3 ECGs to determine whether the participant should be discontinued from the study.
- A participant who meets either bulleted criterion below will be withdrawn from the study.
    - $QT_CF > 500$ msec
    - Change from baseline: $QT_CF > 60$ msec

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

8.1.3. Other study stopping criteria

A participant will be discontinued from the study if they experience a serious adverse event and/or unacceptable adverse events, as determined by the investigator and/or medical monitor. Every effort should be made to complete safety follow-up procedures after a participant is discontinued from study drug.

The study will be halted if there is a SAE or 2 severe AEs, considered to be at least possibly related to the investigational medicinal product (IMP). If following an internal safety review, it is appropriate to restart the trial, a substantial amendment will be submitted to the Medicines and Healthcare Regulatory Authority (MHRA) and Research Ethics Committee (REC). The trial will not restart until the amendment has been approved by the MHRA and REC.

8.1.4. Temporary Discontinuation

A participant withdrawn from the study treatment will no longer continue in the trial.

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.
- If 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.
- The investigator will ask withdrawn participants to consent to a follow-up examination, to check that they have come to no harm as a result of taking part in the trial. Provided that participants agree, they will undergo, at withdrawal from the trial, the medical examination and other tests and procedures planned for the follow-up visit. The investigator will record in the CRF the results of follow-up examination of withdrawn participants, if they give their consent for that.
- Refer to the SoA (Section 2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed, provided the participant gives consent.

8.3. Lost to Follow Up

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

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

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

9. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, 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 (i.e., 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 following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order:
    1. 12-lead ECG
    2. vital signs
    3. blood draws.

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

- The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.
- No more than 533 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

9.1. Efficacy Assessments

There will be no efficacy assessments for this study.

9.2. Adverse Events

Planned time points for all safety assessments are listed in the SoA (Section 2). Additional time points for safety tests (such as vital signs, physical exams and laboratory safety tests) may be added during the course of the study based on newly available data to ensure appropriate safety monitoring.

The definitions of an AE or SAE can be found in Appendix 5.

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

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

- All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 5. 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 5.

9.2.2. Method of Detecting AEs and SAEs

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs (as defined in Section 3.3.1), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 5.

9.2.4. Regulatory Reporting Requirements for SAEs

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

9.2.5. Pregnancy

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

9.3. Treatment of Overdose

For this study, any dose of GSK2269557 greater than 2000 µg within a 24-hour time period will be considered an overdose. For [^{14}C]-GSK2269557, an intravenous dose of

100 µg or an oral dose of 4000 µg within a 24-hour time period will be considered an overdose.

GSK does not recommend specific treatment for an overdose. The Investigator (or physician in charge of the participant at the time) will use clinical judgment to treat any overdose.

In the event of an overdose, the Investigator (or the treating physician) should:

- Contact the Medical Monitor immediately.

Closely monitor the participant for AE/SAE and laboratory abnormalities until [^{14}C]-GSK2269557 can no longer be detected systemically (at least 14 days).

Obtain a plasma sample for PK analysis within 14 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).

Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4. Safety Assessments

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

9.4.1. Physical Examinations

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

9.4.2. Vital Signs

- Vital signs will be measured in a supine or semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate.
- For time points where vital signs are collected in triplicate, only systolic and diastolic blood pressure, and pulse rate should be repeated. There should be at least a 2 minute interval between readings.

- Baseline will be defined as the mean of the 3 pre-dose measurements taken on Day 1 (Treatment 1).

9.4.3. Electrocardiograms

- 12-lead ECGs will be measured in a supine or semi-supine position after 5 minutes rest.
- 12-lead ECGs will be obtained at each time point during the study, as outlined in the SoA (see Section 2). This will be performed using an ECG machine that automatically calculates the heart rate and measures PR interval, QRS duration, QT, and QTcB or QTcF intervals. Refer to Section 8.1.2 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.
- Baseline will be defined as the mean of the 3 pre-dose measurements taken on Day 1 (Treatment 1).

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 6 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 or within 7 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the aetiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 6 must be conducted in accordance with the laboratory manual/SRM and the SoA.

9.4.5. Local Tolerability

Local tolerability at the infusion site will be assessed during treatment period 1, at time points outlined in the SoA (Section 2). Light pressure will be applied at the injection site and record any pain, tenderness, erythema and induration.

Pain and tenderness will be assessed according to the following scale:

- none nothing
- mild easily tolerated
- moderate interferes with daily activities
- severe prevents normal everyday activities or sleep.

Erythema and induration will be measured using a ruler, or a template supplied by the sponsor.

9.5. Pharmacokinetics

Background radioactivity samples (3 samples during period 1) are taken to provide confidence in the determination of endogenous radiocarbon content in the plasma of the participants, and in the processing of those samples to avoid contamination with extraneous radiocarbon.

9.5.1. Blood Sample Collection

Blood samples for plasma total radioactivity, [^{14}C]-GSK2269557, GSK2269557 plasma concentrations, and metabolite profiling will be collected into ethylenediaminetetraacetic acid (EDTA) tubes at the time points indicated in the SoA (Section 2).

The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Processing, storage and shipping procedures are provided in the SRM.

Plasma samples for metabolite profiling will be analysed under a separate GSK Platform Technology Services (PTS) IVIVT protocol. The results of these analyses will be reported separately.

9.5.2. Urine Sample Collection

Urine samples to measure total radioactivity excreted in urine and for metabolite profiling (to be conducted in a separate study) will be collected over the time periods specified in the SoA (Section 2). All participants will be asked to void their bladders before study treatment administration. A blank urine sample will be collected pre-dose. The weight of urine collected during each collection interval will be recorded in the CRF. Further

details of urine sample collection, processing, storage and shipping procedures are provided in the SRM.

9.5.3. Faecal Sample Collection

Faecal samples to measure total radioactivity excreted in faeces and for metabolite profiling (to be conducted in a separate study) will be collected over the time periods specified in the SoA. A faecal sample will be collected from each participant before dosing (the pre-dose sample can be collected up to 48 h before dosing). The weight of faeces collected during each collection interval will be recorded in the CRF. Further details of faecal sample collection, processing, storage and shipping procedures are provided in the SRM.

9.5.4. Bile Collection

Bile samples for analysis of metabolites (to be conducted in a separate GSK PTS IVIVT protocol) will be collected (subject to commercial availability) via the Entero-Test over the time periods specified in the SoA (Section 2). The Entero-Test comprises a gelatine capsule which contains 90 cm or 140 cm of nylon string attached to a 1 g steel weight. One end of the string is attached to the outside of the mouth before swallowing the capsule, so that it can still be retrieved. The gelatine capsule dissolves in the stomach whilst the string and weight continue to the duodenum via peristalsis. Following a food cue to stimulate gall bladder emptying the string is withdrawn. On withdrawal of the string through the mouth the steel weight separates from the string at the pyloric sphincter and is excreted in the faeces. Once the string has been removed from the participant it will be frozen and shipped for metabolite profiling (to be conducted in a separate study). Full details of the Entero-Test sample collection, processing, storage and shipping procedures are provided in the SRM.

9.5.5. Sample Analysis

Total radioactivity measurements in urine samples and faecal homogenates will be determined by LSC at Covance Laboratory (Harrogate, UK) or by accelerator mass spectrometry (AMS) at Xceleron, as appropriate. Total radioactivity measurements from plasma derived from blood will be analysed, as appropriate, by LSC and if required AMS, at GSK, as detailed in the SRM.

[^{14}C]-GSK2269557 and GSK2269557 plasma concentrations will be analysed, as appropriate, at GSK, as detailed in the SRM.

Plasma prepared from blood and aliquots of urine and faecal homogenates will be analysed under a separate GSK protocol for metabolite profiling investigations. Duodenal bile samples collected via the Entero-Test will similarly be analysed under a separate GSK protocol. The results of these analyses will be reported separately.

Analysis of all samples (plasma, urine, faeces, and duodenal bile) will be performed under the control of PTS IVIVT, GlaxoSmithKline, the details of which will be included in the SRM. Raw data will be archived at the bioanalytical site (detailed in the SRM).

Analysis of the PK data collected is explained in details in Section 10.3.1.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Genetics are not evaluated in this study.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Sample Size Determination

No formal sample size calculation has been performed for this study. The primary objective of the study is to gain a better understanding of the compound's excretory and metabolic profile and 4-6 participants are deemed sufficient for this purpose (Penner, 2009). 6 participants will be enrolled into the study in order to achieve at least 4 completed participants.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants Enrolled (APE) Population	All participants for whom a record exists on the study database; includes both screened participants and participants who are not screened but sign the ICF.
Safety Population	Participants in the APE Population who receive at least one dose of study treatment. Participants will be analysed according to the treatment they actually received. The Safety Population will be used for all safety summaries.
PK Population	Participants in the APE Population who receive at least one dose of study treatment and for whom a PK sample was obtained and analysed. Participants will be analysed according to the treatment they actually received. The PK Population will be used for all PK summaries.

10.3. Statistical Analyses

Interim analyses may be conducted to provide preliminary results on plasma PK parameters, see the Reporting and Analysis Plan (RAP) for further details.

10.3.1. Pharmacokinetic Analyses

Plasma GSK2269557 concentration-time data will be listed for each participant and summarised by treatment and planned sampling time. [^{14}C]-GSK2269557 and radioactivity concentrations in plasma will be reported similarly. Individual participant, mean, and median plasma GSK2269557, [^{14}C]-GSK2269557 and total radioactivity concentration-time profiles will be plotted for each treatment on both a linear and semi-log scale.

Pharmacokinetic analysis will be performed by or under the direct auspices of Clinical Pharmacology Modelling & Simulation, GSK. Plasma GSK2269557, [^{14}C] -GSK2269557 and total radioactivity concentration-time data will be analysed by non-compartmental methods with WinNonlin Version 6.3 or above. 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, for GSK2269557, [^{14}C]-GSK2269557 and total radioactivity, as data permits: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-inf)], terminal phase rate constant (λ_z), and apparent terminal phase half-life (t½) following inhaled, oral and IV dosing. Additionally, volume and clearance will be derived following IV dosing. These parameters will be summarised descriptively.

Absolute bioavailability will be estimated for the inhaled and oral doses for each participant and will be summarised.

Derivation of the urine and faecal radioactivity parameters will be the responsibility of the IVIVT department within GSK. The following parameters will be determined from the urine and faecal radiolabelled drug-related material (radioactivity) data, and will be listed and summarised by treatment:

- Absolute amount excreted and percentage excreted in urine (Ae[urine] and Fe%[urine]) within each collection period and cumulative urinary recovery and fraction excreted over the total collection period.
- Absolute amount excreted and percentage excreted in faeces (Ae[faecal] and Fe%[faecal]) with each collection period and cumulative faecal recovery and fraction excreted over the total collection period and cumulatively over the collection period.
- Total excretion (sum of urine and faecal excretion), Ae [total] and Fe% [total] will be calculated by collection interval for each participant.

The urine, faecal and total radioactivity parameters will be listed, summarised and plotted.

All pharmacokinetic data will be stored in the Archives, GlaxoSmithKline Pharmaceuticals, R&D. Production of the summaries, listings and figures of the plasma, urine and faeces data will be performed under the direct auspices of Clinical Statistics, GSK.

Further details regarding the tables, figures and listings to be produced for the study report will be given in the Reporting and Analysis Plan (RAP).

10.3.2. Metabolite profiling

The metabolic profiling/structural characterisation aspect of this work will be performed by GSK under a separate IVIVT protocol and reported separately.

10.3.3. Safety Analyses

Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. Further details will be given in the RAP.

11. REFERENCES

GlaxoSmithKline Document Number 2012N141231_07. GSK2269557 Investigator's Brochure. Date 22 Sep 2017.

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

Penner N, Klunk L, Prakash C. Human radiolabelled mass balance studies: Objectives, utilities and limitations. Biopharm. Drug Dispos. 2009;30:185-203.

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations	
ADME	Absorption Distribution Metabolism Excretion
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AMS	Accelerator Mass Spectrometry
APE	All Participants Enrolled
AST	Aspartate aminotransferase (SGOT)
AUC	Area under concentration-time curve
AUC(0- inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
BMI	Body mass index
BP	Blood pressure
BPM	Beat Per Minute
Bq	Becquerel
C	Carbon
Ci	Curie
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	Maximum observed concentration
CO	Carbon Monoxide
CO_2	Carbon dioxide
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPK	Creatine phosphokinase
CPM	Clinical Project Manager
CRF	Case Report Form
CT	Computed Tomography
δ	Delta
DMPK	Drug Metabolism and Pharmacokinetics
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
F	Absolute bioavailability
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GSK	GlaxoSmithKline
h	Hour(s)
HDPE	High Density Polyethylene
HPLC	High-performance liquid chromatography

Abbreviations	
HBsAg	Hepatitis B surface antigen
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart rate
HMR	Hammersmith Medicines Research
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICRP	International Commission on Radiological Protection
IDSL	Integrated Data Standards Library
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IgM	Immunoglobulin M
IMP	Investigational medicinal product
INR	International normalized ratio
IP	Investigational Product
IRB	Institutional Review Board
IV	Intravenous
IVIVT	In vitro/In vivo Translation
kBq	Kilo Becquerel
Kg	Kilogram
λz	Terminal phase rate constant
L	Litre
LDH	Lactate dehydrogenase
LSC	Liquid Scintillating Counting
µCi	Micro Curie
µg	Microgram
µSv	Micro Sievert
m	Meter
MBq	Megabecquerel
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MDD	Medical Devices Directive
MgSt	Magnesium stearate
MHRA	Medicines and Healthcare Products Regulatory Agency
mL	Millilitre
mmHg	Millimetre of mercury
MSDS	Material Safety Data Sheet
msec	Milliseconds
mSv	Millisievert
nCi	Nano Curie
NOAEL	No-observed-adverse-effect-level
PI3K	Phosphoinositide 3-kinases

Abbreviations	
PIP2	Phosphatidylinositol 4,5-biphosphate
PIP3	Phosphatidylinositol 3,4,5-trisphosphate
PK	Pharmacokinetic
PTS	Platform Technology Services
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red blood cells
REC	Research Ethics Committee
RNA	Ribonucleic acid
SAE	Serious adverse event(s)
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SoA	Schedule of activities
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
Sv	Sievert
t½	Terminal phase half-life
t_{max}	Time of occurrence of Cmax
ULN	Upper limit of normal
WBC	White blood cells
WHO	World Health Organisation
WOCBP	Woman of child bearing potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	**Trademarks not owned by the GlaxoSmithKline group of companies**
DISKUS	Entero-Test
ELLIPTA	WinNonlin

12.2. Appendix 2: Contraceptive Guidance and Collection of Pregnancy Information

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 2, when having penile-vaginal intercourse with a woman of childbearing potential
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame;
- In addition male participants must refrain from donating sperm for duration of study.

Table 2 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 the duration of the study.

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.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- 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/IEC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

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

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH

guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.

Data Protection

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

Publication Policy

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

Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will

have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

- GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study participants, as appropriate.
- The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed 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 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 ICFs, 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 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.

- Definition of what constitutes source data will be documented in a source data agreement.

Study and Site Closure

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

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

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

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

12.4. Appendix 4: Liver Safety: Required Actions and Follow-up Assessments

Phase I Liver chemistry stopping criteria have been designed to assure participant safety and to evaluate liver event aetiology (in alignment with the FDA premarketing clinical liver safety guidance). They are described in Table 3.

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

Table 3 Phase I liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	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

Required Actions and Follow up Assessments following Liver Stopping Event	
Actions	**Follow Up Assessments**
• **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 participant until liver chemistries resolve, stabilise, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT≥3xULN AND bilirubin ≥ 2xULN or INR >1.5** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilise or return to within baseline	• Viral hepatitis serology[3] • Blood sample for pharmacokinetic (PK) analysis, obtained 48 h post 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**

Liver Chemistry Stopping Criteria – Liver Stopping Event	
• 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 liver event follow up assessments within **24-72 hrs** • Monitor participantss weekly until liver chemistries resolve, stabilize or return to within baseline	**INR >1.5:** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]. • 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 participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured, which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
4. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

12.5. Appendix 5: 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 Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or

convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

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

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

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

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, 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.

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT ≥ 3xULN and total bilirubin ≥ 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to participants receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

Refer to Appendix 4 for the required liver chemistry follow-up instructions.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- 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
• The SAE CRF should be transmitted to the SAE coordinator by e-mail. • In rare circumstances and in the absence of other options, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM.

12.6. Appendix 6: Clinical Laboratory Tests

- The tests detailed in Table 4 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 4 Protocol-Required Safety Laboratory Assessments

<table>
<tr><th>Laboratory Assessments</th><th>Parameters</th></tr>
<tr><td>Haematology</td><td>
<table>
<tr><td>Platelet Count</td><td><u>RBC Indices</u>:</td><td><u>White blood cells (WBC) count with Differential</u>:</td></tr>
<tr><td>Red blood cell (RBC) Count</td><td>Mean corpuscular volume (MCV)</td><td>Neutrophils</td></tr>
<tr><td>Hemoglobin</td><td>Mean corpuscular haemoglobin (MCH)</td><td>Lymphocytes</td></tr>
<tr><td>Hematocrit</td><td>Mean corpuscular haemoglobin concentration (MCHC)</td><td>Monocytes</td></tr>
<tr><td></td><td></td><td>Eosinophils</td></tr>
<tr><td></td><td></td><td>Basophils</td></tr>
</table>
</td></tr>
<tr><td>Clinical Chemistry[1]</td><td>
<table>
<tr><td>Urea</td><td>Potassium</td><td>Aspartate aminotransferase (AST) (serum glutamic-oxaloacetic transaminase) (SGOT)</td><td>Triglycerides</td></tr>
<tr><td>Creatinine</td><td>Sodium</td><td>ALT (Serum glutamic pyruvic transaminase) (SGPT)</td><td>Total bilirubin</td></tr>
<tr><td>Glucose, fasting</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Total Protein</td></tr>
<tr><td>Uric Acid</td><td>Chloride</td><td>Gamma GT</td><td>Albumin</td></tr>
<tr><td></td><td>Phosphate</td><td>Cholesterol</td><td>Globulin</td></tr>
</table>
</td></tr>
<tr><td>Routine Urinalysis</td><td>• dipstick test: protein, blood, ketones, glucose, bilirubin, urobilinogen, leukocyte esterase, specific gravity, nitrites, pH;
• Microscopic examination (if leukocyte esterase, nitrites, blood or protein is abnormal)</td></tr>
<tr><td>Other Screening Tests</td><td>• HIV
• Hepatitis B (HBsAg)
• Hepatitis C (Hep C antibody)
• Alcohol, cotinine and drug screen (to include at minimum: amphetamines, barbiturates, cocaine, opiates, cannabinoids and benzodiazepines)</td></tr>
</table>

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 8.1.1 and Appendix 4 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. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

12.7. 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).