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

Title	:	Reporting and Analysis Plan for the effects of GSK2586881 on the responses to acute hypoxia and exercise
Compound Number	:	GSK2586881
Effective Date	:	25-JUN-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 204987.
- 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 Analysis and Statistical Analysis Complete (SAC) deliverables.

RAP Author(s):

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this Reporting and Analysis Plan is to describe all planned analyses and outputs required for the Clinical Study Report (CSR) of study 204987. This amendment covers changes to the study following the interim analysis review of 11 participants.
Protocol	• This RAP amendment is based on the protocol (Dated 23/SEP/2016, GSK Document No.: 2016N283626_00) and protocol amendments 1 & 2 & 3 (Dated:24/FEB/2017, GSK Document No. : 2016N283626_01 & 07/MAR/2017, GSK Document No. : 2016N283626_02 & 06/MAR/2018 GSK Document No. : 2016N283626_03) of study GSK2586881/204987
Study Design	• The study will be a single centre, randomised, placebo-controlled and double blind (sponsor open). Subjects will be randomised to receive a single IV dose of GSK2586881 or saline in a crossover design. Approximately 25 subjects will be enrolled to ensure that a minimum of 20 subjects complete all dosing and critical assessments (the target of 20 may be revised by the sample size re-estimation)
Primary Objective	• To evaluate the effect of a single IV dose of GSK2586881 on the HPV response in healthy volunteers during exercise under hypoxic conditions
Primary Endpoint	• Change from baseline of Pulmonary Artery Systolic Pressure (PASP) measured via Echocardiography
Planned Analyses	• An Interim Analysis was planned after approximately 10 patients had completed periods 1 and 2 of the study, to aid the team in decision making with regards to stopping the study for futility or a re-assessment of sample size. Following the interim (referred to as study Part 1), amendments were made to the study before re-starting Part 2. Further interim reviews are planned when approximately 3 and 6 participants have completed periods 1 and 2 in Part 2 of the study. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze.
Analysis Populations	• All Subjects Screened Population will contain all subjects that complete at least one Visit 1 (Screening) procedure. • The Modified Intent-to-Treat (mITT) Population will comprise all randomised subjects, excluding those who were randomised in error. • The Modified Intent-to-Treat (mITT1) Part 1 Population will comprise all subjects in the mITT Population, who were randomised into Part 1 of the study. • The Modified Intent-to-Treat (mITT2) Part 2 Population will comprise all subjects in the mITT Population, who were randomised into Part 2 of the study • The Pharmacokinetic (PK) Population will comprise all subjects in the mITT Population, for whom a PK sample was obtained and analysed and on active treatment.

Overview	Key Elements of the RAP
	• The Pharmacokinetic (PK1) Population Part 1 will comprise all subjects in the mITT Population, randomised in Part 1 of the study, for whom a PK sample was obtained and analysed and on active treatment. • The Pharmacokinetic (PK2) Population Part 2 will comprise all subjects in the mITT Population, randomised in Part 2 of the study, for whom a PK sample was obtained and analysed and on active treatment.
Hypothesis	• No formal statistical hypotheses are being tested. A Bayesian statistical analysis framework with non-informative priors for model parameters (unless otherwise specified) will be used to obtain posterior distributions for effects of interest. These posterior distributions will be used to obtain a number of probability statements about the magnitude of treatment effects (e.g. probability of **any** treatment related reduction in PASP, or probability that the treatment related reduction in PASP $\geq$ 5 mmHg). A rule of thumb for "end of study success" is if the probability of any treatment related reduction in PASP (T3-T0) exceeds 0.95 (success is also conditional on the probability of (absolute) treatment related reductions in oxygen saturation exceeding 5% being small).
Primary Analyses	• The primary endpoint, change from baseline in PASP following exercise under hypoxic conditions (Ti-T0) will be analysed using a Bayesian repeated measures mixed effects regression model, to compare the effects of Placebo vs GSK2586881. Analyses will be performed for Part 1 and Part 2 separately.
Secondary Analyses	• <u>Pharmacodynamic/Biomarker</u>: RAS peptide responses: Ang II, Ang(1-7), Ang(1-5) will be analysed in a manner similar to the primary endpoint using Bayesian repeated measures mixed modelling to compare the effects of Placebo vs GSK2586881, for Part 2, if data permit. Part 1 data may also be analysed. Data from Part 1 and Part 2 will also be presented descriptively. • <u>Safety</u>: Oxygen saturation will be analysed in a manner similar to the primary efficacy endpoint using Bayesian repeated measures mixed modelling to compare the effects of Placebo vs GSK2586881. Analyses will be performed for Part 1 and Part 2 separately. Vital signs, 12-Lead ECG, AEs and Labs will be tabulated and/or listed by treatment group, study part (Part 1 and 2) and timepoint as appropriate. • <u>Immunogenicity</u>: Data will be tabulated and/or listed. • <u>Pharmacokinetic</u>: Plasma concentrations of GSK2586881 and derived PK parameters will be summarised descriptively/graphically and listed for Part 1 and Part 2 of the study.
Exploratory Analyses	• <u>Pharmacodynamic/Biomarker</u>: The disease biomarker Surfactant Protein D will be analysed in a manner similar to the primary efficacy endpoint using Bayesian repeated measures mixed modelling to

Overview	Key Elements of the RAP
	compare the effects of Placebo vs GSK2586881, for Part 2, if data permit. Part 1 data may also be analysed. Data from Part 1 and Part 2 will also be presented descriptively. Ventilatory parameters (Oxygen consumption (VO2), Carbon dioxide production (CO2), Total Tidal Volume, Inspiratory Tidal Volume, Expiratory Tidal Volume, Total Respiratory Time, Inspiratory Time, Expiratory Time, Duty Cycle, Mean Respiratory Flow and Respiratory rate) will be summarised descriptively and listed, by treatment group, timepoint and study part (Part 1 and 2). Pulmonary vascular resistance (PVR) will be summarised descriptively and listed, by treatment and timepoint, for Part 2. A statistical analysis similar to that described for PASP will also be performed. • Pharmacogenetics Analysis of pharmacogenetic data will be carried out separately by the GSK Genetics team and a separate RAP will be produced. As this is an exploratory endpoint, the results will be available separately to the CSR (or to be included as an appendix).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no major changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 23/SEP/2016) and protocol amendments 1, 2 and 3 (dated 24/FEB/2017, 07/MAR/2017 and 06MAR2018).

This amendment details changes to the display of outputs in relation to separate summaries of Part 1 and 2 data (as detailed in protocol amendment 3).

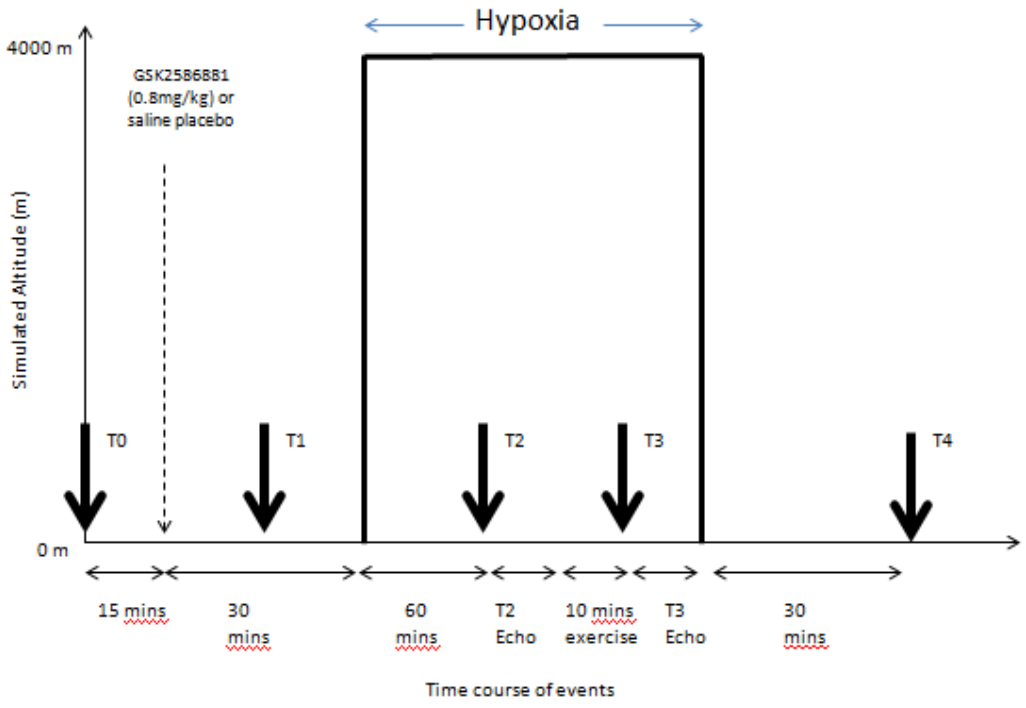
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To evaluate the effect of a single IV dose of GSK2586881 on the HPV response in healthy volunteers during exercise under hypoxic conditions	• Change from baseline of Pulmonary Artery Systolic Pressure (PASP) measured via Echocardiography
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of a single IV dose GSK2586881 on RAS peptide responses	• Effect of GSK2586881 on baseline levels and changes in response to hypoxia and exercise of RAS peptides (e.g. Ang II, Ang(1-7), Ang(1-5))
• To evaluate the safety of a single IV dose of GSK2586881 in healthy volunteers	• Vital signs (heart rate, systolic and diastolic blood pressure) • Oxygen saturation • 12-lead ECGs • Adverse Events (AEs) • Immunogenicity • Clinical laboratory assessments • Continuous pulse oximetry (assessed by the site)
• To evaluate the pharmacokinetics of a single IV dose of GSK2586881	• Plasma concentrations of GSK2586881 • Derived pharmacokinetic parameters
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the effect of a single IV dose of GSK2586881 on ventilatory parameters in healthy volunteers during exercise in hypoxic conditions	Change from baseline of: • Oxygen consumption (VO2) • Carbon dioxide production (CO2) • And other parameters as data permit
• To evaluate the pharmacodynamic activity of a single IV dose of GSK2586881 in healthy volunteers during exercise in hypoxic conditions	• Change from baseline in Surfactant Protein D and/or additional analytes to be determined
• To evaluate the effect of a single IV dose of GSK2586881 on the HPV response in healthy volunteers under hypoxic	• Estimation of pulmonary vascular resistance (PVR) measured via Echocardiography

Objectives	Endpoints
conditions (and during exercise under hypoxic conditions).	
• To evaluate Pharmacogenetics	• Evaluate I/D polymorphisms in the Angiotensin Converting Enzyme (ACE) gene and analyse the impact on Ang II (and possibly other RAS peptides), hypoxic pulmonary vasoconstriction and responses to GSK2586881 administration

2.3. Study Design

Overview of Study Design and Key Features



	The above schematic represents **Part 1** of the study. It is applicable also to **Part 2** of the study, with the following modifications: simulated altitude will be 5000 m, and the T3 echo will be taken 2 minutes into the exercise challenge (rather than at the end of a 10-minute exercise challenge).
Design Features	• Single centre • Randomised • Double-blind (sponsor open) • Placebo-controlled • Two-period crossover • Study duration maximum 56 days
Dosing	• Single IV dose in each study period

Overview of Study Design and Key Features	
Treatment Assignment	• Treatment A: Placebo • Treatment B: GSK2586881 0.8 mg/kg • Subjects will be randomised to one of two treatment sequences AB or BA
Interim Analysis	• Planned after approximately 10 subjects had completed treatment periods 1 and 2 (Part 1). The study may have been stopped if a reasonable change in PASP was not observed or if a review of safety data suggested a change in the benefit-risk profile. Following the interim, the decision was taken to continue the study with modifications to the protocol (Part 2). • In Part 2 an interim review is planned when approximately 3 subjects have completed treatment periods 1 and 2. A further review may take place when approximately 6 subjects have completed treatment periods 1 and 2, dependent on data observed in the earlier review. Subsequent interim reviews may take place, if deemed appropriate.

2.4. Statistical Hypotheses

There are no formal statistical hypotheses. This is an exploratory study and will be analysed, utilising a Bayesian framework.

3. PLANNED ANALYSES

3.1. Interim Analyses

3.1.1. Part 1

An interim analysis was planned after approximately 10 subjects had completed the following critical assessments:

Interim Analysis	Definition / Criteria / Purpose
• PASP at T0 and T3 for both study periods	• Assess treatment differences between GSK2586881 and Placebo in change from pre-dose PASP to hypoxic/exercised PASP [T3-T0]. • To decide whether to continue the study or stop based on futility. • To conduct an advisory sample-size re-estimation with the view to potentially reduce the number of subjects participating in the study below 20. Precision estimates will be updated based on the variability observed from the interim analyses to aid the team in decision making. • PASP data will be summarised and listed. Statistical analysis will be completed as described in Section 7.2 including a graphic of treatment estimates over time.
• Oxygen saturation at T0 and T3 for both study periods	• To estimate treatment differences between GSK2586881 and Placebo in change from pre-dose oxygen saturation to hypoxic/exercised oxygen saturation [T3-T0], with a view to stopping the study if there is evidence that GSK2586881 causes a reduction in oxygen saturation in healthy volunteers. As a non-binding guide high posterior probability of observing ≥5% absolute differences in **mean** oxygenation saturation values between placebo and active arms would be of concern; but clinical judgement would override any statistical methods if, for example, the majority of subjects displayed consistent patterns of reductions e.g. between 2-3%. • Oxygen saturation data will be summarised and listed. Statistical analysis

Interim Analysis	Definition / Criteria / Purpose
	will be completed as described in Section 8.1.2 including a graphic of treatment estimates over time.
• Adverse Events	• To compare adverse events within the two treatment groups and explore any potential safety signals that may emerge. • AEs will be tabulated by treatment group (if there are a sufficient number of events) and listed.
• Angiotensin biomarker concentrations (Ang II, Ang(1-5), Ang(1-7))	• For the first 5 subjects only to allow time for the samples to be analysed by the lab. • Data will be listed only due to expected small sample size. Individual subject plots may be produced. • If Angiotensin data (Ang II, Ang(1-5), Ang(1-7)) is not available at the time of the interim, analysis of the specified eCRF data will still go ahead as planned. A positive outcome in relation to PASP, Oxygen Saturation and AEs would lead to the study continuing without the need to review Angiotensin data. • Should a negative outcome be observed with PASP or Oxygen Saturation, then confirmation of the decision to stop the study for futility would not occur until the Angiotension data from the initial transfer were available and reviewed. • Any negative results with regards to AEs (as agreed by the study team), regardless of other endpoint results, would result in the study stopping.

The interim analysis was to use a data snapshot that had been cleaned to the best extent allowed by the timeframes (i.e. the interim data would not be fully cleaned or fully QC'd data and there would not be a locked database). The date of the source data cut was to be indicated on each interim related output (implemented in HARP via the *d_datadate* macro input parameter in the *ts_setup* macro call). Results were to be restricted to selected members of the study team. Results or discussions were not to be circulated to blinded staff involved in the conduct of the study at the sites.

The following table represents a guide to the outputs to be produced for the interim analysis. All outputs were to be produced in HARP.

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PASP				Y	Y	Y	Y	Y[3]	Y		Y			
Oxygen Saturation				Y	Y	Y	Y	Y[3]	Y		Y			
All AEs				Y[1]			Y[2]							
RAS Peptides (AngII, Ang(1-5), Ang(1-7))						Y	Y							

NOTES :

- Y = Yes display generated.
- 1. Produced if sufficient data
- 2. SAEs will be flagged within this listing

- 3. One table to include statistical analysis medians (95% CrI) and posterior probabilities. Also include within subject correlation as a footnote to support sample size re-estimation.

The sample size re-estimation was to be performed once the primary analysis for the interim had been completed and assuming that no overwhelming data supporting the need to stop for futility was observed. Estimates of standard deviations and within subject correlation were to be obtained from the PASP outputs produced during the interim and/or from SAS outputs from the statistical modelling. The sample size re-estimation was to be performed by re-running programs (using R) used to obtain pre-study precision estimates. The sample size re-estimation program and associated excel outputs of precision estimates were to be archived.

The interim analysis was performed when 11 subjects had been randomised. One subject did not complete both periods 1 and 2 due to withdrawal due to AE, therefore 10 subjects were analysed for the primary endpoint. Following a review of the data, the decision was made to make modifications to the protocol and continue the study (Part 2). Major modifications are a change in the hypoxia chamber altitude from 4000m to 5000m and echo recordings at the T3 timepoint being taken 2 minutes into exercise (due to use of semi-recumbent cycle), rather than at the end of a 10 minute exercise period. Part 1 and 2 of the study will be analysed separately.

3.1.2. Part 2

For Part 2 of the study, up to 14 subjects are planned to be randomised. Two interim analysis reviews are planned as follows:

- Review of PASP, oxygen saturation and AE data when approximately 3 subjects have completed Treatment Periods 1 and 2.
- Review of PASP, oxygen saturation and AE data when approximately 6 subjects have completed Treatment Periods 1 and 2. This second review may not be required and will be dependent on data observed during the first interim review. The timing of this review may be altered, as necessary, dependent on subject recruitment. Further interim reviews may take place, if appropriate.

At each review, the study may be stopped for futility if PASP results are highly variable, or if the PASP profile for the placebo group is not as expected (indicative of the model not working given the alterations to the study) or if review of the safety data suggests a change in the benefit-risk profile. If clear criteria for stopping the study are not met, the study will continue to the next interim analysis review, or on to the planned maximum number of evaluable subjects. Further interim reviews may be performed if deemed appropriate by the study team.
The following table represents a guide to the outputs to be produced for the interim analysis reviews. All outputs were to be produced in HARP. Adverse events (AEs) will be assessed via Inform or a listing produce via HARP.

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PASP						Y	Y							
Oxygen Saturation						Y	Y							
All AEs							Y[1]							

NOTES : Y = Yes display generated, 1. Produced if sufficient data available

3.2. Final Analyses

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

1. All subjects have completed the study as defined in the protocol (and subject to decisions made from the interim analyses).
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met (note that the study is being run as sponsor-unblinded, however, only a partial randomisation schedule will be made available to the GSK programming team for the interim analysis).
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Screened	Comprising of all subjects who complete at least one Visit 1 (Screening) procedure.	• Subject disposition (including reasons for screening failures) • Listing of any AEs/SAEs for non-randomised subjects
Modified Intent-To-Treat (mITT)	Comprising of all randomised subjects, excluding those who were randomised in error. A subject who is recorded as a screen failure, but is randomised and does not receive a dose of study treatment is considered to have been randomised in error. Any other subject who receives a randomisation number will be considered to have been randomised.	• Study Population, Safety & PD/Biomarker listings and selected tables/figures
Modified Intent-To-Treat Part 1 (mITT1)	This will comprise all subjects in the mITT population, who were randomised into Part 1 of the study (planned 4000m altitude)	• Safety & PD/Biomarkers tables and figures (Part 1)
Modified Intent-To-Treat Part 2 (mITT2)	This will comprise all subjects in the mITT population, who were randomised into Part 2 of the study (planned 5000m altitude)	• Safety & PD/Biomarkers tables and figures (Part 2)
Pharmacokinetic (PK)	Subjects in the 'mITT' population, for whom a pharmacokinetic sample was obtained and analysed and on active treatment.	• PK Listings
Pharmacokinetic Part 1 (PK1)	Subjects in the 'mITT' population, randomised in Part 1 of the study, for whom a pharmacokinetic sample was obtained and analysed and on active treatment.	• PK Part 1 tables and figures
Pharmacokinetic	Subjects in the 'mITT' population, randomised	• PK Part 2 tables and

Population	Definition / Criteria	Analyses Evaluated
Part 2 (PK2)	in Part 2 of the study, for whom a pharmacokinetic sample was obtained and analysed and on active treatment.	figures

NOTES :

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, subject management or subject assessment) will be summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A 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

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Time & Events
10.2	Appendix 2: Treatment States
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Biomarker Details
10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
10.9	Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses
10.10	Appendix 10: Abbreviations & Trade Marks
10.11	Appendix 11: List of Data Displays
10.12	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Modified Intent-To-Treat populations (mITT, mITT1 and mITT2, as appropriate), unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated			
	Table	Figure	Listing	Population for displays
Subject Disposition				
Subject Disposition	Y			mITT
Screening Status and Reasons for Screen Failure	Y		Y	All Subjects Screened
Reasons for Subject Withdrawal			Y	mITT
Important Protocol Deviations	Y		Y	mITT
Subjects with Inclusion/Exclusion Criteria Deviations			Y	mITT
Randomised and Actual Treatments			Y	mITT
Subjects for Whom the Treatment Blind was Broken			Y	mITT
Populations Analysed				
Study Populations	Y			All Subjects Screened
Subjects Excluded from Any Population			Y	All Subjects Screened
Demographic and Baseline Characteristics				
Demographic Characteristics	Y		Y	mITT1 and mITT2
Race and Racial Combinations	Y		Y	mITT1 and mITT2
Prior and Concomitant Medications				
Medical Conditions[1]	Y			mITT
Concomitant Medications			Y	mITT
Exposure and Treatment Compliance				
Exposure to Study Treatment			Y	mITT

NOTES :

- Y = Yes display generated.
- 1. Separate summaries for past and current conditions

7. PRIMARY STATISTICAL ANALYSES

7.1. Overview of Planned Analyses

The primary analyses will be based on the Modified Intent-To-Treat populations (mITT, mITT1 and mITT2).

Table 3 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Analyses

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Primary														
Pulmonary Artery Systolic Pressure (PASP)				Y	Y	Y	Y	Y[1]	Y		Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. One table to include statistical analysis medians (95% CrI) and posterior probabilities.

7.2. Planned Statistical Analyses

Primary Statistical Analyses
Endpoint
• Pulmonary Artery Systolic Pressure (PASP)
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 methods used would be fully documented in the CPSR. • The data will be inspected prior to analysis to determine whether a data transformation is required. Any data transformations (e.g. natural logarithm) will be applied to observed individual data prior to any modeling or derivations (e.g. prior to deriving subject baseline) • Separate analyses will be performed for Part 1 and Part 2 of the study. • A Bayesian repeated measures mixed effects model (fitted using SAS PROC MCMC), will be used to model the change from baseline (Ti-T0) in PASP. Based on the study design there are 4 post-dose timepoints (T1, T2, T3 and T4). The timepoint of primary interest is T3; in Part 1 this is immediately after exercise at an altitude of 4000m and in Part 2, this is 2 minutes into a reduced exercise challenge at an altitude of 5000m. • Covariates for period, treatment and timepoint (i.e., T1 to T4) will be included as fixed effects. Adjusted period-specific baseline and subject-level baseline will be included as continuous parameters (see Section 10.3.2.1). Subject will be included as a random effect and timepoint will be included as a repeated effect. Treatment by timepoint and adjusted period-specific baseline by timepoint interactions will be included. An unstructured variance-covariance matrix

Primary Statistical Analyses

will be fitted. Non-informative priors will be used for the model parameters, (see Section 10.8).

- Examination of covariates (for example Age, Weight, Height) may take place, if data permit. In this case, the equivalent model may be fitted in PROC MIXED and the covariate assessed at a 10% alpha level. The final Bayesian model would then be fit based upon the final model (after covariate examination) obtained using PROC MIXED. Alternatively, changes in deviance information criteria (DIC) may be assessed as part of the PROC MCMC modelling to examine covariates.
- Appropriate combinations of the model parameters would be used to obtain posterior distributions for the GSK2586881 vs placebo comparisons at each of the post dosing timepoints (T1 to T4).
- The change from baseline across the different post-dose timepoints will be represented via adjusted posterior medians for GSK2586881 and placebo, as well as associated 95% equi-tailed credible intervals. These results will be presented within tabular and graphical form after data has been back transformed (if applicable).
- The difference between GSK2586881 and placebo, for the change from baseline across post-dose timepoints will be represented via adjusted medians, as well as their associated 95% equi-tailed credible intervals. These results will be presented within tabular form after data has been back transformed (if applicable).
- The posterior distributions will also be used to produce several posterior probability statements, presented in tabular format; the most important being the probability that the change from baseline in PASP is reduced by GSK2586881 at time T3.
- Posterior probabilities of interest include (looking for high probabilities to favour increases to a lesser extent in PASP on GSK2586881):
    - Probability that change from baseline in PASP is reduced by GSK2586881
      (*i.e., probability that a treatment difference is negative, or if a log transformation is applied then the probability that the ratio is less than 1*).
    - Probability that change from baseline in PASP is reduced by >=2.5mmHg and >=5mmHg by GSK2586881
      (*i.e., probability that a treatment difference is <=-2.5 mmHg and <=-5mmHg. In the case of a log-transformation, ratios of interest would be <0.95 and <0.90, representing 5% and 10%difference between groups*)
    - Probability cut-offs may be re-assessed at the time of analysis

Model Checking & Diagnostics

- Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses

Model Results Presentation

- Summary tables for absolute and change from baseline by treatment and timepoint (T0 to T4) (for Part 1 and Part 2)
- Listing of absolute data
- Individual subject profiles by treatment group and timepoint (for Part 1 and Part 2)
- Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at times T1 to T4 along with posterior probabilities of interest (for Part 1 and Part 2)
- Figure of absolute PASP by timepoint (for Part 1 and Part 2)
- Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint (for Part 1 and Part 2)

8. SECONDARY ANALYSES

8.1. Safety Analyses

8.1.1. Overview of Planned Analyses

The safety analyses will be based on the Modified Intent-To-Treat populations (mITT, mITT1 and mITT2), unless otherwise specified.

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Oxygen Saturation														
Oxygen Saturation, measured by continuous pulse oximetry				Y	Y	Y	Y	Y[1]	Y		Y			
Oxygen Saturation vs PASP[2]					Y									
Pulmonary Vascular Resistance														
PVR collected via ECHO				Y	Y	Y	Y	Y[1]	Y		Y			
Adverse Events														
All AEs for Non-randomised Subjects							Y							
All AEs by SOC and PT[3]				Y			Y							
AEs Leading to Study Discontinuation							Y							
Drug-Related AEs by SOC and PT				Y										
All Serious AEs				Y			Y							
All Laboratory[4]														
Laboratory Values of PCI							Y							
All Laboratory Data for Subjects with any Value of PCI							Y							
ECG														
ECG Findings				Y			Y							
ECG Values by Visit				Y							Y			
ECG Values of PCI				Y			Y				Y			
All ECG Values for Subjects with any Value							Y							

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
of PCI														
Vital Signs														
Vital Signs by Visit				Y							Y			
Vital Signs of PCI							Y							
All Vital Signs for Subjects with any Value of PCI							Y							
Immunogenicity														
Immunogenicity				Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated, PCI = Potential Clinical Importance
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. One table to include statistical analysis medians (95% CrI) and posterior probabilities.
- 2. Scatter plot of x vs y (OS vs PASP) by treatment group, timepoint indicated by panel. To be produced for the mITT2 population only.
- 3. Listing will include subject's numbers for individual AE's and AE system organ classes, preferred terms and verbatim term.
- 4. Chemistry and haematology data will be assessed for PCI values.
- Chemistry collected: BUN, Creatinine, Glucose, Potassium, Sodium, Calcium, AST (SGOT), ALT (SGPT), Alkaline phosphatase, Total and direct bilirubin, Total protein, Albumin.
- Haematology collected: Platelet count, RBC count, haemoglobin, hematocrit, MCV, MCH, neutrophils, lymphocytes, monocytes, eosinophils, basophils.
- Urinalysis collected: Specific gravity, pH, glucose, protein, blood and ketones by dipstick, microscopic examination (if blood or protein is abnormal).
- With the exception of Immunogenicity table (mITT) and OS vs PASP scatter plot (mITT2), all tables and figures will be produced separately for the mITT1 and mITT2 populations. Listings will be produced based on the overall mITT population.

8.1.2. Planned Safety Statistical Analyses

Planned Statistical Analyses
Endpoint(s)
• Oxygen Saturation
Model Specification
• Refer to Section 7.2. Oxygen Saturation will be analysed in the same manner as for the primary endpoint PASP. • Posterior probabilities of interest include (looking for very low probabilities to remove any concerns with regards to Oxygen Saturation reduction on GSK2586881):   • Probability that the change from baseline on Oxygen Saturation is reduced by GSK *(i.e., probability that a treatment difference is <0% or if a log transformation is applied then the probability that the ratio < 1).*

Planned Statistical Analyses
• Probability that the change from baseline in Oxygen Saturation is reduced by GSK by >3% and >=5% (absolute difference) compared to placebo. (*i.e., probability that a treatment difference (absolute) is <-3% and <=-5%. In the case of a log-transformation, ratios of interest would be <0.94 and <0.92 representing 6% and 8% difference between groups*) • Probability cut-offs may be re-assessed at the time of analysis
Model Checking
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Summary tables for absolute and change from baseline by treatment and timepoint (T0 to T4) (for Part 1 and Part 2) • Listing of absolute data • Individual subject profiles by treatment group and timepoint (for Part 1 and Part 2) • Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at times T1 to T4 along with posterior probabilities of interest (for Part 1 and Part 2) • Figure of absolute Oxygen Saturation by timepoint (for Part 1 and Part 2) • Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint (for Part 1 and Part 2)

Planned Statistical Analyses
Endpoint(s)
• Pulmonary Vascular Resistance (PVR)
Model Specification
• Refer to Section 7.2. PVR will be analysed in the same manner as for the primary endpoint PASP. • Posterior probabilities of interest to include (looking for high probabilities to favour increases to a lesser extent in PVR on GSK2586881): • Probability that change from baseline in PVR is reduced by GSK2586881 (*i.e., probability that a treatment difference is negative, or if a log transformation is applied then the probability that the ratio is less than 1*). • Probability that change from baseline in PVR is reduced by >=0.1 wood units and >=0.3 wood units (*i.e., probability that a treatment difference is <=-0.1 wood units and <=-0.3 wood units. In the case of a log-transformation, ratios of interest would be <0.95 and 0.90, representing 5% and 10% difference between groups)* • Probability cut-offs may be re-assessed at the time of analysis
Model Checking
• Refer to: Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation (Part 2 only)
• Summary tables for absolute and change from baseline by treatment and timepoint (T0 to T4) • Listing of absolute data • Individual subject profiles by treatment group and timepoint

Planned Statistical Analyses
• Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at times T1 to T4 along with posterior probabilities of interest • Figure of absolute PVR by timepoint • Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint

8.2. Pharmacokinetic Analyses

8.2.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic populations for Part 1 and Part 2, unless otherwise specified.

Table 5 provides an overview of the planned analyses, with full details being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Plasma GSK2586881 concentrations	Y[1, 3]	Y	Y[1,2]	Y				
Pharmacokinetic Parameters		Y		Y		Y		

NOTES :
- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. Linear and Semi-Log plots will be created on the same display.
- 2. One output for one graph per subject and a further output with all subject profiles on the same graphic
- 3. Separate Mean (± SD) and Median plots will be generated.
- All tables and figures will be produced separately for the PK1 and PK2 populations. Listings will be produced for the overall PK population.

8.2.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).

8.2.3. Pharmacokinetic Parameters

8.2.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Win Nonlin Pro V6.3 or greater.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 6 will be determined from the plasma concentration-time data, as data permits.

Table 6 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-2.5h) post-dose	Area under the concentration-time curve over the study period (pre-dose to 30 mins rest post chamber exit).
AUC(0.5-2.0h) post-dose	Area under the concentration-time curve over the time period for the hypoxia challenge (immediately prior to chamber entry to chamber exit).
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
CL	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.

NOTES:

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

8.2.4. Population Pharmacokinetic (PopPK) Analyses

A population PK analysis may be conducted. The plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the specifications of which are provided in Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses.

8.3. Pharmacodynamic and Biomarker Analyses

8.3.1. Overview of Planned Pharmacodynamic and Biomarker Analyses

The pharmacodynamic and biomarker analyses will be based on the Modified Intent-To-Treat populations (mITT, mITT1 and mITT2), unless otherwise specified. Biomarker data will be analysed for those subjects in the Modified Intent-To-Treat populations for whom a sample was obtained and analysed.

Table 7 provides an overview of the planned pharmacodynamic and Biomarker analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 7 Overview of Planned Pharmacodynamic and Biomarker Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
RAS Peptide Responses[1]														
Ang II				Y	Y	Y	Y	Y[1]	Y[1]					
Ang(1-7)				Y	Y	Y	Y	Y[1]	Y[1]					
Ang(1-5)				Y	Y	Y	Y	Y[1]	Y[1]					
Other Biomarkers (Disease Biomarkers)														
Surfactant Protein D				Y	Y	Y	Y	Y[1]	Y[1]					
Ventilatory Parameters[2]														
Oxygen consumption (VO2)				Y			Y							
Carbon Dioxide Production (CO2)				Y			Y							
Total Tidal Volume				Y			Y							
Inspiratory Tidal Volume				Y			Y							
Expiratory Tidal Volume				Y			Y							
Total Respiratory Time				Y			Y							
Inspiratory Time				Y			Y							
Expiratory Time				Y			Y							
Duty Cycle				Y			Y							
Mean Respiratory Flow				Y			Y							
Respiratory Rate				Y			Y							
RAS Peptides vs PASP & Oxygen Saturation[3]														
Ang II vs PASP					Y									
Ang(1-7) vs PASP					Y									
Ang(1-5) vs PASP					Y									
Ang II vs Oxygen Saturation					Y									
Ang(1-7) vs Oxygen Saturation					Y									
Ang(1-5) vs Oxygen Saturation					Y									

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. Statistical analysis of RAS peptides and SPD to be performed for Part 2. Part 1 may also be analysed.
- 2. Parameters will be included in the same summary/figure/listing paging by RAS peptide where applicable
- 3. Scatter plots of x vs y for mITT population, panel by timepoint, include study part in a legend, one plot for PASP, one plot for Oxygen Saturation (page by RAS peptide).
- Unless otherwise stated as in #3, all tables and figures will be produced separately for the mITT1 and mITT2 populations. Listings will be produced based on the mITT population

8.3.2. Planned Pharmacodynamic and Biomarker Statistical Analyses

Planned Statistical Analyses
Endpoint(s)
• **RAS Peptide Responses**: Ang II, Ang(1-7), Ang(1-5) • **Disease Biomarker**: Surfactant Protein D
Model Specification

• Refer to Section 7.2. Change from baseline in PD/Biomarker endpoints will be analysed in a manner similar to the primary endpoint PASP. Data will be assessed prior to analysis to confirm the need for any data transformations. Log transformation highly likely to be required.
• Analyses will be performed for Part 2. Part 1 may also be analysed.
• Repeated measures timepoints of interest will be:
• Pre-dose (T0)
• End of Infusion
• 15 min Post-dose (T1)
• 15-45 min Post-dose
• 60 min post chamber entry (T2)
• Immediately post exercise (T3)
• Immediately post chamber exit
• 30 mins post chamber exit (T4)
  • Posterior probabilities of interest may include:
  • AngII: probability that the ratio <1, <0.50 and <0.25, representing any, 50% and 75% greater reduction in AngII levels on GSK2586881 compared to placebo
  • Ang(1-5) & Ang(1-7): probability that the ratio >1, >1.50 and >1.75, representing any, 50% and 75% greater increase in Ang(1-5) and Ang(1-7) levels on GSK2586881 compared to placebo
  • SPD: probability that the ratio <1, >1 and >1.5, representing any decrease, any increase and a 50% increase in SPD levels on GSK2586881 compared to placebo
  • Probability cut-offs may be re-assessed at the time of analysis

Model Checking
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Summary tables for absolute by treatment and timepoint (as detailed above) (for Part 1 and

Planned Statistical Analyses
Part 2) • Listing of absolute data • Individual subject profiles by treatment group and timepoint (for Part 1 and 2) • Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at ALL timepoints (not just T1 to T4), along with posterior probabilities of interest. (Part 2 and Part 1(as required)) • Figure of absolute data by timepoint (for Part 1 and 2) • Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint (Part 2 and Part 1(as required))

8.4. Pharmacokinetic / Pharmacodynamic Analyses

The pharmacokinetic/pharmacodynamic (PK/PD) analyses will be based on the mITT and mITT2 population, unless otherwise specified. For the RAS peptides, PASP and Oxygen Saturation endpoints, exploratory plots vs pharmacokinetic concentrations will initially be reviewed to identify endpoints where there is a potential trend. If there is evidence for a trend, further PK/PD analyses may be conducted. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the specifications of which are provided in Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses.

Table 8 provides an overview of the planned PK/PD analyses with further details of data displays being presented in Appendix 11: List of Data Displays. Details of missing data imputation specific to PK/PD graphics are provided in Section 10.5.2.

Table 8 Overview of Planned PK/PD Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
RAS Peptide Ang II vs PK concentration		Y[1]		
RAS Peptide Ang(1-7) vs PK concentration		Y[1]		
RAS Peptide Ang(1-5) vs PK concentration		Y[1]		
PASP vs PK concentration		Y[2]		
PASP (T2 & T3) vs AUC(0.5-2.0)		Y[2]		

NOTES :

- Scatter plots, timepoints indicated by panel.
- 1. RAS peptides vs PK will form one graphic, page by RAS peptide. Study part will be identified by a different colour/symbol combination. To be produced for the mITT population.
- 2. Produced for Part 2 only (mITT2 population).
- T = Table, F = Figure, L = Listing, Y = Yes display generated.

9. REFERENCES

GlaxoSmithKline Document Number: 2016N283626_00, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 23-Sep-2016

GlaxoSmithKline Document Number: 2016N283626_01, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 24-Feb-2017

GlaxoSmithKline Document Number: 2016N283626_02, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 07-Mar-2017

GlaxoSmithKline Document Number: 2016N283626_03, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 06-Mar-2018

10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time and Events
Section 10.2	Appendix 2: Treatment States
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Pharmacodynamic and or Biomarkers
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance
Section 10.7	Appendix 7: Biomarker Details
Section 10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Section 10.9	Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses
Other RAP Appendices	
Section 10.10	Appendix 10: Abbreviations & Trade Marks
Section 10.11	Appendix 11: List of Data Displays
Section 10.12	Appendix 12: Example Mock Shells for Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Time & Events

10.1.1.1. Screening and Follow up

Procedure	Screening[1] (up to 28 days prior to Treatment Period 1, Day 1)	Follow up (7-10 days post last dose)	Notes
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Full physical exam, including height and weight	X	X	Height and weight to be measured at screening only. Weight at screening will be used for dosing calculation.
Alcohol, Drugs of Abuse, Smoking test	X		
Medical history (includes substance usage [and family history of premature CV disease])	X		Substances: Drugs, Alcohol, tobacco
Past and current medical conditions [including cardiovascular medical history]	X		
Serum OR urine pregnancy test (WCBP)	X		
HIV, Hep B and Hep C screen	X		
Laboratory assessments (include liver chemistries)	X	X	Non Fasting
Immunogenicity		X	
12-lead ECG	X	X	Triplicate ECG required at screening.
Vital signs	X	X	Triplicate vital signs required at screening.
Spirometry	X		
Echocardiogram	X		
Concomitant Medication review	X	X	
Hypoxia chamber plus exercise	X		**Part 1:** Tolerance to 4000m for 10 mins followed by incremental exercise testing to determine maximum oxygen uptake (VO2max) and calculate 70% of VO2max (to be used for the exercise challenge during the Treatment Periods). **Part 2:** Tolerance to 5000m for 10 mins followed by incremental exercise testing to determine maximum oxygen uptake (VO2max) and calculate 50% of

Procedure	Screening[1] (up to 28 days prior to Treatment Period 1, Day 1)	Follow up (7-10 days post last dose)	Notes
			VO2max (to be used for the exercise challenge during the Treatment Periods)
Pharmacogenetic sample (PGx)	X		Can be taken any time after consent has been signed. Only required once and is optional.
AE/SAE review	X	X	As per timings detailed in protocol Section 7.2.1.1

1. Screening assessments are allowed to be conducted on more than one day

10.1.1.2. Treatment Period 1 and 2

Procedure	Treatment Period 1 and 2 (Washout 3-14 days)											Notes
	Times relative to start of dosing				Hypoxic Challenge ~80 min (Times relative to entry to Chamber)							
	Pre-dose	0h	15 min	15-45 min	0-60 min	60 min	60-70 min	Immediately after exercise	On exit from chamber	After 30 min rest	60 min after exit from Chamber	
Randomisation	X											Treatment Period 1 only. Randomisation can occur up to the day before the first treatment period
Brief physical exam	X											
Vital signs	X			X				X[5]			X	
Immunogenicity	X											
12-lead ECG	X			X							X	
Echocardiogram	X		X			X		X[6 below]		X		
Subject enters chamber					X							Subject enters chamber approximately 30 min after study treatment
Study Treatment (Dosing)		X										
Subject leaves chamber								X				Subject leaves chamber after the fourth echocardiogram, blood samples and vital signs have been taken.
Exercise challenge							X					**Part 1:** exercise at 70% VO2 max for ~5-10 min. Echo conducted immediately after. **Part 2:** exercise at 50% VO2 max for 2 min. Echo started at 2 min into the challenge, and the subject continues exercising.
Ventilatory parameters	X		X			X				X		Measurements to be taken 2 min before echocardiograms.

Procedure	Treatment Period 1 and 2 (Washout 3-14 days)											Notes
	Times relative to start of dosing				Hypoxic Challenge ~80 min (Times relative to entry to Chamber)							
	Pre-dose	0h	15 min	15-45 min	0-60 min	60 min	60-70 min	Immediately after exercise	On exit from chamber	After 30 min rest	60 min after exit from Chamber	
Pulse Oximetry (O2 saturation)	←==========→											Will be continuously monitored for safety. A measurement should be recorded at time of each echocardiogram and databased. **Part 2**: when the echo is recorded during the exercise challenge, pulse oximetry will be recorded immediately prior to initiation of the echo at 2 minutes into exercise.
Telemetry	←==========→											Will be continuously monitored for safety.
RAS Biomarkers	X	X[1]	X[2]	X[3]		X[2]		X[2]	X[4]	X[2]		
SP-D	X	X[1]	X[2]	X[3]		X[2]		X[2]	X[4]	X[2]		
PK sampling	X	X[1]	X[2]	X[3]		X[2]		X[2]	X[4]	X[2]		
AE/SAE review		←==========→										
Concomitant medication review	X											

1. Take at the end of the infusion
2. Taken immediately after echocardiogram
3. Immediately before entering the chamber
4. To be taken as soon as possible after leaving chamber
5. On this occasion ONLY, vital signs to be taken after the blood draw.
6. In Part 2, echo at this time-point taken 2 minutes into the exercise challenge (not immediately after exercise).

10.2. Appendix 2: Treatment States

10.2.1. Treatment States for AE Data

This study is a single dose two period crossover study. As such, AEs will be attributed to the treatment received within the relevant study period based on the dates and times of the AEs in relation to dosing date and time. This is as per IDSL dataset standards. This is detailed in the table below.

10.2.1.1. Treatment States for AE Dates

Treatment State	Definition
Pre-Treatment	AE Start Date / Time < Study Treatment Start Date / Time (Period 1) This will apply to all subjects enrolled into the study, including those not randomised. We may have non-randomised and randomised subjects who have pre-treatment AEs/SAEs. For non-randomised subjects these events will be captured in the 'non-randomised' listing. For randomised subjects these events will be captured in summary listings with treatment group='Pre-Treatment'.
On-Treatment (Period 1)	If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 1) & before Study Treatment Start Date / Time (Period 2). Study Treatment Start Date / Time (Period 1) ≤ AE Start Date / Time < Study Treatment Start Date / Time (Period 2) For randomised subjects, this derivation ensures that AEs starting on or after the Period 1 dose up until the Period 2 dose will be captured and assigned to the Period 1 treatment.
On-Treatment (Period 2)	If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 2) & before Follow-Up. Study Treatment Start Date / Time (Period 2) ≤ AE Start Date / Time ≤ Follow-Up Date For randomised subjects, this derivation ensures that AEs starting on or after the Period 2 dose up until the Follow-up Visit will be captured and assigned to the Period 2 treatment.
Post-Treatment	If AE Start Date is on or after Follow-Up. AE Start Date > Follow-Up Date There shouldn't be any instances of this. Subjects will return for a follow-up and visit and any AEs would be documented at that point (and hence included in Period 2 treatment group). No further follow-up of patients is required.
Onset Time Since 1st Dose (Days/Hours/Mins)	If Study Treatment Start Date / Time (Period 1) ≤ AE Start Date / Time = AE Start Date / Time – Study Treatment Start Date / Time (Period 1) + 1 (min) Missing otherwise. A calculation to assess the time since the Period 1 dose up until the start time of

Treatment State	Definition
	the AE. This will be calculated for all AEs, regardless of which period/treatment the AE was assigned to. Example: If Period 1 Dose was administered at 08:00am 01OCT2016 and Period 1 AE started at 09:10am 01OCT2016, then onset time since **first** dose would be 0d 1h 11m. If Period 2 Dose was administered at 08:30am 08OCT2016 and a Period 2 AE occurred on 08OCT2016 at 10:00am, then onset time since **first** dose would be 7d 2h 1m.
Onset Time Since Period Dose (Days/Hours/Mins)	**[PERIOD 1]** If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 1) & before Study Treatment Start Date / Time (Period 2). = AE Start Date / Time – Study Treatment Start Date / Time (Period 1) +1 (min) **[PERIOD 2]** If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 2) & on or before Follow-Up. = AE Start Date / Time – Study Treatment Start Date / Time (Period 2) + 1 (min) Missing otherwise. A calculation to assess the time since the dose in the relevant Period/treatment to which the AE is attributable to. Example: [PERIOD 1] If Period 1 Dose was administered at 08:00am 01OCT2016 and Period 1 AE started at 09:10am 01OCT2016, then onset time since **period** dose would be 0d 1h 11m (i.e. identical to value in previous row example in this case) [PERIOD 2] If Period 2 Dose was administered at 08:30am 08OCT2016 and a Period 2 AE occurred on 08OCT2016 at 10:00am, then onset time since **period** dose would be 0d 1h 31m
Duration (Days/Hours/Mins)	AE Resolution Date / Time – AE Start 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 eCRF OR value is missing

10.2.2. Treatment States for Concomitant Medication Data

This study is a single dose two period crossover study. As such, Concomitant Medications will be attributed to the treatment received within the relevant study period based on the dates and times of the Concomitant Medications in relation to dosing date and time. This is as per IDSL dataset standards. This is detailed in the table below.

10.2.2.1. Treatment States for Concomitant Medication Dates

Treatment State	Definition
Pre-Treatment	CM Start Date / Time < Study Treatment Start Date / Time (Period 1)
On-Treatment (Period 1)	If CM Start Date / Time is on or after Study Treatment Start Date / Time (Period 1) & before Study Treatment Start Date / Time (Period 2). Study Treatment Start Date / Time (Period 1) ≤ CM Start Date / Time < Study Treatment Start Date / Time (Period 2) For randomised subjects, this derivation ensures that CMs starting on or after the Period 1 dose up until the Period 2 dose will be captured and assigned to the Period 1 treatment group.
On-Treatment (Period 2)	If CM Start Date / Time is on or after Study Treatment Start Date / Time (Period 2) & before Follow-Up. Study Treatment Start Date / Time (Period 2) ≤ CM Start Date / Time ≤ Follow-Up Date For randomised subjects, this derivation ensures that CMs starting on or after the Period 2 dose up until the Follow-up Visit will be captured and assigned to the Period 2 treatment.
Study Day	Should relate to day since first dose i.e the day of the dose administered during Period 1 should be 'Day 1'.
Period Day	Day within the treatment period, for example, Period 1 Day 1 or Period 2 Day 1

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo	Placebo	1
B	GSK2586881 0.8 mg/kg	GSK2586881 0.8 mg/kg	2

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

10.3.2. Baseline Definition & Derivations

10.3.2.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the latest pre-dose assessment. Baseline definitions are applicable to each period.

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose) Time T0	
Safety			
PASP	X	X	T0
Oxygen Saturation		X	T0
Labs	X		Screening
ECGs	X[1]	X	T0
Vital Signs	X[1]	X	T0
Biomarkers/Pharmacodynamic			
RAS peptides		X	T0
Other biomarkers		X	T0
Ventilatory parameters		X	T0

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

For statistical analyses (for example, Bayesian mixed model for PASP):

- Baseline is defined as the measurement taken pre-dose during each treatment period (i.e., time T0). This can also be referred to as '**period-specific baseline**'.
- **Subject-level baseline** is defined as the mean of the two period-specific baseline readings (the pre-dose T0 reading from each of the two treatment periods) for each subject.

- Period-level baseline (or '**adjusted period-specific baseline**') is defined as the difference between the baseline ('period-specific baseline') and 'subject-level baseline' for each period and each subject (i.e., the 'period-specific baseline' minus 'subject-level baseline' in each period).

The statistical modelling will include terms for 'subject-level baseline' and 'adjusted period-specific baseline'.

10.3.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= **Post-Dose Visit Value – Baseline [Ti – T0]**

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.3.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.3.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used to perform all data analyses. Generate tables, figures and listings. • The latest version of R (or alternative supported available packages) will be used in sample size re-estimation for the interim analysis	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Area	: \ARPROD\GSK2586881\204987\Internal_01 : \ARPROD\GSK2586881\204987\Internal_02 : \ARPROD\GSK2586881\204987\Final_01
QC Spreadsheet	: \ARWORK\GSK2586881\204987\Internal_01\documents : \ARWORK\GSK2586881\204987\Internal_02\documents : \ARWORK\GSK2586881\204987\Final_01\documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards (Integrated Data Standards Library) • RAS Peptide data samples for Ang II, Ang(1-5) and Ang(1-7) will be processed by Q2 and data provided to GSK Data Management. • Surfactant Protein D samples and Immunogenicity samples will be processed by GSK and data will be provided to GSK Data Management • Pharmacokinetic samples will be processed by Covance and data will be provided to GSK Data Management	
Generation of RTF Files	
• RTF files will be generated for the interim and final reporting efforts	

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • 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. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures, unless otherwise stated. • 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, %
Descriptive Summary Statistics (Log Transformed Data)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation ($CV_{b/w}$ (%)): CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (NOTE: SD is the SD of log transformed data)
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD)

Reporting Standards	
Summary Statistics (Log Transformed)	of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = √ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data) [2] CV_w (%) = √ (exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Being Log Transformed	Tmax, first point, last point and number of points used in the determination of lambda_z for listings
Listings	Include the first point, last point and number of points used in the determination of lambda_z for listings and R squared
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. General

Multiple Measurements at One 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. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

10.4.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  ○ Any subject with a missing day will have this imputed as day '15'.
  ○ Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

10.4.3. Safety

ECG Parameters

RR Interval

- IF RR interval (msec) is not provided directly, then RR can be derived as :
  [1] If QTcB is machine read & QTcF is not provided, then :

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

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

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

- If ECGs are manually read, the RR value preceding the measurement QT interval should be a collected value THEN do not derive.

Corrected QT Intervals

- When not entered directly in the eCRF, corrected QT intervals by Bazett's (QTcB) and Fridericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements.
- IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as :

$$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Laboratory Parameters

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

10.4.4. Pharmacodynamic and Biomarker

Biomarkers

RAS Peptides

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

Disease Biomarker

- Surfactant Protein D

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.

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as any subject who completes all phases in the study including the follow-up visit. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.5.2. 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 subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
PK	If dosing and/or sampling times are missing, the relevant concentrations will be deleted from the population PK and PK/PD analysis dataset and summarized in a deletion record listing. Samples listed as having no sample (NS), no result (NR) or insufficient sample (IS) will be excluded from the PK data set and also included in the deletion record listing. GSK2586881 concentrations below the lower limit of quantification (LLQ) for the assay will be reported as NQ (Below Quantification Limit). All NQ values will be set to "." (missing) in the population PK and PK/PD dataset. Individuals with all plasma concentrations reported as NQ will be included in the data set. 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 as below. Variables relating to different imputation methods for PK data will be available within the derived A&R PKCNC dataset (e.g. differentiating between setting NQ values to missing or ½ LLQ).
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

Element	Reporting Detail
	(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.

10.5.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

10.5.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	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.

Element	Reporting Detail
Adverse Events	Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. • However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information, then the Week 1 Day 1 date will be assumed to be the start date. • The AE will then be considered to start on-treatment (worst case). • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. The recorded partial date will be displayed in listings.

10.5.2.3. Handling of Missing Data for Statistical Analysis

No missing data imputation methods will be used.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. Laboratory Values

Laboratory parameters have been reviewed against those specified in the protocol and any parameters not specified here have been assigned as not essential for assessment.

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
Hemoglobin	g/L	Male		180
		Female		180
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	g/L		30	
BUN	mmol/L			≥ 2x ULN
Calcium	mmol/L		2	2.75
Creatinine	mmol/L			≥ 1.3x ULN
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

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

10.6.2. 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	

10.6.3. Vital Signs

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

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

10.7. Appendix 7: Biomarker Details

Biomarker Category	Analyte	Method	Lab	Matrix	Total samples expected per subject
RAS Peptides[1] (key endpoints)	Ang II	LCMS	Q2	Blood	8
	Ang (1-5)	LCMS	Q2	Blood	8
	Ang (1-7)	LCMS	Q2	Blood	8
Disease Biomarkers	Surfactant Protein D	Elisa	GSK	Serum	8

NOTES :

- 1. These peptides will be included in the interim analysis.
- Sampling times for each period: Pre-dose (T0), End of Infusion, 15 min Post-dose (T1), 15-45 min Post-dose, 60 min post chamber entry (T2), immediately post exercise (T3), immediately post chamber exit, 30 mins post chamber exit (T4).

10.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	• PASP • Oxygen Saturation • RAS Peptides (AngII, Ang(1-5), Ang(1-7)) • Surfactant Protein D
Analysis	• SAS PROC MCMC: Bayesian repeated measures mixed model

- Fixed effects will be assigned a non-informative prior of N(0, Var=1E6) and may be entered as separate univariate priors or as part of a multivariate distribution (variance covariance structure with zeros for off diagonals) in model hyperpriors.
- The non-informative UN priors should be an inverse Wishart distribution. If the equivalent of an unstructured variance covariance matrix does not fit then an AR(1) w/Random Effect structure may be considered, with non-informative priors ϕ~U[-1,1] for the off diagonal elements and σ^2 ~ invGamma(0.0001, scale=0.0001). Example, for N=3:

$$UN = \begin{pmatrix} \sigma_1^2 & \sigma_{21} & \sigma_{31} \\ \sigma_{21} & \sigma_2^2 & \sigma_{32} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 \end{pmatrix}$$

$$AR(1) = \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} * \sigma^2$$

- Appropriate SAS helper procedures (e.g. PROC TRANSREG) may be used to convert typical "long and thin" PROC MIXED input datasets into a format appropriate for repeated measures modelling in PROC MCMC (e.g. constructing sets of factors for each class level and fixing the final level to zero)
- Centring of continuous covariates will take place at the input dataset stage: (valuei – average) for each subject i.
- Examination of trace plots of samples versus the simulation number and Geweke diagnostics to assess convergence. Autocorrelation plots and lag summary table to assess the degree of autocorrelation. Monte Carlo standard errors compared to posterior standard deviations (a rule of thumb but not binding target would be <0.05). If further diagnostics required a scatterplot matrix plot of the posterior samples of each parameter.
- Number of burn ins, thinning, starting points, number of posterior draws to take (10,000 as a starting default) will be customised to each model and may not be possible to specify in advance but will be modified to ensure satisfactory diagnostics are produced.
- For robustness, where non-informative priors are used the equivalent PROC MIXED model may be fitted (no output from this would be reported) and LS Means and estimates of treatment differences compared to the results obtained from the PROC MCMC analysis. SAS code for the random and repeated statements would be:

```
random int / subject=subjid s vcorr;
repeated visit / subject=subjid*ptrtgrp type=un r rcorr;
```

- Model assumptions will be applied, but appropriate adjustments may be made based on the data.

10.9. Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (Or Biomarker) Analyses

10.9.1. Population PK Dataset File Structure

The PME compliant file structure is a space-delimited file with each row containing the following columns of information. Data from all active treatments will be included (i.e. exclude placebo).

Decision as to whether this will be required will be made following the planned interim analysis (for study Part 2 at approximately N=3 or approximately N=6).

Note that subject numbers up to and including PP were enrolled into Part 1 of the study. Subject numbers from PP onwards will be enrolled into Part 2 of the study.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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=0.8 for 0.8 mg/kg treatment Dose of GSK2586881 (for all events)
PART	Study Part	Integer	-	1=Part 1 or 2=Part 2
PERIOD	Study Period	Integer	-	1=Period 1 or 2=Period 2
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

Variable short name	Assessment description	Format	Unit	Valid Values / Format
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL = 4, TIME = 0 Hours since start of first active infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose/infusion
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 4, TIME = 0 Hours since start of LAST infusion. For pre-dose sample, TRLD is relative to previous dose prior to sample For single dose studies TRFD and TRLD are the same
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
DV	Dependent Variable	Decimal	pg/mL	When LABL=6, observed GSK2586881 concentration at time specified by TRLD. When LABL=4 (dosing record), DV=0
MDV	Missing Data Variable	Integer	-	Either '0' if DV value present or 1 if DV value is non-quantifiable (NQ) or LABL=4
MDV1	Missing data variable	Integer	-	Either '0' if LABL=6 or '1' if LABL=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

Variable short name	Assessment description	Format	Unit	Valid Values / Format
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
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed concentration record for GSK2586881 at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	**pg/mL**

10.9.2. Population PK/PD Dataset File Structure : ANGII

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.

Decision as to whether this will be required will be made following the planned interim analysis (for study Part 2 at approximately N=3 or approximately N=6).

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				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 for placebo treatment **DGRP=0.8 for 0.8 mg/kg treatment Dose of GSK2586881 (for all events)**
PART	Study Part	Integer	-	1=Part 1 or 2=Part 2
PERIOD	Study Period	Integer	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=0 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BLII	AngII concentration record	Decimal		Baseline value (pre-dose value)
DV	AngII concentration record	Decimal		When LABL=6, observed AngII concentration at time specified by TRLD. When LABL=0 or 4, AngII=0
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=0 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=0 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 NQTYPE = '2'
CMT	Compartment data	Integer	-	DOSE event: CMT=1, specifies the

Variable short name	Assessment description	Format	Unit	Valid Values / Format
	item			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
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	

10.9.3. Population PK/PD Dataset File Structure : ANG1-5

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.

Decision as to whether this will be required will be made following the planned interim analysis (for study Part 2 at approximately N=3 or approximately N=6).

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987

Variable short name	Assessment description	Format	Unit	Valid Values / Format
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 for placebo treatment treatment **DGRP=0.8 for 0.8 mg/kg treatment Dose of GSK2586881 (for all events)**
PART	Study Part	Integer	-	1=Part 1 or 2=Part 2
PERIOD	Study Period	Integer	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=0 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				If LABL="0" or "4", TFLAG=6
BL15	Ang1-5 concentration record	Decimal		Baseline value
DV	Angl1-5 concentration record	Decimal		When LABL=6, observed Ang1-5 concentration at time specified by TRLD. When LABL=0or 4, Ang1-5=0
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=0 or,4
MDV1	Missing data variable	Integer	-	'1' if LABL=0 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 NQTYPE = '2'
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event CMT=5 for ANG1-5 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
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	

10.9.4. Population PK/PD Dataset File Structure : ANG1-7

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.

Decision as to whether this will be required will be made following the planned interim analysis (for study Part 2 at approximately N=3 or approximately N=6).

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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 for placebo treatment treatment **DGRP=0.8 for 0.8 mg/kg treatment** **Dose of GSK2586881 (for all events)**
PART	Study Part	Integer	-	1=Part 1 or 2=Part 2
PERIOD	Study Period	Integer	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=0 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BL17	Ang1-7 concentration record	Decimal		Baseline value
ANG1-7	Ang1-7 concentration record	Decimal		When LABL=6, observed Ang1-7 concentration at time specified by TRLD. When LABL=0or ,4, DV=0
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=0 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=0 or 4 "0" when LABL=6
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=4 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.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				Valid values are - 1 – each dosing record for subject 0 - for all other records

Assessments captured in the LABL variable

Label	Description	Units
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	

10.9.5. Population PK/PD Dataset File Structure : Oxygen Saturation/PASP

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.

Decision as to whether this will be required will be made following the planned interim analysis (for study Part 2 at approximately N=3 or approximately N=6).

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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 for placebo treatment treatment **DGRP=0.8 for 0.8 mg/kg treatment Dose of GSK2586881 (for all events)**
PART	Study Part	Integer	-	1=Part 1 or 2=Part 2
PERIOD	Study Period	Integer	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=1 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample, TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BLPASP	PASP	Decimal	mmHg	Baseline Value
PASP	PASP	Decimal	mmHg	When LABL=6, PASP at time specified by TRLD. When LABL=1, or 4, PASP=0
BLOS	Oxygen Saturation	Decimal	%	Baseline Value
OS	Oxygen Saturation	Decimal	%	When LABL=6, Oxygen Saturation at time specified by TRLD. When LABL=1 or 4, Oxygen Saturation=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

Assessments captured in the LABL variable

Label	Description	Units
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR**	

10.10. Appendix 10: Abbreviations & Trade Marks

10.10.1. Abbreviations

Abbreviation	Description
ACE2	Angiotensin converting enzyme type 2
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine aminotransferase (SGPT)
Ang II	Angiotensin II
AST	Aspartate aminotransferase (SGOT)
AUC(0-2.5h)	Area under the concentration-time curve over the study period
AUC(0.5-2.0h)	Area under the concentration-time curve over the hypoxia challenge
A&R	Analysis and Reporting
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed plasma concentration
CO2	Carbon Dioxide
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
GSK	GlaxoSmithKline
GUI	Guidance
HPV	Hypoxic Pulmonary Vasoconstriction
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
mITT	Modified Intent-To-Treat
IV	Intravenous
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
O2	Oxygen
PASP	Pulmonary Artery Systolic Pressure

Abbreviation	Description
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PVR	Pulmonary Vascular Resistance
QC	Quality Control
QTcF	Fridericia'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
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tmax	Time to maximum observed concentration
T1/2	Apparent terminal phase half-life
V	Volume of Distribution
VO2	Oxygen Consumption

10.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP
RANDALL NG

Trademarks not owned by the GlaxoSmithKline Group of Companies
R (Statistical programming package/language)
SAS
WinNonLin

10.11. Appendix 11: List of Data Displays

10.11.1. 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
Pharmacodynamic and / or Biomarker	5.1 to 5.n	5.1 to 5.n
Pharmacokinetic / Pharmacodynamic	6.1 to 6.n	6.1 to 6.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 12: 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
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 / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.11.3. Deliverable [Priority]

Delivery	Description
IA[1]	Interim Analysis (Planned to be completed by GSK) – Study Part 1
IA[2], IA[3]	Interim Analyses (Planned to be completed by GSK) – Study Part 2
SAC*	Final Statistical Analysis Complete (Planned to be completed by FSP)

***Please note that where IA and SAC are noted together next to an output, GSK internal stats and programming team will take responsibility for this output, unless otherwise stated.**

10.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	mITT	ES1A	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.2.	All Subjects Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
Protocol Deviation					
1.3.	mITT	DV1	Summary of Important Protocol Deviations		SAC
Populations Analysed					
1.4.	All Subjects Screened	SP1A	Summary of Study Populations	Include All Screened, mITT, mITT1, mITT2, PK1 and PK2 populations. Footnote that percentages based on those in the mITT population, so mITT1, mITT2, PK1 and PK2 pops will have a percentage.	SAC
Demographic and Baseline Characteristics					
1.5.	mITT1	DM3	Summary of Demographic Characteristics (Part 1)	Age groupings <18, 18-40 and >40 to be used. Due to study entry criteria, only 18-40 will be displayed. Only total column needs to be included for a crossover study.	SAC
1.6.	mITT2	DM3	Summary of Demographic Characteristics (Part 2)	As above (Part 2 population)	SAC
1.7.	mITT1	DM5	Summary of Race and Racial Combinations (Part 1)	Only total column needs to be included for a crossover study.	SAC

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
1.8.	mITT2	DM5	Summary of Race and Racial Combinations (Part 2)	As above (Part 2 population)	SAC
Medical Conditions					
1.9.	mITT	MH1	Summary of Past Medical Conditions	Total column only. To be kept as overall mITT.	SAC
1.10.	mITT	MH1	Summary of Current Medical Conditions	Total column only. To be kept as overall mITT.	SAC

10.11.5. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PASP					
3.1.	mITT1	PFT1	Summary of PASP (Part 1)	IDSL example PFT1 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA[1], SAC (GSK)
3.2.	mITT2	PFT1	Summary of PASP (Part 2)	As above (Part 2 population)	SAC (GSK)
3.3.	mITT1	PFT3	Summary of PASP Change from Baseline (Part 1)	IDSL example PFT3 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA[1], SAC (GSK)

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4.	mITT2	PFT3	Summary of PASP Change from Baseline (Part 2)	As above (Part 2 population)	SAC (GSK)
3.5.	mITT1	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in PASP (Part 1)	As per non-standard example SAFE_T1 but parameter column could be removed. Note that adjusted treatment differences and posterior probabilities (<0, <-2.5, <-5) are included on page 2 of mock example. Please note details regarding treatment differences in Section 7.2 and update output accordingly if a log-transformation is required (SAFE_T2 applies in this case with addition of posterior probabilities to be added).	IA[1], SAC (GSK)
3.6.	mITT2	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in PASP (Part 2)	As above (Part 2 population)	SAC (GSK)
Oxygen Saturation					
3.7.	mITT1	PFT1	Summary of Oxygen Saturation (Part 1)	IDSL example PFT1 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA[1], SAC (GSK)
3.8.	mITT2	PFT1	Summary of Oxygen Saturation (Part 2)	As above (Part 2 population)	SAC (GSK)
3.9.	mITT1	PFT3	Summary of Oxygen Saturation Change from Baseline (Part 1)	IDSL example PFT1 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA[1], SAC (GSK)

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.10.	mITT2	PFT3	Summary of Oxygen Saturation Change from Baseline (Part 2)	As above (Part 2 population)	SAC (GSK)
3.11.	mITT1	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Oxygen Saturation (Part 1)	As per SAFE_T1 but parameter column could be removed. Note that adjusted treatment differences are included on page 2 of mock example. For OS expecting that we'll need to update the Posterior Probability labels, to <0%, <-3%, <-5%, where 5% is the clinical concern level for a treatment difference where GSK reduces OS to a greater extent. Please see Section 8.1.2 with regards to changes required should a log transformation be needed (SAFE_T2 applies in this case with addition of posterior probabilities to be added).	IA[1], SAC (GSK)
3.12.	mITT2	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Oxygen Saturation (Part 2)	As above (Part 2 population)	SAC (GSK)
Pulmonary Vascular Resistance (PVR)					
3.13.	mITT2	PFT1	Summary of Pulmonary Vascular Resistance (PVR) (Part 2)	See comments for PASP	SAC (GSK)
3.14.	mITT2	PFT3	Summary of Pulmonary Vascular Resistance Change from Baseline (PVR) (Part 2)	See comments for PASP	SAC (GSK)
3.15.	mITT2	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Pulmonary Vascular Resistance (PVR) (Part 2)	See comments for PASP. Note that adjusted treatment differences and posterior probabilities would initially be (<0, <0.1, <0.3)	SAC (GSK)

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.16.	mITT1	AE1CP (same as CP_AE1x)	Summary of All Adverse Events by System Organ Class and Preferred Term (Part 1)	Summarise by treatment group. Any pre-treatment AEs to be included in the listing only. Will only be created for interim if sufficient number of AEs are observed.	IA[1] (GSK), SAC (FSP)
3.17.	mITT2	AE1CP (same as CP_AE1x)	Summary of All Adverse Events by System Organ Class and Preferred Term (Part 2)	As above (Part 2 population)	SAC (FSP)
3.18.	mITT1	AE1CP (same as CP_AE1x)	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term (Part 1)	Summarise by treatment group.	SAC
3.19.	mITT2	AE1CP (same as CP_AE1x)	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term (Part 2)	As above (Part 2 population)	SAC
3.20.	mITT1	AE1CP (same as CP_AE1x)	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Part 1)	Production of this will be dependent on the number of SAEs, listing may suffice (based on clin pharm IDSL standards advice, this is a conditional summary). Summarise by treatment group. Any pre-treatment SAEs to be included only in listing.	SAC
3.21.	mITT2	AE1CP (same as CP_AE1x)	Summary of All Serious Adverse Events by System Organ Class and Preferred Term (Part 2)	As above (Part 2 population)	SAC
ECG					
3.22.	mITT1	EG1	Summary of ECG Findings (Part 1)		SAC
3.23.	mITT2	EG1	Summary of ECG Findings (Part 2)		SAC
3.24.	mITT1	EG2	Summary of ECG Values (Part 1)		SAC
3.25.	mITT2	EG2	Summary of ECG Values (Part 2)		SAC
3.26.	mITT1	CP_EG11	Frequency of ECG Values by Pre-Specified PCI Categories (Part 1)	Categories as per PCI details in Section 10.6.2.	SAC

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.27.	mITT2	CP_EG11	Frequency of ECG Values by Pre-Specified PCI Categories (Part 2)	As above (Part 2 population)	SAC
3.28.	mITT1	EG2	Summary of Change from Baseline in ECG Values (Part 1)		SAC
3.29.	mITT2	EG2	Summary of Change from Baseline in ECG Values (Part 2)		SAC
3.30.	mITT1	CP_EG12	Frequency of Change from Baseline ECG Values by Pre-Specified PCI Categories (Part 1)	Categories as per PCI details in Section 10.6.2.	SAC
3.31.	mITT2	CP_EG12	Frequency of Change from Baseline ECG Values by Pre-Specified PCI Categories (Part 2)	As above (Part 2 population)	SAC
Vital Signs					
3.32.	mITT1	VS1	Summary of Vital Signs (Part 1)		SAC
3.33.	mITT2	VS1	Summary of Vital Signs (Part 2)		SAC
3.34.	mITT1	VS1	Summary of Change from Baseline in Vital Signs (Part 1)		SAC
3.35.	mITT2	VS1	Summary of Change from Baseline in Vital Signs (Part 2)		SAC
Immunogenicity					
3.36.	mITT	IMM1	Summary of Positive Immunogenicity Results	Can be kept as mITT overall	SAC

10.11.6. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PASP					
3.1.	mITT1	(non-standard)	Summary of PASP (Absolute) (Part 1)	x-axis will be timepoints T0 to T4, see other mock examples, y-axis will be mean PASP including 95% CI, by treatment groups (add to legend). *If data is log-transformed for the analysis then this graphic will need to show geometric means and 95% CIs.*	IA1, SAC (GSK)
3.2.	mITT2	(non-standard)	Summary of PASP (Absolute) (Part 2)	As above (Part 2 population)	SAC (GSK)
3.3.	mITT1	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in PASP (Part 1)	If possible please also add a horizontal line within the graph to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). *If data is log-transformed for analysis then this graphic will be presenting median ratios.*	IA[1], SAC (GSK)
3.4.	mITT2	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in PASP (Part 2)	As above (Part 2 population)	SAC (GSK)

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5.	mITT1	SAFE_F2 (non-standard)	Individual Subject Profiles of PASP (Part 1)	Adjust as space permits, with fewer subjects per page if needed. X-axis and footnote for illustration, can be amended/improved. Vertical reference lines represent start and stop of hypoxia/chamber period.	IA[1], SAC (GSK)
3.6.	mITT2	SAFE_F2 (non-standard)	Individual Subject Profiles of PASP (Part 2)	As above (Part 2 population)	IA[2], IA[3], SAC (GSK)
Oxygen Saturation					
3.7.	mITT1	(non-standard)	Summary of Oxygen Saturation (Absolute) (Part 1)	x-axis will be timepoints T0 to T4, see other mock examples, y-axis will be mean Oxygen Saturation including 95% CI, by treatment groups (add to legend) *If data is log-transformed for the analysis then this graphic will need to show geometric means and 95% CIs.*	IA[1], SAC (GSK)
3.8.	mITT2	(non-standard)	Summary of Oxygen Saturation (Absolute) (Part 2)	As above (Part 2 population)	SAC (GSK)
3.9.	mITT1	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Oxygen Saturation (Part 1)	As above for PASP figure	IA[1], SAC (GSK)
3.10.	mITT2	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Oxygen Saturation (Part 2)	As above (Part 2 population)	SAC (GSK)
3.11.	mITT1	SAFE_F2 (non-standard)	Individual Subject Profiles of Oxygen Saturation (Part 1)	As above for PASP figure	IA[1], SAC (GSK)

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.12.	mITT2	SAFE_F2 (non-standard)	Individual Subject Profiles of Oxygen Saturation (Part 2)	As above (Part 2 population)	IA[2], IA[3], SAC (GSK)
3.13.	mITT2	PD_F1 (non-standard)	Scatter Plot of Oxygen Saturation vs PASP (Part 2)	mITT2 population only Scatter plot: PASP on y axis, treatment groups side by side, timepoint (T0 to T4) split into panels.	SAC
Pulmonary Vascular Resistance (PVR)					
3.14.	mITT2	(non-standard)	Summary of Pulmonary Vascular Resistance (Absolute) (Part 2)	x-axis will be timepoints T0 to T4, see other mock examples, y-axis will be mean PVR including 95% CI, by treatment groups (add to legend) *If data is log-transformed for the analysis then this graphic will need to show geometric means and 95% CIs.*	SAC (GSK)
3.15.	mITT2	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Pulmonary Vascular Resistance (Part 2)	See PASP comments	SAC (GSK)
3.16.	mITT2	SAFE_F2 (non-standard)	Individual Subject Profiles of Pulmonary Vascular Resistance (PVR) (Part 2)	See PASP comments	SAC (GSK)

10.11.7. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK1	PKCT1 (PK01)	Summary of GSK2586881 Pharmacokinetic Concentration-Time Data (ng/mL) (Part 1)		SAC
4.2.	PK2	PKCT1 (PK01)	Summary of GSK2586881 Pharmacokinetic Concentration-Time Data (ng/mL) (Part 2)		SAC
PK Parameter Data					
4.3.	PK1	PKPT1 (PK03)	Summary Statistics of Derived Plasma GSK2586881 Pharmacokinetic Parameters (Part 1)	See Section 8.2.3.1 for list of parameters to be expected	SAC
4.4.	PK2	PKPT1 (PK03)	Summary Statistics of Derived Plasma GSK2586881 Pharmacokinetic Parameters (Part 2)	As above (Part 2 population)	SAC
4.5.	PK1	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma GSK2586881 Pharmacokinetic Parameters (Part 1)	See Section 8.2.3.1 for list of parameters to be expected and Section 10.3.3 for details of those NOT to be log transformed	SAC
4.6.	PK2	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma GSK2586881 Pharmacokinetic Parameters (Part 2)	As above (Part 2 population)	SAC

10.11.8. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK1	PKCF1X (PK16b)	Individual GSK2586881 Plasma Concentration–Time Plots (Linear and Semi-log) (Part 1)	By Subject plots	SAC
4.2.	PK2	PKCF1X (PK16b)	Individual GSK2586881 Plasma Concentration–Time Plots (Linear and Semi-log) (Part 2)	By Subject plots – Part 2	SAC
4.3.	PK1	PKCF6 (PK24)	Individual GSK2586881 Plasma Concentration–Time Plot (Linear and Semi-log) (Part 1)	All individual subject profiles on the same graphic.	SAC
4.4.	PK2	PKCF6 (PK24)	Individual GSK2586881 Plasma Concentration–Time Plot (Linear and Semi-log) (Part 2)	As above (Part 2 population)	SAC
4.5.	PK1	PKCF2 (PK17)	Mean Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log) (Part 1)		SAC
4.6.	PK2	PKCF2 (PK17)	Mean Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log) (Part 2)		SAC
4.7.	PK1	PKCF3 (PK18)	Median Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log) (Part 1)		SAC
4.8.	PK2	PKCF3 (PK18)	Median Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log) (Part 2)		SAC

10.11.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
RAS Peptides – Key					
5.1.	mITT1	PD_T1 (or modify PFT1 & PFT2	Summary of Key RAS Peptides (Absolute Data) (Part 1)	Log-transformed summary to be included as a second page for each parameter if data is log-transformed for analysis. **Ang II, Ang(1-5), Ang(1-7)**	SAC
5.2.	mITT2	PD_T1 (or modify PFT1 & PFT2	Summary of Key RAS Peptides (Absolute Data) (Part 2)	As above (Part 2 population)	SAC
5.3.	mITT2	SAFE_T2 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Key RAS Peptides (Part 2)	mITT2 only Log transformation likely to be required so output as per SAFE_T2. RAS Peptides are collected at timepoints other than T1 to T4 so these will need to be included. Note that adjusted treatment differences are included on page 2 of mock example. Posterior probabilities see Section 8.3.2. **Ang II, Ang(1-5), Ang(1-7)** *If there is insufficient data to run a statistical analysis from data in Part 2, an analysis of Part 1 may be performed in place – to be discussed at DBF*	SAC
Disease Biomarkers					
5.4.	mITT1	PD_T1 (or modify PFT1 & PFT2	Summary of Surfactant Protein D (Absolute Data) (Part 1)	Log-transformed summary to be included as a second page if data is log-transformed for analysis. **Surfactant Protein D**	SAC

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.5.	mITT2	PD_T1 (or modify PFT1 & PFT2	Summary of Surfactant Protein D (Absolute Data) (Part 2)	As above (Part 2 population)	SAC
5.6.	mITT2	SAFE_T2 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Surfactant Protein D (Part 2)	mITT2 only Log transformation likely to be required so output as per SAFE_T2, otherwise SAFE_T1. SPD is collected at timepoints other than T1 to T4 so these will need to be included. Note that adjusted treatment differences are included on page 2 of mock example. Posterior probabilities see Section 8.3.2. *If there is insufficient data to run a statistical analysis from data in Part 2, an analysis of Part 1 may be performed in place – to be discussed at DBF*	SAC

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Ventilatory Parameters					
5.7.	mITT1	PFT1	Summary of Ventilatory Parameters (Absolute Data) (Part 1)	Ventilatory parameters are collected at the same timepoints as PASP, with the exception of the post exercise timepoint where ventilatory parameters are not collected. Order parameters as follows: Oxygen consumption (VO2), Carbon dioxide production (CO2), Total Tidal Volume, Inspiratory Tidal Volume, Expiratory Tidal Volume, Total Respiratory Time, Inspiratory Time, Expiratory Time, Duty Cycle, Mean Respiratory Flow,Respiratory rate	SAC
5.8.	mITT2	PFT1	Summary of Ventilatory Parameters (Absolute Data) (Part 2)	As above (Part 2 population)	SAC

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Outputs to be confirmed post DBF					
5.9.	mITT1	SAFE_T2 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Key RAS Peptides (Part 1)	mITT1 only Log transformation likely to be required so output as per SAFE_T2. RAS Peptides are collected at timepoints other than T1 to T4 so these will need to be included. Note that adjusted treatment differences are included on page 2 of mock example. Posterior probabilities see Section 8.3.2. **Ang II, Ang(1-5), Ang(1-7)**	Post SAC (*to be confirmed post DBF*)
5.10.	mITT1	SAFE_T2 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Surfactant Protein D (Part 1)	mITT1 only Log transformation likely to be required so output as per SAFE_T2, otherwise SAFE_T1. SPD is collected at timepoints other than T1 to T4 so these will need to be included. Note that adjusted treatment differences are included on page 2 of mock example. Posterior probabilities see Section 8.3.2.	Post SAC (*to be confirmed post DBF*)

10.11.10. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
RAS Peptides – Key					
5.1.	mITT1	(non-standard)	Summary of Key RAS Peptides (Absolute) (Part 1)	x-axis will be timepoints T0 to T4 (plus additional timepoints - see other mock examples), y-axis will be mean RAS including 95% CI, by treatment groups (add to legend). One page per endpoint (3 x RAS endpoints) *A log-transformation is likely to be required for analysis so please present geometric means and 95% CIs on a second page.*	SAC
5.2.	mITT2	(non-standard)	Summary of Key RAS Peptides (Absolute) (Part 2)	As above (Part 2 population)	SAC
5.3.	mITT2	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Key RAS Peptides (Part 2)	mITT2 only See example mock SAFE_F1 but page by endpoint (3 RAS endpoints). *If log-transformed then median ratios will be plotted.* If possible please also add a horizontal line within the graphic to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). Note more timepoints for biomarkers other than T1 to T4. *If there is insufficient data to run a statistical analysis from data in Part 2, an analysis of Part 1 may be performed in place – to be discussed at DBF*	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.4.	mITT1	SAFE_F2 (non-standard)	Individual Subject Profiles of Key RAS Peptides (Part 1)	All subjects on one page, one page per RAS endpoint. X-axis and footnote for illustration and can be amended/improved. Vertical reference lines represent start and stop of hypoxia/chamber period. Note more timepoints for biomarkers other than T1 to T4. *Please note, mock shows raw data scales, but data is very likely to need to be log-transformed so please provide a second page per RAS endpoint with y-axis to accommodate log-transformed data.*	IA[1], SAC
5.5.	mITT2	SAFE_F2 (non-standard)	Individual Subject Profiles of Key RAS Peptides (Part 2)	As above (Part 2 population)	SAC
Disease Biomarkers					
5.6.	mITT1	(non-standard)	Summary of Surfactant Protein D (Absolute) (Part 1)	x-axis will be timepoints T0 to T4 (plus additional timepoints - see other mock examples), y-axis will be mean SPD including 95% CI, by treatment groups (add to legend). *A log-transformation is likely to be required for analysis so please present geometric means and 95% CIs on a second page.*	SAC
5.7.	mITT2	(non-standard)	Summary of Surfactant Protein D (Absolute) (Part 2)	As above (Part 2 population)	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.8.	mITT2	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in SPD (Part 2)	mITT2 only See example mock SAFE_F1. *If log-transformed then median ratios will be plotted.* If possible please also add a horizontal line within the graphic to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). Note more timepoints for biomarkers other than T1 to T4. *If there is insufficient data to run a statistical analysis from data in Part 2, an analysis of Part 1 may be performed in place – to be discussed at DBF*	SAC
5.9.	mITT1	SAFE_F2 (non-standard)	Individual Subject Profiles of Surfactant Protein D by Treatment Group and Timepoint (Part 1)	Adjust as space permits, with fewer subjects per page if needed. X-axis and footnote for illustration and can be amended/improved. Vertical reference lines represent start and stop of hypoxia/chamber period. Note more timepoints for biomarkers other than T1 to T4. *Please note, mock shows raw data scales, but data will most likely need to be log-transformed so in this case please provide a second page with y-axis to accommodate log-transformed data.*	SAC
5.10.	mITT2	SAFE_F2 (non-standard)	Individual Subject Profiles of Surfactant Protein D by Treatment Group and Timepoint (Part 2)	As above (Part 2 population)	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Key RAS Peptides vs PASP & Oxygen Saturation					
5.11.	mITT	PD_F1 (non-standard)	Scatter Plot of RAS Peptides (Ang II, Ang(1-7) and Ang(1-5)) vs PASP (Part 1 and 2 combined)	Scatter plot: PASP on y axis. Page by RAS endpoint, treatment groups side by side, timepoints T0 to T4 within panels (2 columns, 5 rows per page, 3 pages). Plot T0 to T4 timepoints (timepoints that match for the two endpoints of interest). Identify study part by different colour/symbol. *As RAS data is log-transformed, please include a second page y-axis to accommodate log-transformed data.*	SAC
5.12.	mITT2	PD_F1 (non-standard)	Scatter Plot of RAS Peptides (Ang II, Ang(1-7) and Ang(1-5)) vs Oxygen Saturation (Part 1 and 2 combined)	Scatter plot: Oxygen Saturation on y axis. Page by RAS endpoint, treatment groups side by side, timepoints T0 to T4 within panels (2 columns, 5 rows per page, 3 pages). Plot T0 to T4 timepoints (timepoints that match for the two endpoints of interest). Identify study part by different colour/symbol. *As RAS data is log-transformed, please include a second page y-axis to accommodate log-transformed data.*	SAC
Outputs to be confirmed post DBF					
5.13.	mITT1	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Key RAS Peptides (Part 1)	mITT1 only See example mock SAFE_F1 but page by endpoint (3 RAS endpoints). *If log-transformed then median ratios will be plotted.* If possible please also add a horizontal line within the graphic to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). Note more timepoints for biomarkers other than T1 to T4.	Post SAC (*to be confirmed post DBF*)

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.14.	mITT1	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Surfactant Protein D (Part 1)	mITT1 only *If log-transformed then median ratios will be plotted.* If possible please also add a horizontal line within the graphic to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). Note more timepoints for biomarkers other than T1 to T4.	Post SAC (*to be confirmed post DBF*)

10.11.11. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	mITT2	PK_F1	Scatter Plot of Plasma GSK2586881 Concentration vs PASP (Part 2)	mITT2 only Timepoint split into panels (matching timepoints are T0 to T4) Placebo PASP data included at concentration of zero for comparison, see mock example.	SAC
6.2.	mITT	PK_F2	Scatter Plot of Plasma GSK2586881 Concentration vs RAS Peptides (Ang II, Ang(1-5) and Ang(1-7)) (Part 1 and 2 combined)	mITT (Part 1 and 2 identified by colour/symbol) One page per RAS endpoint. Placebo RAS data included at concentration of zero for comparison, see mock example. *Please note, if RAS data is log-transformed then also include a second page per RAS endpoint displaying log-transformed RAS vs concentrations.*	SAC
6.3.	mITT2	PK_F1	Scatter Plot of AUC(0.5-2h) vs PASP (Part 2)	mITT2 only Timepoint T2 and T3 only, to be included as two separate panels *Please include log-transformed AUC graphic on a second page.*	SAC

10.11.12. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	All Screened Subjects	ES7	Listing of Reasons for Screen Failure	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
2.	mITT	ES2	Listing of Reasons for Study Withdrawal	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
3.	mITT	BL2	Listing of Subjects for Whom the Treatment Blind was Broken	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers 20+).	SAC
4.	mITT	CP_TA2	Listing of Randomised and Actual Treatments	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
Protocol Deviations					
5.	mITT	DV2	Listing of Important Protocol Deviations	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
6.	mITT	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
Populations Analysed					
7.	All Screened Subjects	SP3a	Listing of Subjects Excluded from Any Population	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
8.	mITT	DM4	Listing of Demographic Characteristics	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
9.	mITT	DM10	Listing of Race	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
Prior and Concomitant Medications					
10.	mITT	CP_CM4	Listing of Concomitant Medications	For small studies / limited conmed data, a listing can be used in place of summary table, hence no summary table requested for this study. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
Exposure and Treatment Compliance					
11.	mITT	EX4	Listing of Exposure Data	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
12.	All Screened Subjects	AE9CP	Listing of All Adverse Events for Non-randomised subjects	Only output AEs that occurred for non-randomised subjects only. These should be assigned as pre-treatment. If no AEs then list 'No data to report'. Any SAEs will be noted on this listing. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
13.	mITT	AE9CP	Listing of All Adverse Events	Will include AEs for mITT patients, including those that occurred pre-treatment. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	IA[1] (GSK), SAC (FSP)
Serious and Other Significant Adverse Events					
14.	mITT	AE9CPA (same as CP_AE9a)	Listing of Serious Adverse Events	As above Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
15.	mITT	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
All Laboratory					
16.	mITT	LB6	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Concern/Potential Clinical Importance	Group by chemistry and haematology Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
17.	mITT	LB6	Listing of Laboratory Values of Potential Clinical Importance	Group by chemistry and haematology Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
ECG					
18.	mITT	CP_EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
19.	mITT	CP_EG4	Listing of ECG Values of Potential Clinical Importance	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
20.	mITT	CP_EG6	Listing of Abnormal ECG Findings	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
21.	mITT	CP_VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
22.	mITT	CP_VS5	Listing of All Vital Signs Data of Potential Clinical Importance	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC

10.11.13. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Safety					
23.	mITT	PFT9	Listing of PASP	Follow PFT9 IDSL format, replacing the last four FEV columns on the example with one PASP column. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	IA[1], IA[2], IA[3], SAC (GSK)
24.	mITT	PFT9	Listing of Oxygen Saturation	As above Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	IA[1], IA[2], IA[3], SAC (GSK)
25.	mITT	PFT9	Listing of Ventilatory Parameters	Similar format to above except include a parameter column to include all ventilator parameter results at each timepoint. Non-standard modification may be required. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
Biomarkers					
26.	mITT	PD_L1 (non-standard)	Listing of RAS Peptides	See non-standard example PD_L1 Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	IA[1], SAC
27.	mITT	PD_L1 (non-standard)	Listing of Surfactant Protein D	Non-standard example above can be followed Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
28.	mITT	IMM2	Listing of Immunogenicity Results	Note: Subjects should have data recorded at screening or period 1 pre-dose (not at both timepoints) Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
PK					
29.	PK	PKCL1X (PK08)	Listing of GSK2586881 Plasma Pharmacokinetic Concentration–Time Data	Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
30.	PK	PKPL1X (PK14)	Listing of Derived GSK2586881 Plasma Pharmacokinetic Parameters	See Section 8.2.3.1 for list of parameters. To include lambda_z and then additionally the first point, last point and number of points used in the determination of lambda_z for listings and R squared. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC
31.	mITT2	PFT9	Listing of Pulmonary Vascular Resistance	Follow PFT9 IDSL format, replacing the last four FEV columns on the example with one PVR column. Include footnote: Study Part 1 (subject numbers P to PPD Study Part 2 (subject numbers PPD	SAC (GSK)

10.12. Appendix 12: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.

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The GlaxoSmithKline group of companies 204987

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

Title	:	Reporting and Analysis Plan for the effects of GSK2586881 on the responses to acute hypoxia and exercise
Compound Number	:	GSK2586881
Effective Date	:	02-MAY-2017

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 204987.
- 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 Analysis and Statistical Analysis Complete (SAC) deliverables.

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204987

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• The purpose of this Reporting and Analysis Plan is to describe all planned analyses and outputs required for the Clinical Study Report (CSR) of study 204987
Protocol	• This RAP is based on the protocol (Dated 23/SEP/2016, GSK Document No.: 2016N283626_00) and protocol amendments 1 & 2 (Dated:24/FEB/2017, GSK Document No. : 2016N283626_01 & 07/MAR/2017, GSK Document No. : 2016N283626_02) of study GSK2586881/204987
Study Design	• The study will be a single centre, randomised, placebo-controlled and double blind (sponsor open). Subjects will be randomised to receive a single IV dose of GSK2586881 or saline in a crossover design. Approximately 25 subjects will be enrolled to ensure that a minimum of 20 subjects complete all dosing and critical assessments (the target of 20 may be revised by the sample size re-estimation)
Primary Objective	• To evaluate the effect of a single IV dose of GSK2586881 on the HPV response in healthy volunteers during exercise under hypoxic conditions
Primary Endpoint	• Change from baseline of Pulmonary Artery Systolic Pressure (PASP) measured via Echocardiography
Planned Analyses	• An Interim Analysis is planned after approximately 10 patients have completed periods 1 and 2 of the study, to aid the team in decision making with regards to stopping the study for futility or a re-assessment of sample size • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze.
Analysis Populations	• All Subjects Screened Population will contain all subjects that complete at least one Visit 1 (Screening) procedure. • The Modified Intent-to-Treat (mITT) Population will comprise all randomised subjects, excluding those who were randomised in error. • The Pharmacokinetic (PK) Population will comprise all subjects in the mITT Population for whom a PK sample was obtained and analysed and on active treatment.
Hypothesis	• No formal statistical hypotheses are being tested. A Bayesian statistical analysis framework with non-informative priors for model parameters (unless otherwise specified) will be used to obtain posterior distributions for effects of interest. These posterior distributions will be used to obtain a number of probability statements about the magnitude of treatment effects (e.g. probability of **any** treatment related reduction in PASP, or probability that the treatment related reduction in PASP $\geq$ 5 mmHg). A rule of thumb for "end of study success" is if the probability of any treatment related reduction in PASP (T3-T0) exceeds 0.95 (success is also conditional on the probability of (absolute) treatment related reductions in oxygen saturation exceeding 5% being small).

Overview	Key Elements of the RAP
Primary Analyses	• The primary endpoint, change from baseline in PASP following exercise under hypoxic conditions (Ti-T0) will be analysed using a Bayesian repeated measures mixed effects regression model, to compare the effects of Placebo vs GSK2586881.
Secondary Analyses	• Pharmacodynamic/Biomarker: RAS peptide responses: Ang II, Ang(1-7), Ang(1-5) will be analysed in a manner similar to the primary endpoint using Bayesian repeated measures mixed modelling to compare the effects of Placebo vs GSK2586881. • Safety: Oxygen saturation will be analysed in a manner similar to the primary efficacy endpoint using Bayesian repeated measures mixed modelling to compare the effects of Placebo vs GSK2586881. Vital signs, 12-Lead ECG, AEs and Labs will be tabulated and/or listed by treatment group and timepoint as appropriate. • Immunogenicity: Data will be tabulated and/or listed. • Pharmacokinetic: Plasma concentrations of GSK2586881 and derived PK parameters will be summarised descriptively/graphically and listed.
Exploratory Analyses	• Pharmacodynamic/Biomarker: The disease biomarker Surfactant Protein D will be analysed in a manner similar to the primary efficacy endpoint using Bayesian repeated measures mixed modelling to compare the effects of Placebo vs GSK2586881, if data permit. Ventilatory parameters (Oxygen consumption (VO2), Carbon dioxide production (CO2), Total Tidal Volume, Inspiratory Tidal Volume, Expiratory Tidal Volume, Total Respiratory Time, Inspiratory Time, Expiratory Time, Duty Cycle, Mean Respiratory Flow and Respiratory rate) will be summarised descriptively and listed. • Pharmacogenetics Analysis of pharmacogenetic data will be carried out separately by the GSK Genetics team and a separate RAP will be produced. As this is an exploratory endpoint, the results will be available separately to the CSR (or to be included as an appendix).

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no major changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 23/SEP/2016) and protocol amendments 1 and 2 (dated 24/FEB/2017 and 07/MAR/2017).

Some minor changes have been included. The variance/covariance structure to be used to account for repeated measurements has been updated to be unstructured (previously specified as compound symmetry). Statistical modelling described in this RAP will supersede any descriptions of modelling specifics provided in the protocol. In addition, the Intent-to-Treat Population has been renamed as Modified Intent-to-Treat to ensure this accurately reflects the description of the population and for suitability in any future publications.

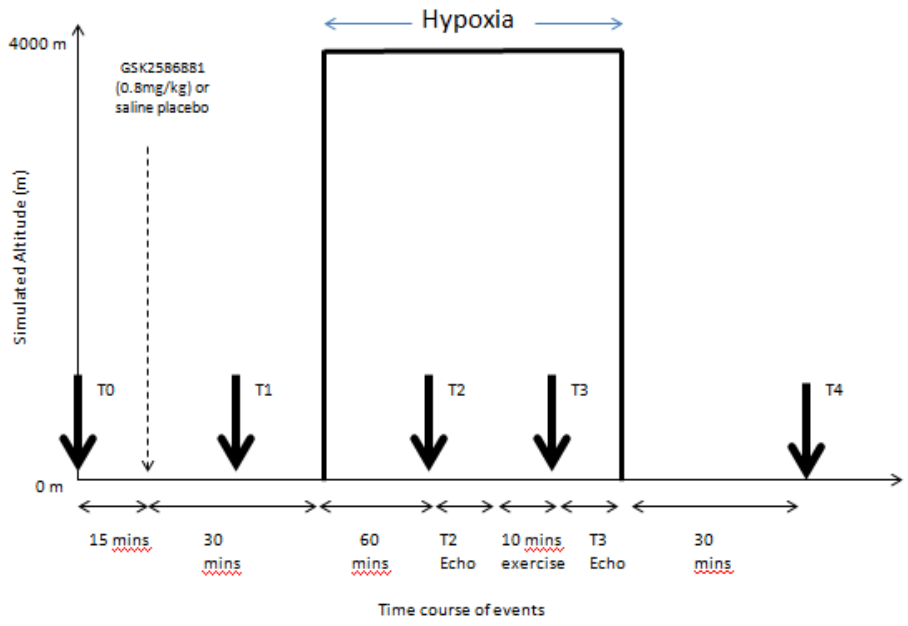
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objective	**Primary Endpoint**
• To evaluate the effect of a single IV dose of GSK2586881 on the HPV response in healthy volunteers during exercise under hypoxic conditions	• Change from baseline of Pulmonary Artery Systolic Pressure (PASP) measured via Echocardiography
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of a single IV dose GSK2586881 on RAS peptide responses	• Effect of GSK2586881 on baseline levels and changes in response to hypoxia and exercise of RAS peptides (e.g. Ang II, Ang(1-7), Ang(1-5))
• To evaluate the safety of a single IV dose of GSK2586881 in healthy volunteers	• Vital signs (heart rate, systolic and diastolic blood pressure) • Oxygen saturation • 12-lead ECGs • Adverse Events (AEs) • Immunogenicity • Clinical laboratory assessments • Continuous pulse oximetry (assessed by the site)
• To evaluate the pharmacokinetics of a single IV dose of GSK2586881	• Plasma concentrations of GSK2586881 • Derived pharmacokinetic parameters
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the effect of a single IV dose of GSK2586881 on ventilatory parameters in healthy volunteers during exercise in hypoxic conditions	Change from baseline of: • Oxygen consumption (VO2) • Carbon dioxide production (CO2) • And other parameters as data permit
• To evaluate the pharmacodynamic activity of a single IV dose of GSK2586881 in healthy volunteers during exercise in hypoxic conditions	• Change from baseline in Surfactant Protein D and/or additional analytes to be determined

Objectives	Endpoints
• To evaluate Pharmacogenetics	• Evaluate I/D polymorphisms in the Angiotensin Converting Enzyme (ACE) gene and analyse the impact on Ang II (and possibly other RAS peptides), hypoxic pulmonary vasoconstriction and responses to GSK2586881 administration

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• Single centre • Randomised • Double-blind (sponsor open) • Placebo-controlled • Two-period crossover • Study duration maximum 56 days
Dosing	• Single IV dose in each study period
Treatment Assignment	• Treatment A: Placebo • Treatment B: GSK2586881 0.8 mg/kg • Subjects will be randomised to one of two treatment sequences AB or BA
Interim Analysis	• Planned after approximately 10 subjects have completed treatment periods 1 and 2. The study may be stopped if a reasonable change in PASP is not observed or if a review of safety data suggests a change in the benefit-risk profile

2.4. Statistical Hypotheses

There are no formal statistical hypotheses. This is an exploratory study and will be analysed, utilising a Bayesian framework.

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim analysis is planned after approximately 10 subjects have completed the following critical assessments:

Interim Analysis	Definition / Criteria / Purpose
• PASP at T0 and T3 for both study periods	• Assess treatment differences between GSK2586881 and Placebo in change from pre-dose PASP to hypoxic/exercised PASP [T3-T0]. • To decide whether to continue the study or stop based on futility. • To conduct an advisory sample-size re-estimation with the view to potentially reduce the number of subjects participating in the study below 20. Precision estimates will be updated based on the variability observed from the interim analyses to aid the team in decision making. • PASP data will be summarised and listed. Statistical analysis will be completed as described in Section 7.2 including a graphic of treatment estimates over time.
• Oxygen saturation at T0 and T3 for both study periods	• To estimate treatment differences between GSK2586881 and Placebo in change from pre-dose oxygen saturation to hypoxic/exercised oxygen saturation [T3-T0], with a view to stopping the study if there is evidence that GSK2586881 causes a reduction in oxygen saturation in healthy volunteers. As a non-binding guide high posterior probability of observing ≥5% absolute differences in **mean** oxygenation saturation values between placebo and active arms would be of concern; but clinical judgement would override any statistical methods if, for example, the majority of subjects displayed consistent patterns of reductions e.g. between 2-3%. • Oxygen saturation data will be summarised and listed. Statistical analysis will be completed as described in Section 8.1.2 including a graphic of treatment estimates over time.
• Adverse Events	• To compare adverse events within the two treatment groups and explore any potential safety signals that may emerge. • AEs will be tabulated by treatment group (if there are a sufficient number of events) and listed.
• Angiotensin biomarker concentrations (Ang II, Ang(1-5), Ang(1-7))	• For the first 5 subjects only to allow time for the samples to be analysed by the lab. • Data will be listed only due to expected small sample size. Individual subject plots may be produced. • If Angiotensin data (Ang II, Ang(1-5), Ang(1-7)) is not available at the time of the interim, analysis of the specified eCRF data will still go ahead as planned. A positive outcome in relation to PASP, Oxygen Saturation and AEs would lead to the study continuing without the need to review Angiotensin data. • Should a negative outcome be observed with PASP or Oxygen Saturation, then confirmation of the decision to stop the study for futility would not occur until the Angiotension data from the initial transfer were available and reviewed.

Interim Analysis	Definition / Criteria / Purpose
	• Any negative results with regards to AEs (as agreed by the study team), regardless of other endpoint results, would result in the study stopping.

The interim analysis will use a data snapshot that has been cleaned to the best extent allowed by the timeframes (i.e. the interim data will not be fully cleaned or fully QC'd data and there will not be a locked database). The date of the source data cut should be indicated on each interim related output (this can be implemented in HARP via the *d_datadate* macro input parameter in the *ts_setup* macro call). Results will be restricted to selected members of the study team. Results or discussions will not be circulated to blinded staff involved in the conduct of the study at the sites.

The following table represents a guide to the outputs to be produced for the interim analysis. All outputs will be produced in HARP.

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PASP				Y	Y	Y	Y	Y[3]	Y		Y			
Oxygen Saturation				Y	Y	Y	Y	Y[3]	Y		Y			
All AEs				Y[1]			Y[2]							
RAS Peptides (AngII, Ang(1-5), Ang(1-7))						Y	Y							

NOTES :

- Y = Yes display generated.
- 1. Produced if sufficient data
- 2. SAEs will be flagged within this listing
- 3. One table to include statistical analysis medians (95% CrI) and posterior probabilities. Also include within subject correlation as a footnote to support sample size re-estimation.

The sample size re-estimation will be performed once the primary analysis for the interim has been completed and assuming that no overwhelming data supporting the need to stop for futility is observed. Estimates of standard deviations and within subject correlation will be obtained from the PASP outputs produced during the interim and/or from SAS outputs from the statistical modelling. The sample size re-estimation will be performed by re-running programs (using R) used to obtain pre-study precision estimates. The sample size re-estimation program and associated excel outputs of precision estimates will be archived.

3.2. Final Analyses

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

1. All subjects have completed the study as defined in the protocol (and subject to decisions made from the interim analyses).
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.

3. All criteria for unblinding the randomisation codes have been met (note that the study is being run as sponsor-unblinded, however, only a partial randomisation schedule will be made available to the GSK programming team for the interim analysis).
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
All Subjects Screened	Comprising of all subjects who complete at least one Visit 1 (Screening) procedure.	• Subject disposition (including reasons for screening failures) • Listing of any AEs/SAEs for non-randomised subjects
Modified Intent-To-Treat	Comprising of all randomised subjects, excluding those who were randomised in error. A subject who is recorded as a screen failure, run-in failure, or stabilisation failure, but is randomised and does not receive a dose of study treatment is considered to have been randomised in error. Any other subject who receives a randomisation number will be considered to have been randomised.	• PD/Biomarkers • Safety
Pharmacokinetic	Subjects in the 'mITT' population for whom a pharmacokinetic sample was obtained and analysed and on active treatment.	• PK

NOTES :

- Please refer to Appendix 11: List of Data Displays which details the population to be used for each display being generated.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, subject management or subject assessment) will be summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
  - Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
  - This dataset will be the basis for the summaries and listings of protocol deviations.
- A 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

Table 1 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 1 Overview of Appendices

Section	Component
10.1	Appendix 1: Time & Events
10.2	Appendix 2: Treatment States
10.3	Appendix 3: Data Display Standards & Handling Conventions
10.4	Appendix 4: Derived and Transformed Data
10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data
10.6	Appendix 6: Values of Potential Clinical Importance
10.7	Appendix 7: Biomarker Details
10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
10.9	Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses
10.10	Appendix 10: Abbreviations & Trade Marks
10.11	Appendix 11: List of Data Displays
10.12	Appendix 12: Example Mock Shells for Data Displays

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Analyses

The study population analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified.

Table 2 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		
Screening Status and Reasons for Screen Failure[1]	Y		Y
Reasons for Subject Withdrawal			Y
Important Protocol Deviations	Y		Y
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Randomised and Actual Treatments			Y
Subjects for Whom the Treatment Blind was Broken			Y
Populations Analysed			
Study Populations	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Race and Racial Combinations	Y		Y
Prior and Concomitant Medications			
Medical Conditions[2]	Y		
Concomitant Medications			Y
Exposure and Treatment Compliance			
Exposure to Study Treatment			Y

NOTES :

- Y = Yes display generated.
- 1. Based on All Screened Population
- 2. Separate summaries for past and current conditions

7. PRIMARY STATISTICAL ANALYSES

7.1. Overview of Planned Analyses

The primary analyses will be based on the Modified Intent-To-Treat population.

Table 3 provides an overview of the planned analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 3 Overview of Planned Analyses

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Primary														
Pulmonary Artery Systolic Pressure (PASP)				Y	Y	Y	Y	Y[1]	Y		Y			

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. One table to include statistical analysis medians (95% CrI) and posterior probabilities.

7.2. Planned Statistical Analyses

Primary Statistical Analyses
Endpoint
• Pulmonary Artery Systolic Pressure (PASP)
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 methods used would be fully documented in the CPSR. • The data will be inspected prior to analysis to determine whether a data transformation is required. Any data transformations (e.g. natural logarithm) will be applied to observed individual data prior to any modeling or derivations (e.g. prior to deriving subject baseline) • A Bayesian repeated measures mixed effects model (fitted using SAS PROC MCMC), will be used to model the change from baseline (Ti-T0) in PASP. Based on the study design there are 4 post-dose timepoints (T1, T2, T3 and T4). The timepoint of primary interest is T3 (immediately after exercise at altitude). • Covariates for period, treatment and timepoint (i.e., T1 to T4) will be included as fixed effects. Adjusted period-specific baseline and subject-level baseline will be included as continuous parameters (see Section 10.3.2.1). Subject will be included as a random effect and timepoint will be included as a repeated effect. Treatment by timepoint and adjusted period-specific baseline by timepoint interactions will be included. An unstructured variance-covariance matrix will be fitted. Non-informative priors will be used for the model parameters, (see Section 10.8).

Primary Statistical Analyses

• Examination of covariates (for example Age, Weight, Height) may take place, if data permit. In this case, the equivalent model may be fitted in PROC MIXED and the covariate assessed at a 10% alpha level. The final Bayesian model would then be fit based upon the final model (after covariate examination) obtained using PROC MIXED. Alternatively, changes in deviance information criteria (DIC) may be assessed as part of the PROC MCMC modelling to examine covariates.
• Appropriate combinations of the model parameters would be used to obtain posterior distributions for the GSK2586881 vs placebo comparisons at each of the post dosing timepoints (T1 to T4).
• The change from baseline across the different post-dose timepoints will be represented via adjusted posterior medians for GSK2586881 and placebo, as well as associated 95% equi-tailed credible intervals. These results will be presented within tabular and graphical form after data has been back transformed (if applicable).
• The difference between GSK2586881 and placebo, for the change from baseline across post-dose timepoints will be represented via adjusted medians, as well as their associated 95% equi-tailed credible intervals. These results will be presented within tabular form after data has been back transformed (if applicable).
• The posterior distributions will also be used to produce several posterior probability statements, presented in tabular format; the most important being the probability that the change from baseline in PASP is reduced by GSK2586881 at time T3.
• Posterior probabilities of interest include (looking for high probabilities to favour increases to a lesser extent in PASP on GSK2586881):
  • Probability that change from baseline in PASP is reduced by GSK2586881 (*i.e., probability that a treatment difference is negative, or if a log transformation is applied then the probability that the ratio is less than 1*).
  • Probability that change from baseline in PASP is reduced by >=2.5mmHg, >=5mmHg and >=7.5mmHg by GSK2586881 (*i.e., probability that a treatment difference is <=-2.5 mmHg, <=-5mmHg and <=-7.5mmHg. In the case of a log-transformation, ratios of interest would be <0.95, <0.90 and <0.85, representing 5%, 10% and 15% difference between groups but may be reassessed at the time of analysis*)

Model Checking & Diagnostics
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Summary tables for absolute and change from baseline by treatment and timepoint (T0 to T4) • Listing of absolute data • Individual subject profiles by treatment group and timepoint • Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at times T1 to T4 along with posterior probabilities of interest. • Figure of absolute PASP by timepoint • Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint

8. SECONDARY ANALYSES

8.1. Safety Analyses

8.1.1. Overview of Planned Analyses

The safety analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified.

Table 4 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 4 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Oxygen Saturation														
Oxygen Saturation, measured by continuous pulse oximetry				Y	Y	Y	Y	Y[1]	Y		Y			
Oxygen Saturation vs PASP[2]					Y									
Adverse Events														
All AEs for Non-randomised Subjects							Y							
All AEs by SOC and PT[3]				Y			Y							
AEs Leading to Study Discontinuation							Y							
Drug-Related AEs by SOC and PT				Y										
All Serious AEs				Y			Y							
All Laboratory[4]														
Laboratory Values of PCI							Y							
All Laboratory Data for Subjects with any Value of PCI							Y							
ECG														
ECG Findings				Y			Y							
ECG Values by Visit				Y							Y			
ECG Values of PCI				Y			Y				Y			
All ECG Values for Subjects with any Value of PCI							Y							
Vital Signs														
Vital Signs by Visit				Y							Y			

Endpoint / Parameter/ Display Type	Absolute							Change from Baseline						
Vital Signs of PCI							Y							
All Vital Signs for Subjects with any Value of PCI							Y							
Immunogenicity														
Immunogenicity				Y			Y							

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated, PCI = Potential Clinical Importance
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. One table to include statistical analysis medians (95% CrI) and posterior probabilities.
- 2. Scatter plot of x vs y by treatment group, timepoint indicated by panel
- 3. Listing will include subject's numbers for individual AE's and AE system organ classes, preferred terms and verbatim term.
- 4. Chemistry and haematology data will be assessed for PCI values.
- Chemistry collected: BUN, Creatinine, Glucose, Potassium, Sodium, Calcium, AST (SGOT), ALT (SGPT), Alkaline phosphatase, Total and direct bilirubin, Total protein, Albumin.
- Haematology collected: Platelet count, RBC count, haemoglobin, hematocrit, MCV, MCH, neutrophils, lymphocytes, monocytes, eosinophils, basophils.
- Urinalysis collected: Specific gravity, pH, glucose, protein, blood and ketones by dipstick, microscopic examination (if blood or protein is abnormal).

8.1.2. Planned Safety Statistical Analyses

Planned Statistical Analyses
Endpoint(s)
• Oxygen Saturation
Model Specification

• Refer to Section 7.2. Oxygen Saturation will be analysed in the same manner as for the primary endpoint PASP.
• Posterior probabilities of interest include (looking for very low probabilities to remove any concerns with regards to Oxygen Saturation reduction on GSK2586881):
  • Probability that the change from baseline on Oxygen Saturation is reduced by GSK *(i.e., probability that a treatment difference is <0% or if a log transformation is applied then the probability that the ratio < 1).*
  • Probability that the change from baseline in Oxygen Saturation is reduced by GSK by >1%, >3% and >=5% (absolute difference) compared to placebo. (*i.e., probability that a treatment difference (absolute) is <-1%, <-3% and <=-5%. In the case of a log-transformation, ratios of interest would be <0.98, <0.94 and <0.92 representing 2%, 6% and 8% difference between groups but may be re-assessed at the time of analysis*)

Model Checking
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses.
Model Results Presentation
• Summary tables for absolute and change from baseline by treatment and timepoint (T0 to T4)

Planned Statistical Analyses
• Listing of absolute data • Individual subject profiles by treatment group and timepoint • Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at times T1 to T4 along with posterior probabilities of interest • Figure of absolute Oxygen Saturation by timepoint • Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint

8.2. Pharmacokinetic Analyses

8.2.1. Overview of Planned Pharmacokinetic Analyses

The pharmacokinetic (PK) analyses will be based on the Pharmacokinetic population, unless otherwise specified.

Table 5 provides an overview of the planned analyses, with full details being presented in Appendix 11: List of Data Displays.

Table 5 Overview of Planned Pharmacokinetic Analyses

Endpoints	Untransformed				Log-Transformed			
	Summary		Individual		Summary		Individual	
	F	T	F	L	F	T	F	L
Plasma GSK2586881 concentrations	Y[1, 3]	Y	Y[1,2]	Y				
Pharmacokinetic Parameters		Y		Y		Y		

NOTES :
- T = Table, F = Figures, L = Listings, Y = Yes display generated.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. Linear and Semi-Log plots will be created on the same display.
- 2. One output for one graph per subject and a further output with all subject profiles on the same graphic
- 3. Separate Mean (± SD) and Median plots will be generated.

8.2.2. Drug Concentration Measures

Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).

8.2.3. Pharmacokinetic Parameters

8.2.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 3: Data Display Standards & Handling Conventions (Section 10.3.3 Reporting Process & Standards).
- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Win Nonlin Pro V6.3 or greater.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 6 will be determined from the plasma concentration-time data, as data permits.

Table 6 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-2.5h) post-dose	Area under the concentration-time curve over the study period (pre-dose to 30 mins rest post chamber exit).
AUC(0.5-2.0h) post-dose	Area under the concentration-time curve over the time period for the hypoxia challenge (immediately prior to chamber entry to chamber exit).
AUC(0-∞)	Area under the concentration-time curve extrapolated to infinity.
Cmax	Maximum observed concentration, determined directly from the concentration-time data.
tmax	Time to reach Cmax, determined directly from the concentration-time data.
t½	Apparent terminal half-life will be calculated as: **t½ = ln2 / lambda_z**
CL	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.

NOTES:

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

8.2.4. Population Pharmacokinetic (PopPK) Analyses

A population PK analysis may be conducted. The plasma concentration-time data may be merged with historical data and analysed as part of a population PK meta-analysis. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the specifications of which are provided in Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses.

8.3. Pharmacodynamic and Biomarker Analyses

8.3.1. Overview of Planned Pharmacodynamic and Biomarker Analyses

The pharmacodynamic and biomarker analyses will be based on the Modified Intent-To-Treat population, unless otherwise specified. Biomarker data will be analysed for those subjects in the Modified Intent-To-Treat population for whom a sample was obtained and analysed.

Table 7 provides an overview of the planned pharmacodynamic and Biomarker analyses, with full details of data displays being presented in Appendix 11: List of Data Displays.

Table 7 Overview of Planned Pharmacodynamic and Biomarker Analyses

Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
RAS Peptide Responses[1]														
Ang II				Y	Y	Y	Y	Y	Y					
Ang(1-7)				Y	Y	Y	Y	Y	Y					
Ang(1-5)				Y	Y	Y	Y	Y	Y					
Other Biomarkers (Disease Biomarkers)														
Surfactant Protein D				Y	Y	Y	Y	Y	Y					
Ventilatory Parameters[1]														
Oxygen consumption (VO2)				Y			Y							
Carbon Dioxide Production (CO2)				Y			Y							
Total Tidal Volume				Y			Y							
Inspiratory Tidal Volume				Y			Y							
Expiratory Tidal Volume				Y			Y							
Total Respiratory Time				Y			Y							
Inspiratory Time				Y			Y							
Expiratory Time				Y			Y							
Duty Cycle				Y			Y							
Mean Respiratory Flow				Y			Y							
Respiratory Rate				Y			Y							
RAS Peptides vs PASP & Oxygen Saturation[2]														
Ang II vs PASP					Y									
Ang(1-7) vs PASP					Y									
Ang(1-5) vs PASP					Y									
Ang II vs Oxygen Saturation					Y									
Ang(1-7) vs Oxygen Saturation					Y									
Ang(1-5) vs Oxygen Saturation					Y									

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- 1. Parameters will be included in the same summary/figure/listing paging by RAS peptide where applicable
- 2. Scatter plots of x vs y, timepoint indicated in a legend, one plot for PASP, one plot for Oxygen Saturation (page by RAS peptide)

8.3.2. Planned Pharmacodynamic and Biomarker Statistical Analyses

Planned Statistical Analyses
Endpoint(s)
• **RAS Peptide Responses**: Ang II, Ang(1-7), Ang(1-5) • **Disease Biomarker**: Surfactant Protein D
Model Specification
• Refer to Section 7.2. Change from baseline in PD/Biomarker endpoints will be analysed in a manner similar to the primary endpoint PASP. Data will be assessed prior to analysis to confirm the need for any data transformations. • Repeated measures timepoints of interest will be: • Pre-dose (T0) • End of Infusion • 15 min Post-dose (T1) • 15-45 min Post-dose • 60 min post chamber entry (T2) • Immediately post exercise (T3) • Immediately post chamber exit • 30 mins post chamber exit (T4)
Model Checking
• Refer to Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Model Results Presentation
• Summary tables for absolute by treatment and timepoint (as detailed above) • Listing of absolute data • Individual subject profiles by treatment group and timepoint • Summary table of statistical analysis, adjusted change from baseline posterior medians and 95% credible intervals by treatment and timepoint, together with estimated posterior median treatment differences (GSK2586881 – Placebo) and 95% credible intervals for the change from baseline at ALL timepoints (not just T1 to T4). • Figure of absolute data by timepoint • Figure of statistical analysis adjusted change from baseline medians and 95% credible intervals by treatment group and timepoint

8.4. Pharmacokinetic / Pharmacodynamic Analyses

The pharmacokinetic/pharmacodynamic (PK/PD) analyses will be based on the mITT population, unless otherwise specified. For the RAS peptides, PASP and Oxygen Saturation endpoints, exploratory plots vs pharmacokinetic concentrations will initially be reviewed to identify endpoints where there is a potential trend. If there is evidence for a trend, further PK/PD analyses may be conducted. The timeline for these analyses will be independent of the analysis described in this RAP. To support this analysis a NONMEM-specific data file will be generated, the specifications of which are provided in Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses.

Table 8 provides an overview of the planned PK/PD analyses with further details of data displays being presented in Appendix 11: List of Data Displays.

Table 8 Overview of Planned PK/PD Analyses

Endpoint	Absolute			
	Summary		Individual	
	T	F	F	L
RAS Peptide Ang II vs PK concentration		Y[1,2]		
RAS Peptide Ang(1-7) vs PK concentration		Y[1,2]		
RAS Peptide Ang(1-5) vs PK concentration		Y[1,2]		
PASP vs PK concentration		Y[1]		
PASP (T2 & T3) vs AUC(0.5-2.0)		Y[1]		

NOTES :

- 1. Scatter plots, timepoints indicated by panel.
- 2. RAS peptides vs PK will form one graphic, page by RAS peptide
- T = Table, F = Figure, L = Listing, Y = Yes display generated.

9. REFERENCES

GlaxoSmithKline Document Number. : 2016N283626_00, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 23-Sep-2016

GlaxoSmithKline Document Number. : 2016N283626_01, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 24-Feb-2017

GlaxoSmithKline Document Number. : 2016N283626_02, The effects of GSK2586881 on the responses to acute hypoxia and exercise: Effective date: 07-Mar-2017

10. APPENDICES

Section	Appendix
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 10.1	Appendix 1: Time and Events
Section 10.2	Appendix 2: Treatment States
Section 10.3	Appendix 3: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 10.4	Appendix 4: Derived and Transformed Data • General, Study Population & Safety • Pharmacodynamic and or Biomarkers
Section 10.5	Appendix 5: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 10.6	Appendix 6: Values of Potential Clinical Importance
Section 10.7	Appendix 7: Biomarker Details
Section 10.8	Appendix 8: Model Checking and Diagnostics for Statistical Analyses
Section 10.9	Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (or Biomarker) Analyses
Other RAP Appendices	
Section 10.10	Appendix 10: Abbreviations & Trade Marks
Section 10.11	Appendix 11: List of Data Displays
Section 10.12	Appendix 12: Example Mock Shells for Data Displays

10.1. Appendix 1: Time & Events

10.1.1. Protocol Defined Time & Events

10.1.1.1. Screening and Follow up

Procedure	Screening[1] (up to 28 days prior to Treatment Period 1, Day 1)	Follow up (7-10 days post last dose)	Notes
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Full physical exam, including height and weight	X	X	Height and weight to be measured at screening only. Weight at screening will be used for dosing calculation.
Alcohol, Drugs of Abuse, Smoking test	X		
Medical history (includes substance usage [and family history of premature CV disease])	X		Substances: Drugs, Alcohol, tobacco
Past and current medical conditions [including cardiovascular medical history]	X		
Serum OR urine pregnancy test (WCBP)	X		
HIV, Hep B and Hep C screen	X		
Laboratory assessments (include liver chemistries)	X	X	Non Fasting
Immunogenicity		X	
12-lead ECG	X	X	Triplicate ECG required at screening.
Vital signs	X	X	Triplicate vital signs required at screening.
Spirometry	X		
Echocardiogram	X		
Concomitant Medication review	X	X	
Hypoxia chamber plus exercise	X		Tolerance to 4000m for 10 mins followed by incremental exercise testing to determine maximum oxygen uptake (VO2max) and calculate 70% of VO2max (to be used for the exercise challenge during the Treatment Periods).
Pharmacogenetic sample (PGx)	X		Can be taken any time after consent has been signed. Only required once and is optional.
AE/SAE review	X	X	As per timings detailed in protocol Section 7.2.1.1

1. Screening assessments are allowed to be conducted on more than one day

10.1.1.2. Treatment Period 1 and 2

Procedure	Treatment Period 1 and 2 (Washout 3-14 days)											Notes
	Times relative to start of dosing				Hypoxic Challenge ~80 min (Times relative to entry to Chamber)							
	Pre-dose	0h	15 min	15-45 min	0-60 min	60 min	60-70 min	Immediately after exercise	On exit from chamber	After 30 min rest	60 min after exit from Chamber	
Randomisation	X											Randomisation can occur up to the day before the first treatment period
Brief physical exam	X											
Vital signs	X			X				X[5]			X	
Immunogenicity	X											
12-lead ECG	X			X							X	
Echocardiogram	X		X			X		X		X		Echocardiogram duration approx 5 min
Subject enters chamber					X							Subject enters chamber approximately 30 min after study treatment
Study Treatment (Dosing)		X										
Subject leaves chamber								X				Subject leaves chamber after the fourth echocardiogram, blood samples and vital signs have been taken.
Exercise challenge							X					For approx 5-10 min
Ventilatory parameters	X		X			X				X		Measurements to be taken 2 min before echocardiograms.
Pulse Oximetry (O2 saturation)	←==========→											Will be continuously monitored for safety. A measurement should be recorded at time of each echocardiogram and databased.
Telemetry	←==========→											Will be continuously monitored for safety.
RAS Biomarkers	X	X[1]	X[2]	X[3]		X[2]		X[2]	X[4]	X[2]		
SP-D	X	X[1]	X[2]	X[3]		X[2]		X[2]	X[4]	X[2]		

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Procedure	Treatment Period 1 and 2 (Washout 3-14 days)											Notes
	Times relative to start of dosing				Hypoxic Challenge ~80 min (Times relative to entry to Chamber)							
	Pre-dose	0h	15 min	15-45 min	0-60 min	60 min	60-70 min	Immediately after exercise	On exit from chamber	After 30 min rest	60 min after exit from Chamber	
PK sampling	X	X[1]	X[2]	X[3]		X[2]		X[2]	X[4]	X[2]		
AE/SAE review		←==========→										
Concomitant medication review	X											

1. Take at the end of the infusion
2. Taken immediately after echocardiogram
3. Immediately before entering the chamber
4. To be taken as soon as possible after leaving chamber
5. On this occasion ONLY, vital signs to be taken after the blood draw.

10.2. Appendix 2: Treatment States

10.2.1. Treatment States for AE Data

This study is a single dose two period crossover study. As such, AEs will be attributed to the treatment received within the relevant study period based on the dates and times of the AEs in relation to dosing date and time. This is as per IDSL dataset standards. This is detailed in the table below.

10.2.1.1. Treatment States for AE Dates

Treatment State	Definition
Pre-Treatment	AE Start Date / Time < Study Treatment Start Date / Time (Period 1) This will apply to all subjects enrolled into the study, including those not randomised. We may have non-randomised and randomised subjects who have pre-treatment AEs/SAEs. For non-randomised subjects these events will be captured in the 'non-randomised' listing. For randomised subjects these events will be captured in summary listings with treatment group='Pre-Treatment'.
On-Treatment (Period 1)	If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 1) & before Study Treatment Start Date / Time (Period 2). Study Treatment Start Date / Time (Period 1) ≤ AE Start Date / Time < Study Treatment Start Date / Time (Period 2) For randomised subjects, this derivation ensures that AEs starting on or after the Period 1 dose up until the Period 2 dose will be captured and assigned to the Period 1 treatment.
On-Treatment (Period 2)	If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 2) & before Follow-Up. Study Treatment Start Date / Time (Period 2) ≤ AE Start Date / Time ≤ Follow-Up Date For randomised subjects, this derivation ensures that AEs starting on or after the Period 2 dose up until the Follow-up Visit will be captured and assigned to the Period 2 treatment.
Post-Treatment	If AE Start Date is on or after Follow-Up. AE Start Date > Follow-Up Date There shouldn't be any instances of this. Subjects will return for a follow-up and visit and any AEs would be documented at that point (and hence included in Period 2 treatment group). No further follow-up of patients is required.
Onset Time Since 1st Dose (Days/Hours/Mins)	If Study Treatment Start Date / Time (Period 1) ≤ AE Start Date / Time = AE Start Date / Time – Study Treatment Start Date / Time (Period 1) + 1 (min) Missing otherwise. A calculation to assess the time since the Period 1 dose up until the start time of the AE. This will be calculated for all AEs, regardless of which period/treatment

Treatment State	Definition
	the AE was assigned to. Example: If Period 1 Dose was administered at 08:00am 01OCT2016 and Period 1 AE started at 09:10am 01OCT2016, then onset time since **first** dose would be 0d 1h 11m. If Period 2 Dose was administered at 08:30am 08OCT2016 and a Period 2 AE occurred on 08OCT2016 at 10:00am, then onset time since **first** dose would be 7d 2h 1m.
Onset Time Since Period Dose (Days/Hours/Mins)	**[PERIOD 1]** If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 1) & before Study Treatment Start Date / Time (Period 2). = AE Start Date / Time – Study Treatment Start Date / Time (Period 1) +1 (min) **[PERIOD 2]** If AE Start Date / Time is on or after Study Treatment Start Date / Time (Period 2) & on or before Follow-Up. = AE Start Date / Time – Study Treatment Start Date / Time (Period 2) + 1 (min) Missing otherwise. A calculation to assess the time since the dose in the relevant Period/treatment to which the AE is attributable to. Example: [PERIOD 1] If Period 1 Dose was administered at 08:00am 01OCT2016 and Period 1 AE started at 09:10am 01OCT2016, then onset time since **period** dose would be 0d 1h 11m (i.e. identical to value in previous row example in this case) [PERIOD 2] If Period 2 Dose was administered at 08:30am 08OCT2016 and a Period 2 AE occurred on 08OCT2016 at 10:00am, then onset time since **period** dose would be 0d 1h 31m
Duration (Days/Hours/Mins)	AE Resolution Date / Time – AE Start 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 eCRF OR value is missing

10.2.2. Treatment States for Concomitant Medication Data

This study is a single dose two period crossover study. As such, Concomitant Medications will be attributed to the treatment received within the relevant study period based on the dates and times of the Concomitant Medications in relation to dosing date and time. This is as per IDSL dataset standards. This is detailed in the table below.

10.2.2.1. Treatment States for Concomitant Medication Dates

Treatment State	Definition
Pre-Treatment	CM Start Date / Time < Study Treatment Start Date / Time (Period 1)
On-Treatment (Period 1)	If CM Start Date / Time is on or after Study Treatment Start Date / Time (Period 1) & before Study Treatment Start Date / Time (Period 2). Study Treatment Start Date / Time (Period 1) ≤ CM Start Date / Time < Study Treatment Start Date / Time (Period 2) For randomised subjects, this derivation ensures that CMs starting on or after the Period 1 dose up until the Period 2 dose will be captured and assigned to the Period 1 treatment group.
On-Treatment (Period 2)	If CM Start Date / Time is on or after Study Treatment Start Date / Time (Period 2) & before Follow-Up. Study Treatment Start Date / Time (Period 2) ≤ CM Start Date / Time ≤ Follow-Up Date For randomised subjects, this derivation ensures that CMs starting on or after the Period 2 dose up until the Follow-up Visit will be captured and assigned to the Period 2 treatment.
Study Day	Should relate to day since first dose i.e the day of the dose administered during Period 1 should be 'Day 1'.
Period Day	Day within the treatment period, for example, Period 1 Day 1 or Period 2 Day 1

10.3. Appendix 3: Data Display Standards & Handling Conventions

10.3.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo	Placebo	1
B	GSK2586881 0.8 mg/kg	GSK2586881 0.8 mg/kg	2

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

10.3.2. Baseline Definition & Derivations

10.3.2.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the latest pre-dose assessment. Baseline definitions are applicable to each period.

Parameter	Study Assessments Considered As Baseline		Baseline Used in Data Display
	Screening	Day 1 (Pre-Dose) Time T0	
Safety			
PASP	X	X	T0
Oxygen Saturation		X	T0
Labs	X		Screening
ECGs	X[1]	X	T0
Vital Signs	X[1]	X	T0
Biomarkers/Pharmacodynamic			
RAS peptides		X	T0
Other biomarkers		X	T0
Ventilatory parameters		X	T0

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

For statistical analyses (for example, Bayesian mixed model for PASP):

- Baseline is defined as the measurement taken pre-dose during each treatment period (i.e., time T0). This can also be referred to as '**period-specific baseline**'.
- **Subject-level baseline** is defined as the mean of the two period-specific baseline readings (the pre-dose T0 reading from each of the two treatment periods) for each subject.

- Period-level baseline (or '**adjusted period-specific baseline**') is defined as the difference between the baseline ('period-specific baseline') and 'subject-level baseline' for each period and each subject (i.e., the 'period-specific baseline' minus 'subject-level baseline' in each period).

The statistical modelling will include terms for 'subject-level baseline' and 'adjusted period-specific baseline'.

10.3.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= **Post-Dose Visit Value – Baseline [Ti – T0]**

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 10.3.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition will be footnoted on all change from baseline displays.

10.3.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used to perform all data analyses. Generate tables, figures and listings. • The latest version of R (or alternative supported available packages) will be used in sample size re-estimation for the interim analysis	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Area	: \ARPROD\GSK2586881\204987\Internal_01 : \ARPROD\GSK2586881\204987\Final_01
QC Spreadsheet	: \ARWORK\GSK2586881\204987\Internal_01\documents : \ARWORK\GSK2586881\204987\Final_01\documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards (Integrated Data Standards Library) • RAS Peptide data samples for Ang II, Ang(1-5) and Ang(1-7) will be processed by Q2 and data provided to GSK Data Management. • Surfactant Protein D samples and Immunogenicity samples will be processed by GSK and data will be provided to GSK Data Management • Pharmacokinetic samples will be processed by Covance and data will be provided to GSK Data Management	
Generation of RTF Files	
• RTF files will be generated for the interim and final reporting efforts	

Reporting Standards	
General	
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics	
Formats	
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • 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. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.	
Unscheduled Visits	
• Unscheduled visits will not be included in summary tables or figures, unless otherwise stated. • 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, %
Descriptive Summary Statistics (Log Transformed Data)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation ($CV_{b/w}$ (%)): CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (NOTE: SD is the SD of log transformed data)
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)
Reporting of Pharmacokinetic Parameters	
Descriptive	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD)

Reporting Standards	
Summary Statistics (Log Transformed)	of logged data and [between and or within] geometric coefficient of variation (CVb/w (%)) will be reported. [1] CV_b (%) = √ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data) [2] CV_w (%) = √ (exp(MSE) - 1) * 100 (MSE = mean square error from mixed effect model of loge-transformed data).
Parameters Not Being Log Transformed	Tmax, first point, last point and number of points used in the determination of lambda_z for listings
Listings	Include the first point, last point and number of points used in the determination of lambda_z for listings and R squared
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

10.4. Appendix 4: Derived and Transformed Data

10.4.1. General

Multiple Measurements at One 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. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from randomisation date :
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

10.4.2. Study Population

Demographics
Age

• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows:
  o Any subject with a missing day will have this imputed as day '15'.
  o Any subject with a missing date and month will have this imputed as '30th June'.
• Birth date will be presented in listings as 'YYYY'.

Body Mass Index (BMI)
• Calculated as **Weight (kg) / [Height (m)]^2**

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Subjects who were randomized but did not report a treatment start date will be categorised as having zero days of exposure.

10.4.3. Safety

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

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

10.4.4. Pharmacodynamic and Biomarker

Biomarkers
RAS Peptides • Ang II, Ang(1-5), Ang(1-7) **Disease Biomarker** • Surfactant Protein D
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.

10.5. Appendix 5: Premature Withdrawals & Handling of Missing Data

10.5.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as any subject who completes all phases in the study including the follow-up visit. • Withdrawn subjects will not be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

10.5.2. 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 subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
PK	If dosing and/or sampling times are missing, the relevant concentrations will be deleted from the population PK and PK/PD analysis dataset and summarized in a deletion record listing. Samples listed as having no sample (NS), no result (NR) or insufficient sample (IS) will be excluded from the PK data set and also included in the deletion record listing. GSK2586881 concentrations below the lower limit of quantification (LLQ) for the assay will be reported as NQ (Below Quantification Limit). All NQ values will be set to "." (missing) in the population PK and PK/PD dataset. Individuals with all plasma concentrations reported as NQ will be included in the data set.
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

Element	Reporting Detail
	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.

10.5.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing. • Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

10.5.2.2. Handling of Partial Dates

Element	Reporting Detail
Concomitant Medications	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.
Adverse Events	Any partial dates for adverse events will be raised to data management. If the full date cannot be ascertained, the following assumptions will be made: • If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month. • However, if these results in a date prior to Week 1 Day 1 and the event could possibly have occurred during treatment from the partial information,

Element	Reporting Detail
	then the Week 1 Day 1 date will be assumed to be the start date. • The AE will then be considered to start on-treatment (worst case). • If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. The recorded partial date will be displayed in listings.

10.5.2.3. Handling of Missing Data for Statistical Analysis

No missing data imputation methods will be used.

10.6. Appendix 6: Values of Potential Clinical Importance

10.6.1. Laboratory Values

Laboratory parameters have been reviewed against those specified in the protocol and any parameters not specified here have been assigned as not essential for assessment.

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
Hemoglobin	g/L	Male		180
		Female		180
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		100	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	20

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
BUN	mmol/L			≥ 2x ULN
Calcium	mmol/L		2	2.75
Creatinine	mmol/L			≥ 1.3x ULN
Glucose	mmol/L		3	9
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150

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

10.6.2. 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	

10.6.3. Vital Signs

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

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

10.7. Appendix 7: Biomarker Details

Biomarker Category	Analyte	Method	Lab	Matrix	Total samples expected per subject
RAS Peptides[1] (key endpoints)	Ang II	LCMS	Q2	Blood	8
	Ang (1-5)	LCMS	Q2	Blood	8
	Ang (1-7)	LCMS	Q2	Blood	8
Disease Biomarkers	Surfactant Protein D	Elisa	GSK	Serum	8

NOTES :

- 1. These peptides will be included in the interim analysis.
- Sampling times for each period: Pre-dose (T0), End of Infusion, 15 min Post-dose (T1), 15-45 min Post-dose, 60 min post chamber entry (T2), immediately post exercise (T3), immediately post chamber exit, 30 mins post chamber exit (T4).

10.8. Appendix 8: Model Checking and Diagnostics for Statistical Analyses

Endpoint(s)	• PASP • Oxygen Saturation • RAS Peptides (AngII, Ang(1-5), Ang(1-7)) • Surfactant Protein D
Analysis	• SAS PROC MCMC: Bayesian repeated measures mixed model

- Fixed effects will be assigned a non-informative prior of N(0, Var=1E6) and may be entered as separate univariate priors or as part of a multivariate distribution (variance covariance structure with zeros for off diagonals) in model hyperpriors.
- The non-informative UN priors should be an inverse Wishart distribution. If the equivalent of an unstructured variance covariance matrix does not fit then an AR(1) w/Random Effect structure may be considered, with non-informative priors of ϕ~U[-1,1] for the off diagonal elements and σ^2 ~ invGamma(0.0001, scale=0.0001). Example, for N=3:

$$UN = \begin{pmatrix} \sigma_1^2 & \sigma_{21} & \sigma_{31} \\ \sigma_{21} & \sigma_2^2 & \sigma_{32} \\ \sigma_{31} & \sigma_{32} & \sigma_3^2 \end{pmatrix}$$

$$AR(1) = \begin{pmatrix} 1 & \phi & \phi^2 \\ \phi & 1 & \phi \\ \phi^2 & \phi & 1 \end{pmatrix} * \sigma^2$$

- Appropriate SAS helper procedures (e.g. PROC TRANSREG) may be used to convert typical "long and thin" PROC MIXED input datasets into a format appropriate for repeated measures modelling in PROC MCMC (e.g. constructing sets of factors for each class level and fixing the final level to zero)
- Centring of continuous covariates will take place at the input dataset stage: (valuei – average) for each subject i.
- Examination of trace plots of samples versus the simulation number and Geweke diagnostics to assess convergence. Autocorrelation plots and lag summary table to assess the degree of autocorrelation. Monte Carlo standard errors compared to posterior standard deviations (a rule of thumb but not binding target would be <0.05). If further diagnostics required a scatterplot matrix plot of the posterior samples of each parameter.
- Number of burn ins, thinning, starting points, number of posterior draws to take (10,000 as a starting default) will be customised to each model and may not be possible to specify in advance but will be modified to ensure satisfactory diagnostics are produced.
- For robustness, where non-informative priors are used the equivalent PROC MIXED model may be fitted (no output from this would be reported) and LS Means and estimates of treatment differences compared to the results obtained from the PROC MCMC analysis. SAS code for the random and repeated statements would be:

```
random int / subject=subjid s vcorr;
repeated visit / subject=subjid*ptrtgrp type=un r rcorr;
```

- Model assumptions will be applied, but appropriate adjustments may be made based on the data.

10.9. Appendix 9: Population PK and Pharmacokinetic / Pharmacodynamic (Or Biomarker) Analyses

10.9.1. Population PK Dataset File Structure

The PME compliant file structure is a space-delimited file with each row containing the following columns of information. Data from all active treatments will be included (i.e. exclude placebo).

Decision as to whether this will be required will be made following the planned interim analysis.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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=0.8 for 0.8 mg/kg treatment Dose of GSK2586881 (for all events)
PART	Study Part	Integer	-	1=Period 1 or 2=Period 2
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
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL = 4, TIME = 0 Hours since start of first active infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose/infusion

Variable short name	Assessment description	Format	Unit	Valid Values / Format
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL = 4, TIME = 0 Hours since start of LAST infusion. For pre-dose sample, TRLD is relative to previous dose prior to sample For single dose studies TRFD and TRLD are the same
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
DV	Dependent Variable	Decimal	pg/mL	When LABL=6, observed GSK2586881 concentration at time specified by TRLD. When LABL=4 (dosing record), DV=0
MDV	Missing Data Variable	Integer	-	Either '0' if DV value present or 1 if DV value is non-quantifiable (NQ) or LABL=4
MDV1	Missing data variable	Integer	-	Either '0' if LABL=6 or '1' if LABL=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

Variable short name	Assessment description	Format	Unit	Valid Values / Format
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
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed concentration record for GSK2586881 at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	**pg/mL**

10.9.2. Population PK/PD Dataset File Structure : ANGII

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.

Decision as to whether this will be required will be made following the planned interim analysis.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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 for placebo treatment **DGRP=0.8 for 0.8 mg/kg treatment** **Dose of GSK2586881 (for all events)**
PART	Study Part	Varchar	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=0 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose

Variable short name	Assessment description	Format	Unit	Valid Values / Format
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BLII	AngII concentration record	Decimal		Baseline value (pre-dose value)
DV	AngII concentration record	Decimal		When LABL=6, observed AngII concentration at time specified by TRLD. When LABL=0 or 4, AngII=0
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=0 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=0 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 NQTYPE = '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

Variable short name	Assessment description	Format	Unit	Valid Values / Format
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
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	

10.9.3. Population PK/PD Dataset File Structure : ANG1-5

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.

Decision as to whether this will be required will be made following the planned interim analysis.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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 –

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				Time of start infusion)
RATE	Rate of Infusion	Decimal	Mg/h	Rate of infusion (AMT/INF)
DGRP	Treatment Identifier	Decimal	-	DGRP=0 for placebo treatment treatment **DGRP=0.8 for 0.8 mg/kg treatment** **Dose of GSK2586881 (for all events)**
PART	Study Part	Varchar	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=0 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BL15	Ang1-5 concentration record	Decimal		Baseline value
DV	AngI1-5 concentration record	Decimal		When LABL=6, observed Ang1-5 concentration at time specified by TRLD. When LABL=0or 4, Ang1-5=0
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=0 or,4
MDV1	Missing data variable	Integer	-	'1' if LABL=0 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 NQTYPE = '2'

Variable short name	Assessment description	Format	Unit	Valid Values / Format
CMT	Compartment data item	Integer	-	DOSE event: CMT=1, specifies the compartment into which DOSE is introduced. OBSERVATION event CMT=5 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 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
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	

10.9.4. Population PK/PD Dataset File Structure : ANG1-7

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.

Decision as to whether this will be required will be made following the planned interim analysis.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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 for placebo treatment treatment **DGRP=0.8 for 0.8 mg/kg treatment** **Dose of GSK2586881 (for all events)**
PART	Study Part	Varchar	-	1=Period 1 or 2=Period 2
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		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=0 or 4, TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BL17	Ang1-7 concentration record	Decimal		Baseline value
ANG1-7	Ang1-7 concentration record	Decimal		When LABL=6, observed Ang1-7 concentration at time specified by TRLD. When LABL=0or ,4, DV=0
MDV	Missing data variable	Integer	-	Either '0' if DV value present or 1 if DV is non-quantifiable (NQ) value or LABL=0 or 4
MDV1	Missing data variable	Integer	-	'1' if LABL=0 or 4 "0" when LABL=6
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=4 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 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
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR, includes non-quantifiable (NQ) data**	

10.9.5. Population PK/PD Dataset File Structure : Oxygen Saturation/PASP

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.

Decision as to whether this will be required will be made following the planned interim analysis.

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
STUD	Protocol Number	Integer	-	204987
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 for placebo treatment treatment **DGRP=0.8 for 0.8 mg/kg treatment** **Dose of GSK2586881 (for all events)**
PART	Study Part	Varchar	-	1=Period 1 or 2=Period 2
DAY	Study day	Integer	-	Maximum 10 characters (numeric or text) N= Day N, Actual Study

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				Day
CTIM	Clock time of Dose or measurement	HH:MM:SS	-	
DATE	Date of record	DD/MM/YYY		
TRFD	Actual time relative to FIRST dose	Decimal	Hours	When LABL=1 or 4 , TIME =0 Hours since start of FIRST infusion (on Day 1). For pre-dose sample, TRFD is relative to FIRST dose
TRLD	Actual time relative to LAST dose	Decimal	Hours	When LABL=0 or 4, TIME=0 Hours since start of LAST dose/infusion. For pre-dose sample,TRLD is relative to previous dose **For single dose studies TRLD = TRFD**
TFLAG	Time Flag	Integer	-	At T0 and LABL=6, TFLAG=0 At T1 and LABL=6, TFLAG=1 At T2 and LABL=6, TFLAG=2 At T3 and LABL=6, TFLAG=3 At T4 and LABL=6, TFLAG=4 Otherwise if LABL=6, TFLAG=5 If LABL="0" or "4", TFLAG=6
BLPASP	PASP	Decimal	mmHg	Baseline Value
PASP	PASP	Decimal	mmHg	When LABL=6, PASP at time specified by TRLD. When LABL=1, or4, PASP=0
BLOS	Oxygen Saturation	Decimal	%	Baseline Value
OS	Oxygen Saturation	Decimal	%	When LABL=6, Oxygen Saturation at time specified by TRLD. When LABL=1 or 4, Oxygen Saturation=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

Assessments captured in the LABL variable

Label	Description	Units
0	Dosing record for placebo	
4	**Dosing records for 0.8 mg/Kg GSK2586881**	
6	**Observed record (concentration or ratio) at time specified by TRLD; excludes NA, IS and NR**	

10.10. Appendix 10: Abbreviations & Trade Marks

10.10.1. Abbreviations

Abbreviation	Description
ACE2	Angiotensin converting enzyme type 2
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
ALT	Alanine aminotranferase (SGPT)
Ang II	Angiotensin II
AST	Aspartate aminotransferase (SGOT)
AUC(0-2.5h)	Area under the concentration-time curve over the study period
AUC(0.5-2.0h)	Area under the concentration-time curve over the hypoxia challenge
A&R	Analysis and Reporting
BUN	Blood urea nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL	Clearance
Cmax	Maximum observed plasma concentration
CO2	Carbon Dioxide
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
GSK	GlaxoSmithKline
GUI	Guidance
HPV	Hypoxic Pulmonary Vasoconstriction
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
mITT	Modified Intent-To-Treat
IV	Intravenous
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
O2	Oxygen
PASP	Pulmonary Artery Systolic Pressure

Abbreviation	Description
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Fridericia'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
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Tmax	Time to maximum observed concentration
T1/2	Apparent terminal phase half-life
V	Volume of Distribution
VO2	Oxygen Consumption

10.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP
RANDALL NG

Trademarks not owned by the GlaxoSmithKline Group of Companies
R (Statistical programming package/language)
SAS
WinNonLin

10.11. Appendix 11: List of Data Displays

10.11.1. 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
Pharmacodynamic and / or Biomarker	5.1 to 5.n	5.1 to 5.n
Pharmacokinetic / Pharmacodynamic	6.1 to 6.n	6.1 to 6.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 12: 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
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 / TST ID / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.11.3. Deliverable [Priority]

Delivery	Description
IA	Interim Analysis (Planned to be completed by GSK)
SAC*	Final Statistical Analysis Complete (Planned to be completed by FSP)

***Please note that where IA and SAC are noted together next to an output, GSK internal stats and programming team will take responsibility for this output, unless otherwise stated.**

10.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable**
Subject Disposition					
1.1.	mITT	ES1A	Summary of Subject Disposition for the Subject Conclusion Record		SAC
1.2.	All Subjects Screened	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
Protocol Deviation					
1.3.	mITT	DV1	Summary of Important Protocol Deviations		SAC
Populations Analysed					
1.4.	mITT	SP1A	Summary of Study Populations	Total column only. Include All Screened, mITT and PK. Footnote that percentages based on those in the mITT population, so only PK pop will have a percentage.	SAC
Demographic and Baseline Characteristics					
1.5.	mITT	DM3	Summary of Demographic Characteristics		SAC
1.6.	mITT	DM5	Summary of Race and Racial Combinations	Only total column needs to be included for a crossover study	SAC
Medical Conditions					
1.7.	mITT	MH1	Summary of Past Medical Conditions		SAC
1.8.	mITT	MH1	Summary of Current Medical Conditions		SAC

10.11.5. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PASP					
3.1.	mITT	PFT1	Summary of PASP	IDSL example PFT1 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA, SAC (GSK)
3.2.	mITT	PFT3	Summary of PASP Change from Baseline	IDSL example PFT3 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA, SAC (GSK)
3.3.	mITT	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in PASP	As per non-standard example SAFE_T1 but parameter column could be removed. Note that adjusted treatment differences and posterior probabilities (<0, <-2.5, <-5, <-7.5) are included on page 2 of mock example. Please note details regarding treatment differences in Section 7.2 and update output accordingly if a log-transformation is required (SAFE_T2 applies in this case with addition of posterior probabilities to be added).	IA, SAC (GSK)

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Oxygen Saturation					
3.4.	mITT	PFT1	Summary of Oxygen Saturation	IDSL example PFT1 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA, SAC (GSK)
3.5.	mITT	PFT3	Summary of Oxygen Saturation Change from Baseline	IDSL example PFT1 can be followed ('Day' won't be needed). *If a log-transformation is required for analysis please include log-transformed summary as a second page using PFT2 example.*	IA, SAC (GSK)
3.6.	mITT	SAFE_T1 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Oxygen Saturation	As per SAFE_T1 but parameter column could be removed. Note that adjusted treatment differences are included on page 2 of mock example. For OS expecting that we'll need to update the Posterior Probability labels, to <0%, <-1%, <-3%, <-5%, where 5% is the clinical concern level for a treatment difference where GSK reduces OS to a greater extent. Please see Section 8.1.2 with regards to changes required should a log transformation be needed (SAFE_T2 applies in this case with addition of posterior probabilities to be added).	IA, SAC (GSK)

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.7.	mITT	AE1CP (same as CP_AE1x)	Summary of All Adverse Events by System Organ Class and Preferred Term	Summarise by treatment group. Any pre-treatment AEs to be included in the listing only. Will only be created for interim if sufficient number of AEs are observed.	IA (GSK), SAC (FSP)
3.8.	mITT	AE1CP (same as CP_AE1x)	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency	Summarise by treatment group.	SAC
3.9.	mITT	AE1CP (same as CP_AE1x)	Summary of All Serious Adverse Events by System Organ Class and Preferred Term	Production of this will be dependent on the number of SAEs, listing may suffice (based on clin pharm IDSL standards advice, this is a conditional summary). Summarise by treatment group. Any pre-treatment SAEs to be included only in listing.	SAC
ECG					
3.10.	mITT	EG1	Summary of ECG Findings		SAC
3.11.	mITT	EG2	Summary of ECG Values		SAC
3.12.	mITT	CP_EG11	Frequency of ECG Values by Pre-Specified PCI Categories	Categories as per PCI details in Section 10.6.2.	SAC
3.13.	mITT	EG2	Summary of Change from Baseline in ECG Values		SAC
3.14.	mITT	CP_EG12	Frequency of Change from Baseline ECG Values by Pre-Specified PCI Categories	Categories as per PCI details in Section 10.6.2.	SAC
Vital Signs					
3.15.	mITT	VS1	Summary of Vital Signs		SAC
3.16.	mITT	VS1	Summary of Change from Baseline in Vital Signs		SAC
Immunogenicity					

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.17.	mITT	IMM1	Summary of Positive Immunogenicity Results		SAC

10.11.6. Safety Figures

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PASP					
3.1.	mITT	(non-standard)	Summary of PASP (Absolute)	x-axis will be timepoints T0 to T4, see other mock examples, y-axis will be mean PASP including 95% CI, by treatment groups (add to legend). *If data is log-transformed for the analysis then this graphic will need to show geometric means and 95% CIs.*	IA, SAC (GSK)

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.2.	mITT	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in PASP	If possible please also add a horizontal line within the graph to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). *If data is log-transformed for analysis then this graphic will be presenting median ratios.*	IA, SAC (GSK)
3.3.	mITT	SAFE_F2 (non-standard)	Individual Subject Profiles of PASP	Adjust as space permits, with fewer subjects per page if needed. X-axis and footnote for illustration, can be amended/improved. Vertical reference lines represent start and stop of hypoxia/chamber period.	IA, SAC (GSK)
Oxygen Saturation					
3.4.	mITT	(non-standard)	Summary of Oxygen Saturation (Absolute)	x-axis will be timepoints T0 to T4, see other mock examples, y-axis will be mean Oxygen Saturation including 95% CI, by treatment groups (add to legend) *If data is log-transformed for the analysis then this graphic will need to show geometric means and 95% CIs.*	IA, SAC (GSK)

Safety : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5.	mITT	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Oxygen Saturation	As above	IA, SAC (GSK)
3.6.	mITT	SAFE_F2 (non-standard)	Individual Subject Profiles of Oxygen Saturation	As above	IA, SAC (GSK)
3.7.	mITT	PD_F1 (non-standard)	Scatter Plot of Oxygen Saturation vs PASP	Scatter plot: PASP on y axis, treatment groups side by side, timepoint (T0 to T4) split into panels.	SAC

10.11.7. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK	PKCT1 (PK01)	Summary of GSK2586881 Pharmacokinetic Concentration-Time Data (ng/mL)		SAC
PK Parameter Data					
4.2.	PK	PKPT1 (PK03)	Summary Statistics of Derived Plasma GSK2586881 Pharmacokinetic Parameters	See Section 8.2.3.1 for list of parameters to be expected	SAC
4.3.	PK	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma GSK2586881 Pharmacokinetic Parameters	See Section 8.2.3.1 for list of parameters to be expected and Section 10.3.3 for details of those NOT to be log transformed	SAC

10.11.8. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration Data					
4.1.	PK	PKCF1X (PK16b)	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)	All individual subject profiles on the same graphic. If N>15 then split over two pages e.g. 8 or more subjects per page	SAC
4.3.	PK	PKCF2 (PK17)	Mean Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log)		SAC
4.4.	PK	PKCF3 (PK18)	Median Plasma GSK2586881 Concentration-Time Plot (Linear and Semi-Log)		SAC

10.11.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
RAS Peptides – Key					
5.1.	mITT	PD_T1 (or modify PFT1 & PFT2	Summary of Key RAS Peptides (Absolute Data)	Log-transformed summary to be included as a second page for each parameter if data is log-transformed for analysis. **Ang II, Ang(1-5), Ang(1-7)**	SAC
5.2.	mITT	SAFE_T2 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Key RAS Peptides	Log transformation likely to be required so output as per SAFE_T2. RAS Peptides are collected at timepoints other than T1 to T4 so these will need to be included. Note that adjusted treatment differences are included on page 2 of mock example. Posterior probabilities not required. **Ang II, Ang(1-5), Ang(1-7)**	SAC
Disease Biomarkers					
5.3.	mITT	PD_T1 (or modify PFT1 & PFT2	Summary of Surfactant Protein D (Absolute Data)	Log-transformed summary to be included as a second page if data is log-transformed for analysis. **Surfactant Protein D**	SAC
5.4.	mITT	SAFE_T2 (non-standard)	Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in Surfactant Protein D	Log transformation likely to be required so output as per SAFE_T2, otherwise SAFE_T1 (no posterior probabilities). SPD is collected at timepoints other than T1 to T4 so these will need to be included. Note that adjusted treatment differences are included on page 2 of mock example. Posterior probability not required.	SAC

Pharmacodynamic and Biomarker : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Ventilatory Parameters					
5.5.	mITT	PFT1	Summary of Ventilatory Parameters (Absolute Data)	Ventilatory parameters are collected at the same timepoints as PASP, with the exception of the post exercise timepoint. Order parameters as follows: Oxygen consumption (VO2), Carbon dioxide production (CO2), Total Tidal Volume, Inspiratory Tidal Volume, Expiratory Tidal Volume, Total Respiratory Time, Inspiratory Time, Expiratory Time, Duty Cycle, Mean Respiratory Flow,Respiratory rate	SAC

10.11.10. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
RAS Peptides – Key					
5.1.	mITT	(non-standard)	Summary of Key RAS Peptides (Absolute)	x-axis will be timepoints T0 to T4 (plus additional timepoints - see other mock examples), y-axis will be mean RAS including 95% CI, by treatment groups (add to legend). One page per endpoint (3 x RAS endpoints) *If a log-transformation is required for analysis please present geometric means and 95% CIs on a second page.*	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.2.	mITT	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Key RAS Peptides	See example mock SAFE_F1 but page by endpoint (3 RAS endpoints). *If log-transformed then median ratios will be plotted.* If possible please also add a horizontal line within the graphic to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). Note more timepoints for biomarkers other than T1 to T4.	SAC
5.3.	mITT	SAFE_F2 (non-standard)	Individual Subject Profiles of Key RAS Peptides	All subjects on one page, one page per RAS endpoint. X-axis and footnote for illustration and can be amended/improved. Vertical reference lines represent start and stop of hypoxia/chamber period. Note more timepoints for biomarkers other than T1 to T4. *Please note, mock shows raw data scales, but data may need to be log-transformed so in this case please provide a second page per RAS endpoint with y-axis to accommodate log-transformed data.*	IA, SAC (GSK)
Disease Biomarkers					
5.4.	mITT	(non-standard)	Summary of Surfactant Protein D (Absolute)	x-axis will be timepoints T0 to T4 (plus additional timepoints - see other mock examples), y-axis will be mean SPD including 95% CI, by treatment groups (add to legend). *If a log-transformation is required for analysis please present geometric means and 95% CIs on a second page.*	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.5.	mITT	SAFE_F1 (non-standard)	Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in Surfactant Protein D	*If log-transformed then median ratios will be plotted.* If possible please also add a horizontal line within the graphic to indicate the 'hypoxia' in chamber period (approx 30 mins post dose to 120 mins post-dose). Add major tick marks for labels indicated in example graphic. Major tick marks to be PTM labels (or shortened version of). Note more timepoints for biomarkers other than T1 to T4.	SAC
5.6.	mITT	SAFE_F2 (non-standard)	Individual Subject Profiles of Surfactant Protein D by Treatment Group and Timepoint	Adjust as space permits, with fewer subjects per page if needed. X-axis and footnote for illustration and can be amended/improved. Vertical reference lines represent start and stop of hypoxia/chamber period. Note more timepoints for biomarkers other than T1 to T4. *Please note, mock shows raw data scales, but data may need to be log-transformed so in this case please provide a second page with y-axis to accommodate log-transformed data.*	SAC
Key RAS Peptides vs PASP & Oxygen Saturation					
5.7.	mITT	PD_F1 (non-standard)	Scatter Plot of RAS Peptides (Ang II, Ang(1-7) and Ang(1-5)) vs PASP	Scatter plot: PASP on y axis. Page by RAS endpoint, treatment groups side by side, timepoints T0 to T4 within panels (2 columns, 5 rows per page, 3 pages). Plot T0 to T4 timepoints (timepoints that match for the two endpoints of interest) *If RAS data is log-transformed, please include a second page y-axis to accommodate log-transformed data.*	SAC

Pharmacodynamic and Biomarker : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.8.	mITT	PD_F1 (non-standard)	Scatter Plot of RAS Peptides (Ang II, Ang(1-7) and Ang(1-5)) vs Oxygen Saturation	Scatter plot: Oxygen Saturation on y axis. Page by RAS endpoint, treatment groups side by side, timepoints T0 to T4 within panels (2 columns, 5 rows per page, 3 pages). Plot T0 to T4 timepoints (timepoints that match for the two endpoints of interest) *If RAS data is log-transformed, please include a second page y-axis to accommodate log-transformed data.*	SAC

10.11.11. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	mITT	PK_F1	Scatter Plot of Plasma GSK2586881 Concentration vs PASP	Timepoint split into panels (matching timepoints are T0 to T4) Placebo PASP data included at concentration of zero for comparison, see mock example.	SAC
6.2.	mITT	PK_F1	Scatter Plot of Plasma GSK2586881 Concentration vs RAS Peptides (Ang II, Ang(1-5) and Ang(1-7))	Timepoint split into panels (matching timepoints are T0 to T4) One page per RAS endpoint. Placebo RAS data included at concentration of zero for comparison, see mock example. *Please note, if RAS data is log-transformed then also include a second page per RAS endpoint displaying log-transformed RAS vs concentrations.*	SAC
6.3.	mITT	PK_F1	Scatter Plot of AUC(0.5-2h) vs PASP	Timepoint T2 and T3 only, to be included as two separate panels *Please include log-transformed AUC graphic on a second page.*	SAC

10.11.12. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure		SAC
2.	mITT	ES2	Listing of Reasons for Study Withdrawal		SAC
3.	mITT	BL2	Listing of Subjects for Whom the Treatment Blind was Broken		SAC
4.	mITT	CP_TA2	Listing of Randomised and Actual Treatments		SAC
Protocol Deviations					
5.	mITT	DV2	Listing of Important Protocol Deviations		SAC
6.	mITT	IE4	Listing of Subjects with Inclusion/Exclusion Criteria Deviations		SAC
Populations Analysed					
7.	All Screened Subjects	SP3a	Listing of Subjects Excluded from Any Population		SAC
Demographic and Baseline Characteristics					
8.	mITT	DM4	Listing of Demographic Characteristics		SAC
9.	mITT	DM10	Listing of Race		SAC
Prior and Concomitant Medications					
10.	mITT	CP_CM4	Listing of Concomitant Medications	For small studies / limited conmed data, a listing can be used in place of summary table, hence no summary table requested for this study.	SAC
Exposure and Treatment Compliance					
11.	mITT	EX4	Listing of Exposure Data		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
12.	All Screened	AE9CP	Listing of All Adverse Events for Non-randomised subjects	Only output AEs that occurred for non-randomised subjects only. These should be assigned as pre-treatment. If no AEs then list 'No data to report'. Any SAEs will be noted on this listing	SAC
13.	mITT	AE9CP	Listing of All Adverse Events	Will include AEs for mITT patients, including those that occurred pre-treatment.	IA (GSK), SAC (FSP)
Serious and Other Significant Adverse Events					
14.	mITT	AE9CPA (same as CP_AE9a)	Listing of Serious Adverse Events	As above	SAC
15.	mITT	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment		SAC
All Laboratory					
16.	mITT	LB6	Listing of All Laboratory Data for Subjects with Any Value of Potential Clinical Concern/Potential Clinical Importance	Group by chemistry and haematology	SAC
17.	mITT	LB6	Listing of Laboratory Values of Potential Clinical Importance	Group by chemistry and haematology	SAC
ECG					
18.	mITT	CP_EG4	Listing of All ECG Values for Subjects with Any Value of Potential Clinical Importance		SAC
19.	mITT	CP_EG4	Listing of ECG Values of Potential Clinical Importance		SAC
20.	mITT	CP_EG6	Listing of Abnormal ECG Findings		SAC

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
21.	mITT	CP_VS5	Listing of All Vital Signs Data for Subjects with Any Value of Potential Clinical Importance		SAC
22.	mITT	CP_VS5	Listing of All Vital Signs Data of Potential Clinical Importance		SAC

10.11.13. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Safety					
23.	mITT	PFT9	Listing of PASP	Follow PFT9 IDSL format, replacing the last four FEV columns on the example with one PASP column.	IA, SAC (GSK)
24.	mITT	PFT9	Listing of Oxygen Saturation	As above	IA, SAC (GSK)
25.	mITT	PFT9	Listing of Ventilatory Parameters	Similar format to above except include a parameter column to include all ventilator parameter results at each timepoint. Non-standard modification may be required.	SAC
Biomarkers					
26.	mITT	PD_L1 (non-standard)	Listing of RAS Peptides	See non-standard example PD_L1	IA, SAC (GSK)
27.	mITT	PD_L1 (non-standard)	Listing of Surfactant Protein D	Non-standard example above can be followed	SAC
Immunogenicity					
28.	mITT	IMM2	Listing of Immunogenicity Results	Note: Subjects should have data recorded at screening or period 1 pre-dose (not at both timepoints)	SAC
PK					
29.	PK	PKCL1X (PK08)	Listing of GSK2586881 Plasma Pharmacokinetic Concentration–Time Data		SAC
30.	PK	PKPL1X (PK14)	Listing of Derived GSK2586881 Plasma Pharmacokinetic Parameters	See Section 8.2.3.1 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

10.12. Appendix 12: Example Mock Shells for Data Displays

Example : SAFE_T1 Page 1 of 2
Protocol : 204987
Population : Modified Intent-To-Treat

Table x.x
Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in XXXX

Parameter	Treatment	Timepoint	N	n	Posterior Median (Std Dev)	95% Credible Interval
XXXX	Placebo	T1: 15 M Post Infusion	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
		T2: 60 M Post Chamber Entry	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
		T3: Immediately Post Exercise	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
		T4: 30 M Post Chamber Exit	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
	GSK2586881 0.8 mg/kg	T1: 15 M Post Infusion	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
		T2: 60 M Post Chamber Entry	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
		T3: Immediately Post Exercise	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)
		T4: 30 M Post Chamber Exit	xx	xx	xx.x (xx.xx)	(xx.x, xx.x)

No transformation has been applied to the data
Non-informative prior used for all modelling parameters
Unstructured covariance matrix fitted

Cont.....

Example : SAFE_T1
Protocol : 204987
Population : Modified Intent-To-Treat

Table x.x
Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in XXXX

Parameter	Comparison	Timepoint	Posterior Median Difference (Std Dev)	95% Credible Interval	Posterior Prob. of True Diff > X(units) <0	<-2.5	<-5	<-7.5
XXXX	GSK2586881 0.8 mg/kg Vs Placebo	T1: 15 M Post Infusion	xx.x (xx.xx)	(xx.x, xx.x)	0.xx	0.xx	0.xx	0.xx
		T2: 60 M Post Chamber Entry	xx.x (xx.xx)	(xx.x, xx.x)	0.xx	0.xx	0.xx	0.xx
		T3: Immediately Post Exercise	xx.x (xx.xx)	(xx.x, xx.x)	0.xx	0.xx	0.xx	0.xx
		T4: 30 M Post Chamber Exit	xx.x (xx.xx)	(xx.x, xx.x)	0.xx	0.xx	0.xx	0.xx

No transformation has been applied to the data
Non-informative prior used for all modelling parameters
Unstructured covariance matrix fitted

Programming Note: Mock assumes no transformation. If transformation is required please update table appropriately (see SAFE_T2) to present back-transformed data e.g. present Adjusted Median Ratios, Posterior Probability Ratio <1, see Section 7.2 and Section 8.1.2. Add any additional footnotes required to clarify analyses performed. Timepoint explanation could be added as footnote if there are column space limitations, example given only. Parameter column could be removed for only one parameter in a summary.

Example : SAFE_T2
Protocol : 204987
Population : Modified Intent-To-Treat

Table x.x
Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in XXXX

Parameter	Treatment	Timepoint	N	n	Posterior Median Ratio (SD(Log))	95% Credible Interval
XXXX	Placebo	T1: 15 M Post Infusion	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
		T2: 60 M Post Chamber Entry	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
		T3: Immediately Post Exercise	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
		T4: 30 M Post Chamber Exit	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
	GSK2586881 0.8 mg/kg	T1: 15 M Post Infusion	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
		T2: 60 M Post Chamber Entry	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
		T3: Immediately Post Exercise	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)
		T4: 30 M Post Chamber Exit	xx	xx	x.xx (x.xxx)	(x.xx, x.xx)

A log-transformation was applied to the raw data prior to analysis. Non-informative prior used for all modelling parameters
Unstructured covariance matrix fitted.

Cont.....

Example : SAFE_T2
Protocol : 204987
Population : Modified Intent-To-Treat

Table x.x
Summary of Repeated Measures Bayesian Statistical Analysis of Change from Baseline in XXXX

Parameter	Comparison	Timepoint	Posterior Median Ratio (SD(Log))	95% Credible Interval
XXXX	GSK2586881 0.8 mg/kg Vs Placebo	T1: 15 M Post Infusion	xx.x (xx.xx)	(xx.x, xx.x)
		T2: 60 M Post Chamber Entry	xx.x (xx.xx)	(xx.x, xx.x)
		T3: Immediately Post Exercise	xx.x (xx.xx)	(xx.x, xx.x)
		T4: 30 M Post Chamber Exit	xx.x (xx.xx)	(xx.x, xx.x)

A log-transformation was applied to the raw data prior to analysis. Non-informative prior used for all modelling parameters
Unstructured covariance matrix fitted.

Programming Note: Mock assumes log transformation. Add any additional footnotes required to clarify analyses performed. Timepoint explanation could be added as footnote if there are column space limitations, example given only. Parameter column could be removed for only one parameter in a summary.

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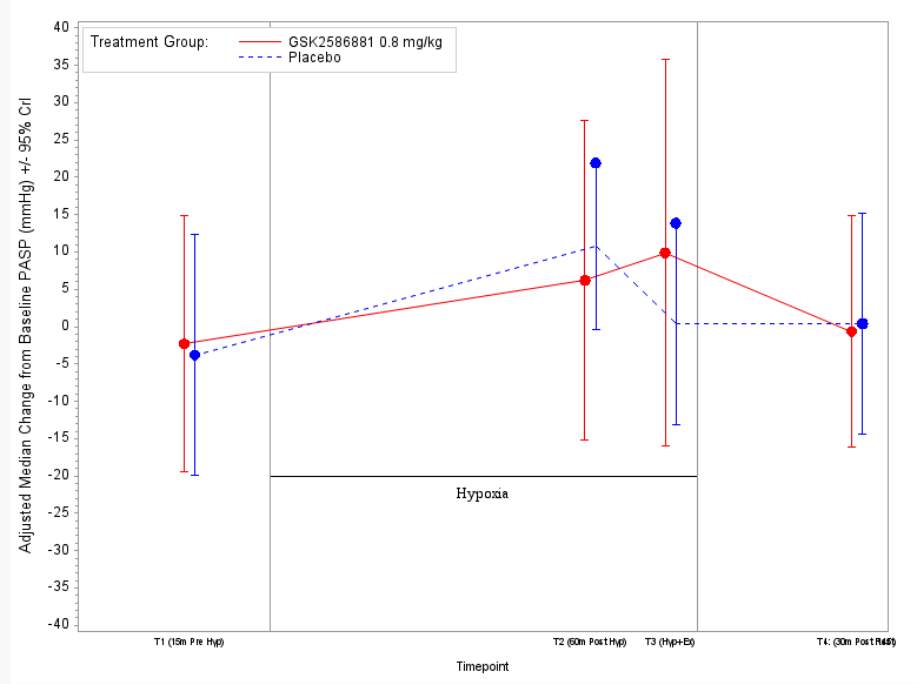
Example : SAFE_F1
Protocol : 204987
Population : Modified Intent-To-Treat

Figure x.x
Adjusted Median Responses and 95% Credible Interval vs Time Profiles of Change from Baseline in XXXX



Programming notes: Major tick marks to be PTM labels (or shortened version of). Adjusted median ratios to be presented if data is log-transformed.

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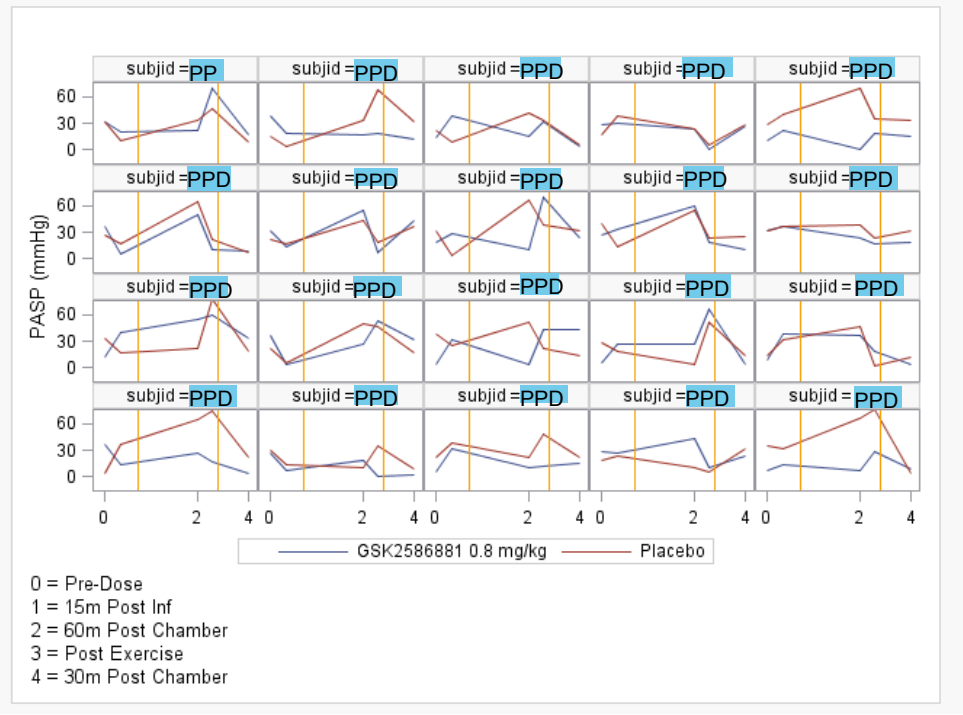
Example : SAFE_F2
Protocol : 204987
Population : Modified Intent-To-Treat

Figure x.x
Individual Subject Profiles of XXXX



Example : PD_T1
Protocol : 204987
Population : Modified Intent-To-Treat

Table x.x
Summary of RAS Peptide Parameters

Analyte	Actual Treatment Group	N	Time	n	n [1]	Mean	SD	Median	Min	Max
AngII (pg/mL)	Placebo	xx	Pre-Dose	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			15 m Post Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			15-45 m Post Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			60 m Post Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			Immediately Post Ex.	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			Post Chamber Exit	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			30 m Post Chm. Exit	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
	GSK2586881 0.8 mg/kg	xx	Pre-Dose	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			15 m Post Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			15-45 m Post Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			60 m Post Infusion	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			Immediately Post Ex.	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			Post Chamber Exit	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x
			30 m Post Chm. Exit	xx	x	xx.xx	xx.xxx	xx.xx	xx.x	xx.x

Ang(1-5) and Ang(1-7).....

[1] Number of imputed observations (imputed using ½ of the LLQ).
NC – value below LLQ, NA – number of imputed values exceeds 75% of total number of evaluable values, CV – Between subject coefficient of variation ***Cont....***

Example : PD_T1
Protocol : 204987
Population : Modified Intent-To-Treat

Table x.x
Summary of RAS Peptide Parameters

Analyte	Actual Treatment Group	N	Planned Relative Time	n	n [1]	Geo. Mean	95% CI of Geo Mean	SD Logs	CV (%)
AngII (pg/mL)	Placebo	xx	Pre-Dose	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			Infusion	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			15 m Post Infusion	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			15-45 m Post Infusion	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			60 m Post Infusion	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			Immediately Post Ex.	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			Post Chamber Exit	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			30 m Post Chm. Exit	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
	GSK2586881 0.8 mg/kg	xx	Pre-Dose	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x
			Infusion	xx	x	xx.xx	(xx.xx, xx.xx)	x.xxx	xx.x

Ang(1-5) and Ang(1-7).....

[1] Number of imputed observations (imputed using ½ of the LLQ).
NC – value below LLQ, NA – number of imputed values exceeds 75% of total number of evaluable values, CV – Between subject coefficient of variation.

Programming notes: Summarise AngII, Ang(1-5) and Ang(1-7) within the summary table, for untransformed and log transformed summary statistics as shown in mock shell.

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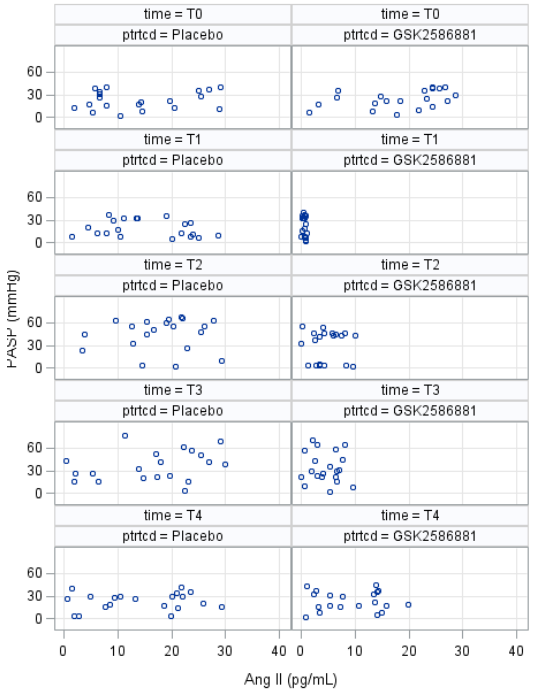
Example : PD_F1
Protocol : 204987
Population : Modified Intent-To-Treat

Figure x.x
Scatter Plot of PASP vs RAS Peptides by Timepoint and Treatment



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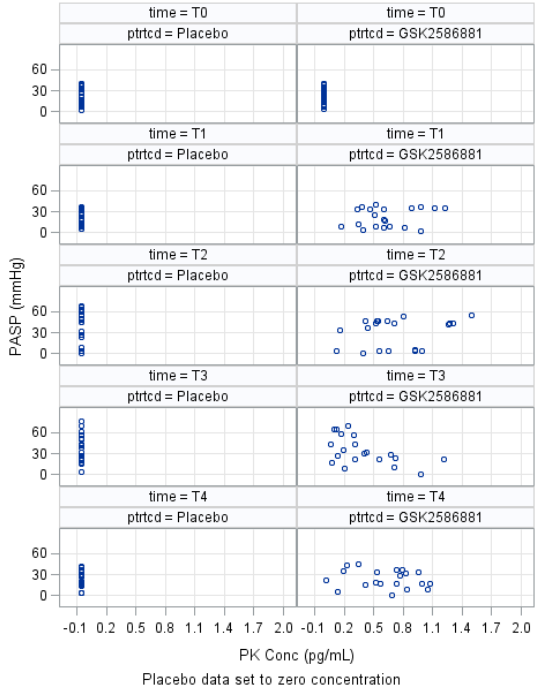
Example : PK_F1
Protocol : 204987
Population : Modified Intent-To-Treat

Figure x.x
Scatter Plot of Plasma GSK2586881 Concentration vs PASP



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Example : PD_L1
Protocol : 204987
Population : Modified Intent-To-Treat

Listing x
Listing of RAS Peptide Parameters

Invid/ Subject	Treatment/ Period	Analyte (units)	Date	Actual Time	Planned Time	Time dev.	Rel. Time To Ref.	Result	Imputed Result
xxxx/ PPD	Placebo/ 1	AngII (pg/mL)	xxPPD xxxx	xx:xx	Pre-Dose	-0.xx	-0.xx	xx.x	
				xx:xx	Infusion	-0.xx	-0.xx	xx.x	
				xx:xx	15 m Post Infusion	-0.xx	-0.xx	xx.x	
				xx:xx	15-45 m Post Infusion	-0.xx	-0.xx	xx.x	
				xx:xx	Imm. Post Exercise	-0.xx	-0.xx	xx.x	
				xx:xx	Post Chamber Exit	-0.xx	-0.xx	xx.x	
				xx:xx	30 m Post Chamber Exit	-0.xx	-0.xx	xx.x	
		Ang(1-5) (pg/mL)	xPPD xx	xx:xx	Pre-Dose	-0.xx	-0.xx	NQ	xx.x
				xx:xx	Infusion	-0.xx	-0.xx	xx.x	
				xx:xx	15 m Post Infusion	-0.xx	-0.xx	xx.x	

.....

Note: NQ = Not Quantifiable (Lower Limit of Quantification shown in parentheses), NA=Not Applicable
Note: “Infusion” sample is drawn at the end of the infusion