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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<thead>
<tr>
<th>Approver</th>
<th>Date</th>
<th>Approval Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPD</td>
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<td>N/A</td>
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### RAP Team Approvals:

<table>
<thead>
<tr>
<th>Approver</th>
<th>Date</th>
<th>Approval Method</th>
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</thead>
<tbody>
<tr>
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<td>e-signature</td>
</tr>
</tbody>
</table>

### Clinical Statistics and Clinical Programming Line Approvals:

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<thead>
<tr>
<th>Approver</th>
<th>Date</th>
<th>Approval Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associate Manager Statistics, ([Future Pipeline Discovery, Quantitative Sciences India], Clinical Statistics)</td>
<td>04-JAN-2018</td>
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<td>Programming Manager ([Future Pipeline Discovery, RD Qsci Clinical Programming Metabolic], Clinical Programming)</td>
<td>02-JAN-2018</td>
<td>e-signature</td>
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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:

<table>
<thead>
<tr>
<th>Document Number</th>
<th>Date</th>
<th>Reason for revision</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017N310967_00</td>
<td>30-MAY-2017</td>
<td>Original</td>
</tr>
<tr>
<td>2017N310967_01</td>
<td>1-SEP-2017</td>
<td>“Promptly” has been changed to “within 24 hours following knowledge of the SAE.”</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Reporting &amp; Analysis Plan</th>
<th>Rationale for Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Subjects: All participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.</td>
<td>Safety: All participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.</td>
<td>To be consistent with current standards for naming population</td>
</tr>
<tr>
<td>Not Defined</td>
<td>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.</td>
<td>This population Required for data disclosure displays.</td>
</tr>
<tr>
<td>Pharmacokinetic: All participants in the ‘Safety’ population for whom sufficient data are available to calculate the derived pharmacokinetic parameters on an as-treated basis.</td>
<td>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).</td>
<td>Definition mentioned in the Protocol is ambiguous from a programming perspective hence standard definition is used after confirming with Study Team.</td>
</tr>
<tr>
<td>Blood sample is collected in time point mentioned in Table 1</td>
<td>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</td>
<td>To capture the immediate decline of drug blood sample is collected in two extra time points.</td>
</tr>
</tbody>
</table>
## 2.2. Study Objective(s) and Endpoint(s)

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

<sup>1</sup> For measured concentrations of daprodustat in blood and plasma, the nomenclature \(^{14}\text{C} \) -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

<table>
<thead>
<tr>
<th>Design Features</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening Period</strong></td>
<td>Participants must be screened within 30 days before the first dose of daprodustat, and must meet all eligibility criteria.</td>
</tr>
<tr>
<td><strong>Treatment Period 1 (oral tablet and intravenous infusion)</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Treatment Period 2 (oral solution)</strong></td>
<td>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.</td>
</tr>
</tbody>
</table>
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 day 7 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 Period 1, each participant will receive 50 μg of radiolabelled GSK1278863 ([14C]-GSK1278863) microtracer by IV infusion, concomitant with a 6 mg oral dose of daprodustat.
- In Treatment Period 2, a single 25 mg dose of [14C]-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 [14C]-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

<table>
<thead>
<tr>
<th>Population</th>
<th>Definition / Criteria</th>
<th>Analyses Evaluated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened</td>
<td>• All participants who sign the ICF. This will be the population for reporting screened population data.</td>
<td>• Study Population</td>
</tr>
<tr>
<td>Enrolled</td>
<td>• 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.</td>
<td>• Study Population</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>• All participants who take at least 1 dose of study treatment.</td>
<td>• Safety and Study population</td>
</tr>
<tr>
<td></td>
<td>• Participants will be analysed according to the treatment they actually received.</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>• 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).</td>
<td>• PK</td>
</tr>
<tr>
<td>(PK)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
<th>Data Displays for Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>GSK1278863 6mg Oral + [14C]-GSK1278863 50 mcg IV</td>
<td>Description (Safety)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Description (PK Analysis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Order [1]</td>
</tr>
<tr>
<td>A1</td>
<td>A</td>
<td>1</td>
</tr>
<tr>
<td>A2</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>B</td>
<td>[14C]-GSK1278863 25 mg Oral Solution</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

**NOTES:**
1. Order represents treatments being presented in TFL, as appropriate.
2. Study population displays will be summarized by total column.
3. 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Study Assessments Considered as Baseline</th>
<th>Baseline Used in Data Display</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td>Screening Day -1 Day 1 (Pre-Dose)</td>
<td>Day 1 (mean pre-dose) [2]</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X [1]</td>
</tr>
<tr>
<td>Laboratory (Haematology+ Clinical chemistry)</td>
<td>X X</td>
<td>Day -1</td>
</tr>
</tbody>
</table>
NOTES:

[1] Taken in triplicate

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:

<table>
<thead>
<tr>
<th>Section</th>
<th>Component</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.3</td>
<td>Appendix 3: Study Phases and Treatment Emergent Adverse Events</td>
</tr>
<tr>
<td>10.4</td>
<td>Appendix 4: Data Display Standards &amp; Handling Conventions</td>
</tr>
<tr>
<td>10.5</td>
<td>Appendix 5: Derived and Transformed Data</td>
</tr>
<tr>
<td>10.6</td>
<td>Appendix 6: Reporting Standards for Missing Data</td>
</tr>
<tr>
<td>10.7</td>
<td>Appendix 7: Values of Potential Clinical Importance</td>
</tr>
</tbody>
</table>
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, $[^{14}C]$-GSK1278863, blood and plasma total radioactivity metabolite and $[^{14}C]$-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
Table 2 Derived Pharmacokinetic Blood and Plasma Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Parameter Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC(0-t)</td>
<td>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.</td>
</tr>
<tr>
<td>( \lambda_z )</td>
<td>The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.</td>
</tr>
<tr>
<td>AUC (0-inf)</td>
<td>Area under the concentration-time curve extrapolated to infinity will be calculated as: [ AUC = AUC(0-t) + \frac{C(t)}{\lambda_z} ]</td>
</tr>
<tr>
<td>%AUCex</td>
<td>The percentage of AUC (0-( \infty )) obtained by extrapolation (%AUCex) will be calculated as: [ \frac{[AUC(0-inf) - AUC(0-t)]}{AUC(0-inf)} \times 100 ]</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum observed concentration, determined directly from the concentration-time data.</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time to reach Cmax, determined directly from the concentration-time data.</td>
</tr>
<tr>
<td>t( \frac{1}{2} )</td>
<td>Apparent terminal half-life will be calculated as: ( t\frac{1}{2} = \frac{\ln 2}{\lambda_z} )</td>
</tr>
<tr>
<td>Vss</td>
<td>Volume of distribution of at steady-state will be calculated as: [ Vss = \frac{CL \times MRT_{iv}}{AUMC(0-inf)/AUC(0-inf)} ] where the mean residence time (MRT) is calculated as AUMC(0-inf) (area under the first moment curve)/AUC(0-inf).</td>
</tr>
<tr>
<td>CL</td>
<td>Total clearance will be calculated as: [ \text{Dose(iv)/AUC(0-inf)} ]</td>
</tr>
<tr>
<td>Treatment period 1</td>
<td>analyte [^{14}\text{C}]- GSK1278863 only.</td>
</tr>
<tr>
<td>Oral F</td>
<td>Absolute bioavailability from the oral tablet and IV doses administered in Period1 for AUC(0-inf) and AUC(0-t) PK parameter calculated as: [ P = \frac{\text{GSK1278863 AUC}<em>{\text{oral}}}{\text{Dose}</em>{\text{oral}}} / \frac{\text{GSK1278863 AUC}<em>{\text{IV}}}{\text{Dose}</em>{\text{IV}}} ]</td>
</tr>
<tr>
<td>Oral and IV Dose will be converted into ng using below conversion values. 1mg=1000000ng 1mcg=1000ng</td>
<td></td>
</tr>
<tr>
<td>[^{14}\text{C}]- GSK1278863/Total radioactivity ratio for Cmax, AUC(0-( \text{t} ))</td>
<td>Cmax Ratio = ([^{14}\text{C}] \text{GSK961081} [\text{Cmax}] / \text{Total radioactivity [Cmax]})</td>
</tr>
<tr>
<td>AUC(0-inf) Ratio = ([^{14}\text{C}] \text{GSK961081} [\text{AUC(0-inf)}] / \text{Total radioactivity [AUC(0-inf)]})</td>
<td></td>
</tr>
<tr>
<td>AUC(0-t) Ratio = ([^{14}\text{C}] \text{GSK961081} [\text{AUC(0-t)}] / \text{Total radioactivity [AUC(0-t)]})</td>
<td></td>
</tr>
</tbody>
</table>
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

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

<table>
<thead>
<tr>
<th><strong>Secondary Endpoint / Variables</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• AUC(0-t), AUC (0-∞) PK parameters of Plasma GSK1278863 from IV and oral dose will be analyzed after loge transformation (PK parameters should be divided by corresponding dose)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Model Specification</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Will be statistically analyzed using a mixed model (MM) for Period1.</td>
</tr>
<tr>
<td>• Terms fitted in the mixed effect ANOVA model will include:</td>
</tr>
<tr>
<td>o Fixed effect : Treatment (IV dose/Oral dose in Period1)</td>
</tr>
<tr>
<td>o Random Effect : Subject</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
<tr>
<td>• 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)</td>
</tr>
</tbody>
</table>
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 \( %CV_w = 100 * (\sqrt{\text{EXP}(\sigma_w^2)} - 1) \) and \( \sigma_w^2 \) 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.
Appendix 2: Schedule of Activities

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)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Day</th>
<th>-30 to -1</th>
<th>-1</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
<th>72</th>
<th>96</th>
<th>120</th>
<th>144</th>
</tr>
</thead>
<tbody>
<tr>
<td>Informed consent</td>
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<td>X</td>
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<tr>
<td>Medical history (including drug/alcohol use)</td>
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<td>X</td>
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<tr>
<td>Demography</td>
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<tr>
<td>Admission to unit</td>
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<td>X</td>
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<tr>
<td>Discharge from unit</td>
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<td>X</td>
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<tr>
<td>Full physical exam, including height, weight and BMI</td>
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<td>X</td>
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<tr>
<td>Brief physical exam</td>
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<td>X</td>
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<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Drugs of abuse screen</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
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<td></td>
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<tr>
<td>Alcohol and cotinine tests, CO breath tests</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>HIV and hepatitis B and C screen</td>
<td></td>
<td></td>
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<td>X</td>
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<td></td>
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<tr>
<td>Laboratory safety tests (including LFTs)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>12-lead ECG</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

1. Pre-dose
2. Procedure performed
3. Procedure performed twice
<table>
<thead>
<tr>
<th>Visit</th>
<th>Screening¹</th>
<th>Treatment Period 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>-30 to -1</td>
<td>-1</td>
</tr>
<tr>
<td>Procedure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs⁴</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>[¹⁴C]-GSK1278863 IV infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral daproductat⁵</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Blood samples for drug assay and radioactivity⁸</td>
<td>X X X X X X X X X X X X X X X X X X X X X X X X</td>
<td></td>
</tr>
<tr>
<td>Urine collection⁶</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Faecal collection⁷</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Entero-Test (duodenal bile)⁹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meals⁸,¹⁰</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

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 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, [¹⁴C]-GSK1278863 analysis, cold daproductat 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 Urate 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)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Day</th>
<th>Treatment Period 2</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>hour</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Admission to unit</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharge from unit</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brief physical exam</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs of abuse screen</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol and cotinine tests, CO breath tests</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory safety tests (including LFTs)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>12-lead ECG</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital signs</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>[14C]-GSK1278863 oral solution</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood samples for drug assay and radioactivity</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Urine collection</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Faecal collection</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meals</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>AE/SAE/concomitant medication review</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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, [14C]-GSK1278863 analysis, cold GSK1278863 analysis, and metabolite profiling will include pre-dose 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

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior</td>
<td>If medication end date is not missing and is before 28 days prior to screening visit</td>
</tr>
<tr>
<td>Concomitant</td>
<td>Any medication that is not a prior, and up to the last scheduled visit</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Treatment State</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment</td>
<td>AE Start Date &lt; Study Treatment Start Date</td>
</tr>
<tr>
<td>On-Treatment</td>
<td>If AE onset date is on or after treatment start date &amp; on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day</td>
</tr>
<tr>
<td>Post-Treatment</td>
<td>If AE onset date is after the treatment stop date. AE Start Date &gt; Study Treatment Stop Date + 1 day</td>
</tr>
</tbody>
</table>

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.
## 10.3.2. Treatment Emergent Flag for Adverse Events

<table>
<thead>
<tr>
<th>Flag</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment Emergent</td>
<td>• If AE onset date is on or after treatment start date &amp; on or before treatment stop date. (plus washout or protocol-specified time limit (e.g. half-life of drug, certain number of days, etc.).&lt;br&gt;• Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 1 day&lt;br&gt;• 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:&lt;br&gt;  Treatment Period Start Date ≤ AE Worsening Date ≤ Study Treatment Stop Date + 1 day</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Continuous Data</th>
<th>Refer to IDSL Statistical Principle 6.06.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorical Data</td>
<td>N, n, frequency, %</td>
</tr>
</tbody>
</table>

### Graphical Displays
- Refer to IDSL Statistical Principals 7.01 to 7.13.

### 10.4.3. Reporting Standards for Pharmacokinetic

#### Pharmacokinetic Concentration Data

<table>
<thead>
<tr>
<th>PC Windows Non-Linear (WNL) File</th>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive Summary Statistics, Graphical Displays and Listings</td>
<td>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.</td>
</tr>
</tbody>
</table>

#### Pharmacokinetic Parameter Derivation

<table>
<thead>
<tr>
<th>PK Parameter to be Derived by Programmer</th>
<th>AUC/Dose, Ratio of plasma [14C] GSK1278863/total radioactivity for Cmax, AUC(0-inf), AUCzt(0-t) Ae[urine], Ae[faeces], Ae[total] Fe%[urine], Fe%[faeces], Fe%[total]</th>
</tr>
</thead>
</table>

#### Pharmacokinetic Parameter Data

<table>
<thead>
<tr>
<th>Is NQ impacted PK Parameters Rule Being Followed</th>
<th>Yes, refer to GUI_51487.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptive Summary Statistics, Graphical Displays and Listings</td>
<td>Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.</td>
</tr>
</tbody>
</table>
## Appendix 5: Derived and Transformed Data

### 10.5.1. General

<table>
<thead>
<tr>
<th>Multiple Measurements at One Analysis Time Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented.</td>
</tr>
<tr>
<td>• 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.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calculated as the number of days from First Dose Date:</td>
</tr>
<tr>
<td>• Ref Date = Missing → Study Day = Missing</td>
</tr>
<tr>
<td>• Ref Date &lt; First Dose Date → Study Day = Ref Date – First Dose Date</td>
</tr>
<tr>
<td>• Ref Data ≥ First Dose Date → Study Day = Ref Date – (First Dose Date) + 1</td>
</tr>
</tbody>
</table>

### 10.5.2. Study Population

<table>
<thead>
<tr>
<th>Demographics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
</tr>
<tr>
<td>• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:</td>
</tr>
<tr>
<td>• Since Year of Birth is recorded in pCRF, date and month will be imputed as ‘30th June’ of that year.</td>
</tr>
<tr>
<td>• Birth date will be presented in listings as ‘YYYY’.</td>
</tr>
<tr>
<td><strong>Body Mass Index (BMI)</strong></td>
</tr>
<tr>
<td>• Calculated as Weight (kg) / [Height (m)]^2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Extent of Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Number of days of exposure to study drug will be calculated based on the formula:</td>
</tr>
<tr>
<td><strong>Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1</strong></td>
</tr>
<tr>
<td>• 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.</td>
</tr>
</tbody>
</table>

### 10.5.3. Safety

<table>
<thead>
<tr>
<th>Laboratory Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 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 ‘&lt;x’ or ‘&gt;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.</td>
</tr>
</tbody>
</table>
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:

     \[
     RR = \left( \frac{QT}{QTcB} \right)^2 \times 1000
     \]

  2. If QTcF is machine read and QTcB is not provided, then:

     \[
     RR = \left( \frac{QT}{QTcF} \right)^3 \times 1000
     \]

- 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:

  \[
  QTcB = \frac{QT}{\sqrt[2]{RR/1000}} \quad QTcF = \frac{QT}{3\sqrt[3]{RR/1000}}
  \]

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

<table>
<thead>
<tr>
<th>Element</th>
<th>Reporting Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• The end of the study is defined as the date of the last contact with the last participant in the study.</td>
</tr>
<tr>
<td></td>
<td>• Withdrawn subjects will not be replaced unless the total number of participants who complete dosing and all critical assessments drops below 4.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
</tbody>
</table>

10.6.2. Handling of Missing Data

<table>
<thead>
<tr>
<th>Element</th>
<th>Reporting Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:</td>
</tr>
<tr>
<td></td>
<td>o These data will be indicated by the use of a “blank” in subject listing displays.</td>
</tr>
<tr>
<td></td>
<td>o Unless all data for a specific visit are missing in which case the data is excluded from the table.</td>
</tr>
<tr>
<td></td>
<td>o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outliers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.</td>
</tr>
</tbody>
</table>

10.6.2.1. Handling of Missing and Partial Dates

<table>
<thead>
<tr>
<th>Element</th>
<th>Reporting Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Partial dates will be displayed as captured in subject listing displays.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Reporting Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 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:</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td>Element</td>
<td>Reporting Detail</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>• 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.</td>
</tr>
<tr>
<td></td>
<td>• Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.</td>
</tr>
<tr>
<td>Concomitant Medications/</td>
<td>• Partial dates for any concomitant medications recorded in the pCRF will be imputed using the following convention:</td>
</tr>
<tr>
<td>Medical History</td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>The recorded partial date will be displayed in listings.</td>
</tr>
</tbody>
</table>
## 10.7. Appendix 7: Values of Potential Clinical Importance

### 10.7.1. Laboratory Values

#### Haematology

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Units</th>
<th>Category</th>
<th>Clinical Concern Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit</td>
<td>Ratio of 1</td>
<td>Male</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Δ from BL</td>
<td>↓0.075</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>g/L</td>
<td>Male</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Δ from BL</td>
<td>↓25</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>x10^9/ L</td>
<td></td>
<td>0.8</td>
</tr>
<tr>
<td>Neutrophil Count</td>
<td>x10^9/ L</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>x10^9/ L</td>
<td></td>
<td>100 - 550</td>
</tr>
<tr>
<td>While Blood Cell Count (WBC)</td>
<td>x10^9/ L</td>
<td></td>
<td>3 - 20</td>
</tr>
</tbody>
</table>

#### Clinical Chemistry

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Units</th>
<th>Category</th>
<th>Clinical Concern Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>mmol/L</td>
<td></td>
<td>2 - 2.75</td>
</tr>
<tr>
<td>Creatinine</td>
<td>µmol/L</td>
<td>Δ from BL</td>
<td>&gt;30% increase from Baseline</td>
</tr>
<tr>
<td>Glucose</td>
<td>mmol/L</td>
<td></td>
<td>3 - 9</td>
</tr>
<tr>
<td>Potassium</td>
<td>mmol/L</td>
<td></td>
<td>3 - 5.5</td>
</tr>
<tr>
<td>Sodium</td>
<td>mmol/L</td>
<td></td>
<td>130 - 150</td>
</tr>
</tbody>
</table>

#### Liver Function

<table>
<thead>
<tr>
<th>Test Analyte</th>
<th>Units</th>
<th>Category</th>
<th>Clinical Concern Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT</td>
<td>U/L</td>
<td>High</td>
<td>≥ 2x ULN</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>U/L</td>
<td>High</td>
<td>≥ 2x ULN</td>
</tr>
<tr>
<td>AlkPhos</td>
<td>U/L</td>
<td>High</td>
<td>≥ 2x ULN</td>
</tr>
<tr>
<td>T Bilirubin</td>
<td>µmol/L</td>
<td>High</td>
<td>≥ 1.5xULN</td>
</tr>
<tr>
<td>T. Bilirubin + ALT</td>
<td>µmol/L</td>
<td>High</td>
<td>1.5xULN T. Bilirubin + ≥ 2x ULN ALT</td>
</tr>
<tr>
<td></td>
<td>U/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 10.7.2. ECG

<table>
<thead>
<tr>
<th>ECG Parameter</th>
<th>Units</th>
<th>Clinical Concern Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Absolute QTc Interval</td>
<td>msec</td>
<td>&gt; 450</td>
</tr>
<tr>
<td>Absolute PR Interval</td>
<td>msec</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>Absolute QRS Interval</td>
<td>msec</td>
<td>&lt; 75</td>
</tr>
<tr>
<td><strong>Change from Baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase from Baseline QTc</td>
<td>msec</td>
<td>&gt; 60</td>
</tr>
</tbody>
</table>

### 10.7.3. Vital Signs

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>Units</th>
<th>Clinical Concern Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mmHg</td>
<td>&lt; 85</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>mmHg</td>
<td>&lt; 45</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>bpm</td>
<td>&lt; 40</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vital Sign Parameter</th>
<th>Units</th>
<th>Clinical Concern Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Decrease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>mmHg</td>
<td>≥ 20</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>mmHg</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>bpm</td>
<td>≥ 15</td>
</tr>
</tbody>
</table>
## Appendix 8: Abbreviations & Trade Marks

### 10.8.1. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&amp;R</td>
<td>Analysis and Reporting</td>
</tr>
<tr>
<td>ADaM</td>
<td>Analysis Data Model</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>Ae</td>
<td>Amount excreted</td>
</tr>
<tr>
<td>Fe</td>
<td>Fecal excreted</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AMS</td>
<td>Accelerator Mass Spectrometry</td>
</tr>
<tr>
<td>AUC(0–inf)</td>
<td>Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time</td>
</tr>
<tr>
<td>AUC(0–t)</td>
<td>Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments</td>
</tr>
<tr>
<td>BIB</td>
<td>Bioanalysis, Immunogenicity and Biomarkers</td>
</tr>
<tr>
<td>CDISC</td>
<td>Clinical Data Interchange Standards Consortium</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum observed concentration</td>
</tr>
<tr>
<td>CPMS</td>
<td>Clinical Pharmacology Modelling &amp; Simulation</td>
</tr>
<tr>
<td>CSR</td>
<td>Clinical Study Report</td>
</tr>
<tr>
<td>CVb / CVw</td>
<td>Coefficient of Variation (Between) / Coefficient of Variation (Within)</td>
</tr>
<tr>
<td>DBF</td>
<td>Database Freeze</td>
</tr>
<tr>
<td>DBR</td>
<td>Database Release</td>
</tr>
<tr>
<td>DOB</td>
<td>Date of Birth</td>
</tr>
<tr>
<td>DP</td>
<td>Decimal Places</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic Case Record Form</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>F</td>
<td>Absolute bioavailability</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>GUI</td>
<td>Guidance</td>
</tr>
<tr>
<td>IA</td>
<td>Interim Analysis</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed Consent Form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>IDMC</td>
<td>Independent Data Monitoring Committee</td>
</tr>
<tr>
<td>IDSL</td>
<td>Integrated Data Standards Library</td>
</tr>
<tr>
<td>IMMS</td>
<td>International Modules Management System</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational Product</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
</tr>
<tr>
<td>mg</td>
<td>Milligrams</td>
</tr>
<tr>
<td>MSE</td>
<td>Mean Square Error</td>
</tr>
<tr>
<td>MMRM</td>
<td>Mixed Model Repeated Measures</td>
</tr>
<tr>
<td>PCI</td>
<td>Potential Clinical Importance</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PDMP</td>
<td>Protocol Deviation Management Plan</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PP</td>
<td>Per Protocol</td>
</tr>
<tr>
<td>QTcB</td>
<td>Bazett’s QT Interval Corrected for Heart Rate</td>
</tr>
<tr>
<td>QTcF</td>
<td>Frederica’s QT Interval Corrected for Heart Rate</td>
</tr>
<tr>
<td>RAP</td>
<td>Reporting &amp; Analysis Plan</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory Rate</td>
</tr>
<tr>
<td>SAC</td>
<td>Statistical Analysis Complete</td>
</tr>
<tr>
<td>SDTM</td>
<td>Study Data Tabulation Model</td>
</tr>
<tr>
<td>SOP</td>
<td>Standard Operation Procedure</td>
</tr>
<tr>
<td>TFL</td>
<td>Tables, Figures &amp; Listings</td>
</tr>
<tr>
<td>μg</td>
<td>Microgram</td>
</tr>
</tbody>
</table>

### 10.8.2. Trademarks

<table>
<thead>
<tr>
<th>Trademarks of the GlaxoSmithKline Group of Companies</th>
<th>Trademarks not owned by the GlaxoSmithKline Group of Companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HARP</td>
<td>Entero-Test</td>
</tr>
<tr>
<td></td>
<td>SAS</td>
</tr>
<tr>
<td></td>
<td>WinNonlin</td>
</tr>
</tbody>
</table>
10.9. Appendix 9: List of Data Displays

10.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

<table>
<thead>
<tr>
<th>Section</th>
<th>Tables</th>
<th>Figures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Population</td>
<td>1.1 to 1.8</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetic</td>
<td>2.1 to 2.13</td>
<td>2.1 to 2.11</td>
</tr>
<tr>
<td>Safety</td>
<td>3.1 to 3.13</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Section</th>
<th>Listings</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICH Listings</td>
<td>1 to 26</td>
</tr>
<tr>
<td>Other Listings</td>
<td>27 to 35</td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>Section</th>
<th>Figure</th>
<th>Table</th>
<th>Listing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic</td>
<td>PK_Fn</td>
<td>PK_Tn</td>
<td>PK_Ln</td>
</tr>
</tbody>
</table>

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

10.9.3. Deliverables

<table>
<thead>
<tr>
<th>Delivery</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR</td>
<td>Dry Run</td>
</tr>
<tr>
<td>SAC</td>
<td>Final Statistical Analysis Complete</td>
</tr>
</tbody>
</table>
## 10.9.4. Study Population Tables

<table>
<thead>
<tr>
<th>Study Population Tables</th>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subject Disposition</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1. Safety</td>
<td>1</td>
<td>Safety</td>
<td>ES1A</td>
<td>Summary of Participant Disposition for the Participant Conclusion Record</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>1.2. Screened</td>
<td>2</td>
<td>Screened</td>
<td>ES6</td>
<td>Summary of Screening Status and Reasons for Screen Failure</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>1.3. Enrolled</td>
<td>3</td>
<td>Enrolled</td>
<td>NS1</td>
<td>Summary of Number of Participant by Country and Site ID</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td><strong>Protocol Deviation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.4. Safety</td>
<td>4</td>
<td>Safety</td>
<td>DV1</td>
<td>Summary of Important Protocol Deviations</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td><strong>Population Analysed</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5. Screened</td>
<td>5</td>
<td>Screened</td>
<td>SP1A</td>
<td>Summary of Study Populations</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td><strong>Demographic and Baseline Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.6. Safety</td>
<td>6</td>
<td>Safety</td>
<td>DM3</td>
<td>Summary of Demographic Characteristics</td>
<td>Include height, weight &amp; BMI.</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>1.7. Enrolled</td>
<td>7</td>
<td>Enrolled</td>
<td>DM11</td>
<td>Summary of Age Ranges</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>1.8. Safety</td>
<td>8</td>
<td>Safety</td>
<td>DM5</td>
<td>Summary of Race and Racial Combinations</td>
<td></td>
<td>DR, SAC</td>
</tr>
</tbody>
</table>
### 10.9.5. Pharmacokinetic Tables

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma GSK1278863 and Plasma [14C] GSK1278863</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1.</td>
<td>PK</td>
<td>pkct1</td>
<td>Summary of Plasma GSK1278863 and [14C] GSK1278863 Concentration by treatment and time</td>
<td>GSK1278863: Summarized for A1 only [14C] GSK1278863: Summarized for A2 and B treatment group only Page by Regimen</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.2.</td>
<td>PK</td>
<td>pkpt1</td>
<td>Summary of Untransformed Plasma GSK1278863 and [14C] GSK1278863 Pharmacokinetic Parameters</td>
<td>GSK1278863: Summarized for A1 only [14C] GSK1278863: Summarized for A2 and B treatment group only Page by Regimen</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.3.</td>
<td>PK</td>
<td>pkpt3</td>
<td>Summary of Loge-transformed Plasma GSK1278863 and [14C] GSK1278863 Pharmacokinetic Parameters</td>
<td>GSK1278863: Summarized for A1 only [14C] GSK1278863: Summarized for A2 and B treatment group only Page by Regimen</td>
<td>DR, SAC</td>
</tr>
<tr>
<td><strong>Plasma Metabolite and [14C] Metabolite</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.4.</td>
<td>PK</td>
<td>pkct1</td>
<td>Summary of Plasma Metabolite and [14C] Metabolite concentration by time</td>
<td>Metabolite: Summarized for A1 only [14C] Metabolite: Summarized for A2 and B treatment group only Page by Regimen</td>
<td>DR, SAC</td>
</tr>
</tbody>
</table>
### Pharmacokinetic: Tables

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
</table>
## Pharmacokinetic: Tables

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

### Urine and Faecal Pharmacokinetic

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.10</td>
<td>PK</td>
<td>PK_T1</td>
<td>Summary of Cumulative Urinary and Faecal Total Radioactivity Pharmacokinetic Parameters (Amount Excreted(unit)) by Time (Treatment Period-2)</td>
<td>Includes (urine), Ae (faeces), Ae (total) parameter.</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.11</td>
<td>PK</td>
<td>PK_T1</td>
<td>Summary of Cumulative Urinary and Faecal Total Radioactivity Pharmacokinetic Parameters (% Excreted) by Time</td>
<td>Fe% (urine), Fe % (faeces), Fe% (total).</td>
<td>DR, SAC</td>
</tr>
</tbody>
</table>
## Pharmacokinetic Figures

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1.</td>
<td>PK</td>
<td>pkcf6</td>
<td>Individual Subject Plasma GSK1278863 and [14C] GSK1278863 Concentration-time Plot (Linear and Semi-log) by Treatment</td>
<td>Different plot symbols will be used for each subject</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.2.</td>
<td>PK</td>
<td>pkcf2</td>
<td>Arithmetic Mean Plasma GSK1278863 and [14C] GSK1278863 Concentration-time Plot (Linear and Semi-log) by Treatment</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.3.</td>
<td>PK</td>
<td>pkcf3</td>
<td>Median Plasma GSK1278863 and [14C] GSK1278863 Concentration-time Plot (Linear and Semi-log) by Treatment</td>
<td></td>
<td>DR, SAC</td>
</tr>
</tbody>
</table>

### Total Radioactivity

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.4.</td>
<td>PK</td>
<td>pkcf6</td>
<td>Individual Subject Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Treatment and Specimen</td>
<td>Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.5.</td>
<td>PK</td>
<td>pkcf2</td>
<td>Arithmetic Mean Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Treatment and Specimen</td>
<td>Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>2.6.</td>
<td>PK</td>
<td>pkcf3</td>
<td>Median Total Radioactivity Concentration-time Plot (Linear and Semi-log) by Treatment</td>
<td>Summarized only for [14C]-863 50 mcg IV and [14C]-GSK863 25 mg Oral Solution -Treatment groups</td>
<td>DR, SAC</td>
</tr>
</tbody>
</table>
### 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 |

### 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 |

### Safety Tables

#### Safety: Tables

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.</td>
<td>Safety</td>
<td>AE1CP</td>
<td>Summary of All Adverse Events by System Organ Class and Preferred Term</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.2.</td>
<td>Safety</td>
<td>AE1CP</td>
<td>Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency</td>
<td></td>
<td>DR, SAC</td>
</tr>
</tbody>
</table>
### Safety: Tables

<table>
<thead>
<tr>
<th>No.</th>
<th>Population</th>
<th>IDSL / Example Shell</th>
<th>Title</th>
<th>Programming Notes</th>
<th>Deliverable [Priority]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3</td>
<td>Safety</td>
<td>AE15</td>
<td>Summary of Common (&gt;=33%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.4</td>
<td>Safety</td>
<td>AE16</td>
<td>Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.5</td>
<td>Safety</td>
<td>LB1</td>
<td>Summary of Chemistry Changes from Baseline</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.6</td>
<td>Safety</td>
<td>LB1</td>
<td>Summary of Laboratory Values</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.7</td>
<td>Safety</td>
<td>LB15</td>
<td>Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.8</td>
<td>Safety</td>
<td>LB1</td>
<td>Summary of Hematology Changes from Baseline</td>
<td>Includes baseline values.</td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.9</td>
<td>Safety</td>
<td>LB1</td>
<td>Summary of Hematology values</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.10</td>
<td>Safety</td>
<td>LB15/</td>
<td>Summary of Worst Case Hematology Results Relative to Normal Range Post-Baseline Relative to Baseline</td>
<td></td>
<td>DR, SAC</td>
</tr>
<tr>
<td>3.11</td>
<td>Safety</td>
<td>EG1</td>
<td>Summary of ECG Findings</td>
<td></td>
<td>DR, SAC</td>
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### 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 |
| 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 |

### Laboratory: Hematology

| 3.8   | Safety | LB1  | Summary of Hematology Changes from Baseline | 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

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### Non-ICH Listings

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## 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

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<th>Planned Relative</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
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<th>Min.</th>
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<td>X</td>
<td>PRE DOSE</td>
<td>X</td>
<td>X.XX</td>
<td>X.XXX</td>
<td>X.XX</td>
<td>X.X</td>
<td>X.X</td>
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<td></td>
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<td></td>
<td>X-XX H</td>
<td>X</td>
<td>X.XX</td>
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Table 2.4
Summary of Statistical Analysis of Log_{e}-transformed Plasma GSK1278863 PK Parameters

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<td>(Test/Ref)</td>
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<td></td>
<td></td>
<td>n Test</td>
<td>n Ref</td>
<td></td>
</tr>
<tr>
<td>AUC(0-inf)(units)</td>
<td>A1 vs A2</td>
<td>x xx.xx</td>
<td>x xx.xx</td>
<td>x.xxxx</td>
</tr>
<tr>
<td>AUC(0-t)(units)</td>
<td>A1 vs a2</td>
<td>x xx.xx</td>
<td>x xx.xx</td>
<td>x.xxxx</td>
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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

Subject xx

Recovery (% of dose)

Actual Mid-Point of Collection (hrs)
Figure 2.8
Arithmetic Mean Cumulative total - Radioactivity Recovered (% of Dose) for Urine, Faeces and Total Excretion
### Listing XX

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

**Treatment:** [14C]GSKXXXX

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<th>Inv./ Subj.</th>
<th>Time</th>
<th>Start Date/ Time</th>
<th>Planned Relative Time</th>
<th>Fe Faeces Ae</th>
<th>Fe Faeces Ae</th>
<th>Faeces Ae</th>
<th>Faeces Ae</th>
<th>Urine Ae</th>
<th>Urine Ae</th>
<th>Total Ae</th>
<th>Total Ae</th>
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<td>PRE DOSE X</td>
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<tr>
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<td>XX:XX</td>
<td>XXJUNXXXX/</td>
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<td>XX:XX</td>
<td>XXJUNXXXX/</td>
<td>XX-XX H</td>
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</tr>
</tbody>
</table>

**Note:** Ae = Amount excreted. NS = No Sample.
Listing of Urinary and Faecal Total Radioactivity Parameters (% Excreted) by Time

Treatment: [14C]GSKXXXX

<table>
<thead>
<tr>
<th>Inv./Subj.</th>
<th>Fe Faeces Start Date/Time</th>
<th>Fe Urine Start Date/Time</th>
<th>Planned Relative Time</th>
<th>Cumulative Fe Faeces</th>
<th>Cumulative Fe Urine</th>
<th>Cumulative Fe Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXXXXXX/</td>
<td>XXJUNXXXX/</td>
<td>XXJUNXXXX/</td>
<td>PRE DOSE X</td>
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<td>X.X</td>
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<td>XX:XX/</td>
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<td>XXJUNXXXX/</td>
<td>X-XX H</td>
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<td>XX:XX</td>
<td>XX:XX</td>
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<td>XX:XX</td>
</tr>
</tbody>
</table>

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