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

Title	:	Reporting and Analysis Plan for a randomised, placebo-controlled, double-blind (sponsor-open), segmental LPS challenge study to investigate the pharmacodynamics of GSK2798745 in healthy participants
Compound Number	:	GSK2798745
Effective Date	:	23-JUN-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 207464
- This RAP is intended to describe the efficacy, biomarker/pharmacodynamics, safety and pharmacokinetics analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the interim analyses and Statistical Analysis Complete (SAC) deliverable.

RAP Author(s):

Approver	Date	Approval Method
PPD Statistician (Respiratory, Clinical Statistics)	Not Applicable	Not Applicable
PPD Senior Director (Respiratory, Clinical Pharmacology)	20-JUN-2018	Pharma TMF

RAP Team Approvals:

Approver	Date	Approval Method
PPD Project Physician Lead (Respiratory TAU)	20-JUN-2018	Email
PPD Clinical Investigational Lead (Respiratory TAU)	20-JUN-2018	Pharma TMF
PPD Operations Study Lead (CPSSO)	20-JUN-2018	Pharma TMF
PPD Data Quality Lead (CPSSO)	21-JUN-2018	Pharma TMF
PPD Translational Scientist and Biomarker Representative (Respiratory TAU)	11-JUN-2018	Email
PPD SERM Director (GCSP)	23-JUN-2018	Pharma TMF

Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Director (Respiratory, Clinical Statistics)	21-JUN-2018	Pharma TMF
PPD Director (Respiratory, Clinical Programming)	20-JUN-2018	Email

TABLE OF CONTENTS

PAGE

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol:

Revision Chronology:		
Original Document Number: 2016N304618_00	24-OCT-2017	Original
Revised Document Number: 2016N304618_01	02-FEB-2018	The primary reason for amending the protocol is to update the number of timepoints for exploratory biomarkers. The number of blood samples for exploratory biomarkers has been reduced.
Revised Document Number: 2016N304618_02	21-MAY-18	The protocol was amended in response to comments from the competent authority.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

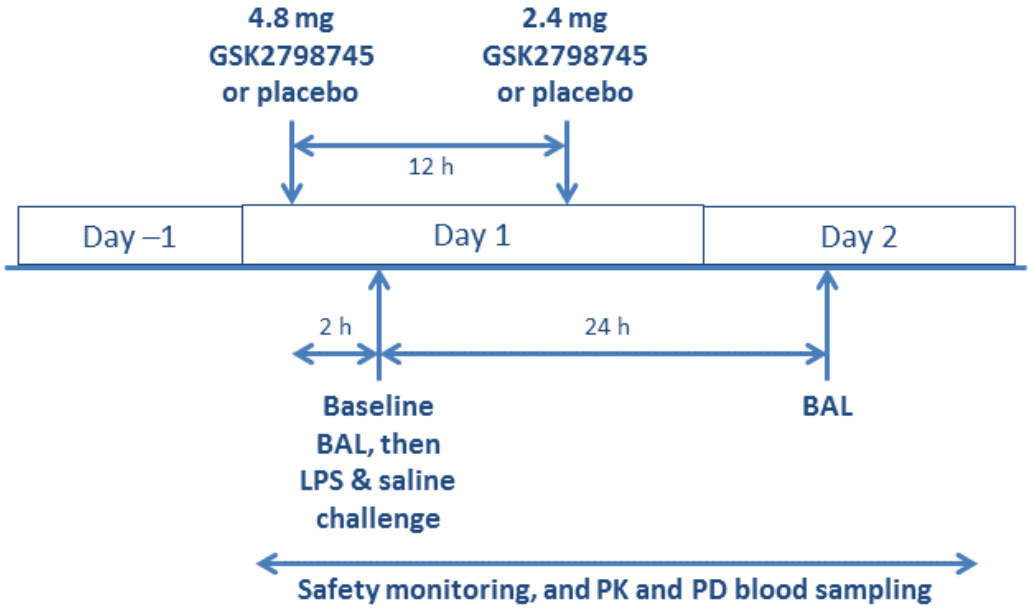
There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 24/OCT/2017).

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

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To investigate the effect of GSK2798745 on alveolar-septal barrier permeability following LPS challenge in healthy participants.	• Baseline adjusted total protein concentration in bronchoalveolar lavage (BAL) samples at 26 h (24 h after segmental LPS challenge).
Secondary Objectives	**Secondary Endpoints**
• To investigate the effect of GSK2798745 on neutrophil levels in LPS-challenged lungs.	• Baseline adjusted total and differential cell count of neutrophils in BAL samples at 26 h (24 h after segmental LPS challenge).
• To assess the safety and tolerability of GSK2798745 in LPS-challenged, healthy participants.	• Adverse events (AEs), laboratory safety assessments, 12-lead electrocardiogram (ECG), physical examination, vital signs, spirometry (forced expiratory volume in 1 second [FEV1] and forced vital capacity [FVC]), faecal occult blood test (FOBT).
• To assess the pharmacokinetics (PK) of GSK2798745 in plasma in LPS-challenged, healthy volunteers	• PK parameters of GSK2798745 in plasma (including AUC (0-26) and Cmax).
Exploratory Objectives	**Exploratory Endpoints**
• To assess concentration of GSK2798745 in BAL	• Levels of GSK2798745 in BAL samples at 2h and 26h after dosing

Objectives	Endpoints
• To investigate the effect of GSK2798745 on exploratory markers of endothelial barrier permeability and/or injury, and inflammation, in LPS-challenged lungs.	• Baseline adjusted levels of exploratory biomarkers in blood and/or BAL.
• To possibly assess metabolite GSK3526876 (major metabolite of GSK2798745) in plasma and BAL samples.	• Plasma and BAL concentrations of metabolite GSK3526876.
• To compare the PK of GSK2798745 with the effect of prophylactic dosing on alveolar-septal barrier permeability following LPS challenge in healthy volunteers.	• Comparison of PK parameters of GSK2798745 in plasma and BAL with baseline corrected total protein concentration in BAL.
• To investigate the effect of GSK2798745 on white blood cell levels (except neutrophils) in LPS-challenged lungs	• Baseline adjusted total and differential cell count of white blood cells (except neutrophils) in BAL samples at 26 h (24 h after segmental LPS challenge).

2.3. Study Design

Overview of Study Design and Key Features **Figure 1 Study Design**	
	
Design Features	• Parallel group study comparing GSK2798745 vs Placebo • Double-blind (sponsor open), placebo-controlled • 26 h study treatment period • Follow-up phone call 2 days after discharge and return to the study site on Day 8 (1 day) for a follow-up visit
Dosing	• 4.8mg GSK2798745 or placebo 2 h before baseline BAL and LPS and saline challenges. This is followed by 2.4mg GSK2798745 or placebo 12h after the initial dose.
Time & Events	• Refer to Appendix 2: Schedule of Activities.
Treatment Assignment	• Participants are randomised to receive GSK2798745 or placebo (1:1 allocation ratio).
Interim Analysis	• An interim analysis will occur after approximately 10 participants per arm have completed the treatment period to assess if the study should stop for futility or continue. Subsequently, if the decision at the first interim is to continue, an interim analysis will occur once approximately 20 participants per arm have completed the treatment period to assess whether the study should continue or stop for success or futility. If at this point the study continues, the maximum 30 participants per arm will be recruited. • The decision to stop or continue will be supported by the predicted probability of success. If the probability of study success is sufficiently high then the study may stop for success. Conversely, if the probability of study success or review is sufficiently low then the study may stop for futility.

2.4. Statistical Analyses

The primary study objective is to investigate the effect of GSK2798745 relative to placebo on BAL total protein at 26 h post first dose (24 hours after segmental LPS challenge). In this study a Bayesian framework will be used (with non-informative priors on all model parameters) to estimate the posterior probability of any mean percentage reduction in 26 h BAL protein level (GSK2798745 relative to placebo). It is anticipated that BAL total protein will be $\log_e$ transformed before model fitting. Following back-transformation treatment comparisons will be expressed as percentage changes.

3. PLANNED ANALYSES

3.1. Interim Analyses

The interim analyses will be undertaken by the study statistician and/or designates and the outputs will only be communicated to key members of the study team which may include the Project Physician Lead, Early Development Lead, Clinical Investigation Lead, Translational Biomarker Representative, Study Statistician, Project Statistician and Study Programmer(s). Following the decision made by this core group, the decision will be communicated to the wider study team. The decision will only be communicated to the site if the decision is made to stop.

The appropriate internal GSK procedures will be followed to ensure that access to unblinded participant level data is restricted to the relevant personnel performing the analysis. A secure directory will be created with restricted access for storage of data, programs, log files and outputs. Only participants contributing data towards the interim analysis will have their treatment codes unblinded as per GSK internal procedures.

Each interim analysis will be based on the predictive probability of meeting the end of study success criteria in the primary endpoint 26h BAL total protein (see Figure 2 and Table 1). An interim analysis will take place once approximately 10 participants per arm have completed the treatment period to determine whether there is sufficient rationale to continue or discontinue the study. If the decision is made to continue then a second interim analysis will occur once approximately 20 participants per arm have been recruited. Sufficient participants will be recruited to obtain up to 30 evaluable participants per arm.

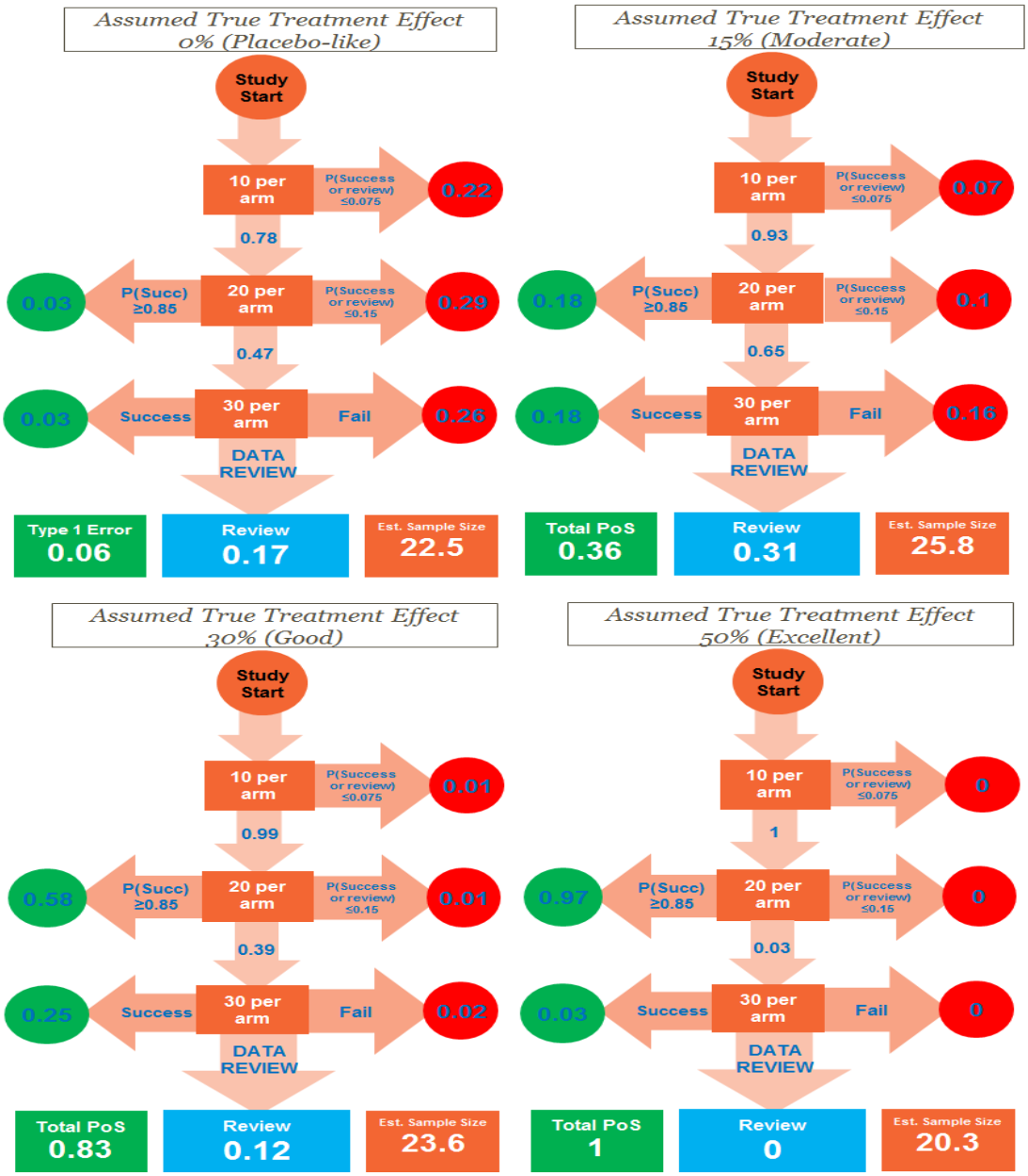
Recruitment into the study will continue whilst the interim analysis is taking place unless data emerges regarding concerns about safety and tolerability. Any communication to the site regarding interim analyses will only take place if a decision to stop the study is made. Should the study be stopped, all ongoing participants will complete their treatment period whilst no further participants will be recruited into the study.

Figure 2 shows the operating characteristics that were evaluated by the study team for the chosen study design during the protocol development stage. It shows the interim analyses set-up under assumed true percentage reductions in total BAL protein for GSK2798745 relative to placebo of 0%, 15%, 30% and 50%, respectively, unconditional on variability. The schematic demonstrates all possible decision pathways the study may take. To obtain the operating characteristics of a given study design, 10,000 studies were simulated with each one taking a particular pathway and finishing in one of the pockets on the left or right of the diagram, or additional data review. The overall proportion of simulated studies reaching a particular conclusion gives the probability of a single study reaching that conclusion.

A stricter posterior probability futility threshold is implemented at the first interim to reduce the probability of incorrectly declaring futility. Furthermore, a minimum of 20 participants per arm must be recruited before declaring success. These rules are shown within the left (success) and right (futile) arrows. Under this design, assuming a true treatment effect of 30%, the overall probability of study success is approximately 83%, unconditional on variability. In addition, the probability of requiring a maximum of 20

participants per arm is approximately 61% (under the same assumption of true treatment effect of 30%). In the case of a placebo-like drug the probability of incorrectly declaring success is approximately 6% (akin to type 1 error rate). The blue boxes at the bottom of the charts show the probability that a study goes to data review, for which the results will be included as part of the headline reporting effort.

Figure 2 Interim Analysis Framework for Range of Assumed True Treatment Effects



The decision made at the interim analysis is supported by the interim predicted probability of success of the study i.e. given the treatment effect and variability observed

from the unblinded participants at the interim, the probability of the study going on to meet the predefined success criteria.

Table 1 shows the stopping criteria for interim analyses. Stopping for success is based upon the predicted probability of success (posterior probability of any percentage reduction in mean BAL total protein for GSK2798745 relative to placebo being at least 95%) whilst stopping for futility is based on the predicted probability of success or data review (posterior probability of any percentage reduction in mean BAL total protein for GSK2798745 relative to placebo being at least 75%). **Note: PP = posterior probability [% reduction in mean BAL total protein for GSK2798745 relative to placebo > 0])**.

Table 1 Success and Futility Criteria for each Interim Analysis

Interim Analysis	**Success**	**Futility**
10 participants per arm	N/A – cannot stop for success at the first interim.	Predictive Prob (PP $\geq$ 0.75) $\leq$ 0.075
20 participants per arm	Predictive Prob (PP $\geq$ 0.95) $\geq$ 0.85	Predictive Prob (PP $\geq$ 0.75) $\leq$ 0.15

Additional analyses/outputs to support the interim analysis decision making

Because the key metric at the interim analysis is simply a probability, the key study team members will be presented with tables, summary statistics and figures for the primary analysis using the interim analysis population to help make an informed decision. Details of the planned displays provided at the interim analyses are provided in Appendix 11: List of Data Displays.

Technical details for calculating predictive probability of success in interim analysis

Note: The method described here is the preferred method of several ways to calculate the predictive probability of success.

The interim analyses utilise predictive inference methods to calculate the predictive probability of success. This predictive probability may be used to help determine whether there is sufficient rationale to continue/discontinue the study.

PROC MCMC in SAS (or other software offering the same methodology) will be used to sample both baseline (2 h) BAL total protein and 26 h BAL total protein (LPS lobe) from their respective interim posterior predictive distributions to generate values for predicted participants (participants yet to be recruited into the study). The number of predicted participants to be generated at the interim analysis is equal to the end of study sample size minus the interim number of participants (Equation 1). The observed and predicted participants are combined together and analysed using the primary analysis model. The end of study success criteria is then applied.

Equation 1

$$n_{predicted,j} = 30 - n_{interim,j}$$

where $j \in (A, P)$ indicates treatment group

There is a degree of uncertainty attached to parameters at the interim (due to the limited data) and for each iteration that fictitious participants are generated the set of predicted participants will look different, due to the random nature of simulations. Thus, to take this uncertainty into account and give an accurate representation of the predictive probability of success based on the interim data, the primary analysis is modelled 10,000 times i.e. the observed data is combined with a different simulated set of future participants 10,000 times. The proportion of primary analyses that trigger the end of study success criteria gives the predictive probability of success if the study was to continue from the interim.

Data is anticipated to require ($\log_e$) transformation before modelling. Baseline will be centred after transformation to improve mixing. General steps to calculating the predictive probability of success at the interim are given here. Consult the GSK statistician for more detailed steps (including the corresponding SAS program).

1. The linear predictor will be the same as the primary analysis model (assuming no further covariates are included) and will include the parameters:

Type	Name (#Levels)	Parameters	Priors
Fixed Categorical	Intercept (1)	#1 Intercept	N(Mean=0, Var=1E6)
	Treatment (2)	#1 Placebo	N(Mean=0, Var=1E6)
		#2 GSK2798745	N/a
Fixed Continuous	Baseline BAL total protein	Linear relationship between baseline and LPS lobe 26h BAL total protein (baseline slope).	N(Mean=0, Var=1E6)

2. The standard deviation parameters will be fitted with non-informative gamma priors with shape=0.001 and scale=0.001.
3. Participant id numbers for future participants will be created to achieve the maximum sample size of 60 (30 per treatment group) as described by Equation 1. Predicted participants will be allocated treatment codes using study-specific treatment block size.
4. The data set to be passed through PROC MCMC will contain complete data for observed interim participants plus treatment and id codes for future participants (baseline (2h) and 26h total protein will be missing).
5. A model statement for baseline BAL total protein will be set up within PROC MCMC with a non-informative prior N(Mean=0, Var=1E6) for mean and non-informative

prior gamma(shape=0.001, scale=0.001) for standard deviation. This allows baseline values to be sampled for future participants from the interim posterior predictive distribution that includes data for current participants.

6. The outpost statement will be used to create an output dataset for posterior predictive samples from each MCMC iteration.
7. A series of diagnostic checks will be undertaken (see Section 7.1.5.1 (model checking & diagnostics) for further details).
8. A series of data manipulation steps are required to merge the observed data with each of the predicted future data sets. The number of data sets is equal to the number of MCMC iterations but all should be contained within one overall data set and labelled according to which MCMC iteration the "study" belongs to.
9. This overall dataset will be passed into PROC MCMC fitting the same primary analysis model but without the predictions. A BY statement will fit the model separately to each dataset (made up of observed and predicted participants). A POSTSUMMARIES option will report summaries of the parameters of interest including the primary endpoint success criteria as a flag variable (*Posterior probability [% reduction in mean BAL total protein for GSK2798745 relative to placebo > 0] ≥ 0.95*) as well as the probability of being within the data review region (*Posterior probability [% reduction in mean BAL total protein for GSK2798745 relative to placebo > 0] ≥ 0.75*).
10. The proportion of complete studies (observed + predicted participants) meeting the success criteria will be computed. The proportion meeting the success criteria gives the predictive probability of success at the interim.
11. The predictive probability of success is compared with the criteria described in Table 1 to support the decision at the interim analysis.

3.2. Final Analyses

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

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR) and database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met.
4. Randomization codes have been distributed according to RandAll NG procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants that signed the ICF and were screened for eligibility	• Study Population
All Subjects	• All randomized participants who received at least one dose of study treatment. • This population will be based on the treatment the participant actually received.	• Study Population • Safety/tolerability
Evaluable	• All participants for whom results of the primary analysis can be determined i.e. all randomised participants who received two correct doses of study treatment, received LPS and saline segmental challenge (in contralateral lobes) and for which results of both baseline (2h) and LPS lobe (26h) BAL samples are evaluable. • This population will be based on the treatment the participant actually received.	• BAL Pharmacodynamic • BAL Biomarker • Blood Biomarker
Pharmacokinetic (PK)	• All participants in the All Subjects population who had at least 1 non-missing PK assessment (Non-quantifiable [NQ] values will be considered as non-missing values).	• Pharmacokinetic

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

4.1. Protocol Deviations

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

Important deviations which result in exclusion from the analysis population will also be summarised and listed. (Please refer to Appendix 1: Protocol Deviation Management and Definitions for Evaluable Population).

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan Version 1.0 (Dated: 18/JUN/2018).

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations and deviations which may lead to exclusion from the analysis are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate 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

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	Placebo	Placebo	1
B	GSK2798745	GSK2798745	2

Treatment comparisons will be displayed as follows using the descriptors as specified:

1. GSK2798745 vs. Placebo

Parameter	Study Assessments Considered as Baseline					Baseline Used in Data Display
	Screening (Days -28 to -2)	Day -1	Day 1 Pre-dose	Day 1 1h	Day 1 2h[1]	
Pharmacodynamic						
BAL Total Protein					X	Day 1 2h
BAL Neutrophil Count (Total and Differential)					X	Day 1 2h
Safety						
12-lead ECG[2]	X	X	X			Day 1 Pre-dose
Vital signs (blood pressure, heart rate)[3]	X	X	X	X		Day 1 Pre-dose
Temperature	X	X	X	X	X	Day 1 Pre-dose
Spirometry (FEV1, FVC)[4]		X	X			Day 1 Pre-dose
Laboratory assessments[5]		X				Day -1
Exploratory Biomarkers						
BAL Biomarkers					X	Day 1 2h

NOTES:
1. Immediately before BAL sampling/LPS challenge
2. Triplicate at Screening, day-1 and day 1 pre-dose. Single measurements at time points after dosing.
3. Blood pressure and heart rate in triplicate.
4. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Triplicate measurements at each time point, the highest of which should be recorded in the case report form.
5. Haematology, clinical chemistry (including liver chemistry), cardiac troponins, urianalysis and coagulation profile.

5.2. Baseline Definitions

If the "baseline used in data display" is missing for a parameter, then the study assessment considered as a baseline closest in time to this will replace this as the baseline used in displays. If all study assessments considered as baseline are missing then no derivation will be performed and baseline will be set to missing.

5.3. Examination of Covariates, Other Strata and Subgroups

5.3.1. Covariates and Other Strata

The list of covariates and other strata may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses. Additional covariates and other strata of clinical interest may also be considered.

Category	Details
Covariates	Baseline (2h) total protein, 26h total protein (saline lobe)

NOTES:
- The covariates listed are those that may be used in analyses.

The default statistical model for BAL markers is to fit an analysis of covariance (ANCOVA) model with baseline (2h BAL) response and treatment group as covariates and 26h BAL response as the response variable. Additional covariates with the use of clinical expertise and statistical tools (raw plots and model selection criteria) may be considered such as age and gender.

5.3.2. Examination of Subgroups

There are no planned subgroup analyses.

5.4. Multiple Comparisons and Multiplicity

Due to the extensive use of a Bayesian framework and the early phase/exploratory nature of this study there will be no explicit multiplicity adjustments. Moreover, the decision framework for study success/fail is predetermined.

5.5. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
12.3	Appendix 3: Assessment Windows
12.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
12.5	Appendix 5: Data Display Standards & Handling Conventions
12.6	Appendix 6: Derived and Transformed Data
12.7	Appendix 7: Reporting Standards for Missing Data
12.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

Study population analyses including analyses of participants' disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 11: List of Data Displays.

7. PHARMACODYNAMIC AND BIOMARKER ANALYSES

7.1. Primary Pharmacodynamic and Biomarker Analyses

7.1.1. Endpoint / Variables

The primary endpoint is defined as BAL total protein (in the lobe in which LPS was administered) at 26h post first dose (24 hours after segmental LPS challenge). A Bayesian framework will be used (with non-informative priors on all model parameters) to estimate the posterior probability of any percentage reduction in mean 26 h BAL protein level (GSK2798745 relative to placebo). It is anticipated that BAL total protein will be $\log_e$ transformed to improve normality before model fitting. Following back-transformation treatment comparisons will be expressed as percentage changes. Details of data transformations are described in Appendix 6: Derived and Transformed Data.

7.1.2. Summary Measure

Following back-transformation, treatment comparison will be expressed as an adjusted median posterior percentage reduction in 26h total protein level for GSK2798745 compared to placebo, along with corresponding 95% credible interval.

7.1.3. Population of Interest

The primary analyses will be based on the Evaluable population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Since this is a proof of mechanism study, the estimand of interest in the primary analysis is the treatment effect (GSK2798745 c.f. placebo) for participants in the Evaluable population i.e. all randomised participants who received the two correct doses of study treatment, received LPS and saline segmental challenge (in contralateral lobes) and for which results for both baseline (2h) and 26h (LPS lobe) BAL samples are evaluable and did not have any major deviations affecting the primary endpoint. Given that the primary analyses are based on the Evaluable population in healthy participants, any intercurrent events such as treatment discontinuation will result in exclusion of the data from the analysis and no missing data imputation will occur.

7.1.5. Statistical Analyses / Methods

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

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

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables

- BAL total protein at 26h (LPS lobe).
- It is anticipated that pharmacodynamic and biomarker endpoints will require $\log_e$-transformation in all analyses to improve the assumption of normality and hence improve model fitting. Following model fitting, back-transformation will occur and treatment effects (GSK2798745 relative to placebo) will be expressed as a percentage change.

Model Specification

- The model described below is the default statistical model for BAL biomarkers with BAL samples taken at 2 h and 26 h. **analyte** in the text below should be replaced by the specific BAL endpoint in the analysis.
- The endpoint will be analysed using an analysis of covariance (ANCOVA) model fitted in a Bayesian framework with covariates having non-informative priors using PROC MCMC in SAS.
- The terms to be fitted in the model:

Type	Name
Dependent variable	• BAL **analyte** at 26 h (**LPS lobe**)
Fixed continuous independent variables	• Baseline (2 h) BAL **analyte**
Fixed categorical independent variables	• Treatment (GSK2798745, Placebo)

Information on the effects and prior distributions for parameters:

Type	Name (#Levels)	Parameters	Priors
Fixed Categorical	Intercept (1)	#1 Intercept	N(Mean= 0, Var=1E6)
	Treatment (2)	#1 Placebo	N/a (constraint = 0)
		#2 GSK2798745	N(Mean=0, Var=1E6)
Fixed Continuous	Baseline (2h) BAL **analyte**	Linear relationship between baseline (2 h) and 26 h LPS lobe BAL **analyte** (baseline slope).	N(Mean=0, Var=1E6)

- The residual variance will be fitted with an non-informative inverse-gamma prior, igamma(shape=0.0001, scale=0.0001).
- Any centering of variables is to occur after any transformation. Baseline (2h) BAL **analyte** is to be centered to improve mixing in PROC MCMC.
- An optional exploration/model building step may take place by adding other covariates to the model that may explain a significant proportion of variance in the response and/or imbalance between treatment groups at baseline and/or be justified by biological rationale/expert

judgment or statistical tools (raw plots and model selection criteria). Only the results of the final model would be reported in the Clinical Study Report (CSR).

- For the final model, appropriate combinations of model parameters should be combined to obtain treatment effects of interest, including performing any back-transformations that are required. For example, assuming $\log_e$ transformation is required, the percentage change in 26h BAL **analyte** will be obtained by computing $exp(\beta_{GSK2798745})$ for each MCMC iteration, which should be programmed between the BEGINNODATA and ENDNODATA statements (within PROC MCMC procedure).
- To obtain probability statements for parameters/effects of interest use binary flag variables. For each MCMC iteration if the condition is satisfied the iteration is flagged as a 1, if not it is flagged as 0. The proportion of iterations flagged as 1 gives the posterior probability of the statement of interest i.e. the proportion of MCMC iterations for which the percentage reduction in BAL **analyte** for GSK2798745 c.f. placebo is greater than zero.
    - For example, the SAS syntax for computing the flag for any percentage reduction in BAL **analyte** would be: *flagsuccess = (ratio < 1);* . Where *ratio* is the parameter used to store the ratio for adjusted posterior medians, GSK2798745 relative to placebo, calculated as $exp(\beta_{GSK2798745})$, and *flagsuccess* being the binary success/fail flag.

Model Checking & Diagnostics

Ways to assess model appropriateness and fit can be assessed using a variety of tools. Some examples of methods are listed here:

- Use the DIC alongside expert judgment/biological rationale to select the most appropriate model. A difference in DIC between two models is >10 is generally considered substantial evidence of an important difference in model fit. Difference in DIC of <5 may be considered negligible.
- Examine trace plots for fixed parameters to evaluate whether there is constant mean and variance, that the chain is moving around the parameter space freely and moving rapidly between the extremes to show that the chain is stationary and mixing.
- Run at least 2 chains starting at different initial values. If all chains converge to the same point, then this is evidence of consistent convergence. Overlapping trace plots give visual reference for this. Running multiple chains is achieved by either by specifying initial values using *begincnst/endcnst* and using a *by* statement to run for each chain, or by using a macro to run PROC MCMC multiple times with initial values specified on the *parms* statement and different seeds specified for each run. Please consult GSK statistician for more details, including SAS syntax.
- The 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 simulation error. The ratio MCSE/SD should typically be ≤ 0.01.
- Autocorrelation plots should be used to assess the correlation between each draw and its kth lag. The further the lag from the original measure the smaller you expect the correlation to be.
- Rather than using the prior distribution to generate starting values for parameters in the model, use raw plots or PROC MIXED (frequentist equivalent to Bayesian) parameter estimates to help determine starting values. This should help the model converge quicker and reduces the number of burn-in iterations required.
- Tailor the number of burn-in iterations, thinning, starting values, number of posterior samples

(10,000 minimum) to ensure satisfactory model fitting and diagnostic plots.

- As an optional check, use residual plots from the PROC MIXED (frequentist equivalent to Bayesian) model to examine model fit (relevant because non-informative priors are used in the analysis). Residuals should be normally distributed (assessed with a histogram or normal probability plot). Residuals and fitted values should be uncorrelated (assessed by plotting against each other and should appear random with no structure). Any pattern suggests that the model is not appropriate. The same plot can be used to examine if there is constant variance.

Model Results Presentation

- Point estimates (median values of posterior distributions), the standard deviation of the posterior distribution (SDs) and 95% credible intervals (CrI) intervals will be presented for each treatment group and treatment comparison (absolute and percentage change). A number of posterior probability statements will also be expressed, as described in Table 2.

Table 2 Posterior Probability Statements of Interest

Posterior Probability Statement (where X = treatment ratio of GSK2798745 / Pbo)	Interpretation
PP (X ≤ 0.25)	Posterior probability of at least a 75% reduction in mean BAL **analyte** GSK2798745 relative to placebo
PP (X ≤ 0.5)	Posterior probability of at least a 50% reduction in mean BAL **analyte** GSK2798745 relative to placebo
PP (X ≤ 0.75)	Posterior probability of at least a 25% reduction in mean BAL **analyte** GSK2798745 relative to placebo
PP (X ≤ 0.9)	Posterior probability of at least a 10% reduction in mean BAL **analyte** GSK2798745 relative to placebo
PP (X ≤ 1)	Posterior probability of any reduction in mean BAL **analyte** GSK2798745 relative to placebo
PP (X > 1)	Posterior probability of any increase in mean BAL **analyte** GSK2798745 relative to placebo
PP (X > 1.1)	Posterior probability of at least a 10% increase in mean BAL **analyte** GSK2798745 relative to placebo
PP (X > 1.25)	Posterior probability of at least a 25% increase in mean BAL **analyte** GSK2798745 relative to placebo
PP (X > 1.5)	Posterior probability of at least a 50% increase in mean BAL **analyte** GSK2798745 relative to placebo
PP (X > 1.75)	Posterior probability of at least a 75% increase in mean BAL **analyte** GSK2798745 relative to placebo

- Point estimates for each treatment group and treatment comparison (absolute and percentage change) will be expressed graphically. See Appendix 11: List of Data Displays for example displays.
- Plots of the posterior distributions for 26 h BAL **analyte** (back-transformed) will be presented for each treatment arm. In addition, the posterior distributions for the absolute difference and percentage change in 26 h BAL **analyte** for GSK2798745 relative to placebo will be presented.

Sensitivity and Supportive Analyses

- Sensitivity analysis 1: Assess whether there is a difference in baseline (2h) concentrations between treatment groups. The design of the study is such that baseline is observed 2 hours after the first dose of study treatment (see Figure 1). Thus, there is opportunity for inhibition of the TRPV4 channel and regulation of endothelial permeability before the baseline (2h) BAL is performed and instillation of LPS and saline challenges. Should there be a significant difference in baseline (2h) **analyte** between treatment arms this may be interpreted as initial concentrations (normal conditions) of **analyte** are being reduced. For example, '745 may reduce baseline BAL **analyte** for GSK2798745 c.f. placebo. This will be investigated through the use of a Bayesian ANOVA model with 2h **analyte** as the dependent variable and treatment group as the independent variable. See Appendix 11: List of Data Displays for further details.
- Sensitivity analysis 2: The primary analysis model may be fitted to include 26 h **analyte** (saline lobe) as a covariate. In a supportive analysis, the model will assess whether administration of saline in the contralateral lobe is associated with 26 h **analyte** in the lobe in which LPS and treatment are administered. If this is the case, then one explanation could be that the segmental LPS may have "spilled over" into other areas of the lungs including the saline lobe. This could also lead to a lower than anticipated LPS dose in the LPS lobe. The analysis would be supported by graphical displays of individual participants and their three lobe measurements (see Appendix 11: List of Data Displays for example displays). Secondly, a positive relationship between contralateral lobes could be interpreted as the BAL procedure resulting in some impact on the endothelial/epithelial lining i.e. the BAL procedure itself results in more irritation of the tissue and stimulates a biological response to a greater extent than anticipated and this results in increased permeability. Thus, by adjusting for 26 h BAL **analyte** (saline lobe) the model is partitioning any effect on BAL total protein due to the procedure and due to the LPS/study treatment. Another reason could be that saline impacts upon permeability. This list is not exhaustive and only speculates on the reasoning behind a significant impact in pulmonary edema in the saline lobe. Further clinical and biological expertise is required to draw any conclusions.
- Sensitivity analysis 3: A sensitivity analysis may be conducted to exclude participants for which their 26 h BAL **analyte** in the saline lobe increases by at least 40% relative to baseline. This is the 95th percentile of the credible interval for 11 participants that underwent segmental LPS challenge over 2 periods (measured at baseline and 26 h) at the Fraunhofer Institute, Germany [Holz, 2015]. The median for 26 h BAL total protein in the saline lobe was 13.7% (95% CrI - 8.8%, 40.4%). This sensitivity analysis is being conducted because some participants may have received a greater dose of LPS than anticipated, be more sensitive to the LPS dose, the BAL procedure may have been more invasive than anticipated, etc. This may confound any observed treatment effect.

7.2. Secondary Pharmacodynamic Analyses

7.2.1. Endpoint / Variables

BAL total and differential neutrophil count (in the lobe in which LPS was administered) at 26 hours. A Bayesian framework will be used (with non-informative priors) to estimate the posterior probability of any percentage reduction in median 26 h (24 h post-LPS) BAL response (GSK2798745 relative to placebo). It is anticipated that BAL analytes will be $\log_e$ transformed to improve normality before model fitting. Following back-transformation treatment comparisons will be expressed as percentage changes. Details of data transformations are described in Appendix 6: Derived and Transformed Data.

7.2.2. Summary Measure

Following back-transformation, treatment comparison will be expressed as an adjusted median posterior percentage reduction in 26 h BAL analyte level for GSK2798745 compared to placebo, along with corresponding 95% highest posterior density interval.

7.2.3. Population of Interest

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

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4.

7.2.5. Statistical Analyses / Methods

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

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

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• BAL total and differential neutrophil count at 26 h (LPS lobe). • It is anticipated that pharmacodynamic and biomarker endpoints will require log-transformation in all analyses to improve the assumption of normality and hence improve model fitting. Following model fitting, back-transformation will occur and treatment effects (GSK2798745 relative to placebo) will be expressed as a percentage change. • The derivation of differential cell count is given in Section 12.6.3.
Model Specification
• See Section 7.1.5.1.
Model Checking & Diagnostics
• See Section 7.1.5.1.
Model Results Presentation
• See Section 7.1.5.1.

7.3. Exploratory Pharmacodynamic and Biomarker Analyses

7.3.1. Endpoint / Variables

Table 3 gives the matrices and sampling schemes for each of the exploratory biomarker endpoints.

Table 3 Exploratory Biomarkers and Corresponding Sampling Schemes

Matrix	Endpoint / Analyte	Sampling Scheme
BAL	Albumin SP-D vWF IL-6 IL-8 TNF-alpha MPO Urea White blood cell counts and differentials (except neutrophils)	2h, 26h
Blood	Total protein (plasma) Albumin (plasma) SP-D (serum) vWF (serum) IL-6 (serum) IL-8 (serum) TNF-alpha (serum) Immature SP-B (serum) urea (plasma) CRP (serum)	2h, 3h, 8h, 26h

7.3.2. Summary Measure

BAL Biomarkers

Exploratory BAL biomarkers will be analysed and reported in the same manner as the primary pharmacodynamic data (without the sensitivity analyses) (refer to Section 7.1 for further details). Treatment comparison will be expressed (following back-transformation) as an adjusted median posterior percentage change for GSK2798745 compared to placebo, along with corresponding 95% credible interval.

Blood Biomarkers

Treatment comparisons will be expressed (following back-transformation) as an adjusted median posterior percentage change for GSK2798745 compared to placebo at each of the sampling timepoints (2h, 3h, 8h and 26h).

7.3.3. Population of Interest

Analyses will be based on the Evaluable population for both the BAL biomarker and blood biomarker analyses.

7.3.4. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4.

7.3.5. Statistical Analyses / Methods

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

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

7.3.5.1. Blood biomarkers

The following text is the general method for analysing and reporting blood biomarkers that follow the sampling scheme in Table 3.

Endpoint / Variables

- Each blood biomarker and the sampling timepoints are listed in Table 3.
- It is anticipated that biomarkers will require log-transformation in all analyses to improve model fitting. Following model fitting, back-transformation will occur and treatment comparisons at each of the sampling timepoints will be expressed as a percentage change for GSK2798745 relative to placebo.

Model Specification

- Each blood biomarker will be analysed using a repeated measures mixed model (MMRM) fitted in a Bayesian framework with all covariates having non-informative priors using PROC MCMC in SAS or other software.
- **analyte** in the text below should be replaced by the specific blood biomarker in the analysis.
- The terms to be fitted in the model:

Type	Name
Dependent variable	• **analyte** response
Fixed categorical independent variables	• Treatment • Sampling timepoint • Sampling timepoint interacted with treatment

Information on the effects and prior distributions for parameters:

Type	Name (#Levels)	Parameters	Priors
Fixed Categorical	Intercept (1)	#1 Intercept	N(Mean= 0, Var=1E6)
	Treatment (2)	#1 Placebo	N/a (constraint=0)
		#2 GSK2798745	N(Mean=0, Var=1E6)
	Sampling Timepoint (4)	#1 2h	N/a (constraint=0)
		#2 3h	N(Mean=0, Var=1E6)
		#3 8h	N(Mean=0, Var=1E6)
		#4 26h	N(Mean=0, Var=1E6)
	Treatment*Sampling Timepoint (8)	#1 Placebo*2h	N/a (constraint=0)
		#2 Placebo*3h	N/a (constraint=0)
		#3 Placebo*8h	N/a (constraint=0)
		#4 Placebo*26h	N/a (constraint=0)
		#5 GSK2798745*2h	N/a (constraint=0)
		#6 GSK2798745*3h	N(Mean=0, Var=1E6)
		#7 GSK2798745*8h	N(Mean=0, Var=1E6)
		#8 GSK2798745*26h	N(Mean=0, Var=1E6)

- The default prior for the VCV matrix would be an Inverse-Wishart with parameters k and **S** (where **S** = (k – p - 1) * **R** and p = dimension of the VCV matrix). Under this framework, **R** can be thought of as a best guess for the VCV of the endpoints/timepoints being modelled. Care should be taken in the choice of k and **R** for each endpoint to ensure it is uninformative.
- Separate variance-covariance matrices will be used for treatment groups if there is sufficient information/data to allow for this, i.e. convergence occurs for all parameters and values do not get "stuck" at zero. If there is not sufficient information then the default position is for treatment groups to share a common variance-covariance matrix.
- An optional exploration/model building step may take place by adding other covariates to the model that may explain a significant proportion of variance in the response and/or imbalance between treatment groups at baseline and/or be justified by biological rationale/expert judgment or statistical tools (raw plots and model selection criteria). Only the results of the final model would be reported in the Clinical Study Report (CSR).
- For the final model, appropriate combinations of model parameters should be combined to obtain treatment effects of interest, including performing any back-transformations that are required. For example, assuming $\log_e$ transformation is required, the percentage change at 8h for GSK2798745 relative to placebo will be obtained by computing $exp(\beta_{GSK2798745} + \beta_{GSK2798745*8h} - \beta_{8h})$ for each MCMC iteration, which should be programmed between the BEGINNODATA and ENDNODATA statements (within PROC MCMC procedure).
- To obtain probability statements for parameters/effects of interest use binary flag variables. For each MCMC iteration if the condition is satisfied the iteration is flagged as a 1, if not it is flagged as 0. The proportion of iterations flagged as 1 gives the posterior probability of the

statement of interest i.e. the proportion of MCMC iterations for which the percentage reduction in the BAL biomarker for GSK2798745 c.f. placebo for the specified sampling timepoint is greater than zero. • For example, the SAS syntax for computing the flag for any percentage reduction in BAL **analyte** would be: *flagsuccess_8h = (ratio_8h < 1);* . Where *ratio_8h* is the parameter used to store the ratio of adjusted posterior medians for GSK2798745 relative to placebo at the 8h sampling timepoint, calculated as $exp(\beta_{GSK2798745} + \beta_{GSK2798745*8h} - \beta_{8h})$, and *flagsuccess_8h* being the binary success/fail flag.
Model Checking & Diagnostics
• See Section 7.1.5.1 (Model Checking and Diagnostics)
Model Results Presentation
• Point estimates (median values of posterior distributions), the standard deviation of the posterior distribution (SDs) and 95% credible intervals (CrI) intervals will be presented for each treatment group and treatment comparison (absolute and percentage change) at each sampling time point. A number of posterior probability statements will also be expressed, as described in Table 2 of Section 7.2.5.1 (Model Results Presentation) for each timepoint. • Point estimates for each treatment group and treatment comparison (absolute and percentage change) at each timepoint will be expressed graphically. See Appendix 11: List of Data Displays for example displays. • Plots of the posterior distributions for each timepoint (back-transformed) will be presented for each treatment arm. In addition, the posterior distributions for the absolute difference and percentage change at each timepoint for GSK2798745 relative to placebo will be presented. • Where appropriate, LLQs and ULQs should be displayed in figures through the use of dashed horizontal lines. • **PD_T2**: The adjusted percentage change in analyte should be expressed as a reduction or increase (GSK2798745 c.f. placebo) depending on the analyte and the desired direction of treatment effect e.g. % reduction/increase GSK2798745 relative to placebo. • **PD_F5**: The adjusted percentage change in analyte should be expressed as a reduction or increase (GSK2798745 c.f. placebo) depending on the specific analyte and the desired direction of treatment effect e.g. % reduction/increase GSK2798745 relative to placebo.

7.3.5.2. BAL exploratory biomarkers

The strategy for analysing and reporting BAL exploratory biomarkers will follow the same structure as the primary analysis (see Section 7.1). Details of outputs can be found in Appendix 11: List of Data Displays.

7.3.5.3. Multivariate Analysis of BAL Total Protein and Total Neutrophils

This analysis may be conducted to better understand the correlation between the endpoints and will be supported by tables and figures.

Endpoint / Variables

- Absolute BAL total protein and total neutrophil counts
- It is anticipated that biomarkers will require log-transformation in all analyses to improve model fitting. Following model fitting, back-transformation will occur and treatment comparisons at each of the sampling timepoints will be expressed as a percentage change for GSK2798745 relative to placebo.

Model Specification

- Each blood biomarker will be analysed using a repeated measures mixed model (MMRM) fitted in a Bayesian framework with all covariates having non-informative priors using PROC MCMC in SAS.
- **analyte** in the text below should be replaced by the specific blood biomarker in the analysis.
- The terms to be fitted in the model:

Type	Name
Dependent variable	• BAL PD Response
Fixed continuous independent variable	• Baseline*PD marker
Fixed categorical independent variables	• Treatment*PD marker

Information on the effects and prior distributions for parameters:

Type	Name (#Levels)	Parameters	Priors
Fixed Continuous	Baseline (2h) * PD marker (2)	#1 Baseline (2h) * Ind[Total Protein = 1]	N(Mean=0, Var=1E6)
		#2 Baseline (2h) * Ind[Neutrophil = 1]	N(Mean=0, Var=1E6)
Fixed Categorical	Treatment * PD marker (4)	#1 Placebo * Ind[Total Protein = 1]	N(Mean=0, Var=1E6)
		#2 Placebo * Ind[Neutrophil = 1]	N(Mean=0, Var=1E6)
		#3 GSK2798745 * Ind[Total Protein = 1]	N(Mean=0, Var=1E6)
		#4 GSK2798745 * Ind[Neutrophil = 1]	N(Mean=0, Var=1E6)
Random	Subjects	Separate value per subject, sampled as i.i.d. ~ N(0,$\sigma^2_{Subject}$)	$\sigma^2_{Subject}$~Gamma(0.001,0.001)

- The default prior for the VCV matrix would be an Inverse-Wishart with parameters k and **S** (where **S** = (k – p - 1) * **R** and p = dimension of the VCV matrix). Under this framework, **R** can be thought of as a best guess for the VCV of the endpoints/timepoints being modelled. Care should be taken in the choice of k and **R** for each endpoint to ensure it is uninformative.
- Separate variance-covariance matrices will be used for treatment groups if there is sufficient

information/data to allow for this (i.e. convergence occurs for all parameters and values do not get "stuck" at zero) to obtain separate estimates for the correlation between the endpoints. If there is not sufficient information then the default position is for treatment groups to share a common variance-covariance matrix.

- An optional exploration/model building step may take place by adding other covariates to the model that may explain a significant proportion of variance in the response and/or imbalance between treatment groups at baseline and/or be justified by biological rationale/expert judgment or statistical tools (raw plots and model selection criteria). Only the results of the final model would be reported in the Clinical Study Report (CSR).
- For the final model, appropriate combinations of model parameters should be combined to obtain treatment effects of interest, including performing any back-transformations that are required. For example, assuming $\log_e$ transformation is required, the percentage change for GSK2798745 relative to placebo in 26h total protein will be obtained by computing $exp(\beta_{GSK2798745,Total\ Protein} - \beta_{Placebo,Total\ Protein})$ for each MCMC iteration, which should be programmed between the BEGINNODATA and ENDNODATA statements (within PROC MCMC procedure).
- To obtain probability statements for parameters/effects of interest use binary flag variables. For each MCMC iteration if the condition is satisfied the iteration is flagged as a 1, if not it is flagged as 0. The proportion of iterations flagged as 1 gives the posterior probability of the statement of interest i.e. the proportion of MCMC iterations for which the percentage reduction in the BAL biomarker for GSK2798745 c.f. placebo for the specified sampling timepoint is greater than zero.
- For example, the SAS syntax for computing the flag for any percentage reduction in BAL total protein as well as neutrophils would be: *flagsuccess_TPROTNEU = (ratio_TPRO < 1 and ratio_TNEU < 1);* . Where *ratio_TPRO* is the parameter used to store the ratio of adjusted posterior medians for GSK2798745 relative to placebo for total protein, calculated as $exp(\beta_{GSK2798745,Total\ Protein} - \beta_{Placebo,Total\ Protein})$ and *flagsuccess_TPROTNEU* being the binary variable where any percentage reduction in both total protein and total neutrophil , active relative to placebo, flags success. This will be computed for a number of different effects of interest: 10%, 25% percentage reduction, etc

Model Checking & Diagnostics

- See Section 7.1.5.1 (Model Checking and Diagnostics)

Model Results Presentation

- Point estimates (median values of posterior distributions), the standard deviation of the posterior distribution (SDs) and 95% credible intervals (CrI) intervals will be presented for each treatment group and treatment comparison (absolute and percentage change) at each sampling time point. A number of posterior probability statements will also be expressed, as described in Table 2 of Section 7.2.5.1 (Model Results Presentation) for each timepoint.
- Point estimates for each treatment group and treatment comparison (absolute and percentage change) for each endpoint will be expressed graphically. See Appendix 11: List of Data Displays for example displays.
- The joint posterior probability statements of interests in Table 2 were correct at the time of writing but may not be limited to these listed.

Table 4 Posterior Probability Statements of Interest

Posterior Probability Statement (where X_{TP} = treatment ratio of GSK2798745 / Pbo for 26h total protein)	Interpretation
PP ($X_{TP} \leq 0.25$ and $X_{NE} \leq 0.25$)	Posterior probability of at least a 75% reduction in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} \leq 0.5$ and $X_{NE} \leq 0.5$)	Posterior probability of at least a 50% reduction in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} \leq 0.75$ and $X_{NE} \leq 0.75$)	Posterior probability of at least a 25% reduction in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} \leq 0.9$ and $X_{NE} \leq 0.9$)	Posterior probability of at least a 10% reduction in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} \leq 1$ and $X_{NE} \leq 1$)	Posterior probability of any reduction in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} > 1$ and $X_{NE} > 1$)	Posterior probability of any increase in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} > 1.1$ and $X_{NE} > 1.1$)	Posterior probability of at least a 10% increase in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} > 1.25$ and $X_{NE} > 1.25$)	Posterior probability of at least a 25% increase in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} > 1.5$ and $X_{NE} > 1.5$)	Posterior probability of at least a 50% increase in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo
PP ($X_{TP} > 1.75$ and $X_{NE} > 1.75$)	Posterior probability of at least a 75% increase in both mean BAL total protein and total neutrophil counts for GSK2798745 relative to placebo

- **PD_F2**: The correlation between endpoints for each treatment arm will be extracted from the statistical analysis and displayed on a panel scatter plot showing 26h total protein against 26h total neutrophils, with separate panels for treatment arm (as it is anticipated the relationship between endpoints will be different between treatment arms).

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

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

8.2. Clinical Laboratory Analyses

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

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified.

The CSSRS questionnaire will be summarised using a listing and summary table. FOBT results will summarised using a listing and summary table.

The details of the planned displays are presented in Appendix 11: List of Data Displays

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Standards for Pharmacokinetic)

9.1.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
Cmax	Plasma GSK2798745 for Day 1
Tmax	Plasma GSK2798745 for Day 1
AUC(0-26)	Plasma GSK2798745 for Day 1 & Day 2

NOTES:

- Additional parameters may be included as required.

9.1.2. Population of Interest

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

9.1.3. Statistical Analyses / Methods

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

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

9.2. Secondary Pharmacokinetic Analyses

9.2.1. Endpoint / Variables

9.2.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 12.5.3 Reporting Standards for Pharmacokinetic)

9.2.1.2. Derived Pharmacokinetic Parameters

Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using the currently supported version of WinNonlin. All calculations of non-compartmental parameters will be based on actual sampling times. Pharmacokinetic parameters listed will be determined from the plasma concentration-time data, as data permits.

Parameter	Parameter Description
Cmax	Plasma metabolite GSK3526876 Day 1
Tmax	Plasma metabolite GSK3526876 Day 1
AUC(0-26)	Plasma metabolite GSK3526876 Day 1 & 2
BAL 2h	BAL metabolite GSK3526876 Day 1
BAL 26h	BAL metabolite GSK3526876 Day 1
BAL 2h	BAL GSK2798745 concentration at 2h
BAL 26h	BAL GSK2798745 concentration at 26h

NOTES:

- Additional parameters may be included as required.

9.2.2. Population of Interest

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

10. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of this analysis is to characterize the pharmacokinetic / pharmacodynamic relationship of GSK2798745 administered orally in the participants.

10.1. Statistical Analyses / Methods

A summary of the planned pharmacokinetic / pharmacodynamic analyses are outlined below:

- Individual plasma GSK2798745 Cmax, will be plotted against corresponding BAL 2h GSK2798745 drug levels. Analysis may be undertaken to assess relationship of drug levels in plasma and target site (BAL).
- Individual plasma GSK2798745 AUC(0-26) and C26 data will be plotted against BAL 26h GSK2798745 drug levels. Regression analysis will be undertaken to assess relationship of drug levels in plasma and target site (BAL)
- Individual plasma GSK2798745 AUC(0-26), C26 and C_{max} data will be plotted against total BAL protein at 26h (primary clinical endpoint). Placebo treatment data (i.e. 0 drug concentration and corresponding total BAL protein will also be included in the PK-PD analysis. Analysis may be undertaken to evaluate the association between GSK2798745 PK parameters and change in BAL total protein.

Data specifications for PK/PD analyses presented in Appendix 11: Pharmacokinetic / Pharmacodynamic Analyses.

11. REFERENCES

Costa M, Fortunato L, Abellan J, Chen G, He Z, Archer G. Bayesian Statistics Best Practice at GSK – Clinical Trials using Bayesian Inference. GlaxoSmithKline; 2017.

Holz O, Tan L, Schaumann L, Müller M, Scholl D, Hidi R,et al. Inter- and intrasubject variability of the inflammatory response to segmental endotoxin challenge in healthy volunteers. *Pulmonary Pharmacology & Therapeutics.* 2015;35:50-9.

12. APPENDICES

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

12.1.1. Exclusions from Evaluable Population

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

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

- The timing and number of planned study assessments, including safety, pharmacokinetic, pharmacodynamics and exploratory biomarker assessments may be altered during the course of the study based on newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

12.2.2. Screening

	Screening (Days –28 to –2)
Outpatient visit	X
Informed consent	X
Inclusion and exclusion criteria	X
Demography	X
Full physical examination	X
Height and weight	X
Medical history	X
Past and current medical conditions	X
HIV, Hepatitis B and C screening	X
FSH and oestradiol[1]	X
Drug, alcohol and cotinine screen	X
C-SSRS	X
Laboratory assessments[2]	X
12-lead ECG[3]	X
Vital signs[4]	X
Spirometry[5]	X
FOBT[6]	X

C-SSRS: Columbia Suicide Severity Rating Scale; ECG: electrocardiogram; FOBT: Faecal Occult Blood Test; HIV: human immunodeficiency virus.

1. Postmenopausal females whose postmenopausal status is in doubt only.
2. Haematology, clinical chemistry (including liver chemistry), cardiac troponins, urinalysis and coagulation profile.
3. In triplicate.
4. Blood pressure and heart rate in triplicate. Single temperature measurement.
5. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Triplicate measurement, the highest of which should be recorded in the case report form.
6. May be measured during the screening window or on Day –1. FOBT cards will be provided at screening and must be returned to the laboratory and analysed before dosing.

12.2.3. Treatment period

	Day –1[2]	Day 1[1]									Day 2[1]			Day 4
		Pre-dose	0 h	1 h	2 h	3 h	6 h	8 h	12 h	14 h	25.5 h	26 h	30 h	
Inpatient stay[2]		←==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========→	
Telephone call[3]														X
Drug, alcohol and cotinine screen	X													
Laboratory assessments[4]	X												X	
12-lead ECG[5]	X	X											X	
Blood pressure and heart rate[5]	X	X		X			X		X	X			X	
Temperature[6]	X	X		X	X		X	X	X	X			X	
Spirometry[7]	X	X					X				X		X	
C-SSRS													X	
Randomisation		X												
Study treatment			X						X					
Pulse oximetry[8]					X							X		
Bronchoscopy, baseline BAL and challenge[9]					X									
Bronchoscopy and post-challenge BAL[10]												X		
Blood sample for exploratory biomarkers[11]					X[11]	X		X				X[11]		
Blood sample for PK		See footnote 12												
AE review		←==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========→	
SAE review	←==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========→	
Concomitant medication review	←==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========	==========→	

AE: adverse event; BAL: bronchoalveolar lavage; ECG: electrocardiogram; PK: pharmacokinetic; SAE: serious adverse event, C-SSRS: Columbia Suicide Severity Rating Scale.

1. Time points relative to the first dose on Day 1.
2. Admission on Day –1, at a time to allow all Day –1 procedures to be done; discharge on Day 2, at least 4 h after the bronchoscopy.
3. To check for any AEs.
4. Haematology, clinical chemistry (including liver chemistry), cardiac troponins, urinalysis and coagulation profile.
5. Triplicate on Day-1 and pre-dose. Single measurements at time points after dosing.
6. Immediately before BAL sampling/LPS challenge at the 2-h time point.
7. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Triplicate measurements at each time point, the highest of which should be recorded in the case report form.
8. Pulse oximetry to be measured during bronchoscopy procedures. Only AEs to be recorded.
9. BAL samples for total protein, neutrophil counts, GSK2798745 and exploratory biomarkers. Baseline BAL sample from a segment in the left lower lobe, followed by segmental challenge of the lungs: LPS in right middle segment; saline control in the lingula segment of the contralateral side. Challenges to be done as close as possible to 2 h post-dose.
10. BAL samples for total protein, neutrophil counts, GSK2798745 and exploratory biomarkers. Baseline and post-dose measurements to be done by the same person, where possible.
11. Blood samples for exploratory biomarkers. The 2- and 26-h blood samples should be taken immediately before BAL sampling.
12. PK samples will be taken pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 6, 8, 12, 12.5, 13, 13.5, 14, 15, 24 and 26 h after the first dose. The 2- and 26-h blood sample should be taken immediately before BAL sampling

12.2.4. Follow-up/Early Withdrawal

	Follow-up/Early Withdrawal (Day 8 [± 1 day])
Outpatient visit	X
Full physical examination	X
Weight	X
Laboratory assessments[1]	X
12-lead ECG[2]	X
Vital signs[3]	X
Spirometry[4]	X
FOBT[5]	X
AE review	X
SAE review	X
Concomitant medication review	X

AE: adverse event; ECG: electrocardiogram; FOBT: Faecal Occult Blood Test; SAE: serious adverse event.

1. Haematology, clinical chemistry (including liver chemistry), cardiac troponins and urinalysis.
2. Single measurement.
3. Blood pressure, heart rate, temperature. Single measurement.
4. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Triplicate measurement, the highest of which should be recorded in the case report form.
5. FOBT cards will be provided upon discharge from the unit and should be returned by the follow-up/early withdrawal visit.

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

Refer to the Study Reference Manual (SRM) for acceptable time deviation windows for study assessments and procedures.

26h PK blood samples that are taken outside of 25.5h-26.5h will be excluded from plasma concentration by time point summary tables as well as displays that include planned timepoint. The 26h blood PK sample has a wider acceptable time deviation window than other blood PK samples due to the requirement for the sample to be aligned with the 26h BAL sample. This may impact on PK summaries.

12.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

12.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the two study treatment doses and LPS/saline challenges.

Study Phase	Definition
Pre-Treatment	Date/Time ≤ Study Treatment Start Date/Time
Post-Treatment	Study Treatment Start Date/Time < Date/Time

NOTES:

- Study Treatment Start relates to the 1st dose received by the individual.

12.4.1.1. Study Phases for Concomitant Medication

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

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

12.4.2. Treatment and LPS Emergent Flag for Adverse Events

The flag assigned to a participant's AE will depend upon the type of AE, the magnitude of the AE and the study phase the AE occurred in. Each adverse event will be considered on a case-by-case basis.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software and R will be used.	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Compound	: \ARPROD\GSK2798745\207464\Internal_01 : \ARPROD\GSK2798745\207464\Internal_02 : \ARPROD\GSK2798745\207464\Headline : \ARPROD\ GSK2798745\207464\Final
Analysis Datasets	
• Analysis datasets will be created according to legacy GSK A&R dataset standards.	
Intermediate Datasets	

- The following instructions are recommended to make modelling and tracking of statistical analyses results easier.
- The Bayesian framework necessitates the storage of intermediate outputs datasets (convention dictates that they be stored in the dddata folder of the reporting effort). **It is strongly recommended that a file naming convention be adopted across all MCMC analyses to allow easy grouping/location of associated items.** The naming convention has to follow the SAS dataset length rules, and any HARP naming conventions.
- The file name is made up of components joined by underscores. This should allow items to automatically group/sort when viewed as a list.
- The components of the file name may change and is included for guidance.

Component ID	Description	Examples	Clarification
1	Three letters for the sample matrix	BAL BLD	Bronchoalveolar Lavage Blood
2	Item/Analyte	TPRO TNEU DNEU TALB <Bicat code>	Total Protein Total Neutrophil Count Differential Neutrophil Count Total Albumin Count <Taken from SI dataset >
3	Single digit Population code	1 2 etc	All Subjects Evaluable (Statistician will need to track assignments)

Component ID	Description	Examples	Clarification
4	Single digit Model ID (may vary depending on the analysis, so model 1 can have different meanings across objectives/sample matrices/endpoints)	1 2 etc	Primary Analysis Sensitivity Analysis 1 (Statistician will need to track assignments on a per objectives/sample matrices/endpoint basis)
5	Double digit Analysis ID (specific to the model)	01 02 03 04 etc	Statistician will need to track on a per item basis
6	MCMC related item	poall pokdein + Others as required	Posterior Summary Stats (processed and ready for display) Posterior samples

- Example for the output dataset produced from PROC MCMC with summary statistics used for T/L/F for the Primary analysis of 26h BAL Total Protein using the Evaluable population using the simplest model (only intercept, baseline and treatment group as covariates): "BAL_TPRO_3_1_01_poall"

Generation of RTF Files

- RTF files will be generated for the final reporting effort.

12.5.2. Reporting Standards

General

- The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  - 4.03 to 4.23: General Principles
  - 5.01 to 5.08: Principles Related to Data Listings
  - 6.01 to 6.11: Principles Related to Summary Tables
  - 7.01 to 7.13: Principles Related to Graphics
- Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings

Formats

- GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated.
- Numeric data will be reported at the precision collected on the eCRF.
- The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Planned time relative to dosing will be used in figures, summaries, statistical analyses and

calculation of any derived parameters, unless otherwise stated.
    - The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- Reporting for Data Listings:
    - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
    - Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits

- Unscheduled visits will not be included in summary tables and/or figures.
- All unscheduled visits will be included in listings.

Descriptive Summary Statistics

Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays

- Refer to IDSL Statistical Principles 7.01 to 7.13.
- Where appropriate, specific SAS attribute maps and formats should be applied to treatments groups or subjects to allow standardisation of graphics. Specific subject level attributes allow tracking and distinguishing subjects across displays and aids interpretation.
- Please consult with GSK statistician to obtain final attributes map.
- Treatment attributes:

Treatment	Colour	Plotting Symbol	Line Style
Placebo	Blue	Circle, Solid	Solid
GSK2798745	Red	Triangle (up), Solid	Solid

- Example of subject attributes:

Subject	Colour	Plotting Symbol	Line Style
PPD	Cyan	Diamond (filled)	Solid
	Salmon	Asterisk	Dashed

12.5.3. Reporting Standards for Pharmacokinetic

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Not applicable.
Pharmacokinetic Parameter Derivation	
PK parameters to be provided to programmer	The following PK parameters will be derived by CPMS and provided to the programmer: [PK parameters, as defined in Section 9.1.1.2 and Section 9.2.1.2)]

Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters, December 2009.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 12.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

12.6.2. Study Population

Treatment Compliance
• Treatment compliance is defined as a participant receiving both doses of study treatment (0 h and 12 h).
Challenge Compliance
• Challenge compliance is defined as undergoing segmental challenge to the lungs, via bronchoscopy, at 2 hours after the first dose of investigational medicinal product (IMP): 10 mL LPS (4 ng/kg) instilled into the right middle segment and 10 mL saline control instilled into the lingula segment of the contralateral side.

12.6.3. Pharmacodynamic and Biomarker

Derivation of BAL White Blood Cell Counts and Differentials
• Differential cell count gives the relative percentage of each type of white blood cell and is calculated as follows. $$Differential\ cell\ type\ count\ (\%) = \frac{Total\ cell\ type\ count\ (cells/mL)}{Total\ white\ blood\ cell\ (leukocyte)\ count\ (cells/mL)}$$ • Equivalently, to calculate absolute cell type count:

Derivation of BAL White Blood Cell Counts and Differentials

$$Total\ cell\ type\ count\ (cells/mL) = Differential\ cell\ type\ count\ (\%) \times total\ WBC\ count\ (cells/mL)$$

- It is anticipated that pharmacodynamic endpoints and biomarkers will require log-transformation in all analyses to improve model fitting. Following model fitting, back-transformation will occur and treatment effects (GSK2798745 relative to placebo) will be expressed as percentage changes.

- Percentage change, active relative to placebo, will be calculated as:
  Percentage change = $\left(\frac{Active\ adjusted\ posterior\ median}{Placebo\ adjusted\ posterior\ median} - 1\right) \times 100$
- Ratio, active relative to placebo, will be calculated as:
  Ratio = $\frac{Active\ adjusted\ median}{Placebo\ adjusted\ median}$

- Urea concentration data in plasma and BAL will be used to calculate the dilution effect of the lavage which is used to extract the sample from the lung compartment. A correction for dilution will be applied to all BAL analytes to derive corrected concentrations i.e. each BAL analyte will be adjusted to account for the magnitude of dilution during the BAL procedure using urea plasma concentration as a reference point. A dilution factor for each BAL sample will be calculated as BAL urea concentration / plasma urea concentration. Each BAL analyte will be multiplied by this dilution factor to "correct". Outputs for BAL analytes adjusted for dilution factor may be produced as an exploratory analysis (See Appendix 11: List of Data Displays). Corrected BAL concentrations for dilution factor will be derived as follows:

  $$Corrected\ concentration\ (pg/ml) = BAL\ concentration\ (pg/ml) \times Dilution\ factor$$

  Where,

  $$Dilution\ factor = \frac{Urea\ plasma\ concentration}{Urea\ BAL\ concentration}\ at\ time\ (t)$$

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Participant study completion (i.e. as specified in the protocol) was defined as completing all phases of the study including the follow-up visit. • Withdrawn participants may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

12.7.2. 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 participant 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
BAL Pharmacodynamic endpoints	• No missing data will be imputed.
Blood Pharmacodynamic endpoints	• Responses unquantifiable due to being below LLQ will be imputed as ½ LLQ. • Responses above ULQ will be imputed as ULQ.

12.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.

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

12.7.2.2. Handling of Missing Data for Statistical Analysis

For BAL endpoints, any participant that has missing data for baseline (2h) or 26h (LPS lobe) does not meet the criteria to be included in the evaluable population and therefore will be excluded from the analysis. No imputation will be performed.

For analyses of repeated measures data (blood biomarkers), responses that are unquantifiable due to being below LLQ will be imputed as ½ LLQ and above ULQ will be imputed as ULQ, whilst for any other missing data SAS PROC MCMC automatically assumes/implements a missing at random/multiple imputation approach if any of the supplied response variables are missing. Given this is a proof of mechanism study, this is deemed sufficient.

12.8. Appendix 8: Values of Potential Clinical Importance

12.8.1. Laboratory Values

Hematology			
Analyte	**Effect**	**Relative – Low (Multipliers of LLN)**	**Relative – High (Multipliers of ULN)**
White Blood Cell Count (x10^9/ L)		0.67	1.82
Neutrophil Count (x10^9/ L)		0.83	
Hemoglobin (g/L)	Male		1.03
	Female		1.13
Hematocrit (ratio of 1)	Male		1.02
	Female		1.17
Platelet Count (x10^9/ L)		0.67	1.57
Lymphocytes (x10^9/ L)		0.81	
Monocytes (x10^9/ L)		0.5	1.8
Red Blood Cell Count (x10^9/ L)		0.7	1.7
Reticulocytes (%)		0	1.5

Chemistry			
Analyte	**Effect**	**Relative – Low (Multipliers of LLN)**	**Relative – High (Multipliers of ULN)**
Calcium (mmol/L)		0.91	1.06
Glucose (mmol/L)		0.71	1.41
Potassium (mmol/L)		0.86	1.10
Sodium (mmol/L)		0.96	1.03
Blood Urea Nitrogen (mmol/L)		0.7	1.5
Total Protein (mg/dL)		0.6	1.7
Creatinine phosphokinase (IU/L)		0	1.8
Direct Bilirubin (umol/L)		0	1.6
Analyte	**Effect**	**Relative – Low (Absolute Value)**	**Relative – High (Absolute Value)**
Creatinine (umol/L)	Chg from Baseline		> 44 umol/L

Urinalysis:
During the study, a dipstick result (positive or negative) will be recorded for each participant at each timepoint. If the dipstick result is positive, a microscopy will be performed. The urinalysis dipstick result at day 8 and day 2 will be compared with day -

1 (pre-dose) and data of PCI will be flagged where a result changes from negative to positive and/or a microscopy is performed.

Faecal Occult Blood Test:
FOBT is performed at screening and follow-up with measurement as haemoglobin (iFOBT) ng/ml. Any positive haemoglobin measurement (≥50ng/ml) will be flagged as potentially clinically important and all results for a participant with at least one flagged result will appear in listings.

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

Other				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Cardiac Troponin (cTn)	ng/ml			>ULN or 2x Baseline Value
Coagulation Profile				
International Normalisation Ratio (INR)			< 0.85	> 1.15
Prothrombin Time (PTT)	%		< 70	> 120
Fibrogen	g/l		< 1.7	> 4.2

12.8.2. ECG

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

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Increase from Baseline QTc	msec		>60

12.8.3. Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	> 90
Heart Rate	bpm	<50	>110

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

12.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

12.9.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

Specification for PK-PD dataset [Proposed dataset name PKPD]

Variable short name	Assessment description	Format	Unit	Valid Values / Format
C	Data Identifier	Integer	-	0
ID	Unique subject number	Numeric		Different ID for different subject
STUD	Protocol Number	Integer	-	207464
SUBJ	Subject identifier in study	Integer	-	Maximum 10 characters (numeric or text). Different identifier for each subject
CENT	Study centre identifier	Integer	-	
DAY	Day of sampling	Integer	See footnotes	See footnotes
C2	Conc of GSK2798745 2 h post first dose	Decimal 3 d.p	ng/mL	Numeric – For placebo TRT arm C2 = 0
C26	Conc of GSK2798745 26 h post first dose	Decimal 3 d.p	ng/mL	Numeric - For placebo TRT arm C26 = 0
AUC26	Area under curve (0-26h)	Decimal 3 d.p	ng.h/mL	Numeric - For placebo TRT arm AUC26 = 0
Analyte	Drug analysed	Integer	-	GSK2798745
Base_PD	Baseline corrected BAL total protein (i.e. before LPS challenge and 2h post dose	Decimal 3 d.p	-	BAL total protein
745_PD	Corrected BAL total protein at 26h post dosing with GSK2798745 (i.e. 24h post LPS challenge)	Decimal 3 d.p		BAL total protein
AGE	Age	Decimal	Yrs	Integer. Age in years at time of screening rounded down to give age at last birthday.
WT	Weight	Decimal	Kg	Weight in kilograms at time of screening.
BMI	Body mass index	Decimal	kg/m^2	Body mass index calculated as weight divided by height squared
SEX	Subject gender	Integer	-	Integer. One of the following - 1 = Male

Variable short name	Assessment description	Format	Unit	Valid Values / Format
				2 = Female
SEXTEXT	Gender Identifier	Character		M = Male, F=Female
TMT	Treatment identifier	Integer	-	Placebo = 0 GSK2798745 =1

Data to be provided to CPMS as csv file shown below

C	ID	STUD	SUBJ	CENT	DAY	C2	C26	AUC26	ANALYTE	Base_PD	745_PD	AGE	WT	BMI	SEX	SEXTEXT	TMT
.	PPD	207464	PPD	1	1	0	0	0.00	745	25	23	50	70	24	1	M	0
.		207464		1	1	15	6	20.00	745	20	18	50	70	24	1	M	1
.		207464		1	1	20	10	30.00	745	25	10	50	70	24	1	M	1
.		207464		2	1	0	0	0.00	745	26	30	50	70	24	1	M	0
.		207464		2	1	22	12	35.00	745	30	15	60	75	24	2	F	1

C2: Conc of GSK2798745 2 h post dose
C26: Conc of GSK2798745 26 h post dose
AUC26: AUC(0-26h) GSK2798745
Base_PD: Baseline corrected total BAL protein (i.e. before LPS challenge and 2h post dose
745_PD: Corrected total BAL protein at 26h post dosing with GSK2798745 (i.e. 24h post LPS challenge)

12.10. Appendix 10: Abbreviations & Trade Marks

12.10.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
ALT/SGPT	Alanine Amino Transferase / Serum Glutamic-Pyruvic Transaminase
AST/SGOT	Aspartate Amino Transferase / Serum Glutamic Oxaloacetic Transaminase
A&R	Analysis and Reporting
BAL	Bronchoalveolar Lavage
BUN	Blood Urea Nitrogen
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CrI	Credible Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CRP	C-reactive Protein
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DIC	Deviance Information Criterion
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
HPD	Highest Posterior Density
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IL	Interleukin
IMMS	International Modules Management System
INR	International Normalisation Ratio
IP	Investigational Product
ITT	Intent-To-Treat
LLQ	Lower Limit of Quantification
LPS	Lipopolysaccharide
MCMC	Monte Carlo Markov Chain
MMRM	Mixed Model Repeated Measures

Abbreviation	Description
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PP	Posterior Probability
PopPK	Population PK
PTT	Prothrombin Time
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
SP-B	Surfactant Protein B
TA	Therapeutic Area
TFL	Tables, Figures & Listings
TNF-alpha	Tumour Necrosis Factor alpha
ULQ	Upper Limit of Quantification
vWF	Von Willebrand Factor

12.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
HARP
RANDALL NG

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

12.11. Appendix 11: List of Data Displays

12.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.13	
Pharmacodynamic and Biomarker	2.1 to 2.17	2.1 to 2.29
Safety	3.1 to 3.18	
Pharmacokinetic	4.1 to 4.8	4.1 to 4.10
Pharmacokinetic / Pharmacodynamic		7.1 to 7.2
Section	**Listings**	
ICH Listings	1 to 32	
Other Listings	33 to 55	

12.11.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 12: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Pharmacodynamic and Biomarker	PD_Fn	PD_Tn	PD_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes'.

12.11.3. Deliverables

Delivery [Priority] [1]	Description
IA1 [X]	Interim Analysis 1
IA2 [X]	Interim Analysis 2
HR [X]	Headline Results During Study (i.e. in-stream data review)
SAC [X]	Statistical Analysis Complete

NOTES:

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

12.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC [1]
1.2.	All Subjects	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC [1]
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC [1]
Protocol Deviation					
1.4.	All Subjects	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [1]
Population Analysed					
1.5.	All Subjects	SP1	Summary of Study Populations	IDSL	SAC [1]
1.6.	All Subjects	SP2	Summary of Exclusions from the Evaluable Population	IDSL	SAC [1]
Demographic and Baseline Characteristics					
1.7.	All Subjects	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC [1]
1.8.	All Subjects	DM11	Summary of Age Ranges	EudraCT	SAC [1]
1.9.	All Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC [1]
Prior and Concomitant Medications					
1.10.	All Subjects	MH1	Summary of Past Medical Conditions	ICH E3	SAC [1]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.11.	All Subjects	MH1	Summary of Current Medical Conditions	ICH E3	SAC [1]
1.12.	All Subjects	CM1	Summary of Concomitant Medications	ICH E3	SAC [1]
Exposure and Treatment Compliance					
1.13.	All Subjects	EX1	Summary of Exposure to Study Treatment	ICH E3 Exclude “Days on study drug” and “Daily Dose” from IDSL template.	SAC [1]

12.11.5. Pharmacodynamic and Biomarker Tables

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL Total Protein					
2.1.	Evaluable	PD_T1	Summary of **BAL Total Protein** by Timepoint (Baseline (2 h) and 26 h), Lung Lobe (LPS and Saline Challenge) and Treatment Group	Separate pages for arithmetic and geometric summary statistics.	IA1 [1], IA2 [1], HR [1], SAC [1]
2.2.	Evaluable	PD_T2	**26 h BAL Total Protein**: Summary of Posterior Distributions and Posterior Probability Statements from the Primary Analysis	Up to 4 pages. Page 1: Raw baseline values and baseline covariates values predictions are made at. Also add values used to determine predictions for any other covariates included in the model. Page 2: Adjusted posterior medians for each treatment group i.e. model adjusted predictions. 75% and 95% CrI. Page 3: Treatment comparisons in the form of adjusted posterior median absolute differences or percentage changes (dependent on endpoint and transformation). 75% and 95% CrI. Page 4: Posterior probability statements of interest.	IA [1], IA2 [1], HR [1], SAC [1]
2.3.	Evaluable	PD_T2	**Sensitivity Analysis: 26 h BAL Total Protein including 26 h Saline Lobe BAL Total Protein as a Covariate**: Summary of Posterior Distributions and Posterior Probability Statements from the Primary Analysis	**Conditional output.** See programming notes above.	SAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	Evaluable	PD_T2	**Sensitivity Analysis: 26h BAL Total Protein Excluding Participants with High Saline Lobe BAL Total Protein Level**: Summary of Posterior Distributions and Posterior Probability Statements from the Primary Analysis	**Conditional output.** See programming notes above.	SAC [1]
2.5.	Evaluable	PD_T2	**26 h BAL Total Protein and Total Neutrophil Count**: Summary of Posterior Distributions and Posterior Probability Statements from the Multivariate Analysis	**Conditional output**. See programming notes above.	SAC [1]
BAL Total Neutrophil Count					
2.6.	Evaluable	PD_T1	Summary of **BAL Total Neutrophil Count** by Timepoint (Baseline (2 h) and 26 h), Lung Lobe (LPS and Saline Challenge) and Treatment Group	Separate pages for arithmetic and geometric summary statistics.	HR [1], SAC [1]
2.7.	Evaluable	PD_T2	**26 h BAL Total Neutrophil Count**: Summary of Posterior Distributions and Posterior Probability Statements from the Analysis	Up to 4 pages. Page 1: Raw baseline values and baseline covariates values predictions are made at. Also add values used to determine predictions for any other covariates included in the model. Page 2: Adjusted posterior medians for each treatment group i.e. model adjusted predictions. 75% and 95% CrI. Page 3: Treatment comparisons in the form of adjusted posterior median absolute differences or percentage changes (dependent on endpoint and transformation). 75% and 95% CrI. Page 4: Posterior probability statements of interest.	HR [1], SAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL Differential Neutrophil Count					
2.8.	Evaluable	PD_T1	Summary of **BAL Differential Neutrophil Count** by Timepoint (Baseline (2 h) and 26 h), Lung Lobe (LPS and Saline Challenge) and Treatment Group	Separate pages for arithmetic and geometric summary statistics.	HR [1], SAC [1]
2.9.	Evaluable	PD_T2	**26h BAL Differential Neutrophil Count**: Summary of Posterior Distributions and Posterior Probability Statements from the Analysis	Up to 4 pages. Page 1: Raw baseline values and baseline covariates values predictions are made at. Also add values used to determine predictions for any other covariates included in the model. Page 2: Adjusted posterior medians for each treatment group i.e. model adjusted predictions. 75% and 95% CrI. Page 3: Treatment comparisons in the form of adjusted posterior median absolute differences or percentage changes (dependent on endpoint and transformation). 75% and 95% CrI. Page 4: Posterior probability statements of interest.	HR [1], SAC [1]
Exploratory BAL Biomarkers					
2.10.	Evaluable	PD_T1	Summary of **Exploratory BAL Biomarkers (excluding WBCs)** by Timepoint (Baseline (2h) and 26h), Lung Lobe (LPS and Saline Challenge) and Treatment Group	One page per analyte. Separate pages for arithmetic and geometric summary statistics.	SAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	Evaluable	PD_T2	**26h Exploratory BAL Biomarkers (excluding WBCs):** Summary of Posterior Distributions and Posterior Probability Statements from the Analyses	Up to 4 pages per analyte. Page 1: Raw baseline values and baseline covariates values predictions are made at. Also add values used to determine predictions for any other covariates included in the model. Page 2: Adjusted posterior medians for each treatment group i.e. model adjusted predictions. 75% and 95% CrI. Page 3: Treatment comparisons in the form of adjusted posterior median absolute differences or percentage changes (dependent on endpoint and transformation). 75% and 95% CrI. Page 4: Posterior probability statements of interest.	SAC [1]
2.12.	Evaluable	PD_T1	Summary of **BAL White Blood Cell Types (Totals and Differentials, except neutrophils):** by Timepoint (Baseline (2h) and 26h), Lung Lobe (LPS and Saline Challenge) and Treatment Group	One page per analyte. Separate pages for arithmetic and geometric summary statistics.	SAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	Evaluable	PD_T2	**26h BAL White Blood Cell Types (Totals and Differentials, except Neutrophils):** Summary of Posterior Distributions and Posterior Probability Statements from the Analyses	Up to 4 pages per analyte. Page 1: Raw baseline values and baseline covariates values predictions are made at. Also. add values used to determine predictions for any other covariates included in the model. Page 2: Adjusted posterior medians for each treatment group i.e. model adjusted predictions. 75% and 95% CrI. Page 3: Treatment comparisons in the form of adjusted posterior median absolute differences or percentage changes (dependent on endpoint and transformation). 75% and 95% CrI. Page 4: Posterior probability statements of interest.	SAC [1]
BAL Pharmacodynamic/Biomarker Corrected for Dilution Factor					
2.14.	Evaluable	PD_T1	Summary of **All BAL Biomarkers Corrected for Dilution Factor** by Timepoint (Baseline (2h) and 26h), Lung Lobe (LPS and Saline Challenge) and Treatment Group	**Conditional output**. One page per analyte. Separate pages for arithmetic and geometric summary statistics.	SAC [1]
2.15.	Evaluable	PD_T2	**All BAL Biomarkers Corrected for Dilution Factor:** Summary of Posterior Distributions and Posterior Probability Statements from the Analyses	**Conditional output.** See programming notes above.	SAC [1]
Exploratory Blood Biomarkers					
2.16.	Evaluable	PD_T1	Summary of **Exploratory Blood Biomarkers** by Timepoint and Treatment Group	Separate pages for arithmetic and geometric summary statistics.	SAC [1]

Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.17.	Evaluable	PD_T2	**Exploratory Blood Biomarkers:** Summary of Posterior Distributions and Posterior Probability Statements from the Analyses	Approximately 7 pages per analyte. Add timepoint as first column. Page 1: Raw baseline values and baseline covariates values predictions are made at. Also. add values used to determine predictions for any other covariates included in the model. Page 2: Adjusted posterior medians at each timepoint i.e. model adjusted predictions. 75% and 95% CrI. Page 3: Treatment comparisons in the form of adjusted posterior median absolute differences or percentage changes (dependent on transformation) for each timepoint. 75% and 95% CrI. Page 4-7: Posterior probability statements of interest for '745 c.f. pbo – separate page for each timepoint.	SAC [1]

12.11.6. Pharmacodynamic and Biomarker Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL Total Protein					
2.1	Evaluable	PD_F1	**BAL Total Protein:** Geometric Means and 95% CI by timepoint and challenge (baseline, 26 h LPS Lobe, 26 h Saline Lobe) and treatment group		IA [1], IA2 [1], HR [1], SAC [1]
2.2	Evaluable	PD_F3	**BAL Total Protein:** Participant Profiles of Baseline (2h) to 26h by Challenge and Treatment Group	Use participant attributes map so each subject has specific marker, line colour, pattern to track participant between plots.	IA [1], IA2 [1], HR [1], SAC [1]
2.3	Evaluable	PD_F4	**BAL Total Protein:** Point Estimates and Credible Intervals from the Primary Analysis	**Separate pages for 75% and 95% CrI.** Page to include 3 column panels. 1st: (Back-transformed) treatment group predictions, 2nd: Treatment group differences, 3rd: Percentage reduction ('745 c.f. Pbo).	IA [1], IA2 [1], HR [1], SAC [1]
2.4	Evaluable	PD_F5	**BAL Total Protein:** Posterior Distribution Density Plots from the Primary Analysis	3 pages in total. Page 1: posteriors for separate treatment groups **overlaid**. Page 2: posterior for absolute difference (GSK2798745 c.f. placebo) Page 3: posterior for percentage reduction (GSK2798745 c.f. placebo)	IA [1], IA2 [1], HR [1], SAC [1]
2.5	Evaluable	PD_F2	Scatter plot of BAL 26h Total Protein v 26h Total Neutrophil counts	Overlay correlation coefficient from multivariate analysis (if performed) for each treatment group.	SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL Total Neutrophil Count					
2.6	Evaluable	PD_F1	**BAL Total Neutrophil Count:** Geometric Means and 95% CI by timepoint and challenge (baseline, 26 h LPS Lobe, 26 h Saline Lobe) and treatment group.		HR [1], SAC [1]
2.7	Evaluable	PD_F3	**BAL Total Neutrophil Count:** Participant Profiles of Baseline (2h) to 26h by Challenge and Treatment Group	Use participant attributes map so each subject has specific marker, line colour, pattern to track participant between plots.	HR [1], SAC [1]
2.8	Evaluable	PD_F4	**BAL Total Neutrophil Count:** Point Estimates and 95% Credible Intervals from the Analysis	Page to include 3 column panels. 1st: (Back-transformed) treatment group predictions, 2nd: Treatment group differences, 3rd: Percentage reduction ('745 c.f. Pbo).	HR [1], SAC [1]
2.9	Evaluable	PD_F5	**BAL Total Neutrophil Count:** Posterior Distribution Density Plots from the Analysis	3 pages in total. Page 1: posteriors for separate treatment groups. Page 2: posterior for absolute difference (GSK2798745 c.f. placebo) Page 3: posterior for percentage reduction (GSK2798745 c.f. placebo)	HR [1], SAC [1]
BAL Differential Neutrophil Count					
2.10	Evaluable	PD_F1	**BAL Differential Neutrophil Count**: Geometric Means and 95% CI by timepoint and challenge (baseline, 26h LPS Lobe, 26h Saline Lobe) and treatment group		HR [1], SAC [1]
2.11	Evaluable	PD_F3	**BAL Differential Neutrophil Count**: Participant Profiles of Baseline (2h) to 26h by Challenge and Treatment Group	Use participant attributes map so each subject has specific marker, line colour, pattern to track participant between plots.	HR [1], SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12	Evaluable	PD_F4	**BAL Differential Neutrophil Count**: Point Estimates and 95% Credible Intervals	Page to include 3 column panels. 1st: (Back-transformed) treatment group predictions, 2nd: Treatment group differences, 3rd: Percentage reduction ('745 c.f. Pbo).	HR [1], SAC [1]
2.13	Evaluable	PD_F5	**BAL Differential Neutrophil Count**: Posterior Distribution Density Plots from the Analysis	3 pages in total. Page 1: posteriors for separate treatment groups. Page 2: posterior for absolute difference (GSK2798745 c.f. placebo) Page 3: posterior for percentage reduction (GSK2798745 c.f. placebo)	HR [1], SAC [1]
Exploratory BAL Biomarkers					
2.14	Evaluable	PD_F1	**Exploratory BAL Biomarkers (excluding WBCs):** Geometric Means and 95% CI of by timepoint and challenge (baseline, 26 h LPS Lobe, 26 h Saline Lobe) and treatment group	One page per biomarker.	SAC [1]
2.15	Evaluable	PD_F3	**Exploratory BAL Biomarkers (excluding WBCs):** Participant Profiles of Baseline (2h) to 26h by Challenge and Treatment Group	One page per biomarker. Use participant attributes map so each subject has specific marker, line colour, pattern to track participant between plots.	SAC [1]
2.16	Evaluable	PD_F4	**Exploratory BAL Biomarkers (excluding WBCs):** Point Estimates and 95% Credible Intervals from the Analyses	One page per biomarker. Page to include 3 column panels. 1st: (Back-transformed) treatment group predictions, 2nd: Treatment group differences, 3rd: Percentage reduction ('745 c.f. Pbo).	SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.17	Evaluable	PD_F5	**Exploratory BAL Biomarkers (excluding WBC):** Posterior Distribution Density Plots from the Analyses	3 pages per analyte. Page 1: posteriors for separate treatment groups. Page 2: posterior for absolute difference (GSK2798745 c.f. placebo) Page 3: posterior for percentage reduction (GSK2798745 c.f. placebo). Treatment comparison for percentage change should be expressed as an increase/reduction depending on desired treatment direction for the specific analyte e.g. % reduction/increase 745 c.f. placebo.	SAC [1]
2.18.	Evaluable	PD_F1	**BAL White Blood Cell Types (Totals and Differentials, except Neutrophils):** Geometric Means and 95% CI by timepoint and challenge (baseline, 26 h LPS Lobe, 26 h Saline Lobe) and treatment group	One page per biomarker.	SAC [1]
2.19.	Evaluable	PD_F3	**BAL White Blood Cell Types (Totals and Differentials, except Neutrophils):** Participant Profiles of Baseline (2h) to 26h by Challenge and Treatment Group	One page per biomarker. Use participant attributes map so each subject has specific marker, line colour, pattern to track participant between plots.	SAC [1]
2.20.	Evaluable	PD_F4	**BAL White Blood Cell Types (Totals and Differentials, except Neutrophils):** Point Estimates and 95% Credible Intervals from the Analyses	One page per biomarker. Page to include 3 column panels. 1st: (Back-transformed) treatment group predictions, 2nd: Treatment group differences, 3rd: Percentage reduction ('745 c.f. Pbo).	SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21	Evaluable	PD_F5	**BAL White Blood Cell Types (Totals and Differentials, except Neutrophils):** Posterior Distribution Density Plots from the Analyses	3 pages per analyte. Page 1: posteriors for separate treatment groups. Page 2: posterior for absolute difference (GSK2798745 c.f. placebo) Page 3: posterior for percentage reduction (GSK2798745 c.f. placebo). Treatment comparison for percentage change should be expressed as an increase/reduction depending on desired treatment direction for the specific analyte e.g. % reduction/increase 745 c.f. placebo.	SAC [1]
BAL Pharmacodynamic/Biomarker adjusted for Dilution Factor					
2.22	Evaluable	PD_F1	**All BAL Biomarkers adjusted for Dilution Factor:** Geometric Means and 95% CI by timepoint and challenge (baseline, 26 h LPS Lobe, 26 h Saline Lobe) and treatment group	**Conditional Output.** Urea-corrected**.** One page per biomarker.	SAC [1]
2.23	Evaluable	PD_F3	**All BAL Biomarkers adjusted for Dilution Factor:** Participant Profiles of Baseline (2h) to 26h by Challenge and Treatment Group	**Conditional Output.** Urea-corrected**.** One page per biomarker. Use participant attributes map so each subject has specific marker, line colour, pattern to track participant between plots.	SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.24	Evaluable	PD_F4	**All BAL Biomarkers adjusted for Dilution Factor:** Point Estimates and 95% Credible Intervals from the Analyses	**Conditional Output.** Urea-corrected**.** One page per biomarker. Page to include 3 column panels. 1st: (Back-transformed) treatment group predictions, 2nd: Treatment group differences, 3rd: Percentage reduction ('745 c.f. Pbo).	SAC [1]
2.25	Evaluable	PD_F5	**All BAL Biomarkers Corrected for Dilution Factor:** Posterior Distribution Density Plots from the Analyses	**Conditional Output.** Urea-corrected**.** 3 pages per analyte. Page 1: posteriors for separate treatment groups. Page 2: posterior for absolute difference (GSK2798745 c.f. placebo) Page 3: posterior for percentage reduction (GSK2798745 c.f. placebo). Treatment comparison for percentage change should be expressed as an increase/reduction depending on desired treatment direction for the specific analyte e.g. % reduction/increase 745 c.f. placebo.	SAC [1]
Exploratory Blood Biomarkers					
2.26	Evaluable	PD_F1	**Exploratory Blood Biomarkers:** Geometric Means and 95% CI by timepoint and treatment group	One page per biomarker.	SAC [1]

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27	Evaluable	PD_F7	**Exploratory Blood Biomarkers:** Participant Time Profiles by Treatment Group	One page per biomarker. Use participant specific attributes map. Use discrete x-axis scale so timepoints 2h and 3h are distinguishable. For each biomarker decided on y-axis on case-by-case basis.	SAC [1]
2.28	Evaluable	PD_F6	**Exploratory Blood Biomarkers:** Time Profiles of Adjusted Posterior Medians and 95% Credible Intervals.	3 pages per biomarker. Page 1: Separate profiles for each treatment group. Page 2: Profile for absolute difference treatment comparison. Page 3: Treatment comparison as percentage change.	SAC [1]
2.29	Evaluable	PD_F5	**Exploratory Blood Biomarkers**: Posterior Distribution Density Plots from the Analyses for each Timepoint	6 pages per biomarker: First 4 pages: posterior for each treatment group on same page, 1 page per timepoint. Page 5: Analyte response absolute difference (GSK2798745 c.f. placebo) for all timepoints. Page 6: Analyte response percentage reduction (GSK2798745 c.f. placebo) for all timepoints.	SAC [1]

12.11.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Subjects	AE1	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.2.	All Subjects	AE1	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency	ICH E3	SAC [1]
Serious and Other Significant Adverse Events					
3.3.	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC [1]
3.4.	All Subjects	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study by System Organ Class and Preferred Term	IDSL	SAC [1]
Laboratory: Chemistry					
3.5.	All Subjects	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC [1]
Laboratory: Haematology					
3.6.	All Subjects	LB1	Summary of Haematology Changes from Baseline	ICH E3	SAC [1]
Laboratory: Urinalysis					
3.7.	All Subjects	LB1	Summary of Urine Concentration Changes from Baseline	ICH E3	SAC [1]
3.8.	All Subjects	UR3	Summary of Urinalysis Dipstick Results	ICH E3	SAC [1]
Laboratory: Hepatobiliary (Liver)					
3.9.	All Subjects	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC [1]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
3.10.	All Subjects	EG1	Summary of ECG Findings	IDSL	SAC [1]
3.11.	All Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC [1]
3.12.	All Subjects	SAFE_T4	Summary of Number of Participants with Maximum ECG Values Meeting or Exceeding Pre-Specified Ranges of Concern by Category, Treatment and Timepoint.		SAC [1]
Vital Signs					
3.13.	All Subjects	VS1	Summary of Change from Baseline in Vital Signs	ICH E3 Include body temperature, heart rate, blood pressure.	SAC [1]
Columbia Suicide Severity Rating Scale (C-SSRS)					
3.14.	All Subjects	CSSRS1 (SAFE_T1)	Summary of C-SSRS Suicidal Ideation or Behaviour	Include Placebo column.	SAC [1]
Laboratory: Other					
3.15.	All Subjects	SAFE_T2	Summary of Faecal Occult Blood Test (FOBT) Data		SAC [1]
3.16.	All Subjects	LB1	Summary of Cardiac Troponin (cTn) Changes from Baseline		SAC [1]
3.17.	All Subjects	LB1	Summary of Coagulation Profile Changes from Baseline		SAC [1]
Spirometry					
3.18.	All Subjects	SAFE_T3	Summary of Spirometry Data		SAC [1]

12.11.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma PK Concentration					
4.1.	PK	PKCT1 / PK01	Summary of GSK2798745 Plasma Pharmacokinetic Concentration-Time Data (ng/mL)		SAC [1]
4.2.	PK	PKCT1 / PK01	Summary of Metabolite GSK3526876 Plasma Pharmacokinetic Concentration-Time Data (ng/mL)	**Conditional output.**	SAC [1]
BAL PK Concentration					
4.3.	PK	PKCT1 / PK01	Summary of GSK2798745 BAL 2h and 26h Concentration Data (ng/mL)	Not urea-corrected.	SAC [1]
4.4.	PK	PKCT1 / PK01	Summary of GSK2798745 BAL 2h and 26h Concentration **Corrected for Dilution Factor Data** (ng/mL)	**Conditional output**. Urea-corrected.	SAC [1]
Plasma PK Parameters					
4.5.	PK	PKPT1 / PK03	Summary of Derived GSK2798745 Plasma Pharmacokinetic Parameters		SAC [1]
4.6.	PK	PKPT3 / PK05	Summary of Log-Transformed Derived GSK2798745 Plasma Pharmacokinetic Parameters		SAC [1]
4.7.	PK	PKPT1 / PK03	Summary of Derived Metabolite GSK3526876 Plasma Pharmacokinetic Parameters	**Conditional output.**	SAC [1]
4.8.	PK	PKPT3 / PK05	Summary of Log-Transformed Derived Metabolite GSK3526876 Plasma Pharmacokinetic Parameters	**Conditional output.**	SAC [1]

12.11.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Plasma PK Concentrations					
4.1.	PK	PKCF1P / PK16a	Individual GSK2798745 Plasma Concentration-Time Plot (Linear and Semi-Log)		SAC [1]
4.2.	PK	PKCF2 / PK17	Mean GSK2798745 Plasma Concentration-Time Plot (Linear and Semi-Log)		SAC [1]
4.3.	PK	PKCF3 / PK18	Median GSK2798745 Plasma Concentration-Time Plot (Linear and Semi-Log)		SAC [1]
4.4.	PK	PKCF1P / PK16a	Individual Metabolite GSK3526876 Plasma Concentration-Time Plot (Linear and Semi-Log)	**Conditional output.**	SAC [1]
4.5.	PK	PKCF2 / PK17	Mean Metabolite GSK3526876 Plasma Concentration-Time Plot (Linear and Semi-Log)	**Conditional output.**	SAC [1]
4.6.	PK	PKCF3 / PK18	Median Metabolite GSK3526876 Plasma Concentration-Time Plot (Linear and Semi-Log)	**Conditional output.**	SAC [1]
BAL PK Concentrations					
4.7.	PK	PK_F1	Individual Participant and Median BAL GSK2798745 Concentration-Time Plot	Not urea-corrected BAL concentration. PK_F1 is a loose example. One active treatment group in this study. Use participant-specific attributes map.	SAC [1]
4.8.	PK	PK_F1	Individual Participant and Median BAL GSK2798745 Concentration-Time Plot (**Concentration Adjusted for Dilution Factor**)	Conditional output. Urea-corrected BAL concentration. PK_F1 is a loose example. One active treatment group in this study. Use participant-specific attributes map.	SAC [1]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
BAL and Plasma PK Concentrations					
4.9.	Evaluable	PKPD_F1	Scatter Plots of Plasma PK Parameters (C_{MAX}, AUC_{0-26}, C_{26}) v BAL GSK2798745 Concentrations (C_2, C_{26}).	Only participants on active treatment. Page 1: Plasma C_{MAX} v BAL C_2. Page 2: Plasma AUC_{0-26} v BAL C_{26} Page 3: Plasma C_{26} v BAL C_{26}	SAC [1]
4.10.	Evaluable	PKPD_F1	Scatter Plots of Plasma PK Parameters (C_{MAX}, AUC_{0-26}, C_{26}) v BAL GSK2798745 Concentrations (C_2, C_{26}). **BAL Concentrations Adjusted for Dilution Factor.**	Only participants on active treatment. Page 1: Plasma C_{MAX} v BAL C_2. Page 2: Plasma AUC_{0-26} v BAL C_{26} Page 3: Plasma C_{26} v BAL C_{26}	SAC [1]

12.11.10. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK / PD					
7.1.	Evaluable	PKPD_F1	Scatter Plots of Plasma PK Parameters (AUC_{0-26}, C_{26}, C_{max}) v 26h BAL Total Protein.	Page 1: Plasma AUC_{0-26} v 26h BAL Total Protein Page 2: Plasma C_{26} v 26h BAL Total Protein Page 3: Plasma C_{MAX} v 26h BAL Total Protein	SAC [1]
7.2.	Evaluable	PKPD_F1	Plots of BAL GSK2798745 Concentrations v 26h BAL Total Protein	Page 1: BAL C_2 v 26h BAL Total Protein Page 2: BAL C_{26} v 26h BAL Total Protein	SAC [1]

12.11.11. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC [1]
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC [1]
3.	All Subjects	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC [1]
4.	All Subjects	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC [1]
5.	All Subjects	TA1 / CP_RD1x	Listing of Planned and Actual Treatments	IDSL	SAC [1]
Protocol Deviations					
6.	All Subjects	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [1]
7.	All Subjects	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [1]
Populations Analysed					
8.	All Subjects	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC [1]
Demographic and Baseline Characteristics					
9.	Screened	DM2	Listing of Demographic Characteristics	ICH E3	SAC [1]
10.	Screened	DM9	Listing of Race	ICH E3	SAC [1]
Prior and Concomitant Medications					
11.	All Subjects	CP_CM3	Listing of Concomitant Medications	IDSL	SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
12.	All Subjects	EX3	Listing of Exposure Data	ICH E3	SAC [1]
Adverse Events					
13.	All Subjects	AE8CP	Listing of All Adverse Events	ICH E3	SAC [1]
14.	All Subjects	AE7	Listing of Participant Numbers for Individual Adverse Events	ICH E3	SAC [1]
15.	All Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC [1]
Serious and Other Significant Adverse Events					
16.	All Subjects	AE8CPa	Listing of Fatal Serious Adverse Events	ICH E3	SAC [1]
17.	All Subjects	AE8CPa	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC [1]
18.	All Subjects	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC [1]
19.	All Subjects	AECP8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC [1]
20.	All Subjects	AECP8	Listing of Other Significant Adverse Events	ICH E3	SAC [1]
Hepatobiliary (Liver)					
21.	All Subjects	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC [1]
22.	All Subjects	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC [1]
All Laboratory					
23.	All Subjects	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC [1]
24.	All Subjects	LB5	Listing of Laboratory Values of Potential Clinical Importance		SAC [1]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
25.	All Subjects	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC [1]
26.	All Subjects	UR2A	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC [1]
ECG					
27.	All Subjects	EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC [1]
28.	All Subjects	EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC [1]
29.	All Subjects	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC [1]
30.	All Subjects	EG5	Listing of Abnormal ECG Findings	IDSL	SAC [1]
Vital Signs					
31.	All Subjects	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC [1]
32.	All Subjects	VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC [1]

12.11.12. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic					
33.	Evaluable	PD_L2	Listing of BAL Total Protein Data		IA1 [1], IA2 [1], HR [1], SAC [1]
34.	Evaluable	PD_L2	Listing of BAL Total Protein Data **Corrected for Dilution Factor.**	**Conditional Output**. Urea-corrected.	SAC [1]
35.	Evaluable	PD_L2	Listing of BAL Neutrophil Data (Total and Percentage)	Percentage in brackets – change template accordingly.	HR [1]
36.	Evaluable	-	**26h BAL Total Protein**: Raw SAS Output from the Primary Analysis		IA1 [1], IA2 [1], HR [1], SAC [1]
37.	Evaluable	-	**Sensitivity Analysis: 26 h BAL Total Protein including 26h Saline Lobe BAL Total Protein as a Covariate**: Raw SAS Output from the Analysis		SAC [1]
38.	Evaluable	-	**Sensitivity Analysis 26 h BAL Total Protein Excluding Participants with High Saline Lobe BAL Total Protein Level**: Raw SAS Output from the Analysis		SAC [1]
39.	Evaluable	-	**Exploratory Analysis: 26 h BAL Total Protein and Total Neutrophil Count:** Raw SAS Output from the Multivariate Analysis	**Conditional Output.**	SAC [1]
40.	Evaluable	-	**26h BAL Total Neutrophil Count**: Raw SAS Output from the Analysis		SAC [1]
41.	Evaluable	-	**26 h BAL Differential Neutrophil Count**: Raw SAS Output from the Analysis		SAC [1]
42.	Evaluable	-	**Exploratory BAL Biomarkers (excluding WBC):** Raw SAS Output from the Analyses		SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
43.	Evaluable	-	**BAL White Blood Cell Types (Totals and Differentials):** Raw SAS Output from the Analyses		
44.	Evaluable	-	**All Exploratory BAL Biomarkers Corrected for Dilution Factor**: Raw SAS Output from the Analysis	**Conditional Output.** Urea-corrected**.**	SAC [1]
45.	Evaluable	-	**Exploratory Blood Biomarkers**: Raw SAS Output from the Analysis		SAC [1]
Safety					
46.	All Subjects	SAFE_L1	Listing of Spirometry Data of Potential Clinical Importance		SAC [1]
47.	All Subjects	CSSRS4 (SAFE_L2)	Listing of C-SSRS Suicidal Ideation or Behaviour Data		SAC [1]
48.	All Subjects	CSSRS5 (SAFE_L3)	Listing of C-SSRS Suicidal Behaviour Details	Production dependent on events occurring.	SAC [1]
49.	All Subjects	SAFE_L4	Listing of Abnormal Faecal Occult Blood Test (FOBT) Data		SAC [1]
Interim Analysis Specific					
50.	Evaluable	PD_L1	Interim Analysis: Raw SAS output from predicting the probability of achieving end of study success		IA1 [1], IA2 [1], HR [1], SAC [1]
Pharmacokinetic					
51.	PK	PKCL1P / PK07	Listing of GSK2798745 Plasma Pharmacokinetic Concentration-Time Data		SAC [1]
52.	PK	PKPL1P / PK13	Listing of Derived GSK2798745 Primary and Secondary Pharmacokinetic Parameters		SAC [1]
53.	PK	PKCL1P / PK07	Listing of Metabolite GSK3526876 Plasma Pharmacokinetic Concentration-Time Data		SAC [1]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
54.	PK	PKPL1P / PK13	Listing of Derived Metabolite GSK3526876 Primary and Secondary Pharmacokinetic Parameters		SAC [1]
55.	PK	PKCL1P / PK07	Listing of GSK2798745 BAL Pharmacokinetic Concentration-Time Data	Not urea-corrected.	SAC [1]
56.	PK	PKCL1P / PK07	Listing of GSK2798745 BAL Pharmacokinetic Concentration-Time Data **Adjusted for Dilution Factor**	**Conditional output**. Urea-corrected.	SAC [1]

12.12. Appendix 12: Example Mock Shells for Data Displays

Example: PD_T1
Protocol: 207464
Population: Evaluable

Table 2.1
Summary of BAL Total Protein by Timepoint (Baseline (2 h) and 26 h), Lung Lobe (LPS and Saline Challenge) and Treatment Group

Parameter	Treatment	Timepoint/Chall	N	n	Arithmetic Mean	Arithmetic 95% CI of Mean	Arithmetic SD	Median	Min	Max
BAL Total Protein (ug/mL)	Placebo	Baseline (2 h)	30	30	92.07	(76.647, 107.49)	41.30	84.07	33.15	190.94
		LPS (26 h)	30	30	290.39	(214.00, 366.79)	204.59	245.46	69.50	1113.5
		Saline (26 h)	30	30	115.20	(105.48, 124.92)	26.02	111.34	65.68	167.58
	GSK2798745	Baseline (2 h)	30	30	91.04	(81.026, 101.06)	26.83	90.58	46.29	145.77
		LPS (26 h)	30	30	150.50	(123.49, 177.51)	72.33	145.34	71.69	370.73
		Saline (26 h)	30	30	100.09	(85.923, 114.26)	37.94	90.11	45.34	194.93

Example: PD _T1
Protocol: 207464
Population: Evaluable

Table 2.1 (continued)
Summary of BAL Total Protein by Timepoint (Baseline and 26 h), Lung Lobe (LPS and Saline Challenge) and Treatment Group

Parameter	Treatment	Timepoint/Chall	N	n	Geometric Mean	95% CI of Geometric Mean	SD Logs
BAL Total Protein (ug/mL)	Placebo	Baseline	30	30	93.81	(58.657, 160.33)	0.29
		LPS (26 h)	30	30	248.80	(95.136, 458.63)	0.48
		Saline (26 h)	30	30	95.15	(44.451, 182.50)	0.44
	GSK2798745	Baseline	30	30	86.07	(52.140, 129.92)	0.30
		LPS (26 h)	30	30	200.01	(85.715, 402.44)	0.51
		Saline (26 h)	30	30	99.37	(60.871, 142.52)	0.30

Example: PD_T2
Protocol: 207464
Page x of x
Population: Evaluable

Data as of xx-xxx-xxxx

Table 2.3 (cont.)
Summary of Posterior Distributions and Posterior Probability Statements
for Primary Analysis of 26 h BAL Total Protein

Endpoint/Analyte	Treatment	Item	n	Median	SD	95% CrI
Total Protein	Placebo	Raw Baseline	x	xxxxxx	xxxx	(xxxx, xxxx)
	GSK2798745	Raw Baseline	x	xxxxxx	xxxx	(xxxx, xxxx)
	N/a	Baseline Value used in Statistical Modelling		xxxxxx		

Example: PD_T2 (continued)
Protocol: 207464
Page x of x
Population: Evaluable

Data as of xx-xxx-xxxx

Table 2.3 (cont.)
Summary of Posterior Distributions and Posterior Probability Statements
for Primary Analysis of 26 h BAL Total Protein

Response/Analyte	Treatment	n	Median	SD	95% CrI	75% CrI	MCSE/SD
26 h Total Protein	Placebo	x	xxxxx	xxxxx	(xxxxx, xxxxx)	(xxxxx, xxxxx)	xxxxx
	GSK2798745	x	xxxxx	xxxxx	(xxxxx, xxxxx)	(xxxxx, xxxxx)	xxxxx

Example: PD_T2 (continued)
Protocol: 207464
Page x of x
Population: Evaluable

Data as of xx-xxx-xxxx

Table 2.3 (cont.)
Summary of Posterior Distributions and Posterior Probability Statements
for Primary Analysis of 26 h BAL Total Protein

Endpoint/Analyte	Comparison	Median	SD	95% CrI	75% CrI	MCSE/SD
26 h Total Protein	Absolute Difference (Active – Placebo)	xxxxx	xxxxx	(xxxxx, xxxxx)	(xxxxx, xxxx)	xxxx
	Percentage Reduction (Active cf. Placebo)	xxxxx	xxxxx	(xxxxx, xxxxx)	(xxxxx, xxxx)	xxxx

Example: PD_T2 (continued)
Protocol: 207464
Page x of x
Population: Evaluable

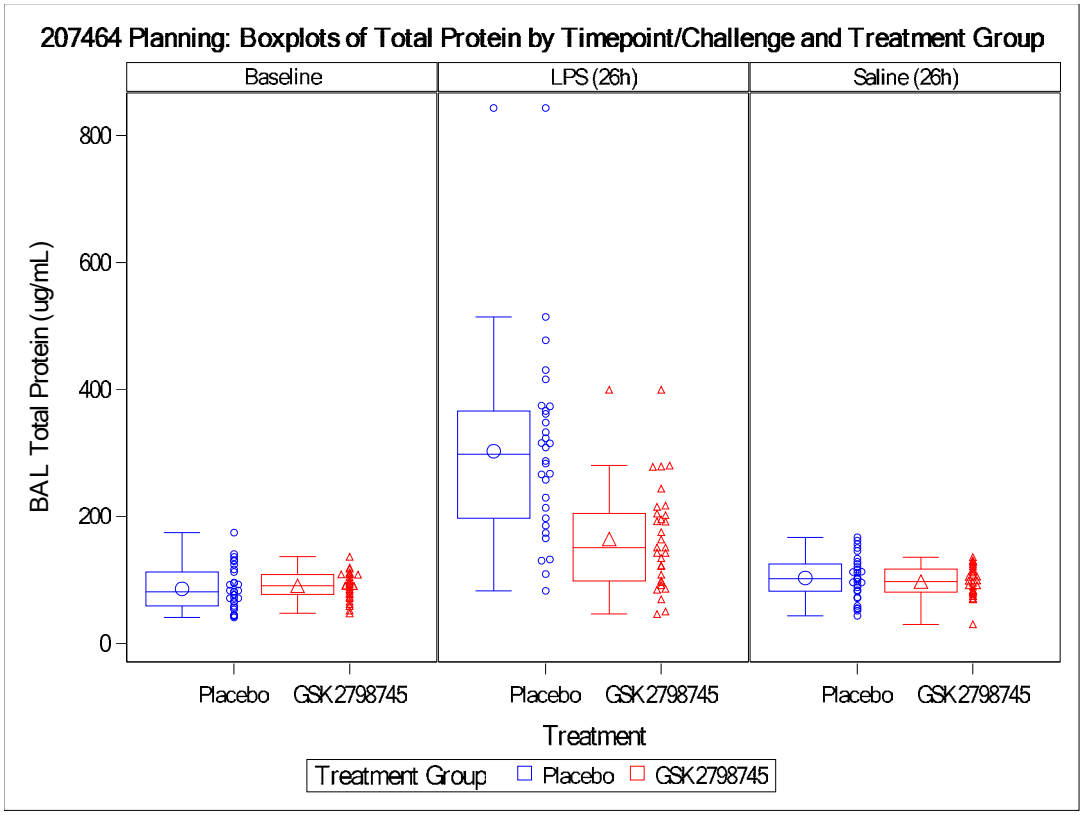
Data as of xx-xxx-xxxx

Table 2.3 (cont.)
Summary of Posterior Distributions and Posterior Probability Statements
for Primary Analysis of 26 h BAL Total Protein

Response	Comparison	Posterior Probability Statement	Value
26 h Total Protein	Median Percentage Change (Active cf. Placebo)	At least a 75% mean reduction (Active c.f. Placebo)	0.002
		At least a 50% mean reduction (Active c.f. Placebo)	0.221
		At least a 25% mean reduction (Active c.f. Placebo)	0.522
		At least a 10% mean reduction (Active c.f. Placebo)	0.721
		Any mean reduction (Active c.f. Placebo)	0.952
		Any mean increase (Active c.f. Placebo)	0.048
		At least a 10% mean increase (Active c.f. Placebo)	0.030
		At least a 25% mean increase (Active c.f. Placebo)	0.018
		At least a 50% mean increase (Active c.f. Placebo)	0.002
		At least a 75% mean increase (Active c.f. Placebo)	0.000

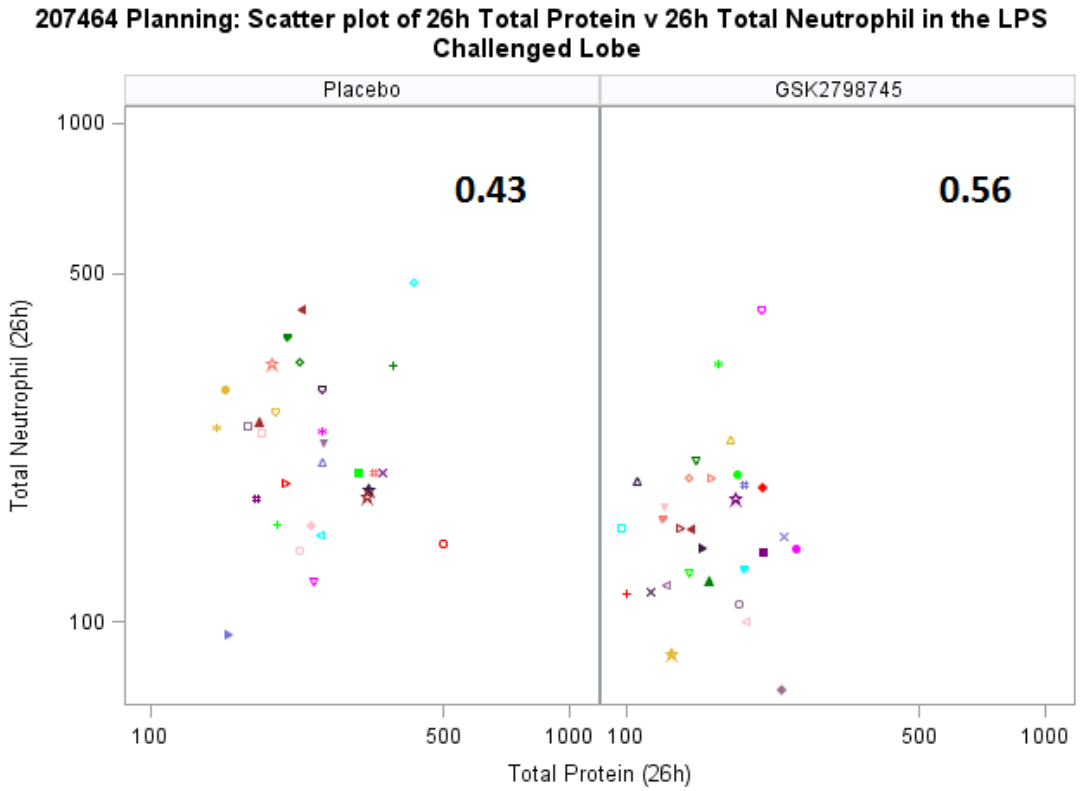
Example: PD _F1
Protocol: 207464
Population: Evaluable

Figure 2.10
Boxplots of Total Protein by Timepoint/Challenge and Treatment Group



Example: PD _F2
Protocol: 207464
Population: Evaluable

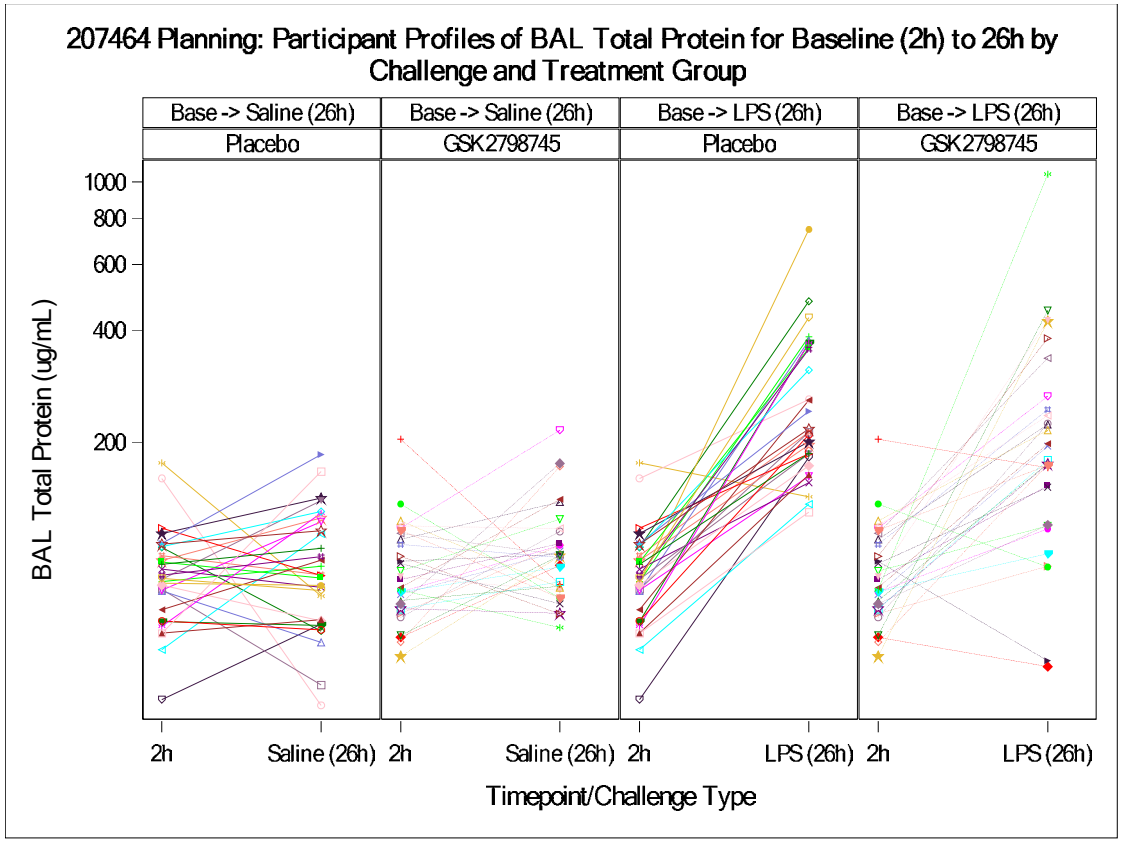
Figure 2.73
Scatter Plot of 26 Total Protein v 26h Total Neutrophil in the LPS Challenged Lobe



Note: correlation is rho value taken from unstructured variance-covariance matrix in multivariate analysis

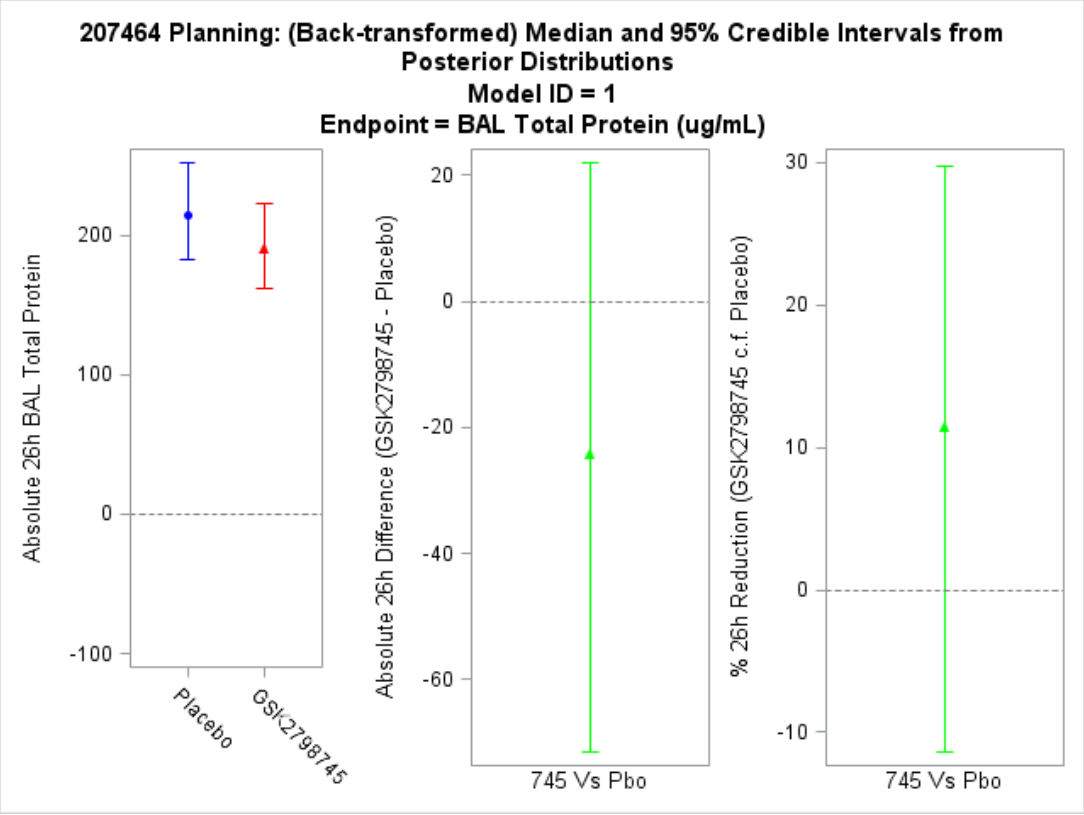
Example: PD _F3
Protocol: 207464
Population: Evaluable

Figure 2.12
Participant Profiles of Baseline (2h), LPS lobe (26h) and Saline Lobe (26h) BAL Total Protein by Treatment Group



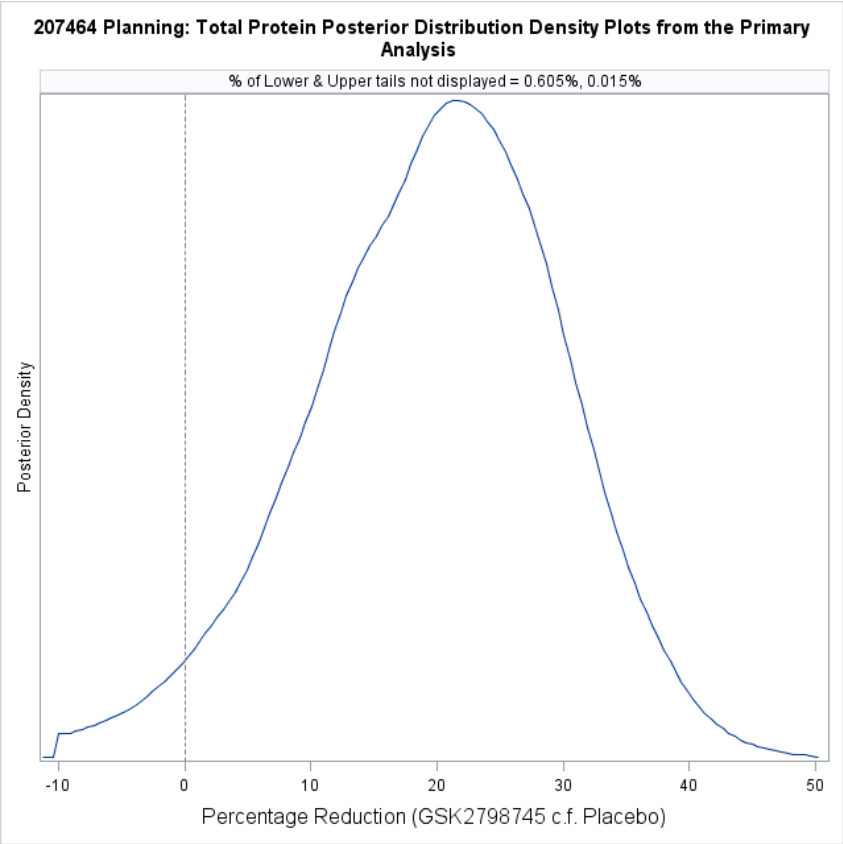
Example: PD _F4
Protocol: 207464
Population: Evaluable

Table 2.13
Total Protein Point Estimates and 95% Highest Posterior Density Intervals from the Primary Analysis



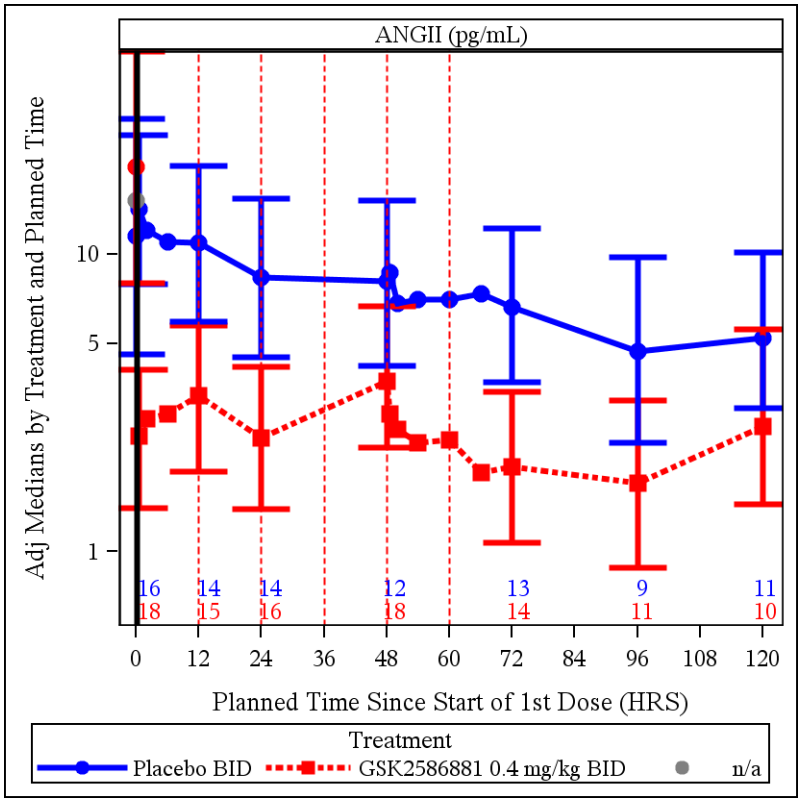
Example: PD _F5
Protocol: 207464
Population: Evaluable

Figure 2.14
Total Protein Posterior Density Plots from the Primary Analysis



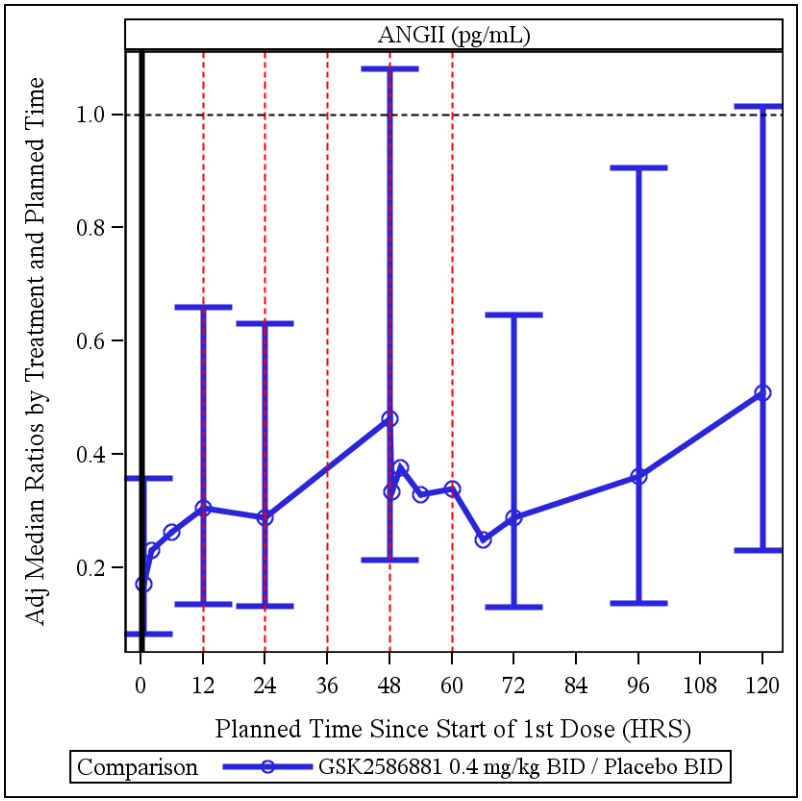
Example: PD _F6
Protocol: 207464
Population: All Subjects

Figure 2.83
Time Profiles of Adjusted Posterior Medians and 95% Credible Intervals for Blood Total Protein



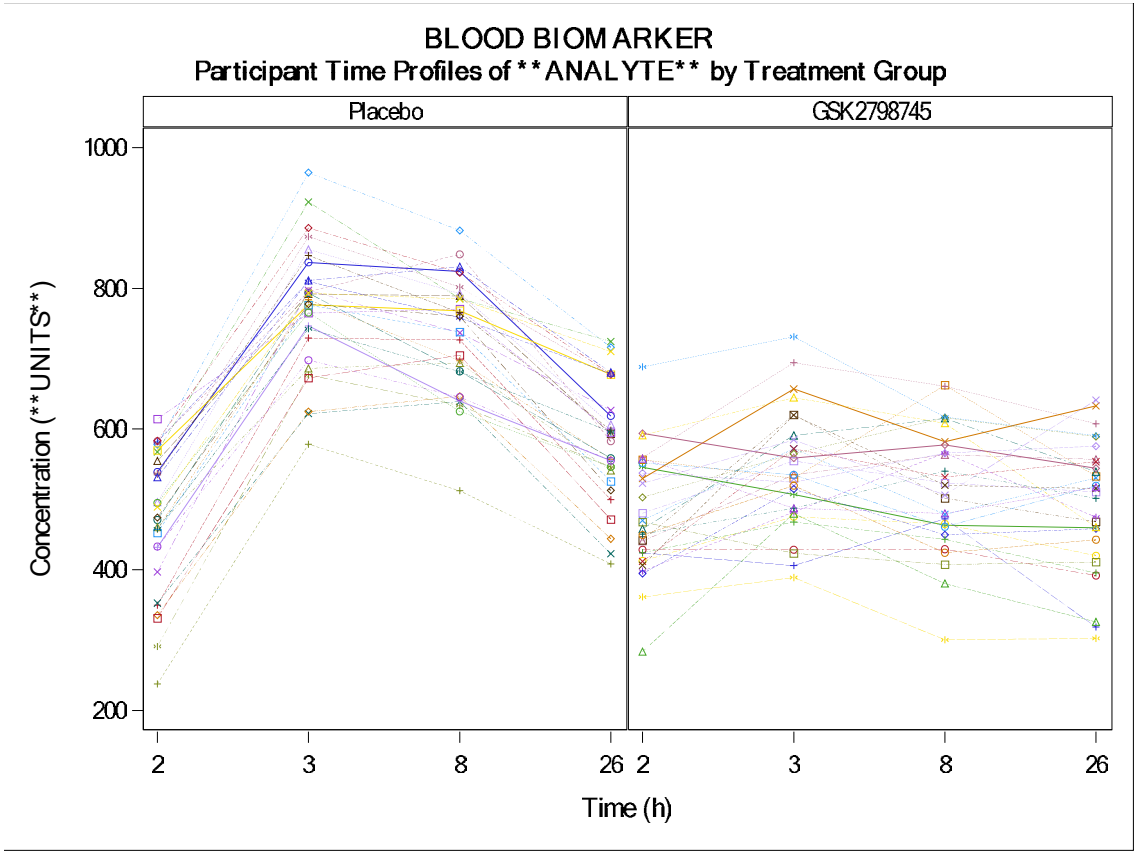
Example: PD _F6 (continued)
Protocol: 207464
Population: All Subjects

Figure 2.83 (continued)
Time Profiles of Adjusted Posterior Medians and 95% Credible Intervals for Blood Total Protein



Example: PD _F7
Protocol: 207464
Population: All Subjects

Figure 2.82
Participant Time Profiles of **BLOOD BIOMARKER** by Treatment Group



Example: PD _L1
Protocol: 207464
Population: Evaluable

Listing 39
Raw SAS Output from Predicting the Probability of Achieving End of Study Success

Success	Frequency (Number of Complete Studies)	Interim Posterior Predictive Probability
Yes	7602	0.76
No	2398	0.24

Note: End of Study Success Definition: Posterior Probability (% reduction Active compared to Placebo) ≥ 0.95

EXAMPLE CSSRS1 (SAFE_T1)
Protocol: GSK123456
Population: All Subjects

Table X
Summary of Participants with C-SSRS Suicidal Ideation or Behaviour during Treatment

	Treatment A (N=78)	Treatment B (N=78)
Number of participants with at least one on-treatment C-SSRS assessment	77	78
Suicidal Ideation or Behaviour (1-10)		
Any event	28 (36%)	34 (44%)
Suicidal Ideation (1-5)		
Any suicidal ideation	28 (36%)	34 (44%)
1 - Passive: Wish to be dead	9 (12%)	11 (14%)
2 - Active: Non-specific (no method, intent, plan)	6 (8%)	8 (10%)
3 - Active: Method, but no intent or plan	6 (8%)	8 (10%)
4 - Active: Method and intent, but no plan	6 (8%)	8 (10%)
5 - Active: Method, intent, and plan	6 (8%)	8 (10%)
Suicidal Behaviour (6-10)		
Any suicidal behaviour	28 (36%)	34 (44%)
6 - Preparatory acts or behaviour	9 (12%)	11 (14%)
7 - Aborted attempt	6 (8%)	8 (10%)
8 - Interrupted attempt	6 (8%)	8 (10%)
9 - Non-fatal actual suicide attempt	6 (8%)	8 (10%)
10 - Completed suicide	6 (8%)	8 (10%)
Self-Injurious Behaviour, no suicidal attempt	6 (8%)	8 (10%)

Note: Percentages are based on the number of participants with at least one on-treatment C-SSRS assessment. For behaviour, the numbers of participants (n) are those with the specified behaviour at least once during treatment. For ideation, n refers to the number whose maximum ideation at any on-treatment assessment is the specified ideation. Participants may have more than one type of suicidal ideation or behavior.
USER ID: directory/ program.sas DDMMMYYYY HH:MM

Example: SAFE_T2
Protocol: 207464
Population: All Subjects

Table 3.15
Summary of Faecal Occult Blood Test (FOBT) Data

Parameter	Treatment	Timepoint/Chall	N	n	Number of Positive Results
Haemoglobin (ng/ml)	Placebo	Screening	30	30	0
		Follow-up	30	30	1
	GSK2798745	Screening	30	30	0
		Follow-up	30	30	3

Example: SAFE_T3
Protocol: 207464
Population: All Subjects

Table 3.17
Summary of Spirometry Data

Treatment	Visit	Planned Relative Timepoint	N	n	PFT (Units)	Mean	95% CI	Mean % Pred FEV1 (L)	95% CI	Mean FEV1/ FVC Ratio	95% CI	# Participants with % Pred FEV1 < 80%	# Participants with % FEV1/FVC Ratio < 70%
Placebo	Screening	Screening	30	29	FEV1 (L)	3.552	3.213, 3.901	82.44	76.72, 88.90			2	
			30	29	FVC (L)					5.505	5.212, 5.987		3
	Day -1	Day -1			FEV1 (L)								
					FVC (L)								
	Day 1	Pre-dose			FEV1 (L)								
					FVC (L)								
	Day 1	6 h			FEV1 (L)								
					FVC (L)								
	Day 2	25.5 h			FEV1 (L)								
					FVC (L)								
	Day 2	30 h			FEV1 (L)								
					FVC (L)								
	Day 8	Day 8			FEV1 (L)								
					FVC (L)								

Example: SAFE_T4
Protocol: IPC103711
Page 1 of 1
Population: All Subjects

Table 12.6
Summary of Number of Participants with Maximum ECG Values meeting or exceeding Pre-specified Ranges of concern by Category, Treatment and Timepoint

Timepoint = Screening Visit

	Placebo (N=12)	066 25mcg QD (N=13)	066 87.5mcg QD (N=12)
QTCB			
n	12	13	12
>450 to <480	1 (8%)	4 (31%)	6 (50%)
>=480 to <500	0	0	0
>=500	0	0	0
QTCF			
n	12	13	12
>450 to <480	0	0	0
>=480 to <500	1 (8%)	0	0
>=500	0	0	0

EXAMPLE SAFE_L1
Protocol: IPC103711
Population: All Subjects

Listing 17
Listing of Spirometry Data

Subj.	Treatment	Visit	Planned Relative Time	Date/ Time	PFT (Units)	Reading 1	Reading 2	Reading 3	Reading Max.	Predicted Normal FEV1 [1]	% Predicted Normal FEV1 [1]	FEV1/ FVC Ratio
PPD	066 87.5mcg QD	SCREENING	SCREENING	10MAR2008/ 10:55	FEV1(L)	5.07	5.01	5.1	5.1	5.041	101.172	
					FVC(L)	6.4	6.39	6.48	6.48			0.79
		DAY 1	PRE-DOSE	PPD / 8:24	FEV1(L)	5.38			5.38			
		DAY 7	PRE-DOSE	PPD / 7:58	FEV1(L)	5			5			
			POST-BRONCH	PPD 14:16	FEV1(L)	5.06			5.06			
		DAY 8	POST-BRONCH	PPD 14:22	FEV1(L)	5.29			5.29			
	066 87.5mcg QD	SCREENING	SCREENING	01APR2008/ 10:41	FEV1(L)	4.18	4.22	4.37	4.37	4.496	97.202	
					FVC(L)	5.76	5.8	5.99	5.99			0.73
		DAY 1	PRE-DOSE	PPD 7:57	FEV1(L)	4.43			4.43			
		DAY 7	PRE-DOSE	PPD 8:04	FEV1(L)	4.38			4.38			
			POST-BRONCH	PPD / 14:29	FEV1(L)	4.2			4.2			
		DAY 8	POST-BRONCH	PPD / 14:05	FEV1(L)	4.31			4.31			

[1]Values have been recalculated from raw data
PPD

EXAMPLE CSSRS4 (SAFE_L2)

Protocol: GSK123456
Population: All Subjects

Listing X
Listing of C-SSRS Suicidal Ideation and Behaviour Data

Treatment: Treatment A

Centre ID/ Subject	Visit/ Evaluation/ Assessment Date/ Study Day	------- Suicidal Ideation (1-5)------ (1) Wish to be Dead	(2) Non-spec. Suicidal Thoughts	(3) Without Intent	(4) Without Plan	(5) With Plan and Intent	---- Suicidal Behaviour (6-10) ----- (6) Prep. Acts/ Beh.	(7) Aborted Attempt	(8) Interrupted Attempt	(9) Non-fatal Actual Attempt	(10) Comp. suicide	Non-Suic. Self-Injurious Beh.
PPD	Visit 2 (Baseline)/ Lifetime/ PPD -14	Yes	Yes	Yes	No	No	No	No	No	No	No	No
	Visit 2 (Baseline)/ Current History/ PPD -14	Yes	Yes	No	No	No						
	VISIT 7 (Week 20)/ Since last visit/ PPD 140	Yes	Yes	No	Yes	No	No	No	Yes	No	No	No
	Visit 2 (Baseline)/ Lifetime / PPD -15	No	Yes	Yes	No	No	No	No	No	No	No	No

Note: The current history period is within the past XX months. If a participant has a lifetime evaluation shown, but not a current history evaluation, this indicates that the participant's most severe suicidal ideation occurred during the current history period. If the participant had an actual suicide attempt which was not a completed suicide, it is considered as (9) Non-fatal actual attempt.
USER ID: directory/program.sas DDMMMYYYY HH:MM
EXAMPLE CSSRS5 (SAFE_L3)

Protocol: GSK123456
Population: e.g., All Subjects, Safety

Listing X
Listing of C-SSRS Suicidal Behaviour Details

Treatment: Treatment A

Centre ID/ Subject	Visit/ Evaluation/ Assessment Date/ Study Day	Suicidal Behaviour/ Number of Events	Description	Actual Attempt Type	If Actual Attempt: Date/ Actual Lethality/ Potential Lethality	Com-pleted Sui-cide?	Date of Most Recent Behavior [1]
PPD	Visit 2 (Baseline)/ Lifetime/ PPD -14	Actual Attempt/ 3	Subject PPD PPD	Most recent	10FEB2005/ No or very minor physical damage/ Behaviour not likely to result in injury		
				Most lethal	10FEB2002/ Minor physical damage/		
				Initial/ First	10JAN2002/ No or very minor physical damage/ Behaviour not likely to result in injury		
		Inter-rupted Attempt/ 1	Subject was prevented from PPD				--FEB2002

[1] This column relates to suicidal behaviour other than actual attempts, for screening/baseline only.

USER ID: directory/program.sas DDMMMYYYY HH:MM

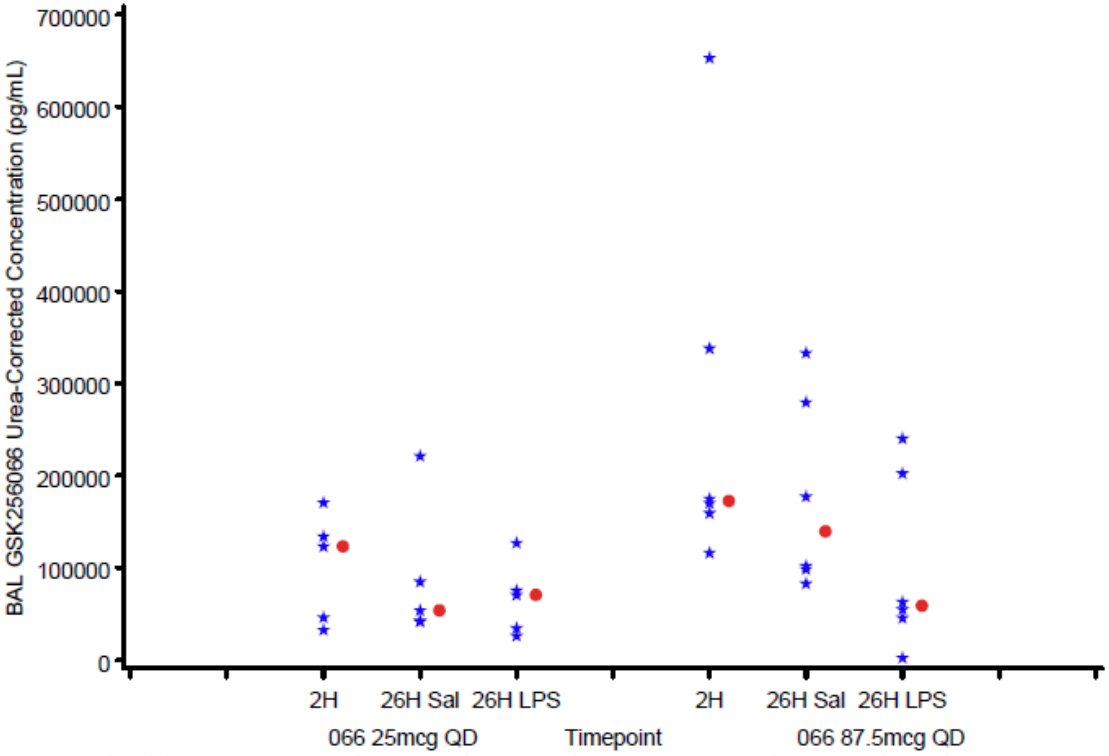
Example: SAFE_L4
Protocol: 207464
Population: All Subjects

Listing 41
Listing of Abnormal Faecal Occult Blood Test (FOBT) Data

Treatment	Participant	Visit	Date	Time	Haemoglobin Value (ng/ml)
Placebo	PPD	Screening	04APR2018	08:09	
		Follow-up	17APR2018	09:09	
		Screening	06APR2018	10:09	
		Follow-up	19APR2018	11:09	
GSK2798745		Screening	03APR2018	12:09	
		Follow-up	18APR2018	13:09	
		Screening	05APR2018	14:09	
		Follow-up	120APR2018	15:09	

Example: PK_F1
Protocol: 207464
Population: All Subjects

Figure 4.7
Individual Participant and Median BAL GSK2798745 Concentration-Time Plot

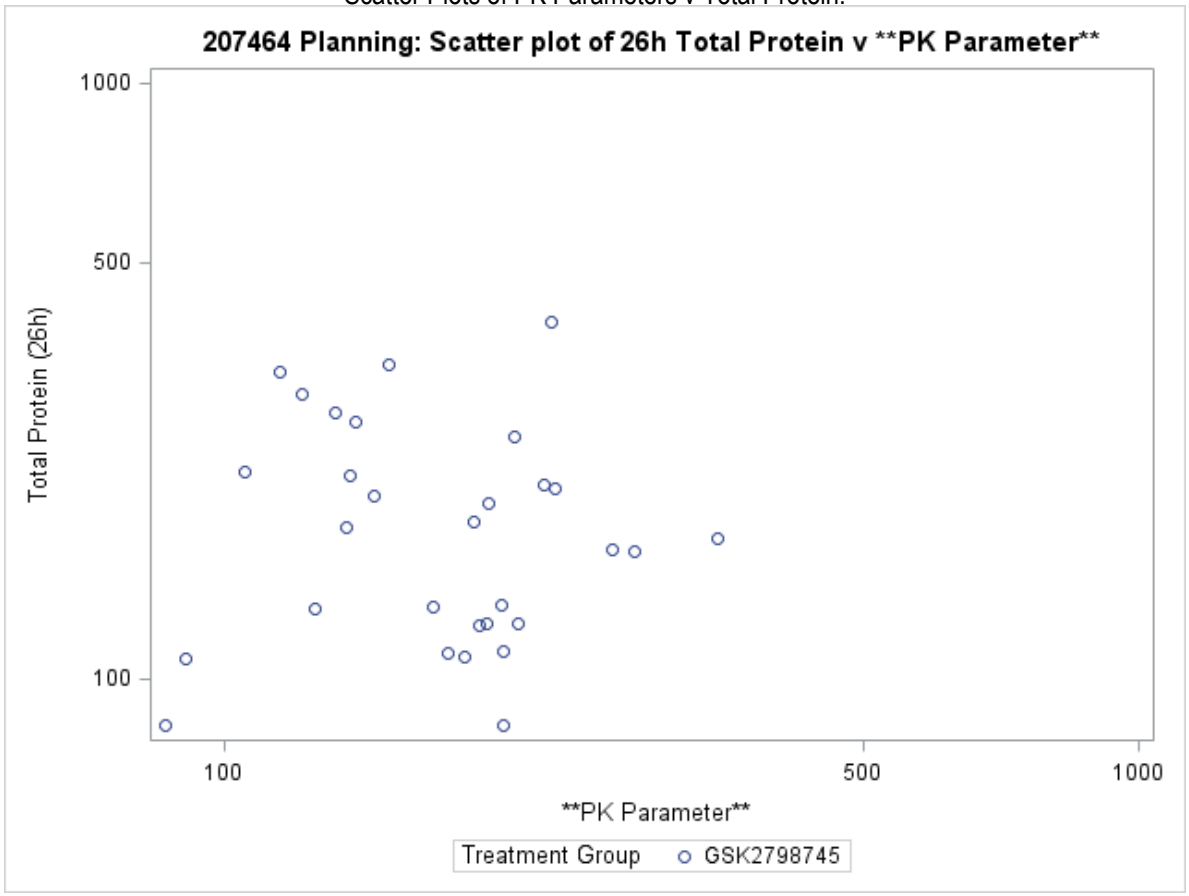


NOTE: For BAL Supernatant the median for the 26H timepoints are zero due to majority of the values being assigned as NQ.

PPD

Example: PKPD_F1
Protocol: 207464
Population: Evaluable

Figure 7.1
Scatter Plots of PK Parameters v Total Protein.



Example: PD_L2
Protocol: 207464
Population: Evaluable

Listing 1
Listing of BAL Total Protein Data

Treatment: Placebo
Analyte: Total Protein (pg/ml)

Subject	Baseline (2h) date/time	26h date/ time	2h Analyte Concn (pg/ml)	BAL	2h Concn Vol (ml)	26h Saline Lobe Analyte (pg/ml)	26h LPS Lobe BAL (pg/ml)	26h BAL Vol. (ml)
PPD	01AUG2018/ 09:45	02AUG2018/ 09:50	168			188	450	

PPD

Example AE2
Protocol: GSK123456
Population: All Subjects

Table 6.2
Listing of Relationship between System Organ Class and Verbatim Text

System Organ Class	Preferred Term	Verbatim Text
Blood and lymphatic system disorders	Lymphadenopathy	ENLARGED LYMPH NODE
Cardiac disorders	Palpitations	HEART PALPITATION
	Tachycardia nos	TACHYCARDIA
Ear and labyrinth disorders	Cerumen impaction	CLOGGED EARS WITH EAR WAX
	Ear pain	EARACHES IN BOTH EARS
		RIGHT EAR PAIN
	Tinnitus	RINGING IN RIGHT EAR
Eye disorders	Asthenopia	TIRED EYES
	Conjunctivitis	BILATERAL ACUTE CONJUNCTIVITIS
		CONJUNCTIVITIS
	Dry eye nos	DRY EYES
	Eye redness	REDDENED EYES
	Vision blurred	BLURRED VISION
		BLURRY VISION
		WORSENING OF BLURRED VISION
Gastrointestinal disorders	Abdominal pain nos	ABDOMEN PAIN
	Abdominal pain upper	MID-EPIGASTRIC AREA PAIN
		STOMACH ACHE
		STOMACH CRAMPS
		STOMACH PAIN
	Abdominal tenderness	LOCALIZED AREA OF TENDERNESS R ABDOMEN
		MILD TENDERNESS RIGHT LOWER ABDOMINAL QUADRANT
	Constipation	CONSTIPATION
	Diarrhoea nos	DIARRHEA
	Dry mouth	DRY MOUTH
	Dyspepsia	DYSPEPSIA
		HEARTBURN