Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for an open-label study in healthy male participants to determine the mass balance, absolute bioavailability and pharmacokinetics of daprodustat, administered as a single intravenous microtracer (concomitant with an oral dose of non-radiolabelled daprodustat) and a single, oral radiolabelled dose**.**
Compound Number	:	GSK1278863 (daprodustat)
Effective Date	:	30-JAN-2018

Description:

- The purpose of this Reporting and Analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol 200232
  - This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

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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:		
Document Number	**Date**	**Reason for revision**
2017N310967_00	30-MAY--2017	Original
2017N310967_01	1-SEP-2017	"Promptly" has been changed to "within 24 hours following knowledge of the SAE."

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were slight deviations to the "Analysis population" and PK collection Time point in Period 2 which is outlined in Table 1. However, no changes to originally planned statistical analysis specified in the protocol amendment 1 [(Dated: 01/SEP/2017)].

Table 1 Changes to Protocol Defined Analysis Plan

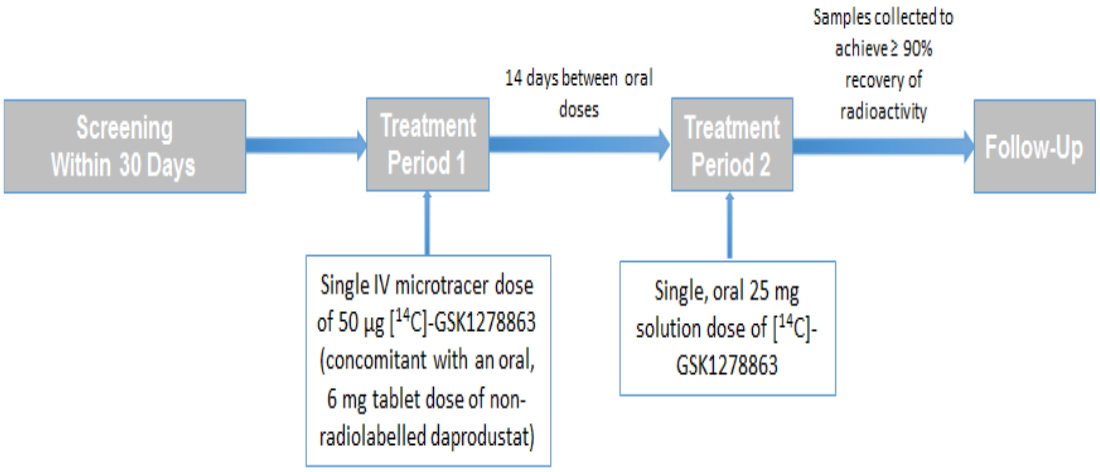
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
• **All Subjects:** All participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.	• **Safety:** All participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.	• To be consistent with current standards for naming population
• Not Defined	• Enrolled: All participants who passed screening and entered the study. Included are: Run-in Failures; And participants who were assigned a treatment in a non-randomised study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• This population Required for data disclosure displays.
• **Pharmacokinetic:** All participants in the 'Safety' population for whom sufficient data are available to calculate the derived pharmacokinetic parameters on an as-treated basis.	• **Pharmacokinetic:** All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• Definition mentioned in the Protocol is ambiguous from a programming perspective hence standard definition is used after confirming with Study Team.
Blood sample is collected in time point mentioned in Table 1	• Blood sample is collected in two additional time points following infusion termination than mentioned in Table 4 (i.e. 2.25 and 2.5hr) to capture the immediate decline of drug	• To capture the immediate decline of drug blood sample is collected in two extra time points.

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

Objectives	Endpoints[1]
Primary Objectives	**Primary Endpoints**
• To determine total radioactivity (drug related material) in blood and plasma following a single IV microtracer dose of [^{14}C] -GSK1278863[1] (concomitant with an oral dose of non-radiolabelled daprodustat[1]) and a single, oral dose of [^{14}C]-GSK1278863.	• AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of total drug-related material (radioactivity) in blood and plasma. • Volume (Vss) and clearance (CL) of total drug-related material (radioactivity) after IV dose only (Treatment Period 1).
• To determine the rate and extent of excretion of total radioactivity in urine and faeces and the total recovery of radioactivity following a single, oral dose of [^{14}C]-GSK1278863.	• Urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time (Treatment Period 2 only).
Secondary Objectives	**Secondary Endpoints**
• To determine parent daprodustat and metabolite concentrations in plasma following a single IV microtracer dose of [^{14}C]-GSK1278863 and both oral doses of daprodustat.	• AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of daprodustat parent and metabolite in plasma from the IV dose and both oral doses. • Volume (Vss) and clearance (CL) of daprodustat parent and metabolite (if possible) after IV dose only (Treatment Period 1).
• To estimate the absolute bioavailability of daprodustat following oral administration.	• F (absolute bioavailability) after oral dosing.
• To generate samples that will be used to characterise the metabolite profile of daprodustat following a single IV microtracer dose of [^{14}C]-GSK1278863 concomitant with an oral dose of non-radiolabelled daprodustat (plasma and duodenal bile) and a single, oral dose of [^{14}C]-GSK1278863 (plasma, urine and faeces).	• Characterisation and quantification of metabolites in plasma, urine, faeces, and duodenal bile (*These analytical investigations will be conducted and the results reported under a separate GSK protocol).*
• To evaluate the safety and tolerability of daprodustat after single IV and oral doses in healthy participants.	• Incidence and severity of adverse events. • Laboratory safety, 12-lead ECG, and vital sign parameters.

[1] For measured concentrations of daprodustat in blood and plasma, the nomenclature [^{14}C]-GSK1278863 describes the parent daprodustat concentration derived via analysis by liquid chromatography (LC) + Accelerator Mass Spectrometry(AMS), whereas daprodustat describes the parent daprodustat concentration derived via liquid chromatography tandem mass spectrometry (LC/MS).

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• This is an open-label, single-centre, non-randomised, 2-period, single-sequence, crossover, mass balance study in 6 healthy male participants. • Each participant will be involved in the study for up to 10 weeks. He will have a screening visit, two treatment periods (Treatment Periods 1 and 2), separated by 14 days, and a follow up visit 1-2 weeks after the last assessment in Treatment Period 2. During both treatment periods, participants will reside in the unit from the afternoon before Day 1 (Day -1) until all procedures are completed on Day 7. Participants may be asked to stay for up to 1 week longer in Treatment Period 2, if excretion of drug-related material takes longer than anticipated. • **Screening Period** Participants must be screened within 30 days before the first dose of daprodustat, and must meet all eligibility criteria. • **Treatment Period 1 (oral tablet and intravenous infusion)** On Day 1 of Treatment Period 1, after an overnight fast of at least 8 h, each participant will take a single 6 mg oral dose of daprodustat. After approximately 1 h, participants will receive 50 µg of [^{14}C]-GSK1278863 by IV infusion over 1 h. Blood samples will be collected for 144 h after oral dosing (until Day 7), while duodenal bile will be collected by Entero-Test. • **Treatment Period 2 (oral solution)** On Day 1 of Treatment Period 2, after an overnight fast of at least 8 h, each participant will receive 25 mg [^{14}C]-GSK1278863 as an oral solution; participants will continue to fast for 4 h after dosing. Blood, urine and faecal samples will be collected for a minimum of 144 h (up to Day 7) after dosing, depending on the amount of radioactivity excreted by each participant.

Overview of Study Design and Key Features	
	Based on the radio quantification results on Days 6 and 7 a decision will be taken regarding continuation in Treatment Period 2, i.e. ○ If ≥ 90% of the administered radioactivity has been recovered and excretion rate is <1% then Participants may be discharged on day7 itself. ○ If excretion rate is >1% or if the results are inconclusive, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals for up to 7 additional days. ○ Once less than 1% of the dose is excreted in 2 consecutive 24-h periods where samples are provided, or ≥ 90% of the radioactivity has been recovered, the participant will be discharged. All remaining participants will be discharged from the unit no later than Day 15. • **Follow-up** Follow-up procedures will be done 7-14 days after the participant's last assessment in Treatment Period 2.
Dosing	• The investigational drug is GSK1278863 (daprodustat). In Treatment Period1, each participant will receive 50 µg of radiolabelled GSK1278863 ([^{14}C]-GSK1278863) microtracer by IV infusion, concomitant with a 6 mg oral dose of daprodustat. • In Treatment Period 2, A single 25 mg dose of [^{14}C]-GSK1278863 will be administered as an oral solution.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• This is an open-label study and all 6 participants will be assigned to the same treatment regimen in a non-randomised manner. All participants will receive IV infusion [concomitant with an oral non-radiolabelled dose] at Treatment Period 1 followed by oral solution dose at Treatment Period 2.
Interim Analysis	• No interim analysis will be performed in this study.

2.4. Statistical Hypotheses / Statistical Analyses

- This is an investigative study to determine the excretion mass balance of daprodustat (GSK1278863) using [^{14}C]-radiolabelled drug substance, administered in Treatment Period 1 as a single intravenous microtracer dose (concomitant with a single oral non-radiolabelled dose) and a single oral solution radiolabelled dose in Treatment Period 2.

- Due to its descriptive nature, there will be no formal statistical hypothesis tested; an estimation approach will be adopted to assess the study objectives.

3. PLANNED ANALYSES

3.1. Interim Analyses

- No Interim Analysis is planned for this study.

3.2. Final Analyses

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

1. All participants 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.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants who sign the ICF. This will be the population for reporting screened population data.	• Study Population
Enrolled	• Enrolled: All participants who passed screening and entered the study. Included are: Run-in Failures; And participants who were assigned a treatment in a non-randomised study. • Note screening failures (who never passed screening even if rescreened) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population as they did not enter the study.	• Study Population
Safety	• All participants who take at least 1 dose of study treatment. • Participants will be analysed according to the treatment they actually received.	• Safety and Study population
Pharmacokinetic (PK)	• All participants in the Safety population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK

Refer to Appendix 9: List of Data Displays which details the population used for each display.
Note: Reason for Deviation in "Analysis Population" from Protocol to RAP is mentioned in the Table 1

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 [6OCT2017and versionV1].

Data will be reviewed prior to DBR 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 listing of all inclusion/exclusion criteria deviations will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions				
Treatment Description		**Data Displays for Reporting**		
Code	**Description**	**Description (Safety)**	**Description (PK Analysis)**	**Order [1]**
A	GSK1278863 6mg Oral + [14C]-GSK1278863 50 mcg IV	A	A1 A2	1 2
B	[14C]-GSK1278863 25 mg Oral Solution	B	B	3

NOTES:

1. Order represents treatments being presented in TFL, as appropriate.

Study population displays will be summarized by total column.

Please add footnote in all the displays as follows for the treatment group

- **Note: For Safety Displays**

  A: GSK1278863 6mg Oral + [14C]-GSK1278863 50 mcg IV

  B: [14C]-GSK1278863 25 mg Oral Solution

- **Note: For PK displays:**

  A1: GSK1278863 6mg Oral

  A2: [14C]-GSK1278863 50 mcg IV

  B: [14C]-GSK1278863 25 mg Oral Solution

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 in the associated treatment period. If time is not collected, Day 1 assessments are assumed to be taken prior to first dose and used as baseline.

Parameter	**Study Assessments Considered as Baseline**			**Baseline Used in Data Display**
	Screening	Day -1	Day 1 (Pre-Dose)	
Safety				
Vital Signs	X		X [1]	Day 1 (mean pre-dose) [2]
Laboratory (Haematology+ Clinical chemistry)	X	X		Day -1

NOTES:

[1] Taken in triplicate

[2] Mean of the triplicate pre-dose assessments.

Unless otherwise stated, if baseline data is missing no derivation will be performed and baseline will be set to missing.

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
10.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
10.4	Appendix 4: Data Display Standards & Handling Conventions
10.5	Appendix 5: Derived and Transformed Data
10.6	Appendix 6: Reporting Standards for Missing Data
10.7	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 Screened/Enrolled/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 summaries 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. 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.

7.3. 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

8.1. Primary and Secondary Pharmacokinetic Analyses

8.1.1. Endpoint / Variables

Primary Endpoint:

- AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of radioactivity in blood and plasma.
- Volume (Vss) and clearance (CL) of radioactivity after IV dose only (Treatment Period 1).
- Urinary and faecal cumulative excretion as a percentage of the total radioactive dose administered over time (Treatment Period 2 only).

Secondary Endpoint:

- AUC(0–inf), AUC(0–t), Cmax, tmax and t1/2 of daprodustat parent and metabolite in plasma from the IV dose and both oral doses.
- Volume (Vss) and clearance (CL) of daprodustat parent and metabolite (if possible) after IV dose only (Treatment Period 1).
- F (absolute bioavailability) after oral dosing of the 6 mg tablet dose.

8.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions(Section 10.4.3 Reporting Standards for Pharmacokinetic)

Plasma daprodustat, [^{14}C]-GSK1278863, blood and plasma total radioactivity, metabolite (GSK2391220, GSK2506104, GSK2487818, GSK2506102, GSK2531398, GSK2531401) and [^{14}C]-metabolite concentration-time data will be listed for each participant and standard summary statistics will be calculated (i.e. arithmetic mean, standard deviation, median, minimum and maximum) by treatment and planned sampling time.

Individual participant, mean and median plasma daprodustat, [14C]-GSK1278863, blood and plasma total radioactivity metabolite and [14C]-metabolite concentration-time profiles will be plotted for each treatment on both a linear and semi-log scale.

8.1.1.2. Derived Pharmacokinetic Parameters

8.1.1.2.1. Deriving Blood and Plasma Pharmacokinetic Parameters

- PK parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin Version 6.3 or above. All calculations of non-compartmental parameters will be based on actual sampling times. PK parameters listed will be determined from the

plasma daprodustat, [^{14}C]-GSK1278863, blood and plasma total radioactivity, metabolite and [^{14}C]-metabolite concentration-time data, as data permits.

Table 2 Derived Pharmacokinetic Blood and Plasma 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.
λ_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
AUC (0-inf)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / λ_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 / λ_z**
Vss	Volume of distribution of at steady-state will be calculated as: $CL*MRT_{iv}$ where the mean residence time (MRT) is calculated as AUMC(0-inf) (area under the first moment curve)/AUC(0-inf). **Treatment period 1**, analyte [^{14}C]- GSK1278863 only.
CL	Total clearance will be calculated as: **Dose(iv)/AUC(0-inf)** **Treatment period 1**, analyte [^{14}C]- GSK1278863 only.
Oral F	Absolute bioavailability from the oral tablet and IV doses administered in Period1 for AUC(0-inf) and AUC(0-t) PK parameter calculated as: $F = \frac{\frac{\text{GSK1278863 AUC}_{(\text{oral})}}{\text{Dose}_{(\text{oral})}}}{\frac{\text{GSK1278863 AUC}_{(\text{IV})}}{\text{Dose}_{(\text{IV})}}}$ Oral and IV Dose will be converted into ng using below conversion values. 1mg=1000000ng 1mcg=1000ng
[^{14}C]-GSK1278863/Total radioactivity ratio for Cmax, AUC(0-	Cmax Ratio = [14C] GSK961081 [Cmax] /Total radioactivity [Cmax] AUC(0-inf) Ratio = [14C] GSK961081 [AUC[0-inf] /Total radioactivity [AUC(0-inf)] AUC(0-t) Ratio = [14C] GSK961081 [AUC[0-t] /Total radioactivity [AUC(0-t)]

Parameter	Parameter Description
inf), AUC(0-t)	

NOTES:
Additional parameters may be included as required.

8.1.1.2.2. Derived Urine and Faecal Pharmacokinetic Parameters

- Derivation of the urine and faecal radioactivity parameters will be the responsibility, or under the direct auspices, of the BIB(Bioanalysis, Immunogenicity and Biomarkers) department within GSK.

- The following parameters will be determined from the urine and faecal radiolabelled drug-related material (total radioactivity) data, and will be listed by subject for each collection interval both in absolute terms and also cumulatively. Cumulative urinary, faecal and total excretion (amount excreted and % of total dose excreted over the study) will be summarised (N, n, arithmetic mean, SD, median, minimum, maximum) for each collection interval.

Table 3 Derived Pharmacokinetic Urine and Faecal Parameters

Parameter	Parameter Description
Ae[urine]	Total radioactivity recovered in the urine (Ae[urine]) calculated for each collection interval as: **(concentration in urine sample x collected sample weight)** for each urine collection interval. In converting urine sample weight to volume, we assume 1g=1mL.
Ae[faeces]	Total radioactivity recovered in the faeces (Ae[faeces]) calculated for each collection interval as: **(concentration in faecal homogenate aliquot analysed x weight of homogenate aliquot analysed) x (total homogenate weight / collected sample weight)** for each faecal collection interval.
Ae[total]	Total radioactivity excretion will be estimated in each collection interval as: **Sum of Ae[urine] and Ae[faeces]**
Fe%[urine]	% of total dose excreted as total radioactivity for each collection interval will be estimated as: **(Ae[urine]) for each collection interval)/Radiolabelled Dose*100** Where radiolabelled dose is either dose(iv) or dose(oral) and excludes the inhaled element of the dose.
Fe%[faeces]	% of total dose excreted as total radioactivity for each collection interval will be estimated as: **(Ae[faeces] for each collection interval)/ Radiolabelled Dose*100** Where radiolabelled dose is either dose(iv) or dose(oral) and excludes the inhaled element of the dose.
Fe%[total]	% of total dose excreted as radioactivity will be estimated in each collection interval as: **Sum of Fe%[urine] and Fe%[faeces]**

When summarising urine and faecal parameters, 'NS' (i.e., no sample provided as subject not voided at particular collection period) or 'NQ' values for these parameters will be imputed with zero.

8.1.2. Summary Measure

- Derived PK parameter estimates (AUC(0-inf), AUC(0-t), Cmax, tmax, t1/2) of plasma daprodustat, plasma metabolite and total radioactivity in blood and plasma for IV and oral along with volume and clearance (Treatment Period 1 after IV dose only) will be summarised/listed.
- Urinary and faecal cumulative excretion as a percentage of the total radioactive dose over time will be summarised and listed (Treatment Period 2 only).

- Absolute bioavailability after oral and IV dosing (Treatment Period 1) will be analysed by using AUC(0-t), AUC (0-∞) parameters.

8.1.3. Population of Interest

The PK analyses will be based on the PK population, unless otherwise specified.

8.1.4. 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 8.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8.1.4.1. Statistical Methodology Specification

Pharmacokinetic Statistical Analyses (Absolute Bioavailability assessment in Treatment Period1)
Secondary Endpoint / Variables
• AUC(0-t), AUC (0-∞) PK parameters of Plasma GSK1278863 from IV and oral dose will be analyzed after $\log_e$ transformation (PK parameters should be divided by corresponding dose)
Model Specification
• Will be statistically analyzed using a mixed model (MM) for Period1. • Terms fitted in the mixed effect ANOVA model will include: o Fixed effect : Treatment (IV dose/Oral dose in Period1) o Random Effect : Subject • 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. • Point estimates for the adjusted means on the loge scale, the mean difference between treatments and associated 90% confidence interval for the contrast (test-reference)

will be constructed using the residual variance.

Model Checking & Diagnostics
• Dose normalized PK parameters should be used for the analysis. • For the Mixed Model analysis, Model assumptions will be applied, but appropriate adjustments may be made based on the data. • Distributional 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 transformations, such as data squared, or square root of data, will be explored.
Model Results Presentation
• The point estimate and confidence interval obtained from MM analysis will be exponentially back-transformed to obtain Adjusted (least square) geometric means for each treatment. • Point estimates (Absolute Bioavailability of GSK1278863) and associated 90% confidence interval for the ratio Oral dose/IV dose along with within-subject variability (%CVw) will be reported. Where %CVw=100*(SQRT (EXP(σ_w^2)-1)) and σ_w^2 is the mean squares error (MSE) from the statistical Mixed model.

9. REFERENCES

GlaxoSmithKline Document Number 2017N310967_00. An open-label study in healthy male participants to determine the mass balance, absolute bioavailability and pharmacokinetics of daprodustat, administered as a single intravenous microtracer (concomitant with an oral dose of non-radiolabelled daprodustat) and a single, oral radiolabelled dose 30-MAY-2017.

GlaxoSmithKline Document Number 2017N310967_01. An open-label study in healthy male participants to determine the mass balance, absolute bioavailability and pharmacokinetics of daprodustat, administered as a single intravenous microtracer (concomitant with an oral dose of non-radiolabelled daprodustat) and a single, oral radiolabelled dose; 01-SEP-2017.

GUI_137354: Information for Authors – Reporting and Analysis Plan, Global; GSK.

SOP_54838: Development, Review & Approval of Reporting & Analysis Plan, Global; GSK.

10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management

A Per Protocol Population is not being defined for this study.
Please Refer to Section 4.1 for handling and Reporting of Protocol Deviations.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

The Schedule of Activities for Treatment Period 1 and Treatment Period 2 is presented in Table 4 and Table 5, respectively.

Table 4 Treatment Period 1 (oral tablet and intravenous infusion)

Visit	Screening[1]		Treatment Period 1																			
Day	-30 to -1	-1	1													2		3	4	5	6	7
Procedure		*hour*	*Pre-dose*	*0*	*0.5*	*1*	*1.25*	*1.5*	*2*	*3*	*4*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*
Informed consent	X																					
Medical history (including drug/alcohol use)	X																					
Demography	X																					
Admission to unit		X																				
Discharge from unit[2]																						X
Full physical exam, including height, weight and BMI	X																					
Brief physical exam		X																				X
Drugs of abuse screen	X	X																				
Alcohol and cotinine tests, CO breath tests	X	X																				
HIV and hepatitis B and C screen	X																					
Laboratory safety tests (including LFTs)	X	X																				X
12-lead ECG[3]	X																					X

Visit	Screening[1]		Treatment Period 1																				
Day	-30 to -1	-1	1													2		3	4	5	6	7	
Procedure		*hour*	*Pre-dose*	*0*	*0.5*	*1*	*1.25*	*1.5*	*2*	*3*	*4*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*	
Vital signs[3,4]	X		X							X													X
[^{14}C]-GSK1278863 IV infusion						←			→														
Oral daprodustat[5]				X																			
Blood samples for drug assay and radioactivity[8]	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine collection[6]			X																				
Faecal collection[7]			X																				
Entero-Test (duodenal bile)[8]			←							→													
Meals[8,9]								X			X			X									
AE/SAE/concomitant medication review[10]	←																						→

Abbreviations: AE: adverse event; ECG: electrocardiogram; HIV: human immunodeficiency virus; IV: intravenous; LFTs: liver function tests; SAE: serious adverse event.

Notes:

[1] Screening will be within 30 days before Day 1.

[2] Participants will be discharged for a washout period prior to dosing in Treatment Period 2; there will be at least 14 days between a participant's oral doses. Participants who withdraw from the study early should be subject to those assessments that would be required at discharge in that treatment period, if participants agree to that.

[3] Single ECG measurements will be taken at at all time points. If any measurement is considered abnormal, triplicate measurements will be taken and the mean of the triplicate measurements used. The pre-dose measurement on Day 1 will be used as baseline.

[4] Triplicate measurements of systolic and diastolic blood pressure; single measurements of oral temperature and respiratory rate.

[5] Participants will fast for at least 8 h before oral dosing.

[6] Samples will be taken for background radiation at screening, Day –1 and pre-dose only, while total radioactivity, [^{14}C]-GSK1278863 analysis, cold daprodustat analysis, and metabolite profiling will include predose and all post-dosing samples. Sampling times are relative to the oral dose on Day 1, unless otherwise indicated. Additional blood samples will be collected at 2.25 and 2.5 hr following infusion termination to capture the immediate decline of drug.

[7] Urine and faeces will be collected at pre-dose (up to 3 h pre-dose for the urine sample; up to 48 h pre-dose for the faecal sample).

[8] The Entero-Test will be swallowed about 3.5 h before the oral dose, while participants are in a fasted state. It will be removed 3 h after the oral dose (about 1 h after the end of the IV infusion). At about 0.5 h after the start of IV infusion (i.e., 1.5 h before string withdrawal) a food cue will be used to stimulate gall bladder emptying.

[9] Meal times are specified for Day 1 only. On all other days, meals will be served at the unit's standard times.

[10] AEs and SAEs will be collected from the start of oral dosing until the final follow-up visit. However, any SAEs assessed as related to study participation (e.g., study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consent to participate in the study.

Table 5 Treatment Period 2 (oral solution)

Visit	Treatment Period 2																					FU[1]
Day	-1	1												2		3	4	5	6	7[2]	8–15[2,3]	
Procedure	*hour*	*Pre-dose*	*0*	*0.5*	*1*	*1.5*	*2*	*3*	*4*	*6*	*8*	*10*	*12*	*24*	*36*	*48*	*72*	*96*	*120*	*144*		
Admission to unit	X																					
Discharge from unit[4]																				X	X	
Brief physical exam	X																			X	X	X
Drugs of abuse screen	X																					
Alcohol and cotinine tests, CO breath tests	X																					
Laboratory safety tests (including LFTs)	X																			X	X	X
12-lead ECG[5]		X																			X	X
Vital signs[5,6]		X						X												X	X	X
[^{14}C]-GSK1278863 oral solution[7]			X																			
Blood samples for drug assay and radioactivity[8]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urine collection[9]		X	←																		→	
Faecal collection[9]		X	←																		→	
Meals[10]									X			X										
AE/SAE/concomitant medication review[11]	←																				→	

Abbreviations: AE: adverse event; ECG: electrocardiogram; FU: follow-up; HIV: human immunodeficiency virus; LFTs: liver function tests; SAE: serious adverse event.

Notes:
[1] Follow-up will be 7–14 days after the participant's last assessment.

[2] Urine and faecal samples will be collected for a minimum of 144 h (up to Day 7) 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 on Day 6 (96–120 h) and Day 7 (120–144 h). If less than 1% of the dose is excreted in each of those 24-h periods for a given participant, he may be discharged on Day 8 (after the LSC results from Days 6 and 7 are available), and no further samples will be collected. If excretion is higher than 1% in the 96–144 h (Day 6–7) collection period, or if the results are inconclusive, the participant will remain at the unit, and urine and faecal collections will continue at 24-h intervals, for up to 7 additional days (until the morning of Day 14). Once less than 1% of the dose is excreted in a 24-h period, or ≥ 90% of the radioactivity has been recovered, that participant will be discharged. Any remaining participants will be discharged from the unit on Day 15. In the unlikely event that excretion is still higher than 1% in the 24-h collection period prior to discharge on Day 15, the participant will continue to collect faecal samples only, at home, at 24-h intervals. Samples will be returned to the unit every 2 to 3 days for analysis.

[3] Brief physical exam, laboratory safety tests, 12-lead ECG and vital signs to be done only on the day of discharge. Blood samples for drug assay and radioactivity to be taken each morning (at the time of dosing on Day 1) until Day 7.

[4] Participants withdrawing from the study early should be subject to those assessments that would be required at discharge.

[5] Single ECG measurements will be taken at all time points. If any measurement is considered abnormal, triplicate measurements will be taken and the mean of the triplicate measurements used. The pre-dose measurement on Day 1 will be used as baseline.

[6] Triplicate measurements of systolic and diastolic blood pressure; single measurements of oral temperature and respiratory rate.

[7] Participants will fast for at least 8 h before oral dosing.

[8] Samples will be taken for background radiation pre-dose only, while total radioactivity, [^{14}C]-GSK1278863 analysis, cold GSK1278863 analysis, and metabolite profiling will include predose and all post-dosing samples.

[9] Urine and faeces will be collected at pre-dose (up to 3 h pre-dose for the urine sample; up to 48 h pre-dose for the faecal sample), then over 24 h collection periods as follows: 0–24 h, 24–48 h, 48–72 h, 72–96 h, 96–120 h and 120–144 h. If participants are required to stay after Day 7, collections will continue at 24-h intervals. An aliquot from each collection period will be taken for metabolic profiling (separate study).

[10] Meal times are specified for Day 1 only. On all other days, meals will be served at the unit's standard times.

[11] AEs and SAEs will be collected until the final follow-up visit.

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

1. 12-lead ECG
2. vital signs
3. blood draws
4. other assessments

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

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

10.3.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not a prior, and up to the last scheduled visit

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.

10.3.1.1. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day
Post-Treatment	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date + 1 day
Onset Time Since 1st Dose (Days, hours, mins)	Start/Stop Time is Collected: (AE Onset Date/time - Treatment Start Date/time) / 60 Start or Stop Time is missing: If Treatment Start Date > AE Onset Date = AE Onset Date - Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date - Treatment Start Date +1 day Missing otherwise.
Duration (Days, hours, Mins)	Start/Stop Time is Collected: Onset Time = (AE Resolution Date/time – AE Onset Date/time) / 60 Start or Stop Time is missing: AE Resolution Date – AE Onset Date + 1 day
Drug-related	If relationship is marked 'YES' on [Inform/CRF OR value is missing].

NOTES:

- If the study treatment stop date is missing, then the AE will be considered to be On-Treatment.

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10.3.2. 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 or protocol-specified time limit (e.g. half-life of drug, certain number of days, etc.). • Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date+ 1 day • 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 + 1 day

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.

10.4. Appendix 4: Data Display Standards & Handling Conventions

10.4.1. Reporting Process

Software	
• The SAS Version 9.4 or above and WinNonlin Version 6.3 or above will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: arenv/arprod/ GSK1278863/mid200232/final_01
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards SDTM IG Version 3.1.3 ADaM IG Version 1.0. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for final SAC.	

10.4.2. 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

Formats
• 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 eCRF. • The reported precision from non eCRF 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 Principals 7.01 to 7.13.	

10.4.3. 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 as per GUI_51487, Noncompartmental Analysis of Pharmacokinetic Data. 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	
PK Parameter to be Derived by Programmer	AUC/Dose, Ratio of plasma [14C] GSK1278863/total radioactivity for Cmax, AUC(0-inf), AUCzl(0-t) Ae[urine], Ae[faeces], Ae[total] Fe%[urine], Fe%[faeces], Fe%[total]
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to GUI_51487.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.

10.5. Appendix 5: Derived and Transformed Data

10.5.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • Participants having both High and Low values for Normal Ranges at any post-baseline visit 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

10.5.2. Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: • Since Year of Birth is recorded in pCRF, date and month will be imputed as '30th June' of that year. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• **Calculated as Weight (kg) / [Height (m)]2**
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • For Period1 consider oral start date and IV stop date for duration of exposure Subjects who were allocated to treatment but did not report a treatment start date will be categorised as having zero days of exposure.

10.5.3. Safety

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 decimal places in the observed values will be used to determine how much to add or subtract in order to impute the corresponding numeric value.

Laboratory Parameters
• Example 1: 2 Decimal Places = '< x' becomes x – 0.01 • Example 2: 1 Decimal Places = '> x' becomes x + 0.1 • Example 3: 0 Decimal Places = '< x' becomes x – 1

ECG Parameters
RR Interval
• IF RR interval (msec) is not provided directly, then RR can be derived as : [1] If QTcB is machine read & QTcF is not provided, then : $$RR = \left[\left(\frac{QT}{QTcB}\right)^2\right] * 1000$$ [2] If QTcF is machine read and QTcB is not provided, 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. • Machine read values of RR should not be replaced with derived values.
Corrected QT Intervals
• When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}}$$ $$QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

10.5.4. Pharmacokinetic

PK Endpoints
AUC(0-t), AUC (0-∞)
• PK endpoints used to assess the bioavailability i.e. AUC(0-t) and AUC (0-∞) will be divided by corresponding dose (converted into ng) before passing to MM model. • Metabolite of interest are GSK2391220, GSK2506104, GSK2487818, GSK2506102, GSK2531398, GSK2531401 • The ratio of plasma [14C] GSK1278863/total radioactivity for Cmax,AUC(0-inf),AUC(0-t) will be calculated and summarized for radiolabelled dose in each period.

10.6. Appendix 6: Reporting Standards for Missing Data

10.6.1. 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 follow-up visit. • The end of the study is defined as the date of the last contact with the last participant in the study. • Withdrawn subjects will not be replaced unless the total number of participants who complete dosing and all critical assessments drops below 4. • 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.

10.6.2. 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: ○ 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. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

10.6.2.1. 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 year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: • Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the 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 as the Month unless this is before the Month of start of the study treatment; in that case the Month of study treatment start will be used. • 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 study treatment stop date will be used. • Missing Month of Stop: December will be used as the Month unless this is after the Month of stop of the study treatment; in that case the Month of study treatment stop, will be used.

Element	Reporting Detail
	• 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. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the pCRF will be imputed using the following convention: o If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month o 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.

10.7. Appendix 7: Values of Potential Clinical Importance

10.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Δ from BL	↓0.075	
Hemoglobin	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
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L		2	2.75
Creatinine	µmol/L	Δ from BL	>30% increase from Baseline	
Glucose	mmol/L		3	9
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

10.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec	> 450	
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec	> 60	

10.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range			
		Decrease		Increase	
		Lower	Upper	Lower	Upper
Systolic Blood Pressure	mmHg	≥ 20	≥ 40	≥ 20	≥ 40
Diastolic Blood Pressure	mmHg	≥ 10	≥ 20	≥ 10	≥ 20
Heart Rate	bpm	≥ 15	≥ 30	≥ 15	≥ 30

10.8. Appendix 8: Abbreviations & Trade Marks

10.8.1. Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
ADaM	Analysis Data Model
AE	Adverse Event
Ae	Amount excreted
Fe	Fecal excreted
ALT	Alanine aminotransferase
AMS	Accelerator Mass Spectrometry
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
BIB	Bioanalysis, Immunogenicity and Biomarkers
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CSR	Clinical Study Report
CVb / CVw	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
F	Absolute bioavailability
FDA	Food and Drug Administration
GSK	GlaxoSmithKline
GUI	Guidance
IA	Interim Analysis
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
IV	Intravenous
mg	Milligrams
MSE	Mean Square Error
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance

Abbreviation	Description
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QTcB	Bazett's QT Interval Corrected for Heart Rate
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RR	Respiratory Rate
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TFL	Tables, Figures & Listings
µg	Microgram

10.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP

Trademarks not owned by the GlaxoSmithKline Group of Companies
Entero-Test
SAS
WinNonlin

10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.8	
Pharmacokinetic	2.1 to 2.13	2.1 to 2.11
Safety	3.1 to 3.13	
Section	**Listings**	
ICH Listings	1 to 26	
Other Listings	27 to 35	

10.9.2. 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 Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln

NOTES:

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

10.9.3. Deliverables

Delivery	Description
DR	Dry Run
SAC	Final Statistical Analysis Complete

10.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1A	Summary of Participant Disposition for the Participant Conclusion Record		DR, SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		DR, SAC
1.3.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID		DR, SAC
Protocol Deviation					
1.4.	Safety	DV1	Summary of Important Protocol Deviations		DR, SAC
Population Analysed					
1.5.	Screened	SP1A	Summary of Study Populations		DR, SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM3	Summary of Demographic Characteristics	Include height, weight & BMI.	DR, SAC
1.7.	Enrolled	DM11	Summary of Age Ranges		DR, SAC
1.8.	Safety	DM5	Summary of Race and Racial Combinations		DR, SAC

10.9.5. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma GSK1278863 and Plasma [^{14}C] GSK1278863					
2.1.	PK	pkct1	Summary of Plasma GSK1278863 and [14C] GSK1278863 Concentration by treatment and time	GSK1278863: Summarized for A1 only [^{14}C] GSK1278863: Summarized for A2 and B treatment group only Page by Regimen	DR, SAC
2.2.	PK	pkpt1	Summary of Untransformed Plasma GSK1278863 and [14C] GSK1278863 Pharmacokinetic Parameters	GSK1278863: Summarized for A1 only [^{14}C] GSK1278863: Summarized for A2 and B treatment group only Page by Regimen	DR, SAC
2.3.	PK	pkpt3	Summary of Loge-transformed Plasma GSK1278863 and [14C] GSK1278863 Pharmacokinetic Parameters	GSK1278863: Summarized for A1 only [^{14}C] GSK1278863: Summarized for A2 and B treatment group only Page by Regimen	DR, SAC
Plasma Metabolite and [^{14}C] Metabolite					
2.4.	PK	pkct1	Summary of Plasma Metabolite and [14C] Metabolite concentration by time	Metabolite: Summarized for A1 only [^{14}C] Metabolite: Summarized for A2 and B treatment group only Page by Regimen	DR, SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.5.	PK	pkpt1	Summary of Untransformed Plasma Metabolite and [14C] Metabolite Pharmacokinetic Parameters	Metabolite: Summarized for A1 only [^{14}C] Metabolite: Summarized for A2 and B treatment group only Page by Regimen	DR, SAC
2.6.	PK	pkpt3	Summary of Loge-transformed Plasma Metabolite and [14C] Metabolite Concentration Pharmacokinetic Parameters	Metabolite: Summarized for A1 only [^{14}C] Metabolite: Summarized for A2 and B treatment group only Page by Regimen	DR, SAC

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Total Radioactivity					
2.7.	PK	pkct1	Summary of Blood and Plasma Total Radioactivity Concentration by Treatment and time	Page by Specimen Type Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups	DR, SAC
2.8.	PK	pkpt1	Summary of Untransformed Plasma Total Radioactivity Pharmacokinetic Parameters	Page by Specimen Type Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups	DR, SAC
2.9.	PK	pkpt3	Summary of Loge-transformed Blood Total Radioactivity Pharmacokinetic Parameters	Pageby Specimen Type Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups	DR, SAC

Urine and Faecal Pharmacokinetic					
2.10.	PK	PK_T 1	Summary of Cumulative Urinary and Faecal Total Radioactivity Pharmacokinetic Parameters (Amount Excreted(unit)) by Time (Treatment Period-2)	*Includes (urine), Ae (faeces), Ae (total) parameter.*	DR, SAC
2.11.	PK	PK_T1	Summary of Cumulative Urinary and Faecal Total Radioactivity Radioactivity Pharmacokinetic Parameters (% Excreted) by Time	*Fe% (urine), Fe %(faeces), Fe% (total).*	DR, SAC

Other Output					
2.12.	PK	pkpt3	Summary of Ratio of plasma [14C] GSK1278863: Total Radioactivity PK parameter ratios by treatment	only for Cmax, AUC(0-t) and AUC(0-inf) parameters	DR, SAC
PK Statistical Analysis					
2.13.	PK	PK_T2	Summary of Statistical Analysis of Loge-transformed Plasma GSK1278863 PK Parameters		DR, SAC

10.9.6. Pharmacokinetic Figures

No.	Population	IDSL / Example Shell	Title	Programming Notes	Deliverable [Priority]
Plasma GSK1278863 and [14C]- GSK1278863					
2.1.	PK	pkcf6	Individual Subject Plasma GSK1278863 and [14C] GSK1278863 Concentration-time Plot (Linear and Semi-log) by Treatment	Different plot symbols will be used for each subject	DR, SAC
2.2.	PK	pkcf2	Arithmetic Mean Plasma GSK1278863 and [14C] GSK1278863 Concentration-time Plot (Linear and Semi-log) by Treatment		DR, SAC
2.3.	PK	pkcf3	Median Plasma GSK1278863 and [14C] GSK1278863 Concentration -time Plot (Linear and Semi-log) by Treatment		DR, SAC
Total Radioactivity					
2.4.	PK	pkcf6	Individual Subject Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Treatment and Specimen	Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups	DR, SAC
2.5.	PK	pkcf2	Arithmetic Mean Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Treatment and Specimen	Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups	DR, SAC
2.6.	PK	pkcf3	Median Total Radioactivity Concentration -time Plot (Linear and Semi-log) by Treatment	Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups	DR, SAC

2.9.	PK	pkcf3	Median Plasma Metabolite and [14C]-Metabolite Concentration Plot (Linear and Semi-log) for GSK1278863 6mg oral dose	Page by metabolites	DR, SAC
Urine and Faecal Pharmacokinetic					
2.10.	PK	PK_F1	Individual Subject Cumulative Total Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion by Subject		DR, SAC
2.11.	PK	PK_F2	Arithmetic Mean Cumulative 14C -Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion		DR, SAC
Metabolite and [14C]-Metabolite					
2.7.	PK	pkcf6	Individual Subject Plasma Metabolite and [14C]-Metabolite Concentration-time Plot (Linear and Semi-log) for GSK1278863 6mg oral dose	Page by metabolites	DR, SAC
2.8.	PK	pkcf2	Arithmetic Mean Plasma Metabolite and [14C]-Metabolite Concentration-time Plot (Linear and Semi-log) for GSK1278863 6mg oral dose	Page by metabolites	DR, SAC

10.9.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term		DR, SAC
3.2.	Safety	AE1CP	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency		DR, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3.	Safety	AE15	Summary of Common (>=33%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)		DR, SAC
Serious and Other Significant Adverse Events					
3.4.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)		DR, SAC
Laboratory: Chemistry					
3.5.	Safety	LB1	Summary of Chemistry Changes from Baseline		DR, SAC
3.6.	Safety	LB1	Summary of Laboratory Values		DR, SAC
3.7.	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline		DR, SAC
Laboratory: Hematology					
3.8.	Safety	LB1	Summary of Hematology Changes from Baseline	Includes baseline values.	DR, SAC
3.9.	Safety	LB1	Summary of Hematology values		DR, SAC
3.10.	Safety	LB15/	Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline		DR, SAC
ECG					
3.11.	Safety	EG1	Summary of ECG Findings		DR, SAC
3.12.	Safety	EG2	Summary of ECG Values		DR, SAC
Vital Signs					
3.13.	Safety	VS1	Summary of Change from Baseline in Vital Signs		DR, SAC

10.9.8. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	DR, SAC
2.	Safety	ES3	Listing of Reasons for Study Withdrawal		DR, SAC
Protocol Deviations					
3.	Safety	DV2A	Listing of Important Protocol Deviations		DR, SAC
4.	Safety	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations		DR, SAC
Demographic and Baseline Characteristics					
5.	Safety	DM4	Listing of Demographic Characteristics		DR, SAC
6.	Safety	DM10	Listing of Race		DR, SAC
Prior and Concomitant Medications					
7.	Safety	CP_CM4	Listing of Concomitant Medications		DR, SAC
Exposure and Treatment Compliance					
8.	Safety	EX4	Listing of Exposure Data		DR, SAC
Adverse Events					
9.	Safety	AE9CP	Listing of All Adverse Events		DR, SAC
10.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		DR, SAC
11.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text		DR, SAC
Serious and Other Significant Adverse Events					
12.	Safety	AE9CPa	Listing of Serious Adverse Events		DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
13.	Safety	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study		DR, SAC
14.	Safety	AE9CP	Listing of Treatment emergent AEs		DR, SAC
Hepatobiliary (Liver)					
15.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		DR, SAC
16.	Safety	MH3	MH3 Listing of Medical Conditions for Subjects with Liver Stopping		DR, SAC
17.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events		DR, SAC
All Laboratory					
18.	Safety	LB6	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance/Outside Normal Range		DR, SAC
19.	Safety	LB6	Listing of Laboratory Values of Potential Clinical Importance		DR, SAC
20.	Safety	UR2b	Listing of Urinalysis Data for Subjects with Positive Dipstick Results		DR, SAC
ECG					
21.	Safety	EG4	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance		DR, SAC
22.	Safety	EG4	Listing of ECG Values of Potential Clinical Importance		DR, SAC
23.	Safety	EG6	Listing of All ECG Findings for Participants with an Abnormal ECG Finding		DR, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
24.	Safety	VS5	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL Required for ClinPharm studies only. Display ALL Vital Signs for a subject who experienced a value of potential clinical importance.	DR, SAC
25.	Safety	VS5	Listing of Vital Signs of Potential Clinical Importance	IDSL Required for ClinPharm studies only.	DR, SAC

10.9.9. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
26.	PK	PK_L1	Listing of Urinary and Faecal Total -Radioactivity Parameters (Amount Excreted) by Time	Include absolute and cumulative for urine, faeces and total Only for Treatment Period-2	DR, SAC
27.	PK	PK_L2	Listing of Urinary and Faecal Total-Radioactivity Parameters (% Excreted) by Time	Include absolute and cumulative for urine, faeces and total Only for Treatment Period-2	DR, SAC
28.	PK	pkcl1x	Listing of Plasma GSK1278863 and [14C] - GSK1278863 Concentration-time Data		DR, SAC
29.	PK	pkpl1x	Listing of Plasma GSK1278863 and [14C] - GSK1278863 Pharmacokinetic Parameters		DR, SAC
30.	PK	pkcl1x	Listing of Blood and Plasma Total-Radioactivity Concentration -time Data		DR, SAC
31.	PK	pkpl1x	Listing of Blood and Plasma Total -Radioactivity Pharmacokinetic Parameters		DR, SAC
32.	PK	pkcl1x	Listing of Plasma Metabolite and [14C]-Metabolite Concentration -time Data		DR, SAC
33.	PK	pkpl1x	Listing of Plasma Metabolite and [14C]-Metabolite Pharmacokinetic Parameters		DR, SAC
34.	PK	N/A	Supportive SAS Output from Statistical Analysis of Loge-transformed Plasma GSK1278863 Pharmacokinetic Parameters		DR,SAC

10.10. Appendix 10: Example Mock Shells for Data Displays

Example : PK_T1
Protocol : 200232
Population : PK

Table 2.10
Summary of Cumulative Urinary and Faecal Total Radioactivity Parameters (Amount Excreted **(unit)**) by Time

Treatment		N	Planned Relative Time	n	Mean	SD	Median	Min.	Max.
14C]GSKXXXX	Ae Faeces	X	PRE DOSE	X	X.XX	X.XXX	X.XX	X.X	X.X
			X-XX H	X	X.XX	X.XXX	X.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XXX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XXX-XXX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
	Ae Urine	X	PRE DOSE	X	X.XX	X.XXX	X.XX	X.X	X.X
			X-XX H	X	X.XX	X.XXX	X.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XXX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XXX-XXX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
	Ae Total (Faeces+Urine)	X	PRE DOSE	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			X-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XX-XXX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X
			XXX-XXX H	X	XX.XX	X.XXX	XX.XX	X.X	XX.X

Example : PK_T2
Protocol : mid200232
Population : PK

Table 2.4
Summary of Statistical Analysis of Log_e-transformed Plasma GSK1278863 PK Parameters

Parameter	Comparison Test vs Reference	Adjusted Geometric Mean (Dose normalised) n Test	n Ref	Ratio (Test/Ref)	90% Confidence Interval for the Ratio	%CVw
AUC(0-inf)(units)	A1 vs A2	x xx.xx	x xx.xx	x.xxxx	(x.xxxx, x.xxxx)	xx.x
AUC(0-t)(units)	A1 vs a2	x xx.xx	x xx.xx	x.xxxx	(x.xxxx, x.xxxx)	xx.x

FOOTNOTE:
Note:
A1: GSK1278863 6mg Oral
A2: [14C]-GSK1278863 50 mcg IV

Figure 2.7
Individual Subject Cumulative Total Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion by Subject

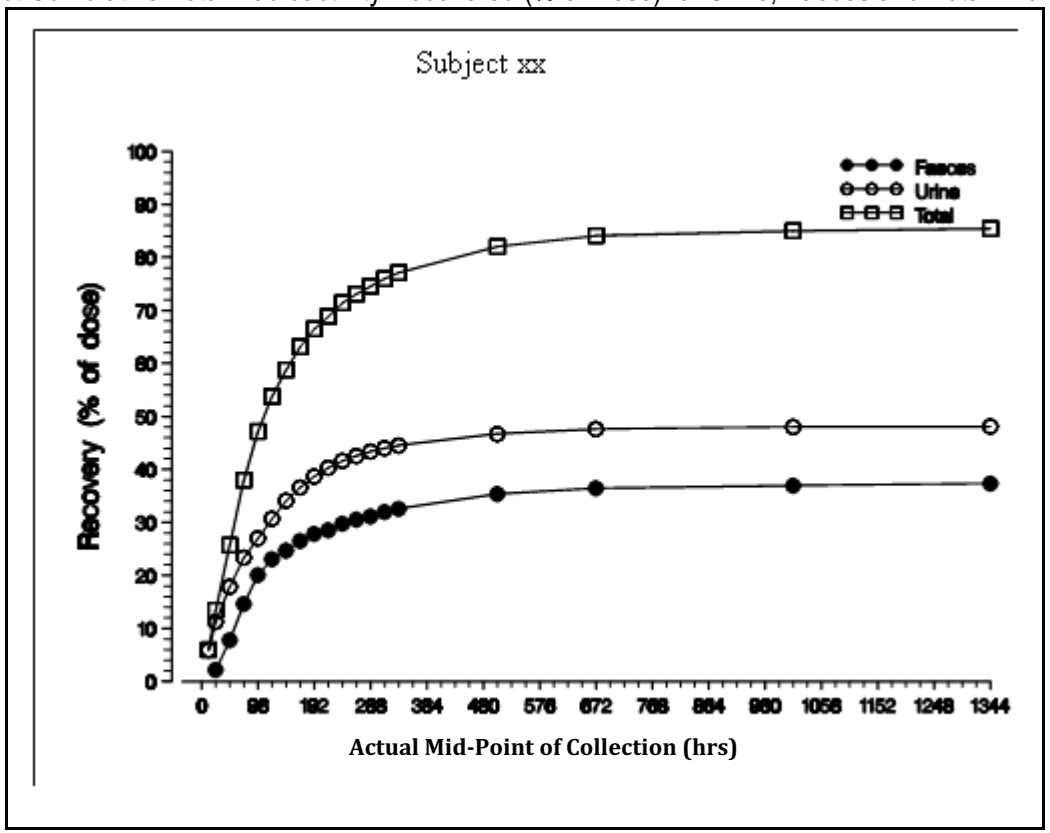
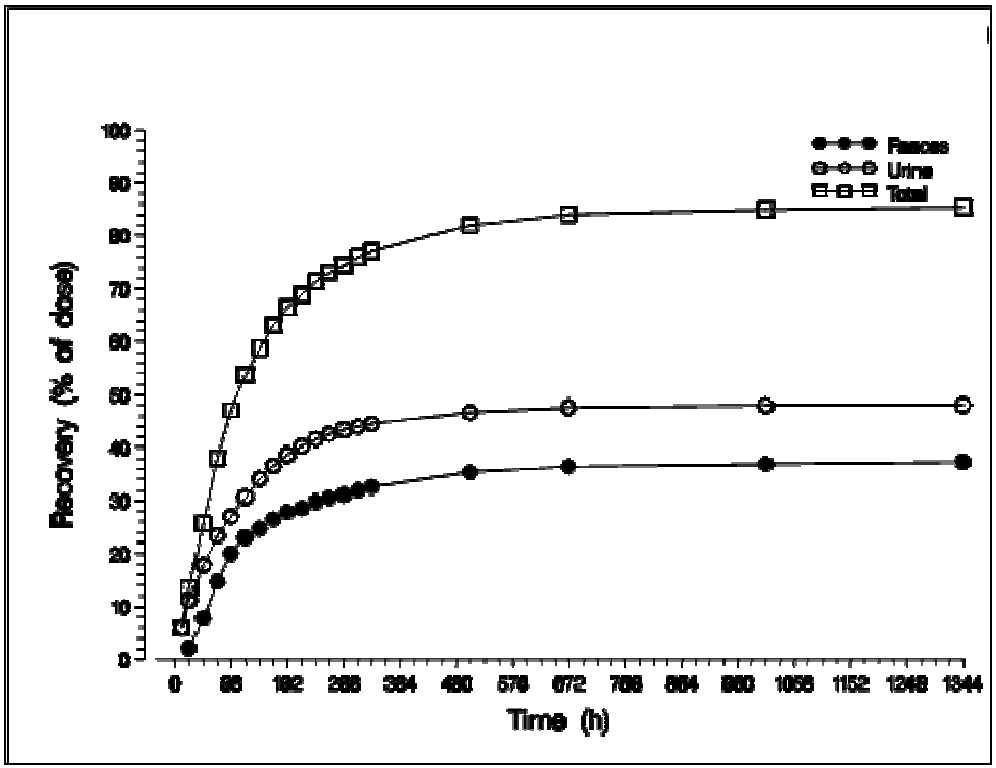


Figure *2.8*
Arithmetic Mean Cumulative total -Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion



Example : PK_L1
Protocol : MID200232
Population : PK

Listing XX
Listing of Urinary and Faecal Total radioactivity Parameters (Amount Excreted) by Time

Treatment: [14C]GSKXXXX

Inv./ Subj.	Fe Faeces Start Date/ Time/ End Date/ Time	Fe Urine Start Date/ Time/ End Date/ Time	Planned Relative Time	Ae Faeces	Cumulative Ae Faeces	Ae Urine	Cumulative Ae Urine	Ae Total	Cumulative Ae Total
XXXXXX/ XXX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ XX:XX/ XXJUNXXXX/ XX:XX	PRE DOSE X	X.X	X.X	X.X	X.X	X.X	X.X
	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	X-XX H	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XX-XX H	XX.X	XX.X	X.X	XX.X	XX.X	XX.X
	XXJUNXXXX/	XXJUNXXXX/	XX-XX H	X.X	XX.X	X.X	XX.X	X.X	XX.X

Note: Ae = Amount excreted. NS = No Sample.

Example : PK_L2
Protocol : MID200232
Population : PK

Listing XX
Listing of Urinary and Faecal Total Radioactivity Parameters (% Excreted) by Time

Treatment: [14C]GSKXXXX

Inv./ Subj.	Fe Faeces Start Date/ Time/ End Date/ Time	Fe Urine Start Date/ Time/ End Date/ Time	Planned Relative Time	Fe Faeces	Cumulative Fe Faeces	Fe Urine	Cumulative Fe Urine	Fe Total	Cumulative Fe Total
XXXXXX/ XXX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ XX:XX/ XXJUNXXXX/ XX:XX	PRE DOSE X	X.X	X.X	X.X	X.X	X.X	X.X
	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	X-XX H	XX.X	XX.X	XX.X	XX.X	XX.X	XX.X
	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XX-XX H	XX.X	XX.X	X.X	XX.X	XX.X	XX.X
	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XXJUNXXXX/ X:XX/ XXJUNXXXX/ X:XX	XX-XX H	X.X	XX.X	X.X	XX.X	X.X	XX.X

Note: Fe = Fraction excreted as a percentage of total radioactive dose. NS = No Sample.