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

Title	:	Reporting and Analysis Plan for A Placebo Controlled, Double-blind, Multi-centre, Single Dose, Parallel Group, Randomised Clinical Trial of GSK2862277 in Patients undergoing Oesophagectomy Surgery
Compound Number	:	GSK2862277
Effective Date	:	17-NOV-2015

Description :

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol TFR116341.
- This RAP is intended to describe the planned efficacy, safety & tolerability, pharmacokinetics and pharmacodynamic analyses required for the study.
- This version includes amendments to the originally approved RAP.
- This RAP will be provided to the study team members to convey the content of i) the interim analyses output (including sample size re-estimation) and ii) the Statistical Analysis Complete (SAC) deliverable.
- Note: Analyses and outputs to support the exploratory translational sub-study will be covered in a separate stand-alone RAP and such outputs are not expected to form part of the SAC deliverable for the main study

Author's Name and Functional Area:

PPD	17-NOV-2015
Manager, Statistics (Clinical Statistics)	
PPD	
Statistician (Clinical Statistics)	

Approved via e-mail by:

PPD	17-NOV-2015
Director (Clinical Statistics)	

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1. REPORTING & ANALYSIS PLAN SYNOPSIS

Overview	Key Elements of the RAP
Purpose	• This RAP details all planned analyses and outputs required for the final Clinical Study Report (CSR) of study GSK2862277 TFR116341.
Protocol	• This RAP is based on protocol amendment 4 (Dated: 16/FEB/2015) of study GSK2862277 (GSK Document No. : 2014N197251_04 and eCRF Version (1).
Primary Objective	• To evaluate whether a single nebulised dose of GSK2862277 prevents peri-operative lung injury compared to placebo, as assessed by measurement of pulmonary vascular permeability (PVPI).
Primary Endpoint	• Baseline adjusted change in PVPI on completion of surgery
Study Design	• A Placebo Controlled, Double-blind, Multi-centre, Single Dose, Parallel Group, Randomised Clinical Trial of GSK2862277 in Patients undergoing Oesophagectomy Surgery • No formal sample size calculations were performed, however, the number of patients is based on computer simulations of baseline adjusted change in PVPI and P_aO_2/F_iO_2 on completion of surgery outcomes. Posterior probabilities of each outcome are assessed in combination against chosen threshold criteria to determine the likelihood of success/failure of the study to detect true treatment differences. A sample size of 40 subjects p.a. has an equivalent of a Type I error rate of 4.65% and a probability of 80.64% of detecting plausible effect sizes. A sufficient number of subjects will be enrolled such that 80 subjects complete dosing and assessments. • Patients enrolled in the study will be scheduled to undergo planned/elective trans-thoracic surgery for oesophagectomy. Prior to surgery patients will receive a single nebulised dose of GSK2862277 or placebo. • A factorial treatment structure is used in the randomisation (Treatment and the lung which BAL is sampled from, both two level factors). Summary tables of the raw/observed data will be produced with all possible groupings (See Section 11.4.1). Although each statistical model will contain adequate terms to account for the full factorial treatment structure the majority of statistical analyses for non BAL related endpoints will implicitly assume that the Treatment by BAL interaction is negligible and present results as treatment comparisons averaged over the levels of the BAL factor; without formally testing for it (mainly due to the small sample size). Informal checking of this assumption may consist of examining the posterior distribution for the interaction term and visually assessing whether it is non zero. If this is deemed to have occurred the corresponding summary tables and analysis outputs will be modified. For BAL related endpoints the starting assumption for summary tables and statistical modelling will be the interaction term is present, but outputs may be modified if the interaction is subsequently deemed negligible. • Due to the nature of the endpoints in this study (e.g. the invasive medical procedures needed to obtain PVPI) it is often not practical/ethical to schedule

Overview	Key Elements of the RAP
	true baseline samples (pre-randomisation / pre-dose). However, in mitigation, it should be noted that the surgical procedure is expected to be the principal factor driving changes in many of these study endpoints (e.g. PVPI and PaO2/FiO2) and the scheduled baseline is measured before the surgical intervention. Therefore, potential interpretational difficulties (e.g. attributing causality: chance result or real treatment effect acting over the dose to baseline time period) should large differences between baseline values on the treatment arms are acknowledged but accepted (this is an exploratory and not confirmatory study). If the observed difference between treatments at baseline is deemed to be large / clinically important appropriate sensitivity analyses may be performed (for example, but not limited to, omitting the baseline term from the corresponding statistical model).
Planned Analyses	• Interim analyses are detailed within Section 3.1 where applicable. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to Database Freeze of the study data.
Analysis Populations	• The 'Safety Population' will be used to evaluate study population andsafety and 'PK' population to evaluate pharmacokinetics. • Per protocol populations have been defined that exclude "open and shut" cases; and will be used as part of efficacy and PD/Biomarkers analyses.
Hypothesis	• The study was designed to estimate the effect of a single nebulised 26 mg dose of GSK2862277 relative to placebo on primary and secondary efficacy endpoints. • No formal statistical hypothesis tests will be conducted; instead an estimation approach will be undertaken.
Primary Analyses	• The protocol proposed an end of study decision pathway, consisting of the primary endpoint and PaO2/FiO2 on completion of surgery (adjusting for the baseline values of each endpoint) • Evaluation of this decision pathway via joint modelling of the 2x endpoints constitutes the primary analysis. • The primary analysis utilises a Bayesian framework with Monte Carlo Markov Chain (MCMC) sampling techniques. The decision pathway will be evaluated via posterior distributions of appropriate combinations of the model parameters. • The decision pathway is not binding upon GSK but provides an *a priori* yardstick to measure the success of the trial against. Note: The marginal distribution of baseline adjusted PVPI on completion of surgery is obtained as part of the steps to evaluate the decision grid (hence this primary analysis does cover the primary objective/endpoint stated in the protocol).
Secondary Analyses	• Baseline adjusted change in PVPI on completion of surgery: Bayesian ANCOVA model(s) with baseline and centre as fixed effects with covariate exploration / model building activities (e.g. duration of surgery and duration of one lung ventilation as plausible continuous covariates). Acts as confirmation

Overview	Key Elements of the RAP
	that the marginal distribution from the Primary analysis is appropriate. • Baseline adjusted change in extravascular lung water index (EVLWI) and baseline adjusted change in PaO2/FiO2, on completion of surgery will be analysed in a similar manner to the Secondary Analysis of PVPI (single time point analysis), described above. • Bayesian repeated measures analysis of post-operative PVPI, EVLWI and PaO2/FiO2 (separate model for each endpoint; assuming a mixed effects model structure). Baseline adjusted medians and 95% credible intervals will be constructed for the differences/ratios between GSK2862277 26 mg and Placebo at each of the post-operative time points. • Safety data will be presented in tabular format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. • Incidence and titres of serum anti-GSK2862277 antibodies post dosing will be summarised by treatment and listed by subject • Individual GSK2862277 plasma concentration-time profiles and median/mean (±SD) profiles will be plotted and listed. Derived PK parameters will be summarised and listed. BAL fluid and plasma urea data, along with the derived Dilution Factor will be summarised and listed. BAL fluid concentrations of GSK2862277, the volume of ELF in BAL fluid and pooled ELF concentration of GSK2862277 will be summarised and graphically presented. No formal statistical analyses will be conducted. • Biomarkers in BAL will be analysed in a Bayesian framework assuming a mixed effects model structure. Summary statistics from derived posterior probability distributions (such as treatment medians and 95% credible intervals) will be constructed for the differences/ratios between GSK286227 26 mg and Placebo at each time point (and possibly within each BAL sampling location too).
Exploratory Analyses	• Daily SOFA scores will be analysed using Bayesian repeated measures analyses. Adjusted medians and 95% credible intervals will be presented in tables and graphically for each treatment by day, together with estimated treatment differences GSK2862277 26 mg – Placebo and the corresponding 95% credible intervals. Note: Strong assumptions will be made to predict a baseline SOFA score for each subject to evaluate change from baseline SOFA (exploratory) • Blood/Cellular Biomarkers will be analysed in a similar fashion to the BAL biomarkers. • Other clinical parameters would be summarised by treatment and listed by subject. Statistical modelling would be conditional on the observed data.

1.1. RAP Amendments

Revision chronology:

RAP Section(s)	Amendment details
Reporting and Analysis Plan Final [10-JUL-2015]	
Reporting and Analysis Plan Final Amendment 1 [17-NOV-2015] – Pre unblinding for IA1	
Cover Page	Indicated RAP contains amended text
1	Clarified Analysis Populations for Efficacy PD/Biomarkers will be Per protocol (i.e. will not include "Open and Shut" cases)
1.1	Added Revision Chronology Table
3.1.2	Clarified IA2 will use mixture of Safety and Per protocol populations
7.1.1 & 8.1.1	Clarified Per Protocol 2 population to be used instead of Safety
8.4.1	Clarified Per Protocol 2 population to be used instead of Safety, except for BAL related outputs where Per Protocol 1 popualtion is required
8.4.1 Table 8	Updated List of Planned Biomarkers to reflect current plans at time of RAP amendment 1
11.1.1	Clarified that an upcoming eCRF version will have a variable indicating if a subject was an "open and shut case" and manual programming may be required to implement the populations if this variable is not retrospectively populated for existing subjects.
11.6.2.1	Added section for missing date/times for surgical procedures and biomarker samples to account for known missing data for subject PPD (known at time RAP amendment #1 written).

RAP Section(s)	Amendment details
Reporting and Analysis Plan Final [10-JUL-2015]	
Reporting and Analysis Plan Final Amendment 1 [17-NOV-2015] – Pre unblinding for IA1	
11.7.1	Based upon medical monitor advice: • Corrected Low Flag value for Hemoglobin (Males and Females) because it was specified in g/dL and not g/L • Changed PR interval Lower and Upper PCI values • Change from Baseline "Increase from Baseline QTc": Moved the range from the Lower to the Upper column (leaving Lower column blank) • Re-drew the Vital Sign Parameter (Change from Baseline) tables to only have one entry for Decreases and Increases respectively
11.8	Updated List of Planned Biomarkers to reflect current plans at time of RAP amendment 1
11.14	Amended populations for efficacy/Biomarker related outputs and corrected typos in timing/priority (e.g. "IA [2]" corrected to "IA2 [1]")

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the substance of the originally planned primary statistical analysis specified in the protocol / protocol amendment 4 (Dated: 16/FEB/2015). Clarification of how the four level treatment structure is incorporated into the decision grid and a mechanism to adjust for other covariates such as centre have been included in this RAP.

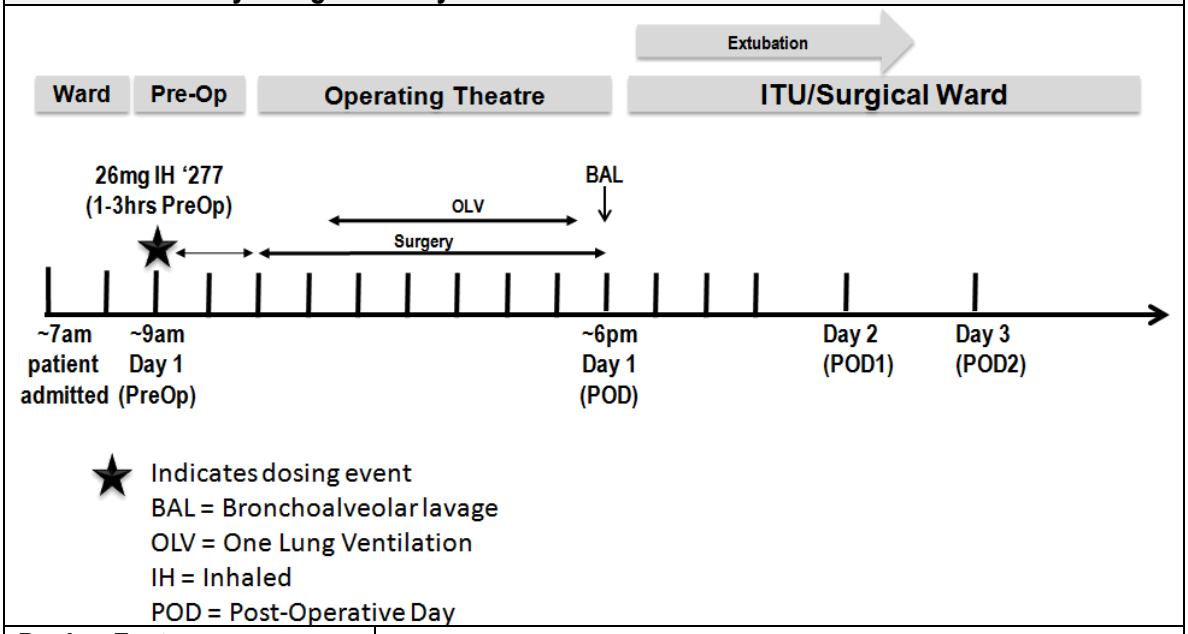
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate whether a single nebulised dose of GSK2862277 prevents peri-operative lung injury compared to placebo, as assessed by measurement of pulmonary vascular permeability.	• Baseline adjusted change in PVPI on completion of surgery
Secondary Objectives	**Secondary Endpoints**
• To evaluate whether a single nebulised dose of GSK2862277 prevents peri-operative lung injury compared to placebo, as assessed by measurement of pulmonary oedema.	• Baseline adjusted change in EVLWI on completion of surgery.
• To evaluate the safety and tolerability of GSK2862277 administered preoperatively	• AEs • Clinical laboratory safety data. • ECG readings • Vital signs
• To evaluate whether a single nebulised dose of GSK2862277 prevents peri-operative lung injury compared to placebo, as assessed by degree of hypoxaemia	• Baseline adjusted change in PaO2/FiO2 on completion of surgery
• To evaluate differences in expression profile of BAL biomarkers from both ventilated and collapsed lungs immediately after surgery	• Levels of BAL biomarkers (e.g. IL-6, sRAGE, protein levels) on completion of surgery.
• To evaluate the effect of a single IH dose of GSK2862277 compared to placebo, on attenuating lung and distal organ injury over the post-operative period	• Change over time in PaO2/FiO2 post-operatively on Day 2 through to Day 4 (as available; SpO2/FiO2 when arterial line removed) • Change over time in PVPI and EVLWI post-operatively on Day 2 through to Day 4 • Daily SOFA scores on Day 2 through to Day 4
• To describe plasma pharmacokinetics of a single inhaled dose of GSK2862277.	• Plasma concentrations of GSK2862277 and derived pharmacokinetic parameters.
• To quantify the concentration of	• BAL concentrations of GSK2862277 and derived

Objectives	Endpoints
GSK2862277 in BAL and to compare to plasma levels of GSK2862277	pharmacokinetic parameters • Ratio of BAL concentration to plasma concentration.
• To evaluate the levels and specificity of any anti-drug antibodies formed following dosing with GSK2862277.	• Incidence and titers of serum anti-GSK2862277 antibodies post dosing
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the effect of GSK2862277 compared to placebo on clinical and patient outcomes.	• Further exploratory evaluation of effectiveness may be conducted where data permit. Endpoints may include, but are not limited to: • Diagnosis of ARDS out to day 28; • 28 day survival; • Ventilator Free Days; ICU & hospital length of stay; • Organ Failure Free Days; • Haemodynamic assessments (e.g. Cardiac Index, Global End Diastolic Volume, etc) • Oxygenation Index
• To evaluate changes in TNFR related and disease biology biomarkers in the blood of patients who have been treated with GSK286227 compared to placebo, on completion of surgery and in the immediate post-operative period.	• Difference from placebo in levels of plasma biomarkers (e.g. IL-6, sRAGE) on completion of surgery and through to Day 4

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• Randomised placebo controlled, double-blind, multi-centre, single dose parallel group, design in patients undergoing Oesophagectomy surgery. •
Dosing	• Single nebulised dose 1-5 hours prior to surgery.
Treatment Assignment	• N=80 subjects randomised across two groups, dosed and completed all assessments (40 patients per group). • GSK RandAll NG used to generate randomisation schedules. • Patients are randomized to receive 26 mg GSK2862277 or Placebo and either ventilated or collapsed lung BAL procedure.
Interim Analysis	• Unblinded safety review after approx 10 patients have completed Day 7 visit; roughly 5 per arm • Unblinded safety review and futility analysis after approx 40 patients have completed Day 7 visit; roughly 20 per arm (includes Sample size re-estimation)

2.4. Statistical Hypotheses

Precision Estimation

No formal statistical hypotheses will be tested in this study. Safety related objectives will be assessed via summary tables, listings and figures.

In addition to summary tables, listings and figures, study objectives relating to efficacy (for example, lung physiology and biomarkers) may be evaluated using posterior distribution(s) for the

effect of GSK2862277 relative to Placebo. Point estimates and corresponding 95% credible intervals will be constructed for the difference between the mean of the test treatment and the mean of the reference treatment, μ(test) - μ(reference). No adjustment for multiplicity will be performed due to the Bayesian analysis framework.

Note: If data require log transformation prior to analysis then point estimates and corresponding 95% credible intervals will be constructed for the ratio of test treatment to placebo treatment μ (test) / μ (reference) in place of those for differences in means.

3. PLANNED ANALYSES

3.1. Interim Analyses

There are two interim analyses planned for this study both of which will use unblinded data (an unblinded sample size re-estimation will be performed as part of interim analysis #2). Further details are given in Section 3.1.1 and Section 3.1.2. The interim analyses will be performed by the study statistician (or designate). The appropriate internal GSK procedures will be followed to ensure that access to unblinded subject level data is restricted to the specific study team members who require access.

3.1.1. Interim analysis #1: Unblinded safety review after approx 10 patients have completed Day 7 visit; roughly 5 per study drug arm.

The principal objective will be to determine whether there are any emerging safety trends/ signals which might require modifications to be made and/or suspension of recruitment pending further data review. Unless there are safety concerns recruitment into the study may continue whilst interim analysis #1 (IA1) is being performed. IA1 will use the "Safety" population applicable at the time of the data cut.

The following safety outputs will be provided:

- Demographic information
- AE/SAEs
- Laboratory data
- Vital signs
- ECG data
- Concomitant medications
- Listing of surgical procedure information for each subject

For further details of the output see Appendix 14.

Note: An additional informal check of the available plasma PK values may be made to give confidence dosing is occurring as intended. Samples will be batched and sent for analysis at designated intervals during the study and the results made available (batches will be timed to coincide with the interim analyses). The check would be basic; namely confirming subjects on active doses of GSK2862277 with available plasma PK concentrations at the time of the interim had at least one quantifiable post dose value of GSK2862277. No outputs will be reported from this step and the timing of the interim analyses will not be delayed on account of this. Appropriate

remedial action(s) would be taken if this check revealed potential problems with the dosing (for example, but not limited to, re-training of selected sites on the use of the equipment, or processing all the collected PK samples with formal PK and/or PK/PD modelling with a view to a dose adjustment – details would be documented in any associated protocol amendment and/or the CSR).

3.1.2. Interim analysis #2: Unblinded safety review, futility analysis and sample size re-estimation after approx 40 patients have completed Day 7 visit; roughly 20 per study drug arm.

A "soft lock" of the database for those subjects in scope for interim analysis #2 (IA2) is planned. This should ensure the IA2 eCRF data are as clean as possible and that data for the potential analyses in Figure 1 are available in a reasonable timeframe. IA2 will use a mixture of the "Safety" and "Per Protocol" populations applicable at the time of the data cut.

In addition a Sample size re-estimation will take place at IA2 to determine if the overall target sample size should remain at 80 subjects (~40 p.a.).

The outcome of interim analysis #2 will be communicated by GSK to the sites as either "Continue" or "Pause and Review".

Upon a "Pause and Review" communication the available data will be reviewed by the study team (un-blinded) and additional data may be requested from the sites to determine whether to:

- Stop the study early for futility
- Modify aspects of its design
- Resume and continue unaltered

Figure 1 indicates the flow of additional data to be reviewed upon a "Pause and Review" outcome and possible actions; although it should be stressed that Figure 1 is non-binding. Emerging patterns in the data may suggest other analyses not described here that may influence the action taken.

Although interim analysis #2 is scheduled to occur after approximately 20 patients p.a. have available data up to Day 7, it is possible that recruitment rates may be lower than anticipated in which case the interim analysis may occur after a fixed time with whatever data are available.

The futility analysis component of Interim analysis #2 will use the baseline adjusted endpoints on completion of surgery:

- PVPI Ratio: Mean Active/Mean Placebo,
- P to F Ratio Difference: Mean Active – Mean Placebo

and will utilise predictive inference, decision pathway and confidence thresholds.

The interim analysis will assume that there is no interaction between study drug (active and placebo) and the location of the BAL lung sampling (collapsed or ventilated). Therefore the 4 treatments will be combined to two treatments (based on study drug) and

references to treatment arms in this section assume usage of Alternative Treatment descriptors #1 (See Section 11.4.1). The algorithm suggested in Section 9.3.1 of the protocol has been modified to allow adjustments for other covariates.

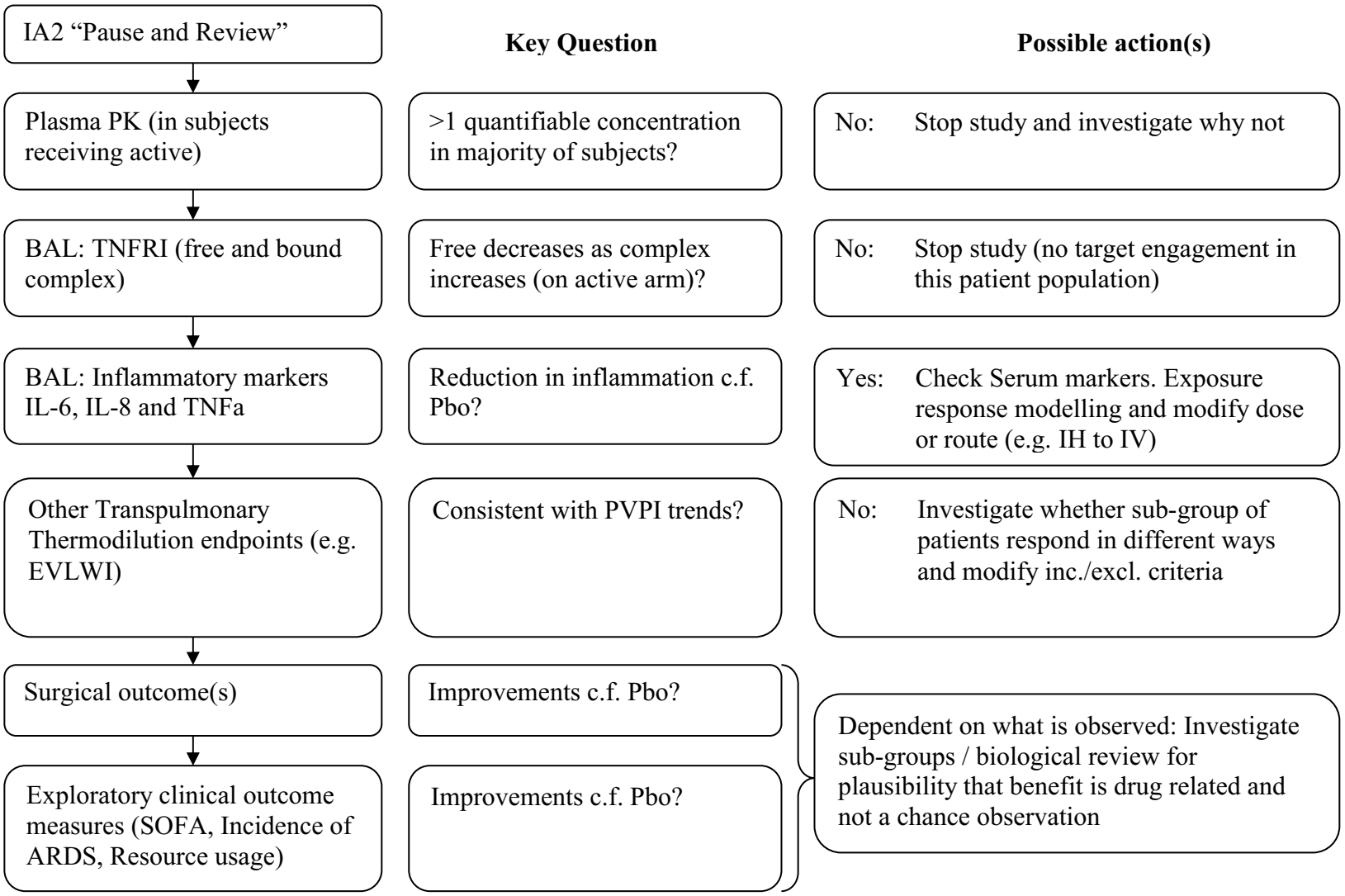
The algorithm for the interim analysis is as follows:

1. Apply any transformations to the endpoint(s) (and baseline(s)) and center any continuous covariates.
2. Fit a model similar in form to that described in Section 7.1.2 to the observed IA2 data. Note: Should use separate variance covariance matrices (one per treatment arm).
3. The equivalent of adjusted least square means will be constructed for each endpoint on each treatment arm.
4. Once MCMC model convergence has been achieved the current iteration's values for the variance covariance matrix and the adjusted least square mean vector define a multivariate normal distribution for a future subjects data (a separate distribution per treatment arm)
5. Use the newly defined multivariate normal distributions to simulate enough subjects to achieve an overall total of 40 per arm
6. Repeat steps 4 & 5 1000 times (i.e. 1,000 samples once the MCMC model has converged).
7. For each treatment arm, use the median values of the adjusted least square means and the median values of each element of the variance covariance matrix to derive the hyperparameters of the Normal-Inverse-Wishart distribution for each treatment (i.e. constructed using the model **adjusted** IA2 immediately post surgical values rather than being derived directly from the raw/observed data) – see Table 14 for how to obtain these parameters.
8. Derive Multivariate sample statistics from each simulated dataset (see Section 11.12.1 for the list of sample statistics to derive). The sample statistics will be used to update the parameters of the Normal-Inverse-Wishart distribution for each treatment (see Table 15).
9. Use the updated Normal-Inverse-Wishart distributions to estimate the end of study mean treatment effects (i.e. condition on the Expected value of the VCV) and then determine the parameters describing the distribution of the mean end of study treatment difference (See Section 11.12.1).
10. Determine whether the probability of observing ANY decrease in PaO2/FiO2 means and Any increase in PVPI means is greater than 0.1
11. If so then record that simulated study as being futile
12. Repeat steps 8 to 10 1000 times
13. Determine the proportion of the 1000 simulated studies which meet the futility threshold
14. If the proportion is larger than 0.3 then the recommendation is to "Pause and Review", otherwise the recommendation is to "Continue"

Interim Analysis #2	Details
Additional details on the Method	• PVPI and P_aO_2/F_iO_2 on completion of surgery • Baseline: PVPI and P_aO_2/F_iO_2 immediately prior to surgery (day 1) • Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics (PVPI is expected to require a Ln (natural logarithm) transformation) • Any observations with missing model covariates (e.g. baseline) would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates) • The above endpoints and baselines will be the average of any replicates available at the planned time points • The model specifications described in Section 7.1.2 (primary analysis) will also apply to the model fitted to the observed set of IA2 data where applicable. Exceptions include only using the burn in and thinning parameters to achieve MCMC model convergence (the number of posterior draws will be limited to 1,000 to match the required number of future simulated study outcomes). In addition the IA2 model does not require directly fitting 4 separate treatment parameters. Therefore the following is an example construction for the adjusted least square equivalent Ln{PVPI} $\hat{\mu}_{Pbo,PVPI} + \left(\sum_{i=1}^{\#centers} Center_i \Big/ \#Centers \right)$
Output	• By subject time profiles of PVPI and PaO2/FiO2 grouped by treatment will be produced using the available IA2 data. • Scatterplots of the observed IA2 data from each subjects will be produced (grouped by treatment and IA2 timepoint) • Descriptive statistics for absolute and change from baseline PVPI and PaO2/FiO2 grouped by treatment will be tabulated. • A set of summary text describing the IA2 process and recommendation will be produced. Note: In addition the full output from SAS PROC MCMC will be produced for statisticians to assess the suitability of the model but this is not expected to be disseminated further due to its technical nature.
Pause and Review	• In the event of a "Pause and Review" recommendation the analyses described in Figure 1 may be attempted in the order described therein. • Analyses in Figure 1 are expected to be the same as their respective end of study analyses (e.g. analyses involving BAL will account for the BAL lung sampled in the statistical modelling and if necessary compare active to placebo within each of those strata). • No formal decision criteria for Figure 1 are specified here. The results of the analyses described in Figure 1 will be used to inform the decision to "Continue", "Modify" or "Stop" in discussions with the study team. Additional analyses may be performed if appropriate and documented in the CPSR.
Sample Size Restimation	• The adjusted sample size (total number of subjects) will be **determined by the clinical study team** after reviewing the outcome of the following exercise. It is

Interim Analysis #2	Details
	expected to be the smallest value from either the current upper limit (80) or the re-estimated value (i.e. it is expected to remain capped at 80 subjects). There is no minimum limit, so it is therefore possible that the re-estimated sample size chosen by the clinical study team is the same value as the observed number of IA2 subjects, and hence the study will cease recruiting new subjects. • The re-estimation will use the median estimates of each of the elements in the VCV matrix obtained from the (adjusted) modelling of the observed IA2 data. It will use the similar methodology to the protocol (see Section 11.12.2 for details of the simulation process), except that total sample size will be varied until the resulting operating characteristics for the "Overall success outcome" using the "Null" and "Minimum desired profile" scenarios match the ones obtained for a total sample size of 80 (roughly 4.65% and 80.64% respectively). If the point estimates for the variances from the observed IA2 data are larger than the assumed values used in the protocol then the procedure will start at 80 subjects and increase by 2 subjects until the criteria are met, and conversely if the observed variances are smaller the process will start at 80 subjects and decrease by 2 subjects until the criteria are met. Note: Larger increments may also be used to arrive in the "ball park" more quickly (e.g. 6, 10 or 20 subject increments)

Figure 1 Flow chart of additional data and questions in the event of IA2 Pause and Review outcome (non-exhaustive list)



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.
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.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screen Failures	• Comprise all subjects who enrolled but are recorded as screen failures	• Screen Failures
Safety	• Comprise of all subjects who receive at least one complete dose of study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Safety • Efficacy
Pharmacokinetic (PK)	• Subjects in the 'Safety' population for whom a pharmacokinetic sample (plasma and/or BAL) was obtained and analysed.	• PK
Per Protocol 1 (PP1)	• Subjects in the 'Safety' population for whom the treatment actually received was the same one they were randomised to (**both** study drug and BAL sampling location) • Met the protocol defined inclusion/exclusion criteria (if criteria are changed during course of study apply the set applicable at the time of their enrolment) • Not an "open and shut" (inoperable) surgical case	• Efficacy
Per Protocol 2 (PP2)	• Subjects in the 'Safety' population for whom the study drug actually received was the same one they were randomised to (study drug) • Met the protocol defined inclusion/exclusion criteria (if criteria are changed during course of study apply the set applicable at the time of their enrolment) • Not an "open and shut" (inoperable) surgical case	• Efficacy

Population	Definition / Criteria	Analyses Evaluated
Per Protocol 3 (PP3)	• Subjects in the 'Safety' population for whom the BAL lung actually sampled was the same one they were randomised to • Met the protocol defined inclusion/exclusion criteria (if criteria are changed during course of study apply the set applicable at the time of their enrolment) • Not an "open and shut" (inoperable) surgical case	• Efficacy
Interim Analysis 1 (IA1)*	• Subjects in the 'Safety' population at the time of the Interim Analysis 1 data cut	• Outputs detailing population membership
Interim Analysis 2 (IA2)*	• Subjects in the 'Safety' population at the time of the Interim Analysis 2 data cut	• Outputs detailing population membership

NOTES :

- Please refer to Appendix 1: List of Data Displays which details the population to be used for each displays being generated.
- *= Population will only be produced to support the end of study reporting. Outputs required to support each of the interim analyses will use the applicable population at the time of the respective interim analysis data cut.

4.1. Protocol Deviations

- Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
    - For subjects involved in the interim analyses every effort will be made to review the (uncleaned) data from those subjects prior to unblinding those individuals. However given the interim database(s) may not be frozen these in-stream decisions may be revised if new information becomes apparent. Any such revision, and justification if necessary, would be noted in the study file.
    - This dataset will be the basis for the summaries and listings of protocol deviations.
- A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the 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
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Treatment States and Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Biomarker Details
11.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
11.10	Appendix 10: PVPI and EVLW – Supplementary Information
11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
11.12	Appendix 12: Details of Simulation exercise that produced operational characteristics used in the protocol
11.13	Appendix 13: Abbreviations & Trade Marks
11.14	Appendix 14: List of Data Displays
11.15	Appendix 15: 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 "Safety" 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 14: List of Data Displays.

Table 2 Overview of Planned Study Population Analyses

Display Type	Data Displays Generated		
	Table	Figure	Listing
Randomisation			
Randomisation			Y
Blind broken (excluding when part of interim analyses)			Y
Subject Accountability			
Study Population membership	Y		Y
Subject Disposition			
Disposition	Y		
Reasons for Screening Failures	Y		Y
Reasons for Withdrawals			Y
Important Protocol Deviations	Y		Y
Inclusion and Exclusion Criteria Deviations			Y
Demography			
Demographic Characteristics	Y		Y
Race & Racial Combinations	Y		Y
European Medicines Agency: Summaries for the European Clinical Trials Database (EudraCT)	Y		
Medical Condition & Concomitant Medications			
Concomitant Medication	Y		Y
Medical Conditions (Current and Past)	Y[1]		Y
Exposure			
Exposure			Y

NOTES :

- Y = Yes display generated.
- 1 = Summarise Current and Past conditions in separate tables

7. PRIMARY STATISTICAL ANALYSES

7.1. Efficacy Analyses

7.1.1. Overview of Planned Efficacy Analyses

Further details regarding Transpulmonary Thermodilution (TPTD) measurements are provided in Appendix 10: PVPI and EVLW – Supplementary Information.

The primary efficacy analyses will be based on the "Per Protocol 2" population, unless otherwise specified.

Table 3 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 14: List of Data Displays.

Table 3 Overview of Planned Efficacy 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
Transpulmonary Thermodilution														
PVPI				Y	Y	Y	Y[1.]				Y			Y[1.]
P_aO_2/F_iO_2				Y	Y	Y	Y[1]				Y			Y[1.]
Joint Modelling of PVPI and P_aO_2/F_iO_2	Y	Y	Y		Y									

NOTES :

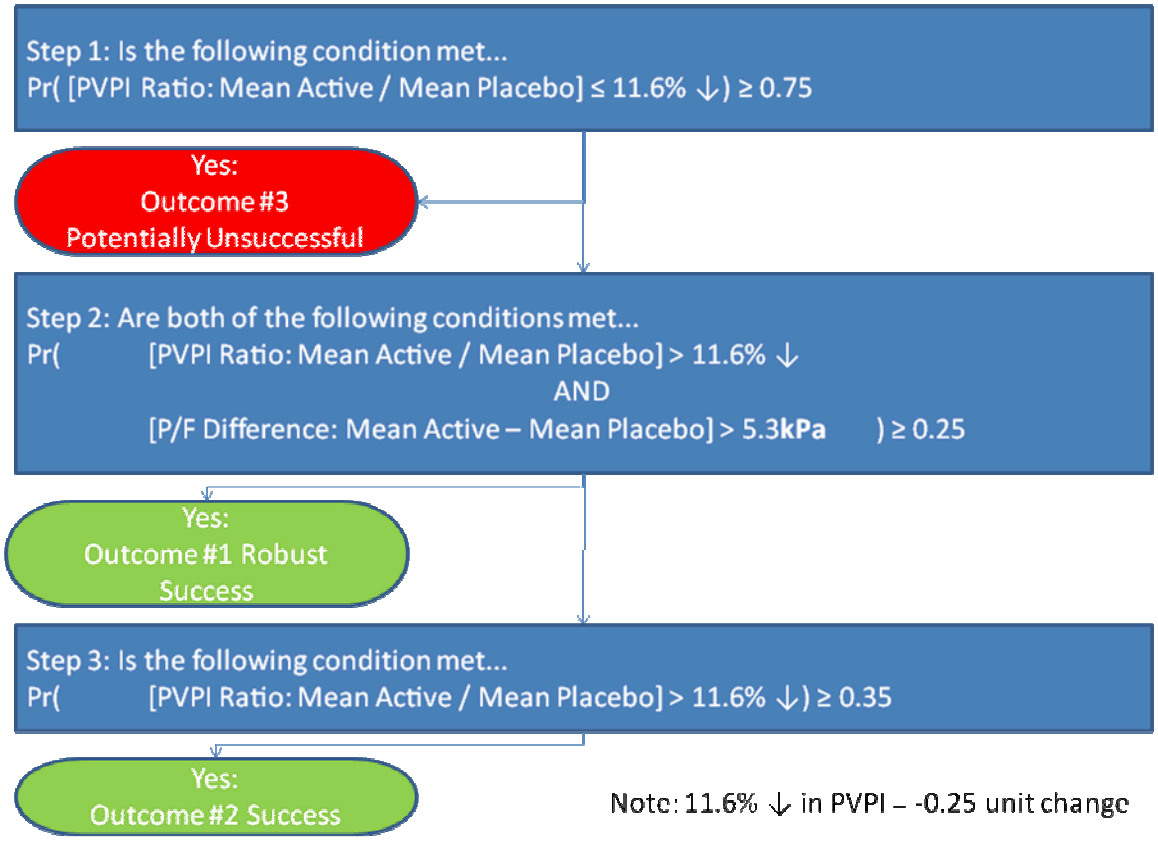
- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Natural logarithms of the observed response will be performed if it is deemed appropriate prior to modelling. If Natural logarithms are used results will be back-transformed for display purposes.

1. Listing should also flag any discrepancies between the eCRF supplied PVPI and any in-house GSK re-derivations.

Figure 2 shows the proposed End of Study Decision Pathway based on joint modelling of PVPI and P_aO_2/F_iO_2.

In crude terms decreases in PVPI and increases in P_aO_2/F_iO_2 (relative to the changes seen on the placebo arm) are the desired outcomes for the study drug.

Figure 2 End of Study Decision Pathway



Note: In Figure 2 statements such as " ≤ 11.6% ↓ " translate as "the decrease (active relative to placebo) is **less** than 11.6%; i.e. when the ratio of the treatment means (Act/Pbo) is **greater** than 0.884". The implication being that there is a 75% chance or more that study drug hasn't decreased PVPI enough and the outcome is "Potentially Unsuccessful".

The posterior probability of each Figure 2 outcome will be derived and, if it exceeds its respective confidence level, that outcome will be deemed to have occurred. Combinations of occurring outcomes imply the following four end of study states:

Overall success	≥1 of the "Success" outcomes	AND	0 "Failures"
Potentially Unsuccessful	0 "Success" outcomes	AND	1 "Failure"
Inconclusive	0 "Success" outcomes	AND	0 "Failures"
Inconsistent	≥1 of the "Success" outcomes	AND	1 "Failure"

Note: The primary analysis will only use the pre-op and immediate post op values of PVPI and P_aO_2/F_iO_2. Secondary analysis (a repeated measures version of the joint modelling) may also include the same set of timepoints and comparisons, but because the estimates across multiple timepoints may be correlated there may be minor differences in the results from the Primary and Secondary analysis models. In such a scenario the primary analysis model will take precedence. Only if the study statistician deems any

discrepancies to be large enough to be of concern will further discussion and/or comment be added to the CSR.

7.1.2. Planned Efficacy Statistical Analyses

Primary Statistical Analyses
Endpoint(s)
• PVPI and P_aO_2/F_iO_2 on completion of surgery • Baseline: PVPI and P_aO_2/F_iO_2 immediately prior to surgery (day 1) • Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics (PVPI is expected to require a Ln (natural logarithm) transformation) • Any observations with missing model covariates (e.g. baseline) would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates) • The above endpoints and baselines will be the average of any replicates available at the planned time points
Model Specification
• The (transformed) endpoints will be assumed to follow a multivariate normal distribution. Linear predictors will be derived for each subject (i.e. obtain a vector of means for the MVN distribution). Each treatment arm will also have a separate variance covariance matrix. • The linear predictors will consist of mean vectors to capture the effect of treatment for each endpoint and a variety of other model terms (an example is given at the end of this text). • Main Treatment Descriptors to be used (i.e. 4 levels of the treatment term) • No intercept terms should be fitted for either endpoint (due to fitting all 4 levels of treatment). • Baseline vectors will be fitted as continuous covariates (baseline values should be centered prior to inclusion in the model, centering to occur after any transformation of the individual subjects responses). • Categorical fixed effect vectors should be added for Center by Endpoint (if recruitment is such that center terms are poorly estimated then appropriate action will be taken, including but not limited to, pooling of centers or removal of the term from the model). • Non-informative priors will be utilized for each model parameter assigned either as a normal distribution centered on 0 with large variance 1E6 or as appropriate to the parameters distribution. • The prior for the variance covariance matrices Σ_{Pbo} and Σ_{Act} will be an inverse Wishart distribution (separate VCVs are not required for the BAL factor levels). • SAS PROC MCMC will be used to combine the non-informative priors with the data observed to obtain sufficient draws from the posterior distribution (after any thinning) such that the MCSE/SD values for parameters of interest are less than 0.01 (anticipated to be in the region of ~100,000 draws). If model convergence is poor then alternative initial parameter values should be considered. • The randomization seed used in PROC MCMC should itself be generated with an element of randomness - but there is no need to formally document this process (e.g. using Excel function RANDBETWEEN [1,9999999] and copying the result into the SAS code) • Combinations of the fitted model parameters will be used to answer the clinically relevant questions.

Primary Statistical Analyses

- Median values of the baseline adjusted response for each endpoint and their associated 95% credible intervals (equi-tailed) will be produced from the posterior distributions obtained via appropriate combinations of the fitted model parameters; akin to lease square means (e.g. Adjusted Pbo PVPI averaging over BAL = $\frac{\hat{\mu}_{PC,PVPI} + \hat{\mu}_{PV,PVPI}}{2} + \left(\sum_{i=1}^{\#centers} Center_i \Big/ \#Centers \right)$).
- The joint (bivariate) posterior probability distribution of the endpoints (averaging over BAL) will be obtained for the comparison(s) implied in Figure 2 by appropriate combinations of the fitted model parameters. The marginal posterior distributions for the comparisons for each endpoint will also be obtained from this joint posterior sample and be used to construct medians and 95% equi-tail credible intervals for individual endpoints.
- Flag variables (taking binary values of 1 or 0) will be created to evaluate the steps in the end of study decision pathway for each simulated draw from the joint posterior distribution (Figure 2). The mean of each flag variable over the MCMC iterations is the estimate of the desired probability, and should be used to assess which study outcome has been observed. These flag variables (and constrained variables) may cause SAS to issue warning or error messages to the log due to their binary nature, especially if the result is clear cut and their value rarely changes (such warnings/errors should be reviewed but may be safely discounted)
- In addition posterior probabilities of the differences (or ratios) for other cut-points (which may be determined upon inspection of the data, or from developing business requirements), may also be computed.
- Where applicable estimates would be derived at the means of any model covariates, akin to least squares means in PROC MIXED, and back transformed if necessary. When covariates are centered before the model fitting their mean is zero so the covariate can be dropped from the derivation.

  The following describes the anticipated linear predictor for an hypothetical subject from center 3, on active treatment, with BAL sampled from the collapsed lung and centered baseline values of -4.1 and -0.5 for P/F and PVPI respectively (note: additional covariates may be explored and added based on the observed data).

Primary Statistical Analyses

$$\begin{bmatrix} {}^{P/F} & {}^{PVPI} \\ \hat{y}_1 & \hat{y}_2 \end{bmatrix} = \begin{bmatrix} -4.1 & 0.5 \end{bmatrix} \begin{bmatrix} \hat{BS}_{P/F} & 0 \\ 0 & \hat{BS}_{PVPI} \end{bmatrix} +$$

$$\begin{bmatrix} I(C_1) & I(C_2) & I(C_3) & I(C_4) & I(C_5) \end{bmatrix} \begin{bmatrix} Center_{1,P/F} & Center_{1,PVPI} \\ Center_{2,P/F} & Center_{2,PVPI} \\ Center_{3,P/F} & Center_{3,PVPI} \\ Center_{4,P/F} & Center_{4,PVPI} \\ \text{Center}_{5,P/F} & \text{Center}_{5,PVPI} \end{bmatrix} +$$

$$I(Pbo, Collapsed) * \begin{bmatrix} \hat{\mu}_{PC,P/F} & \hat{\mu}_{PC,PVPI} \end{bmatrix} +$$
$$I(Pbo, Ventilated) * \begin{bmatrix} \hat{\mu}_{PV,P/F} & \hat{\mu}_{PV,PVPI} \end{bmatrix} +$$
$$I(Act, Collapsed) * \begin{bmatrix} \hat{\mu}_{AC,P/F} & \hat{\mu}_{AC,PVPI} \end{bmatrix} +$$
$$I(Act, Ventilated) * \begin{bmatrix} \hat{\mu}_{AV,P/F} & \hat{\mu}_{AV,PVPI} \end{bmatrix}$$

Where

$Center_5$ term(s) constrained to be zero and $I(\bullet)$ is an Indicator function with value 1 if condition met and zero otherwise [Here I(Pbo, Collapsed), I(Pbo, Ventialted), I(Act, Ventilated) = 0, I(Act, Collapsed) = 1, $I(C_3) = 1$ and $I(C_1), I(C_2), I(C_4)$ & $I(C_5) = 0$]

To link to observed data assume : $\begin{bmatrix} {}^{P/F} & {}^{PVPI} \\ y_1 & y_2 \end{bmatrix} \overset{MVN}{\sim} \left(\begin{bmatrix} {}^{P/F} & {}^{PVPI} \\ \hat{y}_1 & \hat{y}_2 \end{bmatrix}, [\Sigma_{Act}] \right)$ where Σ_{Pbo} & Σ_{Act} are 2x2 Variance Covariance matrices for the treatment arms (ignoring the BAL factor)

Posterior distributions are enumerated with appropriate combinations of $\hat{\mu}_{PC,P/F}, \hat{\mu}_{PC,PVPI}, \hat{\mu}_{PV,P/F}, \hat{\mu}_{PV,PVPI}, \hat{\mu}_{AC,P/F}$ & $\hat{\mu}_{AC,PVPI}, \hat{\mu}_{AV,P/F}$ & $\hat{\mu}_{AV,PVPI}$

e.g Sample from Posterior Distn for Diff in Mean P/F averaging over BAL factor =

$$\left(\frac{\hat{\mu}_{AC,P/F} + \hat{\mu}_{AV,P/F}}{2} \right) - \left(\frac{\hat{\mu}_{PC,P/F} + \hat{\mu}_{PV,P/F}}{2} \right)$$

Model Checking & Diagnostics

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
- Posterior distributions for the Interaction between Study Drug and BAL will be produced and examined as part of the model fitting process (separate distribution per endpoint). If any of the endpoints is deemed to have a non-zero interaction then the treatment comparisons (study drug) will be obtained within each level of BAL, for BOTH endpoints and the same decision pathway will be applied to each. An example of the combinations required to obtain the Interaction term for PVPI is

$$\left(\frac{\hat{\mu}_{PC,P/F} + \hat{\mu}_{AV,P/F}}{2} \right) - \left(\frac{\hat{\mu}_{PV,P/F} + \hat{\mu}_{AC,P/F}}{2} \right)$$

- A SAS coding trick may be required to fit separate variance covariance matrices to work around a known bug in the SASv9.3 TS1M2 MCMC procedure. Separate response variables

Primary Statistical Analyses
may be required for each treatment arm (with all values set to missing if the record was from a subject not on that treatment). Multiple MVN model statements would link these endpoints to a distinct VCV matrix. See MCMC training course notes "An intro. to Bayesian methods using SAS" by PPD GSK, February 2014" Slide 56+ for details.
Model Results Presentation
• Posterior treatment effects (adjusted Active and Placebo means averaging over the levels of BAL) and differences (or ratios) to placebo (marginals from the joint posterior probability distribution of the comparisons) will be displayed graphically. In addition a bivariate contour plot of the joint posterior distribution for the comparisons in Figure 2 may be produced (with the decision criteria overlaid onto it and the marginal distributions displayed) – this may require bespoke programming. • Median and 95% (equi-tail) credible intervals for the LSmean equivalents and Median and 95% (equi-tail) credible intervals for differences (or ratios) to placebo will be summarized. • Posterior probabilities for the end of study decision pathway (and other cut points)

Sensitivity and Supportive Statistical Analyses
• Other potential *a priori* covariates include "Endpoint by duration of surgical procedure" and "Endpoint by duration of one lung ventilation" interaction terms. Each duration term would enter the model as a centered continuous covariate. The study statistician may explore the appropriateness of these terms, and whether they should enter as linear or higher order terms via scatterplots of covariate vs each endpoint. Given the relatively small sample sizes and exploratory nature of the trial the final analysis model used to make inferences may be selected via a combination of expert judgment and formal statistical model selection techniques (e.g. Bayes factors). • Intermediate model building outputs would not need to be formally reported – only the final chosen model would have associated Tables, Figures and Listings. • Optional (at discretion of study statistician): For robustness, assuming non-informative priors are used, the equivalent PROC MIXED model may be fitted and the LSMeans and estimates of differences compared to the results obtained from the PROC MCMC analysis. Output from this analysis may be listed as a stand alone output or as part of the MCMC raw SAS listings (conditional on PROC MIXED being used) – with no corresponding Tables or Figures. • The above analyses may be repeated using the Per Protocol 1 population if deemed necessary by the study statistician

8. SECONDARY STATISTICAL ANALYSES

8.1. Efficacy Analyses

8.1.1. Overview of Planned Efficacy Analyses

The secondary efficacy analyses will be based on the "Per Protocol 2" population, unless otherwise specified.

Table 4 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 4 Overview of Planned Efficacy 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
Transpulmonary Thermodilution[5]														
Joint Modelling of PVPI and P_aO_2/F_iO_2	Y	Y	Y		Y[1]									
Pulmonary Vascular Permeability Index (PVPI)	Y	Y	Y	Y	Y	Y	Y				Y			Y
Extravascular Lung Water Index (EVLWI)[4]	Y	Y	Y	Y	Y	Y	Y[2]				Y			Y[3]
Extravascular Lung Water (EVLW)							Y[2]							
Arterial Line Used				Y[7]			Y							
Cardiac Output (CO)							Y[2]							
Cardiac Index (CI)[4]				Y			Y[2]				Y			Y[3]
Global End-Diastolic Volume (GEDV)							Y[2]							
Global End-Diastolic Volume Index (GEDI)[4]				Y			Y[2]				Y			Y[3]
Mean Arterial Pressure (MAP)				Y			Y				Y			Y
Systemic Vascular Resistance (SVR)							Y							
Systemic Vascular Resistance Index (SVRI)[4]				Y			Y				Y			Y
Stroke Volume Variation (SVV)				Y			Y				Y			Y
Global Ejection Fraction (GEF)				Y			Y				Y			Y
Heart Rate (HR)				Y			Y				Y			Y
Blood Pressure (AP): Systolic and Diastolic				Y			Y				Y			Y
Central Venous				Y			Y				Y			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
Pressure (CVP)														
Predicted Body Weight[4]				Y			Y							
Predicted Body Surface Area[4]				Y			Y							
Body Surface Area[4]				Y			Y							
Oxygenation														
P_aO_2/F_iO_2 [4]	Y	Y	Y	Y	Y	Y	Y				Y			Y
SpO_2/F_iO_2 [4]				Y	Y	Y	Y				Y			Y
Correlation between P_aO_2/F_iO_2 and SpO_2/F_iO_2 [4]					Y[1]									
Mean Airway Pressure (Paw)				Y			Y				Y			Y
Oxygenation Index				Y			Y				Y			Y
SOFA														
SOFA scores[6]	Y	Y	Y	Y		Y	Y				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. Represented as scatterplot matrix
2. List replicate values and the derived mean
3. Derive mean of the replicate values prior to computing the change from baseline
4. Derived in house by GSK from data collected on eCRF.
5. Site instructed to set up machine to display the Absolute values and not the corresponding indexed values. If the site omitted to do this (monitors examining the PDF hard copy of the PiCCO output is an example of how GSK may be alerted) then GSK will derive corresponding absolute versions using the formulas in Section 11.5.4.
6. Add footnotes to change from baseline SOFA outputs explaining the strong assumptions required to obtain the Baseline (see Section 11.4.2.1)
7. Summarise the Number of distinct individuals and % of big N for each Response category

8.1.2. Planned Efficacy Statistical Analyses

Secondary Statistical Analyses (Repeated Measures Joint Modelling of PVPI and PaO2/FiO2)
Endpoint(s)
• All Post Surgery PVPI and P_aO_2/F_iO_2 • Baseline: PVPI and P_aO_2/F_iO_2 immediately prior to surgery (day 1) • Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics (PVPI is expected to require a Ln (natural logarithm) transformation) • Any observations with missing model covariates (e.g. baseline) would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates) • The above endpoints and baselines will be the average of any replicates available at the

Secondary Statistical Analyses (Repeated Measures Joint Modelling of PVPI and PaO2/FiO2)
planned time points
Model Specification
• Repeated measures version of the primary analysis (Section 7.1.2). Only changes related to the repeated measures are described in detail. • 4x Post surgery Planned Timepoints: on completion of surgery day1, day 2 day 3 and day 4 (where available) • Center by endpoint model parameters to be duplicated in the linear predictor (one repeat for each planned timepoint) • Additional model parameters (continuous & centered) to capture the Baseline by planned timepoint interaction • Obtain Bivariate and associated marginal distributions for the active Vs placebo comparisons (averaging over levels of BAL sampling) for each planned timepoint • Care should be taken in how the data are sorted/arranged, since the ordering of variables will now contain information on both endpoint and timepoint. A simplified example linear predictor is shown below for baseline, immediately post op day1 and day 2 timepoints for a hypothetical subject from center 3, on active treatment, with BAL sampled from the collapsed lung with centered baseline values of -4.1 and -0.5 for P/F and PVPI respectively (note: additional covariates may be explored and added based on the observed data and the additional timepoints would be added in a similar style and alternative orderings of the data may be used if easier to implement in SAS) :

Secondary Statistical Analyses (Repeated Measures Joint Modelling of PVPI and PaO2/FiO2)

$$\begin{bmatrix} \overset{P/F}{\underset{D1}{}} & \overset{P/F}{\underset{D2}{}} & \overset{PVPI}{\underset{D1}{}} & \overset{PVPI}{\underset{D2}{}} \\ \hat{y}_1 & \hat{y}_2 & \hat{y}_3 & \hat{y}_4 \end{bmatrix} = \left[I(C_1) \;\; I(C_2) \;\; I(C_3) \;\; I(C_4) \;\; I(C_5) \right] *$$

$$\begin{bmatrix} Center_{1,P/F} & Center_{1P/F} & Center_{1,PVPI} & Center_{1,PVPI} \\ Center_{2,P/F} & Center_{2,P/F} & Center_{2,PVPI} & Center_{2,PVPI} \\ Center_{3,P/F} & Center_{3,P/F} & Center_{3PVPI} & Center_{3,PVPI} \\ Center_{4P/F} & Center_{4,P/F} & Center_{4PVPI} & Center_{4,PVPI} \\ \text{Center}_{5,P/F} & \text{Center}_{5P/F} & \text{Center}_{5,PVPI} & \text{Center}_{5,PVPI} \end{bmatrix} +$$

$$\left[-4.1 \;\; -4.1 \;\; 0.5 \;\; 0.5 \right] \left[Diag\left(\hat{B}S_{D1,P/F} \;\; \hat{B}S_{D2,P/F} \;\; \hat{B}S_{D1,PVPI} \;\; \hat{B}S_{D2,PVPI} \right) \right] +$$

$$I(Pbo, Coll) * \left[\hat{\mu}_{D1,PC,P/F} \;\; \hat{\mu}_{D2,PC,P/F} \;\; \hat{\mu}_{D1,PC,PVPI} \;\; \hat{\mu}_{D2,PC,PVPI} \right] +$$

$$I(Pbo, Vent) * \left[\hat{\mu}_{D1,PV,P/F} \;\; \hat{\mu}_{D2,PV,P/F} \;\; \hat{\mu}_{D1,PV,PVPI} \;\; \hat{\mu}_{D2,PV,PVPI} \right] +$$

$$I(Act, Coll) * \left[\hat{\mu}_{D1,AC,P/F} \;\; \hat{\mu}_{D2,AC,P/F} \;\; \hat{\mu}_{D1,AC,PVPI} \;\; \hat{\mu}_{D2,AC,PVPI} \right] +$$

$$I(Act, Vent) * \left[\hat{\mu}_{D1,AV,P/F} \;\; \hat{\mu}_{D2,AV,P/F} \;\; \hat{\mu}_{D1,AV,PVPI} \;\; \hat{\mu}_{D2,AV,PVPI} \right]$$

Where

$Center_5$ term(s) constrained to be zero and $I(\bullet)$ is an Indicator function

with value 1 if condition met and zero otherwise [Here I(Pbo, Coll), I(Pbo, Vent), I(Act, Vent) = 0, I(Act, Coll) = 1, $I(C_3) = 1$ and $I(C_1), I(C_2), I(C_4)$ & $I(C_5) = 0$]

To link to observed data assume :

$$\begin{bmatrix} \overset{P/F}{\underset{D1}{}} & \overset{P/F}{\underset{D2}{}} & \overset{PVPI}{\underset{D1}{}} & \overset{PVPI}{\underset{D2}{}} \\ y_1 & y_2 & y_3 & y_4 \end{bmatrix} \overset{MVN}{\sim} \left(\begin{bmatrix} \overset{P/F}{\underset{D1}{}} & \overset{P/F}{\underset{D2}{}} & \overset{PVPI}{\underset{D1}{}} & \overset{PVPI}{\underset{D2}{}} \\ \hat{y}_1 & \hat{y}_2 & \hat{y}_3 & \hat{y}_4 \end{bmatrix}, \left[\Sigma_{Act} \right] \right)$$ where Σ_{Act} is a 4x4

Variance Covariance matrix for the active treatment arm

Posterior distributions are enumerated with appropriate combinations of

$\hat{\mu}_{D1,PC,P/F}, \hat{\mu}_{D1,PV,P/F}, \hat{\mu}_{D1,PC,PVPI}, \hat{\mu}_{D1,PV,PVPI}, \hat{\mu}_{D1,AC,P/F}, \hat{\mu}_{D1,AV,P/F}, \hat{\mu}_{D1,AC,PVPI}, \hat{\mu}_{D1,AV,PVPI},$

$\hat{\mu}_{D2,PC,P/F}, \hat{\mu}_{D2,PV,P/F}, \hat{\mu}_{D2,PC,PVPI}, \hat{\mu}_{D2,PV,PVPI}, \hat{\mu}_{D2,AC,P/F}, \hat{\mu}_{D2,AV,P/F}, \hat{\mu}_{D2,AC,PVPI}, \hat{\mu}_{D2,AV,PVPI}$

e.g Sample from Posterior Distn for Day 2 Diff in Mean P/F averaging over BAL =

$$\left(\frac{\hat{\mu}_{D2,AC,P/F} + \hat{\mu}_{D2,AV,P/F}}{2} \right) - \left(\frac{\hat{\mu}_{D2,PC,P/F} + \hat{\mu}_{D2,PV,P/F}}{2} \right)$$

Model Checking & Diagnostics

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
- Checks similar to those for the Primary analysis of the interaction terms for Study Drug and BAL within each timepoint will be produced and if any of them suggest an interaction then ONLY the treatment comparisons within THAT timepoint only will be modified to account for the location of the BAL sampling

Model Results Presentation

- Sets of outputs analogous to the Primary analysis will be produced for each planned timepoint;

Secondary Statistical Analyses (Repeated Measures Joint Modelling of PVPI and PaO2/FiO2)
although the end of study decision pathway would not be applied to the resulting probabilities.
Sensitivity and Supportive Statistical Analyses
• A similar approach will be performed to the primary analysis. Refer to the Sensitivity and Supportive Statistical Analyses within the Primary Analysis Section 7.1.2 • The analysis may be repeated using the exploratory endpoint (Imputed PaO2/FiO2).

Secondary Statistical Analyses (Univariate analyses – post surgery timepoint only)
Endpoint(s)
• PVPI on completion of surgery • EVLWI on completion of surgery • P_aO_2/F_iO_2 on completion of surgery
Model Specification
• A similar Bayesian repeated measures modeling approach will be implemented (c.f. the Joint modeling approach in the Secondary Analysis of PVPI and P_aO_2/F_iO_2; but with only one endpoint). • If deemed necessary natural logarithms of the observed responses may be implemented on a per endpoint basis.
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. • Checks similar to those for the Primary analysis of the interaction terms for Study Drug and BAL within each timepoint may be produced
Model Results Presentation
• Posterior means and treatment ratios will be displayed graphically. • Median, mean and 95% credible intervals for treatment means and ratios of all time points, to immediately prior to surgery. • Posterior probabilities that the ratios at all time points are less than 1, and other specific values
Sensitivity and Supportive Statistical Analyses
• A similar approach will be performed to the primary analysis. Refer to the Sensitivity and Supportive Statistical Analyses within the Primary Analysis Section 7.1.2
Secondary Statistical Analyses (SOFA)
Endpoint(s)
• SOFA scores on Day 2 through to Day 4.
Model Specification
• A Bayesian repeated measures model will be fit to SOFA scores (observed and imputed) measured on Day 2, Day 3 and Day 4. The following categorical terms will be fit in the model: Day, Treatment and Treatment * Day, where Day is the repeated measures factor and treatment uses the 4x main treatment levels. An assessment will be made by the study statistician regarding including Baseline SOFA as a continuous covariate. The model will assume non-informative priors for all parameters. The modeling will implicitly combine the BAL sampling levels by study drug arm. The adjusted means for each Study Drug by Day will be obtained and the posterior distributions of these quantities will be displayed graphically, and the median and 95% credible interval (equi-tailed) will be calculated. Posterior distributions of (combined) Active - Placebo for each post surgery time point will be generated. The posterior

Secondary Statistical Analyses (Univariate analyses – post surgery timepoint only)
probabilities that these differences, representing the true effect size, at each time point are less than 0, less than -1, less than -2 and less than -3 will be produced, in addition to other values which will be determined upon inspection of the data.
Model Checking & Diagnostics
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. • Checks similar to those for the Primary analysis of the interaction terms for Study Drug and BAL within each timepoint may be produced
Model Results Presentation
• Adjusted medians and 95% credible intervals will be presented for each study drug by day, together with the median estimated study drug differences (Active – Placebo) and the corresponding 95% credible intervals. • Plots of medians and 95% credible intervals from the model will be generated for each study drug by time point. Additionally, plots of differences and 95% credible intervals for the comparison of interest will be generated • Bayesian posterior probabilities that the true differences for each of the active treatments and placebo are greater than various levels will be produced, assuming non informative priors
Sensitivity and Supportive Statistical Analyses
• A similar approach will be performed to the primary analysis. Refer to the Sensitivity and Supportive Statistical Analyses within the Primary Analysis Section 7.1.2

8.2. Safety Analyses

8.2.1. Overview of Planned Analyses

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

Table 5 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 5 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
All AE's[1]	Y			Y				
All Drug-related AE's	Y							
Serious AE's	Y			Y				
Withdrawal AE's				Y				
European Medicines Agency: Summaries for the European Clinical Trials Database (EudraCT)	Y							
Clinical Laboratory								
Clinical Chemistry[2]	Y			Y				
Hematology[2]	Y			Y				
Urinalysis[3]	Y							
ECG								
ECG Findings	Y			Y	Y			
ECG Values	Y			Y[4]				
Vital Signs								
Vitals Values	Y			Y				
Immunogenicity								
Immunogenicity results	Y			Y				
Surgical Procedure								
Subject level information related to the Surgical Procedure				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. Listings will include subject's numbers for individual AE's & AE system organ classes, preferred terms and verbatim text.
2. Listings of chemistry (and/or haematology) abnormalities of PCI and all values for subjects with chemistry (and/or haematology) abnormalities of PCI. CRP to be excluded from these summaries (but will be included in the Biomarker outputs)
3. Urinalysis results may be mapped to common nomenclatures prior to summarising
4. Listings of ECG values of PCI and all ECG values for subjects with any PCI

8.3. Pharmacokinetic Analyses

8.3.1. Overview of Planned Pharmacokinetic Analyses

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

Table 6 provides an overview of the planned analyses, with full details being presented in Appendix 14: List of Data Displays.

Table 6 Overview of Planned Pharmacokinetic Analyses

Endpoint / Parameter/ Display Type	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Blood														
Plasma Drug Concentration				Y	Y	Y	Y					Y	Y	
Derived PK Parameters				Y			Y				Y			
BAL														
BAL Drug Concentration							Y							
Plasma Urea & BAL Urea							Y							
Dilution Factor							Y							
Volume of ELF fluid[1.]				Y			Y							
Volume of BAL fluid							Y							
Total Drug in BAL fluid							Y							
Derived ELF Drug Concentration[1.]				Y			Y					Y		

NOTES :

- T = Table, F = Figure, L = Listings, Y = 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. Corrected for Dilution Factor.

8.3.2. Drug Concentration Measures

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

8.3.3. Pharmacokinetic Parameters

8.3.3.1. Deriving Pharmacokinetic Parameters

- Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 11.4.3 Reporting Process & Standards).

- The pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using WinNonLin Phoenix.
- All calculations of non-compartmental parameters will be based on actual sampling times.
- Pharmacokinetic parameters described in Table 7 will be determined from the plasma concentration-time data, as data permits.

Table 7 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
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**

NOTES:

- Additional parameters may be included as required.
- Lambda_z is the terminal phase rate constant estimated by linear regression analysis of the loge transformed concentration-time data

Section 11.5.5 details the BAL PK parameters to be derived, as data permits. These too will be summarised and listed.

8.3.3.2. Statistical Analysis of Pharmacokinetic Parameters

There will be no formal statistical analyses of the pharmacokinetic parameter data. PK parameters will be calculated based on the available data and listed.

8.4. Pharmacodynamic (Biomarker) Analyses

8.4.1. Overview of Planned Pharmacodynamic (Biomarker) Analyses

The pharmacodynamic analyses will be based on the "Per Protocol 2" population, unless otherwise specified (e.g. for BAL related analyses which use "Per Protocol 1"). Further details of the biomarkers can be found in Appendix 8.

Table 8 provides an overview of the **planned** pharmacodynamic (Biomarker) analyses, with full details of data displays being presented in Appendix 14: List of Data Displays. Additional biomarkers may be added (or removed), and will follow a similar analysis strategy and any additional outputs would take the next available number.

Table 8 Overview of Planned Pharmacodynamic (Biomarker) Analyses

Endpoint / Parameter/ Display Type	Untransformed/Transformed as appropriate													
	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
BAL														
Free sTNFR1	Y	Y	Y	Y	Y		Y							
Total sTNFR1	Y	Y	Y	Y	Y		Y							
Complex sTNFR1	Y	Y	Y	Y	Y		Y							
TNFa	Y	Y	Y	Y	Y		Y							
IL-6	Y	Y	Y	Y	Y		Y							
IL-8	Y	Y	Y	Y	Y		Y							
IL-1b	Y	Y	Y	Y	Y		Y							
MCP-1	Y	Y	Y	Y	Y		Y							
CRP$^{\Delta}$	Y	Y	Y	Y	Y		Y							
IL-1ra	Y	Y	Y	Y	Y		Y							
IL-10	Y	Y	Y	Y	Y		Y							
Total protein	Y	Y	Y	Y	Y		Y							
Total protein ratio	Y	Y	Y	Y	Y		Y							
Surfactant Protein D (SP-D)	Y	Y	Y	Y	Y		Y							
RAGE	Y	Y	Y	Y	Y		Y							
CC16	Y	Y	Y	Y	Y		Y							
vWF	Y	Y	Y	Y	Y		Y							
sICAM	Y	Y	Y	Y	Y		Y							
MPO	Y	Y	Y	Y	Y		Y							
Serum (Plasma when suffixed by [Plasma])														
Free sTNFR1	Y	Y	Y	Y	Y	Y	Y				Y			Y
Total sTNFR1	Y	Y	Y	Y	Y	Y	Y				Y			Y
Complex sTNFR1	Y	Y	Y	Y	Y	Y	Y				Y			Y
IL-6	Y	Y	Y	Y	Y	Y	Y				Y			Y
IL-8	Y	Y	Y	Y	Y	Y	Y				Y			Y
CRP$^{\Delta}$	Y	Y	Y	Y	Y	Y	Y				Y			Y
Total Protein [Plasma]	Y	Y	Y	Y	Y	Y	Y				Y			Y
Surfactant Protein D (SP-D)	Y	Y	Y	Y	Y	Y	Y				Y			Y

Endpoint / Parameter/ Display Type	Untransformed/Transformed as appropriate													
	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
RAGE	Y	Y	Y	Y	Y	Y	Y				Y			Y
CC16	Y	Y	Y	Y	Y	Y	Y				Y			Y
vWF	Y	Y	Y	Y	Y	Y	Y				Y			Y
sICAM	Y	Y	Y	Y	Y	Y	Y				Y			Y
MPO	Y	Y	Y	Y	Y	Y	Y				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 (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.
- Δ=Run as part of Clinical Chemistry Labs – and therefore may have different timepoints and require subsequent adjustments to the model / displays. For BAL there is only a single timepoint

8.4.2. Planned Pharmacodynamic (Biomarker) Statistical Analyses

Planned Statistical Analyses (BAL Biomarkers)

Endpoint(s)

- Absolute value of BAL biomarker (separate analysis per biomarker)
- Any observations with missing model covariates would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates)

Model Specification

- For each biomarker, the values will be inspected to determine whether a data transformation is required.
- Main Treatment Descriptors to be used (i.e. 4 levels of the treatment term)
- No intercept terms should be fitted for either endpoint (due to fitting all 4 levels of treatment).
- Categorical fixed effect should be added for Center (if recruitment is such that center terms are poorly estimated then appropriate action will be taken, including but not limited to, pooling of centers or removal of the term from the model).
- Non-informative priors will be utilized for each model parameter assigned either as a normal distribution centered on 0 with large variance 1E6 or as appropriate to the parameters distribution.
- Separate Variance parameters for each treatment arm.
- SAS PROC MCMC will be used to combine the non-informative priors with the data observed to obtain sufficient draws from the posterior distribution (after any thinning) such that the MCSE/SD values for parameters of interest are less than 0.01 (anticipated to be in the region of ~100,000 draws). If model convergence is poor then alternative initial parameter values should be considered.
- The randomization seed used in PROC MCMC should itself be generated with an element of randomness - but there is no need to formally document this process (e.g. using Excel function RANDBETWEEN [1,9999999] and copying the result into the SAS code)
- Combinations of the fitted model parameters will be used to answer the clinically relevant questions.
- Median values of the adjusted response for each level of the main treatment descriptors and their associated 95% credible intervals (equi-tailed) will be produced from the posterior

Planned Statistical Analyses (BAL Biomarkers)
distributions obtained via appropriate combinations of the fitted model parameters; akin to lease square means • Posterior distributions will be obtained for the Active vs Placebo comparison within each level of the BAL sampling. These distributions will be used to determine the probability of any reduction and any increase c.f. placebo. In addition posterior probabilities of the differences (or ratios) for other cut-points (which may be determined upon inspection of the data, or from developing business requirements), may also be computed. • Where applicable estimates would be derived at the means of any model covariates, akin to least squares means in PROC MIXED, and back transformed if necessary. When covariates are centered before the model fitting their mean is zero so the covariate can be dropped from the derivation.
Model Checking
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. • Potential covariates may also be explored (e.g. duration of surgery, age, gender). Only outputs from the final model will be reported
Model Results Presentation
• By subject time profiles of biomarkers will be produced. • Scatterplot matricies of the correlation structures between BAL biomarkers may be produced. • Median and 95% (equi-tail) credible intervals for the LSmean equivalents and Median and 95% (equi-tail) credible intervals for differences (or ratios) to placebo will be summarized. • Posterior probabilities for the cut points

Planned Statistical Analyses (Serum Biomarkers)
Endpoint(s)
• Absolute value of serum biomarker response (separate analysis per biomarker) • Timepoints: Day 1 (on completion of surgery), day 2, day 3, day 4 and day 8 • Baseline: day 1 (Pre-dose) • Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics (all biomarkers are expected to require a Ln (natural logarithm) transformation) • Any observations with missing model covariates (e.g. baseline) would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates)
Model Specification
• The (transformed) endpoints will be assumed to follow a multivariate normal distribution. Linear predictors will be derived for each subject (i.e. obtain a vector of means for the MVN distribution). Each treatment arm will also have a separate variance covariance matrix. • The linear predictors will consist of mean vectors to capture the effect of treatment for each time point and a variety of other model terms (an example is given at the end of this text). • Main Treatment Descriptors to be used (i.e. 4 levels of the treatment term) • No intercept terms should be fitted for either endpoint (due to fitting all 4 levels of treatment). • Baseline vectors will be fitted as continuous covariates (baseline values should be centered prior to inclusion in the model, centering to occur after any transformation of the individual subjects responses).

Planned Statistical Analyses (Serum Biomarkers)
• Categorical fixed effect vectors should be added for Center (if recruitment is such that center terms are poorly estimated then appropriate action will be taken, including but not limited to, pooling of centers or removal of the term from the model). • Non-informative priors will be utilized for each model parameter assigned either as a normal distribution centered on 0 with large variance 1E6 or as appropriate to the parameters distribution. • Each of the 4x variance covariance matrices will use an inverse Wishart distribution as its prior. • SAS PROC MCMC will be used to combine the non-informative priors with the data observed to obtain sufficient draws from the posterior distribution (after any thinning) such that the MCSE/SD values for parameters of interest are less than 0.01 (anticipated to be in the region of ~100,000 draws). If model convergence is poor then alternative initial parameter values should be considered. • The randomization seed used in PROC MCMC should itself be generated with an element of randomness - but there is no need to formally document this process (e.g. using Excel function RANDBETWEEN [1,9999999] and copying the result into the SAS code) • Combinations of the fitted model parameters will be used to answer the clinically relevant questions. • Median values of the baseline adjusted response for each treatment by timepoint combination and their associated 95% credible intervals (equi-tailed) will be produced from the posterior distributions obtained via appropriate combinations of the fitted model parameters; akin to lease square means • Posterior distributions will be obtained for the Active vs Placebo comparison within each level of the BAL sampling for each time point. These distributions will be used to determine the probability of any reduction and any increase c.f. placebo. In addition posterior probabilities of the differences (or ratios) for other cut-points (which may be determined upon inspection of the data, or from developing business requirements), may also be computed. • Where applicable estimates would be derived at the means of any model covariates, akin to least squares means in PROC MIXED, and back transformed if necessary. When covariates are centered before the model fitting their mean is zero so the covariate can be dropped from the derivation.
Model Checking
• Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses. • Potential covariates may also be explored (e.g. duration of surgery, age, gender). Only outputs from the final model will be reported
Model Results Presentation
• By subject time profiles of biomarkers will be produced. • Scatterplot matricies of the correlation structures between BAL biomarkers may be produced (one page per timepoint – including baseline). • Median and 95% (equi-tail) credible intervals for the LSmean equivalents and Median and 95% (equi-tail) credible intervals for differences (or ratios) to placebo will be summarized. • Posterior probabilities for the cut points

9. OTHER STATISTICAL ANALYSES

9.1. Exploratory Statistical Analyses

The strategy for each exploratory endpoint is to list and summarise by Study Medication (i.e. Assume BAL sampling location is irrelevant). Subsequent statistical analysis may be conditional on the observed data (at the discretion of the study statistician) and methods would be documented in the CSR.

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 14: List of Data Displays.

Table 9 Overview of Planned Exploratory Statistical Analyses

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Clinical Outcomes								
Diagnosis of ARDS out to day 28	Y			Y				
28 day survival	Y	Y		Y				
Organ failure free days out to day 28	Y			Y				
Resource Utilisation								
Ventilator Free Days	Y			Y				
ICU Length of Stay	Y			Y				
Hospital Length of Stay	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.

10. REFERENCES

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11. APPENDICES

Section	Component
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Time & Events
11.3	Appendix 3: Treatment States and Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Biomarker Details
11.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
11.10	Appendix 10: PVPI and EVLW – Supplementary Information
11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
11.12	Appendix 12: Details of Simulation exercise that produced operational characteristics used in the protocol
11.13	Appendix 13: Abbreviations & Trade Marks
11.14	Appendix 14: List of Data Displays
11.15	Appendix 15: Example Mock Shells for Data Displays

11.1. Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population

11.1.1. Exclusions from Per Protocol Populations

A subject meeting any of the following criteria will be excluded from the Per Protocol population:

Per Protocol Population ID	Number	Exclusion Description
1	01	Subject did not satisfy all of the inclusion and exclusion criteria (from whichever version of the protocol was active at the time of their enrolment)
	02	Subject did not receive either i) the study drug they were randomised to, or ii) the actual BAL lung sampled was not the one they were randomised to have sampled
	03	Subject was classified as inoperable upon commencement of surgical procedures (an “open and shut” case)
2	01	Subject did not satisfy all of the inclusion and exclusion criteria (from whichever version of the protocol was active at the time of their enrolment)
	02	Subject did not receive the study drug they were randomised to
	03	Subject was classified as inoperable upon commencement of surgical procedures (an “open and shut” case)
3	01	Subject did not satisfy all of the inclusion and exclusion criteria (from whichever version of the protocol was active at the time of their enrolment)
	02	Actual BAL lung sampled for the subject was not the one they were randomised to have sampled
	03	Subject was classified as inoperable upon commencement of surgical procedures (an “open and shut” case)

NOTES:

- The above definitions may be modified during the in-stream protocol deviation reviews (for example, subjects who were deemed to be in-operable upon commencement of their surgical procedure may be added to each of the per protocol populations – this may require anecdotal evidence followed up by bespoke communications between GSK and the sites as it is not possible to guarantee such scenarios could be accurately defined using rules based on duration of surgery alone)
  A planned eCRF update should add a variable indicating if an individual was an “open and shut case”. Prior to this update manual coding may be required to correctly compute the above populations (and also if the new variable is not retrospectively populated for existing subjects, e.g. those in IA1)

11.2. Appendix 2: Time & Events

11.2.1. Protocol Defined Time & Events

Table 10 Time and Events Table (Screening)

Procedures	Screening (7 to 28 days inclusive prior to surgery)	1. Rest the subject in a supine or semi-recumbent position for at least 5 min and then take three measurements 5 minutes apart. 2. HIV testing dependent on local practice 3. If repeat screening is required previous results from ADA screening and Quantiferon-GOLD testing can be used for up to 60 days.
Informed Consent	X	
Demography	X	
Medical History	X	
Smoking Status & History	X	
Quantiferon-GOLD for TB[3]	X	
HepB, HepC, HIV testing[2]	X	
Inclusion/Exclusion Criteria	X	
Concomitant Medication	X	
Physical Examination	X	
Vital Signs	X	
12-lead ECG[1]	X	
Serious Adverse Events	X	
Clinical Labs including Haematology and Chemistry	X	
Pre-existing ADA screening[3]	X	
Pharmacogenetics (PGx) sample[3]	X	
IVRS	X	

Table 11 Time and Events Table Day 1

Procedures	Pre-dose[4]	0 h[1]	1 h	Immediately prior or at start of surgery	On completion of surgery	
Randomisation	X[2]					1. Dosing may occur 1-5 hours prior to surgery 2. Randomisation & associated IVRS activities may be conducted up-to 72 hours prior to administration of study treatment. 3. Only applicable at designated sites 4. Can be taken up to 24 hours prior to dosing 5. If 12 lead ECG is not available, monitoring by 3 lead ECG/telemetry (or similar) is acceptable NB: Time points (except pre-dose) refer to post-start of drug administration on Day 1. Pre-dose is defined as the time from admission to hospital up to the administration of study treatment.
Brief Physical Examination	X					
Concomitant Medication	X					
IVRS	X[2]					
Vital Signs	X		X			
12-lead ECG	X		X[5]			
Adverse Events	X					
Serious Adverse Events	X					
Clinical Labs including Haematology and Chemistry	X					
Blood sample for immunogenicity	X					
Blood sample for PK	X		X		X	
Blood sample for urea and total protein					X	
Blood samples for translational sub-study[3]	X				X	
Sample for Urinalysis	X					
Blood sample for serum biomarkers	X				X	
Nebulised (IH) Study Treatment		X				
Transpulmonary thermodilution				X	X	
P/F Ratio: • Arterial blood sample • Record FiO_2				X	X	
Measure SpO_2 using pulse oximetry				X	X	
BAL Sampling					X	

Table 12 Time and Events Table (Days 2 to 28)

Procedures	Day 2	Day 3	Day 4	Daily until discharge	Day 8[1]	Day of discharge	Day 28 (FU) ±3 days
Concomitant Medication	X	X	X	X		X	X
IVRS						X	X
Transpulmonary thermodilution[2]	X	X	X				
P/F Ratio • Arterial blood sample (as	X	X	X				
Measure SpO_2 using pulse oximetry	X	X	X				
Additional SOFA Components[3] • Glasgow Coma Score (GCS) • Record Mean Arterial Pressure[4] or administration of vasopressors required • Bilirubin • Platelets • Creatinine (or urine output)	X	X	X				
Vital Signs			X			X	X
12-lead ECG	X		X			X	
Adverse Events	X	X	X	X	X	X	X
Serious Adverse Events	X	X	X	X	X	X	X
Clinical Labs including Haematology and Chemistry	X	X	X		X		
Blood sample for serum	X	X	X		X		
Blood samples for translational sub-study[5]	X						
Blood sample for Immunogenicity					X		X
Blood sample for PK	X[6]	X[7]					
Sample for Urinalysis					X		

1. If discharged before Day 8 take blood and urine samples on day of discharge
2. PVPI will be measured via single-indicator transpulmonary thermodilution as long as the subject remains in the ICU with a patent indwelling PiCCO catheter, up to Day
3. Sequential Organ Failure Assessment (SOFA) Score will only be calculated up to Day 4.
4. If no arterial blood sample calculate MAP using equation: 2X diastolic blood pressure + systolic blood pressure. Then divide by 3.
5. Only applicable at designated sites
6. Sample to be taken 24 to 26 hours post-dose of study treatment.
7. Sample to be taken 46 to 50 hours post-dose of study treatment.

Procedures	Day 2	Day 3	Day 4	Daily until discharge	Day 8[1]	Day of discharge	Day 28 (FU) ±3 days	8. Organ Failure Free Days needs to be recorded every day until Day 28 (See SPM).
Organ Failure Free Days							X[8]	
ARDS diagnosis status						X		
Ventilator Free Days							X	
ICU & Hospital Length of Stay						X		
Survival							X	

11.3. Appendix 3: Treatment States and Phases

11.3.1. Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to Study Treatment Start date & time. Since this is a single dose study and the time spent on the nebuliser (On-treatment) is expected to be 3-5 minutes a separate "On-treatment" phase is not required for this study.

Treatment Phase	Definition
Pre-Treatment	Date & Time ≤ Study Treatment Start Date & Time
Post-Treatment	Date & Time> Study Treatment Start Date & Time

11.3.2. Treatment States

Assessments and events will be classified according to time of occurrence relative to the start date & time of the study treatment.

11.3.2.1. Treatment States for AE Data

Treatment State	Definition
Pre-Treatment	AE Start Date & Time ≤ Study Treatment Start Date & Time
Post-Treatment	AE Start Date & Time > Study Treatment Start Date & Time
During Surgery	If Start of Surgery Date & Time ≤ AE Start Date & Time < End of Surgery Date & Time
Onset Time Since 1st Dose (Days Hours Minutes)	AE Onset Date & Time - Treatment Start Date & Time converted to D H M format by tu_times
Duration (Days Hours Minutes)	AE Resolution Date & Time – AE Onset Date &Time converted to D H M format by tu_times If resolution time not available then AE Resolution Date – AE Onset Date + 1
Drug-related	If relationship is marked 'YES' on Inform OR value is missing

11.4. Appendix 4: Data Display Standards & Handling Conventions

11.4.1. Study Treatment & Sub-group Display Descriptors

Main Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo (BAL Collapsed lung)	Placebo (BAL Collapsed lung)	1
B	Placebo (BAL Ventilated lung)	Placebo (BAL Ventilated lung)	2
C	GSK2862277 (BAL Collapsed lung)	GSK2862277 26mg IH (BAL Collapsed lung)	3
D	GSK2862277 (BAL Ventilated lung)	GSK2862277 26mg IH (BAL Ventilated lung)	4

NOTES:

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

In addition two alternative sets of treatment descriptors are required. Unless otherwise stated the outputs should use the main treatment group descriptions

Alternative Treatment Group Descriptions #1			
RandAll NG		Alternative Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo (BAL Collapsed lung)	Placebo	1
B	Placebo (BAL Ventilated lung)		
C	GSK2862277 (BAL Collapsed lung)	GSK2862277 26mg IH	2
D	GSK2862277 (BAL Ventilated lung)		

NOTES:

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

Alternative Treatment Group Descriptions #2			
RandAll NG		Alternative Data Displays for Reporting	
Code	Description	Description	Order [1]
A	Placebo (BAL Collapsed lung)	BAL Collapsed lung	1
C	GSK2862277 (BAL Collapsed lung)		
B	Placebo (BAL Ventilated lung)	BAL Ventilated lung	2
D	GSK2862277 (BAL Ventilated lung)		

NOTES:

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

11.4.2. Baseline Definition & Derivations

11.4.2.1. Baseline Definitions

For all endpoints (expect as noted in baseline definitions) the baseline value will be the latest pre-dose assessment.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Day 1 (Pre-Dose)	Day 1 (Immediately prior to start of surgery)	Day 2	
Primary				
PVPI		X		Day 1 (Immediately prior to start of surgery)
Secondary				
Transpulmonary Thermodilution output		X		Day 1 (Immediately prior to start of surgery)
PaO2/FiO2 Ratio		X		Day 1 (Immediately prior to start of surgery)
SOFA[1]	X			Derived Day 1 (Pre-dose)
Biomarkers				
Biomarker (Blood / Serum)	X			Day 1 (Pre-dose)
Immunogenicity	X			Day 1 (Pre-dose)

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- 1 = See Section 11.5.4 for assumptions required to derive a Baseline SOFA score

11.4.2.2. Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.4.2.1 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.

11.4.3. Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS software will be used.	
Reporting Area (Final reporting effort at end of study)	
HARP Server	: uk1salx00175
HARP Area	: gsk2862277/tfr116341/final
QC Spreadsheet	: gsk2862277/tfr116341/final/documents
Reporting Area (Interim analysis 1)	
HARP Server	: uk1salx00175
HARP Area	: gsk2862277/tfr116341/ia1
QC Spreadsheet	: gsk2862277/tfr116341/ia1/documents
Reporting Area (Interim analysis 2)	
HARP Server	: uk1salx00175
HARP Area	: gsk2862277/tfr116341/ia2
QC Spreadsheet	: gsk2862277/tfr116341/ia2/documents
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards AND/OR the set of CDISC standards implemented at GSK at time of database freeze (SDTM IG Version X.X & AdaM IG Version X.X. • Any interim analysis is expected to be performed using Legacy GSK A&R dataset standards but the final reporting is expected to be performed in CDISC. However, if recruitment rates are high and/or the study is stopped after an interim analysis then the final reporting may also use the Legacy GSK A&R dataset standards. • For creation of ADaM datasets (ADCM/ADAE), the same version of dictionary datasets will be implemented for conversion from SI to SDTM.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort (but will not be generated for the ia1 and ia2 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 Standards	
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. They may also be omitted from figures, summaries and statistical analyses if the time deviation was deemed to be clinically impactful.	

Unscheduled Visits	
• Unscheduled visits will not be included in summary tables. • Unscheduled visits / data points may be included in figures if it is relevant. Relevant outputs would typically be those focused on safety, and unscheduled visits / data points may be included in derivations of some endpoints (e.g. maximum post dose change from baseline body temperature). Less relevant outputs are those which aid activities that would not inherently utilise unscheduled visits / data points such as statistical modelling. For example, an individual subject time profile of body temperature should include any unscheduled temperature values; but a figure summarising body temperatures by treatment prior to statistical modelling should not display the unscheduled visit / data points. • 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, %
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 Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation CVb (%) will be reported. [1] CV_b (%) = $\sqrt{}$ (exp(SD^2) - 1) * 100 (SD = SD of log transformed data)
Parameters Not Being Log	Tmax

Reporting Standards	
Transformed	
Listings	Additionally, include the first point, last point and number of points used in the determination of lambda_z for listings.

Graphical Displays

- Refer to IDSL Statistical Principals 7.01 to 7.13.
- The currently supported versions of the SAS SGxxx graphics procedures should be default choice for graphical displays (except for graphics produced by CPMS who may use their preferred software). If SGxxx cannot produce a required graphic then alternative software may be used. The default graphics options in SGxxx procedures may supersede IDSL Statistical Principals 7.01 to 7.13 (e.g. font choices and styles); since the SGxxx procedures post date the authoring of the principles.
- Whenever possible a treatment attribute map dataset should be used to keep symbols and colour schemes consistent across outputs, and where possible across individual subjects. This should be stored in the refdata area of HARP

11.5. Appendix 5: Derived and Transformed Data

11.5.1. 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 Study Treatment Start Date:
• If the reference has both Dates and Times then the Study Day should be computed using the Datepart only
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Treatment Start Date→ Study Day = Ref Date –Treatment Start Date
  • Ref Date ≥ Treatment Start Date→ Study Day = Ref Date – (Treatment Start Date) + 1

Change from Baseline
• The change from baseline will be calculated by subtracting the baseline values from the individual post-randomisation values.

11.5.2. 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'.
• Age will be computed relative to SCREENING visit (so outputs will match inclusion criteria definition of age at time subjects sign the informed consent form)

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** • Since this is a single dose study duration of exposure outputs may not be displayed

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

11.5.3. 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 Fredericia's (QTcF) formulas will be calculated, in msec, depending on the availability of other measurements. • IF RR interval (msec) is provided then missing QTcB and/or QTcF will be derived as : $$QTcB = \frac{QT}{\sqrt{\frac{RR}{1000}}} \qquad QTcF = \frac{QT}{\sqrt[3]{\frac{RR}{1000}}}$$

Adverse Events
AE'S OF Special Interest
• No AE's of special interest have been defined for this study.

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 • Categorical lab results from Urinanalysis may be mapped to a common nomenclature for the purposes of producing summary tables (for example, but not limited to, "+" , "Pos" and "Positive" may all be summarised under "Positive"). The medical monitor will advise on the mappings based upon the observed categories within each test and a listing of the actual mappings

Laboratory Parameters
applied to each lab test will be produced.

11.5.4. Efficacy

Transpulmonary Thermodilution

Predicted Body Weight

- Males: $BW_{Pred} = 50 + (0.91 * (Height - 152.4))$
  $Where...BW_{Pred}(kg), Height(cm)$
- Females: $BW_{Pred} = 45.5 + (0.91 * (Height - 152.4))$
  $Where...BW_{Pred}(kg), Height(cm)$

Body Surface Area (DuBois formulae)

- $BSA = 0.007184 * Weight^{0.425} * Height^{0.725}$
  $Where...BSA(m^2), Weight(kg), Height(cm)$

Predicted Body Surface Area

- $PBSA = 0.007184 * BW_{Pred}^{0.425} * Height^{0.725}$
  $Where...PBSA(m^2), BW_{Pred}(kg), Height(cm)$

"Indexing" of values using the (Absolute value) data entered into the eCRF

- $CI = \frac{CO}{BSA}$, $where\ CI(\mathrm{L/min/m^2}), CO(\mathrm{L/min})\ \&\ BSA(\mathrm{m^2})$
- $GEDI = \frac{GEDV}{BSA_{Pred}}$, $where\ GEDI(\mathrm{mL/m^2}), GEDV(\mathrm{mL})\ \&\ BSA_{Pred}(\mathrm{m^2})$
- $EVLWI = \frac{EVLW}{BW_{Pred}}$, $where\ EVLWI(\mathrm{mL/kg}), EVLW(\mathrm{mL})\ \&\ BW_{Pred}(\mathrm{kg})$
- $SVRI = SVR * BSA, where\ SVRI(\mathrm{dyn*s*cm^{-5}*m^2}), SVR(\mathrm{dyn*s*cm^{-5}})\ \&\ BSA(\mathrm{m^2})$

Note: These alternative derivations may be used as a rough and ready check of the internal consistency of the parameters but small differences may occur due to rounding so they will not appear in any listings/outputs/analyses:

$SVRI = \frac{(MAP - CVP)}{CI} * 80$ and $SVR = 80 * \frac{(MAP - CVP)}{CO}$.

Recovering the Absolute value from the "Indexed" value

- $CO = CI * BSA, where\ CI(\mathrm{L/min/m^2}), CO(\mathrm{L/min})\ \&\ BSA(\mathrm{m^2})$
- $GEDV = GEDI * BSA_{Pred}, where\ GEDI(\mathrm{mL/m^2}), GEDV(\mathrm{mL})\ \&\ BSA_{Pred}(\mathrm{m^2})$
- $EVLW = EVLWI * BW_{Pred}, where\ EVLWI(\mathrm{mL/kg}), EVLW(\mathrm{mL})\ \&\ BW_{Pred}(\mathrm{kg})$
- $SVR = \frac{SVRI}{BSA}$, $where\ SVRI(\mathrm{dyn*s*cm^{-5}*m^2}), SVR(\mathrm{dyn*s*cm^{-5}})\ \&\ BSA(\mathrm{m^2})$

Secondary Endpoints

Calculation of P_aO_2/F_iO_2 and S_pO_2/F_iO_2

- The P_aO_2/F_iO_2 endpoint will be calculated when patients are intubated and have an arterial line present. Prior to computing the ratio the P_aO_2 will be converted from kPa units to mmHg using the conversion rate 1/0.133 and F_iO_2 will be expressed as a proportion and not a percentage.
- S_pO_2/ F_iO_2 will be calculated as a ratio of percentages, where patients are no longer intubated and the arterial line has been removed.

SOFA (Sequential Organ Failure Assessment)

Table below (SOFA Score points allocation algorithm) details how points should be allocated to each SOFA component. Prior to analysis the CONMEDS dataset will be reviewed by the medical monitor who will flag observations which are adrenergic agents and vasopressors. Adrenergic agents that do not appear in Vincent (1996), and for which a highest dose has been recorded, will be assigned a SOFA score of 2.

Zero points are assigned if none of the points scoring criteria are met. If any of the information required to derive an individual SOFA component score is missing or cannot be obtained then that component score will be set to a missing value.

Derivation of Baseline SOFA value: Not all required SOFA components are being measured on Day 1. When component data are available they should be used (Day 1 Pre-dose: lab samples). Since each subject is about to undergo surgery they will be assumed to have been sufficiently fit to satisfy the following assumptions: Respiration, Central Nervous System and Cardiovascular component scores fixed at 0 and Renal score derived solely from Creatinine Pre-dose lab result.

SOFA Score points allocation algorithm

SOFA Score / Variable (x)	0	1	2	3	4
Respiration: P_aO_2/F_iO_2 (mmHG)	$x \geq 400$	$300 \leq x < 400$	$200 \leq x < 300$	$100 \leq x < 200$	$x < 100$
				With Respiratory support (Note: if P_aO_2/F_iO_2 in these categories but subject not on respiratory support then a score of 2 should be assigned)	
Coagulation: Platelets (10^3 / mm^3)	$x \geq 150$	$100 \leq x < 150$	$50 \leq x < 100$	$20 \leq x < 50$	$x < 20$
Liver: Bilirubin (µmol/L)	$x < 20$	$20 \leq x < 33$	$33 \leq x < 102$	$102 \leq x < 204$	$x \geq 204$

Secondary Endpoints

Calculation of P_aO_2/F_iO_2 and S_pO_2/F_iO_2

Cardiovascular: Hypotension (Adrenergic agents administered for at least one hour; doses are in μg/kg/min)	Mean Arterial Pressure ≥ 70 mmHg	Mean Arterial Pressure < 70 mmHg	Dopamine≤5.0 (μg/kg/min) or any dose of: Dobutamine Or any dose of an adrenergic agent not listed here or in Vincent(1996)	Dopamine 5.1-15.0 (μg/kg/min) or Epinephrine≤0.1 or Norepinephrine≤0.1	Dopamine > 15.0 (μg/kg/min) or Epinephrine>0.1 or Norepinephrine>0.1
Central Nervous System: Glasgow Coma Score	x ≥ 15	13 ≤ x ≤ 14	10 ≤ x ≤ 12	6 ≤ x ≤ 9	x < 6
Renal: Creatinine (μmol/L)	x ≤ 110	110 < x ≤ 170	170 < x ≤ 300	300 < x ≤ 440 [Or Urine output < 500 mL/day]	x > 440 [Or Urine output < 200 mL/day]

Calculation of Oxygenation Index

The oxygenation index will be calculated as:

$$\text{Oxygenation Index (\%)} = \frac{FiO2 * Paw}{PaO2}$$

where Mean Airway Pressure (Paw) and PaO2 are measured in mmHg and FiO2 is entered as a % and not a proportion.

Conversion of Paw units from cmH_2O to mmHg will be performed using the ratio 1 cmH_2O = 1/1.36 mmHg.

Conversion of PaO2 units from kPa to mmHg will be performed using the ratio 1 kPa = 1/ 0.133 mmHg.

11.5.5. Pharmacokinetic

Drug Concentration in BAL

Derivation of BAL/ELF Drug Concentration Data

- Urea concentration data will be used to calculate the dilution effect of the lavage which is used to extract the epithelial lining fluid (ELF) from the lung. A correction for dilution will be applied to BAL drug concentrations as follows:

Epithelial Lining Fluid (ELF) Drug Concentration (pg/mL) =
BAL Drug Concentration (pg/mL) x *Dilution Factor*

Drug Concentration in BAL

where

Dilution Factor= Plasma Urea / BAL Urea

Plasma urea is measured from the plasma samples planned to be taken at a similar time to the BAL sample time.

- Additionally the Volume of ELF in BAL fluid and the Total Drug in BAL fluid will be calculated as follows:

Volume of ELF in BAL Fluid (mL) = BAL Fluid Volume (mL)/Dilution Factor

Total Drug in BAL (pg) = BAL Drug Concentration (pg/mL) x *BAL Volume (mL)*

11.5.6. Pharmacodynamic (Biomarker)

Pharmacodynamic (Biomarker)

Biomarkers

- In general, it is assumed that biomarker endpoints will require variance stabilising transformations, such as taking a $\log_e$ transformation prior to analysis (and that summary statistics appropriate to $\log_e$ normally distributed data will apply for all summaries). However, this assumption will be considered for each endpoint individually prior to the generation of summary tables or statistical analysis, and if deemed more appropriate, a $\log_e$ transformation will not be applied, or non-parametric methods may be employed.
- If transformations are used then the results will be reported on the back-transformed scale unless otherwise stated.

11.5.7. Exploratory Endpoints

Exploratory Endpoints

Predicting missing P_aO_2/F_iO_2 using S_pO_2/F_iO_2

- Rice (2007) describe the following linear model to predict S_pO_2/F_iO_2 using available P_aO_2/F_iO_2 values.

$$S_pO_2/F_iO_2 = 64 + (0.84 * P_aO_2/F_iO_2)$$

- For exploratory purposes (i.e. taking the very strong steps of disregarding the uncertainty of the original linear regression parameter estimates and the inverse estimation aspect of the proposal) the formulae will be re-arranged and used to impute missing P_aO_2/F_iO_2 values when a corresponding S_pO_2/F_iO_2 value is available (e.g. when the arterial line has been removed):

P_aO_2/F_iO_2 (Imputed) = (S_pO_2/F_iO_2 – 64) / 0.84 when P_aO_2/F_iO_2 is missing & S_pO_2/F_iO_2 available
P_aO_2/F_iO_2 (Imputed) = P_aO_2/F_iO_2 when P_aO_2/F_iO_2 is non-missing
P_aO_2/F_iO_2 (Imputed) = Missing in all other cases

11.6. Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who has completed all phases of the study including the follow-up visit. • Withdrawn subjects may be replaced in the study, but any replacement would take the next available randomisation number and not be guaranteed to receive the same treatment as the withdrawn subject. • 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. • In the event that the study is prematurely discontinued, all available data will be listed and a review carried out by the study team to assess which statistical analyses are still considered appropriate.
Surgery	• In some cases, a subject may be randomised to the study and surgery initiated, but subsequently halted due to a decision being made that the case is in fact inoperable. In the event of an open and shut case subjects will be withdrawn from the study by the investigator. As the subjects will have received a dose of study dose prior to surgery, every effort should be made to complete as many of the Day 28 follow-up assessments and procedures as possible, prior to hospital discharge.

11.6.2. Handling of Missing Data

Element	Reporting Detail

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

Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
PVPI and EVLWI	• In the case that PVPI and EVLWI are missing and cannot be derived using the methods described in Section 11.5.4, they will remain missing.
PK	• Urea data: Below the Lower Limit of Quantification (LLQ) values will be imputed with the relevant (BAL fluid) LLQ divided by 2 for the purpose of deriving the Dilution Factor. • Plasma concentrations: Refer to Section 11.5.3 or for further guidance see the PK Guidance document, GUI_00000051487, and the DB/CPMS guidelines

Element	Reporting Detail
	'Standards for the Handling of NQ impacted PK Parameters' for more information.
Biomarkers	• Values below LLQ will be set as LLQ/2 • Values above the upper limit of quantification (ULQ) will be set as ULQ • Imputed values will be used for the purposes of the computation of change from baseline and for summaries, plots and analysis, if deemed applicable. • Number of data imputed will be highlighted in the summaries and listings will report the values as below LLQ or above ULQ. • If multiple LLQ's and ULQ's are available per assay (i.e. multiple runs with different standard curves are utilised) then the LLQ and/or ULQ value used for the above purposes shall be the minimum of the available LLQs and/or the maximum of the BLQ's. • If more than a third of observations are below LLQ or above ULQ then no imputation will be performed for that subject.

11.6.2.1. 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 3: 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.
Surgical Procedures / Biomarker samples (Serum and BAL)	• If the date/time of an event occurring during the surgical procedures is unknown then it shall remain missing. Any associated data values may be listed using the timeslicing keys to determine the chronological ordering. • Since each surgical procedure is bespoke it is not possible to impute a date/time, although depending upon the analysis and endpoint the planned time (or the time of a proximal event) may be sufficiently accurate to be used. Otherwise the data point may be omitted from the analysis and/or form part of a sensitivity analysis (e.g. Subject PPD has unknown BAL sample date/time and the proposed PK modelling may be sensitive to any assumed/imputed value, so the observation may be dropped).

11.6.2.2. 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, 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.

11.6.2.3. Handling of Missing Data for Statistical Analysis

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td>SOFA</td><td>• If any of the information required to derive an individual SOFA component score is missing or cannot be obtained then that component score will be set to a missing value.
• However, in the case of missing P_aO_2/F_iO_2 ratios; S_pO_2/F_iO_2 ratios and the following corresponding thresholds for S_pO_2/F_iO_2 may be used (Pandharipande, 2009):

<table>
<tr><th>SOFA Respiratory Score</th><th>P_aO_2/F_iO_2</th><th>S_pO_2/ F_iO_2</th></tr>
<tr><td>1</td><td>< 400</td><td>< 512</td></tr>
<tr><td>2</td><td>< 300</td><td>< 357</td></tr>
<tr><td>3</td><td>< 200</td><td>< 214</td></tr>
<tr><td>4</td><td>< 100</td><td>< 89</td></tr>
</table>

• If subjects have missing SOFA components data due to procedural / operational causes then those component scores may be populated with the average response at that time point on the corresponding treatment arm. Alternatively if it is the Day 3 value which requires imputation linear interpolation using the Day 2 and Day 4 data may be used.</td></tr>
</table>

11.7. Appendix 7: Values of Potential Clinical Importance

11.7.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male	0.3	0.54
		Female	0.3	0.54
Hemoglobin	g/L	Male	90	180
		Female	90	180
Lymphocytes	$x10^9$/ L		0.6	3.0
Neutrophil Count	$x10^9$/ L		1.5	20
Platelet Count	$x10^9$/ L		100	600
While Blood Cell Count (WBC)	$x10^9$/ L		3	20
Note: For the following lab tests the corresponding normal ranges should be used as the PCI range: Reticulocyte Count, RBC Count, MCV, MCH, MCHC, Monocytes, Eosinophils and Basophils				

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		25	60
Calcium	mmol/L		1.8	2.75
Creatinine	mmol/L		30	160
Glucose	mmol/L		3	9
Potassium	mmol/L		2.5	5.5
Sodium	mmol/L		120	160
Total CO2	mmol/L		16	35
BUN	mmol/L		3	15
Chloride			no PCI required for this study	no PCI required for this study

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 4x ULN
AST/SGOT	U/L	High	≥ 4x ULN
AlkPhos	U/L	High	≥ 4x ULN
T Bilirubin (Note: Direct Bilirubin PCI not required for this study)	µmol/L	High	≥ 2xULN
T. Bilirubin + ALT	µmol/L U/L	High	2xULN T. Bilirubin + ≥ 4x ULN ALT

11.7.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	**Upper**
Absolute			
Absolute QT Interval	msec	≥ 300	≤ 500
Absolute QTc Interval (QTcB or QTcF)	msec	≥ 300	≤ 450
Absolute PR Interval	msec	< 90	> 200
Absolute QRS Interval	msec	< 70	> 120
Absolute RR Interval	msec	< 375	> 1700
Change from Baseline			
Increase from Baseline QTc	msec		> 60

11.7.3. Vital Signs

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

Vital Sign Parameter (Change from Baseline)	Units	Clinical Concern Range	
		Decreases of magnitude	Increases of magnitude
Systolic Blood Pressure	mmHg	>50	>50
Diastolic Blood Pressure	mmHg	>30	>30
Heart Rate	bpm	>50	>50

11.8. Appendix 8: Biomarker Details

Note: These are the planned biomarkers at time of RAP writing. Additional items may be added or existing ones removed.

Parameters (BICATCD Code)	Sample	Unit	LLQ	ULQ
Target Engagement *				
Free sTNFR1	Serum & BAL			
Total sTNFR1	Serum & BAL			
Complex TNFR1	Serum & BAL			
Pro-Inflammatory Biomarkers *				
TNFa	BAL			
IL-6	Serum & BAL			
IL-8	Serum & BAL			
IL-1b	BAL			
MCP-1	BAL			
Anti-Inflammatory Biomarkers *				
CRP (Reactive Protein C) $^{\Delta}$	Plasma & BAL			
IL1-ra	BAL			
IL-10	BAL			
Protein Permeability Index *				
Total Protein in BAL	BAL			
Total Protein in Plasma	Plasma			
Total Protein Ratio (Ratio is derived from BAL and Plasma values)	Plasma & BAL			
Markers of Epithelial Cell Injury				
Surfactant Protein D	Serum & BAL			
RAGE (Receptor for Advanced Glycation End products)*	Serum & BAL			
Club Cell 16 (also known as CC10 and CC16)	Serum & BAL			
Markers of Endothelial Injury				
vWF	Serum & BAL			
sICAM-1*	Serum & BAL			
Markers of Neutrophil Activation*				
MPO	Serum & BAL			

NOTE :

- * Expect biomarker parameters to be increased in oesophagectomy patients.
- Serum sampling times: Day 1 Prior to Surgery,.Day 1 On Completion of Surgery, Day 2, Day 3, Day 4 and Day 8/Day of Discharge.
- BAL sampling time: Day 1 On Completion of Surgery.
- N/A = No ranges are normally provided for parameters.
- Display biomarkers in the order presented in the Table, and use Functional Category labels provided to further group them.
- Δ = Measured in plasma as part of Clinical Chemistry Labs so may have different sampling scheme and require appropriate adjustments to displays and/or models

11.9. Appendix 9: Examination of Covariates, Subgroups & Other Strata

11.9.1. Handling of Covariates, Subgroups & Other Strata

- The randomisation is stratified by Centre (site). However, the number of subjects recruited at a site may be small (it is conceivable that a site may not recruit sufficient subjects to have an individual from each of the four treatment arms). Therefore the statistical models should include a fixed categorical effect for centre by intent, but this centre term may be dropped. Alternatively low recruiting centres may be pooled by NHS region, or another suitable characteristic (e.g. shared research fellow) if deemed appropriate.
- The following is a list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses (such outputs would take the next available number).
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Category	Potential Covariates and / or Subgroups
Randomisation strata	• Centre (site) • Research fellow assisting with study procedures • NHS authority the site belongs to (a potential mechanism to cluster centres that may behave similarly within the UK)
Subject characteristics	• Gender • Age • Race / Ethnicity • Height / Weight / BMI
Medical History	• Prior Oesophageal Chemotherapy • Smoking history • Medical history
Surgical Procedure	• Duration of Surgery • Duration of One Lung Ventilation • Duration of anaesthesia • Inotrope usage

Category	Potential Covariates and / or Subgroups
Immunogenicity	• Did subject develop serum anti-GSK2862277 antibodies
Clinical Outcomes / Resource Utilisation	• Did subject develop ARDS during study • Vent free days • ICU length of stay • Hospital length of stay • Organ failure free days

11.10. Appendix 10: PVPI and EVLW – Supplementary Information

11.10.1. Data derivations to be performed by GSK

When appropriate, "Indexed" versions of the parameters will be derived as per Section 11.5.4.

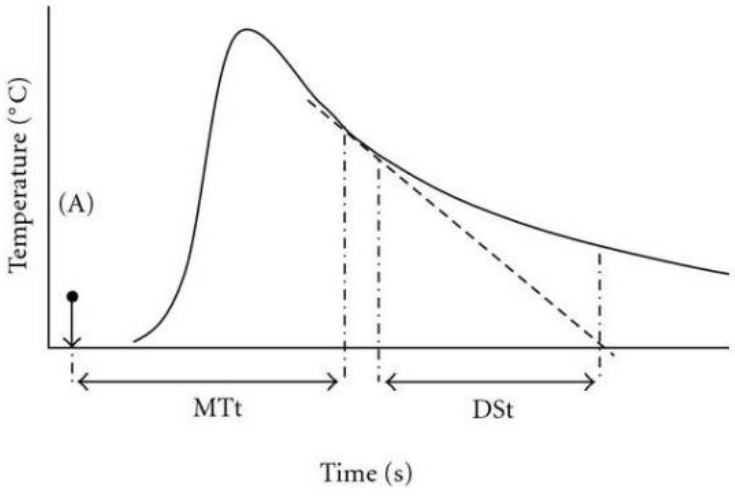
In the event that the sites did not configure their PiCCO machine to display the Absolute parameter sets and the only information available is the Indexed version of a PiCCO parameter then the Absolute value will be recovered from the indexed version using the appropriate equation from Section 11.5.4.

11.10.2. Theoretical Underpinning of Transpulmonary Thermodilution Measurements

This section briefly describes the theory behind the PiCCO machine. Not all of the items described are provided / outputted by the machine (see Table 13 for the parameters databased via the eCRF).

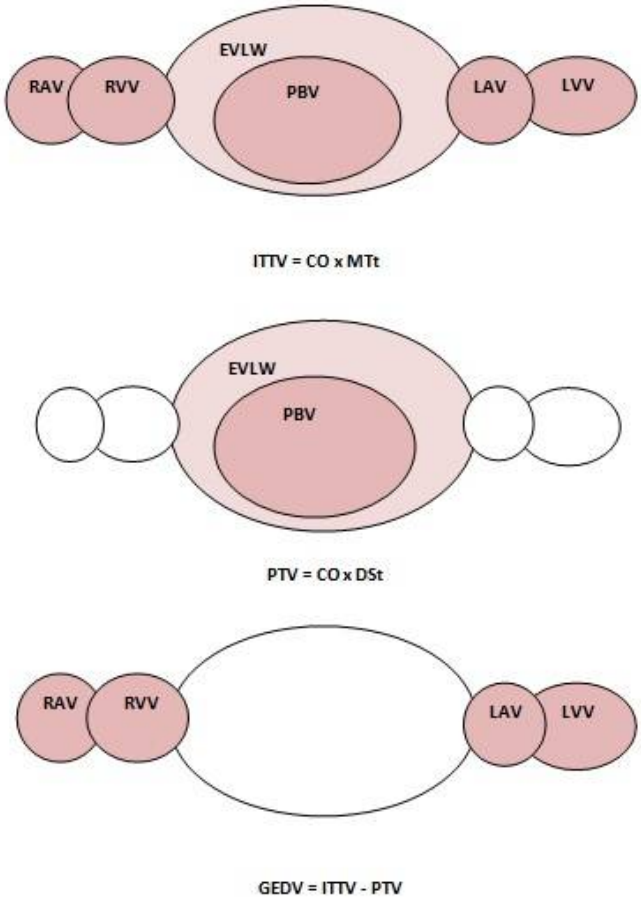
The transpulmonary thermodilution provides the measurement of cardiac output (CO), the global end-diastolic volume (GEDV) and intra-thoracic blood volume (ITBV) by passing a thermal indicator (cold solution) through the right heart, lungs and left heart and measuring the temperature changes at a known distance downstream, typically in the femoral artery. The ITBV (a measure of all the blood contained within the chest), is measured by the GEDV, which is the sum of the end-diastolic volumes of all heart chambers, and pulmonary blood volume (PBV).

Figure 3 **Transpulmonary Thermodilution Curve showing mean transit time and downslope decay time (DSt) of the slope. The time point (A) represents the time of injection. The product of cardiac output and MTt equals the intrathoracic thermal volume. Multiplication of the cardiac output and the DSt equals the pulmonary thermal volume (PTV).**



The product of the CO and the mean transit time (MTt) of the thermal indicator, is the intrathoracic thermal volume (ITTV = ITBV + EVLW), i.e., the distribution volume of the thermal indicator. The product of the CO and exponential downslope time (DSt) is the pulmonary thermal volume (PTV). The GEDV is calculated as the difference between the intrathoracic and pulmonary thermal volume (GEDV = ITTV – PTV). (See Figure 4.)

Figure 4 **Determination of GEDV by transpulmonary thermodilution. The ITTV describes the distribution volume of the thermal indicator, including the volumes in the right atrium (RA), right ventricle (RV), left atrium and left ventricle (LV).**



Intrathoracic blood volume (ITBV) is calculated from the GEDV by assuming a relationship of a constant ratio of 1.25. (ITBV = 1.25 x GEDV). This ratio allows the calculation of ITBV and consequently the calculation of the EVLW (ITTV – ITBV).

PVPI is the ratio between EVLW and the pulmonary blood volume (PBV), which is deduced from the difference between the PTV and EVLW (PBV = PTV – EVLW).

Table 13 Endpoints and abbreviations used in Transpulmonary Thermodilution

Timeframe	Grouping	Abbreviation / Item	Databased	Description
Continuous[1]				
	Continuous cardiac output	Heart Rate	Yes	Heart Rate
		AP	Yes	Arterial Pressures [Systolic Blood Pressure / Diastolic Blood Pressure]
		CVP	Yes	Central Venous Pressure [manually entered into PiCCO machine]
		CPO	No	Cardiac Power Output
		CPI	No	Cardiac Power Index
	Calibrated Continuous cardiac output	PCCO	No	Pulse Contour Cardiac Output: Calculated beat by beat as Stroke Volume * Heart Rate
		PCCI	No	Pulse Contour Cardiac Index
	Stroke Volume	SV	No	Stroke Volume
		SVI	No	Stroke Volume Index: **Assumed** to be Stroke Volume indexed by predicted body surface area
	Afterload	SVR	Yes	Systematic Vascular Resistance: Determinant of afterload. Computed as $\frac{MAP - CVP}{Flow(CO)} * 80$ where Flow(CO)=Pressure/Resistance. Vasoconstriction implied if Flow(CO) is decreasing and Vasodilation implied if Flow(CO) is increasing provided pressure is constant
		SVRI	No	Systematic Vascular Resistance Index: SVR * BSA (Body Surface Area - DuBois)
		MAP	Yes	Mean Arterial Pressure

Timeframe	Grouping	Abbreviation / Item	Databased	Description
	Volume responsiveness	SVV	Yes	Stroke Volume Variation: Variation in Stroke Volume over the breathing cycle for a specific time frame (only available in mechanically ventilated patients in sinus rhythm)
		PPV	No	Pulse Pressure Variation: Variation in Pulse Pressure over the breathing cycle for a specific time frame (only available in mechanically ventilated patients in sinus rhythm)
	Contractility	dPmax	No	Left contractility paramater
Discontinuous	Thermodilution Cardiac Output	CO (also known as CO_{TDa})	Yes (triplicates)	Cardiac Output (thermodilution): Volume of blood pumped by heart in one minute.
		CI	No	Cardiac Index: Cardiac Output indexed by body surface area (DuBois)
	Volumetric Preload	GEDV	Yes (triplicates)	Global End Diastolic Volume: Filling volume of all four heart chambers
		GEDI	No	Global End Diastolic Volume Index: GEDV indexed to predicted body surface area
	Contractility	GEF	Yes	Global Ejection Fraction
		CFI	No	Cardiac Function Index: Measure of contractility (performance of cardiac muscle). Ratio of flow and preload: CFI = CO / GEDV
	Pulmonary Edema	EVLW (also known as ELW)	Yes (triplicates)	Extra Vascular Lung Water: Includes intra-cellular, interstitial and intra-alveolar water (not pleural effusion)
		EVLWI (also known as ELWI)	No	Extra Vascular Lung Water Index: EVLW indexed to predicted body weight

Timeframe	Grouping	Abbreviation / Item	Databased	Description
		PVPI	Yes	Pulmonary Vascular Permeability Index: EVLW indexed to Pulmonary Blood Volume
	Used internally by the PiCCO machine	ITBV	No	Intra-thoracic Blood Volume
		PBV	No	Pulmonary blood volume
		PTV	No	Pulmonary thermal volume
		MTt	No	Mean transit time
		DSt	No	Downslope decay time
		ITTV	No	Intrathoracic thermal volume
		LAV / RAV	No	Left / Right atrium Volume
		LVV / RVV	No	Left / Right ventricle Volume
Constant	Information / Demographics	BSA	No	Body Surface Area (DuBois): Manually derived from observed weight and height
		PBW	No	Predicted Body Weight
		PBSA	No	Predicted Body Surface Area: Derived using same approach as DuBois but uses Predicted body weight instead of observed weight
		Arterial Line Used	Yes	Typically Femoral (Brachial is the other option)

1. A snapshot of the values for the continuous measurements would be taken when the 3x Thermodilutions are performed

11.11. Appendix 11: Model Checking and Diagnostics for Statistical Analyses

11.11.1. Bayesian Analyses (SAS Proc MCMC)

- The following points are for guidance and illustration only and do not guarantee a successful model convergence. They cannot cover all eventualities and do not remove the requirement to do what is best for the specific set of observed data being modelled.
- Unless otherwise stated, data collected at screening and at unscheduled time points will not be included in the statistical analyses, i.e., only planned/scheduled post-screening data will be included.
- All credible intervals reported will be equal tail, unless otherwise specified.
- Convergence for the parameters in the model needs to be verified.
- The randomization seed used in PROC MCMC should itself be generated with an element of randomness - but there is no need to formally document this process (e.g. using Excel function RANDBETWEEN [1,9999999] and copying the result into the SAS code)
- Unless the parameter is a flag variable (e.g. taking binary values of 1 or 0) the medians of the posterior distribution should be used.
- Warnings/Erros in the SAS log regarding flag variables may be safely discounted
- All effects will be entered on the same PARMS statement initially. If necessary to aid model convergence parameters may be split across several PARMS lines.
- Centring of continuous covariates will take place at the input dataset stage, using only individuals who contribute usable data to the model fitting process.
- Individuals with missing covariates would be dropped from the model fitting process (alternative imputation strategies may be explored if required, e.g. substituting the covariate mean for a missing value)
- Bespoke conjugate samplers (functions that can be called from within PROC MCMC) may be used to improve the computational performance and reduce the computational overheads. If such an approach is used it may require different parameterisations / prior specification but it should be set up act commensurate to the approaches described.

11.11.1.1. Prior Distributions

Unless otherwise specified, the following will be the default approach to selecting prior distributions:

- Non-informative priors of the form Normal(0, Var=1E6) will be assigned to each fixed-effect parameter in the proposed statistical model.

- Non-informative inverse-gamma priors of the form IG(a=2.001,b=0.001) will be used for scale parameters (variances). If these parameters do not lead to convergence than choose “a” small and “b” smaller than the expected standard

deviation (the expected standard deviation can be obtained from empirical estimates or by fitting the model using likelihood approaches such as in PROC MIXED).

- For scale parameters (variances) that may take values close to zero a non-informative prior of the form Uniform(0, XXX) may be assigned for the standard deviation (SD) in place of the inverse gamma, where XXX is a suitably chosen range that covers clinically plausible values for the SD.

- For repeated measures models, non-informative Inverse-Wishart priors of the form IW(υ, Σ) will be assigned for the unstructured VCV. The parameter υ represents the dimension of VCV (number of rows or columns) and the matrix Σ is an identity matrix of the same dimension as VCV.

    - If there are issues with these distribution parameters then the identity version of Σ may be replaced with a diagonal matrix that uses best guesses for the residual variance at each repeated measure timepoint (or empirical estimates or the residual estimate from fitting likelihood based models using PROC MIXED). This only needs to be of the correct order of magnitude.

    - Alternatively, a Spatial power (with planned times as the "distances") for the VCV may be explored. The prior for the correlation parameter ρ is Uniform[-1,1], whereas the variance parameter σ^2 is assumed to follow the IG(a=2.001,b=0.001) prior distribution.

It is good practice to ensure that each prior distribution is visualized to ensure it appears sensible, i.e., that it allows parameter values that generate clinically plausible response values and that it is truly non-informative over the region of the likelihood function where the data lies.

Note:

- The Gamma(a, b) density function takes the form

$$p(u) = \frac{b(bu)^{a-1}e^{-bu}}{\Gamma(a)}, u > 0$$

  The mean is a/b and the variance is a/b^2.

- The IG(a, b) density function takes the form

$$p(u) = \frac{b^a u^{-(a+1)}e^{-b/u}}{\Gamma(a)}, u > 0$$

  The mode is b/(a+1), the mean is b/(a-1), if a>1, and the variance is $b^2/[(a-1)^2(a-2)]$, if a>2.

- There is no requirement to formally report the prior visualisation outputs.

11.11.1.2. Initial Values

Unless otherwise specified, initial parameter values of zero will be used for the fixed-effect parameters. For remaining model parameters initial values may be drawn at random from their respected prior distribution. If convergence of the Markov chain Monte Carlo (MCMC) algorithm is problematic then alternative estimates may be used (for example, these could be based on maximum likelihood estimates, or by setting any "intercept" parameter to lie roughly in the region of the observed data values).

11.11.1.3. Convergence Diagnostics

To be able to perform Bayesian inference using MCMC simulations the samples for all the parameters in the model need to be obtained from the corresponding target posterior distribution. To ensure that this is the case the following is a list of convergence diagnostics that can be applied for each parameter:

Comparing MCSE vs posterior standard deviation:

- The Monte Carlo Standard Errors (MCSE) should be compared with the standard deviation of the posterior distribution (SD) to ensure that only a fraction of the posterior variability is due to the simulation, i.e., the ratio MCSE/SD should be as small as possible, typically close to 0.01.

- Adequate values for the number of MCMC samples / thinning / number of burn-in samples should be chosen to ensure that the ratio MCSE/SD for the key parameters in the model is approximately 0.01 (key parameters are those associated with treatment, or pre-specified comparisons of interest).

- For other model parameters, try to get the MCSE/SD values as close to 0.01 as possible, but if there is significant autocorrelation then values below 0.05 would be considered acceptable.

- In addition, if possible, the number of tuning units and maximum number of tuning iterations may be increased to find a better proposal distribution for the model parameters, which in turn may reduce the MCSE/SD ratio.

- Where possible the code should be written to allow the SAS compiler to identify and make use of conjugacy, since this can greatly reduce the corresponding MCSE/SD ratio.

- Models selected with MCSE/SD values > 0.01would need a brief remark/justification added to the CSR to clarify why it was not possible to reach the target and why it is believed the subsequent model still has utility from an inference perspective.

Geweke diagnostics:

- The Geweke diagnostic test checks whether the mean estimates have converged by comparing means from the early and latter part of the Markov chain using a z-score t-test.

- Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.

Diagnostic plots and visual inspection:

- Trace plots of samples versus the simulation index can used to assess some aspects of convergence. The centre of the chain should appear stable with very small fluctuations, i.e., the distribution of points should not change as the chain progresses and the posterior mean and variance are relatively constant.

- Autocorrelation plots can be used to assess degree of autocorrelation (should decline rapidly and show no oscillation patterns).

- The posterior density should look reasonable for each parameter (e.g. for posterior parameters expected to follow a normal distribution, the density plot should not appear bi-modal, but for parameters acting as binary flags, then bi-modal is acceptable).

- Examination of correlation structures between relevant posterior parameters should be used to provide information about what potential issues may be and also what corrective action(s) may be worthwhile attempting (scatterplots of the samples from the posterior distributions of the parameters).

Convergence for all the parameters in the model needs to be verified.

11.11.1.4. Additional Model Checking (optional at the discretion of the study statistician)

Additional model checking can be performed using the posterior predictive distribution.

- For each observation generate as many expected values from the posterior predictive distribution as the number of MCMC samples.

- Residuals for each observation are obtained by subtracting the expected values from the observed values.
- For each subject calculate an average residual and an average expected value.

- Model fitting can be checked by looking for patterns when plotting the average residual versus the average predicted value as in a maximum likelihood estimation setting.

When non-informative priors are used and there is only a small amount of missing data a faster/easier alternative to the posterior predictive distribution model checking would be to fit the equivalent model using a frequentist approach (e.g. in SAS PROC MIXED) and utilise the built in diagnostic tools.

11.11.1.5. Possible corrective actions for non-converging MCMC models

Possible corrective actions include but are not limited to

- Moving parameters (or combinations of parameters) onto separate PARMS statements (to form blocks that are updated independently in the MCMC algorithms)
- Increasing the number of MCMC draws from the posterior distributions
- Increasing the length of the burn in period
- Increasing the thinning parameter (to reduce the autocorrelation)
- Centring covariates (to reduce correlations between the posterior parameters)
- Re-parameterising the model (e.g. using log-normal prior distributions to stop values being sampled that are below zero)
- Re-scaling the parameters (e.g. if one parameter takes values orders of magnitudes different to the other model parameters then dividing it by a suitable constant but back transforming the rescaled parameter prior to its use in any subsequent manipulations)
- Visualising the likelihood function of the dataset to determine if there are more appropriate starting estimates (or profiled versions of the likelihood for subsets of model parameters where difficulties are being encountered if it is a high dimensionality problem)
- Consulting with internal GSK experts to resolve the issues

11.11.2. Mixed modelling assumptions (SAS Proc MIXED)

The following applies to statistical models fitted using SAS Proc MIXED:

- Model assumptions will be applied, but appropriate adjustments maybe made based on the data.
- The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
- An unstructured covariance structure for the R matrix will be used by specifying ‘type=UN’ on the REPEATED line.

  - In the event that this model fails to converge, alternative correlation structures may be considered such as CSH or CS.
  - Akaike's Information Criteria (AIC) will be used to assist with the selection of covariance structure.
- Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the (studentised) residuals and a plot of the (studentisd) residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.

If there are any departures from the distributional assumptions, alternative models may be explored using appropriate transformed data.

11.12. Appendix 12: Details of Simulation exercise that produced operational characteristics used in the protocol

This section describes in detail how simulations were used to choose the cut-off points and probability thresholds included in the protocol decision rules and how simulations were used to assess the operating characteristics of the target sample size (40 per arm).

11.12.1. Simulations supporting interim analysis 2

This section is divided into a broad overview of the strategy and additional sub-sections containing further detail on specific topics

- Feasibility considerations limited maximum number of subjects to 80.
- Assumption of 2x endpoints per subject available at 2x time points (pre-surgery (baseline) and immediately post surgery). PVPI was assumed to require Ln (natural logarithm) transformation. No covariate adjustments were allowed in these simulations, but the actual IA2 analysis may incorporate covariate adjustments (e.g. for centre effects)
- Goal of simulation strategy was to optimise the timing and frequency of interim analyses and the decision rules therein.
- Various scenarios of possible GSK2862277 treatment effects; expressed as differences from the placebo means were evaluated in conjunction with different IA2 recruitment targets (hypothetical placebo means assumed to be the same as the baseline adjusted values estimated from the BALTI dataset (Perkins, 2014)). Table 20 details the possible treatment effects evaluated. Table 16 details the potential IA2 timings and thresholds evaluated.
- For each scenario the simulation process is split into "Outer" and "Inner" loops. Differences over the outer loops explore the impact of the "information content" within data available at the time of IA2. Differences over the inner loops explore the impact of the decision criteria and rules for a given set of "observed" interim data. In practice there will only be one set of observed study data. The *a priori* expectation was that the later the timing of IA2 (with respect to the possible 80 subjects) the more consistent the information content would be across outer loops and, therefore, less variability between outer loop outcomes.
- Logistics of implementing these complex simulations sometimes dictated the approaches taken (e.g. using conjugacy rather than MCMC simulations to enumerate distributions).
- Outer loops: For efficiency 10,000 sets of individual subject level data for the maximum possible study size are generated for each scenario (i.e. 80 subjects per dataset). Repeatedly subsetting these 80 subjects and creating summary statistics from each subsample allows multiple IA2 timings to be evaluated without constantly

having to re-simulate subject level data. Sufficient summary statistics were created using the first 12 subjects (6 per arm.), the first 14 subjects (7 p.a.), etc, through to 78 subjects (39 p.a.) in increments of 2 subjects. Thus, each of the 10,000 sets has 34 associated sets of summary statistics. Operating characteristics of potential IA2 timings (e.g. after 15 subjects per arm) were evaluated by selecting the corresponding 10,000 sets of associated summary statistics and putting each of them through the inner loop process. These are the summary statistics (and dimensions) produced which act as inputs to the inner loop process:

- Placebo Mean Vector [2x1], Variance Covariance matrix [2x2] and Correlation matrix [2x2]
- Number of subjects on Placebo [scalar]
- Active Mean Vector [2x1] Variance Covariance matrix [2x2] and Correlation matrix [2x2]
- Number of subjects on Active [scalar]

Note: This step may be introducing some form of correlation between the simulation runs because the same subject level data is being used repeatedly (e.g. the summary statistics for 6 and 7 subjects per arm will only differ due to the 1x additional subject). Unfortunately computational run time, the number of scenarios and the protocol development timeline prohibited completely independent subject simulations to create the various summary statistics used as inputs to the inner loops.

- Inner loops: The starting assumption for each inner loop was that the "observed" data at the time of the interim have been used to derive multivariate sample summary statistics (computed separately per treatment arm). By using the VCV matrix from the Baseline adjusted BALTI dataset and the baseline adjusted Placebo means in the scenarios simulation of separate baseline data points was not necessary for the inner loops in this exercise.

  Initially these summary statistics are combined with a set of non-informative priors to produce the hyperparameters of a multivariate normal distribution for predicting an individual subjects future response (described for the placebo treatment arm; analogous results for the active arm):

Table 14 Mechanism for updating hyperparameters to simulate remaining subjects (Pbo arm)

Par'	Prior Values	Data (Sample Summary statistics)	Posterior Parameters
$\mu_{0,Pbo}$	$\begin{bmatrix}0\\0\end{bmatrix}$	$\bar{\mathbf{x}}$ (2x1 Vector of Pbo Sample means)	$\mu_{1,Pbo} = \frac{(k_0 * \mu_{0,Pbo}) + (n_{pbo} * \bar{\mathbf{x}})}{(k_0 + n_{pbo})}$
$k_{0,Pbo}$	0	n_{pbo} at IA2	$k_{1,Pbo} = (k_0 + n_{pbo})$
$\nu_{0,Pbo}$	0	n_{pbo} at IA2	$\nu_{1,Pbo} = (\nu_0 + n_{pbo})$
$\Psi_{0,Pbo}$	$\begin{bmatrix}0 & 0\\0 & 0\end{bmatrix}$	$\mathbf{C} = (n_{pbo} - 1) * VCV$ **C** is a 2x2 matrix VCV is sample variance covariance matrix	$\Psi_{1,Pbo} = \Psi_{0,Pbo} + \mathbf{C} + \left(\left(\frac{k_0 * n_{pbo}}{k_0 + n_{pbo}}\right) * (\bar{\mathbf{x}} - \mu_{0,Pbo}) * (\bar{\mathbf{x}} - \mu_{0,Pbo})\right)$

The Posterior parameters (subscripted with a 1) from Table 14 are used to sample the parameters of the Multivariate normal distribution for a future subject and generate sufficient data to "complete the study recruitment for the arm". Each of the following steps constitutes one "inner loop":

- Draw a sample VCV matrix Σ_{Pbo} (Note: Σ_{Pbo} relates to an individual subject, not a mean) from the inverse Wishart distribution parameterized using the posteriors $\Psi_{1,Pbo}$ and $\nu_{1,Pbo}$

- Conditional on the sampled Σ_{Pbo} draw a single sample (denoted $\boldsymbol{\mu}_{\mathbf{Fut,Pbo}}$) from a MVN distribution with a mean vector parameterised using the posterior for $\mu_{1,Pbo}$ and a VCV matrix parameterised using $\frac{\text{Sampled}\,\Sigma_{Pbo}}{k_{1,Pbo}}$

- Draw sufficient subjects to reach a total of 40 per arm from the (same within an inner loop) MVN distribution i.e. from $\overset{MVN}{\sim}(\boldsymbol{\mu}_{\mathbf{Fut,Pbo}}, \Sigma_{Pbo})$. For example if the timing of the interim analysis was after 15 subjects then sample 25 future subjects from the MVN.

- Repeat this inner looping a total of 1,000 times

Conceptually 1,000 hybrid datasets are formed by repeatedly joining the observed data at time of the interim onto the 1,000 simulated sets of future subjects from the inner loops. Each of these "end of study datasets" (Eos) could then be analysed separately to obtain the joint probability of seeing any decrease in mean PaO2/FiO2 in conjunction with any increase in mean PVPI (relative to placebo).

However for computational speed the mechanism of updating the MVN hyperparameters was also used to obtain the end of study posterior distributions for the mean of each treatment arm. This is achieved by deriving the same set of sample summary statistics from each set of future simulated subjects (the "future data") and using the previous posteriors as priors. This results in Table 15. A further assumption uses the expected value of the inverse-Wishart distribution as the "sampled" Σ_{Eos} when obtaining the MVN distribution for the Mean treatment effect parameters for each arm. To further speed computations matrix algebra is used to obtain a MVN distribution for the end of study mean treatment difference parameters.

Using this distribution of mean treatment differences at the end of the study the probability of seeing any decrease in PaO2/FiO2 in conjunction with any increase in PVPI can be determined (since this problem is bivariate the SAS function PROBBNRM may be used).

Table 15 Mechanism for updating hyperparameters for end of study treatment effects (Pbo arm)

Par'	Prior Values	Data (Sample Summary statistics for future subjects)	Posterior
$\mu_{2,Pbo}$	$\mu_{1,Pbo}$ (Table 14)	$\bar{\mathbf{x}}_{\text{Fut,Pbo}}$	$\mu_{2,Pbo} = \frac{(k_1 * \mu_{1,Pbo}) + (n_{rem} * \bar{\mathbf{x}}_{Fut,Pbo})}{(k_{1,Pbo} + n_{rem})}$
$k_{2,Pbo}$	$k_{1,Pbo}$ (Table 14)	$n_{rem} = 80 - n_{pbo}$	$k_{2,Pbo} = (k_{1,Pbo} + n_{rem})$
$\nu_{2,Pbo}$	$\nu_{1,Pbo}$ (Table 14)	$n_{rem} = 80 - n_{pbo}$	$\nu_{2,Pbo} = (\nu_{1,Pbo} + n_{rem})$
$\Psi_{2,Pbo}$	$\Psi_{1,Pbo}$ (Table 14)	$\mathbf{C}_{Fut,Pbo} = (n_{rem} - 1) * VCV_{Fut,Pbo}$	$\Psi_{2,Pbo} = \Psi_{1,Pbo} + \mathbf{C}_{Fut,Pbo} + \left(\left(\frac{k_1 * n_{rem}}{k_1 + n_{rem}}\right) * (\bar{\mathbf{x}}_{Fut,Pbo} - \mu_{1,Pbo}) * (\bar{\mathbf{x}}_{Fut,Pbo} - \mu_{1,Pbo})^T\right)$

$$\text{End of study Mean Pbo effect} = \boldsymbol{\mu}_{Eos,\mathbf{Pbo}} \overset{MVN}{\sim} \left(\mu_{2,Pbo}, \frac{E[\Sigma_{Eos,Pbo}]}{k_{2,Pbo}}\right)$$

Hence

$$\text{EoS Mean Trt Diffs} = \boldsymbol{\mu}_{Eos,Diff} \overset{MVN}{\sim} \left(\left(\mu_{2,Act} - \mu_{2,Pbo}\right), \frac{\left(\frac{\Psi_{2,Pbo}}{\nu_{2,Pbo} - 2 + 1}\right) + \left(\frac{\Psi_{2,Act}}{\nu_{2,Act} - 2 + 1}\right)}{\left(k_{2,Pbo} + k_{2,Act}\right)} \right)$$

Each of the parameters of the EoS Mean Trt Diffs MVN distribution for that inner loop is saved.

The output of the outer and inner loops for a given scenario is a dataset with approximately 10,000 * 34 * 1,000 sets of parameters that describe the end of study MVN distribution of mean treatment differences. In addition, each record also contains sufficient metadata to link it back to its generating circumstances.

Iterative discussions within the study team led to the critical boundaries for the endpoints that would be considered futile (i.e. any decrease in PaO2/FiO2 in conjunction with any increase in PVPI). Once set, the optimisation questions became "*timing of IA2 and how much confidence was required to declare futility*".

These outer/inner loop datasets allow multiple probability trigger thresholds to be evaluated without need to re-simulate (see topics below).

Generation of the individual subject data for the outer loop

Subject level PVPI and PaO2/FiO2 data from BALTI prevention trial (Perkins, 2014) were available for 56 subjects at pre-surgery and immediately post-surgery time points.

PC SAS (v9.3 TS1M2) PROC MCMC was used to fit the model in Equation 1 to the BALTI trial data and, once convergence achieved, simultaneously generate 10,000 sets of 80 subjects (40 per placebo arm using the fitted BALTI means and 40 per active arm using the BALTI means offset by a pre-specified amount; see Table 20). Each endpoint for each of the 80 subjects is represented as a distinct model parameter.

Equation 1 MVN Model fitted to BALTI dataset for the ith Subject

$$\begin{bmatrix} P/F & PVPI \\ \hat{y}_1 & \hat{y}_2 \end{bmatrix}_i = \begin{bmatrix} BSP/F_i & \ln(BSPVPI_i) \end{bmatrix} \begin{bmatrix} \hat{BS}_{P/F} & 0 \\ 0 & \hat{BS}_{PVPI} \end{bmatrix} + \begin{bmatrix} \hat{\mu}_{BALTI,P/F} & \hat{\mu}_{BALTI,PVPI} \end{bmatrix}$$

i = 1 to 56

Where

BSP/F_i = Baseline (pre - surgery) PaO2/FiO2 for ith Subject (Centered)

$BSPVPI_i$ = Baseline (pre - surgery) PVPI for ith Subject (Centered)

To link to observed data assume : $\begin{bmatrix} P/F & PVPI \\ y_1 & y_2 \end{bmatrix}_i \overset{MVN}{\sim} \left(\begin{bmatrix} P/F & PVPI \\ \hat{y}_1 & \hat{y}_2 \end{bmatrix}_i, [\Sigma] \right)$ where Σ is a 2x2

Variance Covariance matrix common to both treatments

Prior distributions are :

$$\begin{bmatrix} \hat{BS}_{P/F} & \hat{BS}_{PVPI} \end{bmatrix} \overset{MVN}{\sim} \left(\begin{bmatrix} 0 & 0 \end{bmatrix}_i, \begin{bmatrix} 1E6 & 0 \\ 0 & 1E6 \end{bmatrix} \right); \text{initial values} \begin{bmatrix} 0.36 & 0.4 \end{bmatrix}$$

$$\begin{bmatrix} \hat{\mu}_{BALTI,P/F} & \hat{\mu}_{BALTI,PVPI} \end{bmatrix} \overset{MVN}{\sim} \left(\begin{bmatrix} 0 & 0 \end{bmatrix}_i, \begin{bmatrix} 1E6 & 0 \\ 0 & 1E6 \end{bmatrix} \right); \text{initial values} \begin{bmatrix} 20 & 0.5 \end{bmatrix}$$

$$\Sigma \overset{iWish}{\sim} \left(2, \begin{bmatrix} 1 & 0 \\ 0 & 1 \end{bmatrix} \right)$$

Example of supplied mean vectors for Placebo and Active arms for the "minimum desired profile"

$$\begin{bmatrix} P/F \\ LN(PVPI) \end{bmatrix} : \mu_p = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix} \mu_a = \begin{bmatrix} 48.6105 \\ 0.602481 \end{bmatrix} \mu_{dif\,\&\,rat} = \begin{bmatrix} 6.3405 \\ -0.16252 \end{bmatrix} \& \begin{bmatrix} 1.15 \\ 0.85 \end{bmatrix} = \begin{matrix} 15\% \uparrow \\ 15\% \downarrow \end{matrix}$$

Distribution used to simulate a future subject for the Placebo and Active arms

$$\begin{bmatrix} y_{Pbo,P/F} & y_{Pbo,PVPI} \end{bmatrix}_k \overset{MVN}{\sim} \left(\begin{bmatrix} 42.27 & 0.765 \end{bmatrix}_i, \Sigma \right)$$

$$\begin{bmatrix} y_{Act,P/F} & y_{Act,PVPI} \end{bmatrix}_k \overset{MVN}{\sim} \left(\begin{bmatrix} 48.6105 & 0.602481 \end{bmatrix}_i, \Sigma \right)$$

k = 1 to 40 and the sampled Σ is the same for each of the 2k subjects within a given MCMC iteration but a new Σ will be drawn for each of the 10,000 MCMC iterations (outer loops)

Generation of the summary statistics for the outer loops

SAS PROC IML was used to read in the PROC MCMC output (a dataset with one row per outer loop containing all subjects data for both treatment arms), and to process each row in turn as follows:

Manipulate/split the row contents into a matrix of dimension 2x40 (separate matrices of endpoints per treatment arm).

Subset each 2x40 matrix into possible interim analysis 2 timings by taking the first 5 observations and then 6th, 7th, etc until reaching the 39th and repeat the following

> Centre each endpoint and derive the sample mean and sample variance covariance matrix (n-1 as the divisor) and also express the sample variance covariance matrix in terms of correlations and save the n per arm at the time of interim
>
> Save each element of these matrices (to give one row per outer loop per possible interim analysis timing containing Pbo and Active summary statistics)

Choice of IA2 timing

Potential IA2 timings examined in this simulation exercise were at 15, 20 and 25 subjects per arm (plus a sanity check of 39 per arm).

Choice of IA2 futility threshold probability (applies within each inner loop)

A series of potential futility threshold probabilities for each inner loop were evaluated (ranging from 0.05 to 0.95 by increments of 0.05 using SAS formats). If the posterior probability of observing any decrease in PaO2/FiO2 in conjunction with any increase in PVPI exceeded the proposed threshold that inner loop was marked as futile.

Choice of IA2 proportion of futile inner loop studies that will trigger the Pause and Review IA2 outcome (applies within each outer loop)

A series of threshold proportions were evaluated (ranging from 0.05 to 0.95 by increments of 0.05 using SAS formats). If the proportion of the (1,000) inner loops marked as futile exceeded the proposed threshold proportion that outer loop was said to have declared a "Pause and Review" outcome.

Selecting the timing and futility threshold

Each inner loop * outer loop * potential IA2 timing * dataset scenario (Table 20) provides a posterior probability of observing any decrease in PaO2/FiO2 in conjunction with any increase in PVPI (giving 1,000*10,000*4*5 = 20,000,000 values).

A series of SAS formats were created to dichotomise each of these 20,000,000 posterior probabilities into binary outcomes (1=Yes/event occurs, 0=No/event did not occur). For example to evaluate 0.1 and 0.65 futility thresholds the following SAS formats would be created:

Low – 0.1 = 0	and	Low – 0.65 = 0
0.1 – High = 1		0.65 – High = 1

In turn, the dataset of posterior probabilities had each SAS formatted applied and was put through PROC FREQ to determine the proportion of inner loops where the posterior probability for futility exceeded the threshold implied by the SAS format (producing a record for each combination of SAS format * outer loop * potential IA2 timing * dataset scenario).

Another set of SAS formats were created and applied in turn to the above dataset. These flagged when the proportion of the inner loops exceeded the proposed value implied by the associated SAS format, i.e. a Pause and Review outcome. Expressing this information as a proportion of Pause and Review outcomes gives a final dataset with one record per potential IA2 timing * dataset scenario combination.

Table 16 details the combinations of dataset scenario, IA2 timing, futility proportions and proportion required to declare Pause and Review that were evaluated. A subset of the simulation results pertinent to the choices made for the protocol are summarised in Table 17. Other results are available on file. The highlighted column in Table 17 reflects the operating characteristics of the IA2 rules/criteria selected by the study team.

Table 16 Factors varied in evaluating IA2 operating characteristics

Every combination of the following factors were evaluated			
Hypothetical Treatment Profile	**Interim Timings (number of observed subjects per arm)**	**Inner loop futility threshold**	**Proportion of inner loops needed to declare "Pause and Review"**
Null Active as BALTI Pre-op Half Active as BALTI Pre-op Quarter Active as BALTI Pre-op Minimum desired profile	39, 25, 20, 15	0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1, 0.05	0.95, 0.9, 0.85, 0.8, 0.75, 0.7, 0.65, 0.6, 0.55, 0.5, 0.45, 0.4, 0.35, 0.3, 0.25, 0.2, 0.15, 0.1, 0.05

Table 17 Selected results from simulation exercise to evaluate IA2 operating characteristics

Hypothetical Treatment Profile	% of simulated outer loops with Pause and Review outcome [Inner loop Futility threshold: 0.1 Proportion of inner loops to declare "Pause and Review": 0.3]			
	IA2 @ 39 p.a.	IA2 @ 25 p.a.	IA2 @ 20 p.a.	IA2 @ 15 p.a.
Null	71.69%	76.15%	76.26%	75.98%
Active as BALTI Pre-op	0.02%	0.31%	1.06%	2.62%
Half Active as BALTI Pre-op	6.17%	15.69%	20.59%	25.82%
Quarter Active as BALTI Pre-op	31.65%	44.41%	48.13%	51.46%
Minimum desired profile	2.24%	7.96%	11.41%	16.46%

Note: Highlighted column (20 per arm) reflects the IA2 choices selected for the study protocol

Note: Whilst writing this RAP a minor error in the SAS code was discovered and corrected (results presented in this RAP reflect the corrected data). The SAS code was not adding dummy records to the first PROC FREQ output dataset to re-include the opposite outcome whenever all inner loops had identical results (i.e. either all 1,000 inner loops were futile, or all 1,000 inner loops were not futile). Therefore the denominators used in subsequent PROC FREQ's (number of input records) were not always as large as they should have been; but this situation was infrequent, so the impact is deemed minimal.

11.12.2. Simulations providing operating characteristics of the target sample size (40 per arm)

The simulated data relating to all 80 subjects within each of the 10,000 outer loops for each dataset scenario were used to obtain sets of sample summary statistics and then to obtain the parameters of the MVN distribution for the End of Study mean treatment differences (see Section 11.12.1 and Table 20). For clarification, since there are no inner loops non-informative priors were used (Table 14) along with the expected value of the inverse-Wishart distribution when deriving the parameters of the MVN distribution for the mean treatment difference.

Discussions within the study team led to the clinically relevant differences that make up Figure 2. The SAS PROBBNRM function was used to obtain the posterior probability of the mean treatment effects being in each region defined by Figure 2, for each outer loop, using the corresponding MVN distribution for the mean treatment difference. This probability only depends upon the location of the clinically relevant differences.

To get the process started an arbitrary probability threshold was assigned as a "trigger" for each region and if the posterior probability of being in the region exceeded the trigger it was deemed to have occurred. Since more than one region may be triggered the algorithm to combined triggered regions to obtain a single outcome was codified as

Overall success	≥1 of the "Success" outcomes	AND	0 "Failures"
Potentially Unsuccessful	0 "Success" outcomes	AND	1 "Failure"
Inconclusive	0 "Success" outcomes	AND	0 "Failures"
Inconsistent	≥1 of the "Success" outcomes	AND	1 "Failure"

Based on the arbitrary trigger thresholds each of the 10,000 outer loops was evaluated to determine which regions (if any) met their probability triggers, and subsequently, which outcome occurred for that outer loop (Note: The language used in Section 9.2.1 of the protocol refers to these probability triggers as "confidence levels"). The operating characteristic of each outcome is the number of observed occurrences expressed as a proportion of the 10,000 outer loops. These were presented to the study team and an iterative process was started to vary these thresholds and observe the impact on operating characteristics.

The "null" and "minimum desired profile" have different desired operating characteristics and the trigger thresholds were varied until the team were comfortable with the operating characteristics of both. This led to the criteria in Figure 2 (probability triggers of 0.75 for Step 1, 0.25 for Step 2 and 0.35 for Step 3; denoted {0.75, 0.25, 0.35}) and the resulting operating characteristics in Table 18 that were presented in Table 5 of the study protocol (re-produced here using all scenarios from Table 20).

Table 18 Results from Simulation exercise assuming 40 p.a. complete

Hypothetical Treatment Profile	% of simulated studies with outcome			
	Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	4.65%	92.81%	2.54%	0%
Active as BALTI Pre-op	92.72%	6.83%	0.45%	0%
Half Active as BALTI Pre-op	40.93%	49.98%	9.09%	0%
Quarter Active as BALTI Pre-op	15.61%	77.13%	7.26%	0%
Minimum desired profile	80.64%	13.63%	5.73%	0%

A well performing end of study decision pathway should not be expected to conclude success for the "Null" profile whilst reliably concluding success for the "minimum desired profile". In the language of frequentist hypothesis testing the "Overall success"

probabilities for the Null and Minimum desired profile are akin to the Type I error rate and power for the study design respectively. These were estimated to be 4.65% and 80.64% respectively so the study design and end of study pathway was deemed acceptable (assuming 40 evaluable subjects per arm and residual variance covariance estimates in line with the BALTI trial (Perkins, 2014)).

An additional step evaluated the operating characteristics of the final end of study decision pathway (Figure 2) using 25, 30 and 35 subjects per arm. Unsurprisingly, the operating characteristics were not as good, given the reduced information content (see Table 19).

This exercise was also repeated using the following sets of probability triggers for the three steps of Figure 2: {0.75, 0.25, 0.50}, {0.70, 0.25, 0.50}, {0.95, 0.25, 0.50}, {0.95, 0.25, 0.35} and {0.75, 0.25, 0.25}; results presented in Table 21, Table 22, Table 23, Table 24 and Table 25 respectively.

Note: Candidate combinations of probability thresholds were selected based upon review of the distributions formed from the 10,000 outer loop probabilities associated with the 3x outcomes described in Figure 2 for each dataset in Table 20 and for 25, 30 , 35 and 40 per arm total sample size. These are shown in Figure 5, Figure 6, Figure 7, Figure 8 and Figure 9. In these figures the boxid's titled "Fail", "Strong Success" and "Success" correspond to the Step 1, Step 2 and Step 3 probability thresholds respectively. A threshold would be a vertical slice placed on the x-axis and the proportion exceeding the slice would be the expected proportion triggering that rule (but the overall outcome requires the codifying rules described above).

Table 19 Results from Sensitivity analysis assuming 25, 30 and 35 p.a. complete

Hypothetical Treatment Profile	n (p.a.)	% of simulated studies with outcome			
		Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	25	9.38%	86.03%	4.59%	0%
	30	7.32%	88.52%	4.16%	0%
	35	5.65%	90.91%	3.44%	0%
Active as BALTI Pre-op	25	88.49%	9.98%	1.53%	0%
	30	90.04%	8.97%	0.99%	0%
	35	91.51%	7.86%	0.63%	0%
Half Active as BALTI Pre-op	25	44.57%	46.42%	9.01%	0%
	30	42.84%	47.68%	9.48%	0%
	35	42.08%	48.64%	9.28%	0%
Quarter Active as BALTI Pre-op	25	21.96%	68.95%	9.09%	0%
	30	19.50%	72.31%	8.19%	0%
	35	17.49%	74.95%	7.56%	0%
Minimum desired profile	25	76.41%	17.06%	6.53%	0%
	30	77.71%	15.91%	6.38%	0%
	35	79.25%	14.9%	5.85%	0%

Table 20 Hypothetical scenarios for generating datasets

DID	DID Desc'	Pbo Vector for Immediate Post-op mean response	Active Vector for Post-op mean response	MAX n p.a.	nmc
1	Null	$\begin{bmatrix} P/F \\ LN(PVPI) \end{bmatrix} : \mu_p = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix}$	$\mu_a = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix} \mu_{dif\,\&rat} = \begin{bmatrix} 0 \\ 0 \end{bmatrix} \& \begin{bmatrix} 1 \\ 1 \end{bmatrix} = NOCHANGE$	40	10000
2	Active as BALTI Pre-op	$\begin{bmatrix} P/F \\ LN(PVPI) \end{bmatrix} : \mu_p = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix}$	$\mu_a = \begin{bmatrix} 53.14 \\ 0.577 \end{bmatrix} \mu_{dif\,\&rat} = \begin{bmatrix} 10.87 \\ -0.188 \end{bmatrix} \& \begin{bmatrix} 1.257 \\ 0.829 \end{bmatrix} = \begin{matrix} 25.7\% \uparrow \\ 17.1\% \downarrow \end{matrix}$	40	10000
3	Half Active as BALTI Pre-op	$\begin{bmatrix} P/F \\ LN(PVPI) \end{bmatrix} : \mu_p = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix}$	$\mu_a = \begin{bmatrix} 47.705 \\ 0.671 \end{bmatrix} \mu_{dif\,\&rat} = \begin{bmatrix} 5.435 \\ -0.094 \end{bmatrix} \& \begin{bmatrix} 1.129 \\ 0.910 \end{bmatrix} = \begin{matrix} 12.9\% \uparrow \\ 9.0\% \downarrow \end{matrix}$	40	10000
4	Quarter Active as BALTI Pre-op	$\begin{bmatrix} P/F \\ LN(PVPI) \end{bmatrix} : \mu_p = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix}$	$\mu_a = \begin{bmatrix} 44.985 \\ 0.718 \end{bmatrix} \mu_{dif\,\&rat} = \begin{bmatrix} 2.715 \\ -0.047 \end{bmatrix} \& \begin{bmatrix} 1.064 \\ 0.954 \end{bmatrix} = \begin{matrix} 6.4\% \uparrow \\ 4.6\% \downarrow \end{matrix}$	40	10000
5	Minimum desired profile	$\begin{bmatrix} P/F \\ LN(PVPI) \end{bmatrix} : \mu_p = \begin{bmatrix} 42.27 \\ 0.765 \end{bmatrix}$	$\mu_a = \begin{bmatrix} 48.6105 \\ 0.602481 \end{bmatrix} \mu_{dif\,\&rat} = \begin{bmatrix} 6.3405 \\ -0.16252 \end{bmatrix} \& \begin{bmatrix} 1.15 \\ 0.85 \end{bmatrix} = \begin{matrix} 15\% \uparrow \\ 15\% \downarrow \end{matrix}$	40	10000

DID = Dataset ID, p.a. = per arm, nmc = Number of MCMC iterations (Outer loops)

Table 21 Results from probability threshold set {0.75, 0.25, 0.50} and Sensitivity analysis assuming 25, 30, 35 and 40 p.a. complete

Hypothetical Treatment Profile	n (p.a.)	% of simulated studies with outcome			
		Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	25	6.06%	86.03%	7.91%	0%
	30	4.46%	88.52%	7.02%	0%
	35	3.52%	90.91%	5.57%	0%
	40	2.65%	92.81%	4.54%	0%
Active as BALTI Pre-op	25	88.15%	9.98%	1.87%	0%
	30	89.75%	8.97%	1.28%	0%
	35	91.31%	7.86%	0.83%	0%
	40	92.57%	6.83%	0.60%	0%
Half Active as BALTI Pre-op	25	40.40%	46.42%	13.18%	0%
	30	39.04%	47.68%	13.28%	0%
	35	37.90%	48.64%	13.46%	0%
	40	37.12%	49.98%	12.90%	0%
Quarter Active as BALTI Pre-op	25	17.42%	68.95%	13.63%	0%
	30	15.24%	72.31%	12.45%	0%
	35	13.32%	74.95%	11.73%	0%
	40	11.38%	77.13%	11.49%	0%
Minimum desired profile	25	73.06%	17.06%	9.88%	0%
	30	74.61%	15.91%	9.48%	0%
	35	76.04%	14.90%	9.06%	0%
	40	77.53%	13.63%	8.84%	0%

Table 22 Results from probability threshold set {0.70, 0.25, 0.50} and Sensitivity analysis assuming 25, 30, 35 and 40 p.a. complete

Hypothetical Treatment Profile	n (p.a.)	% of simulated studies with outcome			
		Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	25	6.06%	87.89%	6.05%	0%
	30	4.45%	90.31%	5.23%	0.01%
	35	3.50%	92.73%	3.75%	0.02%
	40	2.65%	93.96%	3.39%	0%
Active as BALTI Pre-op	25	86.71%	10.60%	1.25%	1.44%
	30	88.46%	9.43%	0.82%	1.29%
	35	89.92%	8.12%	0.57%	1.39%
	40	91.40%	7.01%	0.42%	1.17%
Half Active as BALTI Pre-op	25	39.47%	49.87%	9.73%	0.93%
	30	38.13%	51.15%	9.81%	0.91%
	35	37.13%	51.98%	10.12%	0.77%
	40	36.16%	53.19%	9.69%	0.96%
Quarter Active as BALTI Pre-op	25	17.16%	72.28%	10.30%	0.26%
	30	15.08%	75.27%	9.49%	0.16%
	35	13.12%	78.02%	8.66%	0.20%
	40	11.24%	79.99%	8.63%	0.14%
Minimum desired profile	25	72.40%	19.14%	7.80%	0.66%
	30	73.85%	17.97%	7.42%	0.76%
	35	75.39%	16.76%	7.20%	0.65%
	40	76.92%	15.23%	7.24%	0.61%

Table 23 Results from probability threshold set {0.95, 0.25, 0.50} and Sensitivity analysis assuming 25, 30, 35 and 40 p.a. complete

Hypothetical Treatment Profile	n (p.a.)	% of simulated studies with outcome			
		Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	25	6.06%	65.60%	28.34%	0%
	30	4.46%	71.10%	24.44%	0%
	35	3.52%	75.65%	20.83%	0%
	40	2.65%	79.01%	18.34%	0%
Active as BALTI Pre-op	25	88.15%	2.44%	9.41%	0%
	30	89.75%	2.30%	7.95%	0%
	35	91.31%	1.67%	7.02%	0%
	40	92.57%	1.55%	5.88%	0%
Half Active as BALTI Pre-op	25	40.40%	22.09%	37.51%	0%
	30	39.04%	23.24%	37.72%	0%
	35	37.90%	23.89%	38.21%	0%
	40	37.12%	24.84%	38.04%	0%
Quarter Active as BALTI Pre-op	25	17.42%	42.69%	39.89%	0%
	30	15.24%	46.59%	38.17%	0%
	35	13.32%	49.17%	37.51%	0%
	40	11.38%	52.51%	36.11%	0%
Minimum desired profile	25	73.06%	5.06%	21.88%	0%
	30	74.61%	4.64%	20.75%	0%
	35	76.04%	4.24%	19.72%	0%
	40	77.53%	3.94%	18.53%	0%

Table 24 Results from probability threshold set {0.95, 0.25, 0.35} and Sensitivity analysis assuming 25, 30, 35 and 40 p.a. complete

Hypothetical Treatment Profile	n (p.a.)	% of simulated studies with outcome			
		Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	25	9.38%	65.60%	25.02%	0%
	30	7.32%	71.10%	21.58%	0%
	35	5.65%	75.65%	18.70%	0%
	40	4.65%	79.01%	16.34%	0%
Active as BALTI Pre-op	25	88.49%	2.44%	9.07%	0%
	30	90.04%	2.30%	7.66%	0%
	35	91.51%	1.67%	6.82%	0%
	40	92.72%	1.55%	5.73%	0%
Half Active as BALTI Pre-op	25	44.57%	22.09%	33.34%	0%
	30	42.84%	23.24%	33.92%	0%
	35	42.08%	23.89%	34.03%	0%
	40	40.93%	24.84%	34.23%	0%
Quarter Active as BALTI Pre-op	25	21.96%	42.69%	35.35%	0%
	30	19.50%	46.59%	33.91%	0%
	35	17.49%	49.17%	33.34%	0%
	40	15.61%	52.51%	31.88%	0%
Minimum desired profile	25	76.41%	5.06%	18.53%	0%
	30	77.71%	4.64%	17.65%	0%
	35	79.25%	4.24%	16.51%	0%
	40	80.64%	3.94%	15.42%	0%

Table 25 Results from probability threshold set {0.75, 0.25, 0.25} and Sensitivity analysis assuming 25, 30, 35 and 40 p.a. complete

Hypothetical Treatment Profile	n (p.a.)	% of simulated studies with outcome			
		Overall Success	Potentially Unsuccessful	Inconclusive	Inconsistent
Null	25	12.70%	86.03%	1.27%	0%
	30	10.36%	88.52%	1.12%	0%
	35	8.21%	90.91%	0.88%	0%
	40	6.62%	92.81%	0.57%	0%
Active as BALTI Pre-op	25	88.89%	9.98%	1.13%	0%
	30	90.26%	8.97%	0.77%	0%
	35	91.61%	7.86%	0.53%	0%
	40	92.80%	6.83%	0.37%	0%
Half Active as BALTI Pre-op	25	48.33%	46.42%	5.25%	0%
	30	46.59%	47.68%	5.73%	0%
	35	45.81%	48.64%	5.55%	0%
	40	44.63%	49.98%	5.39%	0%
Quarter Active as BALTI Pre-op	25	26.85%	68.95%	4.20%	0%
	30	23.87%	72.31%	3.82%	0%
	35	21.64%	74.95%	3.41%	0%
	40	19.92%	77.13%	2.95%	0%
Minimum desired profile	25	79.08%	17.06%	3.86%	0%
	30	80.15%	15.91%	3.94%	0%
	35	81.54%	14.90%	3.56%	0%
	40	83.04%	13.63%	3.33%	0%

Figure 5 Hypothetical Treatment Profile used to generate data (subjects)=Null

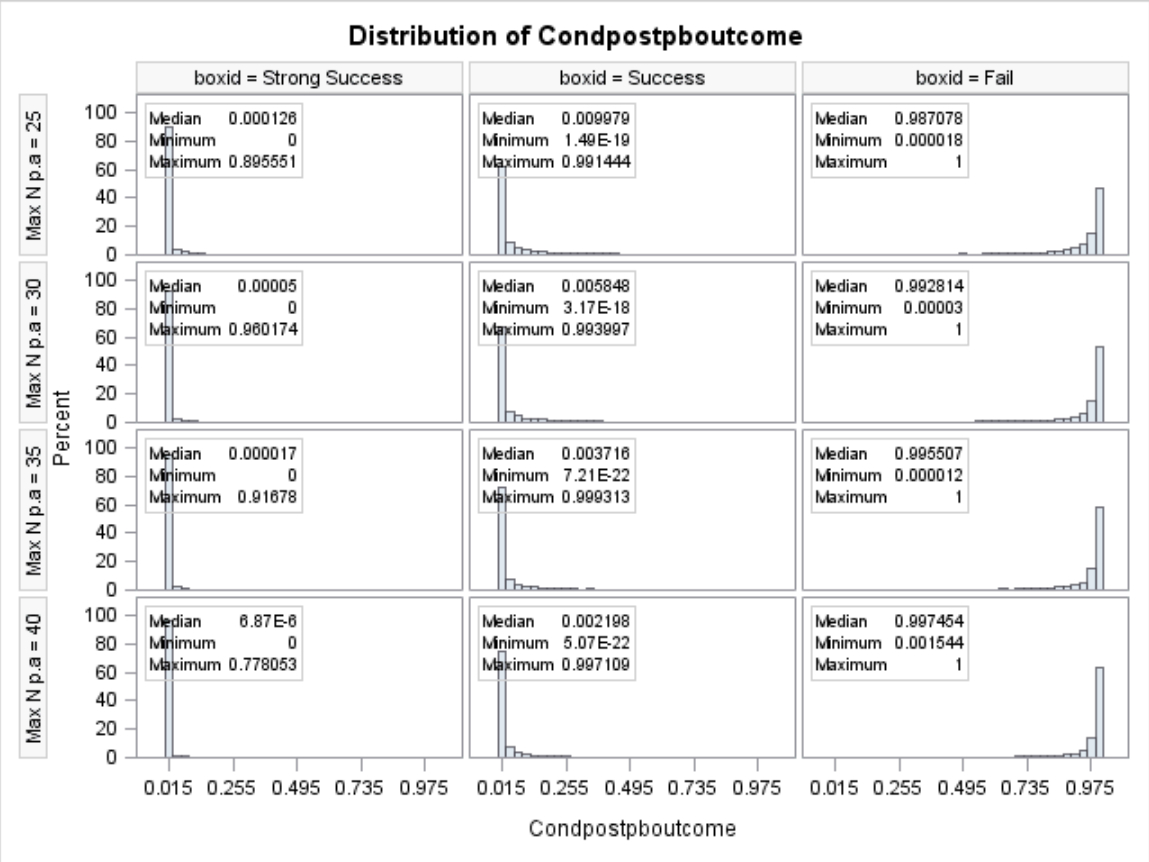


Figure 6 Hypothetical Treatment Profile used to generate data (subjects)= Active as BALTI Pre-op

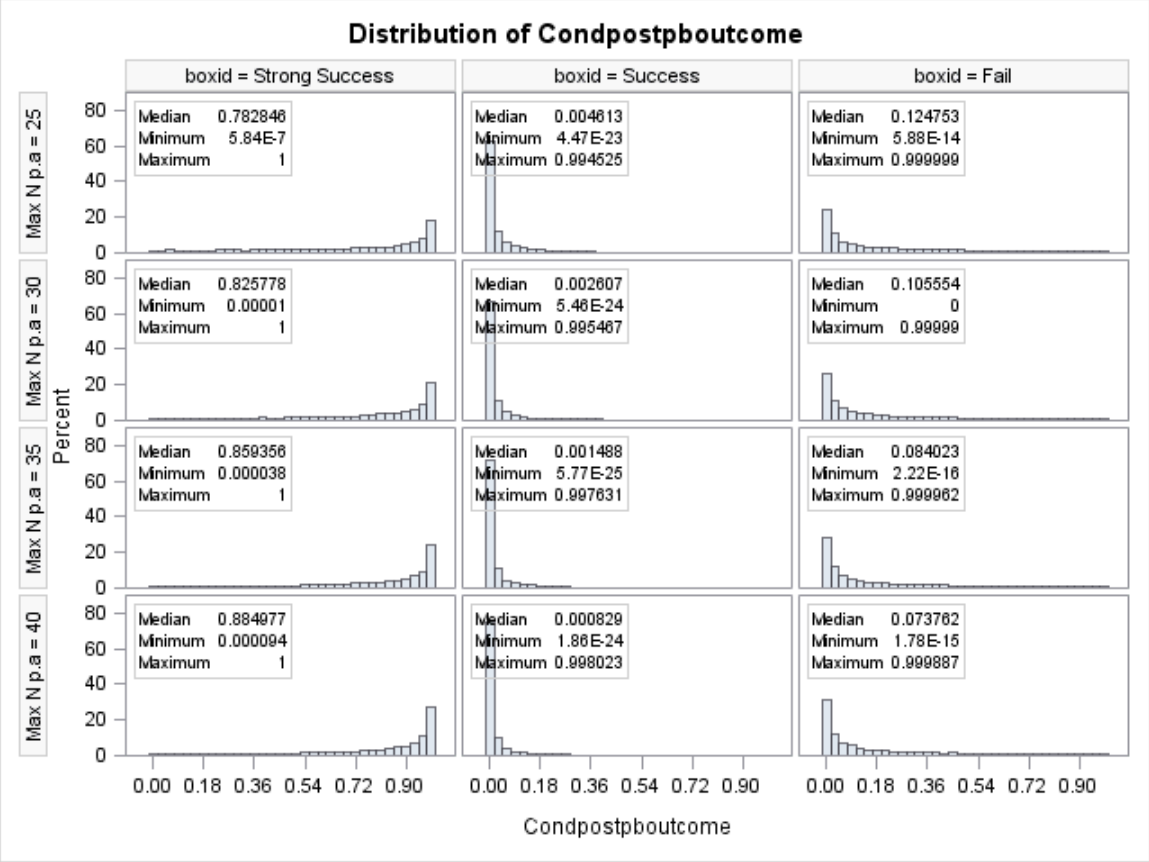


Figure 7 Hypothetical Treatment Profile used to generate data (subjects)= Half Active as BALTI Pre-op

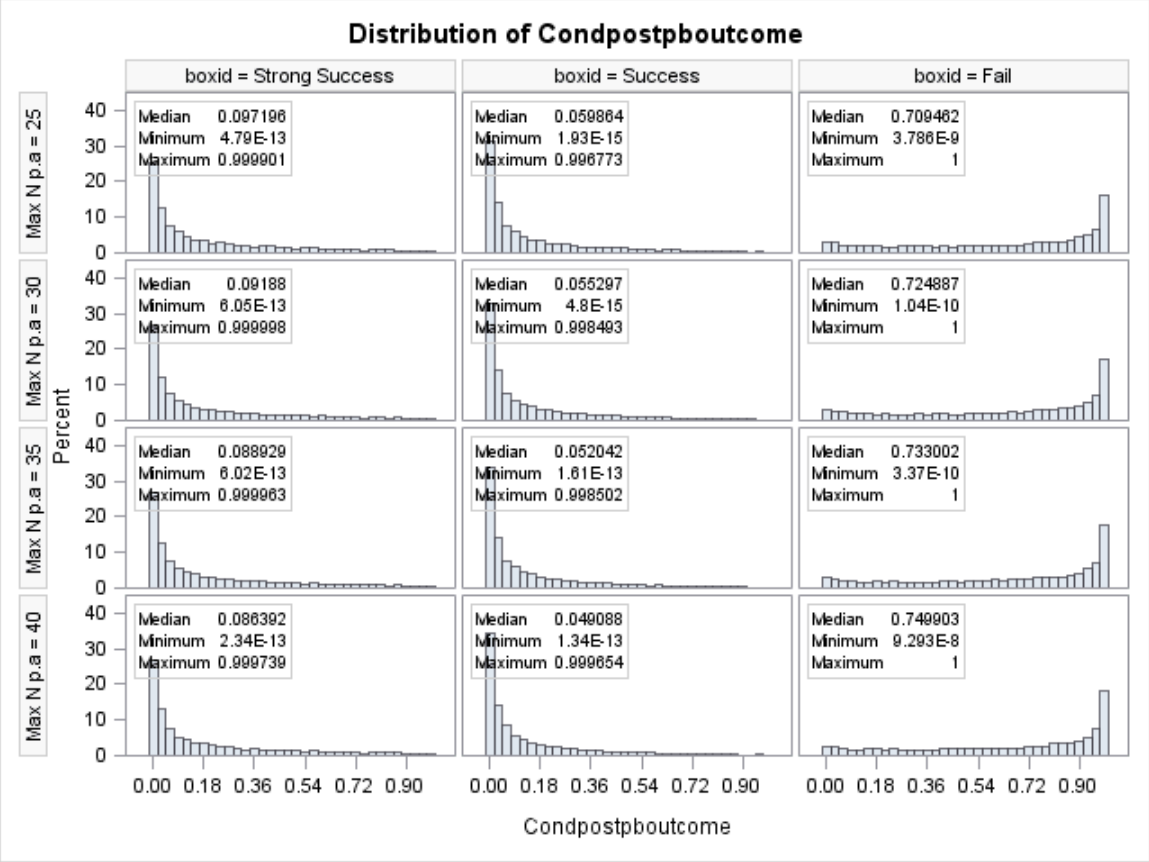


Figure 8 Hypothetical Treatment Profile used to generate data (subjects)= Quarter Active as BALTI Pre-op

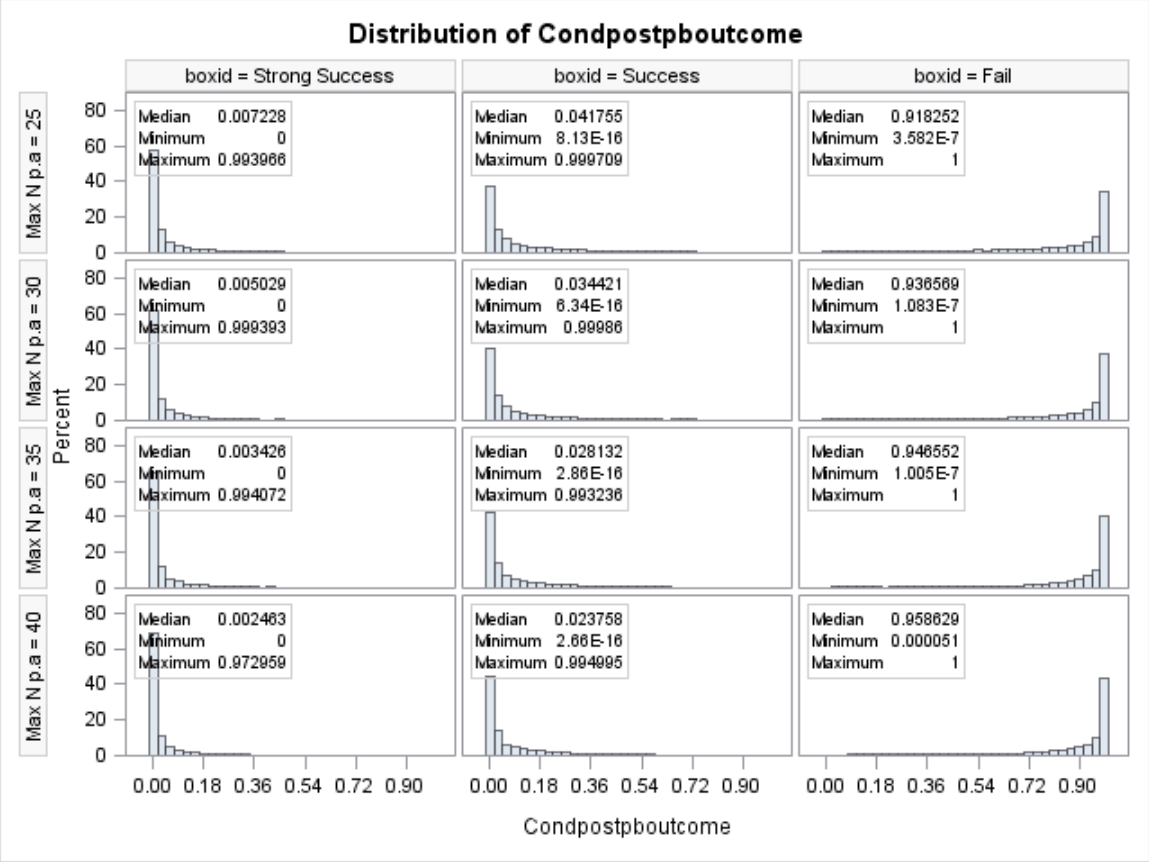
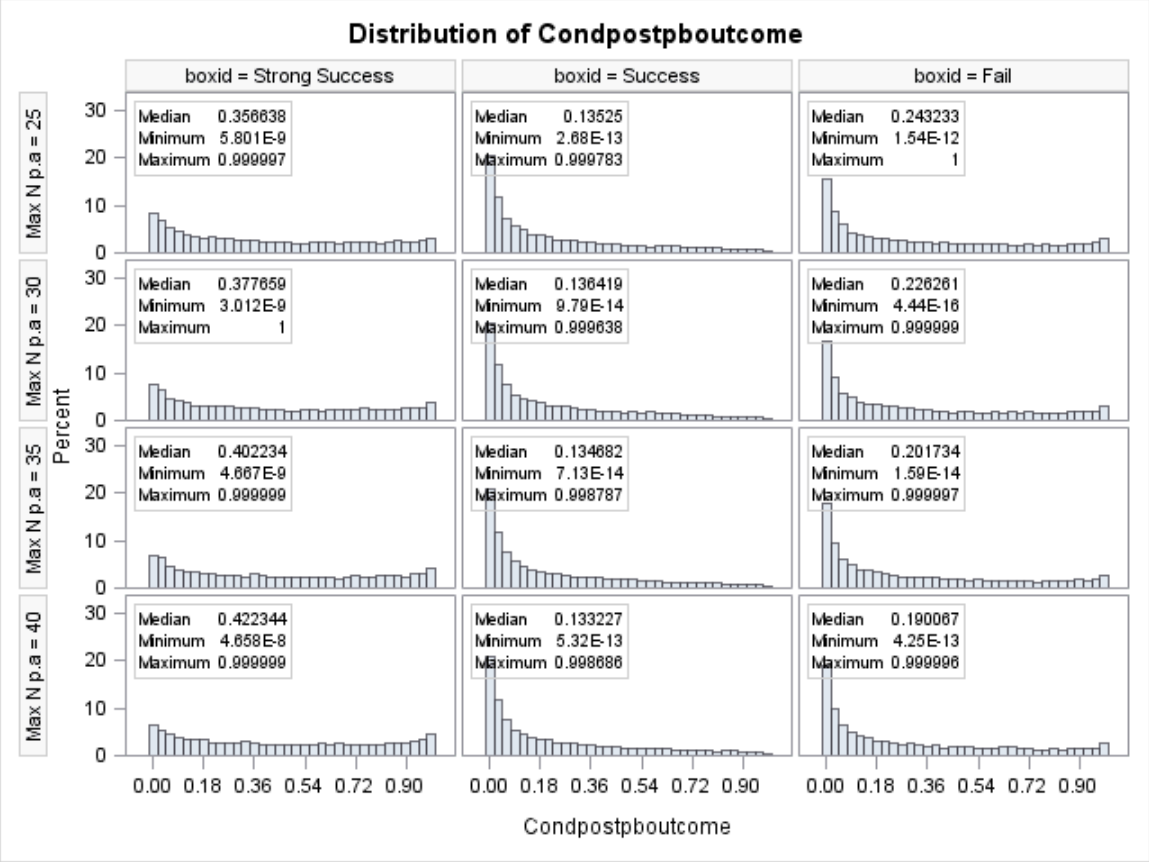


Figure 9 Hypothetical Treatment Profile used to generate data (subjects)= Minimum desired profile



11.13. Appendix 13: Abbreviations & Trade Marks

11.13.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ELF	Epithelial Lining Fluid
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
ITT	Intent-To-Treat
GSK	GlaxoSmithKline
GUI	Guidance
LOC	Last Observation Carries Forward
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
QC	Quality Control
QTcF	Frederica'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
SAC	Statistical Analysis Complete
SDTM	Study Data Tabulation Model
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operation Procedure

Abbreviation	Description
TA	Therapeutic Area
TFL	Tables, Figures & Listings
Note: See Table 13 for abbreviations used in Transpulmonary Thermodilution	

11.13.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
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11.14. Appendix 14: List of Data Displays

11.14.1. 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
Pharmacogenetics	6.1 to 7.n	6.1 to 7.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	(x+1) to z	

11.14.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 15 : 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
Pharmacogenetics	PGX_Fn	PGX_Tn	PGX_Ln

NOTES:

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

11.14.3. Deliverable [Priority]

Delivery [Priority] [1]	Description
DS [X]	During Study
DE [X]	Dose Escalation
IAn [X]	Interim Analysis<n> Statistical Analysis Complete
SAC [X]	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort.

11.14.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Accountability					
1.1.	n/a	POP_T1	Summary of Subject Accountability (subjects constituting each Statistical Analysis Population)	Statistical analysis population by treatment. Create categories for the main treatment descriptors and for each of the alternative sets (grouping by study medication and BAL sampling location)	IA1 [1], IA2 [2], SAC [1]
Subject Disposition					
1.2.	Safety	ES1	Summary of Subject Disposition		SAC [1]
1.3.	Screen Failures	ES6	Summary of Reasons for Screening Failure	Facilitates CONSORT diagram in publications. Therefore also sub-total the inclusion/exclusion category by the applicable individual criteria (e.g. exclusion due to presence of pre-existing ADA antibodies).	SAC [1]
1.4.	Safety	DV1b	Summary of Important Protocol Deviations	Create Separate “block” for each of the three per protocol populations in the style given in the shell.	SAC [1]
Demography					
1.5.	Safety	DM1	Summary of Demographic Characteristics (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
1.6.	Safety	DM1	Summary of Demographic Characteristics (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
1.7.	Safety	DM1	Summary of Demographic Characteristics (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	Safety	DM5	Summary of Race and Racial Combinations Details (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
1.9.	Safety	DM5	Summary of Race and Racial Combinations Details (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
1.10.	Safety	DM5	Summary of Race and Racial Combinations Details (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
1.11.	Safety	SAFE_T1	Number of Subjects per Country by Treatment Group	Macro: EMA_COUNTRY	SAC [1]
1.12.	Safety	SAFE_T2	Number of Subjects in each Age Group by Treatment Group	Macro: EMA_AGEGRP All age categories (in years) will be produced if they exist in the data, and according to the EMA requirements. If age unit is other than year, then programming modifications will be required.	SAC [1]
Medical Condition & Concomitant Medications					
1.13.	Safety	MH4	Summary of Current Medical Conditions (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
1.14.	Safety	MH4	Summary of Current Medical Conditions (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
1.15.	Safety	MH4	Summary of Current Medical Conditions (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
1.16.	Safety	MH4	Summary of Past Medical Conditions (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.17.	Safety	MH4	Summary of Past Medical Conditions (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
1.18.	Safety	MH4	Summary of Past Medical Conditions (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
1.19.	Safety	CP_CM1	Summary of Concomitant Medications by Generic Term (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
1.20.	Safety	CP_CM1	Summary of Concomitant Medications by Generic Term (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
1.21.	Safety	CP_CM1	Summary of Concomitant Medications by Generic Term (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]

11.14.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Analysis					
2.1.	PP1	EFF_T1	Summary Statistics supporting Primary Analysis (Absolute and Change from Baseline): PVPI and PaO2/FiO2 (by Treatment arm)	Use Main Treatment Group Descriptors Only include timepoints associated with the primary analysis (i.e. the two assessments on Day 1: prior to surgery/post surgery).	IA2 [1], SAC [1]
2.2.	PP2	EFF_T1	Summary Statistics supporting Primary Analysis (Absolute and Change from Baseline): PVPI and PaO2/FiO2 (by Study Medication)	Use Alternative Treatment Group Descriptors #1 Only include timepoints associated with the primary analysis (i.e. the two assessments on Day 1: prior to surgery/post surgery).	IA2 [1], SAC [1]
2.3.	PP1	EFF_T1	Summary Statistics supporting Primary Analysis (Absolute and Change from Baseline): PVPI and PaO2/FiO2 (by BAL Location)	Use Alternative Treatment Group Descriptors #2 Only include timepoints associated with the primary analysis (i.e. the two assessments on Day 1: prior to surgery/post surgery).	IA2 [1], SAC [1]
2.4.	PP2	EFF_T2	Summary of Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.	Example shell conditional on the Trt*BAL interaction term being non-significant. Use expert judgement to override the shell if an alternative layout is more informative / easier to review Assign a statistical analysis ID number to each analysis and page by this variable (mechanism to allow sensitivity analyses to be presented if applicable)	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Analyses					
	Transpulmonary Thermodilution				
2.5.	PP1	EFF_T1	Summary Statistics (Absolute and Change from Baseline):Transpulmonary Thermodilution (by Treatment arm)	Use Main Treatment Group Descriptors See Table 4 for endpoints (Arterial Line, Predicted body weight, predicted body surface area and body surface area only do need to be summarised at multiple timepoints).	SAC [1]
2.6.	PP2	EFF_T1	Summary Statistics (Absolute and Change from Baseline):Transpulmonary Thermodilution (by Study Medication)	Use Alternative Treatment Group Descriptors #1 See above comments	SAC [1]
2.7.	PP1	EFF_T1	Summary Statistics (Absolute and Change from Baseline):Transpulmonary Thermodilution (by BAL Location)	Use Alternative Treatment Group Descriptors #2 See above comments	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	PP2	EFF_T2	Summary of Statistical Analysis: Repeated Measures Joint Modelling of PVPI and PaO2/FiO2	Example shell conditional on the Trt*BAL*Time interaction terms being non-significant. Use expert judgement to override the shell if an alternative layout is more informative / easier to review It is not possible to display all elements of the VCV from the actual MCMC modelling using this layout (e.g. the off diagonal elements across planned time). Add footnote to alert user that this has occurred. Assign a statistical analysis ID number to each analysis and page by this variable (mechanism to allow sensitivity analyses to be presented if applicable)	SAC [1]
2.9.	PP2	EFF_T5	Summary of Statistical Analysis: Modelling of PVPI on Completion of Surgery	Example shell conditional on the Trt*BAL interaction term being non-significant. Use expert judgement to override the shell if an alternative layout is more informative / easier to review Assign a statistical analysis ID number to each analysis and page by this variable (mechanism to allow sensitivity analyses to be presented if applicable)	SAC [1]
2.10.	PP2	EFF_T5	Summary of Statistical Analysis: Modelling of EVLWI on Completion of Surgery	See above comments	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
	Oxygenation (especially P_aO_2/F_iO_2)				
2.11.	PP1	EFF_T1	Summary Statistics (Absolute and Change from Baseline):Oxygenation (by Treatment arm)	Use Main Treatment Group Descriptors See Table 4 for endpoints. Also include the imputed version of PaO2/FiO2	SAC [1]
2.12.	PP2	EFF_T1	Summary Statistics (Absolute and Change from Baseline): Oxygenation (by Study Medication)	Use Alternative Treatment Group Descriptors #1 See above comments	SAC [1]
2.13.	PP1	EFF_T1	Summary Statistics (Absolute and Change from Baseline): Oxygenation (by BAL Location)	Use Alternative Treatment Group Descriptors #2 See above comments	SAC [1]
2.14.	PP2	EFF_T5	Summary of Statistical Analysis: Modelling of PaO2/FiO2 on Completion of Surgery	Example shell conditional on the Trt*BAL interaction term being non-significant. Use expert judgement to override the shell if an alternative layout is more informative / easier to review Assign a statistical analysis ID number to each analysis and page by this variable (mechanism to allow sensitivity analyses to be presented if applicable)	SAC [1]
	SOFA				
2.15.	PP2	EFF_T1	Summary Statistics (Absolute and Change from Baseline): Daily SOFA scores by Treatment and Time	Display Total SOFAs (observed then imputed).	SAC [1]
2.16.	PP2	EFF_T5	Summary of Statistical Analysis of Repeated Measures Modelling of SOFA	Make appropriate modifications to account for the repeated measures	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exploratory Analyses					
	Clinical Outcomes				
2.17.	PP2		Summary of Diagnosed ARDS out to day 28 (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC [2]
2.18.	PP2		Summary of 28 day survival status (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC [2]
2.19.	PP2		Summary of Organ Failure Free days out to day 28 (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC [2]
	Resource Utilisation				
2.20.	PP2		Summary of Ventilator Free Days (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC [2]
2.21.	PP2		Summary of ICU Length of Stay (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC [2]
2.22.	PP2		Summary of Hospital Length of Stay (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC [2]
Bespoke outputs to support the Interim Analyses					
2.23.	PP2	EFF_T3	Summary of Futility Statistical Analysis at Interim Analysis 2		IA2 [1]
2.24.	PP2	EFF_T4	Summary of Sample Size re-estimation process at Interim Analysis 2		IA2 [1]

11.14.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Analysis					
2.1.	PP2	EFF_F5	Spaghetti plots of PVPI and PaO2/FiO2 Time Profiles (by Treatment arm)	Separate plot per endpoint. Identify subjects using the main treatment descriptors. Plot Ln(PVPI) by using Ln scale axis Only use Pre-Op and imm.Post Op timepoints	IA2 [1], SAC [1]
2.2.	PP2	EFF_F6	Scatterplots of PVPI Vs PaO2/FiO2 by Study Medication and Timepoint	Identify subjects using the main treatment descriptors Only use Pre-Op and imm.Post Op timepoints	IA2 [1], SAC [1]
2.3.	PP2	EFF_F7	Adjusted Medians and 95% Credible Intervals from the Marginal Posterior Distributions for each Study medication (PVPI and PaO2/FiO2)		IA2 [1], SAC [1]
2.4.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals from the Marginal Posterior Distributions for Study medications comparisons (PVPI and PaO2/FiO2)		IA2 [1], SAC[1]
2.5.	PP2	EFF_F4	Joint Posterior Distribution and associated Marginals used to evaluate End of Study Decision Pathway		IA2 [1], SAC[1]
Secondary Analyses					
	Transpulmonary Thermodilution				
2.6.	PP2	EFF_F1	Individual Subject PVPI and EVLWI Time Profiles	Include all data for the subjects (inc unscheduled). Use actual times. Try to keep all endpoints on the same page per subject and panel by endpoint	SAC[1]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.7.	PP2	EFF_F5	Spaghetti plots of PVPI and EVLWI Time Profiles (by Treatment arm)	Separate plot/page per endpoint.	SAC[1]
2.8.	PP2	EFF_F6	Scatterplots of PVPI Vs PaO2/FiO2 by Study Medication and Timepoint		SAC[1]
2.9.	PP2	EFF_F7	Adjusted Medians and 95% Credible Intervals from the Marginal Posterior Distributions for each Study medication (PVPI and PaO2/FiO2)	Use Planned Timepoint as the x-axis of the plot but offset/group by treatment to avoid overlapping	SAC[1]
2.10.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals from the Marginal Posterior Distributions for Study medications comparisons (PVPI and PaO2/FiO2)	Use Planned Timepoint as the x-axis of the plot	SAC[1]
2.11.	PP2	EFF_F7	Adjusted Medians and 95% Credible Intervals for each Study medication from the Modelling of PVPI on Completion of Surgery		SAC[1]
2.12.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals for Study medication comparisons from the Modelling of PVPI on Completion of Surgery		SAC[1]
2.13.	PP2	EFF_F7	Adjusted Medians and 95% Credible Intervals for each Study medication from the Modelling of EVLWI on Completion of Surgery		SAC[1]
2.14.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals for Study medication comparisons from the Modelling of EVLWI on Completion of Surgery		SAC[1]
Oxygenation (especially P_aO_2/F_iO_2)					
2.15.	PP2	EFF_F3	Individual Subject Oxygenation Time Profiles	Include all data for the subjects (inc unscheduled). Use actual times. If possible put all endpoints on the same panel. Add the imputed PaO2/FiO2 profile as well.	SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	PP2	EFF_F5	Spaghetti plots of PaO2/FiO2 and SpO2/FiO2 Time Profiles (by Treatment arm)	Separate plot/page per endpoint. Also add the impuited PaO2/FiO2	SAC [1]
2.17.	PP2	EFF_F2	Scatterplot of Observed PaO2/FiO2 and the PaO2/FiO2 value imputed from the associated SpO2/FiO2	Only plot data where observed PaO2/FiO2 and SpO2/FiO2 data are present. Identify data points using the main treatment descriptor symbols and the b-splines using the associated line pattern.	SAC[1]
2.18.	PP2	EFF_F7	Adjusted Medians and 95% Credible Intervals for each Study medication from the Modelling of PaO2/FiO2 on Completion of Surgery		SAC[1]
2.19.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals for Study medication comparisons from the Modelling of PaO2/FiO2 on Completion of Surgery		SAC[1]
SOFA					
2.20.	PP2	EFF_F1	Individual Subject SOFA Time Profiles	Include all data for the subjects (inc unscheduled). Use actual times.	SAC [1]
2.21.	PP2	EFF_F7 / EFF_F1	Adjusted Medians and 95% Credible Intervals for each Study medication from the Repeated Measures Modelling of SOFA	Use Planned Timepoint as the x-axis of the plot but offset/group by treatment to avoid overlapping	SAC[1]
2.22.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals for Study medication comparisons from the Repeated Measures Modelling of SOFA	Use Planned Timepoint as the x-axis of the plot	SAC[1]
Exploratory Analyses					
Clinical Outcomes					
2.23.	PP2		Kaplan Meier survival curves for Day 28 Survival status (and approx 95% CIs) (by Study Medication)	Use Alternative Treatment Group Descriptors #1	SAC[2]

11.14.7. Safety Tables

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	CP_AE1p	Summary of All Serious Adverse Events (by Treatment arm)	Sort by System Organ Class Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.2.	Safety	CP_AE1p	Summary of All Serious Adverse Events (by Study Medication)	Sort by System Organ Class Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.3.	Safety	CP_AE1p	Summary of All Serious Adverse Events (by BAL Location)	Sort by System Organ Class Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
3.4.	Safety	CP_AE1p	Summary of All Adverse Events (by Treatment arm)	Sort by System Organ Class Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.5.	Safety	CP_AE1p	Summary of All Adverse Events (by Study Medication)	Sort by System Organ Class Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.6.	Safety	CP_AE1p	Summary of All Adverse Events (by BAL Location)	Sort by System Organ Class Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
3.7.	Safety	CP_AE1p	Summary of Drug-Related Adverse Events (by Treatment arm)	Sort by System Organ Class Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.8.	Safety	CP_AE1p	Summary of Drug-Related Adverse Events (by Study Medication)	Sort by System Organ Class Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.9.	Safety	CP_AE1p	Summary of Drug-Related Adverse Events (by BAL Location)	Sort by System Organ Class Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.10.	Safety	AE2	Relationship between System Organ Class and Verbatim Text		IA1 [1], IA2 [2], SAC [1]
3.11.	Safety	SAFE_T3	All Non-Serious Adverse Event Counts that Occur in at least 5% of Any Treatment Group	Macro: EMA_AE	SAC [2]
3.12.	Safety	SAFE_T4	All Serious Adverse Event Counts	Macro: EMA_AE The 'Number of Related Fatalities' is only required at the Preferred Term level for reporting and is intentionally left out of the 'Any events' group	SAC [2]
Laboratory Values					
3.13.	Safety	LB1	Summary of Chemistry Laboratory Values (by Treatment arm)	Exclude Pa02 from this summary Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.14.	Safety	LB1	Summary of Chemistry Laboratory Values (by Study Medication)	Exclude Pa02 from this summary Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.15.	Safety	LB1	Summary of Chemistry Laboratory Values (by BAL Location)	Exclude Pa02 from this summary Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
3.16.	Safety	LB1	Summary of Hematology Laboratory Values (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.17.	Safety	LB1	Summary of Hematology Laboratory Values (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.18.	Safety	LB1	Summary of Hematology Laboratory Values (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.19.	Safety	UR3b	Summary of Urinalysis Dipstick Results (by Treatment arm)	Use Main Treatment Group Descriptors Note: Consult with medical monitor to "map" results within each test to a common nomenclature prior to summarising	IA1 [1], IA2 [2], SAC [1]
3.20.	Safety	UR3b	Summary of Urinalysis Dipstick Results (by Study Medication)	Use Alternative Treatment Group Descriptors #1 Note: Consult with medical monitor to "map" results within each test to a common nomenclature prior to summarising	IA1 [1], IA2 [2], SAC [1]
3.21.	Safety	UR3b	Summary of Urinalysis Dipstick Results (by BAL Location)	Use Alternative Treatment Group Descriptors #2 Note: Consult with medical monitor to "map" results within each test to a common nomenclature prior to summarising	IA1 [1], IA2 [2], SAC [1]
ECG					
3.22.	Safety	EG1	Summary of ECG Findings (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.23.	Safety	EG1	Summary of ECG Findings (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.24.	Safety	EG1	Summary of ECG Findings (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
3.25.	Safety	EG2	Summary of ECG Values (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.26.	Safety	EG2	Summary of ECG Values (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.27.	Safety	EG2	Summary of ECG Values (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
3.28.	Safety	EG2	Summary of Change from Baseline in ECG Values (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.29.	Safety	EG2	Summary of Change from Baseline in ECG Values (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.30.	Safety	EG2	Summary of Change from Baseline in ECG Values (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]
Vital Signs					
3.31.	Safety	VS1	Summary of Vital Signs (by Treatment arm)	Use Main Treatment Group Descriptors	IA1 [1], IA2 [2], SAC [1]
3.32.	Safety	VS1	Summary of Vital Signs (by Study Medication)	Use Alternative Treatment Group Descriptors #1	IA1 [1], IA2 [2], SAC [1]
3.33.	Safety	VS1	Summary of Vital Signs (by BAL Location)	Use Alternative Treatment Group Descriptors #2	IA1 [1], IA2 [2], SAC [1]

Safety : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
3.34.	Safety	IMM1	Summary of Treatment emergent Positive Immunogenicity results (by Study Medication)	Use Alternative Treatment Group Descriptors #1 Note: The screening test results are not being databased (pre-requisite for Negative test was an inclusion criterion). Therefore this table should only contain treatment emergent positive samples	SAC [2]

11.14.8. Safety Figures

No Safety figures are currently planned. Spotfire is intended to be used in-stream to review safety data in an ongoing manner. If appropriate selected Spotfire visualisations may be reproduced within HARP.

11.14.9. Pharmacokinetic Tables

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma					
4.1.	PK	PKCT1	Summary of Plasma GSK2862277 Pharmacokinetic Concentration – Time Data (by Treatment arm)	Use Main Treatment Group Descriptors Planned time points: Day1: 0h, 1h, On completion of surgery; Day 2: 24 h, Day 3: 48 h	SAC [1]
4.2.	PK	PKCT1	Summary of Plasma GSK2862277 Pharmacokinetic Concentration – Time Data (by Study Medication)	Use Alternative Treatment Group Descriptors #2 Planned time points: Day1: 0h, 1h, On completion of surgery; Day 2: 24 h, Day 3: 48 h	SAC [1]
4.3.	PK	PKPT1	Summary of Derived Plasma GSK2862277 Pharmacokinetic Parameters (by Treatment arm)	Use Main Treatment Group Descriptors	SAC [1]
4.4.	PK	PKPT1	Summary of Derived Plasma GSK2862277 Pharmacokinetic Parameters (by Study Medication)	Use Alternative Treatment Group Descriptors #2	SAC [1]
4.5.	PK	PKPT3	Summary of Derived Plasma GSK2862277 Pharmacokinetic Parameters (log transformed) (by Treatment arm)	Use Main Treatment Group Descriptors	SAC [1]
4.6.	PK	PKPT3	Summary of Derived Plasma GSK2862277 Pharmacokinetic Parameters (log transformed) (by Study Medication)	Use Alternative Treatment Group Descriptors #2	SAC [1]
BAL					
4.7.	PK	Non-standard PK_T1	Summary of Derived Lung ELF Drug Concentrations and Volume Data (by Treatment arm)	Use Main Treatment Group Descriptors Exclude Placebo data. Only expecting pooled wash and pooled volume in this study.	SAC [1]

Pharmacokinetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.8.	PK	Non-standard PK_T1	Summary of Derived Lung ELF Drug Concentrations and Volume Data (by Study Medication)	Use Alternative Treatment Group Descriptors #2 Exclude Placebo data. Only expecting pooled wash and pooled volume in this study.	SAC [1]

11.14.10. Pharmacokinetic Figures

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma					
4.1.	PK	PKCF3	Median Plasma GSK2862277 Concentration-Time Plots (Linear and Semi-log) (by Treatment arm)	Use Main Treatment Group Descriptors Planned time points: Day1: 0h, 1h, On completion of surgery; Day 2: 24 h, Day 3: 48 h. Add a horizontal line at y-axis at LLQ and add footnote LLQ = ...	SAC [1]
4.2.	PK	PKCF3	Median Plasma GSK2862277 Concentration-Time Plots (Linear and Semi-log) (by Study Medication)	Use Alternative Treatment Group Descriptors #2 Planned time points: Day1: 0h, 1h, On completion of surgery; Day 2: 24 h, Day 3: 48 h. Add a horizontal line at y-axis at LLQ and add footnote LLQ = ...	SAC [1]
4.3.	PK	PKCF1	Individual Subject Plasma GSK2862277 Concentration – Time Plots (Linear and Semi-log) (by Treatment arm)	Use Main Treatment Group Descriptors Plot Planned time points: Day1: 0h, 1h, On completion of surgery; Day 2: 24 h, Day 3: 48 h and actual time points. Paginate by time point type.	SAC [1]
4.4.	PK	PKCF1	Individual Subject Plasma GSK2862277 Concentration – Time Plots (Linear and Semi-log) (by Study Medication)	Use Alternative Treatment Group Descriptors #2 Plot Planned time points: Day1: 0h, 1h, On completion of surgery; Day 2: 24 h, Day 3: 48 h and actual time points. Paginate by time point type.	SAC [1]

Pharmacokinetic : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL					
4.5.	PK	Non-Standard PK_F1 (Study PII11115117 can provide examples)	Median Plasma and Individual Subject Derived Lung ELF GSK2862277 Concentrations Plot (Semi-Log) (by Treatment arm)	Use Main Treatment Group Descriptors Exclude Placebo data. Legend to identify subjid. Plasma based on planned rel. Time. Elf on actual rel. Time of Pooled wash. Elf data will be the pooled sample value. Include footnotes. Adjust x-axis to represent planned time points 0h, 1h, On completion of surgery; 24 h, 48 h. Use common y-axis range over this plot and the sister plot by study medication	SAC [1]
4.6.	PK	Non-Standard PK_F1	Median Plasma and Individual Subject Derived Lung ELF GSK2862277 Concentrations Plot (Semi-Log) (by Study Medication)	Use Alternative Treatment Group Descriptors #2 Exclude Placebo data. Legend to identify subjid. Plasma based on planned rel. Time. Elf on actual rel. Time of Pooled wash. Elf data will be the pooled sample value. Include footnotes. Adjust x-axis to represent planned time points 0h, 1h, On completion of surgery; 24 h, 48 h.	SAC [1]

11.14.11. Pharmacodynamic (Biomarker) Tables

Pharmacodynamic (Biomarker) : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL Biomarkers					
5.1.	PP1	EFF_T1	Summary Statistics of BAL Biomarkers On Completion of Surgery (by Treatment arm)	No change form Baseline Add additional page by variable of the functional category of the biomarker Use Main Treatment Group Descriptors	SAC [1]
5.2.	PP1	EFF_T1	Summary Statistics of BAL Biomarkers On Completion of Surgery (by Study Medication)	No change form Baseline Add additional page by variable of the functional category of the biomarker Use Alternative Treatment Group Descriptors #1	SAC [1]
5.3.	PP1	EFF_T1	Summary Statistics of BAL Biomarkers On Completion of Surgery (by BAL Location)	No change form Baseline Add additional page by variable of the functional category of the biomarker Use Alternative Treatment Group Descriptors #2	SAC [1]
5.4.	PP1		Summary of Statistical Analyses of BAL Biomarkers	Group by functional categories and Repeat table layouts for each BAL Biomarker Present only the final model per biomarker	SAC [1]
Serum Biomarkers					
5.5.	PP1	EFF_T1	Summary Statistics (Absolute and Change from Baseline): Serum Biomarkers by Time (by Treatment arm)	Add additional page by variable of the functional category of the biomarker Use Main Treatment Group Descriptors	SAC [1]

Pharmacodynamic (Biomarker) : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.6.	PP2	EFF_T1	Summary Statistics (Absolute and Change from Baseline): Serum Biomarkers by Time (by Study Medication)	Add additional page by variable of the functional category of the biomarker Use Alternative Treatment Group Descriptors #1	SAC [1]
5.7.	PP1	EFF_T1	Summary Statistics (Absolute and Change from Baseline): Serum Biomarkers by Time (by BAL Location)	Add additional page by variable of the functional category of the biomarker Use Alternative Treatment Group Descriptors #2	SAC [1]
5.8.	PP2		Summary of Statistical Analysis in Serum Biomarkers	Group by functional categories and Repeat table layouts for each BAL Biomarker Present only the final model per biomarker	SAC [1]

11.14.12. Pharmacodynamic (Biomarker) Figures

Pharmacodynamic (and or Biomarker) : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL Biomarkers					
5.1.	PP1		Box Plots of the BAL Biomarkers by Treatment Arm	Use imputed result. For each biomarker also plot individual data points alongside each box. Plot treatment arms side by side. Include LLQ and ULQ as reference lines where it makes sense to and footnote appropriately	SAC [1]
Serum Biomarkers					
5.2.	PP2		Raw Time profiles of the Serum Biomarkers by Subject	Paginate by Treatment. For each subject plot biomarkers within a functional class on a single graph when units permit. Include LLQ and ULQ as reference lines where it makes sense to and footnote appropriately	SAC [1]
5.3.	PP2		Spaghetti plots of the Serum Biomarkers by Treatment arm	For each biomarker plot time profiles of individuals within a treatment on a single graph. Use common axis ranges across pages/panels for each biomarker Include LLQ and ULQ as reference lines where it makes sense to and footnote appropriately	SAC [1]

Pharmacodynamic (and or Biomarker) : Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.4.	PP2		Spaghetti plots of the Serum Biomarkers by Study Medication	For each biomarker plot time profiles of individuals within a study medication on a single graph. Plot study medications side by side but identify the BAL location within each study medication. Use common axis ranges across pages/panels for each biomarker Include LLQ and ULQ as reference lines where it makes sense to and footnote appropriately	SAC [1]
5.5.	PP2		Scatterplot matrix of Serum Biomarkers by Treatment Arm	Plot all patients on same scatterplot. Indicate treatment groups by using different colours. Paginate by planned sampling times	SAC [1]
5.6.	PP2		Scatterplot matrix of Serum Biomarkers by Time	Plot all patients and time points on same scatterplot. Indicate individual timepoints by using different colours. Paginate by Treatment Arm	SAC [1]
5.7.	PP2	EFF_F7 / EFF_F1	Adjusted Medians and 95% Credible Intervals for each Study medication from the Repeated Measures Modelling of Serum Biomarkers	Repeat for each biomarker Use Planned Timepoint as the x-axis of the plot but offset/group by treatment to avoid overlapping	
5.8.	PP2	EFF_F8	Adjusted Medians and 95% Credible Intervals for Study medication comparisons from the Repeated Measures Modelling of Serum Biomarkers	Repeat for each biomarker Use Planned Timepoint as the x-axis of the plot	

11.14.13. Pharmacogenetic Tables

Pharmacogenetic : Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacogenetics					
6.1.	Safety	GN1	Summary of Genetics Subject Accountability		SAC [2]
6.2.	Safety	GN2	Summary of Genetic Consent Not Obtained / Withdrawn		SAC [2]

11.14.14. ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Accountability					
1.	n/a	POP_L1	Listing of Subject Accountability (subjects constituting each Statistical Analysis Population)	Also list out the subject IDs who will participate in the Translational Sub-Study	IA1 [1], IA2 [2], SAC [1]
Randomisation					
2.	Safety	CP_TA1	Listing of Randomised and Actual Treatments	Omit cohort column Include Site ID Include Randomisation number and Randomisation Date/Time (if only date available then modify column labels) Split Actual Treatment column into two separate columns (“Actual Study Medication” and “Actual BAL Sampled”) Create corresponding Deviation columns for each actual treatment column	IA1 [1], IA2 [2], SAC [1]
3.	Safety	BL1	Listing of Subjects for whom Treatment Blind was Broken (excluding when broken to support the interim analyses)		SAC [2]
Subject Disposition					
4.	Screen Failures	ES7	Listing of Reasons for Screening Failure	See notes for corresponding summary table	SAC [2]
5.	Safety	DV2	Listing of Important Protocol Deviations	Add additional columns to cover the 3x per protocol populations	IA1 [1], IA2 [2], SAC [1]
6.	Safety	IE3	Listing of subjects with Inclusion/Exclusion Criteria Deviations		SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
7.	Safety	CP_ES10x	Listing of Subjects who Withdrew from Study	Modify the contents and re-label the cross over related column names as appropriate to a parallel group design. Keep the date of last contact.	SAC [2]
Demography					
8.	Safety	DM2	Listing of Demographic Characteristics		IA1 [1], IA2 [2], SAC [1]
9.	Safety	DM9	Listing of Race		IA1 [1], IA2 [2], SAC [1]
Medical Condition & Concomitant Medications					
10.	Safety	MH2	Listing of Current and Past Medical Conditions	Combine both current and past items into one listing	IA1 [1], IA2 [2], SAC [1]
11.	Safety	CP_CM3	Listing of Concomitant Medications by Generic Term		IA1 [1], IA2 [2], SAC [1]
Exposure					
12.	Safety	EX3	Listing of Exposure Data		SAC [2]
Adverse Events					
13.	Safety	CP_AE8a	Listing of All Serious Adverse Events		IA1 [1], IA2 [2], SAC [1]
14.	Safety	CP_AE8	Listing of All Adverse Events		IA1 [1], IA2 [2], SAC [1]
15.	Safety	CP_AE8	Listing of Adverse Events Leading to Withdrawal from Study		IA1 [1], IA2 [2], SAC [1]
16.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events		IA1 [1], IA2 [2], SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory Values					
17.	Safety	CP_LB5	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance		IA1 [1], IA2 [2], SAC [1]
18.	Safety	CP_LB5	Listing of All Clinical Chemistry Laboratory Data for Subjects with PCI Abnormalities		IA1 [1], IA2 [2], SAC [1]
19.	Safety	CP_LB5	Listing of Hematology Abnormalities of Potential Clinical Importance		IA1 [1], IA2 [2], SAC [1]
20.	Safety	CP_LB5	Listing of All Hematology Laboratory Data for Subjects with PCI Abnormalities		IA1 [1], IA2 [2], SAC [1]
21.	n/a	LB13	Listing of Laboratory Tests and Associated Reference Ranges	Add centre/site column if necessary to distinguish different sets of normal ranges (and add corresponding date range(s) if normal ranges have changed within a site during conduct of study)	IA1 [1], IA2 [2], SAC [1]
22.	Safety	Base on AE2	Relationship between Urinalysis Summary Table Categories and Verbatim Text	Describes the mapping of test results to categories used in corresponding summary table. Base on AE2 shell (System Organ class becomes the Lab test name, Preferred term becomes the Category result was mapped onto)	IA1 [1], IA2 [2], SAC [1]
ECG					
23.	Safety	CP_EG3	Listing of All ECG Values for Subjects with any Value of Potential Clinical Importance		IA1 [1], IA2 [2], SAC [1]
24.	Safety	CP_EG3	Listing of ECG Values of Potential Clinical Importance		IA1 [1], IA2 [2], SAC [1]

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
25.	Safety	CP_EG5	Listing of Abnormal ECG Findings		IA1 [1], IA2 [2], SAC [1]
Vital Signs					
26.	Safety	CP_VS4	Listing of Vital Signs of Potential Clinical Importance		IA1 [1], IA2 [2], SAC [1]
27.	Safety	CP_VS4	Listing of All Vital Signs of for Subjects with any Value of Potential Clinical Importance		IA1 [1], IA2 [2], SAC [1]
Immunogenicity					
28.	Safety	IMM2	Listing of Immunogenicity results	Omit drug concentration units column. Omit titre column if not applicable to observed data.	SAC [2]

11.14.15. Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Efficacy Endpoints					
29.	Safety	EFF_L2	Listing of Transpulmonary Thermodilution Data		IA2 [1] SAC [1]
30.	Safety	EFF_L3	Listing of Oxygenation Data		IA2 [1] SAC [1]
31.	Safety	EFF_L3	Listing of Change from Baseline Oxygenation Data	Keep Baseline record (actual values) but post baseline entries should contain the change values (Vent mode changes should be flagged)	IA2 [1] SAC [1]
32.	Safety	EFF_L4	Listing of SOFA Data		SAC [1]
33.	PP2	Non-standard	SAS Output from Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.		SAC [1]
34.	PP2	Non-standard	SAS Output from Statistical analysis: Modelling of PVPI on Completion of Surgery		SAC [1]
35.	PP2	Non-standard	SAS Output from Statistical analysis: Modelling of PaO2/FiO2 on Completion of Surgery		SAC [1]
36.	PP2	Non-standard	SAS Output from Statistical analysis: Modelling of EVLWI on Completion of Surgery		SAC [1]
37.	PP2	Non-standard	SAS Output from Statistical analysis: Repeated Measures Modelling of SOFA		SAC [1]
38.	PP2	Non-standard	SAS Output from PROC MCMC Futility analysis at Interim Analysis 2	Interim analysis #2 only.	IA2 [1]
39.	PP2	Non-standard	SAS Output from Sample Size Re-estimation at Interim Analysis 2	Interim analysis #2 only.	IA2 [1]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Surgical Procedure					
40.	Safety	EFF_L1	Listing of Information relating to the surgical procedure by Subject	New page per subject. Group and order subjects by Treatment, Centre and ID	IA1 [1], IA2 [2], SAC [1]
PK (Plasma and BAL)					
41.	PK	PKCL1p	Listing of GSK2862277 Plasma Pharmacokinetic Concentration - Time Data	Use Main Treatment Descriptors	SAC [1]
42.	PK	PKPL1p	Listing of Derived GSK2862277 Plasma Pharmacokinetic Parameters	Use Main Treatment Descriptors	SAC [1]
43.	PK	PKLU1p	Listing of Derived GSK2862277 Lung ELF concentrations	Use Main Treatment Descriptors	SAC [1]
44.	PK	Non-standard	Listing of Data required to obtain Lung ELF concentrations	Use Main Treatment Descriptors Create bespoke by-subject listing that includes the BAL Drug concentration, Plasma Urea and BAL Urea, dilution factor, Volume of ELF, Volume of BAL and Total drug in BAL fluid	SAC [1]
Pharmacodynamic (and or Biomarker)					
	BAL Biomarkers				
45.	Safety		Listing of BAL Biomarker data		SAC [1]
46.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker Free sTNFR1		SAC [1]
47.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker Total sTNFR1		SAC [1]
48.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker Complex sTNFR1		SAC [1]
49.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker TNFa		SAC [1]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
50.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker IL-6		SAC [1]
51.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker IL-8		SAC [1]
52.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker IL-1b		SAC [1]
53.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker MCP-1		SAC [1]
54.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker CRP		SAC [1]
55.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker IL1-ra		SAC [1]
56.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker IL-10		SAC [1]
57.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker Total Protein		SAC [1]
58.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker SP-D		SAC [1]
59.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker RAGE		SAC [1]
60.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker CC16		SAC [1]
61.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker vWF		SAC [1]
62.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker sICAM-1		SAC [1]
63.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker MPO		SAC [1]
64.	PP1	Non-standard	SAS Output from Statistical Modelling of BAL biomarker Total Protein Ratio		SAC [1]
Serum Biomarkers					
65.	Safety		Listing of Serum Biomarker data		SAC [1]
66.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker Free sTNFR1		SAC [1]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
67.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker Total sTNFR1		SAC [1]
68.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker Complex sTNFR1		SAC [1]
69.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker IL-6		SAC [1]
70.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker IL-8		SAC [1]
71.	PP2	Non-standard	SAS Output from Statistical Modelling of Plasma biomarker CRP		SAC [1]
72.	PP2	Non-standard	SAS Output from Statistical Modelling of Plasma biomarker Total Protein		SAC [1]
73.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker SP-D		SAC [1]
74.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker RAGE		SAC [1]
75.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker CC16		SAC [1]
76.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker vWF		SAC [1]
77.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker sICAM-1		SAC [1]
78.	PP2	Non-standard	SAS Output from Statistical Modelling of Serum biomarker MPO		SAC [1]
Exploratory					
79.	Safety	EFF_L7	Listing of Subjects Diagnosed with ARDS out to day 28		SAC [2]
80.	Safety	EFF_L5	Listing of day 28 survival status		SAC [2]
81.	Safety	EFF_L6	Listing of Organ Failure Free days	Keep Subject and metadata and replace Vent free days with Organ failure free days	SAC [2]
82.	Safety	EFF_L6	Listing of day 28 Resource Usage		SAC [2]

11.15. Appendix 15: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request

Appendix 15: Example Mock Shells for Data Displays

Example : PK_T1 Page 1 of n
Protocol : TFR116341
Population : Pharmacokinetic

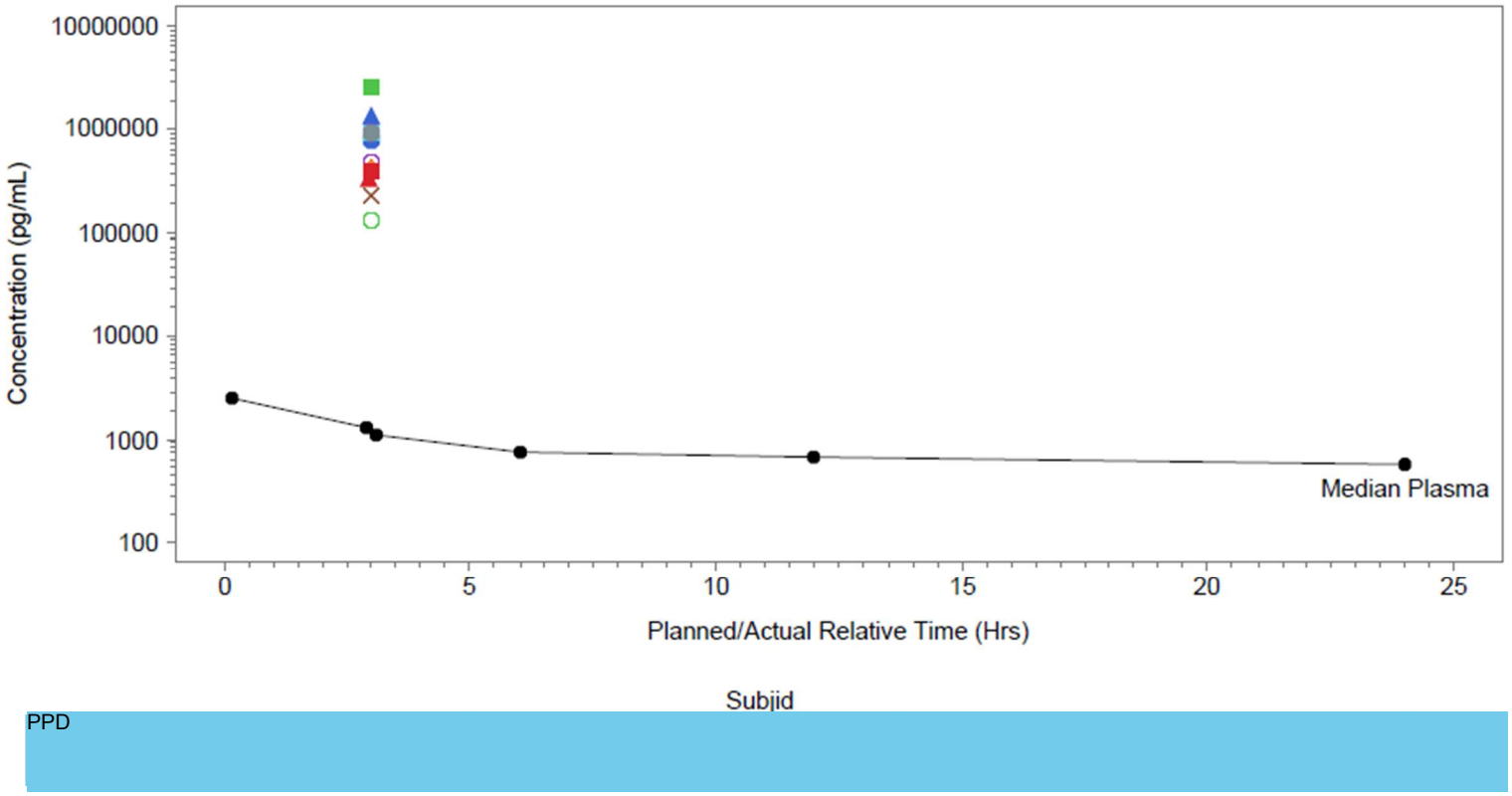
Table X.X
Summary of Derived Lung ELF Drug Concentrations and Volume Data

Treatment: 26.0 mcg

	Planned Relative Time	N	Geometric Mean	90% CI (Lower,Upper)	SD Logs	CVb (%)
ELF Drug Conc (pg/mL)	Day 1(1)	10	110133.4	(52983.6,228927.1)	1.09	151.6
	Day 1(2)	10	63196.2	(40464.7,98697.4)	0.66	74.7
	Day 1(3)	10	48241.2	(35806.4,64994.2)	0.44	46.8
Pooled ELF Drug Conc (pg/mL)	Day 1 (Pooled Washes)	10	55374.3	(39768.3,77104.4)	0.49	52.6
Volume of ELF in BAL Fluid (mL)	Day 1 (1)	10	0.0330	(0.0164,0.0662)	1.042	140.1
	Day 1(2)	10	0.0996	(0.0526,0.1886)	0.953	121.6
	Day 1(3)	10	0.1970	(0.1000,0.3882)	1.012	133.7

Example : PK_F1 Page 1 of n
Protocol :TFR116341
Population : Pharmacokinetic

Table X.X
Median Plasma and Individual Subject Derived Lung ELF GSK2862277 Concentrations Plot (Semi-Log) Pooled Washes



Example : EFF_T1

Population: Biomaker

Table 12.1

Summary of Raw Immune Function Biomarker data and change from Baseline

Endpoint (unit): PVPI (xxx)

Treatment	N	Item	Visit [1]	Planned Relative Time	n	n imp [2]	Mean [3]	95% CI of Mean	SD	Median	Min [4]	Max
0.002 mg/kg IV SD	6	Analyte numeric result	P1D1	PRE-DOSE (BL)	6	0	8.40	(6.65, 10.15)	1.664	8.60	5.6	10.5
				2 HOUR	6	0	7.95	(6.17, 9.73)	1.697	7.55	5.8	10.8
				6 HOUR	6	0	8.30	(5.88, 10.72)	2.308	7.40	6.2	11.9
				24 HOUR	6	0	9.03	(6.46, 11.60)	2.449	8.80	6.3	12.1
				48 HOUR	6	0	8.42	(5.99, 10.84)	2.309	7.90	5.7	11.8
		Change from Baseline	P1D1	2 HOUR	6	0	-4.86	(-15.68, 5.97)	10.318	-1.37	-23.4	3.6
				6 HOUR	6	0	-0.79	(-20.78, 19.20)	19.046	0.20	-21.3	19.5
				24 HOUR	6	0	7.47	(-11.68, 26.62)	18.245	7.09	-18.2	33.3
				48 HOUR	6	0	-0.19	(-15.45, 15.07)	14.543	-2.64	-16.0	20.7

[1] P=Study Part, D=Study day relative to 1st dose
[2] Number of imputed observations (imputed using 1/2 of the LLQ)
[3] NA = Not Applicable (due to >= 75% of values being LLQ)
[4] NC = Non-Calculable (due to presence of LLQ values)

PPD

Programming Notes: Paginate by endpoint. Indicate the baseline timepoint (e.g. suffix with “(BL)”). If no imputations for the endpoints then drop the nimp column and any associated footnotes. Modify as appropriate to the endpoint(s) being summarised.

Example : EFF_T1 (contd)

Population: Biomaker

Table 12.1

Summary of Raw Immune Function Biomarker data and percentage change from Baseline

Endpoint (unit): PVPI (xxx)

Treatment	N	Item	Visit [1]	Planned Relative Time	n	n imp [2]	Geo. Mean	95% CI of Geo. Mean	SD Logs	CV (%)
0.002 mg/kg IV SD	6	Analyte numeric result	P1D1	PRE-DOSE (BL)	6	0	8.25	(6.57, 10.35)	0.216	21.9
				2 HOUR	6	0	7.81	(6.27, 9.72)	0.209	21.1
				6 HOUR	6	0	8.05	(6.11, 10.62)	0.263	26.8
				24 HOUR	6	0	8.76	(6.56, 11.69)	0.275	28.0
				48 HOUR	6	0	8.16	(6.14, 10.85)	0.272	27.7
		Change from Baseline	P1D1	2 HOUR	6	0	NA	NA	NA	NA
				6 HOUR	6	0	NA	NA	NA	NA
				24 HOUR	6	0	NA	NA	NA	NA
				48 HOUR	6	0	NA	NA	NA	NA

[1] P=Study Part, D=Study day relative to 1st dose
[2] Number of imputed observations (imputed using 1/2 of the LLQ)
[3] NA = Not Applicable (due to >= 75% of values being LLQ)
[4] NC = Non-Calculable (due to presence of LLQ values)

Example : EFF_T2

Protocol: TFR116341

Population: Safety

Table 12.207

Summary of Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.

---------- Statistical Analysis ID=1 ----------

Treatment	N	Planned. Relative Time	Endpoint	n	Sample Mean Vector	Sample Variance Covariance Matrix		Sample Correlation
Placebo (BAL Collapsed lung)	20	Pre-Op (BL)	Ln{PVPI}	XX	XX.X	XX.XXX	XX.XXX	X.XX
			PaO2/FiO2	XX	XX.X	XX.XXX	XX.XXX	
		Imm. Post Op.	Ln{PVPI}	XX	XX.X	XX.XXX	XX.XXX	X.XX
			PaO2/FiO2	XX	XX.X	XX.XXX	XX.XXX	
Placebo (BAL Ventilated lung)	20	Pre-Op (BL)	Ln{PVPI}	XX	XX.X	XX.XXX	XX.XXX	X.XX
			PaO2/FiO2	XX	XX.X	XX.XXX	XX.XXX	
		Imm. Post Op.	Ln{PVPI}	XX	XX.X	XX.XXX	XX.XXX	X.XX
			PaO2/FiO2	XX	XX.X	XX.XXX	XX.XXX	
GSK2862277 26mg IH (BAL Collapsed lung)	20	Pre-Op (BL)	Ln{PVPI}	XX	XX.X	XX.XXX	XX.XXX	X.XX
			PaO2/FiO2	XX	XX.X	XX.XXX	XX.XXX	
		Imm. Post Op.	Ln{PVPI}	XX	XX.X	XX.XXX	XX.XXX	X.XX
			PaO2/FiO2	XX	XX.X	XX.XXX	XX.XXX	

Example : EFF_T2 (Contd)

Population: Safety

Table 12.207
Summary of Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.

Statistical Analysis ID=1

Item	Planned. Relative Time	Endpoint	Median Mean Vector	Median Variance Matrix	Covariance	Median Correlation
Adjusted Placebo (averaging over BAL)	Imm. Post Op.	Ln{PVPI}	XX.X	XX.XXX	XX.XXX	X.XX
		PaO2/FiO2	XX.X	XX.XXX	XX.XXX	
Adjusted Active (averaging over BAL)	Imm. Post Op.	Ln{PVPI}	XX.X	XX.XXX	XX.XXX	X.XX
		PaO2/FiO2	XX.X	XX.XXX	XX.XXX	
Adjusted Active Vs Placebo Joint Distribution (averaging over BAL)	Imm. Post Op.	PVPI Ratio	XX.X	XX.XXX	XX.XXX	X.XX
		PaO2/FiO2 Diff	XX.X	XX.XXX	XX.XXX	

Example : EFF_T2 (Contd)

Population: Safety

Table 12.207
Summary of Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.

---------- Statistical Analysis ID=1 ----------

Item (units)	Planned. Relative Time	Median	95% Credible Interval	MCSE/SD
Adjusted Pbo PVPI averaging over BAL (xxx)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX
Adjusted Pbo PaO2/FiO2 averaging over BAL (kPa)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX
Adjusted Act PVPI averaging over BAL (xxx)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX
Adjusted Act PaO2/FiO2 averaging over BAL (kPa)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX

Note: Values used for continuous covariates in model adjustment: Baseline PVPI = xxx (unit), Baseline PaO2/FiO2 = xxx (unit), Age = 36 Years, Height = xx cm, etc

PPD

Example : EFF_T2 (contd)

Population: Safety

Table 12.207
Summary of Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.

Statistical Analysis ID=1

Item (units)	Planned. Relative Time	Median	95% Credible Interval	MCSE/SD
Ratio of Act/Pbo PVPI averaging over BAL	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX
Difference Act-Pbo P/F averaging over BAL (kPa)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX

Note: Values used for continuous covariates in model adjustment: Baseline PVPI = xxx (unit), Baseline PaO2/FiO2 = xxx (unit), Age = 36 Years, Height = xx cm, etc

Example : EFF_T2 (contd)

Population: Safety

Table 12.207
Summary of Primary Statistical Analysis: Joint Modelling of PVPI and PaO2/FiO2.

---------- Statistical Analysis ID=1 ----------

End of Study Decision Pathway	Criteria	Threshold Probability	Observed Probability	Met
Outcome 1: Robust Success	Pr(PVPI ratio (A/P) < 0.884 AND PaO2/FiO2 Diff (A-P) >= 5.3 kPa)	0.25	0.0328	N
Outcome 2: Success	Pr(PVPI ratio (A/P) < 0.884)	0.35	0.0856	N
Outcome 3: Potentially Unsuccessful	Pr(PVPI ratio (A/P) >= 0.884)	0.75	0.9144	Y
OVERALL END OF STUDY OUTCOME	Potentially Unsuccessful			

PPD

Programming note: Use more appropriate descriptors for the labels (e.g. update when timeslicing keys are set). Add any other posterior probability statements in a similar manner to those in GSK2586881 ACE114622 (e.g. PD Table 12.207), for example....

Item (units)	Comparison	Posterior Probability Statement	Value
XXXXX	(Act / Pbo) Imm. Post Op.	< 0.10 i.e. More than 90% reduction	0.0740

Example : EFF_T3
Protocol : TFR116341
Population : Safety

Table X.XX

The SAS System

TFR116341 Interim Analysis 2 (IA2) Statistical Analysis Outcome

"PAUSE and REVIEW"

Number of Observed Placebo Subjects at IA2 = 22

Number of Observed Active Subjects at IA2 = 18

Number of Placebo Subjects required (per simulated dataset) to reach end of study target of 40 = 18

Number of Active Subjects required (per simulated dataset) to reach end of study target of 40 = 22

Number of simulated datasets = 1000

Futility criteria for each simulated dataset: If the joint probability of {Any Decrease in P/F AND Any Increase in PVPI} is > 0.1 then simulated study is futile

If the proportion of future simulated datasets meeting futility criteria is > 0.3 then statistcial analysis recommendation is to "Pause and Review", otherwise recommendation is to "Continue"

Note: As per protocol, this statistcial analysis recommendation is not binding and may be over-ruled by expert judgement of GSK Study Team if deemed appropriate

Proportion of future datasets meeting futility criteria = 0.932, therefore...

Statistical analysis recommendation is to "PAUSE and REVIEW"

Example : EFF_T4
Protocol : TFR116341
Population : Safety

Table X.XX

<<< Precise specification up to the expert judgement of the statistician/programmer. Should contain...

Selected SAS output from sample size re-estimation procedure: Assumed VCV matrix used in protocol, the estimated VCV matrix from the IA2 data, and the recommended number of subjects and the operating characteristics under the re-estimated number assuming a Null and Minimum desired profile for the remaining (unobserved) subjects

>>>

Example : EFF_T5

Population: Safety

Table 12.207

Summary of Statistical Analysis: Modelling of PVPI on Completion of Surgery.

---------- Statistical Analysis ID=1 ----------

Item (units)	Planned. Relative Time	Median	95% Credible Interval	MCSE/SD
Adjusted Pbo PVPI averaging over BAL (xxx)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX
Adjusted Act PVPI averaging over BAL (xxx)	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX

Note: Values used for continuous covariates in model adjustment: Baseline PVPI = xxx (unit), Baseline PaO2/FiO2 = xxx (unit), Age = 36 Years, Height = xx cm, etc

Example : EFF_T5 (contd)

Population: Safety

Table 12.207
Summary of Statistical Analysis: Modelling of PVPI on Completion of Surgery.

Statistical Analysis ID=1

Item (units)	Planned. Relative Time	Median	95% Credible Interval	MCSE/SD
Ratio of Act/Pbo PVPI averaging over BAL	Imm. Post Op.	XX.XX	(X.XXX, XX.XXX)	X.XXX

Note: Values used for continuous covariates in model adjustment: Baseline PVPI = xxx (unit), Baseline PaO2/FiO2 = xxx (unit), Age = 36 Years, Height = xx cm, etc

PPD

Example : EFF_T5 (contd)

Table 12.207
Summary of Statistical Analysis: Modelling of PVPI on Completion of Surgery.

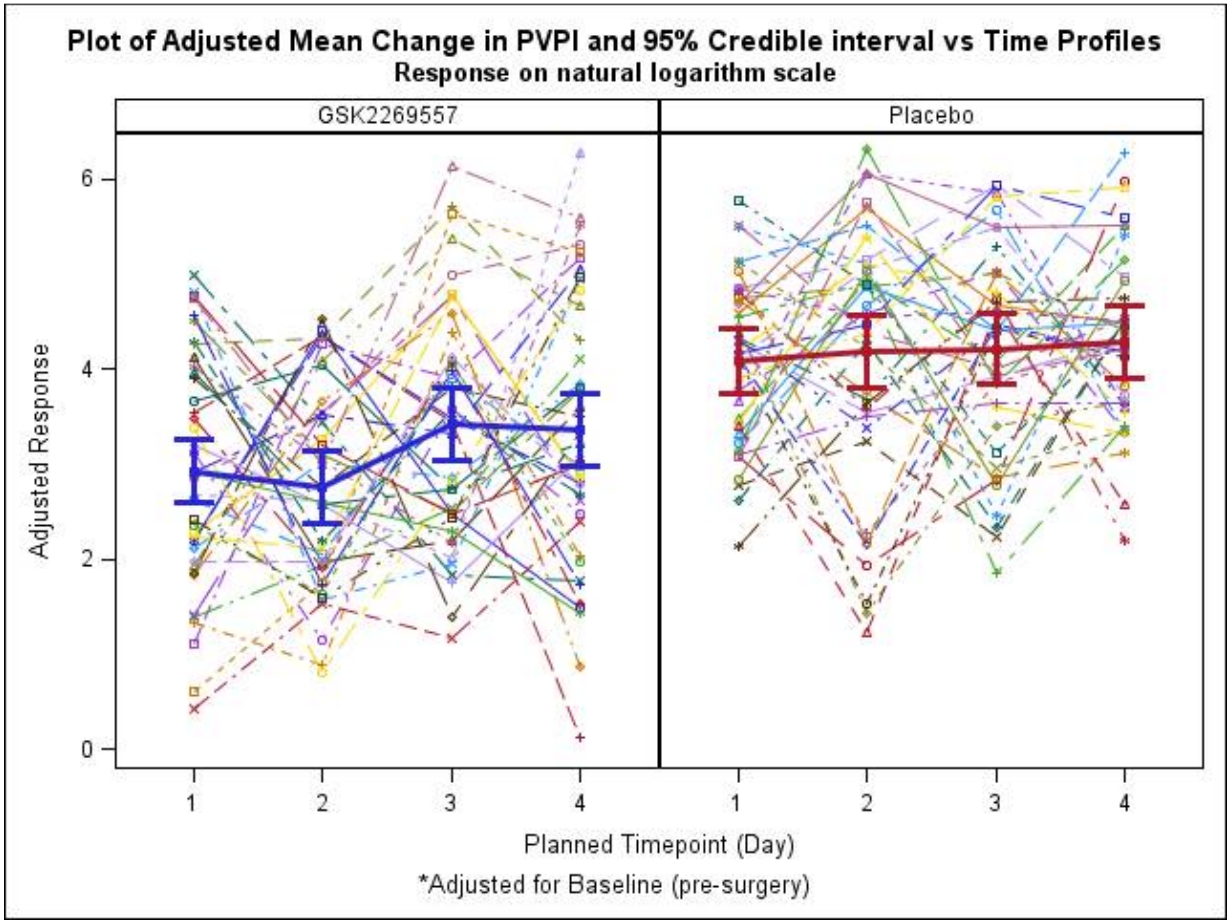
Item (units)	Comparison	Posterior Probability Statement	Value
Statistical Analysis ID=1			
Ratio of Act/Pbo	(Act / Pbo) Imm. Post Op.	< 1.00 i.e. Any reduction	0.6740
PVPI averaging over BAL		< 0.10 i.e. More than 90% reduction	0.0740

PPD

Programming note: Use more appropriate descriptors for the labels (e.g. update when timeslicing keys are set). Add any other posterior probability statements in a similar manner to those above

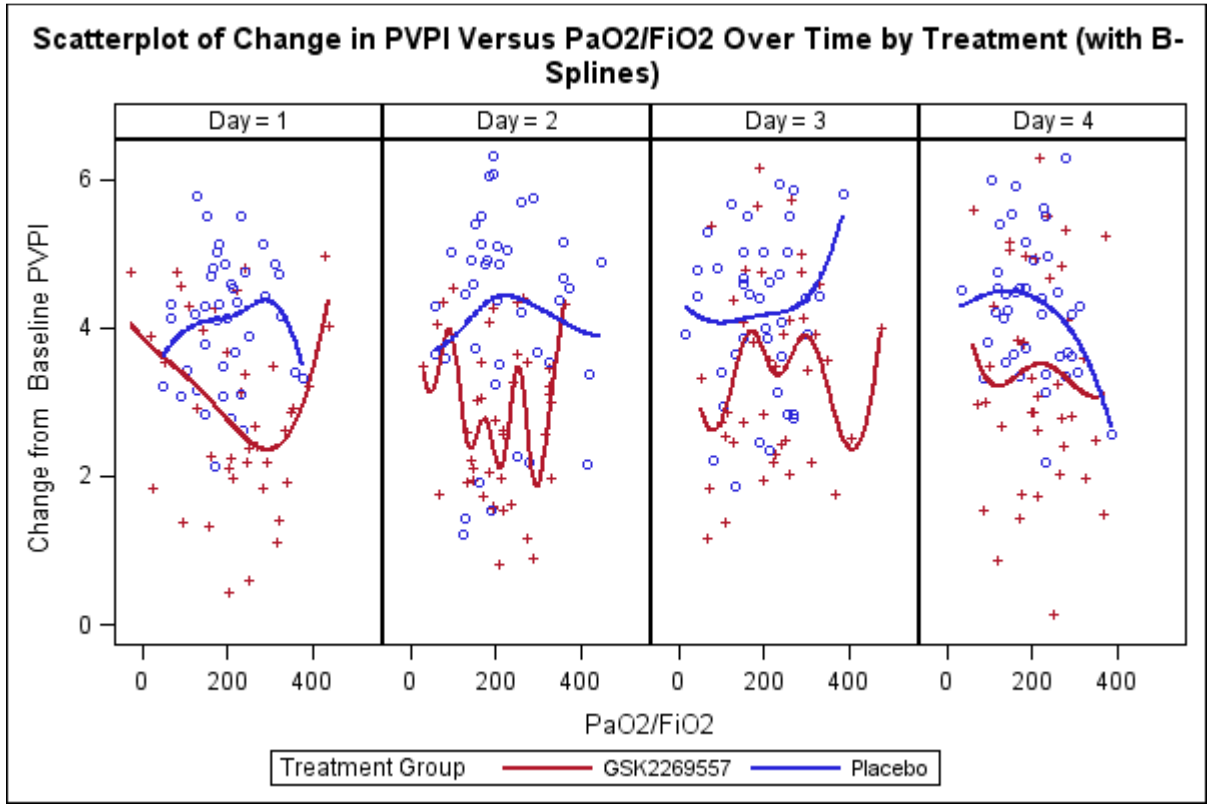
Example : EFF_F1
Protocol : TFR116341
Population : Safety

Figure X.XX



Example : EFF_F2
Protocol : TFR116341
Population : Safety

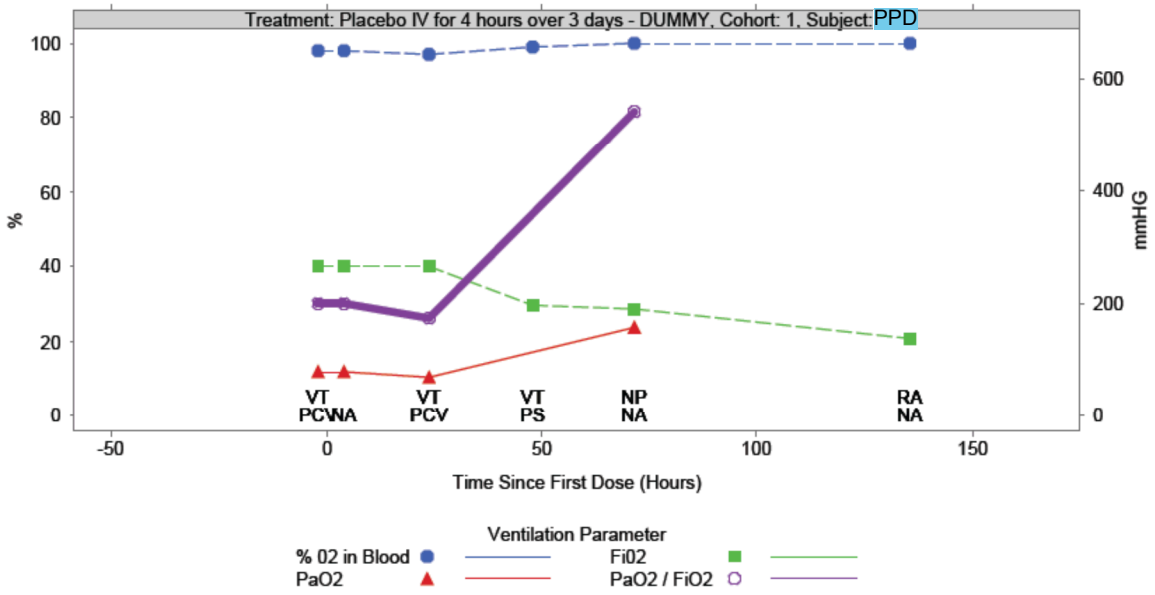
Figure X.XX



Example : EFF_F3
Protocol : TFR116341
Population : Safety

Figure X.XX

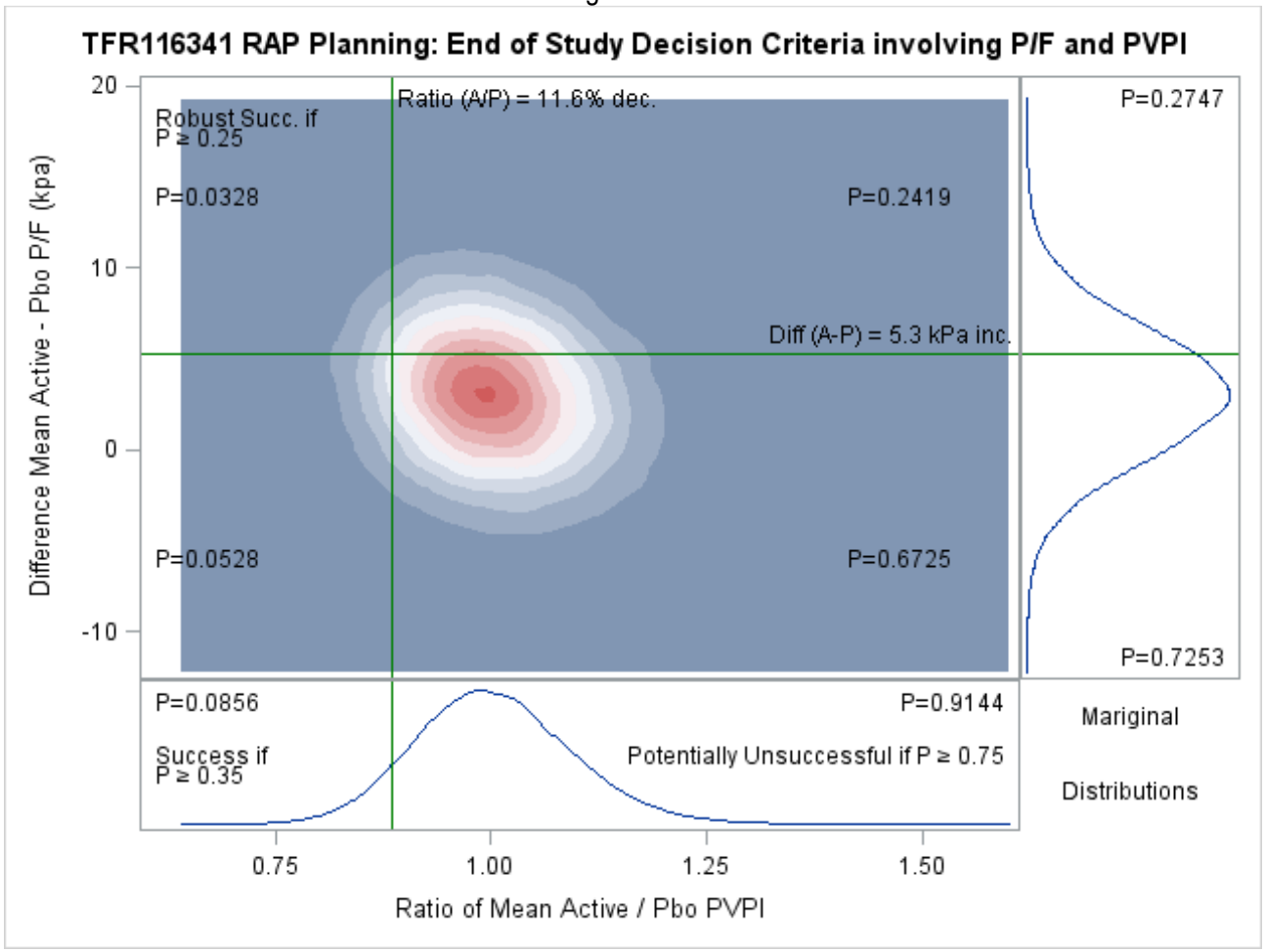
Figure 10.998
By Subject Time Profiles of SaO2, PaO2, FiO2 and P/F ratio



Note: RA = Room Air, NP = Nasal Prongs, FM = Face Mask and VT = Ventilator. Dashed lines left axis, Solid lines right axis
Note: NA = Not Applicable (not on Ventilator), IMV = IMV/sIMV, PCV = Pressure controlled ventilation, PS = Pressure support
N ote: NI PPV = Non-invasive positive pressure ventilation and Other = Other method (see listings for details)
PPD

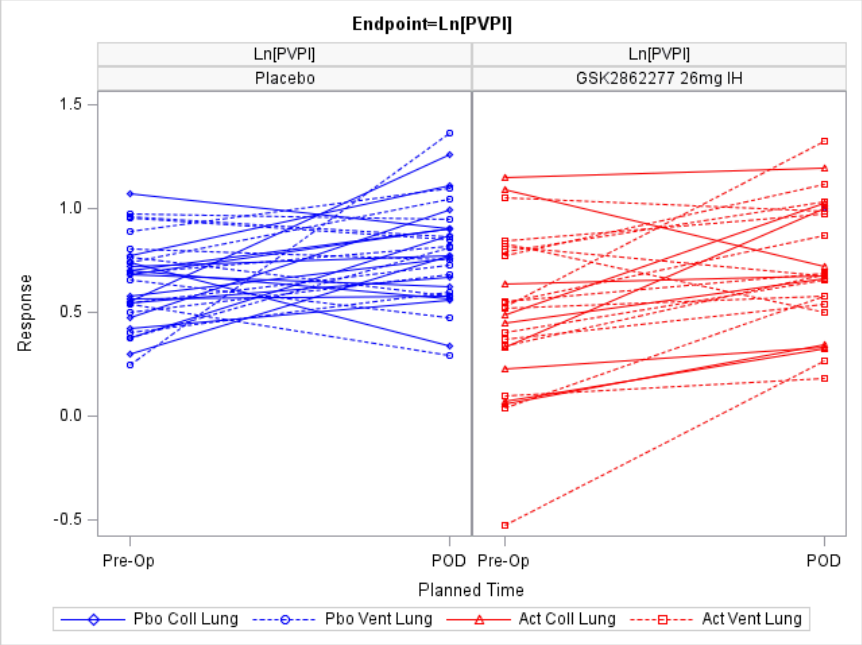
Example : EFF_F4
Protocol : TFR116341
Population : Safety

Figure X.XX



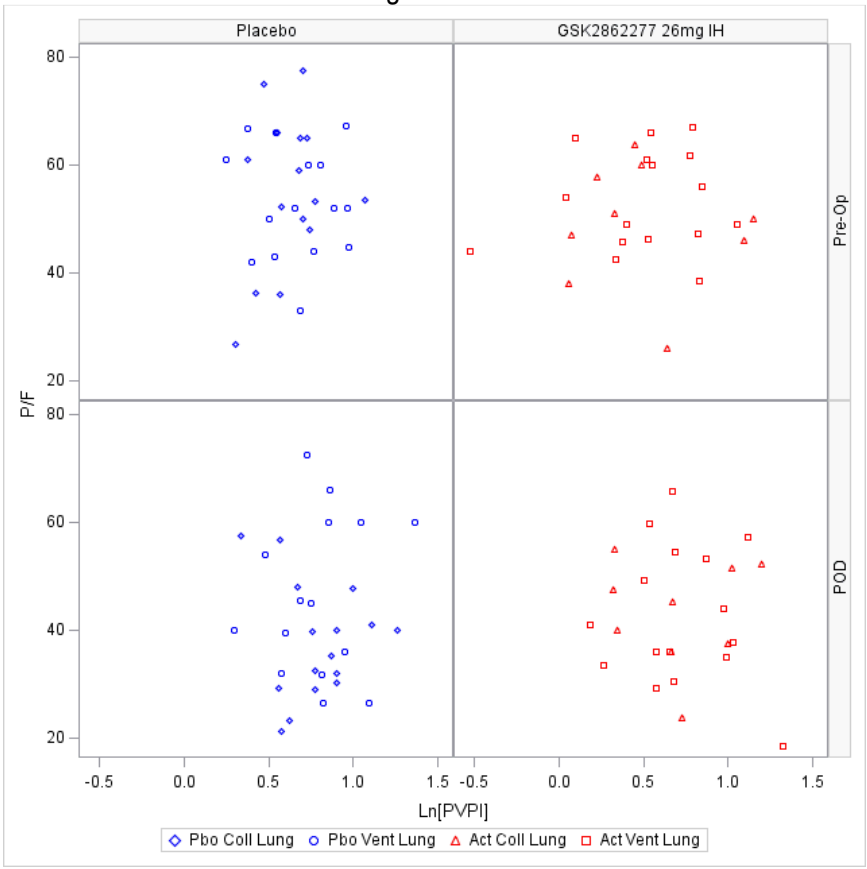
Example : EFF_F5
Protocol : TFR116341
Population : Safety

Figure X.XX



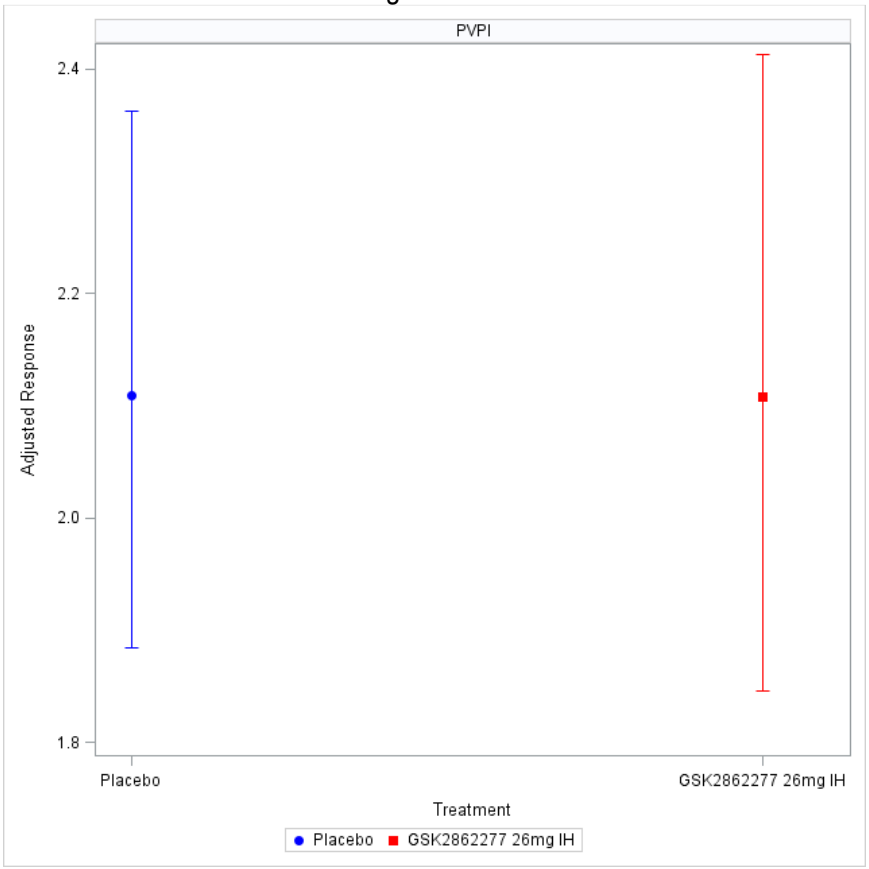
Example : EFF_F6
Protocol : TFR116341
Population : Safety

Figure X.XX



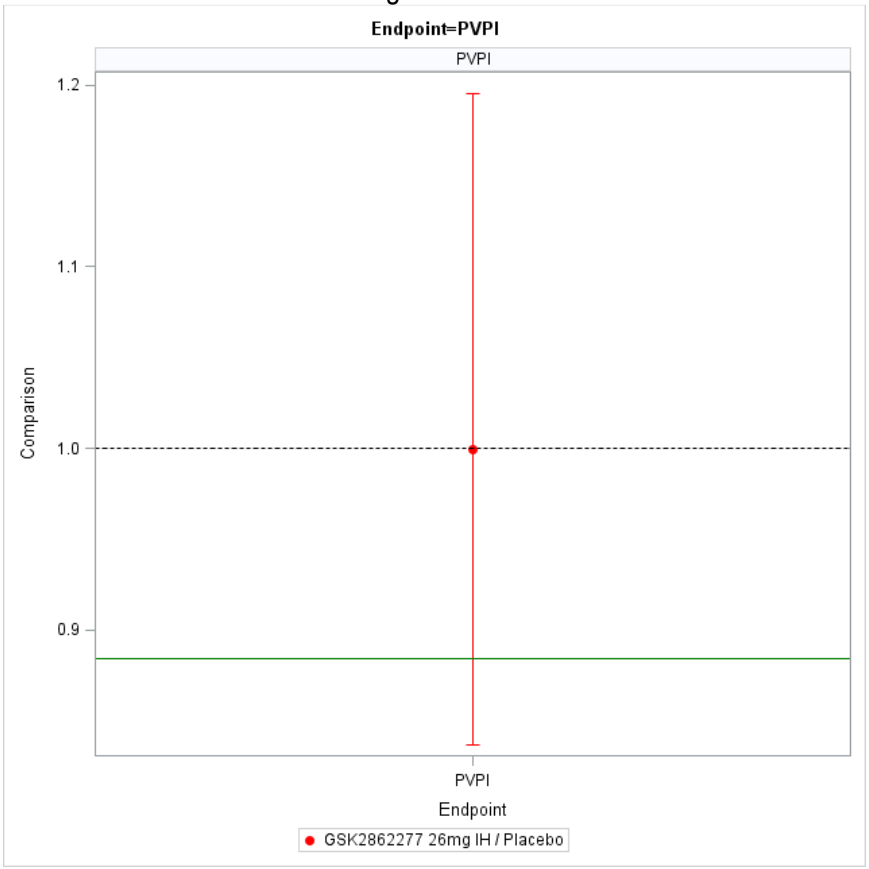
Example : EFF_F7
Protocol : TFR116341
Population : Safety

Figure X.XX



Example : EFF_F8
Protocol : TFR116341
Population : Safety

Figure X.XX



Example : EFF_L1
Protocol : TFR116341
Population : Safety

Listing X.XX
Actual Treatment: Placebo BAL Collapsed Lung, Subject ID xxx, (Inv ID: xxx)

Subject Demographics

Derived Age

Sex

Race

Subject Background

Prior Oesophageal Chemotherapy : [No] or [Yes and end date of treatment]

Smoking History: [Never Smoked] or [Current Smoker] or [Former Smoker and date last smoked]

Medical History: {Exclude the GSK cardiovascular risk factor items, Group by Past and Current}

Study treatment

Actual Study Drug received: [Name and date/time of Start of nebulisation]

Oesophagectomy procedure

Type of Surgery: [Trans Thoracic Oesophagectomy] or [Free text box from eCRF]

Start (rel to Dosing): [Start date and time of procedure] ([Start of procedure relative to dosing (hh:mm)])

Stop (rel to Dosing): [Stop date and time of procedure] ([End of procedure relative to dosing (hh:mm)])

Duration of Oesophagectomy procedure: [Duration of procedure (hh:mm)]

Did subject receive blood transfusion (amount and units): [Yes: amount and units] or [No]

Ventilation: Two Lung Ventilation

Example : EFF_L1 (Contd)
Protocol : TFR116341
Population : Safety

Listing X.XX
Actual Treatment: Placebo BAL Collapsed Lung, Subject ID xxx, (Inv ID: xxx)

All information from "Two-lung ventilation (At start of ventilation)" item of eCRF: [Mode of Ventilation, Tidal Volume, PEEP, Peal Pressure and Plateau Pressure]

Did ventilation continue post surgery: [No] or [Yes and Mode of ventilation]

Ventilation: One Lung Ventilation (OLV)

Start of OLV (rel to Dosing and Surgery): [Start date and time of OLV] ([Start of OLV relative to dosing (hh:mm)],[Start rel' to surgery (hh:mm)])

End of OLV: [End date/time of OLV] ([End of OLV relative to dosing (hh:mm)],[End rel' to surgery (hh:mm)])

Duration of One Lung Ventilation: [Duration of One Lung ventilation (hh:mm)]

All information from "One-lung ventilation (baseline)" item of eCRF: [Mode of Ventilation, Tidal Volume, PEEP, Peal Pressure and Plateau Pressure]

Anaesthetic

Start of anaesthia (rel to Dosing and Surgery): [Start date and time of anaesthia] ([Start of anaesthia relative to dosing (hh:mm)],[Start rel' to surgery (hh:mm)])

End of anaesthia (rel to Dosing and Surgery): [End of anaesthia],[End of anaesthia relative to dosing (hh:mm)],[End rel' to surgery (hh:mm)]

Duration of anaesthia: [Duration of anaesthia (hh:mm)]

Anaesthetic and operative agents: [Epidural Anasthesia] or [free text box from eCRF]

Method of maintenance: [Volatile anaesthetic] or [TIVA]

Was Inotrope used intra-op?: [No] or [Drug Used and For how long (hh:mm)]

Was Inotrope used post-op?: [No] or [Drug Used and For how long (hh:mm)]

Example : EFF_ L1 (Contd)
Protocol : TFR116341
Population : Safety Listing X.XX

Actual Treatment: Placebo BAL Collapsed Lung, Subject ID xxx, (Inv ID: xxx)

BAL Procedure

Start of BAL (rel to Dosing and Surgery): [Start date and time of BAL] ([Start of BAL relative to dosing (hh:mm)],[Start rel' to surgery (hh:mm)])

Lung BAL performed on: [Left] or [Right]

Actual Lung BAL performed on: [Deflated (Collapsed)] or [Inflated (Ventilated)]

Fluid balance in 24hr period from start of surgery

Fluid intake start date/time: [Fluid intake start date/time]

Fluid intake stop date/time: [Fluid intake stop date/time]

Total Input (ml): [Total input]

Total Output (ml): [Total output]

Net total: [Derived as Total Input – Total Output]

Urine Output (ml): [Urine output]

Other Output (ml): [Other output]

Post operative complications

Did the subject receive antibiotics for a suspected respiratory tract infection?: [Yes] or [No]

Did the subject develop a significant pleural effusion?: [Yes] or [No]

Did the subject develop an Empyema?: [Yes] or [No]

Did the patient suffer from aspiration pneumonitis?: [Yes] or [No]

Example : EFF_L2
Protocol : TFR116341
Population : Safety

Listing X.XX
Listing of Transpulmonary Thermodilution Data

Treatment/ Inv ID/ Subject	Weight (kg)/ Pred. Weight (kg)/ Pred. BSA (m**2)	Visit / Planned Relative Time	Actual Date/Time	Time since start of Surgery	Item (units)	Result	Change from Baseline (BL)
Placebo (BAL Collapsed lung)/ PPD	89/ 100/ 233	Day 1 / Imm. Prior to Surgery (BL)	DDMMMYYY / HH:MM	+/- XXh XXm	Arterial Line used	Femoral	n/a
					Cardiac output rep1 (xxx)	XX	n/a
					Cardiac output rep2 (xxx)	XX	n/a
					Cardiac output rep3 (xxx)	XX	n/a
					Cardiac output Mean (xxx)	XX	n/a
					Mean Arterial Pressure (xxx)	XX	n/a
					etc		
		Day 1 / Imm. Post Surgery	DDMMMYYY / HH:MM	+/- XXh XXm	Arterial Line used	Femoral	
					Cardiac output rep1 (xxx)	XX	n/a
					Cardiac output rep2 (xxx)	XX	n/a
					Cardiac output rep3 (xxx)	XX	n/a
					Cardiac output Mean (xxx)	XX	XX
					Mean Arterial Pressure (xxx)	XX	XX

Example : EFF_L3
Protocol : TFR116341
Population : Safety

Listing X.XX
Listing of Oxygenation Data

Treatment: Placebo (BAL Collapsed lung) Inv.ID:PPD Subject:PPD

Visit/ Planned Relative Time/Time Since Dose Planned Actual	Vent	Pa02 (mmHg)	Fi02 (%)	Pa02/ Fi02	Oxy. Ind. (%)	Sa02 (%)	SaO2/ FiO2	PaO2/ FiO2 (Imp)	Vent Mode	Peep (cm H20)	Peak Vent. Pr. (cm H20)	Plateau Vent. Pr. (cm H20)	Mean Airway Pressure (cm H2O)	Tidal Volume (mL)
SCREENING/ SCREENING/ -0.38	Y 4	XX	XX	XX	XX.X	XX	XX	XX	Pressure controlled	XX	XX	XX	XX.X	XXX.XX
PART B/ 0.5 H/ 0.02	Y 4	XX	XX	XX	XX.X	XX	XX	XX	Pressure controlled	XX	XX	XX	XX.X	XXX.XX

Example : EFF_L4
Protocol : TFR116341
Population : Safety

Listing 227
Listing of SOFA and Change from Baseline SOFA Scores (Sequential Organ Failure Assessment)

Treatment: Placebo BID

Inv.ID /Subj	Visit	Study Day	SOFA Component {1} Respiration	Coagulation	Liver	Central Nervous System	Renal	Observed SOFA Score (Total)	Observed Chg. Baseline SOFA [2]
XXXXXX/ XXXXX	Baseline	1	4	0	1	4	0	12	0
	Day 4	4							
	Follow-up Day 7	7							
XXXXXX/ XXXXX	Baseline	1	1	0	2	4	0	11	0
	Day 4	4	2	2	2	1	2	11	0
	Follow-up Day 7	7		3	2	2	2		

[1]: Individual organ function scored on a 0-4 point scale (0: Normal, 4: Most Abnormal)
[2]: String Assumptions made to obtain a baseline SOFA value

PPD

Example : EFF_L5
Protocol : TFR116341
Population : Safety

Listing of Day 28 Survival Status

Treatment: Placebo BID

Inv./ Subj.	Age/ Sex	Randomization Date/ Event or Censoring Date	Endpoint Description for 28 Day Survival	28 Day Survival (days)
PPD XXXXX	XX/ Male	XXOCT201X/ XXOCT201X	Event: Died	6
PPD XXXXX	XX/ Male	XXAPR201X/ XXMAY201X	Censor: Last adequate asmt	28

PPD

Example : EFF_L6
Protocol : TFR116341
Population : Safety

Listing 225
Listing of Day 28 Resource usage

Treatment: Placebo BID

Subject	Inv. ID/Sex/Age/ Race/Death Date (blank if alive)	Hospital-isation Start/ End Date/ Discharged	ICU Start/ End Date/ Discharged	Vent. free days	Days Alive in Hospital	Days Alive in ICU
XXXXX	XXXXXX/M/XX/White - White/Caucasian/European Heritage/XXOCT201X	XXOCT201X/ XXOCT201X/ Y	XXOCT201X/ XXOCT201X/ Y	0	6	6
XXXXX	XXXXXX/M/XX/White - White/Caucasian/European Heritage/	XXAPR201X/ / N	XXAPR201X/ XXAPR201X/ Y	8	28	4

Note: Evaluation Interval: Day of first dose to Day of first dose +27 days
Note: Partial days rounded up during computations

Example : EFF_L7 Page 1 of n
Protocol : TFR116341
Population : Safety

Listing 229
Listing of Date and Time of Individual Subjects Surgical Procedures

Treatment	Invid./ Subj.	Did the subject develop ARDS while in hospital?
Placebo BID	XXXXXX/ XXXXXX	Y

Example : POP_T1
Protocol : TFR116341
Population : n/a

Summary X.XX
Summary of Subject Accountability (subjects constituting each Statistical Analysis Population)

Treatment Descriptors	Treatment	Number of individuals in population							
		Screen Failures	Safety	PK	PP1	PP2	PP3	IA1	IA2
Screening failures	n/a	23	0	0	0	0	0	0	0
Main Treatment Group Descriptions	Placebo (BAL Collapsed lung)	0	15	x	x	x	x	x	x
	Placebo (BAL Ventilated lung)	0	25	x	x	x	x	x	x
	GSK2862277 26mg IH (BAL Collapsed lung)	0	18	x	x	x	x	x	x
	GSK2862277 26mg IH (BAL Ventilated lung)	0	22	x	x	x	x	x	x
Alternative Treatment Group Descriptions #1	Placebo	0	40	x	x	x	x	x	x
	GSK2862277 26mg IH	0	40	x	x	x	x	x	x
Alternative Treatment Group Descriptions #2	BAL Collapsed lung	0	33	x	x	x	x	x	x
	BAL Ventilated lung	0	47	x	x	x	x	x	x

Note: n/a = not applicable, PP = Per Protocol

Example : POP_L1
Protocol : TFR116341
Population : n/a

Listing X.XX
Listing of Subject Accountability (subjects constituting each Statistical Analysis Population)

Inv ID	Screening ID or Subject ID	Actual treatment	Screen Failures	Safety	PK	PP1	PP2	PP3	IA1	IA2	Translational Sub-Study
PPD		n/a	Y	.	.	.	.	.	.	.	.
		n/a	Y	.	.	.	.	.	.	.	.
		n/a	Y	.	.	.	.	.	.	.	.
		Placebo BAL Collapsed	.	Y	Y	Y	Y	Y	Y	Y	.
		Placebo BAL Collapsed	.	Y	Y	.	.	Y	.	.	Y

Note: n/a = not applicable, PP = Per Protocol, Y = Included in population, "." = Excluded from population

Programming note: Label Center ID as Inv Id. If a subject was not a screen failure use their Subject ID. Break on Centres. Add additional columns if required