Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)

Title	:	Reporting and Analysis Plan for an open-label study in healthy male subjects, to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK2269557, administered as a single intravenous microtracer (concomitant with an inhaled non-radiolabelled dose) and a single oral dose
Compound Number	:	GSK2269557
Effective Date	:	09-JAN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 206764.
- This RAP is intended to describe the safety and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver
PPD Study Statistician (Clinical Statistics)

RAP Team Approvals:

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
2017N324843_00	09-AUG-2017	Original
2017N324843_01	30-OCT-2017	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.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 1 [(Dated: 30/Oct/2017)], however additional PK parameters have been requested.

2.2. Study Objective(s) and Endpoint(s)

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.

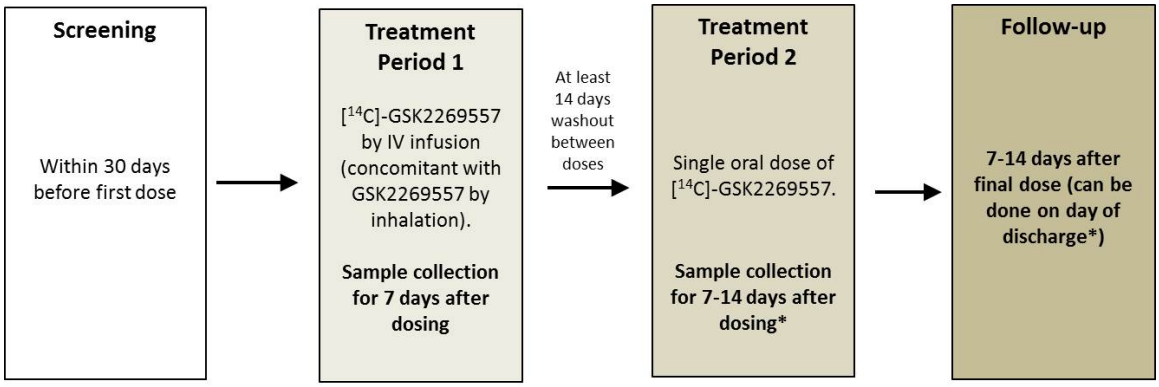
Objective	Endpoint
Secondary	
• To determine parent GSK2269557 concentration in plasma following a single IV microtracer of [^{14}C]-GSK2269557 concomitant with an inhaled non-radiolabelled GSK2269557 dose and a single oral dose of [^{14}C]-GSK2269557.	• AUC(0-inf), AUC(0–t), Cmax, tmax, and t1/2 of 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).

Note: the above table is as presented in the protocol amendment, subsequently additional PK parameters have been requested including: plasma AUC(0-24) and %AUCex for parent GSK2269557 and total radioactivity analytes; plasma ML(iv), ML(po), Fg, EH, Fabs; parent GSK2269557/ total radioactivity ratios for the plasma PK parameters Cmax, AUC(0-t), AUC(0-24) and AUC(0-∞); and CLr derivations are described in Section 8.

2.3. Study Design

Overview of Study Design and Key Features



*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).

Design Features	• open-label • single centre • non-randomised • 2-period single-sequence crossover • mass balance study • approximately 6 healthy male participants will be enrolled • there will be a washout period of at least 14 days between doses
Dosing	• The investigational drug is nemiralisib (GSK2269557). Each subject will receive a 10 µg radiolabelled version of GSK2269557 ([^{14}C]-GSK2269557) microtracer administered by IV infusion, concomitant with an inhaled non-radiolabelled 1000 µg dose of GSK2269557, in period 1 and a single 800 µg dose of [^{14}C]-GSK2269557 administered as an oral dose in period 2.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• This is an open label, non-randomised, 2-period single-sequence crossover study. • All subjects will receive [^{14}C]-GSK2269557 administered as a single IV dose (concomitant with an inhaled non-radiolabelled dose) at period 1 followed by [^{14}C]-GSK2269557 administered as a single oral dose at period 2

2.4. Statistical Hypotheses / Statistical Analyses

- No formal hypotheses will be tested or treatment comparisons performed. Data will be summarised using descriptive methods only.

3. PLANNED ANALYSES

3.1. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management. Note: pharmacokinetic concentration and pharmacokinetic parameter raw file generation start after GSK DBF – take approx. 18 working days after DBF. All other datasets available at DBF.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
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 informed consent form (ICF).	• Screen Failure
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	• Study Population • Safety
Pharmacokinetic (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	• PK

Refer to Appendix 9: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.

- Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the pCRF.

The study endpoints will be reported using the populations detailed in Section 4 of this document regardless of whether the subjects deviate from the protocol.

If there are subjects with protocol deviations that may potentially impact the PK endpoints, exploratory sensitivity summaries may be considered. If further summaries of the data are produced, they will be detailed in the clinical study report.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
		Data Displays for Reporting [1]	
Code	Description	Description	Order [2]
A	GSK2269557 1000 mcg Inhaled + [14C]-GSK2269557 10 mcg IV	557 IH + 14C-557 IV	1
B	[14C]-GSK2269557 800 mcg Oral	14C-557 ORAL	2

NOTES:

1. The following footnote will be presented on each display:
   557 IH + 14C-557 IV = Intravenous radiolabelled 10 mcg GSK2269557 co-administered with inhaled 1000 mcg GSK2269557; 14C-557 ORAL = 800 mcg radiolabelled GSK2269557 administered orally
2. Order represents treatments being presented in TFL, as appropriate

5.2. Baseline Definitions

For all endpoints (except as noted in baseline definitions) the baseline value will be the latest pre-dose assessment with a non-missing value, including those from unscheduled visits. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline. Baseline definitions defined in the table are applicable to each "period" for this crossover study.

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
12-Lead ECG	X	X	X	Day 1 (Pre Dose)
Vital Signs	X	X	X	Day 1 (Pre Dose)
Haematology	X	X	X	Day 1 (Pre Dose)
Clinical Chemistry	X	X	X	Day 1 (Pre Dose)
Liver Function	X	X	X	Day 1 (Pre Dose)

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing. The mean of triplicate measurements at any given time point will be used as the value for that time point unless otherwise stated.

5.3. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.3	Appendix 3 Study Phases and Treatment Emergent Adverse Events
11.4	Appendix 4 Data Display Standards & Handling Conventions
11.5	Appendix 5 Derived and Transformed Data
11.6	Appendix 6 Reporting Standards for Missing Data
11.7	Appendix 7 Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the "Safety" population, unless otherwise specified.

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9 List of Data Displays.

7. SAFETY ANALYSES

The safety analyses will be based on the "Safety" population, unless otherwise specified.

7.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 9 List of Data Displays.

7.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. The details of the planned displays are provided in Appendix 9 List of Data Displays.

7.3. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 9 List of Data Displays.

7.4. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 9 List of Data Displays.

8. PHARMACOKINETIC ANALYSES

The plasma pharmacokinetic concentrations will have different nomenclatures dependent on the method of measuring. For measured concentrations of GSK2269557 in blood plasma, the nomenclature [14C]-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). It is expected that, for period 1, the radiolabelled iv dose will be measured using LC+AMS and will be labelled "[^{14}C]-GSK2269557", the non-radiolabelled inhaled dose will be measured using LC/MS and will be labelled "GSK2269557". For period 2, the radiolabelled oral dose will be measured using LC/MS and will be labelled "GSK2269557". For each period the total radioactivity will be measured by AMS and will be labelled "Total Radioactivity". However, these methods may be adapted if necessary.

The reconciliation of the PK Case Report Form (CRF) and SMS2000 data will be performed by, or under the direct auspices of, Clinical Pharmacology Science and Study Operations (CPSSO), GlaxoSmithKline.

Derivation of plasma pharmacokinetic parameters for [^{14}C]-GSK2269557, total radioactivity and GSK2269557 will be performed by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline.

Derivation of urine/faeces total radioactivity parameters will be performed by, or under the direct auspices of Bioanalysis, Immunogenicity and Biomarkers (BIB), PTS IVIVT, GlaxoSmithKline.

8.1. Endpoint / Variables

8.1.1. Drug Concentration Measures

Refer to Appendix 4 Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic)

8.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times.

Pharmacokinetic parameters listed in Table 1 will be determined from the plasma concentration-time data, as data permits, for each subject, analyte (total radioactivity, GSK2269557 and [^{14}C]-GSK2269557) and treatment period unless otherwise stated.

Pharmacokinetic parameters listed in Table 2 will be determined from the urine and faeces concentration-time data, as data permits, for each collection interval, subject and treatment period unless otherwise stated.

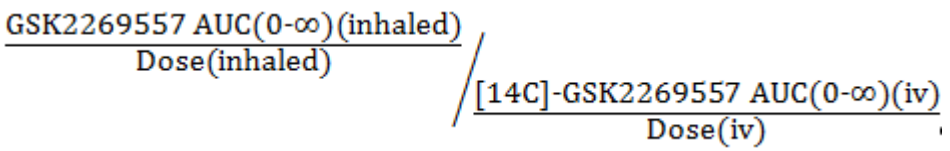
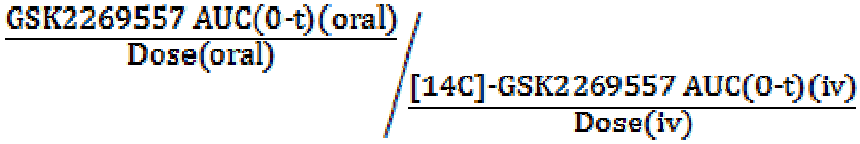
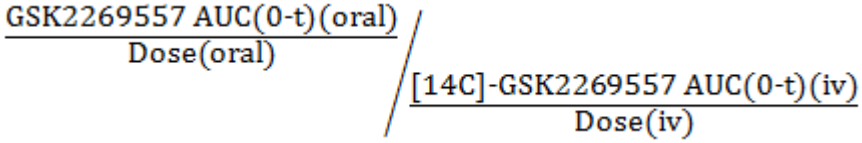
Table 1 Derived Plasma Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-24)	Area under the concentration-time curve from time zero to 24 hours post dose (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: **[AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100**
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
CL(iv)	Total iv clearance will be calculated as: CL(iv)=Dose(iv)/AUC(0-∞) Treatment period 1, analyte [^{14}C]-GSK2269557 only where Dose(iv) is the actual iv dose calculated as [weight of full syringe (g) minus syringe weight after dose (g)] multiplied by nominal concentration (µg/g)

CLr	If Plasma AUC(0-∞) is calculable then
	CLr= Cumulative Ae[urine] for treatment period 1/Plasma AUC(0-∞)
	If Plasma AUC(0-∞) is not calculable then
	CLr= Cumulative Ae[urine] for treatment period 1/Plasma AUC(0-t)
	Where cumulative Ae from excretion data for treatment period 1 and AUC from NCA PK analysis of Treatment period 1, analyte [^{14}C]-GSK2269557 only.

V(c)	$Dose(IV)/AUC(0\text{-}\infty)$ Treatment period 1, analyte [^{14}C]-GSK2269557 only. Where Dose(IV) is the radiometric dose as described in Table 1.
V(dss)	$Dose(IV) \times AUMC(0\text{-}\infty)/\left(AUC(0\text{-}\infty)\right)^2$ Treatment period 1, analyte [^{14}C]-GSK2269557 only. Where AUMC is the area under the moment curve and Dose(IV) is the radiometric dose as described in Table 1.

Parameter	Parameter Description
ML(iv)	Metabolite load following intravenous administration is calculated as: $\frac{\text{Total Radioactivity AUC}(0\text{-}\infty) - \text{[14C]-GSK2269557 AUC}(0\text{-}\infty)}{\text{Total Radioactivity AUC}(0\text{-}\infty)}$ Treatment period 1 only
ML(po)	Metabolite load following oral administration is calculated as: $\frac{\text{Total Radioactivity AUC}(0\text{-}\infty) - \text{GSK2269557 AUC}(0\text{-}\infty)}{\text{Total Radioactivity AUC}(0\text{-}\infty)}$ Treatment period 2 only. Note: GSK2269557 AUC(0-∞) may be updated depending on the sample analysis conducted but refers to the parent GSK2269557 from oral dose.
Fg	Fraction metabolised by gut wall as a fraction of the oral dose will be calculated as follows: Fg= 1 –(ML(po)–ML(iv))
E_H	Hepatic extraction ratio is calculated (Davis, B et al, 1993) as follows: E_H = CL(iv)/1450 mL/min
F_{abs}	Fraction absorbed following an oral dose is calculated as follows: $F_{abs} = \frac{\frac{\text{Oral F}(0\text{-}\infty)}{1 - E_H}}{F_g}$
Dose(IV)	Radiometric IV dose will be calculated by Covance
Dose(oral)	Radiometric Oral dose will be calculated by Covance
Dose(inhaled)	Nominal inhaled dose
Oral F (0-∞)	Oral absolute bioavailability based on AUC(0-∞) calculated as: $\frac{\frac{\text{GSK2269557 AUC}(0\text{-}\infty)(\text{oral})}{\text{Dose(oral)}}}{\frac{\text{[14C]-GSK2269557 AUC}(0\text{-}\infty)(\text{iv})}{\text{Dose(iv)}}}$ Per subject. Note: Radiometric dose will be used for oral and iv as described in Table 1. GSK2269557 AUC(0-∞)(oral) may be updated depending on the sample analysis

Parameter	Parameter Description
	conducted but refers to the parent GSK2269557 from oral dose.
Inhaled F (0-∞)	Inhaled absolute bioavailability based on AUC(0-∞) calculated as  Per subject. Note: Radiometric dose will be used for oral and iv as described in Table 1.
Oral F (0-t)	Oral absolute bioavailability based on AUC(0-t) calculated as:  Per subject. Note: Radiometric dose will be used for oral and iv as described in Table 1. . GSK2269557 AUC(0-∞)(oral) may be updated depending on the sample analysis conducted but refers to the parent GSK2269557 from oral dose.
Inhaled F (0-t)	Inhaled absolute bioavailability based on AUC(0-t) calculated as  Per subject. Note: Radiometric dose will be used for oral and iv as described in Table 1.
GSK2269557 /Total radioactivity ratio for Cmax,	Cmax Ratio = Exp { [loge(GSK2269557 Cmax] - [loge(Total radioactivity Cmax]} Per subject for radiolabelled oral dose. GSK2269557 may be updated depending on the sample analysis conducted but refers to the parent GSK2269557 from oral dose
GSK2269557 /Total radioactivity ratio for AUC(0-inf)	AUC(0-inf) Ratio = Exp { [loge(GSK2269557 AUC(0-inf)] - [loge(Total radioactivity AUC(0-inf)] } Per subject for radiolabelled oral dose. GSK2269557 may be updated depending on the sample analysis conducted but refers to the parent GSK2269557 from oral dose
GSK2269557 /Total radioactivity	AUC(0-t) Ratio = Exp { [loge(GSK2269557 AUC(0-t)] - [loge(Total radioactivity AUC(0-t)] }

Parameter	Parameter Description
ratio for AUC(0-t)	Per subject for radiolabelled oral dose. GSK2269557 may be updated depending on the sample analysis conducted but refers to the parent GSK2269557 from oral dose
[^{14}C]-GSK2269557 /Total radioactivity ratio for Cmax,	Cmax Ratio = Exp { [loge([^{14}C]-GSK2269557 Cmax] - [loge(Total radioactivity Cmax]} Per subject for radiolabelled IV dose.
[^{14}C]-GSK2269557 /Total radioactivity ratio for AUC(0-inf)	AUC(0-inf) Ratio = Exp { [loge([^{14}C]-GSK2269557 AUC(0-inf)] - [loge(Total radioactivity AUC(0-inf)] } Per subject for radiolabelled IV dose.
[^{14}C]-GSK2269557 /Total radioactivity ratio for AUC(0-t)	AUC(0-t) Ratio = Exp { [loge([^{14}C]-GSK2269557 AUC(0-t)] - [loge(Total radioactivity AUC(0-t)] } Per subject for radiolabelled IV dose.

NOTES:

- Additional parameters may be included as required.
- Lambda_z is the terminal phase rate constant.
- The 10 PK parameters AUC(0-t), AUC(0-24), AUC(0-inf), AUCex, Cmax, tmax, t1/2, CL, Vdss and Vc will be derived from phoenix and sent to S&P. The radiometric IV and oral dose will be calculated by Covance and sent to S&P. Additional parameters will be derived by S&P including CLr, ML(iv), ML(po), F_g, E_H, F_{abs}, F and the treatment ratios

Table 2 Derived Urine and Faeces Pharmacokinetic Parameters

Parameter	Parameter Description
Ae[urine]	Total radioactivity recovered in the urine (Ae[urine]) calculated for each collection interval per subject and treatment period as: Ae[urine]= (concentration in urine sample x collected sample weight) for each urine collection interval, eg 0-6, 6-24, 24-48, etc.
Cumulative Ae[urine]	Cumulative total radioactivity recovered in the urine (Cumulative Ae[urine]) calculated for each cumulative collection interval per subject and treatment period as: Cumulative Ae[urine]= summation of Ae[urine] for each urine collection within the cumulative urine collection interval, eg 0-24, 0-48, etc.
Fe%[urine]	% of total dose excreted as total radioactivity (Fe%[urine]) for each collection interval per subject and treatment period, will be estimated as: Fe%[urine]=(Ae[urine]) for each collection period)/Dose*100. Where the dose is the radiolabelled [^{14}C]-GSK2269557, that is in period 1 radiometric iv dose, in period 2 radiometric oral dose
Cumulative Fe%[urine]	Cumulative % of total dose excreted as total radioactivity (Cumulative Fe%[urine]) for each cumulative collection interval per subject and treatment period, will be estimated as: Cumulative Fe%[urine]=summation of Fe%[urine] for each urine collection within the cumulative urine collection interval, eg 0-24, 0-48, etc.

Parameter	Parameter Description
Ae[faeces]	Total radioactivity recovered in the faeces (Ae[faeces]) calculated for each collection interval per subject and treatment period as Ae[faeces] = (concentration in faecal homogenate aliquot analysed x weight of homogenate aliquot analysed) x (total homogenate weight / collected sample weight) for each faecal collection interval, eg 0-24, 24-48, etc
Cumulative Ae[faeces]	Cumulative total radioactivity recovered in the faeces (Cumulative Ae[faeces]) calculated for each cumulative collection interval per subject and treatment period as Cumulative Ae[faeces]= summation of Ae[faeces] for each faecal collection within the cumulative faecal collection interval, eg 0-24, 0-48, etc
Fe%[faeces]	% of total dose excreted as total radioactivity (Fe%[faeces]) for each collection interval per subject and treatment period will be estimated as: Fe%[faeces] =(Ae[faeces] for each collection period)/Dose*100. Where the dose is the radiolabelled [^{14}C]-GSK2269557, that is in period 1 radiometric iv dose, in period 2 radiometric oral dose
Cumulative Fe%[faeces]	Cumulative % of total dose excreted as total radioactivity (Cumulative Fe%[faeces]) for each cumulative collection interval per subject and treatment period will be estimated as: Cumulative Fe%[faeces]=summation of Fe%[faeces] for each faecal collection within the cumulative faecal collection interval, eg 0-24, 0-48, etc.
Ae[total]	Total radioactivity recovered in total excretion (sum of urine and faecal excretion), Ae[total] will be estimates by collection interval for each subject and treatment period as: Ae[total]=Ae[urine]+ Ae[faeces]
Cumulative Ae[total]	Total radioactivity recovered in total excretion (sum of urine and faecal excretion), cumulative Ae[total] will be estimates by cumulative collection interval per subject and treatment period as: Cumulative Ae[total]= summation of Ae[total] for each total excretion collection within the cumulative total excretion collection interval, eg 0-24, 0-48, etc
Fe%[total]	% of total dose excreted as total radioactivity (Fe%[total]) for each collection period will be estimated for each subject and treatment period as: Fe%[total]= Fe%[urine]+ Fe%[faeces]
Cumulative Fe%[total]	Cumulative % of total dose excreted as total radioactivity (Cumulative Fe%[total]) for each cumulative collection period will be estimated for each subject and treatment period as: Cumulative Fe%[total]= Cumulative Fe%[urine]+ Cumulative Fe%[faeces] for each total excretion collection within the cumulative total excretion collection interval, eg 0-24, 0-48, etc

NOTES:

- Additional parameters may be included as required.

8.2. Primary Pharmacokinetic Analyses

8.2.1. Endpoint / Variables

8.2.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic)

8.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated as described in Section 8.1.2.

8.2.2. Summary Measure

A primary objective is to determine total radioactivity (drug related material) in plasma following a single IV microtracer of [14C]-GSK2269557 (concomitant with an inhaled non-radiolabelled GSK2269557 dose) and a single oral dose of [14C]-GSK2269557. To assess this, the plasma PK parameters: AUC (0-inf), AUC (0–t), AUC (0–24), %AUCex, Cmax, tmax, t1/2 of total drug-related material (radioactivity) will be summarised and listed.

The additional primary objective is 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 [14C]-GSK2269557 (concomitant with an inhaled non-radiolabelled dose) and a single oral dose of [14C]-GSK2269557. To assess this, the PK parameters: Ae and Fe% will be summarised and listed for urine faeces and total (Urine + Faeces).

8.2.3. Population of Interest

The primary pharmacokinetic analyses will be based on the “Pharmacokinetic” population, unless otherwise specified.

8.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9 List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.3. Secondary Pharmacokinetic Analyses

8.3.1. Endpoint / Variables

8.3.1.1. Drug Concentration Measures

Refer to Appendix 4 Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Standards for Pharmacokinetic)

8.3.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated as described in Section 8.1.2.

8.3.2. Summary Measure

A secondary objective is to determine parent GSK2269557 concentration in plasma following a single IV microtracer of [14C]-GSK2269557 (concomitant with an inhaled non-radiolabelled GSK2269557 dose) and a single oral dose of [14C]-GSK2269557. To assess this, the plasma PK parameters: AUC (0-inf), AUC (0–t), AUC (0–24), %AUCex, Cmax, tmax, t1/2 of parent GSK2269557 ([14C]-GSK2269557 and GSK2269557) will be summarised and listed and the volume (Vdss and Vc) and clearance of parent GSK2269557 ([14C]-GSK2269557) after IV dose only will be summarised and listed.

Another secondary objective is to estimate the absolute bioavailability of GSK2269557 following inhaled and oral administration. To assess this, the oral and inhaled bioavailability (F) will be summarised and listed.

To assess metabolism, the plasma PK parameters: ML(iv), ML(po), F_g, E_H, F_{abs} will be summarised and listed. To assess exposure and metabolite ratio in humans, the ratio of Parent GSK2269557/total radioactivity will be calculated for the plasma PK parameters: Cmax, AUC(0-t), AUC(0-24) and AUC(0-∞), results will be summarised, listed and statistical analyses will be conducted as described in Section 8.3.4.1. To assess renal clearance, the PK CLr will be summarised and listed if bioanalysis can quantify parent GSK2269557 in urine collection intervals (i.e. if Ae is quantifiable for collection intervals).

8.3.3. Population of Interest

The secondary pharmacokinetic analyses will be based on the Pharmacokinetic population, unless otherwise specified.

8.3.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9 List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 8.3.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.3.4.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data is available (i.e. if participants have well defined plasma profiles).

Endpoint / Variables
• Parent GSK2269557/Total radioactivity ratio for Cmax, AUC(0-t), AUC(0-24) and AUC(0-∞)
Model Specification
NOTE: The description below describes the current thinking of how to analyse these endpoints. The

proposed models will be assessed, and if not appropriate alternative models could be used.

[^{14}C]-GSK2269557/ Total radioactivity ratio for Cmax, AUC(0-t), AUC(0-24) and AUC(0-∞) - Period 1 IV Dose

Following sample analyses the Parent GSK2269557 for the IV dose is likely to be presented as [14C]-GSK2269557 depending on the method, this is in addition to the Parent GSK2269557 for the inhaled dose and the total radioactivity. Analysis has been described for the [^{14}C]-GSK2269557 analyte however may be adapted if alternate sample analysis is conducted.

For each period, following loge-transformation of plasma pharmacokinetic parameters of [^{14}C]-GSK2269557 (from period 1 IV dose) and total radioactivity (from period 1 IV dose), AUC(0-∞), AUC(0-24), AUC(0-t) and Cmax will be separately analysed using a mixed effects model fitting a fixed effect term for analytes ([^{14}C]-GSK2269557 (from period 1 IV dose) and total radioactivity (from period 1 IV dose)) and a random effect for subject. The Kenward & Roger (KR) degrees of freedom approach will be used. Point estimates for the mean difference between the [^{14}C]-GSK2269557 and total radioactivity analytes, and associated 95% confidence interval will be constructed using the residual variance.

GSK2269557/ Total radioactivity ratio for Cmax, AUC(0-t), AUC(0-24) and AUC(0-∞) - Period 2 oral dose

Following sample analyses the Parent GSK2269557 will be presented as either GSK2269557 or [14C]-GSK2269557 depending on the method, in addition to total radioactivity. Analysis has been described for parent GSK2269557 analyte and should be adapted to the appropriate analyte as appropriate.

For each period, following loge-transformation of plasma pharmacokinetic parameters of Parent GSK2269557 (from period 2 oral dose) and total radioactivity (from period 2 oral dose), AUC(0-∞), AUC(0-24), AUC(0-t) and Cmax will be separately analysed using a mixed effects model fitting a fixed effect term for analytes (Parent GSK2269557 (from period 2 oral dose) and total radioactivity (from period 2 oral dose)) and a random effect for subject. The Kenward & Roger (KR) degrees of freedom approach will be used. Point estimates for the mean difference between the Parent GSK2269557 and total radioactivity analytes, and associated 95% confidence interval will be constructed using the residual variance.

Model Checking & Diagnostics

- Model assumptions will be applied, but appropriate adjustments may be made based on the data
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- Normality assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
- If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data

Model Results Presentation

- Point estimates for the mean difference between the Parent GSK2269557 and total radioactivity analytes, and associated 95% confidence interval will be constructed using the residual variance. The point estimate and confidence interval will then be exponentially back-transformed to obtain point estimates and associated 95% confidence interval for the ratio Parent GSK2269557/total radioactivity. These will be presented in a tabular form.

Sensitivity Analyses

- Data will be reviewed and if there are deviation that may affect the PK results, sensitivity analyses may be conducted as appropriate which may include excluding individual time points or excluding individual subjects as appropriate.

9. EXPLORATORY ANALYSES

As outlined in the protocol, there is an exploratory endpoint of characterisation and quantification of metabolites in plasma, urine, faeces, and duodenal bile. These analytical investigations may be conducted by GSK PTS IVIVT and the results reported in a separate GSK PTS IVIVT report.

10. REFERENCES

Davis,B and Morris,T. Physiological Parameters in Laboratory Animals and Humans. Pharmaceutical ResearchVol10.No.7.1093-1095.1993.

PKOne and relevant information on Standards for the Transfer and Reporting of PK Data using HARP available within IDSL standards, 2008.

Protocol Deviation Management Plan for an open-label study in healthy male subjects, to determine the excretion balance and pharmacokinetics of [^{14}C]-GSK2269557, administered as a single intravenous microtracer (concomitant with an inhaled non-radiolabelled dose) and a single oral dose, 2017

11. APPENDICES

11.1. Appendix 1: Protocol Deviation Management

- As detailed in Section 4.1, Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan and a listing and summary of important Protocol Deviations will be provided.
- A Per Protocol Population is not being defined for this study. However additional exploratory sensitivity summaries may be considered, if there are protocol deviations that may affect the primary PK endpoints. Any additional sensitivity summaries will be documented in the CSR.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

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
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							

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
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
	Day									(7-14 days post-last dose)[2,3]
	-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								
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.

11.3. Appendix 3: Study Phases and Treatment Emergent Adverse Events

11.3.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the start and/or stop time/date of the study treatment within the period (for period 1 the inhaled and IV dose, for period 2 the oral dose).

These treatment phases are already defined in the Time and Event table in Appendix 2 Schedule of Activities (Section 11.2).

Treatment Phase	Definition
Pre-Treatment	Date/Time ≤ Study Treatment Start Date/Time
On-Treatment	Study Treatment Start Date/Time < Date/Time ≤ Study Treatment Stop Date/Time
Post-Treatment	Date/Time > Study Treatment Stop Date /Time

11.3.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 6: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

11.3.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	• If AE onset date is on or after treatment start date & on or before treatment stop date plus washout. • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 14 days. • For studies with greater than one treatment period (e.g., crossover study), if AE onset is during one period and worsens during a later period it would be counted in both periods. For the initial period the logic would be as above. For the later period the logic would use the treatment dates associated with the later period: • Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date +14 days.

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.
- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SAL00175
HARP Compound	: GSK2269557
HARP Study	: mid206764
Analysis Datasets	
• Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards. If the Study Data Standardization Plan (SDSP) exists for a study, ensure the CDISC versions are consistent.	
Generation of RTF Files	
• RTF files will be generated for summary tables.	

11.4.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the pCRF. • The reported precision from non pCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the subject's listings.

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables and/or figures. • All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

11.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to PKOne. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
Pharmacokinetic Parameter Derivation	
Plasma PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: CLr, ML(iv), ML(po), Fg, E_H, F_{abs}, F(Oral, (0-t)), F(Oral, (0-∞)), F(inhaled, (0-t)), F (inhaled, (0-∞)) and the Parent GSK2269557/ Total Radioactivity ratio for Cmax, AUC(0-t), AUC(0-24) and AUC(0-∞). note: Parent GSK2269557/ Total Radioactivity ratios will be either GSK2269557/ Total Radioactivity or [14C]-GSK2269557/ Total Radioactivity depending on the method of sample analyses and are of interest for the radiolabelled IV and oral dose.
Urine and Faeces PK Parameter to be Derived by Programmer	The following PK parameters will be derived by the Programmer: cumulative Ae, Fe% and cumulative Fe%.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	No.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to PKOne

11.5. Appendix 5: Derived and Transformed Data

11.5.1. General

Multiple Measurements at One Analysis Time Point
• Triplicate measures of 12-lead ECG and vital signs (HR and BP) will be taken at screening and pre dose for period 1. The mean of the measurements will be calculated and used in any derivation of summary statistics but if listed all data will be presented. • There are no other scheduled multiple measurements however, if multiple measurements are recorded at a given time point the following process will be followed: [1] Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. [2] If there are two values within a time window (as per Section 11.2) the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. [3] Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day
• Calculated as the number of days from First Dose Date: • Ref Date = Missing → Study Day = Missing • Ref Date < First Dose Date → Study Day = Ref Date – First Dose Date • Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1

11.5.2. Study Population

Study Population
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Any subject with a missing day will have this imputed as day '15'. ○ Any subject with a missing date and month will have this imputed as '30th June'. ○ The year of the birth date will be captured in the pCRF Age will then be derived as the integer value of [(DoB- date of Screening)/365.25] • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m) 2]
Treatment Compliance
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) at each visit will be calculated. • Planned Treatment Duration is defined as 1 day in period 1 and 1 day in period 2.
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula:

Study Population
Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1 • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days x Total Daily Dose)** • If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

11.5.3. Safety

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as: [1] If QTcF is machine read, then: $$RR = \left[\left(\frac{QT}{QTcF}\right)^{3}\right] * 1000$$ • If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.
Corrected QT Intervals
• When not entered directly in the pCRF, corrected QT intervals by Fridericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcF will be derived as: $$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Laboratory Parameters
• If a laboratory value which is expected to have a numeric value for summary purposes, has a non-detectable level reported in the database, where the numeric value is missing, but typically a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, the number of significant digits in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value. o Example 1: 2 Significant Digits = '< x ' becomes x – 0.01 o Example 2: 1 Significant Digit = '> x' becomes x + 0.1 o Example 3: 0 Significant Digits = '< x' becomes x – 1 This imputation should be performed on the raw data before the conversion of units in CDISC studies to ensure correct imputation of missing data.

11.6. Appendix 6: Reporting Standards for Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who has completed all phases of the study including the last visit. • If participants prematurely discontinue the study, additional replacement participants may be enrolled at the discretion of the sponsor and in consultation with the investigator • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.
Liver Chemistry Stopping Criteria	• Study treatment will be stopped for a subject if the following liver chemistry stopping criteria is met: o ALT ≥ 3 x ULN; or o ALT ≥ 3 X ULN and total bilirubin ≥ 2 x ULN (> 35% direct bilirubin); or o ALT ≥ 3 x ULN and INR > 1.5 (INR is not a Protocol requirement) Note: Refer to Appendix 4 of Protocol for details of the required assessments if a subject meets the above criteria.
QTc Stopping Criteria	• A subject who meets either bulleted criterion below will be withdrawn from the study: o QTcF > 500 msec o Change from baseline: QTcF > 60 msec

11.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a “blank” in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The pCRF allows for the possibility of partial dates (i.e., only month and/or year) to be recorded for AE start and end dates; that is, the day or the month of the date may be missing. • Any fully or partially missing dates for adverse events will be raised to data management for resolution before DBR.

Element	Reporting Detail
	• If fully or partially missing dates are available following DBF, the following conventions will be applied for calculating the time to onset and the duration of the event: Partially Missing Dates: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the latest study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3 Study Phases and Treatment Emergent Adverse Events. ○ Missing Start Month: January will be used unless this is before the start date of study treatment; in this case the month of the latest study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3 Study Phases and Treatment Emergent Adverse Events. ○ Missing Start Year: Current year will be used unless this is before the start date of study treatment; in this case the year of the latest study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3 Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the latest study treatment stop date will be used. ○ Missing Stop Month: December will be used, unless this is after the stop date of study treatment; in this case the latest month of study treatment stop date will be used. ○ Missing Stop Year: Current year will be used, unless this is after the stop date of study treatment; in this case the latest year of study treatment stop date will be used. Fully Missing Dates: Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Haematocrit	Ratio of 1	Male		0.54
		Δ from BL	↓0.075	
Haemoglobin	g/L	Male		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
White Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L			1.3 x ULN
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2x ULN
AST/SGOT	U/L	High	≥ 2x ULN
AlkPhos	U/L	High	≥ 2x ULN
T Bilirubin	µmol/L	High	≥ 1.5xULN
T. Bilirubin + ALT	µmol/L U/L	High	1.5xULN T. Bilirubin + ≥ 2x ULN ALT

11.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		≤ 450
Absolute PR Interval	msec	< 120	< 220
Absolute QRS Interval	msec		≤ 120
Absolute Ventricular rate	beats/min	<35	>100
Change from Baseline			
Increase from Baseline QTc	msec		> 60

11.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	≥ 90	≤ 140
Diastolic Blood Pressure	mmHg	≥ 40	≤ 90
Heart Rate	bpm	≥ 40	≤ 90
Respiration rate	breaths/min	≥ 8	≤ 20
Oral Temperature	°C	≥ 35.5	≤ 37.8

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range	
		Decrease	Increase
Systolic Blood Pressure	mmHg	≥ 40	≥ 40
Diastolic Blood Pressure	mmHg	≥ 20	≥ 20
Heart Rate	bpm	≥ 30	≥ 30

11.8. Appendix 8: Abbreviations & Trade Marks

11.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
pCRF	Paper Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model

Abbreviation	Description
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

11.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
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SAS
WinNonlin

11.9. Appendix 9: List of Data Displays

11.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.11	N/A
Pharmacokinetic	2.1 to 2.20	2.1 to 2.17
Safety	3.1 to 3.11	N/A
Section	**Listings**	
ICH Listings	1 to 30	
Other Listings	31 to 46	

11.9.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 10: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	N/A	N/A	N/A
Pharmacokinetic	N/A	N/A	N/A
Safety	N/A	N/A	SAFE_L1

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.9.3. Deliverables

Delivery	Description
SAC	Final Statistical Analysis Complete

11.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	Safety	ES1A	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	Safety	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC
1.3.	Safety	ES4	Summary of Participant Disposition at Each Study Epoch	ICH E3	SAC
1.4.	APE	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
Protocol Deviation					
1.5.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
1.6.	Safety	IE2	Summary of Inclusion/Exclusion Criteria Deviations		SAC
Population Analysed					
1.7.	Safety	SP1	Summary of Study Populations	IDSL	SAC
Demographic and Baseline Characteristics					
1.8.	Safety	DM3	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.9.	Safety	DM11	Summary of Age Ranges	EudraCT	SAC
1.10.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
1.11.	Safety	CM1	Summary of Concomitant Medications	ICH E3	SAC

11.9.5. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma					
2.1.	PK	PK01	Summary of Plasma Total Radioactivity Concentrations by Treatment and Time	Include un transformed concentrations	SAC
2.2.	PK	Refer to Programming Notes	Summary of Log Transformed Plasma Total Radioactivity Concentrations by Treatment and Time	Include log transformed concentrations use standard macro for sumstatsinrows for log transformed variable, present similar to example shell PK01 but present geometric mean and SD (Log) rather than mean and SD respectively.	SAC
2.3.	PK	PK03	Summary of Derived Plasma Total Radioactivity PK Parameters by Treatment	Include columns for parameter, period, treatment, N, n, arithmetic mean, 95% CI of arithmetic mean, standard deviation (SD), median, minimum and maximum.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.4.	PK	PK05	Summary of Log-Transformed Derived Plasma Total Radioactivity PK Parameters by Treatment	Include columns for parameter, period, treatment, N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data, median, minimum, maximum and between subject geometric coefficient of variation (CVb (%)). Refer to Section 11.4.3 for parameters that should be log transformed refer to gsk2269557/pii115119/part_a/drivers/t_pk_sum_log (Table 4.3)	SAC
2.5.	PK	PK01	Summary of Plasma [14C]-GSK2269557 Concentrations by Treatment and Time	Include un transformed concentrations	SAC
2.6.	PK	Refer to Programming Notes	Summary of Log Transformed Plasma [14C]-GSK2269557 Concentrations by Treatment and Time	Include log transformed concentrations use standard macro for sumstatsinrows for log transformed variable, present similar to example shell PK01 but present geometric mean and SD (Log) rather than mean and SD respectively.	SAC
2.7.	PK	PK03	Summary of Derived Plasma [14C]-GSK2269557 PK Parameters by Treatment	Include columns for parameter, period, treatment, N, n, arithmetic mean, 95% CI of arithmetic mean, standard deviation (SD), median, minimum and maximum. In addition to standard [14C]-GSK2269557 pk parameters include Clearance (CL(iv) and CLr) and volume (Vdss and Vc).	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.8.	PK	PK05	Summary of Log-Transformed Derived Plasma [14C]-GSK2269557 PK Parameters by Treatment	Include columns for parameter, period, treatment, N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data, median, minimum, maximum and between subject geometric coefficient of variation (CVb (%)). Refer to Section 11.4.3 for parameters that should be log transformed. In addition to standard [14C]-GSK2269557 pk parameters include Clearance (CL(iv) and CLr) and volume (Vdss and Vc). refer to gsk2269557/pii115119/part_a/drivers/t_pk_sum_log (Table 4.3)	SAC
2.9.	PK	PK01	Summary of Plasma GSK2269557 Concentrations by Treatment and Time	Include un transformed concentrations	SAC
2.10.	PK	Refer to Programming Notes	Summary of Log Transformed Plasma GSK2269557 Concentrations by Treatment and Time	Include log transformed concentrations use standard macro for sumstatsinrows for log transformed variable, present similar to example shell PK01 but present geometric mean and SD (Log) rather than mean and SD respectively.	SAC
2.11.	PK	PK03	Summary of Derived Plasma GSK2269557 PK Parameters by Treatment	Include columns for parameter, period, treatment, N, n, arithmetic mean, 95% CI of arithmetic mean, standard deviation (SD), median, minimum and maximum.	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.12.	PK	PK05	Summary of Log-Transformed Derived Plasma GSK2269557 PK Parameters by Treatment	Include columns for parameter, period, treatment, N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data, median, minimum, maximum and between subject geometric coefficient of variation (CVb (%)). Refer to Section 11.4.3 for parameters that should be log transformed refer to gsk2269557/pii115119/part_a/drivers/t_pk_sum_log (Table 4.3)	SAC
2.13.	PK	PK06	Summary of Oral and Inhaled Absolute Bioavailability	Refer to Section 11.4.3 for parameters that should be log transformed. Include PK Parameters: Inhaled F (0-∞), Inhaled F (0-t), Oral F (0-∞) and Oral F (0-t), Dose(Inhaled), Dose(iv) and Dose(Oral). Note: Dose(iv) and Dose(Oral) is radiometric dose, Dose(Inhaled) is nominal	SAC
2.14.	PK	PK06	Summary of Metabolic, Hepatic Extraction and Absorption Parameters	Refer to Section 11.4.3 for parameters that should be log transformed. Include PK Parameters: ML(iv), ML(po), F_g, E_H and F_{abs}	SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.15.	PK	[Non-Standard] Refer to Programming notes	Summary of Parent GSK2269557/Total Radioactivity Ratio for Cmax, AUC(0-24), AUC(0-∞) and AUC(0-t)	Include columns for: period, parent GSK2269557/total radioactivity ratio (GSK2269557/total radioactivity or 14C-GSK2269557/ total radioactivity), parameter (Cmax, AUC(0-24), AUC(0-∞) or AUC(0-t)), geometric mean for ratio, SD(log), 95% CI, median, minimum, maximum and between subject geometric coefficient of variation (CVb (%)).	SAC
2.16.	PK	[Non-Standard] Refer to Programming notes	Summary of Statistical Analyses for Parent GSK2269557/Total Radioactivity Ratio for Cmax, AUC(0-24), AUC(0-∞) and AUC(0-t)	Include columns for: period, parent GSK2269557/total radioactivity ratio (GSK2269557/total radioactivity or 14C-GSK2269557/ total radioactivity), parameter (Cmax, AUC(0-24), AUC(0-∞) or AUC(0-t)), estimate for ratio, SD(log) and 95% CI	SAC
Urine/Faeces					
2.17.	PK	PK02	Summary of Urinary and Faecal –Total Radioactivity Pharmacokinetic Parameters (Amount Excreted) by Treatment and Time	Include Ae(urine), Ae(faeces) and Ae(total).	SAC
2.18.	PK	PK02	Summary of Urinary and Faecal –Total Radioactivity Pharmacokinetic Parameters (Cumulative Amount Excreted) by Treatment and Time	Include cumulative Ae(urine), Cumulative Ae(faeces) and Cumulative Ae(total).	SAC
2.19.	PK	PK02	Summary of Urinary and Faecal –Total Radioactivity Pharmacokinetic Parameters (% of Dose Excreted) by Treatment and Time	Include Fe%(urine), Fe%(faeces) and Fe%(total).	SAC
2.20.	PK	PK02	Summary of Urinary and Faecal –Total Radioactivity Pharmacokinetic Parameters (Cumulative % of Dose Excreted) by Treatment and Time	Include cumulative Fe%(urine), Cumulative Fe%(faeces) and Cumulative Fe%(total).	SAC

11.9.6. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma					
2.1.	PK	PK16a	Individual Subject Plasma Total Radioactivity-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. N (likely 6) lines for each treatment with legend to identify subjects Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/mid201003/final/f_pk_21 (Table 2.1)	SAC
2.2.	PK	PK19	Arithmetic Mean (+SD) Plasma Total Radioactivity-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/ mid201003/ final/ f_pk_22 (Table 2.2)	SAC
2.3.	PK	PK20	Median (Range) Plasma Total Radioactivity-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/ mid201003/ final/ f_pk_23 (Table 2.3)	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.4.	PK	PK16a	Individual Subject Plasma [14C]-GSK2269557 Concentration-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. N (likely 6) lines for each treatment with legend to identify subjects Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/mid201003/final/f_pk_21	SAC
2.5.	PK	PK19	Arithmetic Mean (+SD) Plasma [14C]-GSK2269557 Concentration-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/ mid201003/ final/ f_pk_22	SAC
2.6.	PK	PK20	Median (Range) Plasma [14C]-GSK2269557 Concentration-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/ mid201003/ final/ f_pk_23	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.7.	PK	PK16a	Individual Subject Plasma GSK2269557 Concentration-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. N (likely 6) lines for each treatment with legend to identify subjects Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/mid201003/final/f_pk_21	SAC
2.8.	PK	PK19	Arithmetic Mean (+SD) Plasma GSK2269557 Concentration-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/ mid201003/ final/ f_pk_22	SAC
2.9.	PK	PK20	Median (Range) Plasma GSK2269557 Concentration-time Plot (Linear and Semi-log) by Treatment	Linear and log plot on same page. Separate page per treatment. Time = Planned time post dose (h) Include the LLOQ as a reference line and footnote refer to GSK961081/ mid201003/ final/ f_pk_23	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Urine and Faeces					
2.10.	PK	PK_F4	Individual Subject Absolute –Total Radioactivity Recovered (Amount Excreted) for Urine, Faeces and Total Excretion by Time and Treatment	Ae(urine), Ae(faeces), Ae(total). Linear scale only. Separate page per subject and treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_210	SAC
2.11.	PK	PK_F5	Arithmetic Mean Absolute –Total Radioactivity Recovered (Amount Excreted) for Urine, Faeces and Total Excretion by Time and Treatment	Ae(urine), Ae(faeces), Ae(total). Linear scale only. Separate page per Treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_212	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.12.	PK	PK_F4	Individual Subject Cumulative –Total Radioactivity Recovered (Cumulative Amount Excreted) for Urine, Faeces and Total Excretion by Time and Treatment	Cumulative Ae(urine), Cumulative Ae(faeces), Cumulative Ae(total). Linear scale only. Separate page per subject and treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_210	SAC
2.13.	PK	PK_F5	Arithmetic Mean Cumulative –Total Radioactivity Recovered (Cumulative Amount Excreted) for Urine, Faeces and Total Excretion by Time and Treatment	Cumulative Ae(urine), Cumulative Ae(faeces), Cumulative Ae(total). Linear scale only. Separate page per Treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_212	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.14.	PK	PK_F4	Individual Subject Absolute –Total Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion by Time and Treatment	Fe%(urine), Fe%(faeces), Fe%(total). Linear scale only. Separate page per subject and treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_210	SAC
2.15.	PK	PK_F5	Arithmetic Mean Absolute –Total Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion by Time and Treatment	Fe%(urine), Fe%(faeces), Fe%(total). Linear scale only. Separate page per Treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_212	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
2.16.	PK	PK_F4	Individual Subject Cumulative –Total Radioactivity Recovered (Cumulative % of Dose) for Urine, Faeces and Total Excretion by Time and Treatment	Cumulative Fe%(urine), Cumulative Fe%(faeces), Cumulative Fe%(total). Linear scale only. Separate page per subject and treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_210	SAC
2.17.	PK	PK_F5	Arithmetic Mean Cumulative –Total Radioactivity Recovered (Cumulative % of Dose) for Urine, Faeces and Total Excretion by Time and Treatment	Cumulative Fe%(urine), Cumulative Fe%(faeces), Cumulative Fe%(total). Linear scale only. Separate page per Treatment. 3 lines per plot with legend to identify Urine Faeces and Total Excretion Time = actual mid-point of collection post dose (h). refer to GSK961081/ mid201003/ final/ f_pk_212	SAC

11.9.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Adverse Events (AEs)					
3.1.	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC
3.2.	Safety	AE1CP	Summary All Drug-Related Adverse Events	ICH E3	SAC
Serious and Other Significant Adverse Events					
3.3.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
3.4.	Safety	AE1CP	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	IDSL	SAC
Laboratory: Chemistry					
3.5.	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC
Laboratory: Hematology					
3.6.	Safety	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC
Laboratory: Urinalysis					
3.7.	Safety	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
3.8.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
ECG					
3.9.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.10.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
Vital Signs					
3.11.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC

11.9.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.	APE	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	APE	ES9	Listing of Subjects Who Were Rescreened		SAC
3.	Safety	ES3	Listing of Reasons for Study Withdrawal	ICH E3	SAC
4.	Safety	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3.	SAC
5.	Safety	CP_TA2	Listing of Planned and Actual Treatments	IDSL non randomised study so do not say "randomised" use "Planned" instead	SAC
Protocol Deviations					
6.	Safety	DV2A	Listing of Important Protocol Deviations	ICH E3	SAC
7.	Safety	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
8.	APE	SP3a	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
9.	Safety	DM4	Listing of Demographic Characteristics	ICH E3	SAC
10.	Safety	DM10	Listing of Race	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Prior and Concomitant Medications					
11.	Safety	CP_CM4	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
12.	Safety	EX4	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
13.	Safety	AE9CP	Listing of All Adverse Events	ICH E3	SAC
14.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC
15.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
16.	Safety	AE9CPa	Listing of Serious Adverse Events	ICH E3 Include fatal and non fatal	SAC
17.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC
18.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3 Include fatal and non fatal	SAC
Hepatobiliary (Liver)					
19.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
20.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
All Laboratory					
21.	Safety	LB6	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
22.	Safety	LB6	Listing of Laboratory Values of Potential Clinical Importance		SAC
23.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC
24.	Safety	UR2B	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC
ECG					
25.	Safety	CP_EG4	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
26.	Safety	CP_EG4	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
27.	Safety	CP_EG6	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
28.	Safety	CP_EG6	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
29.	Safety	VS5	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
30.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

11.9.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Plasma PK					
31.	PK	PK08	Listing of Plasma Total Radioactivity-Time Data		SAC
32.	PK	PK14	Listing of Derived Plasma Total Radioactivity Pharmacokinetic Parameters		SAC
33.	PK	PK08	Listing of Plasma [14C]-GSK2269557 Concentration-Time Data		SAC
34.	PK	PK14	Listing of Derived Plasma [14C]-GSK2269557 Pharmacokinetic Parameters	In addition to standard [14C]-GSK2269557 pk parameters include Clearance (CL(iv) and CLr) and volume (Vdss and Vc).	SAC
35.	PK	PK08	Listing of Plasma GSK2269557 Concentration-Time Data		SAC
36.	PK	PK14	Listing of Derived Plasma GSK2269557 Pharmacokinetic Parameters		SAC
37.	PK	PK14	Listing of Oral and Inhaled Absolute Bioavailability	Include PK Parameters: Inhaled F (0-∞), Inhaled F (0-t), Oral F (0-∞) and Oral F (0-t), Dose(Inhaled), Dose(iv) and Dose(Oral). Note: Dose(iv) and Dose(Oral) is radiometric dose, Dose(Inhaled) is nominal	SAC
38.	PK	PK14	Listing of Metabolic, Hepatic Extraction and Absorption Parameters	Include PK Parameters: ML(iv), ML(po), F_g, E_H and F_{abs}	SAC
39.	PK	PK15	Listing of Individual Subject Parent GSK2269557/Total Radioactivity Ratio for Cmax, AUC(0-∞), AUC(0-24) and AUC(0-t)		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Urine and Faeces PK					
40.	PK	[Non-Standard] Refer to programming notes	Listing of Urinary and Faecal Total Radioactivity Parameters (Amount Excreted) by Time	Ae(urine), Ae(faeces), Ae(total) and cumulative Ae(urine), cumulative Ae(faeces), cumulative Ae(total) refer to GSK961081/ mid201003/ final/ l_pk_ae (listing 35)	SAC
41.	PK	[Non-Standard] Refer to programming notes	Listing of Urinary and Faecal Total Radioactivity Parameters (% Excreted) by Time	Fe%(urine), Fe%(faeces), Fe%(total) and cumulative Fe%(urine), cumulative Fe%(faeces), cumulative Fe%(total) refer to GSK961081/ mid201003/ final/ l_pk_fe (listing 36)	SAC
Liver Monitoring					
42.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC
43.	Safety	LIVER7	Listing of Liver Biopsy Details		SAC
44.	Safety	LIVER8	Listing of Liver Imaging Details		SAC
45.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC
Entero-Test					
46.	Safety	[Non-Standard] SAFE_L1	Listing of Entero-Test Administration and Removal		SAC

11.10. Appendix 10: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request