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

Title	:	Reporting and Analysis Plan for Open-label, Dose-escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Single Doses of GSK2586881 in Participants with Pulmonary Arterial Hypertension
Compound Number	:	GSK2586881
Effective Date	:	15-FEB-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 206246.
- This RAP is intended to describe the safety, pharmacodynamic and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Interim Analyses and Statistical Analysis Complete (SAC) deliverable.

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TABLE OF CONTENTS

PAGE

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:		
2016N290015_00	04/APR/2017	Original
2016N290015_01	03/MAY/2017	Amendment 1
2016N290015_02	07/NOV/2017	Amendment 2
2016N290015_03	01/DEC/2017	Amendment 3

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

To support internal decision making, some additional analyses have been included to output posterior probabilities for the primary hemodynamic measurements and also for Cardiac Index (CI) in relation to change from baseline (ratio to baseline).

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

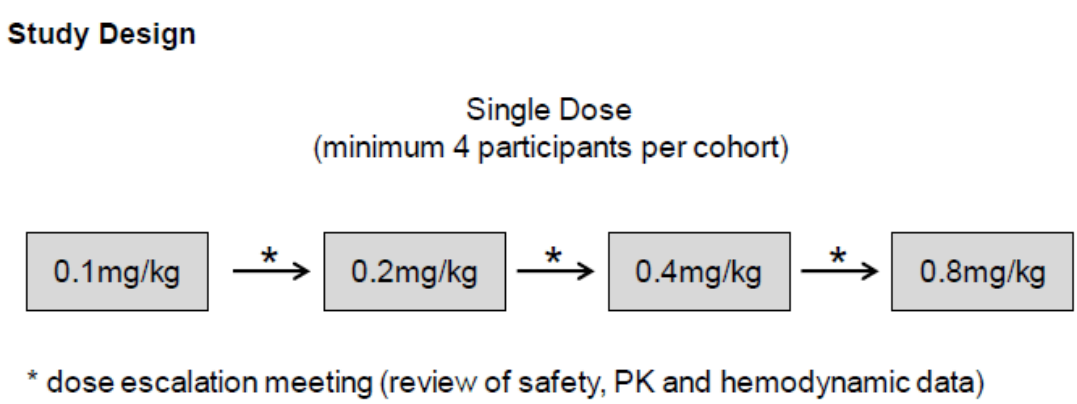
Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To evaluate changes in the pulmonary hemodynamics after single IV doses of GSK2586881 administered to participants with PAH receiving background PAH therapy.	• Change from baseline in pulmonary vascular resistance (PVR), cardiac output (CO) and mean pulmonary artery pressure (mPAP), as data permit
Secondary Objectives	**Secondary Endpoints**
• To evaluate the safety and tolerability of single IV doses of GSK2586881 administered to participants with PAH receiving background PAH therapy.	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), pulse oximetry and immunogenicity.
• To evaluate the effect of single IV doses of GSK2586881 on RAS peptide concentrations in participants with PAH receiving background PAH therapy.	• Change from baseline of pulmonary wedge and systemic RAS peptides (e.g. Ang II, Ang(1-7), Ang(1-5) and AngII/Ang(1-7) ratio) (a)
• To evaluate the effect on biomarkers of disease activity after single IV doses of GSK2586881 administered to participants with PAH receiving background PAH therapy.	• Change from baseline in NT pro-BNP, NO and cardiac troponin I.
• To evaluate the pharmacokinetics (PK) of GSK2586881 after single IV doses of GSK2586881 in participants with PAH receiving background PAH	• Plasma concentrations of GSK2586881 and derived PK parameters.

Objectives	Endpoints
therapy.	
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate PK/PD relationships after single IV doses of GSK2586881	• RAS peptides (systemic and pulmonary wedge) and/or pulmonary vascular hemodynamic measurements compared with PK exposure. (b)
• To evaluate pharmacogenetics (PGx).	• Evaluate I/D polymorphisms in the Angiotensin Converting Enzyme (ACE) gene and analyze the impact on Ang II (and possibly other RAS peptides), and responses to GSK2586881 administration.

(a) Note for reporting the terms 'venous (systemic) RAS peptides' and 'pulmonary wedge RAS peptides' will be presented to clearly distinguish between the systemic venous sampling and the arterial venous pulmonary wedge sampling.

(b) Note this endpoint has been updated slightly from the current protocol amendment which states "Pulmonary wedge RAS peptides, and/or pulmonary vascular hemodynamic measurements compared with PK exposure" to clarify that both venous (systemic) and pulmonary wedge RAS data will be evaluated.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Open-label, phase IIa, dose-escalation study in participants with PAH (as defined in the eligibility criteria) whose symptoms have been clinically stable for 8 weeks prior to enrolment and who have had no change in PAH-specific therapy in the 12 weeks prior to enrolment.
Dosing	• Single dose
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Each participant will be assigned to a single dose at one dose level as shown above
Interim Analysis	• Review of Safety, PK and hemodynamics after 4 subjects have completed each dose level

2.4. Statistical Hypotheses / Statistical Analyses

There are no statistical hypotheses for this study. Data will be presented descriptively with supportive posterior probabilities for selected hemodynamic endpoints in relation to changes from baseline (ratio to baseline).

3. PLANNED ANALYSES

3.1. Interim Analyses

The planned dose levels for the study are 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg and 0.8 mg/kg. Each cohort will recruit a minimum of 4 subjects to a dose level. After the final participant has completed dosing within a given cohort and data are available, a dose escalation meeting will take place. If additional participants are added to a particular dose level, a further meeting may be held to review the additional data.

The study review team may include the following (or delegates as appropriate): Clinical Statistics, CPMS, GCSP, CIL, OSL, Medical Monitor and DQL. Other functions may be invited as required. The data will be used to support the decision to move to the next dose level as planned. Decisions made at each meeting in relation to a given dose, will be documented in the CPSR. For dose escalation decision making, the data to be reviewed will be preliminary safety, PK and hemodynamics. RAS peptide data, if available, will also be reviewed in stream.

Prior to each dose escalation meeting, unblinded safety data for this open-label study will be made available to the study team via listings from Inform and Q2 Results Viewer. In addition, CPMS will obtain the interim unblinded PK concentration data from SMS2000 via HARP according to current working practices. If any process changes occur which affect the way in which SMS2000 data is obtained during the study, then the applicable process at the time will be followed and any changes in processes between dose escalations will be documented. Descriptive tabular summaries (geometric mean, CV(%), median and range) for PK parameters and graphical presentation of PK concentration data will be produced, as appropriate, based on nominal times.

Preliminary hemodynamic data for the primary endpoints PVR, CO, mPAP and also Cardiac Index (CI) will be summarised descriptively by the Statistics and Programming team (S&P). Summary statistics and a data listing will be produced by endpoint, for each dose escalation review. In addition, a graphic will be produced for each endpoint, displaying all subjects within the given dose group, by timepoint (i.e. overlaid time profiles for each subject).

To support internal team decision making (particularly around the lower doses of 0.1 mg/kg and 0.2 mg/kg), a Bayesian analysis of change from baseline (ratio to baseline) in PVR, CO, mPAP and CI will be performed and posterior probabilities produced (see Section 7.1.5). Only analyses carried out at the final reporting effort, once all dose groups have completed, will be included in the CPSR. In addition, for the hemodynamic parameters and available RAS data, individual participant profiles may be presented alongside profiles from a previous investigator led study (NCT01884051) for visual comparison.

A summary of the dose escalation meetings is provided in the table below. The steps below assume no changes to the planned doses, however, there is flexibility to adapt/change a dose if required during the study and the format of the dose escalations below would be modified to accommodate any dose changes. In addition, flexibility is

allowed within the study to recruit additional participants to a previous cohort (post dose escalation review) if a need for further data is required. Any additional participants would be summarised as part of the final (all dose groups) reporting.

Dose Escalation [DE] Level	Data to be Reviewed/Output after a minimum of 4 participants have completed
• Review of Dose Level 1: 0.1 mg/kg (planned) • DE[1]	• Safety: Via Q2 Results Viewer and Inform • PK: CPMS to use SMS2000 data based on nominal times and generate summaries, and graphs. • PD (PVR, CO, mPAP & CI): S&P will generate a summary table, listing and individual subject graphic (all subjects on one graph) for each endpoint based on SI data provided by Data Management via HARP. Outputs may be produced using PC SAS or HARP. • Posterior probabilities (PVR, CO, mPAP & CI). • Review of RAS data (if available or post dose escalation meeting).
• Review of Dose Level 2: 0.2 mg/kg (planned) • DE[2]	• Safety: Via Q2 Results Viewer and Inform • PK: CPMS to use SMS2000 data based on nominal times and generate summaries, and graphs. • PD (PVR, CO, mPAP & CI): S&P will generate a summary table, listing and individual subject graphic (all subjects on one graph) for each endpoint based on SI data provided by Data Management via HARP. Outputs may be produced using PC SAS or HARP. • Posterior probabilities (PVR, CO, mPAP & CI). • Review of RAS data (if available or post dose escalation meeting)
• Review of Dose Level 3: 0.4 mg/kg (planned) • DE[3]	• Safety: Via Q2 Results Viewer and Inform • PK: CPMS to use SMS2000 data based on nominal times and generate summaries, and graphs. • PD (PVR, CO, mPAP & CI): S&P will generate a summary table, listing and individual subject graphic (all subjects on one graph) for each endpoint based on SI data provided by Data Management via HARP. Outputs may be produced using PC SAS or HARP. • Posterior probabilities (PVR, CO, mPAP & CI). • Review of RAS data (if available or post dose escalation meeting)
• Final Reporting (SAC)	• Data for all dose levels including the planned 4th dose of 0.8 mg/kg will be summarised in the final reporting.

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.
3. All criteria for unblinding the randomization codes have been met (*the study is open-label but randomisation numbers are still generated for each cohort)*.
4. Randomization codes have been distributed according to RandAll NG procedures (*the study is open-label but a Randall dataset is still generated*)

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who sign the ICF	Screening summaries
Safety	All participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received.	Study Population & Safety
Evaluable	Evaluable: All participants who are in the Safety population who complete all Day 1 assessments (including up to 24 hours post dose) and were not deemed to have had major protocol deviations (as defined within the PDMP)	PD
Pharmac-okinetic	Subjects in the 'Safety' population for whom a pharmacokinetic sample was obtained and analysed.	PK

Refer to Appendix 11: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

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

- Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis 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. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		**Data Displays for Reporting**	
Code	**Description**	**Description**	**Order in TLF**
A	Dose 1	GSK2586881 i.v. 0.1 mg/kg	1
B	Dose 2	GSK2586881 i.v. 0.2 mg/kg	2
C	Dose 3	GSK2586881 i.v. 0.4 mg/kg	3
D	Dose 4	GSK2586881 i.v. 0.8 mg/kg	4

NOTES: Order represents treatments being presented in TFL, as appropriate.

As this is a small study, for graphical representation, each participant may be assigned a unique combination of plotting symbol / line style / colour based on the attribute map facility using SAS SG procedures. The GSK statistician will provide further details to the study team. The unique characterisation will apply to all graphics of by subject data. In the case that an alternative statistical package is used, every effort will be made to apply a unique set of graphical characterisations for subjects.

In addition, for graphics summarising data by dose group, colours/symbols for each dose group will be made consistent throughout. For example:

GSK2586881 i.v. 0.1 mg/kg - blue diamond
GSK2586881 i.v. 0.2 mg/kg - red square
GSK2586881 i.v. 0.4 mg/kg - green circle
GSK2586881 i.v. 0.8 mg/kg - black star.

5.2. Baseline Definitions

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

Parameter	**Study Assessments Considered As Baseline**		**Baseline Used in Data Display**
	Screening	**Day 1 (Pre-Dose)**	
Safety			
Labs	X	X	Day 1
ECGs	X [1]	X [1]	Day 1 [1]
Vital Signs	X [1]	X	Day 1
Pulse Oximetry	X	X	Day 1
Immunogenicity		X	Day 1

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose)	
Biomarkers/Pharmacodynamic			
RAS peptides, disease activity biomarkers		X	Day 1
Hemodynamics (e.g., PVR, CO, mPAP & CI)		X	Day 1

[1] Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.

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
13.3	Appendix 3: Study Phases and Treatment Emergent Adverse Events
13.4	Appendix 4: Data Display Standards & Handling Conventions
13.5	Appendix 5: Derived and Transformed Data
13.6	Appendix 6: Reporting Standards for Missing Data
13.7	Appendix 7: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of subject's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Data collected for functional class, 6-minute walking distance and PAH underlying cause will also be summarised. Details of the planned displays are presented in Appendix 11: List of Data Displays.

6.2. Concomitant Medications for PAH

PAH medications (reason for medication) will be reviewed by the medical monitor. Two reviews will be planned; one prior to DBF to enable pre-programming and a final review on receipt of final concomitant medication data at DBF. An intermediate review will take place if required. A spreadsheet of the databased concomitant medications will be generated by S&P for review by the medical monitor, who will add a flag to records that are relevant to PAH. S&P will then use the spreadsheet when creating the derived A&R CMANAL dataset to include the flagged records for use within the corresponding output.

In addition, to support the programming of PCI ranges for International Normalized Ratio (INR), Prothrombin time (PT) and PTT (see Section 13.7.1) medications of Heparin or Warfarin will need to be confirmed per participant by review of related concomitant medication terms. This will require non-standard coding for the programming of PCI ranges.

7. PHARMACODYNAMIC AND BIOMARKER ANALYSES

7.1. Primary Analyses

7.1.1. Endpoint / Variables

The primary endpoints are hemodynamic measurements of:

- Pulmonary Vascular Resistance (PVR)
- Cardiac Output (CO)
- Mean Pulmonary Artery Pressure (mPAP)

Additional hemodynamic endpoints are:

- Right Atrial Pressure
- Pulmonary Artery Systolic Pressure
- Pulmonary Artery Diastolic Pressure
- Pulmonary Capillary Wedge Pressure
- Cardiac Index (CI)
- Pulmonary Artery Oxygen Saturation

7.1.2. Summary Measure

Absolute and change from baseline will be the summary measures of interest for hemodynamic endpoints. Hemodynamic measurements will also be log transformed to aid further analysis and therefore the change from baseline geometric means at each post-dose timepoint, will represent a percentage increase/decrease from baseline (presented as a ratio to baseline).

7.1.3. Population of Interest

The primary efficacy analyses will be based on the Evaluable population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Hemodynamic data will be collected according to the timepoints referenced in Appendix 2: Schedule of Activities. Missing data will not be replaced.

The Evaluable population defined in Section 4, utilises patients who complete all Day 1 assessments. If a consistent pattern of withdrawals prior to the completion of Day 1 is noted (for example, sensitivity to the catheter causing it to be removed early) which causes a lower than expected Evaluable population, then additional reviews of available data for those not included in the Evaluable population may take place.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

A Bayesian analysis will be conducted by dose group and timepoint displaying posterior probabilities as detailed in Section 7.1.5.1.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• PVR, CO, mPAP and CI
Model Specification
• The description below describes the current thinking of how to analyse this endpoint. The proposed model will be assessed, and if not appropriate alternative models could be used. Reasons for and a full description of alternative modeling/analysis methods used would be fully documented in the CPSR. • Separate Bayesian repeated measures mixed effect models (one model per endpoint) will be used to assess changes from baseline for dose group and post-treatment timepoint combinations. Individual patient data will be log-transformed prior to analysis and change from baseline (CFB) calculated on transformed data. The Baseline values (BS) used in the model should also have been log-transformed prior to their use. Note: The modeling described below should be appropriately modified for the 1st interim analysis (e.g. to remove terms involving dose). Response: CFB = BS*Time + Time + Dose + Dose*Time Fixed effects: (class) Time [3 levels, 1H, 2H and 4H], Dose level [either 0.1, 0.2, 0.4 or 0.8 mg/kg as appropriate to the timing of the <interim> analysis]. Fixed effects: (continuous): Baseline value (on the Ln scale) Repeated measures on Time, Subject=Subject, Unstructured Variance Co-Variance (VCV) matrix (3x3) Appropriate combinations of the fitted model parameters will be used to obtain posterior distributions (one per planned comparison). The planned comparisons are the equivalent of the LSMeans for each timepoint within each dose level (on a back transformed scale their interpretation is the fold change c.f. baseline). • Non-informative priors should be assumed for all model parameters. Therefore, unless there is a large proportion of missing data, the posterior probabilities may be obtained by fitting the proposed model using SAS PROC MIXED and extracting the appropriate pieces of information. • However, if PROC MCMC is used then the default prior for each fixed effect model parameter should be Normal~(Mean=0, Var=1E6). The default prior for the VCV matrix would be an Inverse-Wishart with parameters k and **S** (where **S** = (k – p - 1) * **R** and p = dimension of the

VCV matrix). Under this framework **R** can be thought of as a best guess for the VCV of the endpoint being modelled. Care should be taken in the choice of k and **R** for each endpoint. The default should set k = 5 (p + 2) and **R** should be set to the following for each endpoint, in order to obtain the value of **S** to put into the inverse-Wishart prior:

CO (L/min)	CI (L/Min/m**2)	PVR (Wood units)	mPAP (mmHg)
$\begin{pmatrix} 0.160 & 0.096 & 0.017 \\ 0.096 & 0.064 & 0.014 \\ 0.017 & 0.014 & 0.005 \end{pmatrix}$	$\begin{pmatrix} 0.160 & 0.096 & 0.017 \\ 0.096 & 0.064 & 0.014 \\ 0.017 & 0.014 & 0.005 \end{pmatrix}$	$\begin{pmatrix} 0.323 & 0.204 & 0.070 \\ 0.204 & 0.544 & 0.111 \\ 0.070 & 0.111 & 0.030 \end{pmatrix}$	$\begin{pmatrix} 0.031 & 0.031 & 0.007 \\ 0.031 & 0.039 & 0.017 \\ 0.007 & 0.017 & 0.018 \end{pmatrix}$

These values of **R** were obtained from a historical study (GSK ID 204696) and unit conversion may be required to match this study.

(Note: depending on the software used and parameterization the above may need to be adjusted to use a Wishart instead of the inverse-Wishart).

Given the small sample sizes in this study the above priors may be more informative/influential than intended. An optional sanity check may be made by comparing the observed sample VCV matrix to the prior. If there are large discrepancies alternative priors may be attempted/evaluated as part of sensitivity analyses (and the output from the most appropriate model reported in the CPSR along with a brief justification/discussion on any switched priors). For example **R** may be replaced by the observed sample VCV matrix (on the log transformed scale) once the study data are available.

- Posterior medians and 95% credible intervals will be presented for each posterior distribution. <As stated previously estimates will be back-transformed so that the difference from baseline represents a ratio.>
- The posterior distributions will be used to produce several probability statements, presented in tabular format. This will include but are not limited to:
  - PVR, the probability of any % reduction from baseline (<0%), <-20% and <-30% (equivalent to <1, <0.8 and <0.7 in terms of a ratio from baseline)
  - CI, the probability of any % increase from baseline (>0%), >20% and >30% (equivalent to >1, >1.2 and >1.3 in terms of a ratio from baseline)
  - CO probability of >0% increase (or >1 in terms of a ratio from baseline)
  - mPAP probability of <0% (or <1 in terms of a ratio from baseline)

Model Checking & Diagnostics

- Assumptions regarding normality will apply if the analysis is conducted using proc mixed. Should major violations occur (caveat being that the sample sizes will be small) then a non-parametric Wilcoxon signed rank test may be considered.

Model Results Presentation

- A summary table will be produced for each endpoint by dose group and timepoint, displaying medians and 95% credible intervals for the change from baseline (ratio to baseline) endpoints along with the posterior probabilities as described above.

7.2. Secondary Analyses

7.2.1. Endpoint / Variables

The secondary biomarker endpoints are:

Venous (systemic) RAS Peptides:

- Ang II
- Ang(1-7)
- Ang(1-5)
- Ang II / Ang(1-7)

Pulmonary Wedge RAS Peptides:

- Ang II
- Ang(1-7)
- Ang(1-5)
- Ang II / Ang(1-7)

Disease Activity Biomarkers:

- NT pro-BNP
- Serum NO
- Cardiac troponin I

7.2.2. Summary Measure

Absolute and change from baseline will be the summary measures of interest for RAS Peptides and Disease Activity Biomarkers. As a log-transformed summary for biomarkers will be included, the change from baseline geometric means will represent a percentage increase/decrease from baseline (presented as a ratio to baseline).

7.2.3. Population of Interest

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

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

Venous (systemic) RAS peptide data will be collected at timepoints in line with the PK. Pulmonary wedge RAS peptides will be collected in line with hemodynamic data pre-dose to 4 hours post dose. Disease activity biomarkers will be collected at timepoints up to 24 hours. For details on data collection timepoints, refer to Appendix 2: Schedule of Activities. Missing data will not be replaced but data recorded as NQ will be imputed based on details given in Appendix 6: Reporting Standards for Missing Data.

7.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 11: List of Data Displays.

8.2. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Hematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 11: List of Data Displays.

8.3. 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 11: List of Data Displays.

For systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR), in addition to standard tables and listings, the change from baseline over time by dose group will displayed graphically along with individual subject profiles.

9. PHARMACOKINETIC ANALYSES

9.1. Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 13.4.3 Reporting Standards for Pharmacokinetic).

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin Pro. For the final reporting effort (see Section 3.1 for interim details of pharmacokinetic analyses), all calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity will be calculated as: **AUC = AUC(0-t) + C(t) / lambda_z**
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
Clast	Last observed quantifiable concentration
tlast	Time of the last observed quantifiable concentration
CL	Plasma clearance
V	Volume of distribution
Lambda_z	The first order rate constant associated with the terminal (log-linear) portion of the concentration-time curve.
Lambda_z_lower	First time point used in computing Lambda_z.
Lambda_z_upper	Last time point used in computing Lambda_z.
#pts	Number of points used in computing Lambda_z.
r-squared	R-squared of Lambda_z computation.

- Additional parameters may be included as required
- Lambda_z is the terminal phase rate constant

9.1.2. Population of Interest

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

9.1.3. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 11: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 9.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

A population PK analysis, to characterize the population pharmacokinetics of GSK2586881 administered IV in participants with PAH, may be conducted, if appropriate. To support this analysis, a NONMEM-specific data file will be generated, the specifications of which are provided in Appendix 8: Population Pharmacokinetic (PopPK) Analyses. Specific details of the analysis, which may be part of a population PK meta-analysis with historical data, will be appropriately documented in a separate RAP and report which will be written by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline, as required. The timeline for these analyses will be independent of the analysis described in this RAP.

11. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of these exploratory analyses are to investigate the pharmacokinetic / pharmacodynamic relationship(s) of GSK2586881 administered IV in participants with PAH. Graphics of RAS Peptides vs PK concentrations and hemodynamic endpoints vs PK concentrations using the PK population, unless otherwise specified, will be initially used to assess any potential relationships. If data permit, the potential association between systemic exposure of GSK2586881 and RAS peptides (Ang II, Ang(1-7), Ang(1-5) and AngII/Ang(1-7) from both venous (systemic) and pulmonary wedge sampling) and clinical endpoints (e.g., PVR, CO, mPAP and CI) may be studied. To support any analyses that is required based on the initial graphical assessment, NONMEM-specific data files will be generated, the specifications of which are provided in Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses. Specific details of any PK/PD analysis, which may be part of a population PK meta-analysis with historical data, will be appropriately documented in a separate RAP and report which will be written by, or under the direct auspices of, Clinical Pharmacology Modelling and Simulation (CPMS), GlaxoSmithKline, as required. The timeline for these analyses will be independent of the analysis described in this RAP.

12. REFERENCES

Not Applicable

13. APPENDICES

13.1. Appendix 1: Protocol Deviation Management and Definitions for Evaluable Population

13.1.1. Exclusions from Evaluable Population

Subjects with major/important protocol deviations will be excluded from Evaluable Population. The Protocol Deviation Management Plan (PDMP) will be used to determine major/important protocol deviations that will lead to exclusion from the Evaluable Population.

13.2. Appendix 2: Schedule of Activities

13.2.1. Protocol Defined Schedule of Events

Procedure	Screening (up to 28 days before dosing)	Treatment Period									Follow-up Day 7-14	Follow-up Day 28 ± 3 days	Notes
		Pre-dose[1]	0h	0.08h (5 min)[2]	0.5h	1h	2h	4h	8h	24h			
Informed consent	X												
Genetics consent	X												
Inclusion and exclusion criteria	X												Recheck clinical status before randomization and/or 1st dose of study medication
Demography	X												
Full physical examination including height and weight	X												
Medical history (includes substance usage and family history of premature CV disease)	X												Substances: drugs, alcohol, tobacco and caffeine
Past and current medical conditions	X												

Procedure	Screening (up to 28 days before dosing)	Treatment Period									Follow-up Day 7-14	Follow-up Day 28 ± 3 days	Notes
		Pre-dose[1]	0h	0.08h (5 min)[2]	0.5h	1h	2h	4h	8h	24h			
Serum OR urine pregnancy test (WOCBP only)	X	X									X		
FSH and estradiol test (postmenopausal females only as needed)	X												
Human Immunodeficiency Virus (HIV), Hepatitis B and C screening	X												If test performed within 3 months prior to first dose of study treatment, testing at screening is not required
Functional classification	X												
6 Minute Walk Distance	X[3]												
Admission		X											Participants may be admitted the day before dosing to enable completion of required pre-dose time point assessments.
Brief physical		X									X		
Study Treatment			X										

Procedure	Screening (up to 28 days before dosing)	Treatment Period									Follow-up Day 7-14	Follow-up Day 28 ± 3 days	Notes
		Pre-dose[1]	0h	0.08h (5 min)[2]	0.5h	1h	2h	4h	8h	24h			
Vital Signs	X	X			X	X	X	X	X	X	X		Vital signs will be measured after 5 minutes supine at all time points. Triplicate blood pressure (BP) will be taken at screening only.
Pulse Oximetry (SpO_2)	X	X			X	X	X	X	X	X	X		Pulse oximetry will be measured and recorded with each blood pressure assessment
Laboratory assessments (include liver chemistries, haematology panel and coagulation panel)	X	X								X	X		
Urinalysis	X									X			
12-lead ECG	X	X						X		X	X		Triplicate will be performed at Screening and Pre-dose

Procedure	Screening (up to 28 days before dosing)	Treatment Period									Follow-up Day 7-14	Follow-up Day 28 ± 3 days	Notes
		Pre-dose[1]	0h	0.08h (5 min)[2]	0.5h	1h	2h	4h	8h	24h			
Telemetry		←----------								----------→			Monitoring to start 30min prior to treatment administration and continue throughout the study until 24h after dosing
Right heart catheter Insertion		←----------								----------→			RHC inserted prior to dose and removed after the 4h hemodynamic measurement
Blood sample for biomarkers of disease activity		X					X	X		X			
Blood sample for Nitric Oxide		X					X	X		X			
Blood sample for PK		X		X	X	X	X	X	X	X			
Blood sample for immunogenicity		X									X	X	

Procedure	Screening (up to 28 days before dosing)	Treatment Period									Follow-up Day 7-14	Follow-up Day 28 ± 3 days	Notes
		Pre-dose[1]	0h	0.08h (5 min)[2]	0.5h	1h	2h	4h	8h	24h			
Blood sample for renin-angiotensin system biomarkers		X		X	X	X	X	X	X	X	X		
Blood sample for transpulmonary RAS biomarkers		X				X	X	X					
Hemodynamic measurements		X				X	X	X					
Genetic sample		X											Can be taken any time after consent
Discharge										X			
AE review		←==========								==========→	X		
SAE review	X	←==========								==========→	X		
Concomitant medication review[4]	X	X									X		

1. Pre-dose measurements may be taken any time after admission up until dosing.
2. Procedures will be completed immediately after dosing has completed.
3. If the six minute walk(6MW) has been performed in the last 6 months, and participant has been stable on current medications then there is no need to repeat. Historical data will be databased.
4. Concomitant medications for the 30 days prior (8 weeks prior for PAH medications) will be reviewed/recorded at screening to evaluate eligibility and changes will be recorded throughout the study.

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

13.3.1. Study Phases

This is a single dose study. Assessments and events will be classified according to time of occurrence relative to the start date and time of the study treatment.

Treatment State	Definition
Pre-Treatment	AE Start Date / Time < Study Treatment Start Date / Time This will apply to all subjects enrolled into the study, including those who were not assigned to a dose (screen failures). For screening failures, any SAEs will be captured in the relevant listing. For dosed subjects included in the Safety population, these events will be captured in summary listings with treatment group='Pre-Treatment'.
On-Treatment	Study Treatment Start Date / Time ≤ AE Start Date / Time ≤ Follow-up (Day 7-14) Date
Post-Treatment	AE Start Date > Follow-Up (Day 7-14) Date There shouldn't be any instances of this. Subjects return for a follow-up visit between Days 7 and 14 and AEs/SAEs prior to this will be recorded. Subjects then return for a Day 28 follow-up but AEs/SAEs will not be recorded.
Onset Time Since 1st Dose (Days/Hours/Mins)	If Study Treatment Start Date / Time ≤ AE Start Date / Time = AE Start Date / Time – Study Treatment Start Date / Time + 1 (min) Missing otherwise. A calculation to assess the time since the single dose up until the start time of the AE. Example: If Dose was administered at 08:00am 01OCT2017 and AE started at 09:10am 01OCT2017, then onset time since **first** dose would be 0d 1h 11m.
Duration (Days/Hours/Mins)	AE Resolution Date /Time – AE Onset Date / Time + 1 (min) Example: AE started at 08:00am and resolved at 08:30am on the same day, then duration would be 0d 0h 31m
Drug-related	If relationship is marked 'YES' on Inform OR value is missing.

13.3.1.1. 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

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.

13.4. Appendix 4: Data Display Standards & Handling Conventions

13.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: \\UK1SALX00175.corpnet2.com\ARENV\
HARP Compound	: \ARPROD\GSK2586881\206246\Internal_01 : \ARPROD\GSK2586881\206246\Internal_02 : \ARPROD\GSK2586881\206246\Internal_03 : \ARPROD\GSK2586881\206246\Internal_04 : \ARPROD\GSK2586881\206246\Final_01
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

13.4.2. 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
• Subject level listings in the main body of the GSK Clinical Study Report. All subject level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• 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 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.	

13.4.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487. 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: For standard PK outputs concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only. For PK/PD graphics only which are generated by S&P, ½ LLQ can be used for NQ PK data to coincide with methods used for Biomarker data (see Section 13.6.2). Variables relating to different imputation methods for PK data will be available within the derived A&R PKCNC dataset.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 13.8.1 Population Pharmacokinetic (PopPK) Dataset Specification.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the data specification detailed in Section 13.9.1 Pharmacokinetic/Pharmacodynamic Dataset Specification.
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to [Standards for Handling NQ Impacted PK Parameters].
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. The following PK parameters will not included in summary tables: Lambda_z, lambda_z_lower, lambda_z_upper, #pts, R squared

13.5. Appendix 5: Derived and Transformed Data

13.5.1. 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. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • 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

13.5.2. Study Population

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** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

13.5.3. Pharmacodynamic and Biomarker

Pharmacodynamic	
Pulmonary Hemodynamics	
Pulmonary Vascular Resistance (PVR) Cardiac Output (CO) Mean Pulmonary Artery Pressure (mPAP) Cardiac Index (CI) Right Atrial Pressure Pulmonary Artery Systolic Pressure Pulmonary Artery Diastolic Pressure Pulmonary Capillary Wedge Pressure Pulmonary Artery Oxygen Saturation	[All endpoints will be provided in SI datasets]
Variance stabilising transformations (e.g. taking natural logarithms of the observed responses) may be implemented on a per endpoint basis, if deemed necessary by the study statistician. If transformations are used the results will be reported on the back-transformed response scales. When assessing change from baseline, the individual timepoint values will be log-transformed prior to calculating a change from baseline difference (in log transformed values). Back transformation and summaries of the geometric mean and 95% CI of the back-transformed change from baseline calculations will represent percentage increase/decrease from baseline (presented as a ratio to baseline).	
Biomarker	
RAS Peptides	
RAS Venous (systemic) Samples: • Ang II, Ang(1-5), Ang(1-7) will be provided in SI datasets • Ang II / Ang(1-7) ratio will be derived in A&R datasets RAS Pulmonary Wedge Samples: • Ang II, Ang(1-5), Ang(1-7) will be provided in SI datasets • Ang II / Ang(1-7) ratio will be derived in A&R datasets	
Disease Activity Biomarkers	
NT Pro-BNP, NO and Cardiac Troponin I will be provided in SI datasets	
For biomarkers, variance stabilising transformations (e.g. taking natural logarithms of the observed responses) may be implemented on a per endpoint basis, if deemed necessary by the study statistician. If transformations are used the results will be reported on the back-transformed response scales. When assessing change from baseline, the individual timepoint values will be log-transformed prior to calculating a change from baseline difference (in log transformed values). Back transformation and summaries of the geometric mean and 95% CI of the back-transformed change from baseline calculations will represent percentage increase/decrease from baseline.	

Pharmacodynamic						
Source of Biomarker Data						
Biomarker Category	**Analyte**	**Sample**	**Method**	**Lab**	**Matrix**	**Total samples expected per subject**
RAS Peptides[1]	Ang II	Venous	LC/MS	Q2	Plasma	9
	Ang (1-5)	Venous	LC/MS	Q2	Plasma	9
	Ang (1-7)	Venous	LC/MS	Q2	Plasma	9
RAS Peptides[2]	Ang II	Pulmonary Wedge	LC/MS	Q2	Plasma	4
	Ang (1-5)	Pulmonary Wedge	LC/MS	Q2	Plasma	4
	Ang (1-7)	Pulmonary Wedge	LC/MS	Q2	Plasma	4
Disease Biomarkers[3]	NT pro-BNP	Venous	Elisa	Q2	Serum	4
	Nitric Oxide	Venous	Chemical Method	Q2	Plasma	4
	Cardiac troponin I	Venous	Elisa	Q2	Serum	4

NOTES :

1. Sampling times: Pre-dose, End of Infusion, 0.5h, 1h, 2h, 4h, 8h, 24h, follow-up day 7-14
2. Sampling times: Pre-dose, 1h, 2h and 4h
3. Sampling times: Pre-dose, 2h, 4h and 24h

13.6. Appendix 6: Reporting Standards for Missing Data

13.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as a participant who has completed all phases of the study including the follow up visit and the last scheduled procedure • Withdrawn subjects may be replaced in the study at the discretion of the sponsor. • All available data from participants 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.

13.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. o Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Biomarkers	• Any values below the Lower Limit of Quantification (LLQ) will be assigned a value of ½ LLQ for display purposes in Figures and for computation of summary statistics. Any values above the Upper Limit of Quantification (ULQ) will be assigned to the ULQ for display purposes in Figures and for computation of summary statistics. If multiple LLQ and /or ULQ values are available per assay (for example if multiple runs with different standard curves are utilised) then the LLQ and/or ULQ value used for the above imputation shall be the minimum of the available LLQs and/or the maximum of the ULQs. • If the number of LLQ (and/or ULQ) values is large for an individual biomarker then alternative analysis strategies may be required. "Large" is hard to define prospectively and may depend upon the dataset in question but a general rule of thumb is if >30% of values are LLQ and/or ULQ. If "large" numbers of LLQ and/or ULQ values are observed methodologies to summarise and analyse the responses similar to those detailed in "Standards for the Handling of NQ impacted PK Parameters" (Respiratory DB and CPMS - 14th December 2009) may be employed. Any such methodology will be documented in the statistical contributions to the clinical study report.

For the derivation of the pulmonary wedge and venous (systemic) AngII / Ang(1-7) **ratios**, the following will apply:

Flags		Numerator (ANGII)			
		BLQ	**Data**	**ALQ**	**Missing**
Denominator (ANG1-7)	**BLQ**	(1/2 LLQ of ANGII) / (1/2 LLQ of Ang(1-7))	ANGII / (1/2 LLQ of Ang(1-7))	(ULQ of ANGII) / (1/2 LLQ of Ang(1-7))	Missing
	Data	(1/2 LLQ of ANGII) / Ang(1-7)	ANGII / Ang(1-7)	(ULQ of ANGII) / Ang(1-7)	Missing
	ALQ	(1/2 LLQ of ANGII) / (ULQ of Ang(1-7))	ANGII / (ULQ of Ang(1-7))	(ULQ of ANGII) / (ULQ of Ang(1-7))	Missing
	Missing	Missing	Missing	Missing	Missing
LLQ / ULQ = Lower / Upper Limit of Quantification, **BLQ / ALQ** = Below / Above Limit of Quantification					

Note: The status of the numerator and denominator should be stored within derived datasets so they can be used in subsequent Summary Tables to display the amount of imputation necessary.

In addition, to support the PK/PD file to be generated (see Section 13.9.1), which will include the AngII/Ang(1-7) ratio, a variable will be included based on non-imputed data i.e., for this variable, the ratio will only be calculated if both AngII and Ang(1-7) have non-missing numeric values, otherwise the ratio will be set to missing.

13.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• Missing or partial dates of AEs will not be allowed in this study.

Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month
	  ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month.
	• The recorded partial date will be displayed in listings.

13.7. Appendix 7: Values of Potential Clinical Importance

13.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		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
RBC Count	TI/L		0.93 x LLN	1.07 x ULN
MCV	FL		0.25 x LLN	2 x ULN
MCH	PG		0.85 x LLN	1.1 x ULN
%Reticulocytes	%		0.5 x LLN	5 x ULN
Monocytes	$x10^9$/ L		0.25 x LLN	2 x ULN
Eosinophils	$x10^9$/ L		0	2 x ULN
Basophils	$x10^9$/ L		0	5 x ULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Calcium	mmol/L		2	2.75
Creatinine	mmol/L			↑ 1.3 x ULN
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
BUN	mmol/L		0.7x	1.6x
Direct Bilirubin	umol/L			1.5x ULN
Total Protein	G/L			1.25x
International normalized ratio (INR)		On Warfarin		4 x
		Not on Warfarin		1.5 x
Prothrombin time (PT)	sec	On Warfarin		4 x ULN
		Not on Warfarin		1.2 x ULN

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
PTT	Sec	On Heparin		4 x ULN
		Not on Heparin		1.2 x ULN

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
Direct Bilirubin			1.5 x ULN

13.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QTc Interval	msec		≥ 500
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

13.7.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	< 90	> 150
Diastolic Blood Pressure	mmHg	< 50	> 100
Heart Rate	bpm	< 35	> 130

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

13.8. Appendix 8: Population Pharmacokinetic (PopPK) Analyses

13.8.1. Population Pharmacokinetic (PopPK) Dataset Specification

The PME compliant file structure is a space-delimited file with each row containing the following columns of information.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg)*WT For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	h	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP = 0.1 for 0.1 mg/kg treatment DGRP = 0.2 for 0.2 mg/kg treatment DGRP = 0.4 for 0.4 mg/kg treatment DGRP = 0.8 for 0.8 mg/kg treatment
PART	Study Part	Integer	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock Time of Event	HH:MM:SS	-	Clock Time of Event
DATE	Date of Record	(DD/MM/YYYY)	-	Date of Record
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
DV	Dependent Variable	Decimal	pg/mL	When LABL=5, observed GSK2586881 concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0

Variable short name	Assessment description	Format	Unit	Valid Values / Format
MDV	Missing Data Variable	Integer	-	Either '0' if DV value present or 1 if DV value is non-quantifiable (NQ) or LABL = 1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	Either '0' if LABL=5 or '1' if LABL= 1, 2, 3 or 4
TYPE	F-Flag	Integer	-	If MDV1 = '1' then TYPE ='0', If DV value present (but not NQ) TYPE= '1' If DV value NQTYPE = '2'
LLQ	Lower Limit of quantification	Integer	pg/mL	Lower limit of quantification for specific analyte SMS dataset (PCLLQ)
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT =1, specifies compartment from which observation is obtained.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Indentifcation data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
5	Observed concentration record for GSK2586881 at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	pg/mL

13.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

13.9.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

Specification for ANG II Venous (Systemic) [Proposed dataset name PKPDAIIV]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	h	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BLII	AngII concentration record	Decimal		Baseline value (pre-dose value) from venous (systemic) RAS sampling

Variable short name	Assessment description	Format	Unit	Valid Values / Format
DV	AngII concentration record	Decimal		When LABL=6, observed AngII concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from venous (systemic) RAS sampling
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL= 1, 2, 3, or 4
MDV1	Missing data variable	Integer	-	'1' if LABL= 1, 2, 3 or 4 "0" when LABL=6
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If DV value present (but not NQ) TYPE= '1' If DV value NQ TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT=3 for DV (ANGII) observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
6	Observed venous (systemic) sample ANGII record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANG II Pulmonary Wedge [proposed dataset name PKPDAIIP]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	h	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	to LAST dose			Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BLII	AngII concentration record	Decimal		Baseline value (pre-dose value) from pulmonary wedge RAS sampling
DV	AngII concentration record	Decimal		When LABL=11, observed AngII concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from pulmonary wedge RAS sampling
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL= 1, 2, 3, or 4
MDV1	Missing data variable	Integer	-	'1' if LABL= 1, 2, 3 or 4 "0" when LABL=11
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If DV value present (but not NQ) TYPE= '1' If DV value NQ TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT=3 for DV (ANGII) observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
11	Observed pulmonary wedge sample ANGII record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANG(1-5) Venous (Systemic) [proposed dataset name PKPDA15V]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	H	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	to LAST dose			Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BL15	Ang1-5 concentration record	Decimal		Baseline value, from venous (systemic) RAS sampling
DV	AngI1-5 concentration record	Decimal		When LABL=7, observed Ang1-5 concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from venous (systemic) RAS sampling
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=1, 2, 3 or 4 "0" when LABL=7
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If DV value present (but not NQ) TYPE= '1' If DV value NQ TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event CMT=4 for ANG1-5 observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
7	Observed venous (systemic) sampling ANG15 record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANG(1-5) Pulmonary Wedge [proposed dataset name PKPDA15P]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	H	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		

Variable short name	Assessment description	Format	Unit	Valid Values / Format
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BL15	Ang1-5 concentration record	Decimal		Baseline value, from pulmonary wedge RAS sampling
DV	AngI1-5 concentration record	Decimal		When LABL=12, observed Ang1-5 concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from pulmonary wedge RAS sampling
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=1, 2, 3 or 4 "0" when LABL=12
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If DV value present (but not NQ) TYPE= '1' If DV value NQ TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event CMT=4 for ANG1-5 observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
12	Observed pulmonary wedge sampling ANG15 record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANG(1-7) Venous (Systemic) [proposed dataset name PKPDA17V]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	H	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	to LAST dose			Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BL17	Ang1-7 concentration record	Decimal		Baseline value, from venous (systemic) RAS sampling
DV	Ang1-7 concentration record	Decimal		When LABL=8, observed Ang1-7 concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from venous (systemic) RAS sampling
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=1, 2, 3 or 4 "0" when LABL=8
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If ANG1-7 value present (but not NQ) TYPE= '1' If ANG1-7 value NQ TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT=5 for ANG1-7 observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
8	Observed venous (systemic) sampling ANG17 record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANG(1-7) Pulmonary Wedge [proposed dataset name PKPDA17P]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	H	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	to LAST dose			Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BL17	Ang1-7 concentration record	Decimal		Baseline value, from pulmonary wedge RAS sampling
DV	Ang1-7 concentration record	Decimal		When LABL=13, observed Ang1-7 concentration at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from pulmonary wedge RAS sampling
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=1, 2, 3 or 4 "0" when LABL=13
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If ANG1-7 value present (but not NQ) TYPE= '1' If ANG1-7 value NQTYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT=5 for ANG1-7 observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
13	Observed pulmonary wedge sampling ANG17 record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANGII/ANG(1-7) Venous (Systemic) [proposed dataset name PKPDARTV]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	H	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	

Variable short name	Assessment description	Format	Unit	Valid Values / Format
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BLRT	AngII/Ang1-7 ratio concentration record	Decimal		Baseline value, from venous (systemic) RAS sampling Refer to Section 13.6.2 for details of data to include.
DV	AngII/Ang1-7 ratio concentration record	Decimal		When LABL=10, observed AngII/Ang1-7 ratio at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from venous (systemic) RAS sampling Refer to Section 13.6.2 for details of data to include.
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or missing value or LABL=1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=1, 2, 3 or 4 "0" when LABL=10
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If ANGII/ANG1-7 value present (but not NQ) TYPE= '1' If ANGII/ANG1-7 value NQ (or missing) TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT=6 for ANGII/ANG1-7 observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
10	Observed venous (systemic) sampling ANGII/ANG17 record (ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for ANGII/ANG(1-7) Pulmonary Wedge [proposed dataset name PKPDARTP]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in that record	Integer	See footnotes	See footnotes
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	H	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)

Variable short name	Assessment description	Format	Unit	Valid Values / Format
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BLRT	AngII/Ang1-7 ratio concentration record	Decimal		Baseline value, from pulmonary wedge RAS sampling Refer to Section 13.6.2 for details of data to include.
DV	AngII/Ang1-7 ratio concentration record	Decimal		When LABL=14, observed AngII/Ang1-7 ratio at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0, from pulmonary wedge RAS sampling Refer to Section 13.6.2 for details of data to include.
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or missing value or LABL=1, 2, 3 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=1, 2, 3 or 4 "0" when LABL=14
TYPE	F-Flag	Integer	-	If MDV1= '1' then TYPE ='0', If ANGII/ANG1-7 value present (but not NQ) TYPE= '1' If ANGII/ANG1-7 value NQ (or missing) TYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event: CMT=6 for ANGII/ ANG1-7 observation event.
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				screening.
HT	Height	Decimal	Cm	Height in centimetres at time of screening.
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = male 2 = female
ETHN	Subject ethnicity	Integer	-	Integer. Code as CRF
RACE	Subject race	Integer	-	Integer. Code as CRF
BMI	Body mass index	Decimal	kg/m^2	body mass index calculated as weight divided by height squared
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
14	Observed pulmonary wedge sampling ANGII/ANG17 record (ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

Specification for PVR/CO/mPAP/CI

The PME compliant file structure is a space-delimited file with each row containing the following columns of information. Data from all treatments will be included.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	206246
DRUG	Name of Drug	Integer	-	Maximum 10 characters (numeric or text). 2586881
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
LABL	Indicator field describing the type of assessment in	Integer	See footnotes	See footnotes

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	that record			
AMT	Dose of GSK2586881	Decimal	Mg	Amount of drug given = Total GSK2586881 dose (mg/kg) * WT. AMT=0 when LABL=0 For dosing events: total dose of GSK2586881 taken For concentration events: 0
INF	Infusion Time	Decimal	h	Time during which total dose infused. (Time at end of infusion – Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0.1 for 0.1 mg/kg treatment DGRP=0.2 for 0.2 mg/kg treatment DGRP=0.4 for 0.4 mg/kg treatment DGRP=0.8 for 0.8 mg/kg treatment
PART	Study Part	Varchar	-	1=Study Period 1
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 1, 2, 3, or 4 TRLD is Time (Hours) since start of LAST infusion. For pre-dose sample, TRLD=0
BLPVR	PVR	Decimal	mmHg	Baseline Value
PVR	PVR	Decimal	mmHg	When LABL=9, PVR at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), PVR=0
PVRFLD	PVR ratio to baseline (fold change)	Decimal	-	When LABL=9, PVRFLD fold change at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), PVRFLD=0
PVRCHG	PVR change from baseline	Decimal	mmHg	When LABL=9, PVRCHG at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), PVRCHG=0
BLCO	Cardiac Output	Decimal	L/min	Baseline Value
CO	Cardiac Output	Decimal	L/min	When LABL=9, CO at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 CO=0
COFLD	Cardiac Output ratio to baseline (fold change)	Decimal	-	When LABL=9, COFLD fold change at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 COFLD=0
COCHG	Cardiac Output	Decimal	L/min	When LABL=9, COCHG at time

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	change from baseline			specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 COCHG=0
BLCI	Cardiac Index	Decimal	L/min/m2	Baseline Value
CI	Cardiac Index	Decimal	L/min/m2	When LABL=9, CI at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 CI=0
CIFLD	Cardiac Index ratio to baseline (fold change)	Decimal	-	When LABL=9, CIFLD fold change at time specified by TRLD. When LABL=1, 2, 3 or 4 (dosing record), DV=0 CIFLD=0.
CICHG	Cardiac Index change from baseline	Decimal	L/min/m2	When LABL=9, CICHG at time specified by TRLD. When LABL=1, 2, 3 or 4 (dosing record), DV=0 CICHG=0.
BLMPAP	mPAP	Decimal	mmHg	Baseline Value
MPAP	mPAP	Decimal	mmHg	When LABL=9, mPAP at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 mPAP=0
MPAPFLD	mPAP ratio to baseline (fold change)	Decimal	-	When LABL=9, mPAPFLD at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 mPAPFLD=0
MPAPCHG	mPAP change from baseline	Decimal	mmHg	When LABL=9, mPAPCHG at time specified by TRLD. When LABL= 1, 2, 3 or 4 (dosing record), DV=0 mPAPCHG=0
EVID	Event Identification data item	Integer	-	Flag indicating whether LABL contains dosing admin info or drug concentration data. Valid values are - 1 – each dosing record for subject 0 - for all other records

Label	Description	Units
1	Dosing records for 0.1 mg/Kg GSK2586881	
2	Dosing records for 0.2 mg/Kg GSK2586881	
3	Dosing records for 0.4 mg/Kg GSK2586881	
4	Dosing records for 0.8 mg/Kg GSK2586881	
9	Observed hemodynamic record at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data	

13.10. Appendix 10: Abbreviations & Trade Marks

13.10.1. Abbreviations

Abbreviation	Description
ACE2	Angiotensin converting enzyme type 2
AE	Adverse Event
Ang	Angiotensin
A&R	Analysis and Reporting
AUC(0-t)	Area under the concentration time curve from time zero to the time of the last quantifiable concentration
AUC(0-∞)	Area under the concentration time curve extrapolated to infinity
CI	Cardiac Index
CI	Confidence Interval
CIL	Clinical Investigative Lead
CL	Clearance
Clast	Last observed quantifiable concentration
Cmax	Maximum observed plasma concentration
CO	Cardiac Output
CPMS	Clinical Pharmacology Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CS	Clinical Statistics
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
DQL	Data Quality Lead
eCRF	Electronic Case Record Form
GCSP	Global Clinical Safety and Pharmacovigilance
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonisation
ICF	Informed Consent Form
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
IV	Intravenous
GUI	Guidance
mmHg	Millimeter of Mercury
mPAP	Mean Pulmonary Artery Pressure
NO	Nitric Oxide
NT-proBNP	N-terminal pro-brain natriuretic peptide
OSL	Operational Study Lead
PAH	Pulmonary Arterial Hypertension
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan

Abbreviation	Description
PK	Pharmacokinetic
PT	Preferred Term
PVR	Pulmonary Vascular Resistance
QC	Quality Control
QTcF	Friderica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RAS	Renin-Angiotensin-System
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operation Procedure
S&P	Statistics and Programming
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tlast	Time of the last observed quantifiable concentration
Tmax	Time to reach Cmax
T1/2	Apparent terminal half-life
V	Volume of distribution

13.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP
RANDALL NG

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS
WinNonlin

13.11. Appendix 11: List of Data Displays

13.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Efficacy	2.1 to 2.n	2.1 to 2.n
Safety	3.1 to 3.n	3.1 to 3.n
Pharmacokinetic	4.1 to 4.n	4.1 to 4.n
Population Pharmacokinetic (PopPK)	5.1 to 5.n	5.1 to 5.n
Pharmacodynamic and / or Biomarker	6.1 to 6.n	6.1 to 6.n
Pharmacokinetic / Pharmacodynamic	7.1 to 7.n	7.1 to 7.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

13.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

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

13.11.3. Deliverables

Delivery	Description
DE [1]	Dose Escalation Dose 1 **(Responsibility of GSK)**
DE [2]	Dose Escalation Dose 2 **(Responsibility of GSK)**
DE [3]	Dose Escalation Dose 3 **(Responsibility of GSK)**
SAC / SAC(GSK)	Final Statistical Analysis Complete / Final Statistical Analysis Complete (Responsibility of GSK)

13.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Safety	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.3.	Safety	NS1	Summary of Number of Participants by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.4.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC
Population Analysed					
1.5.	Safety	SP1	Summary of Study Populations	IDSL	SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC
1.7.	Safety	DM11	Summary of Age Ranges	EudraCT	SAC
1.8.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.9.	Safety	**POP_T1**	Summary of Baseline Characteristics	Include Functional Class (I, II, III) (frequencies) and 6MWD (summary stats) and PAH underlying causes (frequencies) by dose group and overall	SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.10.	Safety	MH1	Summary of Past Medical Conditions	ICH E3	SAC
1.11.	Safety	MH1	Summary of Current Medical Conditions	ICH E3 Separate summaries for Current & Past conditions, if collected.	SAC
1.12.	Safety	CM1	Summary of Concomitant Medications	ICH E3	SAC
1.13.	Safety	CM1	Summary of Concomitant Medications for PAH	Will be based on a spreadsheet review by the medical monitor to flag those records within the conmed dataset that were applicable to PAH. This flag will be read in and merged when creating the CMANAL dataset. One review prior to DBF for pre-programming and a final review (quick turnaround) at DBF.	SAC
Exposure and Treatment Compliance					
1.14.	Safety	EX3	Listing of Exposure to Study Treatment	ICH E3	SAC

13.11.5. 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	ICH E3	SAC
3.2.	Safety	AE1CP	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency	ICH E3 .	SAC
Serious and Other Significant Adverse Events					
3.3.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC
ECG					
3.4.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
3.5.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC
3.6.	Safety	CP_EG11	Frequency of ECG Values by Pre-Specified PCI Categories	Categories as per PCI details in Section 13.7.2	SAC
3.7.	Safety	CP_EG12	Frequency of Change from Baseline ECG Values by Pre-Specified PCI Categories	Categories as per PCI details in Section 13.7.2	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
3.8.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC
Pulse Oximetry					
3.9.	Safety	VS1	Summary of Oxygen Saturation	Collected at same timepoints as vital signs (but no triplicates at pre-dose)	SAC
Immunogenicity					
3.10.	Safety	IMM1	Summary of Positive Immunogenicity Results	Results will be categorised by visit (Day 7, Day 28) and dose group within the table.	SAC

13.11.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	**SAF_F1**	Summary of Change from Baseline (95% CI) in Systolic Blood Pressure by Dose Group	Data from VITALS dataset. See example, x-axis will be post-dose timepoint with each dose group mean ±95% CI plotted (dose groups offset) Include a horizontal dashed grey line at zero. Please use symbols as indicated in Section 5.1	SAC
3.2.	Safety	**SAF_F1**	Summary of Change from Baseline (95% CI) in Diastolic Blood Pressure by Dose Group	Data from VITALS dataset. See example, x-axis will be post-dose timepoint with each dose group mean ±95% CI plotted (dose groups offset) Include a horizontal dashed grey line at zero. Please use symbols as indicated in Section 5.1	SAC
3.3.	Safety	**SAF_F1**	Summary of Change from Baseline (95% CI) in Heart Rate by Dose Group	Data from VITALS dataset. See example: x-axis will be post-dose timepoint with each dose group mean ±95% CI plotted (dose groups offset) Include a horizontal dashed grey line at zero. Please use symbols as indicated in Section 5.1	SAC

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4.	Safety	**SAF_F2**	Summary of Individual Systolic Blood Pressure by Dose Group	Data from VITALS dataset. See example: One plot per dose group, with all subject profiles on each dose group plot, 4 pages per output	SAC
3.5.	Safety	**SAF_F2**	Summary of Individual Diastolic Blood Pressure by Dose Group	Data from VITALS dataset. See example: One plot per dose group, with all subject profiles on each dose group plot, 4 pages per output	SAC
3.6.	Safety	**SAF_F2**	Summary of Individual Heart Rate by Dose Group	Data from VITALS dataset. See example: One plot per dose group, with all subject profiles on each dose group plot, 4 pages per output	SAC

13.11.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK	PKCT1 (PK01)	Summary of GSK2586881 Pharmacokinetic Concentration-Time Data (ng/mL)	By dose group	SAC
PK Parameter Data					
4.2.	PK	PKPT1 (PK03)	Summary Statistics of Derived Plasma GSK2586881 Pharmacokinetic Parameters	By dose group. See Section 9.1.1.2 for full list of parameters to be expected	SAC
4.3.	PK	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma GSK2586881 Pharmacokinetic Parameters	By dose group. See Section 9.1.1.2 for full list of parameters to be expected (Tmax, lambda_x variables, #pts and R2 not included)	SAC

13.11.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK	PKCF1P (PK16a)	Individual GSK2586881 Plasma Concentration–Time Plots (Linear and Semi-log)	By Subject plots	SAC
4.2.	PK	PKCF6 (PK24)	Individual GSK2586881 Plasma Concentration–Time Plot (Linear and Semi-log)	Page by dose group, all subjects on a plot for each dose group	SAC
4.3.	PK	PKCF2 (PK17)	Mean Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log)	Include a legend for dose groups	SAC
4.4.	PK	PKCF3 (PK18)	Median Plasma GSK2586881 Concentration-Time Plot	Include a legend for dose groups	SAC
4.5.	PK	(PK28)	Plot of Individual (+Geometric Mean and 95% CIs) GSK2586881 Cmax versus Dose		SAC
4.6.	PK	(PK28)	Plot of Individual (+Geometric Mean and 95% CIs) GSK2586881 AUC(0-t) versus Dose		SAC
4.7.	PK	(PK28)	Plot of Individual (+Geometric Mean and 95% CIs) GSK2586881 AUC(0-inf) versus Dose		SAC

13.11.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hemodynamics					
6.1.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Pulmonary Hemodynamics (Absolute)	**Interim Tables** Include PVR, CO mPAP & CI only for dose group being assessed at the time (can be indicated in the title 'Dose Group = xx mg/kg') Provide second page with geometric means etc (from log-transformation) **SAC Table** By dose group and endpoint (**x9 PVR, CO, mPAP, Right Atrial Pressure etc**). n[1] in mock not required for Hemodynamic endpoints. Log-transformed summary to be included as a second page for each parameter (see mock). Timepoints are Pre-dose, 1h, 2h and 4h.	**DE[1], DE[2], DE[3]** & SAC

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.2.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Change from Baseline in Pulmonary Hemodynamics	**Interim Tables** Include PVR, CO mPAP & CI only for dose group being assessed at the time (can be indicated in the title 'Dose Group = xx mg/kg') Provide second page with geometric means etc (from log-transformation) **SAC Table** By dose group and endpoint (**x9 PVR, CO, mPAP, Right Atrial Pressure etc**). Pre-dose excluded. n[1] in mock not required for Hemodynamic endpoints. Log-transformed summary to be included as a second page for each parameter (see mock). Timepoints are 1h, 2h and 4h.	**DE[1], DE[2], DE[3]** & SAC
6.3.	Evaluable	**PD_T3**	Summary of Statistical Analysis of PVR, CO, mPAP and CI	**Interim Tables** Utilising Bayesian version of repeated measures mixed effect modelling results for dose group(s) of interest at the time. Posterior probabilities to be included, see Section 7.1.5.1. **SAC table** As above, with consideration to all dose groups, discuss with team to ensure probabilities of interest are displayed as further probabilities may be required in addition to those quoted in Section 7.1.5.1.	**DE[1], DE[2], DE[3],** SAC (GSK)

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
RAS					
6.4.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Venous (Systemic) RAS Peptides (Absolute Data)	By dose group and analyte. Log-transformed summary to be included as a second page for each parameter. To include **AngII, Ang(1-7), Ang(1-5)**. Timepoints are Pre-dose, 0.5h, 1h, 2h, 4h, 8h, 24h and Day(7-14) FU	SAC
6.5.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Pulmonary Wedge RAS Peptides (Absolute Data)	By dose group and analyte. Log-transformed summary to be included as a second page for each parameter. To include **Ang II, Ang(1-7), Ang(1-5)**. Timepoints are Pre-dose, 1h, 2h and 4h only.	SAC
6.6.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Change from Baseline in Venous (Systemic) RAS Peptides	By dose group and analyte. Log-transformed summary to be included as a second page for each parameter. To include **AngII, Ang(1-7), Ang(1-5).** Timepoints are 0.5h, 1h, 2h, 4h, 8h, 24h and Day(7-14) FU	SAC
6.7.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Change from Baseline in Pulmonary Wedge RAS Peptides	By dose group and analyte. Log-transformed summary to be included as a second page for each parameter. To include **Ang II, Ang(1-7), Ang(1-5)**. Timepoints are 1h, 2h and 4h only.	SAC
6.8.	Evaluable	**PD_T2**	Summary of Venous (Systemic) RAS AngII/Ang(1-7) Ratio	By dose group. Log-transformed summary to be included as a second page. Timepoints are Pre-dose, 0.5h, 1h, 2h, 4h, 8h, 24h and Day(7-14) FU	SAC
6.9.	Evaluable	**PD_T2**	Summary of Pulmonary Wedge RAS AngII/Ang(1-7) Ratio	By dose group. Log-transformed summary to be included as a second page. Timepoints are Pre-dose, 1h, 2h, 4h	SAC

Pharmacodynamic (and or Biomarker): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Biomarkers					
6.10.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Disease Activity Biomarkers (Absolute Data)	By dose group and analyte. Log-transformed summary to be included as a second page for each parameter. To include **NT pro-BNP, serum NO, cardiac tropinin I**. Timepoints are Pre-dose, 2h, 4h and 24h only.	SAC
6.11.	Evaluable	**PD_T1** (or modify PFT1 & PFT2)	Summary of Change from Baseline in Disease Activity Biomarkers	By dose group and analyte. Log-transformed summary to be included as a second page for each parameter. To include **NT pro-BNP, serum NO, cardiac tropinin I**. Timepoints are 2h, 4h and 24h only.	SAC

13.11.10. Pharmacodynamic and Biomarker Figures

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hemodynamics					
6.1.	Evaluable	**PD_F3a**	Individual Subject Profiles of Pulmonary Hemodynamics (Absolute)	**Interim Plots**: All subjects on one plot. Page by endpoint CO, PVR, mPAP and CI. Include 'Dose Group = XX' within title Include a second page (similar for PD_F7) that displays the dose group profiles from 206246 side by side with the data from previous ISS study – for each parameter **SAC Plots** All subjects on one plot. One page per dose group. Page also by endpoint **CO, PVR, mPAP and CI** only. Include a second page with log10 axes.	**DE[1], DE[2], DE[3]** & SAC
6.2.	Evaluable	**PD_F1**	Summary of Pulmonary Hemodynamics (Absolute)	X-axis will be timepoints Pre-dose, 1h, 2h, 4h. Y-axis will be mean endpoint including 95% CI, by treatment groups (add to legend). Offset doses at each timepoint. Page by endpoint **CO, PVR, mPAP and CI only** Present geometric means and 95% CIs on second page. Please use symbols as indicated in Section 5.1	SAC

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.3.	Evaluable	**PD_F2**	Summary of Change from Baseline in Pulmonary Hemodynamics	X-axis will be timepoints 1h, 2h, 4h. Y-axis will be mean endpoint including 95% CI, by treatment groups (add to legend). Offset doses at each timepoint. Page by endpoint **CO, PVR, mPAP and CI only** Present geometric means and 95% CIs on second page. Please use symbols as indicated in Section 5.1	SAC
6.4.	Evaluable	**PD_F4**	Linear Regression Plots for Post-dose Changes from Baseline vs Dose in PVR, CO, mPAP and CI	To include data from all dose groups (similar to PD_F4 but with data points plotted for 0.8 mg/kg also). One page per timepoint (1h, 2h and 4h)	SAC

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
RAS Biomarkers					
6.5.	Evaluable	**PD_F3b**	Individual Subject Profiles of Venous (Systemic) RAS Biomarkers	**Interim Plots (as required based on data availability)** All subjects on one plot, one page per dose group and endpoint. Include a second page (similar to PD_F8) that displays the dose group profiles from 206246 side by side with the data from previous ISS study – primarily for AngII and Ang(1-7). **SAC Plot** All subjects on one plot, one page per dose group. AngII x 4 pages, Ang(1-5) x 4 pages, Ang(1-7) x 4 pages. Timepoints are Pre-dose, 0.5h, 1h, 2h, 4h, 8h, 24h and Day(7-14) FU Include a second page with log10 axes for each endpoint/dose group	**DE[1], DE[2], DE[3]** & SAC
6.6.	Evaluable	**PD_F3b**	Individual Subject profiles of Pulmonary Wedge RAS Biomarkers	All subjects on one plot, one page per dose group: Ang II x 4 pages, Ang(1-5) x 4 pages, Ang(1-7) x 4 pages, Ang II/Ang(1-7) x 4 pages. Timepoints are Pre-dose, 1h, 2h and 4h only. Include a second page with log10 axes for each endpoint/dose group.	SAC

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.7.	Evaluable	**PD_F1**	Summary of Venous (Systemic) RAS Biomarkers (Absolute)	X-axis will be timepoints Pre-dose, 0.08h, 0.5h, 1h, 2h, 4h, 8h, 24h, FU7-14. Y-axis will be **geometric** mean RAS including 95% CI, by dose groups (add to legend). One page per endpoint (4 x RAS endpoints). *Presenting geometric means from log-transformed data (see matching table).* *Include **AngII, Ang(1-7), Ang(1-5) and AngII/Ang(1-7)*** Please use symbols as indicated in Section 5.1	SAC
6.8.	Evaluable	**PD_F1**	Summary of Pulmonary Wedge RAS Biomarkers (Absolute)	X-axis will be timepoints Pre-dose, 1h, 2h, 4h. Y-axis will be **geometric** RAS including 95% CI, by dose groups (add to legend). One page per endpoint (4 x RAS endpoints). *Presenting geometric means from log-transformed data (see matching table).* *Include **AngII, Ang(1-7), Ang(1-5) and AngII/Ang(1-7)*** Please use symbols as indicated in Section 5.1	SAC
6.9.	Evaluable	**PD_F5**	Correlation plot for Venous (Systemic) RAS Biomarkers	Scatter plot of Ang II vs Ang(1-7) on page 1, Ang II vs Ang(1-5) on page 2 and Ang(1-5) vs Ang(1-7) on page 3. Venous RAS timepoints. To be plotted on log-log scales. Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.10.	Evaluable	**PD_F5**	Correlation plot for Pulmonary Wedge RAS Biomarkers	Scatter plot of Ang II vs Ang(1-7) on page 1, Ang II vs Ang(1-5) on page 2 and Ang(1-5) vs Ang(1-7) on page 3. Pulmonary wedge RAS timepoints. To be plotted on log-log scales. Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC
Disease Activity Biomarkers					
6.11.	Evaluable	**PD_F1**	Summary of Disease Activity Biomarkers (Absolute)	X-axis will be timepoints Pre-dose, 2h, 4h, 24h. Y-axis will be **geometric** mean endpoint including 95% CI, by treatment groups (add to legend). One page per endpoint (3 x endpoints) *Presenting geometric means from log-transformed data (see matching table).* Please use symbols as indicated in Section 5.1	SAC
6.12.	Evaluable	**PD_F3b**	Individual Subject profiles of Disease Activity Biomarkers	All subjects on one plot, one page per dose group: NT pro-BNP x 4, NO x 4 and cardiac troponin I x 4 pages. Include a second page with log10 axes for each endpoint/dose group.	SAC
RAS Biomarkers vs Hemodynamics					
6.13.	Evaluable	**PD_F6**	Scatter Plot (log-log) of Venous (Systemic) RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs PVR	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on PVR. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.14.	Evaluable	**PD_F6**	Scatter Plot (log-log) of Venous (Systemic) RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs CO	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on CO. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC
6.15.	Evaluable	**PD_F6**	Scatter Plot (Semi-log) of Venous (Systemic) RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs mPAP	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on mPAP. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC
6.16.	Evaluable	**PD_F6**	Scatter Plot (log-log) of Venous (Systemic) RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs CI	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on CI. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC
6.17.	Evaluable	**PD_F6**	Scatter Plot (Semi-log) of Pulmonary Wedge RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs PVR	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on PVR. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC

Pharmacodynamic (and or Biomarker): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.18.	Evaluable	**PD_F6**	Scatter Plot (Semi-log) of Pulmonary Wedge RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs CO	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on CO. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC
6.19.	Evaluable	**PD_F6**	Scatter Plot (Semi-log) of Pulmonary Wedge RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs mPAP	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on mPAP. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC
6.20.	Evaluable	**PD_F6**	Scatter Plot (Semi-log) of Pulmonary Wedge RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) vs CI	3 pages, 1 for each RAS, 4 dose groups on each page, dose/timepoint indicated in legend. Timepoints of interest based on CI. Log-log axes Please provide clear dose/timepoint labels within the legend, mock-up is basic example only.	SAC

13.11.11. Pharmacokinetic / Pharmacodynamic and Biomarker Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK / RAS Peptides					
7.1.	PK	**PK_F1**	Scatter plot (Log-log) of PK Concentration vs Venous (Systemic) Ang II, Ang(1-5), Ang(1-7) and AngII/Ang(1-7)	Scatter plot of PK conc vs Ang II on page 1, PK conc vs Ang(1-5) on page 2, PK conc vs Ang(1-7) on page 3 and PK conc vs AngII/Ang(1-7) on page 4. Timepoints of interest based on PK. To be plotted on log-log scales. Please provide clear dose/timepoint labels within the legend, mock-up is basic example only. Note: For PK/PD plots only, PK concentration data recorded as NQ can be imputed following the same method for biomarker data i.e., replace with ½ LLQ. The imputed variable for PK should be available in the PKCNC dataset. See Section 13.4.3 Footnote to include: '*Note: Values below Lower Limit of Quantification (LLQ) replaced with ½ LLQ. LLQ for PK concentration = xx ng/mL, LLQ for AngII = xx pg/mL, LLQ for Ang(1-5) = xx pg/mL and LLQ for Ang(1-7) = xx pg/mL.*'	SAC

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
7.2.	PK	**PK_F1**	Scatter plot (Log-log) of PK Concentration vs Pulmonary Wedge Ang II, Ang(1-5), Ang(1-7) and AngII/Ang(1-7)	Scatter plot of PK conc vs Ang II on page 1, PK conc vs Ang(1-5) on page 2, PK conc vs Ang(1-7) on page 3 and PK conc vs AngII/Ang(1-7) on page 4. Timepoints of interest based on Pulmonary Wedge RAS. To be plotted on log-log scales. Please provide clear dose/timepoint labels within the legend, mock-up is basic example only. Note: For PK/PD plots only, PK concentration data recorded as NQ can be imputed following the same method for biomarker data i.e., replace with ½ LLQ. The imputed variable for PK should be available in the PKCNC dataset. See Section 13.4.3 Footnote to include: '*Note: Values below Lower Limit of Quantification (LLQ) replaced with ½ LLQ. LLQ for PK concentration = xx ng/mL, LLQ for AngII = xx pg/mL, LLQ for Ang(1-5) = xx pg/mL and LLQ for Ang(1-7) = xx pg/mL.*'	SAC

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
7.3.	PK	**PK_F1**	Scatter Plot (Log-log) of PK Concentration vs PVR, CO, mPAP and CI	Scatter plot of PK conc vs PVR on page 1, PK conc vs CO on page 2, PK conc vs mPAP on page 3 and PK conc vs CI on page 4. Timepoints of interest based on hemodynamics. To be plotted on log-log scales. Please provide clear dose/timepoint labels within the legend, mock-up is basic example only. Note: For PK/PD plots only, PK concentration data recorded as NQ can be imputed following the same method for biomarker data i.e., replace with ½ LLQ. The imputed variable for PK should be available in the PKCNC dataset. See Section 13.4.3. Footnote to include: '*Note: Values below Lower Limit of Quantification (LLQ) replaced with ½ LLQ. LLQ for PK concentration = xx ng/mL.*'	SAC

13.11.12. 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	SAC
2.	Safety	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
4.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
5.	Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
6.	Safety	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
7.	Safety	DM2	Listing of Demographic Characteristics	ICH E3	SAC
8.	Safety	DM9	Listing of Race	ICH E3	SAC
Prior and Concomitant Medications					
9.	Safety	CP_CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
10.	Safety	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
11.	Safety	AE8CP	Listing of All Adverse Events	ICH E3	SAC
12.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
13.	Safety	AE8CPa	Listing of Serious Adverse Events	ICH E3	SAC
14.	Safety	AECP8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC
All Laboratory					
15.	Safety	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance/Outside Normal Range	ICH E3	SAC
16.	Safety	LB5	Listing of Laboratory Values of Potential Clinical Importance		SAC
ECG					
17.	Safety	EG3/CP_EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
18.	Safety	EG3/CP_EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC
19.	Safety	EG5/CP_EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
20.	Safety	EG5/CP_EG5	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
21.	Safety	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
22.	Safety	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC

13.11.13. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Baseline Characteristics					
23.	Safety	**POP_L1**	Listing of Baseline Characteristics		SAC
Pharmacodynamic					
24.	Safety	**PD_L2**	Listing of Hemodynamic Endpoints	**Interim Listings:** Produce for relevant dose group. Include % change from baseline (presented as a ratio to baseline based on back-transformed data) **SAC Listing:** Produce for all dose groups. Include % change from baseline (presented as a ratio to baseline based on back-transformed data)	**DE[1], DE[2]. DE[3]** & SAC
25.	Safety	PFT8	Listing of Oxygen Saturation	Follow PFT8 IDSL format, replacing last 4 columns with Oxygen Saturation endpoint.	SAC
Biomarkers					
26.	Safety	**PD_L1**	Listing of Venous (Systemic) RAS Peptides	See non-standard example PD_L1. To include AngII, Ang(1-5) and Ang(1-7)	SAC
27.	Safety	**PD_L1**	Listing of Pulmonary Wedge RAS Peptides	See non-standard example PD_L1 (4 timepoints only) To include AngII, Ang(1-5) and Ang(1-7)	SAC
28.	Safety	**PD_L1**	Listing of Disease Biomarkers	See non-standard example PD_L1 (4 timepoints only)	SAC
Immunogenicity					
29.	Safety	IMM2	Listing of Immunogenicity		SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK					
30.	PK	PKCL1P (PK07)	Listing of GSK2586881 Plasma Pharmacokinetic Concentration–Time Data		SAC
31.	PK	PKPL1P (PK13)	Listing of Derived GSK2586881 Plasma Pharmacokinetic Parameters	See Section 9.1.1.2 for list of parameters. To include lambda_z and the additionally the first point, last point and number of points used in the determination of lambda_z for listings and R squared.	SAC

13.12. Appendix 13: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request