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

Title	:	Reporting and Analysis Plan for A randomised, double-blind (sponsor open), placebo-controlled, parallel group, 8-week treatment study to investigate the safety, pharmacodynamics, and effect of the TLR7 agonist, GSK2245035, on the allergen-induced asthmatic response in subjects with mild allergic asthma
Compound Number	:	GSK2245035
Effective Date	:	27-FEB-2017

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report (CSR) for Protocol 205540.
- 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 Statistical Analysis Complete (SAC) deliverable.

Author's Name and Functional Area:

PPD Director (Clinical Statistics)	10-FEB-2017
PPD Principal Statistician (Clinical Statistics)	10-FEB-2017
PPD Director (Clinical Pharmacology)	10-FEB-2017

Approved via email:

PPD Director (Clinical Statistics)	27-FEB-2017

TABLE OF CONTENTS

PAGE

1 REPORTING & ANALYSIS PLAN SYNPOSIS

Overview	Key Elements of the RAP
Purpose	• To describe the planned efficacy, biomarker/pharmacodynamics, safety, and pharmacokinetics analyses and output to be included in the Clinical Study Report.
Protocol	• This RAP is based on the Protocol Amendment 2 (Dated: 17/AUG/2016) of Study 205540 (GSK Document No.: 2015N264314_02) and eCRF Version 2.
Primary Objective	• To evaluate the effect of treatment with i.n. GSK2245035 20 ng once weekly (qw) compared to placebo on the allergen-induced late asthmatic response (LAR) in subjects with allergic asthma.
Primary Endpoint	• LAR: minimum FEV_1 between 4-10 hours following allergen challenge one week after treatment. • LAR: weighted mean (WM) FEV_1 between 4-10 hours following allergen challenge one week after treatment.
Study Design	• Randomised (stratified by centre and allergen exposure ('presumed'/'unknown')), double-blind (sponsor open), placebo-controlled, parallel group, 8-week treatment in mild allergic asthmatics
Planned Analyses	• The planned Interim analysis is detailed within Section 3.1 (including details of sample size adjustment). • Pre-Database Freeze (DBF) headline data using FUV1 FEV1 BAC challenge results will be produced for internal GSK review/decision making but these outputs will not be formally reported, since they will be superseded by the final analysis. • All decisions regarding final analysis, as defined in this RAP document, will be made prior to DBF of the study data.
Analysis Populations	• Primary analysis: Per-Protocol Population (comprised of subjects who receive at least one dose of study treatment and commence a BAC at follow-up, i.e. mITT subjects who are not major protocol violators). • Modified Intent-To-Treat Population / Safety / Sputum Producers & PK are other analysis populations that would be used (See Section 4) for full details
Hypothesis	• No formal statistical hypotheses are to be tested. The primary study objective will assess the effect of a weekly dose of 20ng GSK2245035 vs Placebo by precision estimation and credible intervals to estimate the magnitude of underlying effect sizes. A Bayesian approach will be utilised to obtain the posterior distribution for the mean treatment effects for the endpoints in the study (e.g. posterior distributions for percentage attenuation for the endpoint LAR: minimum FEV_1 between 4-10 hours following allergen challenge one week after treatment.). • Other objectives will assess other pharmacodynamic effects and safety and tolerability of GSK2245035.

Overview	Key Elements of the RAP
Primary Analyses	• Statistical models will be fitted separately to each LAR endpoint (weighted mean and minimum FEV_1 change from saline at the FUV1 visit). These parameters will be analysed using a Bayesian version of a mixed effects model (centre as a random effect, and baseline as a covariate). A series of nested models will be fitted to determine if the allergen strata (and interaction with treatment) are necessary. • The principal inferences are expected to come from models with non-informative priors. Sensitivity analyses using informative priors based on AZ data may also be attempted.
Secondary Analyses	• Statistical models will be fitted separately to each EAR endpoint (weighted mean and minimum FEV_1 change from saline at the FUV1 visit). These parameters will be analysed using the same modelling approach as the Primary analysis.

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 Amendment 2 (Dated: 17/AUG/2016).

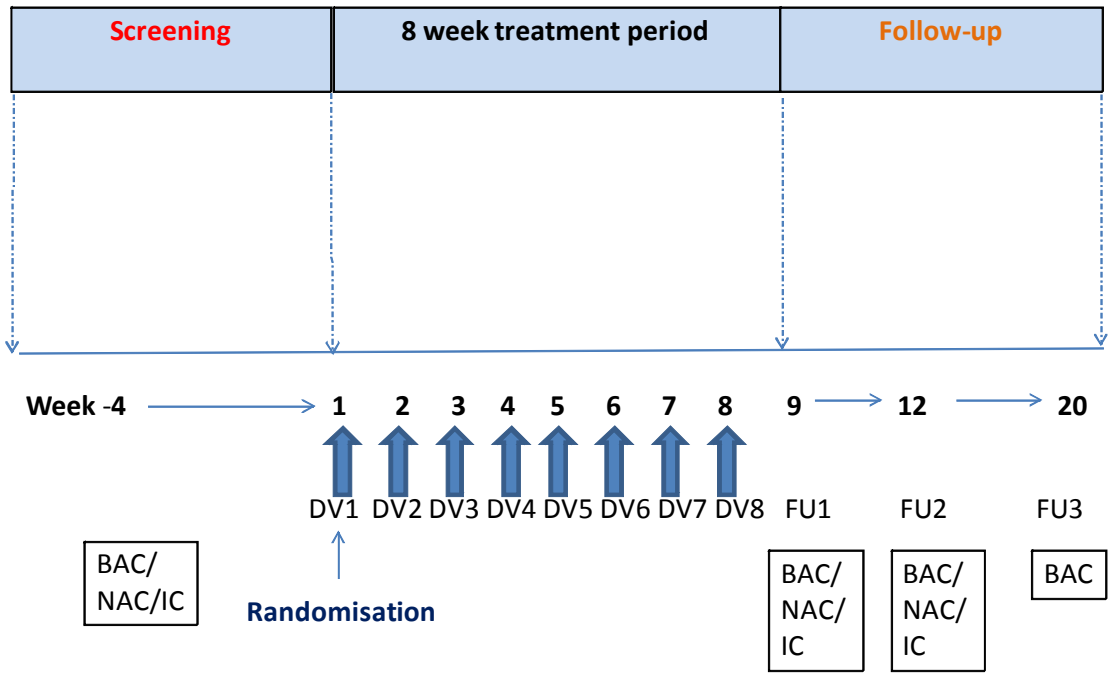
2.2 Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the effect of treatment with i.n. GSK2245035 compared to placebo on the allergen-induced late asthmatic response (LAR) in subjects with allergic asthma.	• LAR: minimum FEV_1 between 4-10 hours following allergen challenge one week after treatment. • LAR: weighted mean FEV_1 between 4-10 hours following allergen challenge one week after treatment
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of treatment with i.n. GSK2245035 compared to placebo on the allergen-induced early asthmatic response (EAR) in subjects with allergic asthma.	• EAR: minimum FEV_1 between 0-2 hours following allergen challenge one week after treatment. • EAR: weighted mean FEV_1 between 0-2 hours following allergen challenge one week after treatment.
Safety Objectives	**Safety Endpoints**
• To evaluate the safety and tolerability of treatment with eight weekly doses of 20 ng i.n. GSK2245035	• General safety endpoints including adverse events (AEs), peak expiratory flow (PEF), rescue salbutamol use, and clinical laboratory parameters
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the duration of effect of treatment with i.n. GSK2245035 compared to placebo on the allergen-induced asthmatic responses (LAR and EAR) in subjects with allergic asthma.	• LAR: minimum and weighted mean FEV_1 between 4-10 hours following allergen challenge approximately 4 and 12 weeks after treatment. • EAR: minimum and weighted mean FEV_1 between 0-2 hours following allergen challenge approximately 4 and 12 weeks after treatment.
• To evaluate the induction of TLR7-associated pharmacodynamic (PD) biomarkers and exhaled nitric oxide (FeNO) following treatment with i.n. GSK2245035	• TLR7-induced blood PD biomarkers. • TLR7 induced gene expression changes in blood • TLR7-induced nasal fluid PD biomarkers • FeNO levels

Objectives	Endpoints
• To evaluate the effect of treatment with i.n. GSK2245035 compared to placebo on Bronchial Allergen Challenge associated allergic biomarkers	• Allergic biomarkers in induced sputum • Allergic biomarkers in blood • FeNO levels
• To evaluate the effect of treatment with i.n. GSK2245035 compared to placebo on Nasal Allergen Administration associated allergic biomarkers	• Allergic biomarkers in nasal fluids • Cellular profile of nasal mucosa
• To evaluate the effect of treatment with i.n. GSK2245035 compared to placebo on Intradermal allergen challenge	• Mean diameter early phase response • Mean diameter late phase response
• To evaluate the effect of treatment with i.n. GSK2245035 compared to placebo on total nasal symptoms	• Total nasal symptoms score (TNSS) assessed daily (AM and PM) throughout the study treatment phase
• To evaluate systemic pharmacokinetics (PK) after administration of i.n. GSK2245035	• Plasma GSK2245035 concentrations

2.3 Study Design

Overview of Study Design and Key Features



BAC -Bronchial allergen challenge; NAC – Nasal allergen challenge/administration
IC – Intradermal challenge; DV – Dosing Visit; FU – Follow-up

Design Features	• parallel group study comparing GSK2245035 vs Placebo • double-blind, placebo-controlled • randomisation stratified by centre and allergen exposure ('presumed'/'unknown') • 8-week study treatment • mild allergic asthmatics • follow-up visits at 1, 4, and 12 weeks after last dose where BAC will be conducted
Dosing	• GSK2245035 20 ng intranasal spray once weekly (QW) (10 ng actuation per nostril making 20 ng total dose)
Treatment Assignment	• Subjects are centrally block randomised and stratified according to centre and type of allergen exposure. Allergen exposure status is assessed as 'unknown' or 'presumed' during the treatment phase according to whether the subject has exposure to that allergen outside of the BAC (see Protocol Section 4.4 for further rationale regarding the allergen exposure status). • The Randomisation Schedule was produced using validated internal software RandAll NG and treatment assigned using the interactive voice response system (IVRS) RAMOS NG.
Interim Analysis	• An interim analysis will be conducted to assess how many subjects on placebo do not experience an LAR (these subjects will be termed 'non-LAR responders') as such subjects will reduce the chances of establishing the primary objective of this study. This interim analysis will determine whether:

Overview of Study Design and Key Features	
	i) further recruitment into the trial should continue (i.e. a futility analysis); or ii) additional subjects should be enrolled to counteract the impact of subjects who do not experience an LAR on placebo. • The timing of the interim is linked to the enrolment rates and will be triggered by whichever occurs first: i) approximately 1 year after the first subject successfully completes the Follow Up 1 assessment; or ii) when 28 subjects have successfully completed the Follow Up 1 assessments.
Headline Analysis	• Selected efficacy outputs will be produced once all subjects' BAC FEV_1 at Follow-Up 1 are available. The results will be produced on unblinded data and produced before DBF for the purposes of internal decision making. Ultimately, the headline results will be superseded by final end of study results produced after DBF.

2.4 Statistical Hypotheses

No formal hypotheses will be tested. The primary study objective will assess the effect of a weekly dose of 20 ng GSK2245035 vs Placebo by precision estimation and credible intervals to estimate the magnitude of underlying effect sizes. A Bayesian approach will be utilised to obtain the posterior distribution for the underlying treatment effects for the endpoints in the study (e.g. posterior distributions of percentage attenuation for the endpoint LAR: minimum FEV_1 between 4-10 hours following allergen challenge one week after treatment.).

Other objectives will assess other pharmacodynamic effects and safety and tolerability of GSK2245035.

3 PLANNED ANALYSES

3.1 Interim Analyses

The interim analyses will be undertaken by the study statistician (or designate) and the boards/personnel who may be privy to this data are:

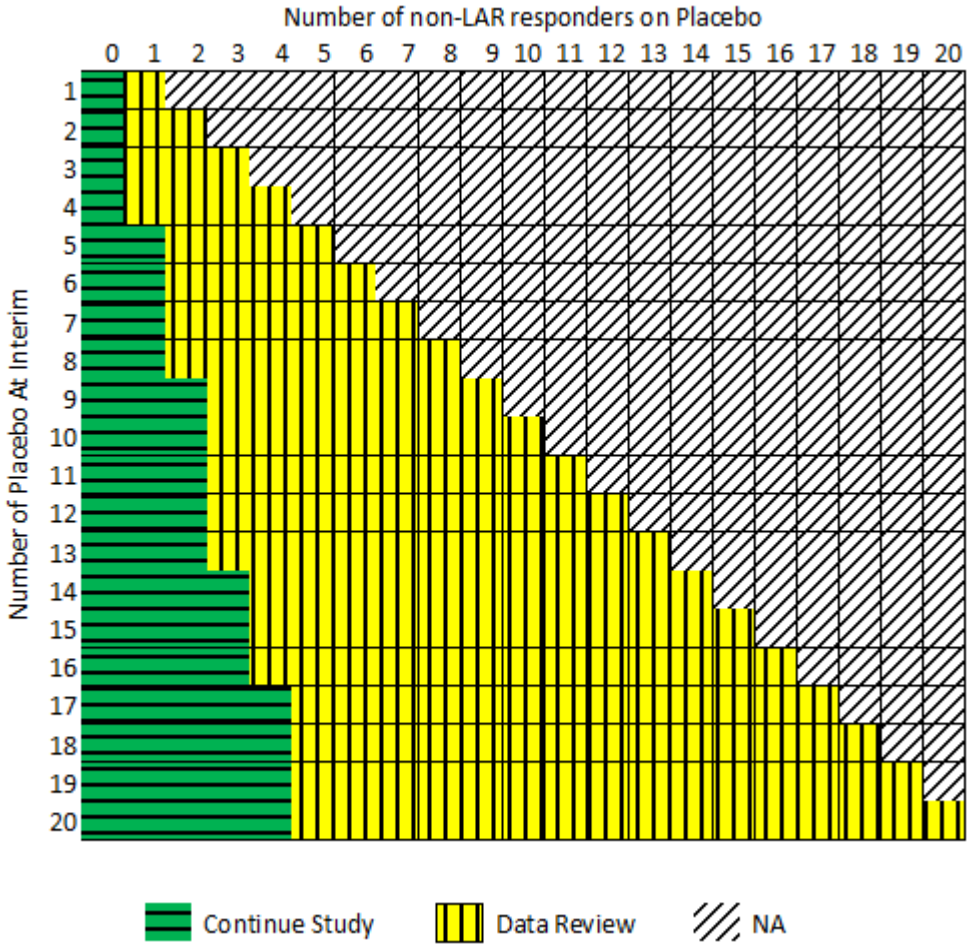
- key members of the Study Team including Medical Monitor, Clinical Operations Representative, Study Statistician(s), Study Programmer(s)

The appropriate internal GSK procedures will be followed to ensure that access to unblinded subject level data is restricted to the specific study team members who require access e.g. storing of data and related outputs in a secure, restricted directory area. Only subjects contributing data towards the interim analysis will have their treatment codes unblinded.

Recruitment into the study will continue whilst the interim analysis is taking place.

The interim analysis will require knowledge of which subjects are in the Placebo arm and determine how many of those Placebo subjects failed to meet the screening inclusion criteria for LAR in their follow up 1 visit (i.e. did not show three FEV_1 decreases of $\geq$ 15 % relative to saline baseline between 4 and 10 hours, with two FEV_1 decreases being at consecutive time points). The number of subjects on placebo who do not exhibit an LAR (non-LAR responders) will be determined from the available interim data (using the All Subjects population at the time of Interim Analysis 1 (IA1)). This number will be checked against Table 1 to advise whether the study should continue or whether further review of the interim analysis data is required to assess the impact. For example, if at the time the interim analysis occurs 10 subjects were on Placebo and 4 of those 10 did not demonstrate an LAR response then the interim analysis would recommend reviewing the data further.

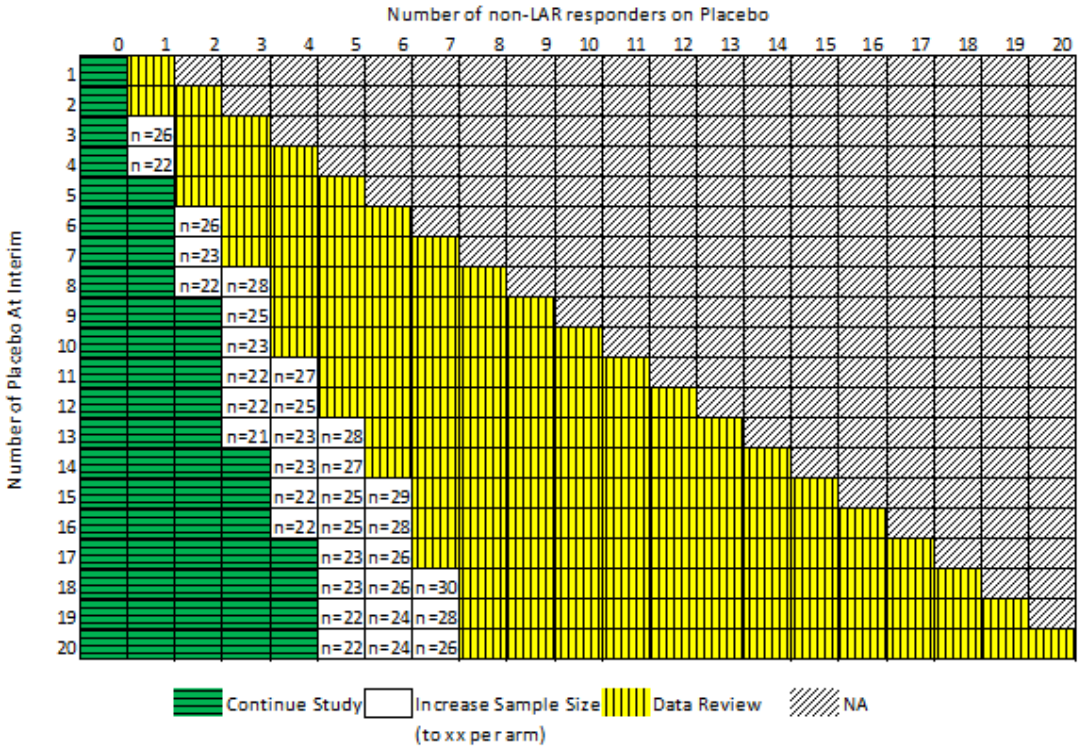
Table 1 Lookup table for Interim Analysis Decision Pathway



Assessing impact of non-LAR response rate:

To evaluate whether recruiting additional subjects may counteract the impact of the non-LAR responders alternative version(s) of Table 1 were constructed using the same methodology, but using final sample sizes that range from 20 to 30 subjects per arm. At each cell, if the probability of success was within 10% of the original operating characteristic for that endpoint (i.e. the characteristics derived under the assumption of zero non-LAR responders) the study would continue; but requiring additional subjects (the smallest number that satisfied the continuation criteria). These additional tables have been compressed into Table 2, which shows the smallest number of subjects (per arm) required to continue the study (if the continuation criteria were still not met with 30 subjects per arm the cell is flagged as recommending further data review).

Table 2 Lookup Table for Interim decision and revised sample sizes (per arm)



Additional analyses / outputs to support the interim analysis decision making

Equivalent versions of the planned summary statistics and figures supporting the primary endpoint/analyses.

Posterior distributions for the percentage attenuation of the primary endpoints (WM and Minimum LAR at FUV1) by GSK2245035 would be constructed from the available interim data using the same methodology as for the planned final analysis; except that a simplifying assumption will be used and terms relating to allergen exposure in the model will be excluded; since there may not be enough information in each strata at the time of the interim to facilitate their estimation (see Section 7 for details of the planned Primary analysis).

Non-binding *"Rule of thumb"* for amending protocol/termination of further enrolment (existing subjects would complete the study as planned)

If either the recommendation of Table 1 and/or Table 2 is for further data review OR the model obtained medians (point estimates) for the observed treatment effects are dramatically different to the assumed effects from the AstraZeneca (AZ) study (27% attenuation for WM LAR and 18% attenuation for Minimum LAR) (Leaker, 2012), the study team may wish to predict the probability of success at the end of the study for each endpoint, using the interim information as a basis for the projection. In the event that this probability of success is low (relative to the ~80% operating characteristic from the protocol) the study team may decide to review any of the other available data items at the interim prior to amending the protocol/terminating further enrolment (and share these outputs with appropriate internal GSK governance boards/senior management). Examples

of outputs might include the biomarkers of TLR7 target engagement and/or downstream allergic reactivity changes.

Technical details for predicting the end of study success using the interim data

For each treatment arm the (joint) posterior predictive distribution of an individual subject's primary endpoints will be obtained (separate Variance Covariance (VCV) matrices for each treatment arm are preferred to cover the case where variability is also a function of treatment; but there may not be sufficient information in the interim dataset to estimate the required parameters, in which case a pooled VCV matrix across treatment arms would be acceptable). The predictive distributions will be used to simulate a sufficient number of future subjects to achieve the end of study sample size (planned to be 20 per arm, but may be revised upwards to a value between 21 and 30 per arm depending on the observed placebo non-LAR responder rates). Summary statistics (sample mean and sample variance covariance matrix) will be derived using each set of simulated subjects for each treatment. These summary statistics are used as informative prior distributions for the treatment parameters in models fitted to the observed interim data (with the simplifying assumption that these models exclude allergen exposure covariate(s)). If the resulting posterior probability of any attenuation exceeds 0.7 (for either endpoint) the hypothetical end of study result is a success. By repeating the process of simulating sets of future subjects (10,000 times); producing informative priors for the treatment parameters from those simulated subjects and combining with the (unchanging) observed interim dataset in a model to evaluate individual study success an expected probability of a successful outcome can be obtained if the study were allowed to continue past the interim (i.e. the number of simulated sets flagged as successful / total number of simulated sets of subjects).

The advantage of utilising posterior predictive distributions is that they also account for the uncertainty in the true values of the parameters (caused by having to estimate them using only the interim data). Note: Each simulated subject can be thought of as being generated using the average of each of the covariate values. Therefore sample statistics are used as priors for the treatment related parameters only in the subsequent modelling step. This avoids having to generate covariate values for the simulated subjects (e.g. assign them to a centre, or generate a baseline response for them).

Further details are given below:

Interim Analyses to estimate end of study success

Step 1: Obtain posterior predictive distribution for a future subject (separate distribution for each treatment arm)

- The endpoints (transformed if necessary) will be assumed to follow a multivariate normal (MVN) distribution. Linear predictors will be derived for each subject (i.e. a vector of means for the MVN distribution). Each treatment arm will also have a separate variance covariance matrix, i.e.

  To link to observed data assume : $\begin{bmatrix} WM & Min \\ y_1 & y_2 \end{bmatrix}_i \overset{MVN}{\sim} \left(\begin{bmatrix} WM & Min \\ \hat{y}_1 & \hat{y}_2 \end{bmatrix}_i, [\Sigma_{<Trt\,b>}] \right)$ where Σ_{Pbo} & Σ

  - are separate 2x2 Variance Covariance matrices for each treatment arm

  and $\begin{bmatrix} WM & Min \\ \hat{y}_1 & \hat{y}_2 \end{bmatrix}$ represents the linear predictor for the ith subject for the two endpoints

  The linear predictors will consist of mean vectors to capture i) the effect of treatment for each endpoint, ii) a continuous baseline for each endpoint and iii) a random centre effect for each endpoint (drawn from Normal(0, $SD_{endpoint\ <x>}$) distribution).
- Baseline vectors will be fitted as continuous covariates (baseline values should be centered prior to inclusion in the model, centering to occur after any transformation of the individual subjects responses).
- Non-informative priors will be utilized for each model parameter assigned either as a normal distribution centered on 0 with large variance 1E6 or as appropriate to the parameters distribution.
- The prior for the variance covariance matrices Σ_{Pbo} and Σ_{Act} will be an inverse Wishart distribution.
- SAS PROC MCMC will be used to combine the non-informative priors with the observed interim data to obtain sufficient draws from the posterior distribution (after any thinning) such that the MCSE/SD values for parameters of interest are less than 0.01 (anticipated to be in the region of ~100,000 draws). If model convergence is poor then alternative initial parameter values should be considered. Note: A SAS coding trick may be required if the MCMC procedure does not automatically detect the conjugacy (occurs in SAS v9.3 when fitting separate variance covariance structures to treatments in a multivariate normal distribution and may occur in SAS v9.4 as well). The trick involves setting up duplicate sets of variables in the input dataset with some populated as missing values and having 2x model statements (see GSK study statistician for details if required).
- The randomization seed used in PROC MCMC should itself be generated with an element of randomness - but there is no need to formally document this process (e.g. using Excel function RANDBETWEEN [1,9999999] and copying the result into the SAS code)
- The following describes the anticipated linear predictor for a hypothetical subject from center 3 (out of 5), on active treatment with centered baseline values of -4.1 and -0.5 for BS1 (*WM*) and BS2 (*Min*) respectively (Note: although not anticipated additional covariates may be explored and added based on the observed data).

Interim Analyses to estimate end of study success

$$\begin{bmatrix} \hat{y}_1^{WM} & \hat{y}_2^{Min} \end{bmatrix} = \begin{bmatrix} -4.1 & -0.5 \end{bmatrix} \begin{bmatrix} \hat{BS1}_{WM} & 0 \\ 0 & \hat{BS2}_{Min} \end{bmatrix} +$$

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

$$I(Placebo) * \begin{bmatrix} \hat{\mu}_{P,WM} & \hat{\mu}_{P,Min} \end{bmatrix} +$$

$$I(Active) * \begin{bmatrix} \hat{\mu}_{A,WM} & \hat{\mu}_{A,Min} \end{bmatrix} +$$

Where

$I(\bullet)$ is an Indicator function with value 1 if condition met and zero otherwise

[Here I(Placebo) = 0, I(Active) = 1,

$I(C_3) = 1$ and $I(C_1), I(C_2), I(C_4)$ & $I(C_5) = 0$]

$Centre_{i,WM} \overset{i.i.d}{\sim} N\left(0, \hat{SD}_{CentreWM}\right)$ and

- $Centre_{i,Min} \overset{i.i.d}{\sim} N\left(0, \hat{SD}_{CentreMin}\right)$
- Each MCMC iteration will produce values for model parameters $\begin{bmatrix} \hat{\mu}_{P,WM} & \hat{\mu}_{P,Min} \end{bmatrix}$, $\begin{bmatrix} \hat{\mu}_{A,WM} & \hat{\mu}_{A,Min} \end{bmatrix}$ and each of the elements within the Σ_{Pbo} and Σ_{Act} variance covariance matrices.
- For each MCMC iteration sufficient placebo and active future subjects data will be drawn from the following multivariate normal distributions (denoting the number of remaining subjects to be $Nrem_{Pbo}$ and $Nrem_{Act}$):
- Placebo: $\begin{bmatrix} y_1^{WM} & y_2^{Min} \end{bmatrix}_{fut,Pbo} \overset{i.i.d.\ MVN}{\sim} \left(\begin{bmatrix} \hat{\mu}_{P,WM} & \hat{\mu}_{P,Min} \end{bmatrix}, \begin{bmatrix} \Sigma_{Pbo} \end{bmatrix}\right)$
- Active: $\begin{bmatrix} y_1^{WM} & y_2^{Min} \end{bmatrix}_{fut,Act} \overset{i.i.d.\ MVN}{\sim} \left(\begin{bmatrix} \hat{\mu}_{A,WM} & \hat{\mu}_{A,Min} \end{bmatrix}, \begin{bmatrix} \Sigma_{Act} \end{bmatrix}\right)$

Step 2: Compute Sample Statistics and obtain Priors for each treatment arm

- The sample mean and sample variance covariance matrices will be derived for each treatment arm using the corresponding set of $Nrem_{Pbo}$ and $Nrem_{Act}$ subjects (and keeping the association with each MCMC iteration)
- Placebo: $\text{Sample Mean Vector}\begin{bmatrix} \bar{x}_1^{WM} & \bar{x}_2^{Min} \end{bmatrix}_{Pbo}$ $\text{Sample VCV}\begin{bmatrix} S^2_{\text{WM}} & S_{WM}S_{Min} \\ S_{WM}S_{Min} & S^2_{\text{Min}} \end{bmatrix}_{Pbo}$
- Active: $\text{Sample Mean Vector}\begin{bmatrix} \bar{x}_1^{WM} & \bar{x}_2^{Min} \end{bmatrix}_{Act}$ $\text{Sample VCV}\begin{bmatrix} S^2_{\text{WM}} & S_{WM}S_{Min} \\ S_{WM}S_{Min} & S^2_{\text{Min}} \end{bmatrix}_{Act}$

Interim Analyses to estimate end of study success

- In the statistical model fitted to the WM endpoint the priors are:

$$\hat{\mu}_{P,WM} \sim N\left(\bar{x}^{WM}_{1,Pbo}, \frac{S^2_{WM,Pbo}}{Nrem_{Pbo}}\right) \quad \hat{\mu}_{A,WM} \sim N\left(\bar{x}^{WM}_{1,Act}, \frac{S^2_{WM,Act}}{Nrem_{Act}}\right),$$

- In the statistical model fitted to the Min endpoint the priors are

$$\hat{\mu}_{P,Min} \sim N\left(\bar{x}^{Min}_{2,Pbo}, \frac{S^2_{Min,Pbo}}{Nrem_{Pbo}}\right) \quad \hat{\mu}_{A,Min} \sim N\left(\bar{x}^{Min}_{2,Act}, \frac{S^2_{Min,Act}}{Nrem_{Act}}\right),$$

Step 3: Fit model and flag success or failure

- To facilitate easy use of the prior distributions a re-parameterized version of Primary analysis Model M3 can be used (Intercept term removed and the zero constraint on the 2nd treatment level removed).
- Separate models will be fitted to each of the endpoints (WM and Min)
- If the posterior probability that $\hat{\mu}_P < \hat{\mu}_A$ exceeds 0.7 (using the informative prior from the ith MCMC iteration) then the ith MCMC iteration is flagged as resulting in a successful end of study result.
- The overall probability of success is the number of successful MCMC iterations / total number of MCMC iterations

Technical details for deriving the individual tables contributing to Table 2

To determine the probability of success in the presence of non-LAR responders simulations were performed for each possible combination of number of available placebo subjects (n) and number showing no LAR response (r) using the AZ point estimates as the true percentage attenuation (separate procedure for each of the primary endpoints):

Let K represent the number of subjects per arm to be evaluated with each value of K producing a different table and K ranging from 21 to 30 by 1.

The rate of non-LAR response (p) is assumed to be the same for Placebo and GSK2245035 arms. A Beta(0.1, 0.1) prior distribution is assumed for the rate, which is updated using conjugate formulae as Beta(0.1 + r, 0.1 + n – r) and a value sampled from this posterior distribution. The number of future subjects on placebo with a non-LAR response is sampled from a Binomial distribution using the sampled value of p and (K – n) observations (the total is a mixture of observed interim data and this sampled value). Similarly the number of non-LAR responders on the GSK2245035 arm is sampled from a Binomial distribution with the same value of p and K observations. Each non-responding individual is assigned a constant value for the response, and the collection of non-responders are combined with the collection of LAR responders (values for the LAR responders are generated in a similar way to the subjects used in the operating characteristics, as described in the protocol, i.e. using the random effects meta-analysis to obtain the expected responses). The probability of success is determined for each of the combined datasets and the median derived. If this median was more than 10% smaller than the original operating characteristic the recommendation is to further review the data. The recommendations from the two primary endpoints will be determined

separately but combined into a single table. Wherever there is disagreement between cells across endpoints the review data decision is chosen.

Table 2 is obtained by examining each cell entry one at a time over all of the additional tables and taking the smallest value of K associated with a non-data review outcome.

Sensitivity analyses showed the outcome of this approach is highly dependent on the value of the constant used for the non-LAR responses (the further the choice from the range of plausible values for LAR responders the more likely the recommendation was to review data). As before, the choice of value is arbitrary in nature, but the same value as used in the protocol planning stage was selected; namely -0.45 for Minimum Change from Saline and -0.20 for Weighted Mean Minimum Change from Saline, based upon applying the LAR criteria to seven historical studies and deriving the mean responses of all non-LAR responding subjects.

See Section 11.13 for details of the outputs to be produced at the Interim analysis.

3.2 Headline Analyses Prior to Database Freeze (DBF)

The following is conditional on the study not being stopped early by the interim analysis. To facilitate internal GSK decision making a data snapshot will be taken when the last subject's BAC FEV_1 data (and derived LAR endpoints) from FUV1 are available. The associated planned efficacy outputs (see Section 11.13.4-Section 11.13.16) will be produced from that (unblinded) snapshot and shared internally with the GSK study team and internal GSK governance boards/senior management. As this data snapshot will be pre-DBF its results will not be formally reported as they will be superseded by the formal end of study results. A separate reporting effort for the headline analyses will be created in the HARP system.

3.3 Safety Review Team (SRT)

Safety Review Team meetings are planned for this study as per GSKs standard pharmacovigilance policies. The SRT is expected to meet on a regular basis to review ongoing safety data, usually via TSCG (Spotfire) and standard TFLs. The SRT meetings are beyond the scope of this RAP and will be documented separately as part of their operating processes.

3.4 Final Analyses

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

1. All subjects have completed the study as defined in the protocol i.e., once all subjects have completed the last follow-up visit or lost to follow-up.
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 (remaining) randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

4 ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprise of all subjects who were screened for inclusion into the study and have any value databased in the eCRF.	• Study Population
Enrolled[1]	• Comprise of all subjects who were enrolled ie, randomised to study treatment. • Only required for 'Summary of Age Ranges' data display; necessary for disclosure purposes to EudraCT and FDAAA.	• Demographics
All Subjects	• Comprise of all subjects who receive at least one dose of study treatment. • This population will be based on the treatment the subject actually received.	• Study Population • Safety • Biomarkers
Run in failures	• Comprise of all subjects who were assigned a randomisation number (even if it was assigned in error) but did not receive any doses of study treatment	• Study Population
Modified Intent-To-Treat (mITT)	• Comprise of all randomised subjects who receive at least one dose of study treatment and commence a BAC at follow-up. • This population will be based on the treatment the subject received. • Any subject who receives a treatment randomisation number will be considered to have been randomised.	• Efficacy
Per-Protocol (PP)	• Comprise of all mITT subjects who comply with the protocol. • Protocol deviations that would exclude subjects from the PP population are defined in Section 4.1 (Protocol Deviations) and Appendix 1 (Protocol Deviation Management and Definition for Per-Protocol Population).	• Efficacy
Pharmacokinetic (PK)	• Subjects in the 'All Subjects' Population for whom a pharmacokinetic sample is obtained and analysed.	• Pharmacokinetic
Sputum Producers (Sputum)	• Subjects in the 'All Subjects' Population for whom a viable pre- or post-challenge sputum sample is obtained (at Screening).	• Sputum Biomarkers
Interim Analysis (IA1)	• Subjects contributing data points used in an Interim analysis (Note: The planned headline analysis is not counted as an interim analysis)	• Study Population

Population	Definition / Criteria	Analyses Evaluated
	• If more than one interim analysis occurs then a separate population will be created for each subsequent interim, using sequential names (e.g. IA2, IA3, etc)	

NOTES :

- Please refer to Appendix 13: List of Data Displays which details the population to be used for each display being generated.

1. If the 'All Subjects' Population contains the same subjects as 'Enrolled' Population, the 'Enrolled' Population will be dropped and 'All Subjects' used instead.

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 Per Protocol Population).
- Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan.
    - Data will be reviewed prior to 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/listing will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5 CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Table 3 provides an overview of appendices within the RAP for outlining general considerations for data analyses and data handling conventions.

Table 3 Overview of Appendices

Section	Component
11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
11.2	Appendix 2: Assessment Windows
11.3	Appendix 3: Treatment States and Phases
11.4	Appendix 4: Data Display Standards & Handling Conventions
11.5	Appendix 5: Derived and Transformed Data
11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data
11.7	Appendix 7: Values of Potential Clinical Importance
11.8	Appendix 8: Multicentre Studies
11.9	Appendix 9: Examination of Covariates, Subgroups & Other Strata
11.10	Appendix 10: Multiple Comparisons & Multiplicity
11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
11.12	Appendix 12: Abbreviations and Trade Marks
11.13	Appendix 13: List of Data Displays

6 STUDY POPULATION ANALYSES

6.1 Overview of Planned Analyses

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

Table 4 provides an overview of the planned study population analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 4 Overview of Planned Study Population Analyses

Endpoint / Parameter / Display Type	Data Displays Generated		
	Table	Figure	Listing
Subject Disposition			
Subject Disposition	Y		
Screening Status and Reasons for Screen Failure	Y		Y
Subjects by Country and Centre	Y		
Subjects by Country and Centre and Allergen Exposure Strata	Y		
Reasons for Subject Withdrawal			Y
Subjects for Whom the Treatment Blind was Broken			Y
Planned and Actual Treatments			Y
Protocol Deviations			
Important Protocol Deviations	Y		Y[1]
Subjects with Inclusion/Exclusion Criteria Deviations			Y
Populations Analysed			
Study Populations and Exclusions	Y		
Subjects Excluded from Any Population			Y
Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
Summary of Age Ranges	Y		
Race and Racial Combinations	Y		Y[2]
Skin Prick Test at Screening	Y		Y
Medical Conditions and Prior and Concomitant Medications			
Current/Past Medical Conditions	Y		Y
Concomitant Medications	Y		Y
Exposure and Treatment Compliance			
Exposure to Study Treatment			Y

NOTES :

- Y = Yes display generated.

[1] Listing also includes analysis population exclusions.
[2] Listing of race.

7 PRIMARY STATISTICAL ANALYSES

7.1 Efficacy Analyses

7.1.1 Overview of Planned Efficacy Analyses

The primary efficacy analyses will be based on the PP population, unless otherwise specified. As a potential sensitivity analysis the final primary analysis model structure (derived using the PP population) may also be run using the mITT population (conditional on the PP and mITT populations differing).

Table 5 provides an overview of the planned efficacy analyses, with full details of data displays being presented in Appendix 13: List of Data Displays.

Table 5 Overview of Planned Efficacy Analyses

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
LAR							
Min and WM FEV_1 absolute change from saline at Week 9 (FUV1)	Y	Y	Y	Y	Y	Y	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

7.1.2 Planned Efficacy Statistical Analyses

Primary Statistical Analyses

Endpoint(s)

- LAR: minimum <change from saline baseline> FEV_1 between 4-10 hours following allergen challenge 1 week after treatment i.e. FUV1.
- LAR: weighted mean of <change from saline baseline> FEV_1 between 4-10 hours following allergen challenge 1 week after treatment i.e. FUV1.
  Note: Text in <> added for clarity, since the wording in the protocol and objectives is familiar to clinical experts in the field, but may be confusing given there are also absolute FEV1 values measured at those times too.
- The "raw" data (replicate (absolute) FEV1 values transcribed into the eCRF) require processing before the Primary analysis. Each planned timepoint may be associated with replicate FEV1 values, which need to be condensed down into a single value (giving a single FEV1 value per timepoint per subject; the timepoints determine how the data are condensed, i.e. some timepoints use the minimum of the replicates others use the maximum). In addition the Screening Visit 2 Incremental BAC challenge may also contain additional FEV1 values relating to the selection procedure for the bolus BAC concentration. Such FEV1 values are not used in the statistical analyses (subjects may differ in the amounts of additional FEV1 data to be excluded). Once the single time profile of absolute FEV1 values is available per subject the Saline baseline is subtracted from each to leave a time profile of change from saline baseline FEV1 values. The minimum and weighted means endpoints are derived from this change from saline baseline time profile. Further details are given in Section 11.5.4.
- Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics
- Any observations with missing model covariates (e.g. baseline) would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates)

Model Specification

- Each endpoint will be analysed separately using a Bayesian Mixed effects model fitted within Proc MCMC in SAS using the following approach:
- Assume equal variances across treatment arms and use a pooled estimate of residual variability (Note: if the posterior predictive distributions produced to support the interim analysis suggest this assumption may be invalid then the modelling approach may be modified to estimate separate variance terms for each treatment arm).
- Step 1: Fit all three of the following models (report output from each model in the same listing – along with the DIC values and changes in DIC values between models). Using a combination of changes in the DIC criteria, **and expert judgment** (see Section 11.9.1), select a single model.
- M1: Intercept + Centre + Treatment + Allergen Exposure + Treatment*Allergen Exposure + Baseline
- M2: Intercept + Centre + Treatment + Allergen Exposure + Baseline
- M3: Intercept + Centre + Treatment + Baseline
- See Section 11.4.2 for Baseline definitions (Screening visit 2 BAC endpoint).

Primary Statistical Analyses

Where in each of the models (M1, M2 and M3) the effects are:

Type	Name (#Levels)	Parameters	Prior(s)
Fixed Categorical	Intercept (1)	#1 Intercept	N (0, Var=1E6)
	Treatment (2)	#1 Placebo	N (0, Var=1E6)
		#2 20ng	n/a (constraint = 0)
	Allergen Exposure (2)	#1 Presumed	N (0, Var=1E6)
		#2 Unknown	n/a (constraint = 0)
	Treatment * Allergen Exposure (4)	#1 Pbo*P	N (0, Var=1E6)
		#2 Pbo*U	n/a (constraint = 0)
		#3 20ng*P	n/a (constraint = 0)
		#4 20ng*U	n/a (constraint = 0)
Fixed Continuous*	Baseline	Baseline slope	N(0, Var=1E6)
Random	Centre (planned 6 centres)	Separate value per contributing centre sampled as i.i.d ~ N(0, σ^2_{Centre})	σ^2_{Centre} ~Gamma(Shape=0.048, Scale=0.830) Weakly informative prior based on 6x in-house GSK datasets – same prior for both endpointsΔ

*=Centre covariates prior to fitting model (do not use observations that will not contribute to the planned model when centering) and if applicable the centering is to occur after any transformations have been applied

Δ=If chain is not mixing (i.e. sticking at values close to zero) an additional mixture prior may be considered to act as a lower boundary constraint, or the centre term excluded from the model.

- Step 2 (optional): Explore adding other covariate terms to the Step 1 model (for example, but not limited to, Age, Gender, Dose per kg, Blood eosinophil levels). Use expert judgment and changes in DIC to determine final model to take to Step 3. Include any Step 2 models in the listing output and add the associated DIC / changes in DIC values to those produced in Step 1.
- Step 3: For the finally selected model use appropriate combinations of the model parameters (back transforming the combination if necessary) to obtain posterior distributions for the quantities of interest described in the Model Results Presentation. Binary flag variables can be used to evaluate the probability statements, by tracking the instances of the desired event happening over each MCMC iteration and taking the mean of the flag variable as the probability.

  For example, if Model 3 is selected then the posterior distribution for the Placebo can be

Primary Statistical Analyses

obtained from adding model parameters Intercept + Treatment[#1] Note: The baseline term is centered and drops out of the expression since it is evaluated at its centered mean of zero; similarly the random centre effect also has mean zero.

The treatment difference (Active – Placebo) would be –Treatment[#1] because the Treatment[#2] parameter is constrained to be zero and the other model terms cancel out.

The Percentage attenuation would be 100 * (1 – (Intercept / (Intercept + Treatment[#1])))

The SAS syntax for setting up indicator flags to obtain the probability of any percentage attenuation is Myflag = (pctann > 0); where pctann is the variable storing the Percentage attenuation.

Programming technical note(s): i) Use of flag variables may result in several error/warning messages in the SAS log (for example, but not limited to, warnings about large autocorrelation and/or zero variance); which should be reviewed but may be safely discounted – if in doubt consult the study statistician. ii) To facilitate summary outputs where results from multiple models are displayed simultaneously (large) intermediate datasets from Proc MCMC may need to be stored to ensure consistency (i.e. no differences due to simulation error between model re-runs). Suitable naming conventions should be used to label these files which group related items together.

- The randomization seed used in PROC MCMC should itself be generated with an element of randomness - but there is no need to formally document this process (e.g. using Excel function RANDBETWEEN [1,9999999] and copying the result into the SAS code)
- In addition posterior probabilities relating to differences and/or percentage attenuations for other cut-points (which may be determined upon inspection of the data, or from developing business requirements), may also be produced.

Model Checking & Diagnostics

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.

Model Results Presentation

- Point estimates (median values of the posterior distributions), the standard deviation of the posterior distribution (SDs) and 95% & 70% equi-tailed credible intervals will be presented for each treatment together with estimated treatment differences relative to Placebo and their corresponding 95% and 70% credible intervals. The treatment differences will also be expressed as percentage attenuations relative to Placebo (and posterior distribution of the percentage attenuation obtained). The posterior probability of any treatment reduction (any percentage attenuation) will also be displayed, along with the posterior probability of the percentage attenuation exceeding the corresponding AZ point estimate (27% attenuation for WM LAR and 18% attenuation for Minimum LAR) (Leaker, 2012).
- Plots of the point estimates for the treatment effects (median values of the corresponding posterior distributions) and 95% & 70% credible intervals from the model will be generated for each treatment. Additionally, plots of differences and 95% & 70% credible intervals for the comparison of GSK2245035 vs Placebo may be generated (for the absolute difference and percent attenuation representations).
- Note: In the event that Model M1 is selected as final (or the final model includes an interaction

Primary Statistical Analyses

term involving treatment and another fixed categorical covariate) the outputs should be adjusted accordingly to present treatment comparisons within each level of the covariate. If the interaction term involving treatment is with a continuous covariate the mean value of the covariate should be used and the outputs clearly labeled that the prediction is made at the specified covariate value.

Sensitivity and Supportive Statistical Analyses

- A scatterplot of each subject's two derived primary endpoints (each endpoint is an axis) – with appropriate identification of subjects belonging to the four distinct treatment & allergen exposure combinations. Include i) the (overall) Pearson correlation coefficient and optionally ii) corresponding density estimates for each combination and axis as plot margin panels
- As an informal check the weakly informative prior on the variance component of the centre effect may be replaced by a non-informative prior and the treatment estimates compared, provided both models converge, to confirm the prior is not more informative than was intended (outputs from this check do not need to be formally reported)
- Informative priors based on AZ published data/effect sizes may be explored for the treatment terms. Priors that need to be modified in models M1, M2 and M3 are indicated below (Priors for WM LAR endpoint only, and analysis would only be required for PP population):

Type	Name (#Levels)	Parameters	Prior(s)
Fixed Categorical	Intercept (1)	#1 Intercept	N (-0.7081, Var=0.4472^2 / 26)
	Treatment (2)	#1 Placebo	N (-0.2619, Var=0.4472^2 * (1/25 – 1/26))
		#2 20ng	n/a (constraint = 0)

- A sensitivity analysis applying the final model to the mITT population may be performed
- Exploration of the relationship between treatment effect sizes and (potential) sub-populations based on eosinophil levels in blood: A model building exercise would take place using a similar strategy as that used to explore the importance of allergen exposure status. However, the base model will start with the simplifying assumption that allergen exposure is not necessary (i.e. use the M3 form of model). The base model will be compared to the fit of a model containing an additional term for the (log transformed if necessary and centered) absolute blood eosinophil from the Baseline visit (SV2, fitted as a continuous covariate). This is similar to model form M2 but with the continuous covariate taking the place of the allergen exposure term. Additionally the benefit of adding a term for the interaction between treatment and this continuous covariate will be explored (similar to the M1 form). If any model terms involving blood eosinophils are included in the model it will be used to predict the mean response for each treatment arm using the following blood eosinophil levels (values presented here may require transformation so they are incorporated into the model prediction on the appropriate scale): 100 cells/mL and 200 cells/mL. Also the treatment difference at each of those eosinophil levels should be evaluated. Non-informative priors would be used for the parameters representing these additional term(s). To produce the descriptive summary tables the blood eosinophil variable will be grouped and summarized by the categories described in Section 11.9.1. Note: If data permit the allergen exposure status may also be added to the model (although there may not be sufficient subjects to estimate the required number of model

Primary Statistical Analyses
parameters; especially when trying to estimate the multi-way interactions involving treatment, allergen exposure and eosinophil levels).

8 SECONDARY STATISTICAL ANALYSES

8.1 Efficacy Analyses

8.1.1 Overview of Planned Efficacy Analyses

The secondary (and exploratory) efficacy analyses presented in this section will be based on the PP population, unless otherwise specified (the exception being the repeated measures version of the primary efficacy endpoint analysis which will also be run using the mITT population (conditional on the PP and mITT populations differing)). Note: For ease of review the exploratory repeated measures analyses for LAR and EAR endpoints are also described in this section.

Table 6 provides an overview of the planned efficacy analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 6 Overview of Planned Efficacy Analyses

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
LAR							
Min and WM FEV_1 absolute change from saline from FUV1, FUV2 and FUV3 visits (Repeated measures)	Y	Y	Y	Y	Y	Y	Y
EAR							
Min and WM FEV_1 absolute change from saline at Week 9 (FUV1)	Y	Y	Y	Y	Y	Y	Y
Min and WM FEV_1 absolute change from saline from FUV1, FUV2 and FUV3 visits (Repeated measures)	Y	Y	Y	Y	Y	Y	Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.1.2 Planned Efficacy Statistical Analyses

Secondary Statistical Analyses: EAR at FUV1
Endpoint(s)
• EAR: minimum <change from saline baseline> FEV_1 between 0-2 hours following allergen challenge 1 week after treatment i.e. FUV1 • EAR: weighted mean of <change from saline baseline> FEV_1 between 0-2 hours following allergen challenge 1 week after treatment i.e. FUV1. • Note: Text in <> added for clarity, since the wording in the protocol and objectives is familiar to clinical experts in the field, but may be confusing given there are also absolute FEV1 values measured at those times too.
Model Specification
• as per Primary Statistical Analysis (see Section 7.1.2).
Model Checking & Diagnostics
• as per Primary Statistical Analysis (see Section 7.1.2).
Model Results Presentation
• as per Primary Statistical Analysis (see Section 7.1.2).
Sensitivity and Supportive Statistical Analyses
• Scatterplots to investigate correlation between endpoints as per Primary Statistical Analysis (see Section 7.1.2). • As an informal check the weakly informative prior on the variance component of the centre effect may be replaced by a non-informative prior and the treatment estimates compared, provided both models converge, to confirm the prior is not more informative than was intended (outputs from this check do not need to be formally reported) • Sensitivity analyses exploring blood eosinophil levels as a covariate (see Section 7.1.2).

Exploratory Statistical Analyses: Repeated measures version LAR Primary analysis model
Endpoint(s)
• LAR: minimum <change from saline baseline> FEV_1 between 4-10 hours following allergen challenge at the three follow up visits (i.e. FUV1, FUV2 and FUV3). • LAR: weighted mean of <change from saline baseline> FEV_1 between 4-10 hours following allergen challenge at the three follow up visits (i.e. FUV1, FUV2 and FUV3). • Note: Text in <> added for clarity, since the wording in the protocol and objectives is familiar to clinical experts in the field, but may be confusing given there are also absolute FEV1 values measured at those times too. • Any transformation of a response variable is also expected to be applied to the corresponding baseline variable. Final decisions on transformations will be based on the observed data and model diagnostics • Any observations with missing model covariates (e.g. baseline) would be excluded from the model fitting process (i.e. also excluding the record from any centering of covariates)
Model Specification
• Each endpoint will be analysed separately using a Bayesian Mixed effects repeated measures model fitted within Proc MCMC in SAS using the following approach: • Assume equal variances across treatment arms and use a pooled estimate of residual

Exploratory Statistical Analyses: Repeated measures version LAR Primary analysis model

variability (i.e. a 3x3 Variance Covariance Matrix). Note: if the posterior predictive distributions produced to support the interim analysis suggest this assumption may be invalid then the modelling approach may be modified to estimate separate variance covariance matrices for each treatment arm.

- Step 1: Fit all three of the following models (report output from each model in the same listing – along with the DIC values and changes in DIC values between models). Using a combination of changes in the DIC criteria, **and expert judgment** (see Section 11.9.1), select a single model.
- R1: Intercept + Centre + Baseline*Visit + Treatment + Visit + Allergen Exposure + Treatment*Visit + Allergen Exposure*Visit + Treatment*Allergen Exposure + Treatment*Allergen Exposure*Visit
- R2: Intercept + Centre + Baseline*Visit + Treatment + Visit + Allergen Exposure + Treatment*Visit + Allergen Exposure*Visit
- R3: Intercept + Centre + Baseline*Visit + Treatment + Visit + Treatment*Visit
- See Section 11.4.2 for Baseline definitions (Screening visit 2 BAC endpoint).

Where in each of the models (R1, R2 and R3) the effects are:

Type	Name (#Levels)	Parameters	Prior(s)
Fixed Categorical	Intercept (1)	#1 Intercept	N (0, Var=1E6)
	Treatment (2)	#1 Placebo	N (0, Var=1E6)
		#2 20ng	n/a (constraint = 0)
	Allergen Exposure (2)	#1 Presumed	N (0, Var=1E6)
		#2 Unknown	n/a (constraint = 0)
	Visit (3)	#1 FUV1	N (0, Var=1E6)
		#2 FUV2	N (0, Var=1E6)
		#3 FUV3	n/a (constraint = 0)
	Treatment * Allergen Exposure (4)	#1 Pbo*P	N (0, Var=1E6)
		#2 Pbo*U	n/a (constraint = 0)
		#3 20ng*P	n/a (constraint = 0)
		#4 20ng*U	n/a (constraint = 0)
	Allergen Exposure * Visit (6)	#1 P*FUV1	N (0, Var=1E6)
		#2 P*FUV2	N (0, Var=1E6)

Exploratory Statistical Analyses: Repeated measures version LAR Primary analysis model				
			#3 P*FUV3	n/a (constraint = 0)
			#4 U*FUV1	n/a (constraint = 0)
			#5 U*FUV2	n/a (constraint = 0)
			#6 U*FUV3	n/a (constraint = 0)
		Treatment * Visit (6)	#1 Pbo*FUV1	N (0, Var=1E6)
			#2 Pbo*FUV2	N (0, Var=1E6)
			#3 Pbo*FUV3	n/a (constraint = 0)
			#4 20ng*FUV1	n/a (constraint = 0)
			#5 20ng*FUV2	n/a (constraint = 0)
			#6 20ng*FUV3	n/a (constraint = 0)
		Treatment * Allergen Exposure * Visit (12)	#1 Pbo*P*FUV1	N (0, Var=1E6)
			#2 Pbo*P*FUV2	N (0, Var=1E6)
			#3 Pbo*P*FUV3	n/a (constraint = 0)
			#4 Pbo*U*FUV1	n/a (constraint = 0)
			#5 Pbo*U*FUV2	n/a (constraint = 0)
			#6 Pbo*U*FUV3	n/a (constraint = 0)
			#7 20ng*P*FUV1	n/a (constraint = 0)
			#8 20ng *P*FUV2	n/a (constraint = 0)
			#9 20ng *P*FUV3	n/a (constraint = 0)
			#10 20ng *U*FUV1	n/a (constraint = 0)
			#11 20ng *U*FUV2	n/a (constraint = 0)
			#12 20ng *U*FUV3	n/a (constraint = 0)
	Fixed Categorical / Continuous*	Baseline*Visit (3)	#1 Baseline slope for FUV1	N(0, Var=1E6)
			#2 Baseline slope for FUV2	N(0, Var=1E6)
			#3 Baseline slope	N(0, Var=1E6)

Exploratory Statistical Analyses: Repeated measures version LAR Primary analysis model

		for FUV3	
Random	Centre (planned 6 centres)	Separate value per contributing centre sampled as i.i.d ~ N(0, σ^2_{Centre})	σ^2_{Centre}~Gamma(Shape=0.048, Scale=0.830) Weakly informative prior based on 6x in-house GSK datasets – same prior for both endpointsΔ
*=Centre covariates prior to fitting model (do not use observations that will not contribute to the planned model when centering) and if applicable the centering is to occur after any transformations have been applied Δ=If chain is not mixing (i.e. sticking at values close to zero) an additional mixture prior may be considered to act as a lower boundary constraint, or the centre term excluded from the model			

- Step 2 (optional): Explore adding other covariate terms to the Step 1 model (for example, but not limited to, Age, Gender, Dose per kg, Blood eosinophil levels). Use expert judgment and changes in DIC to determine final model to take to Step 3. Include any Step 2 models in the listing output and add the associated DIC / changes in DIC values to those produced in Step 1.
- Step 3: For the finally selected model use appropriate combinations of the model parameters (back transforming the combination if necessary) to obtain posterior distributions for the quantities of interest described in the Model Results Presentation. Binary flag variables can be used to evaluate the probability statements, by tracking the instances of the desired event happening over each MCMC iteration and taking the mean of the flag variable as the probability.
- Similar MCMC model fitting options and techniques to the Primary Statistical Analysis will be employed (see Section 7.1.2).
- In addition posterior probabilities of the differences (and/or percentage attenuations) for other cut-points (which may be determined upon inspection of the data, or from developing business requirements), may also be computed.

Model Checking & Diagnostics

- Refer to Appendix 11: Model Checking and Diagnostics for Statistical Analyses.
- This analysis can also be used to confirm the results of the Primary Statistical Analysis (see Section 7.1.2). Further investigation should be undertaken if results between the single timepoint Bayesian model (Primary) and Bayesian Repeated Measures model at FUV1 are inconsistent (*a priori* the most likely causes would be related to missing data influencing the estimates of the respective model's variance covariance parameters and/or the centre effects being a function of all three visits in the repeated measures modeling).

Model Results Presentation

- The information derived for each of the three visits would be similar to that presented for the Primary Statistical Analysis (see Section 7.1.2) (i.e. focus on comparison of GSK2245035 vs Placebo within each visit; except that at FUV2 and FUV3 the additional probability statements for the percentage attenuations exceeding AZ estimates are not required).

Exploratory Statistical Analyses: Repeated measures version LAR Primary analysis model
Sensitivity and Supportive Statistical Analyses
• By subject time profiles of the derived endpoints, split by treatment arm with separate identifiers (plotting symbols) for the allergen exposure strata • If data permit, the repeated measures equivalent of the models exploring the blood eosinophil levels would be attempted (see Sensitivity analysis in Section 7.1.2).This would also make the simplifying assumption that allergen exposure terms are not required and build up the equivalent of models R1-R3 using (log transformed and visit centered) blood eosinophil values in place of the allergen exposure term(s). Predictions would be made for the treatment means and differences at each visit using the same set of eosinophil values as Section 7.1.2.

Exploratory Statistical Analyses: EAR Repeated measures model
Endpoint(s)
• EAR: minimum <change from saline baseline> FEV_1 between 0-2 hours following allergen challenge at the three follow up visits (i.e. FUV1, FUV2 and FUV3). • EAR: weighted mean of <change from saline baseline> FEV_1 between 0-2 hours following allergen challenge at the three follow up visits (i.e. FUV1, FUV2 and FUV3). • Note: Text in <> added for clarity, since the wording in the protocol and objectives is familiar to clinical experts in the field, but may be confusing given there are also absolute FEV1 values measured at those times too.
Model Specification & All other details
• As per LAR repeated measures analysis described in this section; including the sensitivity analyses exploring blood eosinophil levels as a covariate.

8.2 Safety Analyses

8.2.1 Overview of Planned Adverse Events Analyses

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

Table 7 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 7 Overview of Planned Adverse Event Analyses

Endpoint	Absolute		
	Summary		Individual
	T	F	L
Adverse Events (AEs)			
All AEs by SOC and Maximum Grade / Severity	Y		Y
All Drug-Related AEs by SOC Class and Maximum Grade / Severity	Y		
Subject Numbers for Individual AEs			Y
Relationship Between AE SOCs, Preferred Term & Verbatim Text			Y
Disease Related Events (DREs) AEs			
All DRE AEs			Y
Cytokine Release Syndrome (CRS) AEs			
All CRS AEs by SOC and Maximum Grade / Severity	Y		Y
All CRS AEs by SOC and Maximum Grade / Severity by Week	Y		Y
Frequency of CRS events by Dosing Visit	Y		
Frequency of CRS events per Patient		Y	
Serious and Other Significant AEs			
Non-Fatal Serious AEs			Y
Serious AEs by SOC	Y		
Reasons for Considering as a Serious AE			Y
Drug-Related Serious AEs by SOC	Y		
AEs Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment by Overall Frequency			Y

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, SOC = System Organ Class.
- Summary = Represents TF related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.2 Overview of Planned Clinical Laboratory Analyses

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

Table 8 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 8 Overview of Planned Clinical Laboratory Analyses

Endpoint	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
Chemistry						
Chemistry Changes from Baseline				Y		
Emergent Chemistry Results by PCI Criteria	Y					
Chemistry Results of PCI			Y			
All Chemistry Results for Subjects with a Value of PCI			Y			
Haematology						
Haematology Changes From Baseline				Y		
Emergent Haematology Results by PCI Criteria	Y					
Haematology Values of PCI			Y			
All Haematology Results for Subjects with a Value of PCI			Y			
Urinalysis						
Urinalysis Abnormal Laboratory Values			Y			
All Urinalysis Results for Subjects with an Abnormal Value			Y			
Hepatobiliary (Liver) – Conditional on observed data						
Liver Monitoring/Stopping Event Reporting	Y					
Medical Conditions for Subjects with Liver Stopping Events			Y			
Substance Use for Subjects with Liver Stopping Events			Y			
All Laboratory						
Laboratory Tests and Associated Reference Ranges			Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.2.3 Overview of Planned Other Safety Analyses

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

Table 9 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 9 Overview of Planned Other Safety Analyses

Endpoint	Absolute			Change from BL		
	Summary		Individual	Summary		Individual
	T	F	L	T	F	L
ECG						
ECG Findings	Y					
Change from Baseline in ECG Values by Week				Y		
All ECG Values for Subjects with a Value of PCI			Y			
ECG Values of PCI			Y			
Abnormal ECG Findings			Y			
Vital Signs						
Change From Baseline in Vital Signs by Week				Y		
All Vital Signs for Subjects with a Value of PCI			Y			
Vital Sign Values of PCI			Y			
Rescue Salbutamol Medication (excluding that given as part of BAC procedure)						
Rescue Medication usage	Y		Y			
Peak Expiratory Flow (PEF)						
Mean PEF Profiles		Y	Y			
Mean Morning PEF Profiles		Y	Y			
Mean Evening PEF Profiles		Y	Y			
Weekly Maximum PEF	Y		Y			
Weekly WM PEF	Y		Y			
Nasal Examination						
Frequency of Abnormalities	Y		Y			

NOTES:

- T = Table, F = Figures, L = Listings, Y = Yes display generated, PCI = Potential Clinical Importance
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.3 Pharmacokinetic Analyses (Exploratory)

8.3.1 Overview of Planned Pharmacokinetic Analyses

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

Table 10 provides an overview of the planned analyses, with full details being presented in Appendix 13: List of Data Displays.

Table 10 Overview of Planned Exploratory PK Analyses

Endpoint	Untransformed							Log-Transformed						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
PK Concentrations							Y				C	C		

NOTES :

- T = Table, F = Figure, L = Listings, Y = Display generated,
- C = Conditionally produced if quantifiable concentrations exist for at least 20% of subjects at a particular time point,
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

8.3.2 Drug Concentration Measures

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

8.3.3 Pharmacokinetic Parameters

8.3.3.1 Deriving Pharmacokinetic Parameters

Note that there will be no PK Parameters calculated for GSK2245035 due to there being too few time points of PK sample collections to adequately define the PK Parameters. Additionally, the expectation is that all PK concentrations will be non-quantifiable making the derivation of PK Parameters inconsequential. If these assumptions are incorrect and further work on PK parameters is performed it will be documented in the CPSR.

8.4 Pharmacodynamic and Biomarker Analyses (Exploratory)

8.4.1 Overview of Planned Pharmacodynamic and Biomarker Analyses

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

Table 11 and Table 12 provide an overview of the types of biomarkers collected, their sampling schemes and how they contribute towards the overall assessment of the effect of GSK2245035 on various aspects of immune biology.

Table 13 associates each planned/potential analyte with a higher level grouping (denoted "functional class") and describes the ordering when multiple analytes are to be displayed. It also indicates which of the analytes the study team strongly expect to be available and which may be provided, conditional on other factors.

Full details of data displays being presented can be found in Appendix 13: List of Data Displays.

Table 11 Overview of Biomarkers: Planned sampling scheme and display labelling to use

T&E procedure	"Informal" description / rationale for samples	T&E Timepoints		Data Display Labelling for Statistical Modelling activities/outputs	
		Visit	"T&E" descriptions of within Visit Sampling Times	Visit	Planned Time
Sputum induction and processing for BAC associated sample collection	Changes over time (Pre-BAC timepoint) Direct BAC changes (Post Vs Pre BAC)	SV1	Pre-BAC	SV	Pre-BAC
		SV2 (24h)	BAC+24h		24h Post BAC
		DV8	Dose+24h	FUV1	Pre-BAC
		FUV1 (24h)	BAC+24h		24h Post BAC
		FUV2 (Wk 11)	Pre-BAC	FUV2	Pre-BAC
		FUV2 (24h)	BAC+24h		24h Post BAC
		FUV3 (Wk19)	Pre-BAC	FUV3	Pre-BAC
		FUV3 (24h)	BAC+24h		24h Post BAC
Laboratory assessments (haematology only)	Blood (WBC & Differentials): Changes over time (Pre-BAC timepoint) Direct BAC changes (Post Vs Pre BAC)	SV2	Pre-BAC	SV	Pre-BAC
		SV2 (24h)	BAC+24h		24h Post BAC
		FUV1 (Wk 9)	Pre-BAC	FUV1	Pre-BAC
		FUV1 (24h)	BAC+24h		24h Post BAC
		FUV2 (Wk 12)	Pre-BAC	FUV2	Pre-BAC
		FUV2 (24h)	BAC+24h		24h Post BAC
		FUV3 (Wk 20)	Pre-BAC	FUV3	Pre-BAC
		FUV3 (24h)	BAC+24h		24h Post BAC
Blood Samples for PBMC preparations	BAC induced allergic inflammatory cell populations	SV2	Pre-BAC	SV	Pre-BAC
			BAC+6h		6h Post BAC
		FUV1 (Wk 9)	Pre-BAC	FUV1	Pre-BAC
			BAC+6h		6h Post BAC
		FUV2 (Wk 12)	Pre-BAC	FUV2	Pre-BAC
			BAC+6h		6h Post BAC
		FUV3 (Wk 20)	Pre-BAC	FUV3	Pre-BAC
			BAC+6h		6h Post BAC

T&E procedure	"Informal" description / rationale for samples	T&E Timepoints		Data Display Labelling for Statistical Modelling activities/outputs	
		Visit	"T&E" descriptions of within Visit Sampling Times	Visit	Planned Time
Nasal lavage	Changes over time (Background timepoint) Direct NAC effects	SV2 (24h)	Background	SV	Background
			Pre-NAC		Pre-NAC
			NAC+5m		5m Post NAC
			NAC+6h		6h Post NAC
		FUV1 (24h)	Background	FUV1	Background
			Pre-NAC		Pre-NAC
			NAC+5m		5m Post NAC
			NAC+6h		6h Post NAC
		FUV2 (24h)	Background	FUV2	Background
			Pre-NAC		Pre-NAC
			NAC+5m		5m Post NAC
			NAC+6h		6h Post NAC
	TLR7 Induced changes (confirm target engagement)	DV1	Pre-Dose	DV1	Pre-Dose
			Dose+24h		24h Post Dose
		DV4	Pre-Dose	DV4	Pre-Dose
			Dose+24h		24h Post Dose
		DV8	Pre-Dose	DV8	Pre-Dose
			Dose+24h		24h Post Dose
Nasal filter collection	Changes over time (Background timepoint) Direct NAC effects	SV2 (24h)	Background	SV	Background
			Pre-NAC		Pre-NAC
			NAC+5m		5m Post NAC
			NAC+6h		6h Post NAC
		FUV1 (24h)	Background	FUV1	Background
			Pre-NAC		Pre-NAC
			NAC+5m		5m Post NAC
			NAC+6h		6h Post NAC

T&E procedure	"Informal" description / rationale for samples	T&E Timepoints		Data Display Labelling for Statistical Modelling activities/outputs	
		Visit	"T&E" descriptions of within Visit Sampling Times	Visit	Planned Time
		FUV2 (24h)	Background	FUV2	Background
			Pre-NAC		Pre-NAC
			NAC+5m		5m Post NAC
			NAC+6h		6h Post NAC
Nasal scrape	Changes over time	SV2 (24h)	NAC+6h	SV	6h Post NAC
		FUV1 (24h)	NAC+6h	FUV1	6h Post NAC
		FUV2 (24h)	NAC+6h	FUV2	6h Post NAC
Genetic sample	PGx	1x at any of DV1-DV8	n/a	n/a	n/a
Blood sample for biomarker analysis	TLR7 Induced changes (confirm target engagement)	DV1	Pre-Dose	DV1	Pre-Dose
			Dose+24h		24h Post Dose
		DV8	Pre-Dose	DV8	Pre-Dose
			Dose+24h		24h Post Dose
Blood sample for RNA analysis	TLR7 induced gene changes in the periphery	DV1	Pre-Dose	DV1	Pre-Dose
		DV8	Dose+24h	DV8	24h Post Dose
		FUV2 (Wk 12)	Pre-BAC	FUV2	Pre-BAC
FeNO measurement	Treatment induced FeNO changes	All Dosing Visits (DV1 to DV8 inclusive)	Pre-Dose	DV1, DV2, DV3, etc..., DV8	Pre-Dose
	BAC induced FeNO changes	SV1	Prior to Sputum	SV	Pre-BAC
		SV2 (24h)	BAC+24h		24h Post BAC
		FUV1 (Wk 9)	Pre-BAC	FUV1	Pre-BAC
		FUV1 (24h)	BAC+24h		24h Post BAC
		FUV2 (Wk 12)	Pre-BAC	FUV2	Pre-BAC
		FUV2 (24h)	BAC+24h		24h Post BAC
		FUV3 (Wk 20)	Pre-BAC	FUV3	Pre-BAC
		FUV3 (24h)	BAC+24h		24h Post BAC

Table 12 Overview of Biomarkers: Types of samples, data vendors and expected analytes

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
Sputum induction and processing for BAC associated sample collection	Changes over time (Pre-BAC timepoint) Direct BAC changes (Post Vs Pre BAC)	Cell Pellet	Sputum differentials	BIOSPIT	Absolute values (*Cells/g sputum)* and *%* (of Total Non-Squamous Cells) for: Eosinophils, Neutrophils, Lymphocytes, Macrophages, Bronchial Epithelial Cells & Total Non-Squamous Cells	*BAC may increase Sputum EOS (Absolute values and %)*	*Reduced Sputum EOS (Absolute values and/or %) relative to Placebo for i) Baseline (Pre-BAC) or ii) BAC induced increase (Post/Pre ratio)*
		PBS Wash	Inflammatory mediators	GSK (Stevenage)	IL-5, IL-13 *Conditional: IL-16, IL-33, TSLP, Eotaxin, MDC, TARC, ECP*	*BAC may increase inflammatory mediator levels e.g. IL-5 & IL-13*	*Reduced sputum TH2 mediators (IL-5 & IL-13) relative to Placebo for i) Baseline (Pre-BAC) or ii) BAC induced increase (Post/Pre ratio)*
		Cell Pellet RNA	Inflammatory gene expression	Expression Analysis	Affy CHIP Note: Data generation conditional on sufficient cells remaining in	*BAC may increase inflammatory gene expression*	*Reduction or change in nature of BAC induced gene expression*

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
					sample and sufficient sputum producers		*(Post/Pre) or the Baseline (pre BAC) gene expression*
Laboratory assessments (haematology only)	Blood (WBC & Differentials): Changes over time (Pre-BAC timepoint) Direct BAC changes (Post Vs Pre BAC)	Blood	Blood WBC and differentials	Q2	Absolute values (*Cell counts)* and *%* (of Total WBC) for: Eosinophils, Neutrophils, Lymphocytes, Monocytes, Basophils, & Total WBC Note: Neutrophils refers to Total Neutrophils (Segs + Bands), as described in dataset manager codelists	*Blood EOS may increase (either Absolute counts or %) after the BAC*	*Reduction in (Pre-BAC) blood EOS (as absolute count or %) from SV and/or Reduction in BAC induced increase in blood EOS after treatment compared to pbo*
Blood Samples for PBMC preparations	BAC induced allergic inflammatory cell populations	Blood PBMC	n/a	ZKW	Conditional on other study endpoints showing positive signals Reported outside of CPSR as data generation may take a long time	*To be defined, analysis of BAC induced allergic inflammatory populations in PBMC.*	*To be defined, reduction in BAC induced allergic inflammatory populations in PBMC.*

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
Nasal lavage	Changes in time (Background timepoint) Direct NAC effects	Lavage	Immuno-globulins Eosinophil mediators	GSK (Stevenage)	Background Pre-NAC & 6h Post NAC samples only (Allergens are "Birch", "House Dust Mite", "Cat" and "Grass" – Expecting one result per subject using the allergen they were challenged with – but re-label to "Allergen Specific IgA" for displays; only German sites expected to provide Birch Allergen data) ECP, Allergen Specific IgA	*NAC should increase inflammatory mediators*	*Treatment related changes compared to screening of either background levels or the NAC induced increase at 6 hrs (6h/Pre-NAC ratio)* *Eosinophil mediators should go down or not increase on NAC if drug is working & IgA should increase*
			Mast Cell mediators	GSK (Stevenage)	Pre-NAC & 5m Post NAC samples only Histamine Tryptase *Conditional:*	*Mast cell mediators should increase in 5 min post NAC sample*	*Reduction in the NAC (5 min/pre-NAC ratio) induced response after treatment*

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
					Prostaglandin D2		*compared to the SV*
	TLR7 Induced changes (confirm target engagement)	Lavage	"TLR7" Target engagement	GSK (Stevenage)	IP-10	*Within visit ratio (24h / Pre-dose) should be approximately one*	*Increase in within visit fold changes to confirm target engagement. Investigate whether the magnitude of fold changes at DV4 and DV8 are similar*
Nasal filter collection	Changes in time (Background timepoint) Direct NAC effects	Nasal Lining fluid	Inflammatory mediators	GSK (Stevenage)	Background Pre-NAC & 6h Post NAC samples only IL-5 IL-16 *Conditional: IL-13, IL-33, TSLP, Eotaxin, MDC, TARC, IL-10, IFNg*	*NAC should increase inflammatory mediators*	*Treatment related reduction (compared to screening) of either background and or reduction of NAC 6h induced response.* *Th2 cytokines should all go down if drug is working* *Th1/Treg cytokines should increase*

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
			Mast Cell mediators	GSK (Stevenage)	Pre-NAC & 5m Post NAC samples only Histamine, Tryptase, Conditional:Prostaglandin D2 Note: Data generation conditional on sufficient sample remaining. Would only be assayed if mast cell mediators cannot be detect in Nasal lavage fluid samples	*Mast cell mediators should increase in 5 min post NAC sample*	*Reduction in the NAC (5min/pre-NAC ratio) induced response after treatment compared to the SV*

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
Nasal scrape	Changes in time	Nasal Cells	n/a	ZKW	Samples to be held by ZKW, if we are able to get good samples and study is positive will be analysed. Reported outside of CPSR as data generation may take a long time	*n/a*	*n/a*
Genetic sample	PGx	Blood	Whole blood	GSK (Stevenage)	Stored for genomic DNA can only be used if individual consent is signed, could be used to see why someone is a non-responder	n/a	n/a
Blood sample for biomarker analysis	TLR7 Induced changes (confirm	Serum	"TLR7" Target engagement	Q2	IP-10, IFNa, IFNb, IL-1b, IL-6, TNFa, MCP-1	*Within visit ratio (24h / Pre-dose) should be approximately one*	*Increase in within visit fold changes to confirm target engagement*

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
	target engagement)	PBMC	n/a	ZKW	To be used in association with Haematology cell counts to define which populations of cells are changing post dose i.e. in more detail that just "Lymphocytes". . Can also use pre BAC samples at FUV1 and FUV2 to see if ("Lymphocyte") phenotype is restored 1 and 4 weeks after treatment. Reported outside of CPSR as data generation may take a long time	n/a	n/a

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
Blood sample for RNA analysis	TLR7 induced gene changes in the periphery	PAX-gene tubes for TLR7/AFFY chip gene expression in blood	Whole blood RNA	Expression Analysis	Affy CHIP	*No changes*	*Change from pre DV1 of TLR7 induced gene expression in blood 24h after 8th dose and do they return to baseline 4 weeks after treatment*
FeNO measurement	Treatment induced FeNO changes	eCRF data					

T&E procedure	"Informal" description / rationale for samples	Matrix	Functional Categories	Vendor (Δ)	Analyte(s)	Comments	
						Anticipated Placebo profile	Characteristics of Successful drug effect
	BAC induced FeNO changes	eCRF data					
Notes: (Δ) Vendors provided to indicate likely packages/deliverables for pre-programming "ZKW" = Zellkraftwerk, "Q2" = Quest and Quintiles, "BIOSPIT" = Quintiles (BIOSPIT), "GSK (Stevenage)" = PPD team, "<TBC>" = To be confirmed							

Table 13 Functional Categories of Analytes and Display Orders (irrespective of originating matrix) for anticipated analytes at RAP writing

Functional Category (Direction supporting further drug development)			Analyte	Display order within Category	Data Availability*
"TLR7" Target engagement (Increases indicative of target pathway engagement)			IP-10	1	E
			MCP-1	2	E
			IFNa	3	E
			IFNb	4	E
			IL-1b	5	E
			IL-6	6	E
			TNFa	7	E
Sputum Differentials (Absolute and %) (Decreases in Eosinophils desired)			Eosinophils	1	E
			Neutrophils	2	E
			Lymphocytes	3	E
			Macrophages	4	E
			Bronchial Epithelial Cells	5	E
			Total Non-Squamous Cells	6	E
Blood WBC and Differentials (Absolute and %) (Decreases in Eosinophils desired)			Eosinophils	1	E
			Neutrophils$^{\Delta}$	2	E
			Lymphocytes	3	E
			Monocytes	4	E
			Basophils	5	E
			Total WBC	6	E
Immunoglobulins (Increases)			Allergen Specific IgA	1	E
Mast Cell & Eosinophil Mediators (Decreases)			Histamine	1	E
			Tryptase	2	E
			Prostaglandin D2	3	C
			ECP	4	E
Inflammatory Mediators	TH1/Treg Panel (Increases)		IFNg	1	C
			IL-10	2	C
	TH2 Panel (Decreases)	Cytokines	IL-5	1	E
			IL-13	2	Sput':E, Lav':C
			IL-16	3	Sput':C, Lav':E
			IL-33	4	C
			TSLP	5	C
		Chemokines	Eotaxin	1	C
			MDC	2	C
			TARC	3	C

*: E = Expected to be available at final reporting; C = Conditional – not guaranteed to be in final data package (e.g. reasons for absence of analyte may include, but not be limited to i) responses (or lack of) in other data or ii) satisfactory completion of lab assay development by the time of sample processing)
Δ=Neutrophils refers to Total Neutrophils (Segs. + Bands)

8.4.2 Planned Pharmacodynamic and Biomarker Statistical Analyses

Individual biomarkers referred to in the RAP were correct at time of writing, but may not represent the final / definitive list of analytes. The structure / framework of the univariate statistical analyses will be described for a generic biomarker of a given class & proposed sampling scheme. Additional biomarkers would be assigned to the appropriate class & sampling scheme and would be analysed using a similar methodology.

The proposed multivariate analyses / composite endpoints would be modified accordingly if new biomarkers/analytes are assayed and deemed relevant for inclusion.

Additional analyses would use the next available output numbering and changes (additions / planned analyses that were not performed) would be documented in the CPSR.

Several biomarker sampling types will be collected and stored and reporting performed outside of the CPSR and/or SAC deliverable. These have been captured here for completeness and any details on methodology / comparisons would be included in the respective reporting processes.

Pharmacodynamic/Biomarker
General Considerations
• Imputations described in Section 11.4.2.3 would be applied to the response variables prior to any further activities. • Listings should also display original and any imputed versions of the response variable. • Unless otherwise stated all planned analyses will use the imputed response variable. If the baseline value is imputed then the imputed value will be included in the statistical analyses (and any change from baseline responses will be computed as the change from imputed baseline). Only if there are many time points and dose levels with imputed values will sensitivity analyses be performed (e.g. by re-fitting the statistical model without the imputed data points). Any sensitivity analyses will be described in the CPSR (separate outputs from these sensitivity analyses may not be included in the final CPSR if the conclusions from the original statistical analysis do not change). • Each of the biomarkers will be examined to determine if a log transformation should be applied prior to any statistical analyses (no outputs will be produced from this step). Log base 2 will be used unless otherwise stated (including on any Figures requiring a logarithmic y-axis). Based on previous experience with biomarker data the default assumption will be that the variable will require a Log base 2 transformation. • If a transformation is necessary then the transformation should be applied to any associated baseline responses prior to them being centred (applies when fitting models using SAS PROC MCMC). • Transformations of the response variable and/or alternative analysis techniques will be explored on an as needed basis if model assumptions appear invalid (these techniques would be documented in the CPSR). • Use will be made of the recommendations contained in the internal DB – Respiratory guidance document on handling PK values below the limit of quantification when summarising the PD data. For the purposes of this study a “large” amount of missing data is defined as ≥75% of

Pharmacodynamic/Biomarker

values. For example if the experimental design has 8 potential values for a given time-point and 6 or more are LLQ then selected summary statistics (mean, SD, geometric mean and 95% CI for geometric mean, SD logs and CVb(%) will be set to NA).

- Default sets/layouts of descriptive Summary Tables and Figures will be produced for each biomarker where data permit (these are based on the raw data values and not on statistical model outputs); layouts described below.
- Subsequent statistical analyses will only be performed if the study statistician (or delegate) deems that such analysis may provided additional information / value over and above the descriptive Figures and summary tables (for example, if the majority of responses for biomarker X were below Limit of Quantification on all treatment arms, further statistical modelling are not likely to provide much information and would not be attempted).
- Unless otherwise stated model checking will include examination of Studentised residual plots and Q-Q plots for frequentist based statistical analyses and utilise the techniques in Section 11.11 for Bayesian based analyses.
- Panel plots of selected posterior distributions (using groupings and layouts appropriate to the data being summarised) may also be attempted to bring together the results of (Bayesian) statistical modelling to facilitate easier review to obtain an idea of the behaviour of GSK2245035. These would take the next available display numbers but would not be labelled as post-hoc in their titles because they are summarising existing analyses (the exception to this would be if any of their content utilised modelling results from a post-hoc model).
- Exploratory scatter plots involving different combinations of endpoints (and time points) may be produced to investigate possible correlation structures and biological activity (for example, relating Visit 1 IP-10 fold changes in nasal lavage supernatant to post allergen challenge IL-5 levels at follow up visits). It is not possible to pre-specify these in advance (they will be guided by the observed data). These exploratory scatter plots need not be formally reported unless they are required to support statements made in the CPSR (in which case they would be assigned the next available free number and be labelled as post-hoc). Any subsequent statistical analyses resulting from the exploratory figures would be described in the CPSR and also labelled as post-hoc.

Descriptive data summaries (Figures and Tables)

Figures

- **PD_F1**: Displaying Individual Subject level data: Aim to achieve one page per analyte and treatment combination, containing panels of individual subject data (use judgement on the best layout; expected to be 4 columns and 5 rows but it is allowable to use more than one page if necessary to maintain readability). The x-axis and y-axis ranges should be common across all subjects within the analyte (i.e. Placebo page uses same x-axis and y-axis range as 20ng GSK2245035 page to allow comparability; but different analytes can have different y-axis ranges). The x-axis should be discrete and ordered chronologically. Responses within a visit should be joined but there should be gaps between data points from different visits. Use the colour scheme for the treatment and allergen stratum combination described in Section 11.4.3 for each subject (but do not include a legend). The y-axis should be spaced on an appropriate scale (e.g. Log 2) but the labels can be the untransformed values to allow for greater clinical interpretability. The imputed responses should be displayed. If necessary use abbreviations for labelling visit/time combinations, and footnote accordingly. LLQs and ULQs should be displayed as horizontal dashed lines whenever appropriate (e.g. do not put the LLQ line on if none of the subjects values are near the LLQ value, as it will only extend the y-axis range and make the

Pharmacodynamic/Biomarker

subjects data harder to distinguish). However the corresponding LLQ (and the ULQ if defined) can be displayed in the sub-title (or by line) associated with the graph, even if the reference lines are omitted. Display the analytes in the order given by Table 13. Arrange the subject panels so that they are grouped by allergen exposure stratum, centre and subject ID (if space is constrained each panel label should contain the allergen exposure (P or U) and the subject ID as centre information is implied by the ranges of subject ID numbers). Omit unscheduled data points from these figures (only add an appropriate footnote when required, e.g. "Note: Unscheduled data excluded – see corresponding listing for values")

- **PD_F2**: Displaying Individual Subject level data grouped by treatment arm (all timepoints): Aim to achieve one page per analyte; using a grid layout (Placebo 1st row, 20ng GSK2245035 2nd row). Each column is a visit, arranged chronologically from left to right (try to get all visits on the same page but use more than one page to display visits if necessary). The x-axis and y-axis ranges should be common within each analyte. The x-axis should be discrete and ordered chronologically. Use the colour scheme for the treatment and allergen stratum combination described in Section 11.4.3 for each subject. Overlay the means and approximate 95% CI from the corresponding summary tables in thicker lines with different colours; sufficiently offsetting their x-axis values from the individual subject data so that the 95% Cis do not obstruct the individual data markers and/or the other means (if no CI is available due to n* being too low then just plot the mean); i.e. a total of three items to be overlaid; giving the most emphasis to the overall treatment mean. The summary statistics selected should be appropriate to the planned transformations (e.g. if the endpoint is to be log transformed then the mean and associated Cis should be for the geometric mean but if no transformation is planned then they can be for the arithmetic mean). For the individual subject data display the imputed responses using only the planned time-points (omit any unscheduled data). The criteria for y-axis scale/labels, footnotes, LLQ/ULQs and display ordering are the same as PD_F1. The legend should include both i) individual subjects data symbols/line types and ii) the sets of overlaid items (3x means and associated 95% Cis). If the lower and/or upper bound of any CI is negative and the y-axis involves a log transformation then the negative value should be replaced with a suitable small constant (e.g. 10% of the LLQ) and an appropriate footnote added to the display to indicate some of the Cis are altered for display purposes.
- **PD_F3**: Displaying Individual Subject level data grouped by treatment arm (Background or Pre-Challenge (or Pre-Dose) timepoints only): This will use the same principles as PD_F2, except that there are not separate panels (columns) for visits. Instead Visit will form the x-axis categories (ordered chronologically from left to right) and the column label will be the timepoint within the visit (e.g. "Background" or "Pre-Challenge" or "Pre-Dose").
- **PD_F4**: Displaying Individual Subject Fold changes grouped by treatment arm (for analytes unrelated to demonstrating TLR7 target engagement): Aim to achieve one page per analyte, containing panels of individual subject fold-change data; with one panel for each visit/timepoint combination (ordered chronologically from left to right). Within each panel the x-axis is the treatment arm (categorical – ascending dose levels; offset the points by the Stratum level if possible). Use a grid layout; rows contain the reference timepoint (denominator in the fold change ratio) and columns are the visit/timepoint combinations (numerators in the fold change ratio). For example, there may only be one row, which might be labelled as "Pre-BAC for the Visit" and four columns "SV 24h Post BAC", "FUV1 24h Post BAC", "FUV2 24h Post BAC" and "FUV3 24h Post BAC". Use the colour scheme for the treatment and allergen stratum combination described in Section 11.4.3 for each subjects fold change value (include this

Pharmacodynamic/Biomarker
information in a legend). Draw a horizontal dashed reference line at 1. If necessary use a log base y-axis. • **PD_F5**: Displaying Individual Subject Fold changes grouped by treatment arm (for analytes related to demonstrating TLR7 target engagement): This will use the same principles as PD_F4 but will consist of two rows (1st row showing fold changes relative to the true baseline (i.e. before the 1st dose was administered (DV1 Pre-Dose)) and the 2nd row showing fold changes relative to the pre-dose baseline associated with that visit. Note: If i) the timepoint (column) is the reference value in row 2 or ii) no pre-dose value was taken at the corresponding timepoint then the row 2 panel can be left blank/empty.
Tables
• Analytes should be presented in the order described in Table 13. For each analyte the summary statistics should be derived and presented for i) the overall treatments (Placebo and 20ng GSK2245035) and then by ii) the Treatment and Allergen exposure strata combinations (Placebo Presumed, Placebo Unknown, 20ng GSK2245035 Presumed and 20ng GSK2245035 Unknown); each visit and planned time combination (ordered chronologically) within the treatment grouping. The descriptive summary statistics to be presented are detailed in Section 11.4.3. Most biomarkers would require log transformations (i.e. the associated tables will also include the geometric means etc). The tables should be modified to include the n* column (see the internal DB – Respiratory guidance document on handling PK values below the limit of quantification). To facilitate presentation with the same layouts use "Overall" for the stratum value when presenting the overall treatment means.
Default approach for Bayesian MCMC Modelling output
Items and Comparisons of interest and required Probability statements for each comparison
• Assuming that the final model is not of the "R1" form (See Section 11.9.1) then treatment comparisons of interest are the equivalents to the frequentist counterpart LSMeans estimates for Treatment*Visit in a model fitted in SAS PROC MIXED. The posterior distributions of these quantities will be obtained and the median and 95% credible interval (equi-tail) will be tabulated and displayed graphically. Additionally, appropriate combinations of model parameters will be constructed to obtain the posterior distributions of the ratio of Active / Placebo for each planned time point (equivalent to extracting out relevant back transformed LSmean diffs from a PROC MIXED call for a log-transformed response variable). The posterior probabilities that the ratios at each planned timepoint exceeded the cut-points described Table 14 will be computed, along with the median and 95% credible interval (equi-tail) of the distribution. The posterior distributions for the ratios will be displayed graphically and the aforementioned items tabulated. Note: These posterior probabilities relate to events in the current study, and the mean responses on the treatment arms. Predictions relating to i) an individual subject in a future trial and ii) the mean response in a future trial with N subjects per arm will not be produced as part of the reporting of this study, but may be obtained as part of experimental design activities for any future clinical trials involving GSK22454035. • If the model is of the "R1" form (See Section 11.9.1) then the approach will be modified to obtain and display LSMean equivalents of Treatment*Visit*Allergen and the comparisons would be the ratio of Active/Placebo within each Allergen strata within each visit. The same set of default posterior probability cut points will be used for each comparison.

Pharmacodynamic/Biomarker

Table 14 Default Posterior Probability (PP) cut-points of interest for Pharmacodynamic/Biomarkers analyses

Item	X = Treatment ratio (Active / Placebo) at each planned time point
1	PP(X<0.10) "More than a 90% reduction in mean response relative to Placebo"
2	PP(X<0.25) "More than a 75% reduction in mean response relative to Placebo"
3	PP(X<0.50) "More than a 50% reduction in mean response relative to Placebo"
4	PP(X<0.75) "More than a 25% reduction in mean response relative to Placebo"
5	PP(X<0.90) "More than a 10% reduction in mean response relative to Placebo"
6	PP(X<1.00) "Any reduction in mean response relative to Placebo"
7	PP(X≥1.00) "Any increase in mean response relative to Placebo"
8	PP(X>1.10) "More than a 10% increase in mean response relative to Placebo"
9	PP(X>1.25) "More than a 25% increase in mean response relative to Placebo"
10	PP(X>1.50) "More than a 50% increase in mean response relative to Placebo"
11	PP(X>2.00) "More than a 2-fold increase in mean response relative to Placebo"
12	PP(X>10) "More than a 10-fold increase in mean response relative to Placebo"
Note: If the response is untransformed then the cut-points will be computed using the median of the posterior (adjusted) distribution for Placebo and the above ratios to determine the equivalent absolute difference (e.g. If Pbo median = 76 then Item 1 would be PP(Difference (A-P) < -68.4)) Note: Shortened versions of the labels may be used in the TLFs as appropriate (e.g. PP(X<0.10) or PP(Any Reduction c.f. Pbo))	

8.4.2.1 Biomarkers supporting the BAC related exploratory objective(s)

8.4.2.1.1 Sputum

Analyses described in Section 8.4.2.1.1 will use the Sputum producers population. If this population is deemed too small (e.g. less than 3 evaluable subjects per treatment arm/strata combination) a review of each of the planned modelling activities may take place to determine which (if any) of them would be attempted.

Cell Pellet: Sputum Differential cell counts

These analysis models assume all of the required data manipulation steps have been completed and that two response variables are derived per subject; namely a (derived) Total count (in Cells/g sputum – sometimes referred to as Absolute counts in display titles) and a Percentage (% of the Total Non-Squamous Cells). It is expected that a large proportion of subjects may not produce samples and/or viable/evaluable samples at all of the planned timepoints. **Inspection of the amount and pattern of missing data will be conducted, to determine if any form of statistical modelling should take place.** Note: The data manipulation steps add on a small constant in the eventuality that zero counts were recorded for a cell type so there should be no value that cannot be subjected to a log transformation.

Descriptive summary tables will be produced for "%" and Absolute count versions of the endpoints.

Figures of type PD_F1 and PD_F2 should be produced for each combination of response variable (absolute and %) and the cell type (Eosinophils, Neturophils, etc) using all of the available timepoints.

The most pertinent of the differential cell types are the Eosinophils; although the same modelling process would be attempted for the other cell types (Neutrophils, Lymphocytes, Macrophages, Bronchial Epithelial Cells and Total Non-Squamous cells).

Statistical analysis of "Pre-BAC" Samples

- Additional Figures of type PD_F3
- Separate Bayesian repeated measures mixed effect models (per response variable and cell differential type), with non-informative priors for all model parameters, will be fitted to each transformed response over the planned post Screening time points (FUV1, FUV2 and FUV3).
- Baseline: (Transformed) SV Pre-BAC
- The additional terms to include in the chosen "R" model (see Section 11.9.1) are:

  Fixed Categorical: Intercept
  Fixed Continuous Covariates: Baseline*Visit
- The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (3x3).

Statistical analysis of "Direct BAC effect" Samples (All Samples)

- Additional Figures of type PD_F4
- Separate Bayesian repeated measures mixed effect models (per response variable and cell differential type), with non-informative priors for all model parameters, will be fitted to each of the transformed responses collected from an individual subject (i.e. 8 data points per subject; the combinations of Visit and Sample times SV Pre-BAC, SV 24 Post BAC, FUV1 Pre-BAC, FUV1 24h Post BAC, FUV2 Pre-BAC, FUV2 24h Post BAC, FUV3 Pre-BAC and FUV3 24h Post BAC).
- For the purposes of assessing models R1 to R3 (see Section 11.9.1) consider "Visit" in those models to be a eight level term covering the data recorded per subject with these additional terms:

  Fixed Categorical: Intercept
  The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (8x8).

- In this model parameterization the usual "Baseline" timepoints (Pre-BACs) are modeled as response variables and not covariates. Therefore posterior distributions for the quantities of interest; namely treatment effect on "within visit fold changes (Post/Pre) adjusted for the screening visit and placebo fold changes"; use fold changes representing the mean predicted response at the timepoint (and not the average of the individual subjects fold changes).

- The model can provide several layers of useful information that should be presented instead of the default set of comparisons. The following should be modified if the model form is "R1". The Back transformed predicted response for each treatment arm (x2) and visit (x8) combination should be produced. The next stage is to determine the fold change of the predicted response (Predicted Post BAC / Predicted Pre-BAC) within each of the four visits (SV, FUV1, FUV2 and FUV3) for each treatment. For each treatment arm its respective SV fold change can be subtracted from the FUV1, FUV2 and FUV3 visits. This quantity can then be compared across the treatment arms (within each of FUV1, FUV2 and FUV3); to provide an estimate of the screening visit and placebo adjusted change in BAC induced response.

PBS Wash: Allergic Mediators

A similar approach to the analysis of Sputum Differential Cell Counts data will be used for each of the available inflammatory mediators; with the exception being the direction of interest (increases or decreases) may change depending upon which analyte is being modelled (see Table 13 for which direction to prioritise for the biomarker classes).

Cell Pellet RNA

NOT PART OF SAC DELIVERABLE: Conditional on sufficient sample remaining (priority is Cell Pellet and PBS wash data). If available it would produce Affy CHIP data, which would be analysed in a similar fashion to Section 8.4.2.3.4.

8.4.2.1.2 Blood WBC and Differential Cell Counts

As with sputum, the emphasis is on the Eosinophils. These are expected to increase upon BAC challenge (i.e. increases on Placebo c.f. pre-BAC values), and GSK2245035 should "blunt" this increase (*a priori* it is not certain if the treatment effect is sufficiently strong that it causes decreases, rather than a reduced level of increase c.f. Placebo).

The analysis approach is similar to Section 8.4.2.1.1; except that the All Subjects population is to be used and the list of differential cell types from the Blood Haematology samples is different (no Macrophages, BEC or Total Non-Squamous Cells but Monocytes and Basophils are expected). Also and if present in the source data only the total Neutrophils should be descriptively summarised/analysed (not Segs and Bands). Total WBC should also be modelled.

8.4.2.1.3 Blood PBMC

NOT PART OF SAC DELIVERABLE: These samples will be stored and further processing would be subject to study outcome determined from the other endpoints (statistical analyses would be reported separately and methods documented in the corresponding write up / report). The Statistical analysis methodology depends upon what methodology is used to process the samples, as the data structure/content will depend on that choice.

8.4.2.1.4 FeNO (Exhaled Nitric Oxide)

This section has been written assuming that FeNO response will require a log transformation. If it is not the case then appropriate modification should be made (e.g. comparisons expressed as differences rather than ratios (fold changes)).

Statistical Analysis of "Direct BAC effect" FeNO Samples

- Tables of descriptive summary statistics and Figures of type PD_F1, PD_F2 and PD_F4
- A Bayesian repeated measures mixed effect model, with non-informative priors for all model parameters, will be fitted to each of the transformed responses collected from an individual subject (i.e. 8 data points per subject; the combinations of Visit and Sample times SV Pre-BAC, SV 24 Post BAC, FUV1 Pre-BAC, FUV1 24h Post BAC, FUV2 Pre-BAC, FUV2 24h Post BAC, FUV3 Pre-BAC and FUV3 24h Post BAC).
- For the purposes of assessing models R1 to R3 (see Section 11.9.1) consider "Visit" in those models to be a eight level term covering the data recorded per subject with these additional terms:

  Fixed Categorical: Intercept
  The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (8x8).

- In this model parameterization the usual "Baseline" timepoints (Pre-BACs) are modeled as response variables and not covariates. Therefore posterior distributions for the quantities of interest; namely treatment effect on "within visit fold changes (Post/Pre) adjusted for the screening visit and placebo fold changes"; use fold changes representing the mean predicted response at the timepoint (and not the average of the individual subjects fold changes).
- The model can provide several layers of useful information that should be presented instead of the default set of comparisons. The following should be modified if the model form is "R1". The Back transformed predicted response for each treatment arm (x2) and visit (x8) combination should be produced. The next stage is to determine the fold change of the predicted response (Predicted Post BAC / Predicted Pre-BAC) within each of the four visits (SV, FUV1, FUV2 and FUV3) for each treatment. For each treatment arm its respective SV fold change can be subtracted from the FUV1, FUV2 and FUV3 visits. This quantity can then be compared across the treatment arms (within each of FUV1, FUV2 and FUV3); to provide an estimate of the screening visit and placebo adjusted change in BAC induced response.

8.4.2.2 Biomarkers Supporting the NAC related exploratory objective(s)

The Background samples should be analysed separately from the others as their intent is to capture changes in condition over the season (longer term changes).

The Pre-NAC, 5min and 6 hours are designed to measure the direct (within day) impact of the NAC procedure. The pre-wash (applied as part of the process to obtain the background sample) should also make the pre-NAC values more consistent (essentially zero) and should ensure that subjects should begin from a similar nasal condition (i.e. with a clean nose). Thus challenge related changes should be more consistent as mediators induced by the challenge should be the dominant items detected.

However, although all post NAC samples may be collected, not all of the biomarker types will be evaluated in the first instance. Pre-NAC samples will be evaluated for all biomarker types (mast cell mediators and inflammatory mediators). Mast cell mediators will also be evaluated from the 5min sample and Inflammatory mediators will be also be evaluated for the 6h sample.

Whilst the statistical analysis may split the data initial summaries will be produced using the complete dataset (i.e. a "PD_F1" format Figure and summarised in descriptive tables).

8.4.2.2.1 Nasal Lavage Fluid & Nasal Lavage Filters

Nasal Lavage Fluid samples are expected to provide the Mast Cell Mediator results (plus ECP and allergen specific IgA). Nasal Filters are expected to provide the Inflammatory mediators (chemokines and cytokines).

Statistical Analysis of "Background" Samples

- Additional Figures of type PD_F3
- Separate Bayesian repeated measures mixed effect models (per analyte), with non-informative priors for all model parameters, will be fitted to each transformed response over the planned post Screening time points (FUV1 and FUV2).
- Baseline: (Transformed) SV Background
- The additional terms to include in the chosen "R" model (see Section 11.9.1) are:

  Fixed Categorical: Intercept
  Fixed Continuous Covariates: Baseline*Visit
  The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (2x2).

Statistical Analysis of "Direct NAC effect" Samples

- Additional Figures of type PD_F2 and PD_F4
- Separate Bayesian repeated measures mixed effect models (per analyte), with non-informative priors for all model parameters, will be fitted to each of the transformed responses collected from an individual subject (i.e. 6 data points per subject; the combinations of Visit and Sample times SV Pre-NAC, SV Post NAC, FUV1 Pre-NAC, FUV1 Post NAC, FUV2 Pre-NAC and FUV2 Post NAC; where Post-NAC is either 5m or 6h depending whether the biomarker is a mast cell mediator (5m) or inflammatory (6h)).
- For the purposes of assessing models R1 to R3 (see Section 11.9.1) consider "Visit" in those models to be a six level term covering the data recorded per subject with these additional terms:

  Fixed Categorical: Intercept
  The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (6x6).

- In this model parameterization the usual “Baseline” timepoints (Pre-NACs) are modeled as response variables and not covariates. Therefore posterior distributions for the quantities of interest; namely treatment effect on “within visit fold changes (Post/Pre) adjusted for the screening visit and placebo fold changes”; use fold changes representing the mean predicted response at the timepoint (and not the average of the individual subjects fold changes).
- The model can provide several layers of useful information that should be presented instead of the default set of comparisons. The following should be modified if the model form is “R1”. The Back transformed predicted response for each treatment arm (x2) and visit (x6) combination should be produced. The next stage is to determine the fold change of the predicted response (Predicted Post NAC / Predicted Pre-NAC) within each of the three visits (SV, FUV1, and FUV2) for each treatment. For each treatment arm its respective SV fold change can be subtracted from the FUV1 and FUV2 visits. This quantity can then be compared across the treatment arms (within each of FUV1 and FUV2); to provide an estimate of the screening visit and placebo adjusted change in NAC induced response.

8.4.2.2.2 Nasal Scrapes

NOT PART OF SAC DELIVERABLE: These samples will be stored and further processing would be subject to study outcome determined from the other endpoints (statistical analyses would be reported separately and methods documented in the corresponding write up / report). Note: Nasal scrape data are not going to be processed as in previous GSK2245045 studies (i.e. not planning to obtain a gene expression panel); samples may be analysed by CHIP-Cytometry.

8.4.2.3 Biomarkers supporting the Induction of TLR7 (target engagement) exploratory objective(s)

8.4.2.3.1 Nasal Lavage

- Tables of descriptive summary statistics and Figures of type PD_F1, PD_F2 and PD_F5
- Separate Bayesian repeated measures mixed effect models (per analyte), with non-informative priors for all model parameters, will be fitted to each of the transformed post DV1 baseline responses collected from an individual subject (i.e. 5 data points per subject; the combinations of Visit and Sample times excluding DV1 Pre-Dose; namely DV1 24h Post Dose, DV4 Pre-Dose, DV4 24h Post Dose, DV8 Pre-Dose and DV8 24h Post Dose).
- Baseline: (Transformed) DV1 Pre-Dose
- For the purposes of assessing models R1 to R3 (see Section 11.9.1) consider “Visit” in those models to be the five level effect covering the data recorded per subject (excluding DV1 Pre-Dose) with these additional terms:

  Fixed Categorical: Intercept
  Fixed Continuous Covariates: Baseline*Visit
  The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (5x5).
- Only items 6 and 7 from the default set of cut-points (Table 14) should be evaluated for the each of the default within visit treatment comparisons.
- Appropriate combinations of the model parameters should be used to evaluate the following two additional comparisons of interest (all cut point items from Table 14 should be applied to

the posterior distributions obtained for these additional comparisons and also this one:
Posterior Probability the quantity (X) is {NOT[(0.8 ≤ X ≤ 1.25)]})

- 24h response at DV4 vs DV1 for the 20ng GSK2245035 arm (adjusting for equivalent changes on Placebo). This is equivalent to
  "[20ng Post at DV4 / 20ng Post at DV1] / [Pbo Post at DV4 / Pbo Post at DV1]"
- Analogous comparison for DV8 Vs DV1
- The above additional comparisons are investigating if there is any evidence for gross amplification or tolerisation of the TLR7 induced responses after 4 and 8 weeks of weekly dosing, using the placebo data to adjust for any drift in the biomarker changes that may be caused by other factors (e.g. seasonal changes in allergen exposure).

8.4.2.3.2 Blood PD (Serum)

A similar approach to Section 8.4.2.3.1 will be used, except that "Visit" is a three level term (DV1 24h Post Dose, DV8 Pre-Dose and DV8 24h Post Dose) and only the additional comparison involving DV8 is relevant. Baseline is still DV1 Pre-Dose.

8.4.2.3.3 Blood PBMC

NOT PART OF SAC DELIVERABLE: These samples will be stored and further processing would be subject to study outcome determined from the other endpoints (statistical analyses would be reported separately and methods documented in the corresponding write up / report). Possible processing would involve CHIP-cytometry with an interest in characterising differences in cell populations (e.g. B cells and T-cells) between the treatment arms after dosing with drug.

8.4.2.3.4 Blood sample for RNA analysis

Gene expression (Affy CHIP) data. Standard GSK processes for QC of each CHIP and the normalisation procedure will be employed (e.g. using Array Studio software).

The model to be fitted to each probeset will be a repeated measures model (this may be fitted in SAS PROC MIXED). It will be based on the appropriate "R" model (See Section 11.9.1) using (transformed) DV1 Pre-Dose as Baseline, Visits are DV8 and FUV2 with the following additional terms.

Fixed Categorical: Intercept
Fixed Continuous Covariates: Baseline*Visit
The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (2x2).

Back transformed adjusted within visit Treatment comparisons (fold changes) and p-values (from a null hypothesis that the fold change=1) would be provided to the Computational Biology group within GSK for each probeset. That group will follow its processes (e.g. apply an appropriate false discovery rate correction (and possibly a threshold on the magnitude of fold change)) and place the resulting subset of genes into a pathway analysis. The Computational Biologist (or designate) would contribute directly to the corresponding CPSR sections with the interpretation of the pathway analysis outcome(s); and to describe any additional methodologies.

8.4.2.3.5 FeNO (Exhaled Nitric Oxide)

This section has been written assuming that FeNO response will require a log transformation. If it is not the case then appropriate modification should be made (e.g. comparisons expressed as differences rather than ratios (fold changes)).

Statistical Analysis of "Treatment induced changes" FeNO Samples

- Tables of descriptive summary statistics and Figures of type PD_F1 (but modified to use the PD_F3 axis layouts; i.e. one panel per subject with visit as the x-axis category and join the pre-dose values together for each subject across visits) and PD_F3.
- A Bayesian repeated measures mixed effect model, with non-informative priors for all model parameters, will be fitted to each of the post DV1 transformed responses collected from an individual subject (i.e. 7 data points per subject; the Pre-Dose values for DV2 to DV8 inclusive).
- Baseline: (Transformed) DV1 Pre-Dose
- The additional terms to include in the chosen "R" model (see Section 11.9.1) are:

  Fixed Categorical: Intercept
  Fixed Continuous Covariates: Baseline*Visit
  The repeated measures term is Visit (Subject = Subject), with an Unstructured variance covariance matrix common to each treatment arm (7x7).

8.4.2.4 PGx Samples

These samples will be stored and further processing would be subject to study outcome determined from the other endpoints (statistical analyses would be reported separately and methods documented in the corresponding write up / report).

8.4.3 Multivariate / Composite endpoint analyses

Given the exploratory nature and timing in the overall clinical development program of this study, it is anticipated that further post-hoc analyses would be conducted on the data beyond those specified in this section. However, these would be data driven and difficult to pre-specify. Any post-hoc analyses would be labelled as such in their title, take the next available display number(s) and be described in the CPSR.

8.4.3.1 Correlation between Sputum and WBC cell differentials

Using the Sputum population scatterplots of BAC Sputum and WBC Differential cell results (both absolute counts and percentage variables) will be produced for each cell differential evaluated that is comparable over both sampling matrices. Simple linear regression lines may be overlaid onto the plot for i) each individual treatment arm and ii) all data combined (i.e. these would be simple regressions that do not account for the repeated measures on individuals when estimating the regression parameters and are intended to act as a rough indicator for how translatable conclusions drawn from analyses of WBC Differentials may be to the lung (BAC Sputum)). The plots will display all of the available data from all visits.

8.4.3.2 Defining responder / non-responder status for an individual subject using only their datapoints

For each subject the criteria in Table 15 will be evaluated. If the endpoint relating to a question is missing then the subject's response will be set to missing and they would not contribute to the denominator when deriving any proportions.

Table 15 Criteria to be derived/applied at an individual subject level

ID	Area	Question(s)	Statistical Population	Endpoint(s)	Criteria / Responder algorithm (for non-missing endpoints)	Expected rate on Pbo Arm
A1	Target Engagement	Sustained activation of GSK2245035 target pathway?	Per Protocol	Within visit fold change in Nasal Lavage IP-10 (24h / Pre-Dose) at DV1 and DV8	Yes: Fold change >= 2 for BOTH DV1 and DV8 visits No: Any other outcome	<5% from 3x Previous studies (TL7114450, TL7116392, TL7116958)
B1 (FUV1) B2 (FUV2) B3 (FUV3)	Clinical BAC endpoint(s)	At least 20% attenuation of LAR Response c.f. SV?	Per Protocol	FUV1: WM and Min LAR FEV1 absolute change from saline FUV2: WM and Min LAR FEV1 absolute change from saline FUV3: WM and Min LAR FEV1 absolute change from saline	Derive Separately for each FU Visit Yes: >=20% Attenuation (c.f. SV) observed for either WM or Min LAR endpoint No: Any other outcome	~40% from 8x Historical GSK Allergen challenge studies (EL110002, HZA113126, INO102141, IPA101985, LPA111834, RES104385, RES114748 and SIG110762)
C1 (FUV1) C2 (FUV2) C3 (FUV3)	Clinical BAC endpoint(s)	At least 20% attenuation of EAR Response c.f. SV?	Sputum Producer	FUV1: WM and Min EAR FEV1 absolute change from saline FUV2: WM and Min EAR FEV1 absolute change from saline FUV3: WM and Min EAR FEV1 absolute change from saline	Derive Separately for each FU Visit Yes: >=20% Attenuation (c.f. SV) observed for either WM or Min EAR endpoint No: Any other outcome	~50% from 8x Historical GSK Allergen challenge studies
D1 (FUV1) D2 (FUV2) D3	Pre-BAC Endpoint(s)	Any Reduction in Pre-BAC Sputum EOS c.f. SV	Sputum Producer	Pre-BAC Sputum EOS (%) for FUV1, FUV2 and FUV3	Derive Separately for each FU Visit Yes: FU visit Sputum EOS % < corresponding SV % No: Any other outcome	~50% (Assumption of no underlying change)

ID	Area	Question(s)	Statistical Population	Endpoint(s)	Criteria / Responder algorithm (for non-missing endpoints)	Expected rate on Pbo Arm
(FUV3)						
E1 (FUV1) E2 (FUV2) E3 (FUV3)	BAC Induced Changes in Endpoint(s)	Reduced Fold change in Sputum EOS (24h Post BAC/Pre-BAC) c.f. SV	Sputum Producer	Within Visit fold change in Sputum EOS (%) [24h Post BAC / Pre-BAC] at FUV1, FUV2 and FUV3	Derive Separately for each FU Visit Yes: FU visit Fold change < corresponding SV fold change No: Any other outcome	~50% (Assumption of no underlying change)
F1 (FUV1) F2 (FUV2) F3 (FUV3)	Pre-BAC Endpoint(s)	Any Reduction in Pre-BAC Blood EOS c.f. SV	Sputum Producer	Pre-BAC Blood EOS (%) for FUV1, FUV2 and FUV3	Derive Separately for each FU Visit Yes: FU visit Blood EOS % < corresponding SV % No: Any other outcome	~50% (Assumption of no underlying change)
G1 (FUV1) G2 (FUV2) G3 (FUV3)	BAC Induced Changes in Endpoint(s)	Reduced Fold change in Blood EOS (24h Post BAC/Pre-BAC) c.f. SV	Per Protocol	Within Visit fold change in Blood EOS (%) [24h Post BAC / Pre-BAC] at FUV1, FUV2 and FUV3	Derive Separately for each FU Visit Yes: FU visit Fold change < corresponding SV fold change No: Any other outcome	~50% (Assumption of no underlying change)
H1 (FUV1) H2 (FUV2)	Pre-NAC Endpoint(s)	Any Reduction in Pre-NAC Nasal Lavage IL-5 c.f. SV	Per Protocol	Pre-NAC Nasal Lavage IL-5 for FUV1 and FUV2	Derive Separately for each FU Visit Yes: FU visit NL IL-5 < corresponding SV value No: Any other outcome	~50% (Assumption of no underlying change)
I1 (FUV1) I2 (FUV2)	NAC Induced Changes in Endpoint(s)	Reduced Fold change in Nasal Lavage IL-5 (6h Post NAC/Pre-NAC)	Per Protocol	Within visit fold change in Nasal Lavage IL-5 [6h Post NAC / Pre-NAC] at FUV1 and FUV2	Derive Separately for each FU Visit Yes: FU visit Fold change < corresponding SV fold change No: Any other outcome	~50% (Assumption of no underlying change)

ID	Area	Question(s)	Statistical Population	Endpoint(s)	Criteria / Responder algorithm (for non-missing endpoints)	Expected rate on Pbo Arm
		c.f. SV				
J1 (FUV1) J2 (FUV2)	Pre-NAC Endpoint(s)	Any Reduction in Pre-NAC Nasal Lavage ECP c.f. SV	Per Protocol	Pre-NAC Nasal Lavage ECP for FUV1 and FUV2	Derive Separately for each FU Visit Yes: FU visit NL ECP < corresponding SV value No: Any other outcome	~50% (Assumption of no underlying change)
K1 (FUV1) K2 (FUV2)	NAC Induced Changes in Endpoint(s)	Reduced Fold change in Nasal Lavage ECP (6h Post NAC/Pre-NAC) c.f. SV	Per Protocol	Within visit fold change in Nasal Lavage ECP [6h Post NAC / Pre-NAC] at FUV1 and FUV2	Derive Separately for each FU Visit Yes: FU visit Fold change < corresponding SV fold change No: Any other outcome	~50% (Assumption of no underlying change)
L1 (FUV1) L2 (FUV2) *	Pre-NAC Endpoint(s)	Any Reduction in Pre-NAC Nasal Filter Eotaxin c.f. SV	Per Protocol	Pre-NAC Nasal Filter ECP for FUV1 and FUV2	Derive Separately for each FU Visit Yes: FU visit NF ECP < corresponding SV value No: Any other outcome	~50% (Assumption of no underlying change)
M1 (FUV1) M2 (FUV2) *	NAC Induced Changes in Endpoint(s)	Reduced Fold change in Nasal Filter Eotaxin (6h Post NAC/Pre-NAC) c.f. SV	Per Protocol	Within visit fold change in Nasal Filter Eotaxin [6h Post NAC / Pre-NAC] at FUV1 and FUV2	Derive Separately for each FU Visit Yes: FU visit Fold change < corresponding SV fold change No: Any other outcome	~50% (Assumption of no underlying change)
* = Only included if the Nasal Filter Eotaxin biomarker was processed / evaluated						

A subject level listing will be produced to display the results of each question in Table 15 (and any additional post-hoc data driven questions). The proportion of individuals in the Yes category will be derived for each treatment arm and question, using both the main and alternative set of treatment descriptors (i.e. derive a separate proportion for each descriptor). These proportions will be listed and also displayed on starcharts (sometimes called radar plots), with a separate spoke per question and a separate chart per visit, with the treatment profiles overlaid on the individual panels (answers to questions which do not naturally have a visit structure will be duplicated across each visit/starchart). Aim to get all visits on the same page and align question B to the top spoke and present the questions in the following clockwise order: B, C, D, F, H, E, G, I, J, K, L, M and A. If possible use the same axis scale for each spoke, but question A may produce a wide range of proportions and therefore it is acceptable to present some questions on a different spoke axis scale to aid interpretation of any questions where smaller treatment differences are observed. To allow for (data driven) modifications to the number and/or ordering of the question a listing linking the abbreviated IDs to the actual questions/criteria will also be produced and any new questions/criteria not in Table 15 should be appropriately identified (e.g. using a lower case "p" as a suffix to the new question ID).

8.4.3.3 Multivariate Statistical Analysis Strategy

The following is a top level description of the (exploratory) analysis strategy; further refinements may be required once the number of endpoints and their distribution are known (i.e. data driven modifications to the planned analysis may be made during study reporting). Please consult the GSK study statistician for further details if required. Further details of the methodology used would be included in the CPSR.

- Whenever possible, to preserve the maximum amount of information contained within them, continuous variables should not be dichotomised.

- Imputed biomarker responses would be used in this analysis (e.g. responses below LLQ would be assigned ½ LLQ).

- Missing data / covariate values: Given the exploratory nature and relatively small number of subjects strong simplifying assumptions will be made. A missing at random assumption will be made for response variables. Initially for simplicity, covariates that are missing would be replaced with the corresponding treatment arm mean. A possible extension may use multiple imputation methodology to sample 5 sets of complete cases (via MCMC sampling methodology since the missingness patterns are not expected to be monotonic), analyse each of the 5 datasets separately and combine them using Rubin's rules (e.g. via SAS PROC MI and PROC MIANALYZE). This extension would be considered if the number of missing covariates is deemed large by the GSK study statistician.

- Two approaches would be attempted each aiming to explore the magnitude and duration of any GSK2245035 drug related as assessed using a range of endpoints. If the observed data do not permit their use or their assumptions are unlikely to be valid these methods may not be attempted.

- Profile regression (via the PReMiuM R package) – see Liverani (2015).
  - Response variable: BAC LAR outcomes (continuous Primary endpoint(s)). Separate modelling for each of the two primary endpoints
  - For simplicity, the repeated measures aspect will be ignored and data from each visit for an individual will be assumed to be independent.
  - For display purposes the endpoints will be grouped by (biomarker) functional category listed in Table 13; with the option to explore the inclusion of other variables via additional functional categories; for example but not limited to FeNo and diary card WM TNSS value(s).
  - If necessary biomarkers from a functional category may be omitted if there appears to be a larger amount of multicolinearity.
  - Log transformed data used, individual variables may be standardised prior to model fitting.
  - Treatment and visit information would not be provided to the model fitting process.
  - A desirable outcome is if the number of clusters roughly matches the treatment and visit combinations (approximately 6) and/or that individuals from the same treatment arms are consistently clustering together. Also it is desirable that the expected response associated with any "GSK2245035 clusters" is lower than "placebo clusters".
- Unsupervised clustering of individuals and visits followed by Canonical Correspondence analysis / Principal co-ordinates analysis to identify patterns when grouping results by treatment and visit – See Valles (2014)
  - The strategy described in Valles (2014) would be modified to reflect the continuous data in this study (rather than binary presence/absence in their data).
  - Each variable may be standardised prior to model fitting.
  - For each subject and visit combination their associated two primary response variables and the potential set of biomarkers described above for profile regression (plus the option to include other variables, for example but not limited to FeNo and diary card WM TNSS value(s)) would be put through an unsupervised clustering algorithm and the resulting dendrogram would also identify the timepoint and treatment associated with each sample

as well as colour coding by the standardised absolute values (see Fig 3 of the Valles (2014) paper).

- Additionally Canonical Correspondence analysis / Principal co-ordinates analysis would be used to explore patterns in samples belonging to the same treatment and visit. As in Fig 4 of Valles (2014) convex hulls may be drawn around the data points relating to samples from each treatment and timepoint combination and the areas of overlap determined and compared. Separately for each treatment arm and taking its respective Screening visit convex hull area as a reference, the area of overlap from the follow up visits would be expressed as a percentage of screening. Additionally and separately for each visit the convex hull area of GSK2245035 would be expressed relative to the Placebo convex hull area. The relative changes in these areas can potentially inform on magnitude and duration of treatment effects.

- Desirable outcomes would be distinct clusters by treatment arm(s) and lasting changes (across FUV1, FUV2 and FUV3) in convex hull areas on active that are not observed on the placebo.

9 EXPLORATORY STATISTICAL ANALYSES

9.1 Exploratory Analyses

9.1.1 Overview of Planned Exploratory Analyses

The exploratory analyses will be based on different populations depending on what the endpoint is.

Table 16 provides an overview of the planned exploratory analyses, with further details of data displays being presented in Appendix 13: List of Data Displays.

Table 16 Overview of Planned Exploratory Analyses

Endpoint	Absolute						
	Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L
TNSS							
WM TNSS by Week	Y	Y	Y	Y	Y		Y
WM Individual Components of TNSS by Week	C	C	C	C	C		Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated, C=Display conditional on other results.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Intradermal Allergen Challenge	Log Untransformed													
	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Mean Diameter Early Phase Response (15m)														
Wheal/Flare data	C	C	C	Y			Y				Y	Y		Y
Mean Diameter Late Phase Response (6h)														
Wheal/Flare data	C	C	C	Y			Y				Y	Y		Y

NOTES :

- T = Table, F = Figure, L = Listing, Y = Yes display generated, C=Display conditional on other results.
- Stats Analysis = Represents TFL related to any formal statistical analyses (i.e. modelling) conducted.
- Summary = Represents TFL related to any summaries (descriptive statistics) of the observed raw data.
- Individual = Represents FL related to any displays of individual subject observed raw data.

Weighted Mean TNSS

The weighted means of the TNSS values (AM and PM values combined into an overall daily score prior to deriving WM) will be derived for each diary card week. They will be analysed using a similar model to FeNO (Section 8.4.2.3.5) except the response is not anticipated to require any transformation, so the model should be modified to examine differences and not ratios and to account for the additional Follow Up Visit timepoints.

Baseline would be the Day 1 AM TNSS value and Visit would be the week (of each weighted mean).

Conditional on the above output the following may be attempted (and would be assigned the next available output number):

Modelling repeated as above for AM and PM weighted means (derived separately; with Baseline being Day 1 AM TNSS in both models)

Each individual TNSS component may have weekly Weighted Means determined and modelled (for overall and separate AM and PM endpoints; with baseline term being the respective TNSS component from Day 1 AM).

Intradermal Allergen Challenge

Summary statistics for the absolute and change from baseline values will be produced, along with a Figure of the change from baseline values. Further Statistical modelling is conditional on i) review of these summary outputs and ii) other study results / outcomes and would be similar to the other repeated measures models fitted in this study (main aim to compare the treatment effects within each visit). Further details of any statistical modelling would be provided in the CPSR.

Note: Intradermal Allergen Challenge test procedures will not be performed on subjects if the allergen manufacturer is “Allergopharma” (i.e. no data for those individuals). This manufacturer is being used as a solution in response to anticipated supply issues during the clinical study, and may impact on a number of individuals. If the proportion of missing data is large then statistical modelling may not take place.

10 REFERENCES

- GSK Document No.: 2015N264314_02, Study 205540: A randomised, double-blind (sponsor open) placebo-controlled, parallel group, 8-week treatment study to investigate the safety, pharmacodynamics, and effect of the TLR7 agonist, GSK2245035, on the allergen-induced asthmatic response in subjects with mild allergic asthma, 27-Feb-2017.
- Leaker B, Singh D, Lindgren S, Kallen A, Almqvist G, Young B, O'Connor B. The Effects Of The Novel Toll-Like Receptor 7 (TLR7) Agonist AZD8848 On Allergen-Induced Responses In Patients With Mild Asthma. American Thoracic Society International Conference; San Francisco, California, USA, 2012.
- Liverani S., Hastie D I, Azizi, L., Papathomas, M., Richardson, S. PReMiuM: An R Package for Profile Regression Mixture Models Using Dirichlet Processes. Journal of Statistical Software March 2015 Volume 64 Issue 7, 2015.
- Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Culver B, Enright P, Hankinson J, M lp, Zheng J, Stocks J. Multi-Ethnic Reference Values for Spirometry for the 3-95 yr Age Range: The Global Lung Function 2012 Equations. European Respiratory Journal, 2012.
- Spiegelhalter, D. J, Best, N. G., Carlin, B. P., Van der Linde, A. Bayesian Measures of Model Complexity and Fit, Journal of the Royal Statistical Society, Series B, 64(4), 583–616, with discussion, 2002.
- Valles Y, Artacho A, Pascual-Garcia A, Ferrus ML, Gosalbes MJ, Abellán JJ, Francino MP Microbial Succession in the Gut: Directional Trends of Taxonomic and Functional Change in a Birth Cohort of Spanish Infants. PLoS Genet 10(6): e1004406. Doi:10.1371/journal.pgen.1004406, 2014.

11 APPENDICES

Section	Appendix
RAP Section 4 : Analysis Populations	
Section 11.1	Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population
RAP Section 5 : General Considerations for Data Analyses & Data Handling Conventions	
Section 11.2	Appendix 2: Assessment Windows
Section 11.3	Appendix 3: Treatment States & Phases
Section 11.4	Appendix 4: Data Display Standards & Handling Conventions • Study Treatment & Sub-group Display Descriptors • Baseline Definitions & Derivations • Reporting Process & Standards
Section 11.5	Appendix 5: Derived and Transformed Data • General, Study Population & Safety • Efficacy • Pharmacokinetic • Pharmacodynamic and or Biomarkers
Section 11.6	Appendix 6: Premature Withdrawals & Handling of Missing Data • Premature Withdrawals • Handling of Missing Data
Section 11.7	Appendix 7: Values of Potential Clinical Importance • Laboratory Values • ECG • Vital Signs
Section 11.8	Appendix 8: Multicentre Studies
Section 11.9	Appendix 9: Examination of Covariates and Subgroups
Section 11.10	Appendix 10: Multiple Comparisons and Multiplicity
Section 11.11	Appendix 11: Model Checking and Diagnostics for Statistical Analyses
Other RAP Appendices	
Section 11.12	Appendix 12: Abbreviations & Trade Marks
Section 11.13	Appendix 13: List of Data Displays
Section 11.14	Appendix 14: Example Mock Shells for Data Displays (see separate document: RAP-Mock Tables-205540.doc)

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

11.1.1 Exclusions from Per Protocol Population

The Protocol Deviation Management Plan (PDMP) contains more detail on the specific items that may cause subjects to be excluded from the per protocol population. In general a subject meeting any of the following criteria is expected to be excluded from the Per Protocol population (as described in the PDMP reviews and decisions will occur on a case by case basis):

Number	Exclusion Description
01	Failure of any inclusion/exclusion criteria, but subject is still enrolled.
02	Subject took short-acting beta-agonist (SABA) more than 2 days per week on average.
03	Subject did not receive all 8 doses of planned medication (Placebo or GSK2245035).
04	Subject did not receive the same allergen dose during study period as that determined at Screening (except for cases where the dose was reduced for safety reasons- in which case the same (reduced) dose must be used at all follow up challenges (otherwise the individual should be excluded)).

11.2 Appendix 2: Assessment Windows

11.2.1 Definitions of Assessment Windows for Analyses

Data Management are responsible for documenting and implementing the visit windows in this study. If an item is within its visit window it should be transferred to statistics and programming using the corresponding timeslicing key (items that fall outside of the window may be transferred using unscheduled timeslicing keys with the corresponding planned items containing no data). In addition this should also be captured in the protocol deviations dataset. For the purposes of AE, DRE and CRS assignments the algorithms described in Section 11.3.2 should be used.

11.3 Appendix 3: Treatment States and Phases

11.3.1 Treatment Phases

Assessments and events will be classified according to the time of occurrence relative to dosing.

Treatment Phase	Definition
Pre-Treatment	Date/Time < Study Treatment Start Date/Time
On-Treatment*	Study Treatment Start Date/Time ≤ Date/Time ≤ Study Treatment Stop Date/Time+7
Post-Treatment*	Date/Time+7 > Study Treatment Stop Date/Time

NOTES:

- * Treatment phase assumes that the effects of study treatment duration will last a week.
- Study Treatment Start relates to the 1st dose received by the individual and the Study Treatment Stop relates to the final dose received by the individual

11.3.2 Treatment States

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

11.3.2.1 Treatment States for AE (and DRE) Data

Treatment State	Definition
Pre-Treatment	AE Start Date/Time < Study Treatment Start Date/Time
On-Treatment*	If AE onset date/time is on or after treatment start date/time & on or before treatment stop date/time. Study Treatment Start Date/Time ≤ AE Start Date/Time ≤ Study Treatment Stop Date/Time + 7
Post-Treatment*	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date + 7
Onset Time Since 1st Dose (Days)	If Treatment Start Date > AE Onset Date = AE Onset Date – Treatment Start Date If Treatment Start Date ≤ AE Onset Date = AE Onset Date – Treatment Start Date + 1 Missing otherwise.
Duration (Days)	AE Resolution Date – AE Onset Date + 1
Drug-related$^{\Delta}$	If relationship is marked 'YES' on eCRF OR value is missing

NOTES:

- * Treatment phase assumes that the effects of study treatment duration will last a week.
- Study Treatment Start relates to the 1st dose received by the individual and the Study Treatment Stop relates to the final dose received by the individual. If the study treatment stop date is missing then the AE will be considered to be On-Treatment.
- Δ=Not applicable/required for DRE

11.3.2.2 Treatment States for CRS Events Data

Treatment State	Definition
Pre-Treatment	CRS Start Date/Time < Study Treatment Start Date/Time
On-Treatment Week i i=1, 2, 3, …, 7	If CRS Start Date/Time is on or after i^{th} dose of treatment start date/time & on or before $(i+1)^{th}$ dose of treatment stop date/time. I^{th} Study Treatment Dose Start Date/Time ≤ CRS Start Date/Time ≤ $(i+1)^{th}$ Study Treatment Start Date/Time
Post-Treatment*	If CRS onset date is after the last dose of treatment start date/time + 7 ie, CRS Start Date/Time > Study Treatment Stop Date/Time + 7.
Onset Time Since 1st Dose (Days)	If Treatment Start Date > CRS Onset Date = CRS Onset Date – Treatment Start Date If Treatment Start Date ≤ CRS Onset Date = CRS Onset Date – Treatment Start Date + 1 Missing otherwise.
Duration (Days)	CRS Resolution Date – CRS Onset Date + 1
Drug-related	If relationship is marked 'YES' on eCRF OR value is missing

NOTES:

- * Treatment phase assumes that the effects of study treatment duration will last a week.
- If the study treatment stop date is missing then the CRS event will be considered to be On-Treatment during Week 1.

11.4 Appendix 4: Data Display Standards & Handling Conventions

11.4.1 Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions (Main / default)			
RandAll NG		Data Displays for Reporting	
Code	Description	Description [1]	Order [2]
A	Placebo intranasal once weekly	Placebo	1
B	GSK2245035 20ng i.n. once weekly	20 ng GSK2245035 i.n. once weekly	2

NOTES:

1. Abbreviated versions of the treatment descriptions are also permissible if space is restricted e.g., 20ng GSK2245035.
2. Order represents treatments being presented in TFL, as appropriate.

Alternative Treatment Group Descriptions #1			
RandAll NG		Data Displays for Reporting	
Description	Stratum	Description [1]	Order [2]
Placebo	Presumed Allergen	Placebo: Presumed Allergen	1
	Unknown Allergen	Placebo: Unknown Allergen	2
20 ng GSK2245035 i.n. once weekly	Presumed Allergen	20 ng GSK2245035 i.n. once weekly: Presumed Allergen	3
	Unknown Allergen	20 ng GSK2245035 i.n. once weekly: Unknown Allergen	4

NOTES:

1. Abbreviated versions of the treatment descriptions are also permissible if space is restricted e.g., 20ng GSK2245035: Pres, 20ng GSK2245035: Unk; or Pbo P, Pbo U, 20ng P, 20ng U
2. Order represents treatments being presented in TFL, as appropriate.

11.4.2 Baseline Definition & Derivations

11.4.2.1 Baseline Definitions

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

Parameter	Study Assessments Considered As Baseline					Baseline Used in Data Display/ Analysis
	Screening Visit 1	Screening Visit 2	24H After Screening Visit 2	Day 1 Pre-dose	Pre-Dose on Corresponding Dosing Visit	
Efficacy						
LAR Minimum FEV_1		X				Screening Visit 2
LAR: WM FEV_1		X				Screening Visit 2
EAR Minimum FEV_1		X				Screening Visit 2
EAR: WM FEV_1		X				Screening Visit 2
Laboratory						
Chemistry				X		Day 1 Pre-dose
Haematology				X		Day 1 Pre-dose
Safety						
ECG				X		Day 1 Pre-dose
Vital Signs (excluding body temperature)				X		Day 1 Pre-dose
Nasal Examination				X		Day 1 Pre-dose
Body Temperature					X	DV<x> Pre-Dose
Pharmacodynamic and Biomarker (including FeNO) (See Specific model details in Section 8.4.2)						
Other Exploratory Endpoints (excluding Diary Card data)						
IAC Wheal/Flare Early Phase		X (15M)				Screening Visit 2 (15M)

Parameter	Study Assessments Considered As Baseline					Baseline Used in Data Display/ Analysis
	Screening Visit 1	Screening Visit 2	24H After Screening Visit 2	Day 1 Pre-dose	Pre-Dose on Corresponding Dosing Visit	
IAC Wheal/Flare Late Phase		X (6H)				Screening Visit 2 (6H)

NOTES :

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

11.4.2.2 Derivations and Handling of Missing Baseline Data

Definition	Reporting Details
Change from Saline[1]	=Highest Challenge Value – Highest Saline Value
% Change from Saline[1]	= 100 x [(Highest Challenge Value – Highest Saline Value) / Highest Saline Value]
% Attenuation of Reference Response	= 100 x [1-(Test Mean/Reference Mean)]
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Maximum Change from Baseline	= Calculate the change from baseline at each given time point and determine the maximum change

NOTES :

- Unless otherwise specified, the baseline definitions specified in Section 11.4.2.1 Baseline Definitions will be used for derivations for endpoints / parameters and indicated on summaries and listings.
- Unless otherwise stated, if baseline data is missing no derivation will be performed and will be set to missing.
- The baseline definition should be footnoted on all change from baseline displays.

1. Example of calculations of Change and % Change from Saline in the BAC:

Challenge concentration (squ/mL)	Planned relative time	FEV1 (L)	Max FEV1 (L)	FEV1 Change from Max Saline (L)	(%)
Saline	2 M	3.79	**4.02**		
	3 M	4.02			
	4 M	3.83			
45250	5 M	4.11	4.11	0.09	2.2
	10 M	4.08	4.08	0.06	1.5
	15 M	3.86	3.86	-0.16	-4.0
	20 M	3.97	3.97	-0.05	-1.2
	30 M	4.16	4.16	0.14	3.5
	45 M	4.12	4.12	0.10	2.5
	1 H-READ 1	4.14	4.14	0.12	3.0
	1 H-READ 2	3.76			

11.4.2.3 Imputation for Values Below and Above Limit of Quantification

PD responses which are below the assay's respective lower limit of quantification (LLQ) will be imputed using half of the LLQ value.

PD responses which are above the assay's respective upper limit of quantification (ULQ) will be imputed using the ULQ value.

In the event that multiple LLQ/ULQ values are present the minimum for that analyte (for LLQ) and maximum for that analyte (ULQ) should be used in the imputations. If any LLQ values are zero then a suitable small constant may be used in place, to allow the data to be log transformed (for example half of the smallest observed non-zero value).

11.4.3 Reporting Process & Standards

Reporting Process	
Software	
• The currently supported versions of SAS and S-Plus software will be used.	
Reporting Area	
HARP Server	uk1salx00175
HARP Area*	\arprod\gsk2245035\mid205540\final (for CSR) \arprod\gsk2245035\mid205540\headline (for Headline Results) \arprod\gsk2245035\mid205540\interim (for Interim Analysis)
QC Spreadsheet	\arwork\gsk2245035\mid205540\final\documents (for CSR) \arwork\gsk2245035\mid205540\headline\documents (for Headline Results) \arwork\gsk2245035\mid205540\interim\documents (for Interim Analysis)
*=upcoming functionality change in HARP v7 may impose naming conventions which would supersede these suggestions for reporting effort names	
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards	
Intermediate Datasets	
• 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 imposed in the upcoming v7 release and existing limitations on special characters, but the following is proposed (it may be modified as necessary/appropriate): • The file name is made up of components joined by underscores. This should allow items to automatically group/sort when viewed as a list.	

Component ID	Description	Examples	Clarification
1	Three letters aligning item to its closest study objective	BAC NAC TL7	Bronchial Allergen Challenge Nasal Allergen Challenge Target engagement

Reporting Process

		IDX	Intradermal Challenge
2	Single letter if the response variable was Univariate or Multivariate	U M	Univariate Multivariate
3	Three letters for the sample matrix	FEV SPU NLS NLF SRM	FEV1 (Lung data) Sputum Nasal Lavage Fluid Nasal Lavage Filters Serum
4	Up to 5 letters for the Item/Analyte (can exceed 5 if BICATCD values are longer)	LARWM LARMI EARWM EARMI <Bicat code>	LAR WM 4-10h CFB FEV1 LAR Min CFB FEV1 EAR WM 0-2h CFB FEV1 EAR Min CFB FEV1 <Taken from SI.BIOMARK and/or dataset manager>
5	Single digit Population code	1 2 3 4 etc	All Subjects Per Protocol mITT Sputum Producers (Statistician will need to track assignments)
6	Single digit Model ID (may vary depending on the analysis, so model 1 can have different meanings across objectives/sample matricies/endpoints)	1 2 etc	Pre-BAC Samples only All BAC Samples (Statistician will need to track assignments on a per objectives/sample matricies/endpoint basis)
7	Double digit Analysis ID (specific to the modelling, can be used to store the R1-R3 outputs and models fitted whilst covariate building or the models with informative priors)	01 02 03 04 etc	Statistician will need to track on a per item basis
8	MCMC related item	dsetin poall pokdein + Others as required	The dataset that was passed to MCMC Posterior Summary Stats (processed and ready for display) Posterior samples

- Example for the input dataset passed to PROC MCMC for the Primary analysis of LAR WM4-10h CFB Saline Baseline using the PP population (analysis ID 01):

Reporting Process
"BAC_U_FEV_LARWM_2_1_01_dsetin" • Example for the Output statistics (Medians and credible intervals) for the Background samples of Nasal Lavage IL-5 using the All Subjects population: "NAC_U_NLS_IL5_1_1_01_poall" • The above naming convention (excluding item 8) can also be used to name the respective reporting effort SAS programs / macros that implement the different analyses
Generation of RTF Files
• RTF files will be generated for all reporting efforts.

Reporting Standards
General
• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated: o 4.03 to 4.23: General Principles o 5.01 to 5.08: Principles Related to Data Listings o 6.01 to 6.11: Principles Related to Summary Tables o 7.01 to 7.13: Principles Related to Graphics
Formats
• All data will be reported according to the actual treatment the subject received unless otherwise stated. • GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time
• Reporting for tables, figures and formal statistical analyses : • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated. • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate. • Reporting for Data Listings: • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1). • Unscheduled or unplanned readings will be presented within the subject's listings. • Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from figures, summaries and statistical analyses.

Reporting Standards

Unscheduled Visits

- Unscheduled visits will not be included in summary tables.
- Unscheduled visits will not be included in 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, %
Reporting of Pharmacokinetic Concentration Data	
Descriptive Summary Statistics	Refer to IDSL Statistical Principle 6.06.1 Assign zero to NQ values (Refer to GUI_51487 for further details)

Graphical Displays

- Refer to IDSL Statistical Principles 7.01 to 7.13.
- Where possible the following colour scheme will be adopted noting that treatment comparisons against Placebo will utilise the style of GSK2245035 treatment:

Treatment	Colour	Plotting Symbol	Line Style
Placebo once weekly	Blue	Circle, Solid	Solid
20 ng GSK2245035 i.n. once weekly	Orange	Triangle (up), Solid	Solid

If applicable, eg individual subject profile plots, a different line style can be applied to distinguish Allergen Exposure in the Efficacy Figures.

Treatment	Allergen Exposure Strata	Colour	Plotting Symbol	Line Style
Placebo once weekly	Presumed	Blue	Circle, Solid	Solid
	Unknown	Blue	Circle, Hollow	ShortDash
20 ng GSK2245035 i.n. once weekly	Presumed	Orange	Triangle (up), Solid	Solid
	Unknown	Orange	Triangle (up), Hollow	ShortDash

In some displays the visits need to be distinguished, in which case the following colour scheme should be used whenever possible

Reporting Standards

Visit	Colour (SAS Syntax)	Plotting Symbol	Line Style
Screening Visit 1	bioy	Circle, Solid	Solid
Screening Visit 2	green	Diamond, Solid	Solid
Dosing Visit 1	pink	Circle, Solid	LongDash
Dosing Visit 2	brown	Diamond, Solid	LongDash
Dosing Visit 3	dep	HomeDown, Solid	Solid
Dosing Visit 4	lime	Square, Solid	LongDash
Dosing Visit 5	parp	Star, Solid	LongDash
Dosing Visit 6	salmon	Triangle, Solid	Solid
Dosing Visit 7	vlib	TriangleDown, Solid	Solid
Dosing Visit 8	magenta	TriangleLeft, Solid	Solid
Follow Up Visit 1	red	Star, Solid	Solid
Follow Up Visit 2	cyan	Square, Solid	Solid
Follow Up Visit 3	purple	TriangleRight, Solid	Solid

Note: If there is a need to also distinguish the allergen exposure strata then use of Solid/Hollow symbols and Solid/ShortDashed lines can be made, as in the above treatment example (with any LongDash mapping to Dot)

11.5 Appendix 5: Derived and Transformed Data

11.5.1 General

Multiple Measurements at One Time Point
• Generally, mean of the measurements will be calculated, unless replicate FEV_1 or PEF measurements exist in which case the maximum will be utilised, and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window the value closest to the target day for that window will be used. If values are the same distance from the target then the mean will be taken. • Subjects having both High and Low values for Normal Ranges at any post-baseline visits for safety parameters will be counted in both the High and Low categories of 'Any visit post-baseline' row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

11.5.2 Study Population

Demographics
Age
• GSK standard IDSL algorithms will be used for calculating age where birth date will be imputed as follows: ○ Date and month will be imputed as '30th June' for every subject. • Birth date will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg)/Height $(m)^2$
Predicted FEV_1
• Calculated using (Quanjer, 2012), the website www.ers-education.org/guidelines/global-lung-function-initiative has resources such as a SAS macro and an Individual Subject Excel Spreadsheet downloadable from the Tools section of the website that will be provided to the sites (see SRM).

Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Number of Weekly Doses** • Subjects who were randomised but did not report a treatment start date and stop date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of Total Weekly Doses**

11.5.3 Safety

ECG Parameters

RR Interval

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

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

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

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

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

Corrected QT Intervals

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

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

Adverse Events

- MedDRA version 19.0 or later will be used for coding of AE's.

Disease Related Events

- The following DREs are common in subjects with mild allergic asthma and can be serious/life threatening:
  - wheeziness
  - chest tightness or chest heaviness
  - coughing

The start and stop date/time would be recorded for each DRE. The time since 1st dose and time since most recent dose should be computed for each DRE.

Cytokine Release Syndrome (CRS)

- CRS events will be captured on a modified version of GSK's standard non-serious AE eCRF page. The modification captures whether the item is a CRS event and, if it is, its CRS grading score.
- For the purposes of summarising data the GSK AE preferred terms (as coded by the dictionary groups using the latest version of MEDDRA) will be mapped to the CRS categories as shown below:

CRS Category	Examples of GSK AE (Verbatim) Terms that might be mapped to each CRS category via MEDDRA	MEDDRA Preferred terms (Codes) Note: Should be cross checked at time of analysis since codes may be superseded if MEDDRA version changes
Headache	Headache	Headache (10019211) Sinus headache (10040744)
Fever	High temperature, feeling hot and cold & shivering	Pyrexia (10037660) Body temperature increased (10005911) Feeling hot (10016334) Hyperhidrosis (10020642)
Chills/Rigors	Shivering & trembling	Chills (10008531) Feeling cold (10016326) Influenza like illness (10022004)
Nausea	Feeling sick	Nausea (10028813)
Vomiting	Being sick	Vomiting (10047700)
Diarrhoea	Loose stools & frequent bowel movements	Diarrhoea (10012735)
Arthralgia	Arthralgia	Arthralgia (10003239) Musculoskeletal stiffness (10052904)
Myalgia	Achy Muscles	Myalgia (10028411) Back pain (10003988) Neck pain (10028836) Pain (10033371) Pain in extremity (10033425)
Hypotension	Low blood pressure	Hypotension (10021097)

Note: The above may not be an exhaustive list. Therefore, prior to unblinding the medical monitor shall review a list of distinct AE preferred terms observed in the study and ensure that they are all assigned/mapped to a single CRS category (if the preferred term does not relate to a CRS category then it can be mapped as non-CRS; further queries may be raised with the sites if a term was not marked by the site as a CRS event but maps to a CRS category via its MEDDRA coding).

- In the event that multiple terms with different CRS grading scores are mapped to the same CRS category the worst case score (highest severity) should be used in any TLFs.
- For each CRS category the total number of occasions (visits) each subject experienced any non-zero grade of CRS event should be derived (should range between 0 and 8 if the subject completed all dosing visits as planned). This should also be expressed as a proportion of the actual dosing visits attended by the subject.

- For each subject and dosing visit combination the number of different CRS event categories should be derived (where the subjects reported any non-zero grade event); e.g. Subject P experienced 3 different CRS event types at dosing visit 1, 0 CRS event types at dosing visit 2, 4 CRS event types at dosing visit 3, etc.

Rescue Medication

Rescue medication (e.g. Salbutamol) administered as part of the BAC procedures will not be reported separately (it may be reported as part of the con med listings).

Prior to DBF the medical monitor should review the unique medications in the con med dataset to flag any items that should be classified as rescue medications.

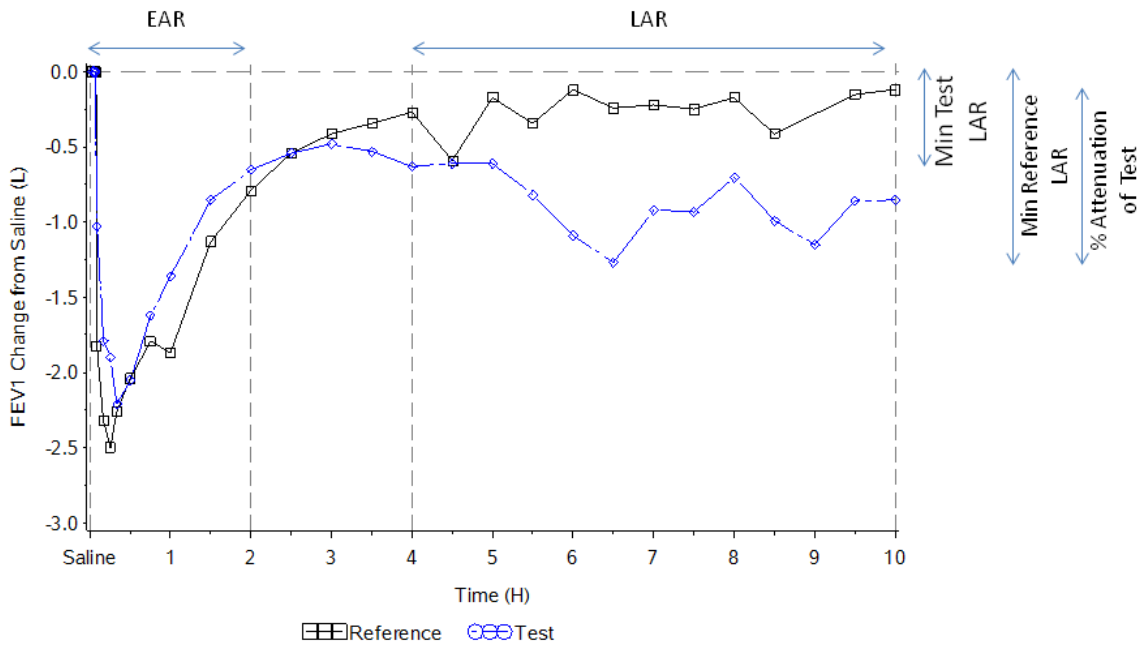
Laboratory Parameters

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

11.5.4 Efficacy

LAR and EAR

Schematic



Weighted Mean is defined using the area under the curve divided by the duration of the interval (details below).

$$\text{Percentage } \textit{Attenuation} \text{ of Reference Response} = \left(1 - \frac{\text{Test Adjusted Mean}}{\text{Reference Adjusted Mean}}\right) \times 100$$

LAR

General Considerations

- FEV_1 measurements taken following the administration of saline will be used as the time zero assessment.
- In the event that the administration of saline was repeated for safety reasons (saline values must be within 10% of the pre-saline values) the latest saline FEV_1 values prior to the administration of allergen will be used.
- Pre-saline FEV_1 values and the FEV1 values recorded as part of the allergen concentration selection phase in the Incremental BAC challenge (Screening visit 2) are not expected to be used in the statistical analysis of the BAC data but will be included in the subject listings if available (e.g. should the coasting procedure occur then it is only planned to database the FEV1 values associated with the final outcome but any repeat pre-saline values may be captured).

Weighted Mean LAR

- Weighted mean will be calculated for FEV_1 using the linear trapezoidal rule (see formula below).
- Actual relative times will be used for the calculation except where actual times are missing. If any actual times are missing, planned relative time will be used for these

LAR and EAR

observations. Actual relative time will be the time relative to the last inhalation stop time.

- The weighted mean will be calculated as the $AUC_{(tf-tl)}$ divided by the t_f- t_l hrs time interval for each subject (t_f = time of first observation, t_l = time for last observation).

$$\text{Weighted Mean}\,(f-l) = \frac{1}{2}\sum_{f-l}\frac{(C_{i+1}+C_i)(t_{i+1}-t_i)}{t_f - t_l}$$

where,

C_i = highest FEV_1 value at planned relative time point I

t_i = actual time for planned relative time point i

i = planned relative time of assessment relative to challenge (i.e. 4 hrs, 4.5 hrs, 5 hrs, 5.5 hrs, 6 hrs, 6.5 hrs, 7 hrs, 7.5 hrs, 8 hrs, 8.5 hrs, 9 hrs, 9.5 hrs and 10 hrs)

f = first I

l = last I

- If an observation is missing between two non-missing observations, the AUC will be linearly interpolated between the two non-missing values i.e., the subject's profile will be assumed to be linear between the two available values. No imputation will be made if either the first or last observation is missing.
- If the number of missing values is considered to be substantial, or if the data is not considered to be missing at random, a sensitivity analysis will be carried out with respect to methods of handling missing data in the calculation of the weighted mean.
- The weighted mean will be set to missing for the relevant challenge if any of the following occurs:
  - A short-acting inhaled β-agonist is taken within 8 hours at any time prior to the challenge
  - The dose of allergen administered is different to that of the Screening dose. Note that the dose of allergen used during the treatment period may be modified from the total dose received at screening, for safety reasons, at the discretion of the investigator. However, in this case, the modified dose used must be consistent for all follow up visits. [In these cases the baseline will be set to missing.]
- The weighted mean LAR will be set to missing if the subject took rescue medication prior to the LAR period i.e., between 0 and 4 hours post-saline.
- If rescue medication is administered during the LAR period prior to the completion of the 10 hour FEV_1 assessment, all FEV_1 values recorded after the administration of rescue medication for that challenge will be set to the last recorded FEV_1 value prior to the administration of rescue medication. The LAR does not have the same natural recovery as the EAR, hence this is the most appropriate derivation for the LAR. The weighted mean LAR will then be calculated as above, using the imputed data set.
- If the use of rescue medication is widespread and/or appears to follow a trend, appropriate sensitivity analyses to examine the impact of the derivations may be conducted. For example, if a large number of subjects are rescued at around 8 hours, the weighted mean LAR over 4-8 hours may be derived and analysed as a sensitivity analysis. All sensitivity analyses will be documented in the CPSR.
- There may be other conditions that effect the LAR response. In such situations it may be necessary to set the respective response to missing. Such scenarios will be

LAR and EAR

identified and documented before unblinding or DBF. Appropriate, sensitivity analyses may be conducted if other situations are noted following unblinding or DBF.

Minimum LAR

- Minimum FEV_1 over 4-10 hrs post–saline challenge will be the minimum value of all the post-saline time points between 4 to 10 hours post-allergen challenge, inclusive of 4 hrs and 10 hrs time points i.e., minimum over 4 hrs, 4.5 hrs, 5 hrs, 5.5 hrs, 6 hrs, 6.5 hrs, 7 hrs, 7.5 hrs, 8 hrs, 8.5 hrs, 9 hrs, 9.5 hrs and 10 hrs.
- Note that the maximum FEV_1 value at each planned relative time point will be derived, where replicates are taken, for every subject and period, before the minimum values are calculated over the specified time period above.
- The minimum will be set to missing for the relevant challenge if either of the following occurs:
  - The subject did not receive the correct dose of study medication at any of the 8-weekly visits.
  - A short-acting inhaled β-agonist is taken within 8 hours at any time prior to the challenge.
  - If subject took rescue medication prior to the LAR period i.e. between 0 and 4 hours post-saline administration.
- The incorrect dose of allergen is administered for the respective BAC. Note that the dose of allergen used during the treatment period may be modified from the total dose received at screening for safety reasons at the discretion of the investigator. However, in this case, the modified dose used must be consistent for all follow up visits. In these cases only the baseline value will be set to missing (essentially removing the subject from any statistical modelling that has the baseline term as a covariate).

There may be other conditions that affect the LAR response. In such situations it may be necessary to set the respective response to missing. Such scenarios will be identified and documented before unblinding. Appropriate, sensitivity analyses may be conducted if other situations are noted following unblinding.

EAR

Weighted Mean EAR

- Weighted mean EAR will be calculated for FEV_1 using the linear trapezoidal rule as per LAR (see above) except using the appropriate EAR time points (i.e., 0 m, 5 m, 10 m, 15 m, 20 m, 30 m, 45 m, 1 hr, 1.5 hrs and 2 hrs).
- In the event that rescue medication is administered prior to the completion of the 2 hour FEV_1 assessment, the weighted mean will be calculated using only FEV_1 values up to the point of administration of rescue medication. This is considered the most appropriate derivation, given the natural self-limiting profile of the EAR.

Minimum EAR

- Minimum EAR will be calculated for FEV_1 as per LAR (see above) except using the appropriate EAR time points (see above) ie, 0-2 hrs post-saline challenge will be the minimum value of all the post-allergen challenge time points up to and including 2 hours post-allergen challenge i.e., minimum over 5 m, 10 m, 15 m, 20 m, 30 m, 45 m and 1 hr, 1.5 hrs and 2 hrs. Note, saline time point (i.e. 0 hr value) will not be included in this calculation.

11.5.5 Pharmacodynamic and Biomarker

Pharmacodynamic/Biomarker

TRL7 Induced Blood PD Biomarkers

- Fold changes should be computed relative to the Visit 1 pre-dose response (DV1 Pre-Dose), and if applicable, to the corresponding pre-dose value from that dosing visit (one value per subject per visit and time point combination). Fold changes should be computed using the imputed responses.

Sputum Differential Cell Counts

This section is based on understanding of the process and expected data items at time of RAP writing. Please consult with GSK Study Statistician at reporting time to confirm what manipulation steps are required, as process details may be changed in-stream as experience is gained (modifications wouldn't be captured via a formal RAP amendment but would be documented by the GSK study statistician via a note to file - if no changes are required then there will be no related note to file).

The following will be provided as source data from the eCRF. The vendor counting the slides would not have access to these values, hence why additional data manipulation is required by GSK Stats and Programming.

- 'Total Cell Count (Total Non-Squamous Cells in sample)'
  [Equation 4 in the Sputum processing worksheet]

- 'Total Leukocytes Count (Total Non-Squamous Cells) per Gram of Selected Sputum Cells'
  [Equation 6 in the Sputum processing worksheet]

- '% Viable Leukocytes (% Viability of non-squamous cells)'
  [Equation 1 in the Sputum processing worksheet]

Pertinent information to the planned data manipulations that the vendor counting the slides would return to GSK data management is:

- Was the slide rejected (Y/N) (and if Y the reasons for rejection)

- For each slide reader (up to three readers possible): Cell counts of the following types: eosinophils, neutrophils, macrophages, lymphocytes, BEC (bronchial epithelial cells) and squamous cells. These counts are from a representative set of cells counted on each slide (vendor expect to count a maximum of ~600 cells to get a minimum of ~400 non-squamous cells on each slide).

- The actual numbers of cells counted on the slide are also provided as "Total Cell Count" (sum of all cell types) and "Total non-squamous cell count" (sum of cell types; eosinophils, neutrophils, macrophages, lymphocytes and BEC). As a sanity check the supplied slide totals (per reader) should match those slide totals derived by hand using the individual cell type count results.

Only two readers per slide are expected but the vendor may provide readings from a third reader if the results of the initial two readers are sufficiently different (according to the vendor's standard

Pharmacodynamic/Biomarker

operating procedure, currently > 10% for the major cell types eosinophils, macrophages and neutrophils). When >2 readers are supplied whichever pair of readers are closest to each other would be used in the subsequent derivations but data from all readers would be listed (and the reader pair indicated , e.g. R1R3 if Reader1 and Reader 3 used or R1R2 if Reader 1 and Reader 2 used).

The percentage of each leukocyte cell type observed on the slide will be derived for the i^{th} reader as follows (leukocyte cells are eosinophils, neutrophils, macrophages, lymphocytes and BEC)

$$\%\ \text{Leukocyte Cell Type on Slide}_i = \frac{Absolute\ Number\ of\ Leukocyte\ Cell\ Type_i}{Absolute\ Total\ Non\text{-}Squamous\ Cell\ Count_i}$$

Prior to statistical analysis the results for each reader and slide would be "scaled up" to reflect the counts for the sample the slide was constructed with. This requires [Equation 6] information from the eCRF page.

The Absolute Leukocyte Cell Types Counts per gram of sputum for the i^{th} reader are derived as

$$\text{Absolute Leukocyte Cell Type x}10^6\ \text{cells / g sputum}_i = \%\text{Leukocyte Cell Type on Slide}_i * [\text{Equation 6}]$$

The geometric mean of the (two) readers would be derived and used in the statistical analyses that refer to the Absolute Cells/g sputum endpoint (separate variable for each cell type).

A new total non-squamous cell count variable will be created as the sum of the geometric mean's of the Leukocyte cell types. This total would be used to derive the percentage of each leukocyte cell type in the sample (ensures the percentages will sum to 100%) as
"(Geo Mean Abs Leuk Cell Count / Total) * 100".

These % endpoints would be used in statistical analyses (separate variable for each cell type)

The following scenarios may result in a sample being deemed as non evaluable (even if the vendor provided data back):

- Slide not read or rejected
- If the value entered in the eCRF for [Equation 1] $\leq$ 70% (implying more than 30% of the non-squamous cells were not viable). Note: This threshold is study specific and may be altered upon review of the complete dataset in consultation with the GSK biology group
- > 50% squamous cells of the proportion counted
- < 200 total cells counted on the slide
- **Note:** When zero counts are observed for a cell type it complicates the derivation of the geometric means. A constant should be added onto all results in the dataset prior to deriving the reader geometric mean (separate value for the constant for each cell type). The constant should be set to half the smallest observed non-zero scaled up absolute count in the entire dataset for

Pharmacodynamic/Biomarker

that cell type, and if all values are zero in the dataset for the cell type then the variable would not be analysed but the means would be set to zero.

- The following is a worked example for two visits for the same subject.

Values entered on eCRF:

Visit	% Viable Leukocytes (% Viability of non-squamous cells) [Equation 1]	Total cell count (10^6 cells) (Total non-squamous cells in sample) [Equation 4]	Total Leukocytes count (Total non-squamous cell count) per gram of selected sputum (10^6 cells/g) [Equation 6]
1	85	1.062	7.080
2	74	1.11744	6.984

Values supplied by vendor

Visit	Reader	Eos	Neut	Mac	Lym	BEC	Squamous	Tot Non-Squ	Total cells
1	1	2	371	38	0	0	96	411	507
1	2	0	348	43	0	0	109	391	500
2	1	4	342	42	0	2	111	390	501
2	2	0	290	50	0	0	160	340	500

Derived % on slides

Visit	Reader	Eos	Neut	Mac	Lym	BEC			
1	1	0.49	90.27	9.25	0.00	0.00			
1	2	0.00	89.00	11.00	0.00	0.00			
2	1	1.03	87.69	10.77	0.00	0.51			
2	2	0.00	85.29	14.71	0.00	0.00			

Cell counts scaled up to sample and small constant added on to each to allow for zeros (e.g. Add to all scaled up BEC values the constant of 0.0178092 = 0.5 * 0.0051 * 6.984)

Visit	Reader	Eos	Neut	Mac	Lym	BEC			
1	1	0.052038	6.391116	0.6549	0.00	0.018054			
1	2	0.017346	6.3012	0.7788	0.00	0.018054			
2	1	0.089281	6.12427	0.752177	0.00	0.053428			
2	2	0.017346	5.956654	1.027346	0.00	0.017809			

Pharmacodynamic/Biomarker

Geometric Means and Percentages used in statistical analyses (Lym has imputed Geo mean of zero)

Visit	Item	Eos	Neut	Mac	Lym	BEC		Tot Non-Squ	
1	Abs (10^6 cells/g sputum)	0.030044	6.345999	0.714168	0	0.017809		7.108265	
1	%	0.42	89.28	10.05	0	0.25			
2	Abs (10^6 cells/g sputum)	0.039353	6.03988	0.87906	0	0.030846		6.98914	
2	%	0.56	86.42	12.58	0	0.44			

WBC Differentials

- **Note:** When zero percentages are observed the corresponding cell count is also zero. Therefore if the count data require log transformations the constant to add on should be set at half the smallest observed non-zero count in the corresponding dataset

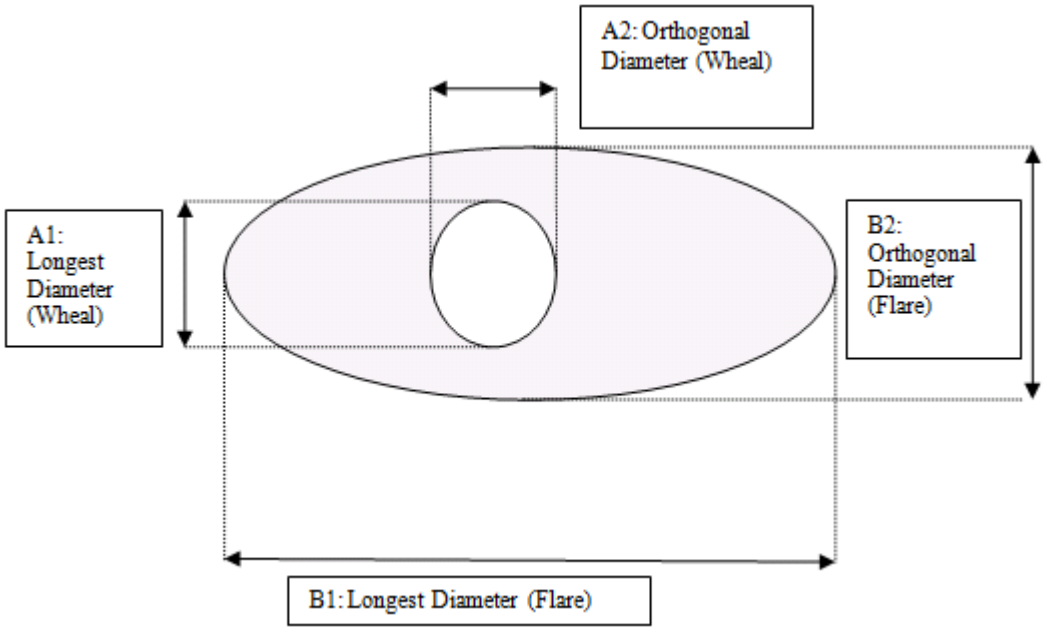
11.5.6 Exploratory Analyses

Intradermal Allergen Challenge

Wheal/Flare Derivations

- The wheal and flare derived value to be used in the summaries and figures will be calculated as follows:
- At each planned timepoint both the Wheal (also referred to as Induration in some study documents) and Flare components will have two measurements databased; namely the longest and orthogonal diameters. The mean diameter for each component is the average of these two values. For display purposes the label “Wheal” should be used rather than “Induration”. An example is illustrated below

Intradermal Allergen Challenge



- Mean Diameter (Wheal) = (A1+A2) / 2
- Mean Diameter (Flare) = (B1+B2) / 2

- For each subject and planned sampling time the Mean Diameter Wheal values for each allergen should be compared to the corresponding Negative control value as an additional data validation check. A flag variable should capture if the Mean Diameter Wheal response on Challenge not at least 3mm larger than the corresponding Negative control value (i.e. flag if Wheal Mean Diameter Challenge – Wheal Mean Diameter Negative Control Challenge <= 3mm).

Total Nasal Symptom Score (Diary card)

Daily Score Derivation (TNSS and its individual components) – daily scores sometimes referred to as "Overall"

- The Daily Score is calculated as the mean of the (non-missing) respective AM and PM assessments (e.g. Daily TNSS = Mean of AM TNSS and PM TNSS values; Daily nasal congestion score = Mean of AM nasal congestion score and PM nasal congestion score, etc. A daily score would only be recorded as missing if both the AM and PM assessment are missing on that day.

Weekly Weighted Mean Derivation

- Each diary card week begins on the planned day of dosing (relative to the date of dosing at DV1) and contains 7 days of data, i.e. Week 1 contains days 1 to 7 inclusive, Week 2 contains days 8 to 14 inclusive etc.
- The weekly weighted means are derived from the 7 days of data using a similar approach to the BAC endpoints. The exceptions are i) no actual time, but only planned times, starting at 1 and ending at 7 for each weeks worth of data, ii) the first and last values (day 1 and 7 within the week) may be missing and a valid WM derived (the

Total Nasal Symptom Score (Diary card)
WM would only not be derived if 4 or more days within the week were missing; in which case the Weekly WM would also be set to missing) and iii) No BAC specific rules e.g. setting WM means to missing based on rescue medication, SABA or incorrect BAC allergen administration. • If the number of missing WM values is considered to be substantial, or if the data is not considered to be missing at random, a sensitivity analysis may be carried out with respect to methods of handling missing data in the calculation of the weighted mean.

11.6 Appendix 6: Premature Withdrawals & Handling of Missing Data

11.6.1 Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as one who has completed all phases of the study including all of the follow-up visits. • Withdrawn subjects may be replaced in the study. • All available data from subjects who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.

11.6.2 Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument : ○ These data will be indicated by the use of a "blank" in subject listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	• Any subjects excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

11.6.2.1 Handling of Missing Dates

Element	Reporting Detail
General	Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 3: Treatment States and Phases. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.

Element	Reporting Detail
	• Start or end dates which are completely missing (i.e. no year specified) will remain missing, with no imputation applied.

11.6.2.2 Handling of Partial Dates

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

11.6.2.3 Handling of Missing Data for Statistical Analysis

The SAS PROC MCMC framework automatically assumes/implements a missing at random / multiple imputation approach if any of the supplied response variables are missing. This is deemed to be sufficient given the exploratory nature of the study. However, if a large proportion of data are missing then alternative approaches may be considered.

Several analyses are specified as being conditional on there being sufficient non-missing data to take place (e.g. Sputum and biomarkers with large proportions of LLQ values).

If model covariates are missing (e.g. Baseline) then the best approach will be selected on a case by case basis, but may involve omitting the record or imputing a response based on other data prior to fitting the observation model.

Given the exploratory nature of this study and the large number of endpoints it is not possible to pre-specify/cover all eventualities but any missing data approaches investigated would be documented in the CPSR and if deemed important included in the outputs as sensitivity analyses.

11.7 Appendix 7: Values of Potential Clinical Importance

11.7.1 Laboratory Values

Hematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.67	1.82
Neutrophil Count		0.83	
Lymphocytes		0.81	
Hemoglobin	Male		1.03
	Female		1.13
Hematocrit	Male		1.02
	Female		1.17
Platelet Count		0.67	1.57
		Absolute – Low	**Absolute – High**
MCV (fL)		< 80	> 100
MCH (pg/cell)		< 25.78	> 34
Monocytes (K/mL)		< 0.1	> 0.9
Eosinophils (K/mL)		< 0	> 0.6
Basophils (K/mL)		< 0	> 0.9

Chemistry Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Albumin (mmol/L)		0.86	
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

Liver Function			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT/SGPT	U/L	High	≥ 2×ULN
AST/SGOT	U/L	High	≥ 2×ULN
Alkaline Phosphatase	U/L	High	≥ 2×ULN
Total Bilirubin	µmol/L	High	≥ 1.5×ULN
Total Bilirubin + ALT	µmol/L	High	1.5×ULN Total Bilirubin
			+
	U/L		≥ 2×ULN ALT

Note: The following lab tests are being collected in this study but have not had PCI ranges defined: RBC Count, BUN, Creatinine, Direct Bilirubin and Total Protein. The maximum and minimum observed values will be reported as part of the lab summary tables and this is deemed sufficient to identify potentially extreme values which would then be investigated further if required.

11.7.2 ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTc Interval	msec		> 450
Absolute PR Interval	msec	< 110	> 220
Absolute QRS Interval	msec	< 75	> 110
Change from Baseline			
Increase from Baseline QTc	msec		> 60

11.7.3 Vital Signs

Vital Sign Parameter (Absolute)	Units	Clinical Concern Range	
		Lower	Upper
Systolic Blood Pressure	mmHg	< 85	> 160
Diastolic Blood Pressure	mmHg	< 45	> 100
Heart Rate	bpm	< 40	> 110
Body Temperature	°C	< 36.0	> 37.5

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
		Clinical Concern Range			
		Lower		Upper	
Body Temperature	°C	< -1		> +1	

11.8 Appendix 8: Multicentre Studies

11.8.1 Methods for Handling Centres

- See Section 11.9.1 for details of how centres will be handled in the statistical modelling.

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

11.9.1 Handling of Covariates, Subgroups & Other Strata

- The following is a list of covariates that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses.
- Additional covariates of clinical interest may also be considered.
- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.
- To avoid parameter estimation problems caused by the small sample size (i.e. empty cells in the possible combinations of centre, treatment and allergen exposure) the default approach (unless specified otherwise) for fitting centre in statistical models is to handle it as a random effect (Normally distributed with mean zero and a SD appropriate to the endpoint). Where possible historical data would be used to form a weakly informative prior for the SD, with the specific value described in the corresponding RAP section. If historical data are not available then the distribution for the random centre effects would use a SD value of 1000.
- For analyses without repeated measures over visit, the output from fitting three nested models (M1-M3) to each statistical analysis should be available (e.g. listing form); but inferences (summary tables and figures) would be produced from the final chosen model only. The three models represent possible combinations of centre (fitted as a random effect), treatment and allergen exposure status (fitted as fixed effects). The models may include other terms appropriate to the analysis, but any further covariate exploration activity would start using the selected model (M1, M2 or M3) as its base:
    - **M1**: Centre + Treatment + Allergen Exposure + Treatment*Allergen Exposure + <other terms>
    - **M2**: Centre + Treatment + Allergen Exposure + <other terms>
    - **M3**: Centre + Treatment + <other terms>

      Where Treatment = “Placebo” or “20ng GSK2245035”, Allergen Exposure = “Presumed allergen” or “Unknown allergen” and Centre is the random effect drawn from the N(0, SD) distribution.
    - The DIC criteria (which may be overruled by expert judgement) would be used to select from Models M1-M3 (see Section 11.11.1). To aid review DIC values from models M1 to M3 should also be summarised in one location in the listing. Examples of expert judgement would be rejecting model M1, even if the DIC

suggested otherwise, if the effect size was deemed to be too small to be clinically important/relevant (i.e. differences in the point estimates for the presumed and unknown allergen exposure responses are clinically unimportant). Other examples of expert judgement include making an overarching decision on the model structure based on all endpoints of a similar nature (e.g. choosing a model form (M1, M2 or M3) for both primary endpoints, or for all serum biomarkers measuring TLR7 induction).

- An analogous set of three models should be used when comparisons of treatment within multiple visits are of interest:
  - **R1**: Centre + Treatment + Visit + Allergen Exposure + Treatment*Visit + Allergen Exposure*Visit + Treatment*Allergen Exposure + Treatment*Allergen Exposure*Visit + <other terms>
  - **R2**: Centre + Treatment + Visit + Allergen Exposure + Treatment*Visit + Allergen Exposure*Visit + <other terms>
  - **R3**: Centre + Treatment + Visit + Treatment*Visit + <other terms>
- If any of the models M1-M3 (or R1-R3) cannot be fitted then the formal process to select models described above is not possible and the default approach should be to use the simplest model form that has acceptable model convergence.

Category	Covariates and / or Subgroups
Centre	One level per site contributing evaluable data to the analysis. Sites may be grouped by country for display purposes. If pooling of centres is deemed necessary the strategy would be to pool centres within the same country before attempting to pool centres over different countries.
Country	Currently planned to be either "UK" or "Germany" but other countries may be utilised.
Allergen Exposure	"Presumed allergen" or "Unknown allergen"
Blood Eosinophil Levels (Cells/mL)	Although the planned statistical modelling will fit this term as a continuous covariate the following categorical variables may be derived based on i) Baseline (SV2) Blood Eosinophils: <150 Cells/mL and >= 150 Cell/mL ii) BAC visit Blood Eosinophil Levels: <150 Cells/mL and >= 150 Cell/mL
Sputum Eosinophil Levels (%) Note: Only if data are available	Although only derivable for subjects/timepoints where sputum samples were produced and were viable the following variables should be created for use as potential categorical covariates based on i) Baseline (SV2) Sputum Eosinophils: <= 2% and > 2% ii) BAC visit Sputum Eosinophils: <= 2% and > 2% iii) Baseline (SV2) Sputum Eosinophils: <= Median of Observed values and > Median of Observed values

Category	Covariates and / or Subgroups
	iv) BAC visit Sputum Eosinophils: <= Median of Observed values and > Median of Observed values
FeNo (Ppb)	Potential categorical covariate based on i) <= 25 ppb and > 25 ppb

11.10 Appendix 10: Multiple Comparisons & Multiplicity

11.10.1 Handling of Multiple Comparisons & Multiplicity

Due to the extensive use of a Bayesian framework and the early phase / exploratory medicine nature of this study there will be no explicit multiplicity adjustments.

11.11 Appendix 11: Model Checking and Diagnostics for Statistical Analyses

11.11.1 Statistical Analysis Assumptions

Endpoint(s)	• All which are modelled using a Bayesian framework
Analysis	• Bayesian (Proc MCMC)

General Considerations for Bayesian Analyses (PROC MCMC):

The following points are for guidance and illustration and do not guarantee a successful model convergence. They cannot cover all eventualities and do not remove the requirement to do what is best for the specific set of observed data being modelled.

Priors:

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

- Non-informative priors of the form Normal(0, Var=1E6) would be assigned to each fixed effect in the proposed statistical model.
- Non-informative Inverse-gamma priors of the form IGamma(0.001,0.001) would be assigned to stand-alone variance parameters that are not expected to take values near zero (e.g. for the residual variance rather than a random effect variance component)
- For stand-alone variance parameters that may take values close to zero a non-informative prior of the form Uniform(0, XXX) may be assigned for the SD
- For repeated measures models non-informative Inverse-Wishart priors will be assigned for the Variance Covariance matrix (VCV). They would use degrees of freedom equal to the dimension of the VCV matrix and an Identity matrix (of the same dimension).
- If there are issues with those variance parameters then the Identitity matrix may be replaced with a diagonal matrix that uses best guesses for the residual variance at each repeated measure time point (or the residual estimates from fitting simple models)
- It is good practice to ensure that each prior distribution is visualised to ensure it appears sensible and allows clinically plausible response values, whilst not allowing impossible values to be drawn with high probability and that if it is intended to be non-informative it is doing so over the region of the likelihood function.
  Note: There is no requirement to formally report these visualisation outputs.

Initial Values:

Unless otherwise specified initial parameter values of zero would be used for the fixed effect parameters and for remaining model parameters initial values may be drawn at random from their respective prior distribution. If model converge is problematic then alternative estimates, more suited to the particular dataset being modelled, may be used (for example, these could be based on visual inspection of the raw data and/or parameter estimates from fitting simpler models).

Checking Convergence and Other Diagnostics:

The key model diagnostic output is the MCSE/SD ratio for each parameter:

- Adequate values for the number of MCMC samples / thinning / number of burn in

samples should be chosen to ensure that the **MCSE/SD for the key parameters is below 0.01** (e.g. key parameters those associated with treatment, or as pre-specified comparisons of interest) in each final model.

- For other model parameters, try to get the **MCSE/SD values as close to 0.01 as possible**, but if there is significant autocorrelation then values **below 0.05 would be considered acceptable.**
- In addition, the number of tuning units and maximum number of tuning iterations may be increased to find a better multivariate normal approximation to the parameters, which in turn may reduce the MCSE/SD values
- Where possible the code should be written to allow the SAS compiler to identify and use conjugate sampling, since this can greatly reduce the corresponding MCSE/SD values
- Models selected with MCSE/SD values above 0.01 (for key parameters) or 0.05 (for other parameters) would need a brief remark/justification added to the QC log and/or CPSR to clarify why it was not possible to reach the targets and why it is believed the subsequent model still has utility.

Use of the default SAS PROC MCMC diagnostic plots should be made and where possible:

- Autocorrelation should decline rapidly and show no oscillation patterns
- Worm plots should show the chain appears to be stationary and mixing, i.e.
  - Constant mean, constant variance
  - Moving around the parameter space freely (not getting "stuck" at similar values for a large number of iterations before moving on again)
  - Moving rapidly between extremes
- The posterior density should look reasonable for each parameter (e.g. for posterior parameters expected to follow a normal distribution the density plot should not appear bi-modal, but for parameters acting as binary flags then bi-modal is acceptable)

Use of a bespoke GSK utility macro "*%ScatterHist*" is encouraged to examine correlation structures between relevant posterior parameters (and/or parameters in each PARMS block). This can provide information about what potential issues may be and also what corrective action(s) may be worthwhile attempting.

(SAS macro code of the most up to date version including any refinements would be available from GSK internal training course materials – modifications may be made to improve axis scales and legibility as required).

Possible corrective actions:
Possible corrective actions include but are not limited to:

- Moving parameters (or combinations of parameters) onto separate PARMS statements (to form blocks that are updated independently in the MCMC algorithms)
- Increasing the number of MCMC draws from the posterior distributions
- Increasing the length of the burn in period
- Increasing the thinning parameter (to reduce the autocorrelation)
- Centring covariates (to reduce correlations between the posterior parameters)
- Re-parameterising the model (e.g. using log-normal prior distributions to stop values being

sampled that are below zero)

- Re-scaling the parameters (e.g. if one parameter takes values orders of magnitudes different to the other model parameters then dividing it by a suitable constant but back transforming the rescaled parameter prior to its use in any subsequent manipulations)
- Visualising the likelihood function of the dataset to determine if there are more appropriate starting estimates (or profiled versions of the likelihood for subsets of model parameters where difficulties are being encountered if it is a high dimensionality problem)
- Consulting with internal GSK experts to resolve the issues

Model selection / Criteria for assessing covariates:

The following is a "rule of thumb" only; the study statistician's expert judgment based on the observed data / context of the endpoint / scientific & biological rationale for including a covariate may override this:

- Changes in Deviance Information Criterion (DIC) may be used to compare models that have been fitted to the same dependent variable (endpoint). In general the model with the lowest DIC would be preferred; although the simpler models would be selected if the differences in DIC were sufficiently small (see below for guidance on what constitutes sufficiently small).
- Since most of the proposed MCMC modeling is undertaken using non-informative priors the DIC approximates Akaike Information Crikteria (AIC) and therefore the AIC "rules of thumb" may be used to guide the selection as follows: Suppose there are R candidate models. Let DIC_1, DIC_2, …, DIC_R be the Deviance Information Criteria for each model and let DIC_{min} be the minimum of these values.
- *"Models receiving DIC within 1–2 of the 'best' (DIC_{min}) deserve consideration, and models within 3–7 have considerably less support"* (Spiegelhalter, 2002). These boundaries have been modified so that there are no gaps as follows: if the difference in DIC is < 1 then choose the simpler model, refine the "deserve consideration" range to be 1< Diff DIC <= 2.5 and the "less support" range to be 2.5 < Diff DIC <=7. Models receiving DIC in excess of 7 from DIC_{min} should not be considered unless there is sufficient scientific/biological rationale for favoring the additional model / covariates.

Utilising the posterior distributions:

- In the relevant statistical analysis sections pre-specified quantities of interest are supplied to be obtained from the posterior distribution (e.g. Table 14). These lists should not be considered exhaustive and may be amended as further information becomes available (for example, but not limited to, if competitors publish results that set a new benchmark then GSK2245035 may be compared to that benchmark by adding it to the list of cut points). Results from any additions should appear after the pre-specified quantities in the corresponding outputs.
- Equi-tail credible intervals should be used, since they are invariant under transformation of the parameter space (unlike Highest Posterior Density).
- In addition, truncation of the x-axis ranges for posterior distributions may be necessary if there are a small number of extreme value posterior samples that would otherwise inhibit interpretation of where the bulk of the distribution lies. Appropriate footnotes should indicate whether axes have been truncated and give an indication of the level of truncation (e.g. 5 values are truncated, or less than 0.1% of posterior samples are truncated).

- To facilitate review the posterior distributions may be grouped into lattice plots to move more towards the "big picture on one page". SAS PROC MCMC uses the density statement in GTL to produce its internal diagnostic figures from the dataset of posterior samples; hence it is possible to re-produce and add customisations to those density plots (such as displaying them in a lattice layout); although it may require on the fly combinations of several of the temporary datasets that store the individual MCMC samples.

11.12 Appendix 12 – Abbreviations & Trade Marks

11.12.1 Abbreviations

Abbreviation	Description
A&R	Analysis and Reporting
Act	Active Drug *in this study 20 ng GSK2245035 i.n. once weekly*
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
ALQ	Above Limit of Quantification
ALT/SGPT	Alanine Amino Transferase / Serum Glutamic-Pyruvic Transaminase
AST/SGOT	Aspartate Amino Transferase / Serum Glutamic Oxaloacetic Transaminase
AZ	AstraZeneca
BAC	Bronchial Allergen Challenge
BEC	Bronchial Epithelial Cells
BLQ	Below Limit of Quantification
BUN	Blood Urea Nitrogen
CB / CFB	Change from Baseline
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
CPMS	Clinical Pharmacology Modelling & Simulation
CrI	Credible interval (may also be denoted CI if context is clear that it refers to an interval)
CRS	Cytokine Release Syndrome
CS	Clinical Statistics
CSR / CPSR	Clinical Study Report / Clinical Pharmacology Study Report (terms can be used interchangeably)
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DIC	Deviance Information Criterion
DOB	Date of Birth
DP	Decimal Places
DVx	x^{th} Dosing Visit (x = 1 to 8)
EAR	Early Asthmatic Response
eCRF	Electronic Case Record Form
EudraCT	European Clinical Trials Database
FDAAA	Food and Drug Administration Amendments Act
FeNO	Fractional exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in 1 Second
FUVx	x^{th} Follow Up Visit (x = 1 to 3)
GSK	GlaxoSmithKline

Abbreviation	Description
GUI	Guidance
HARP	Harmonisation for Analysis of the Reporting Program
IA	Interim Analysis
IAC and/or IAD	Intradermal Allergen Challenge
IC and/or ID	Intradermal Challenge
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
IVRS	Interactive Voice Response System
LAR	Late Asthmatic Response
LLQ	Lower Limit of Quantification
LOC	Last Observation Carries Forward
Max	Maximum
MCMC	Markov Chain Monte Carlo
Min	Minimum
mITT	Modified Intent-To-Treat
MMRM	Mixed Model Repeated Measures
MVN	Multivariate normal distribution
NAC	Nasal Allergen Challenge
Pbo	Placebo
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PP	Per-Protocol
PP	Posterior Probability
QC	Quality Control
QTcB	Bazett's QT Interval Corrected for Heart Rate
QTcF	Fridericia's QT Interval Corrected for Heart Rate
RAMOS (NG)	Randomization & Medication Ordering System (Next Generation)
RAP	Reporting & Analysis Plan
SABA	Short-acting beta-agonist
SAC	Statistical Analysis Complete
SAS	Statistical Analysis System
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SE	Standard Error
SOC	System Organ Class
SOP	Standard Operation Procedure
SVx	x^{th} Screening Visit
TA	Therapeutic Area

Abbreviation	Description
TFL	Tables, Figures & Listings
TLR7	Toll Like Receptor 7
TNSS	Total Nasal Symptom Score
TSCG	TIBCO Spotfire Clinical Graphics
ULQ	Upper Limit of Quantification
VCV	Variance Co-Variance
WM	Weighted Mean

11.12.2 Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS
TSCG

11.13 Appendix 13: List of Data Displays

11.13.1 Data Display Numbering

The following numbering will be applied for RAP generated displays:

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

11.13.2 Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required an example mock-up displays provided in Appendix 14: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Pharmacodynamic and Biomarker	PD_Fn	PD_Tn	PD_Ln
Exploratory	EXP_Fn	EXP_Tn	EXP_Ln

NOTES:

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

11.13.3 Deliverable [Priority] and Responsibility (including AR datasets)

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

NOTES:

1: Indicates priority (i.e. order) in which displays will be generated for the reporting effort [1] = Highest priority, [2] = 2nd highest priority, etc.

Unless indicated otherwise GSK will be responsible for producing each planned output. Outputs marked “FSP” in the “Deliverable Priority” column should be produced by the associated Full Service Provider.

The FSP should discuss with GSK whether they are also responsible for the associated analysis and reporting dataset (AR dataset) if it is not obvious. For example, the ECG outputs are solely the responsibility of the FSP and thus the AR ECG dataset would naturally be their responsibility too, but some outputs can be split between organisations and it may be that additional variables are requested for a common AR dataset by either organisation. For example, the AE dataset has to be modified to contain the study specific CRS related variables, and it is likely that GSK will assume responsibility for the production and QC of this modified AR AE dataset as they will produce it to allow in stream reviews by the Safety Review Team and the production of the related CRS outputs; but that this same dataset will be used by the FSP to produce the standard AE Tables and Listings using the standard macros. The (shared study) QC spreadsheet will document these agreements on the number/names of the AR datasets required to report the study and the associated accountability and QC duties (preliminary discussions / assignments to occur at the GSK and FSP study kick off meeting).

In some instances additional outputs may be required. To avoid GSK and the FSP(s) re-using the same number the (shared study) QC spreadsheet will be the definitive source of output numbers for the study that are not already pre-specified in the RAP. It should be consulted and a record added to allocate/reserve the next available number(s) before creating new display(s) in the HARP system.

11.13.4 Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects	ES1	Summary of Subject Disposition	ICH E3, GSK CTR, FDAAA, EudraCT	IA 1, HR 1, SAC 1
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements Used with Summary of Study Populations and Summary of Subject Disposition to create Consort diagram.	FSP: SAC 1
1.3.	All Subjects	NS1	Summary of Number of Subjects by Country and Centre	EudraCT	IA 1, HR 1, SAC 1
1.4.	All Subjects	NS1	Summary of Number of Subjects by Country, Centre and Allergen Exposure Strata		IA 1, HR 1, SAC 1
Protocol Deviation					
1.5.	All Subjects	DV1	Summary of Important Protocol Deviations	ICH E3	IA 1, HR 1, SAC 1
Population Analysed					
1.6.	Screened	SP1 and SP2	Summary of Study Populations and Exclusions	Use IDSL terminology Combine the SP1 and SP2 structures into the same display. Summary table may not be necessary if there are few study populations (e.g., only Safety and PK, and the sample sizes are apparent from other outputs).	IA 1, HR 1, SAC 1

Study Population Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.7.	All Subjects	DM1	Summary of Demographic Characteristics	ICH E3, GSK CTR, FDAAA, EudraCT	IA 1, HR 1, SAC 1
1.8.	Enrolled	DM11	Summary of Age Ranges	FDAAA, EudraCT	FSP: SAC 1
1.9.	All Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, GSK CTR, FDAAA, EudraCT	IA 1, HR 1, SAC 1
1.10.	All Subjects	POP_T1	Summary of the Selected Allergen from the Skin Prick Tests at Screening		IA 1, HR 1, SAC 1
Prior and Concomitant Medications					
1.11.	All Subjects	MH4	Summary of Past Medical Conditions	ICH E3	FSP: SAC 2
1.12.	All Subjects	MH4	Summary of Current Medical Conditions	ICH E3	FSP: SAC 2
1.13.	All Subjects	CM1	Summary of Concomitant Medications	ICH E3	FSP: SAC 2

11.13.5 Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LAR					
2.1.	PP	EFF_T1 (also see gw685698_gw642444 Study hza113126 final reporting effort Table 10.1)	Summary of Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline by Visit	Include an additional column for Visit between the Shell columns "Treatment" & "N" (group items by treatment then visit) and modify Parameter names as appropriate to the information being displayed	IA 1, HR 1, SAC 1
2.2.	PP	EFF_T1	Sensitivity Analysis: Summary of Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline by Visit and Blood Eosinophil Level	As per main summary table with additional column for the Blood Eosinophil group (arranged so that groups from the same visit appear in consecutive rows)	SAC 2

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	PP	EFF_T2 (also see gsk2245035 mid204509 final Table 5.2)	Summary of Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Primary Analysis Minimum and Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1)	Four (or Three part Table if no baseline terms). 1st Part: Raw Baseline values and Baseline covariate value predictions made at. Also add values used to determine predictions for any other covariates included in final model. 2nd part "Model Adjusted" predictions for Treatment and Timepoint combinations; 3rd part Summarises the posterior distributions for each comparison and 4th part lists the posterior probabilities evaluated from each comparison Include the SD from the posterior distribution inbetween the "Median" and "95% CrI" columns (Parts 2 and 3). Also include the 70% CrI (Parts 2 and 3) Also present the results as percentage attenuations in the Comparisons and Probability statements parts Replace/relabel Analyte(units) to be the Parameter/response from the modelling. Add column for Allergen Strata after the "Treatment" column if the final model used for inferences requires it.	IA 1, HR 1, SAC 1
2.4.	mITT	EFF_T2	Summary of Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1)	Conditional on PP and mITT populations differing. As per PP equivalent	SAC 1

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.5.	PP	EFF_T2	Sensitivity Analysis: Summary of Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1) using Informative Priors	Sensitivity analysis: Display priors as footnotes / or as appropriate in the output	HR 2, SAC 2
2.6.	PP	EFF_T2	Sensitivity Analysis: Summary of Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1) using Blood Eosinophil level as a covariate	Modify Table structure to also indicate which value of esoinophils the prediction/item is associated with	SAC 2
2.7.	PP	EFF_T2	Summary of Repeated Measures Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline	As per single timepoint version (the Planned Time column should contain the Visit and Timepoints within visits, e.g. FUV1, FUV2)	SAC 2
2.8.	mITT	EFF_T2	Summary of Repeated Measures Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline	Conditional on PP and mITT populations differing. As per PP equivalent version	SAC 2
2.9.	PP	EFF_T2	Sensitivity Analysis Summary of Repeated Measures Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean LAR Absolute Change from Saline using Blood Eosinophil level as a covariate	As per PP equivalent version but modify Table structure to also indicate which value of esoinophils the prediction/item is associated with	SAC 2
EAR					
2.10.	PP	EFF_T1	Summary of Bronchial Allergen Challenge Minimum and Weighted Mean EAR Absolute Change from Saline by Visit	As per LAR equivalent	SAC 1
2.11.	PP	EFF_T1	Sensitivity Analysis: Summary of Bronchial Allergen Challenge Minimum and Weighted Mean EAR Absolute Change from Saline by Visit and Blood Eosinophil Level	As per LAR equivalent	SAC 2

Efficacy: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.12.	PP	EFF_T2	Summary of Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean EAR Absolute Change from Saline at Week 9 (FUV1)	As per LAR equivalent	SAC 1
2.13.	PP	EFF_T2	Sensitivity Analysis: Summary of Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean EAR Absolute Change from Saline at Week 9 (FUV1) using Blood Eosinophil level as a covariate	As per LAR equivalent	SAC 2
2.14.	PP	EFF_T2	Summary of Repeated Measures Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean EAR Absolute Change from Saline	As per LAR equivalent	SAC 2
2.15.	PP	EFF_T2	Sensitivity Analysis: Summary of Repeated Measures Posterior Distributions and Posterior Probability statements - Bronchial Allergen Challenge Minimum and Weighted Mean EAR Absolute Change from Saline using Blood Eosinophil level as a covariate	As per LAR equivalent	SAC 2

11.13.6 Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
LAR					
2.1.	PP	EFF_F2	Boxplots of derived LAR endpoints By Visit and Treatment/Allergen Strata Combinations	Overlay individual data points next to boxes (but do not obscure key features such as mean/median symbols and whiskers/outliers) Use default SAS boxplot type Deviate from treatment/strata colour schemes if necessary to display all information types (e.g. use different box fill colours/patterns for presumed and unknown allergen strata)	IA 1, HR 1, SAC 1
2.2.	PP	EFF_F7	By Subject time profiles of derived LAR endpoints grouped by Treatment/Allergen Strata Combinations	Separate Page per endpoint Separate spaghetti plots for each treatment arm/allergen strata (arrange in lattice with treatment as columns and allergen strata as rows). Join individual subjects visits (use separate colours/symbols/line styles for each subject) but use same legend across both endpoints. If space permits include the subject IDs in a legend (however it is anticipated that there will not be sufficient space and the legend would be omitted). Use same y-axis and x-axis range for each of the panels on a page	IA 1, HR 1, SAC 1

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	PP	EFF_F3 and EFF_F4	Bronchial Allergen Challenge Scatterplots of Minimum Vs Weighted Mean LAR Absolute Change from Saline by Visit	One page per BAC visit. 1st set of 4 pages should use Main treatment descriptors (EFF_F3) and 2nd set of 4 pages should use Alternative treatment descriptors (EFF_F4) Diagonal reference line (y=x) Marginal panels are Kernel Density Estimate smoothers, Pearson correlation coefficient for overall dataset (not split by treatments)	IA 1, HR 1, SAC 1
2.4.	PP	EFF_F5	Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the Primary Analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1)	Display results from Primary analysis (i.e. not repeated measures model output) Median plus 70% & 95% CrI If final model uses allergen strata then split the treatments by strata and present comparisons within strata Separate page per endpoint (WM and Min) and confidence level for the credible intervals (70% and 95%); i.e. four pages in total To facilitate production of presentations / publications include each individual panel on its own page at the end of the display.	IA 1, HR 1, SAC 1

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.5.	PP	EFF_F6 & Fig12.135 (idslfinal reporting effort of GSK2245035 TL7116958 study)	Bronchial Allergen Challenge Posterior Distribution Density Plots from the Primary Analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1)	Display results from Primary analysis (i.e. not repeated measures model output) for the quantities of interest presented in the corresponding point estimate figure. One page per density curve, if necessary truncate the density curve (e.g. if outliers distort axis scales) – but indicate how much truncation has occurred. Use appropriate x-axis/by-line labels to identify the items. Display "Absolutes", then "differences in absolutes" and then "% Attenuations", sorting by chronological order (visits) and treatment/allergen strata within each of these types. When the item is a comparison (vs Pbo) use vertical reference lines to indicate when equality occurs (i.e. zero for a difference, one for a ratio)	IA 1, HR 1, SAC 1
2.6.	mITT	EFF_F5	Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1)	Conditional on PP and mITT populations differing. As per PP Version	SAC 1
2.7.	mITT	EFF_F6	Bronchial Allergen Challenge Posterior Distribution Density Plots from the analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1)	Conditional on PP and mITT populations differing. As per PP Version	SAC 1

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	PP	EFF_F5	Sensitivity Analysis: Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1) using Informative Priors	Sensitivity analysis: Display priors as footnotes / or as appropriate in the output	HR 2, SAC 2
2.9.	PP	EFF_F6	Sensitivity Analysis: Bronchial Allergen Challenge Posterior Distribution Density Plots from the analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1) using Informative Priors	Sensitivity analysis: Display any corresponding prior on each item (or the implied prior if item is a combination of model parameters which had priors put on them). Also display the likelihood function derived from the observed data (but scale it to have AUC of 1 to allow comparability with the probability distributions and appropriately indicate it is a scaled likelihood in any legends)	HR 2, SAC 2
2.10.	PP	EFF_F5	Sensitivity Analysis: Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1) using Blood Eosinophil level as a covariate	Modify x-axis labels/groups as appropriate to incorporate the value of eosinophils the precition/item is associated with	SAC 2
2.11.	PP	EFF_F6	Sensitivity Analysis: Bronchial Allergen Challenge Posterior Distribution Density Plots from the analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints at Week 9 (FUV1) using Blood Eosinophil level as a covariate	Modify x-axis labels/groups as appropriate to incorporate the value of eosinophils the precition/item is associated with	SAC 2
2.12.	PP	EFF_F5	Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the Repeated Measures analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints	Notes as for the FUV1 timepoint version, but within each sub-panel present the results by visit	SAC 2

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	PP	EFF_F6	Bronchial Allergen Challenge Posterior Distribution Density Plots from the Repeated Measures analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints	Notes as for the FUV1 timepoint version	SAC 2
2.14.	mITT	EFF_F5	Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the Repeated Measures analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints	Conditional on PP and mITT populations differing. As per PP repeated measures version	SAC 2
2.15.	mITT	EFF_F6	Bronchial Allergen Challenge Posterior Distribution Density Plots from the Repeated Measures analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints	Conditional on PP and mITT populations differing. As per PP repeated measures version	SAC 2
2.16.	PP	EFF_F5	Sensitivity Analysis: Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the Repeated Measures analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints using Blood Eosinophil level as a covariate	As per PP equivalent version but modify structure to also indicate which value of esoinophils the prediction/item is associated with	SAC 2
2.17.	PP	EFF_F6	Sensitivity Analysis: Bronchial Allergen Challenge Posterior Distribution Density Plots from the Repeated Measures analysis of LAR Minimum and Weighted Mean LAR Absolute Change from Saline endpoints using Blood Eosinophil level as a covariate	As per PP equivalent version but modify structure to also indicate which value of esoinophils the prediction/item is associated with	SAC 2
EAR					
2.18.	PP	EFF_F2	Boxplots of derived EAR endpoints By Visit and Treatment/Allergen Strata Combinations	See notes for LAR boxplot figure	IA 1, HR 1, SAC 1
2.19.	PP	EFF_F3 and EFF_F4	Bronchial Allergen Challenge Scatterplots of Minimum Vs Weighted Mean EAR Absolute Change from Saline by Visit	See notes for EAR scatterplot figure	IA 1, HR 1, SAC 1
2.20.	PP	EFF_F7	By Subject time profiles of derived EAR endpoints grouped by Treatment/Allergen Strata Combinations	See notes for EAR equivalent figure	IA 1, HR 1, SAC 1

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21.	PP	EFF_F5	Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints at Week 9 (FUV1)	As per LAR equivalent (except no AZ benchmark)	SAC 1
2.22.	PP	EFF_F6	Bronchial Allergen Challenge Posterior Distribution Density Plots from the analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints at Week 9 (FUV1)	As per LAR equivalent	SAC 1
2.23.	PP	EFF_F5	Sensitivity Analysis: Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints at Week 9 (FUV1) using Blood Eosinophil level as a covariate	As per LAR equivalent (except no AZ benchmark)	SAC 2
2.24.	PP	EFF_F6	Sensitivity Analysis: Bronchial Allergen Challenge Posterior Distribution Density Plots from the analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints at Week 9 (FUV1) using Blood Eosinophil level as a covariate	As per LAR equivalent	SAC 2
2.25.	PP	EFF_F5	Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the Repeated Measures analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints	As per LAR equivalent (except no AZ benchmark)	SAC 2
2.26.	PP	EFF_F6	Bronchial Allergen Challenge Posterior Distribution Density Plots from the Repeated Measures analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints	As per LAR equivalent	SAC 2

Efficacy: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.27.	PP	EFF_F5	Sensitivity Analysis: Bronchial Allergen Challenge Point estimates and Credible Intervals (70% and 95%) from the Repeated Measures analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints using Blood Eosinophil level as a covariate	As per LAR equivalent (except no AZ benchmark)	SAC 2
2.28.	PP	EFF_F6	Sensitivity Analysis: Bronchial Allergen Challenge Posterior Distribution Density Plots from the Repeated Measures analysis of EAR Minimum and Weighted Mean EAR Absolute Change from Saline endpoints using Blood Eosinophil level as a covariate	As per LAR equivalent	SAC 2
Bronchial Allergen Challenge					
2.29.	All Subjects	EFF_F1	By Subject plots of Bronchial Allergen Challenge Absolute Change from Saline FEV_1 time profiles by Visit	Order pages by Country, Centre Treatment (Pbo 1st) and Allergen Strata (Presumed 1st). Use same y-axis range for all panels. Use the plotting symbols in 11.4.3 Choose appropriate number of subject panels per page to minimise "wasted space" Shell provides structure/layout; labels and text etc should be modified as appropriate to the data presented.	IA 1, HR 1, SAC 1
2.30.	All Subjects	EFF_F1	By Subject plots of Bronchial Allergen Challenge Absolute FEV_1 time profiles by Visit	Use Programming notes from above figure of change from saline baseline FEV1 and same layout/structure	IA 1, SAC 1

11.13.7 Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Subjects	CP_AE1p	Summary of All Adverse Events by System Organ Class	ICH E3	FSP: SAC 1
3.2.	All Subjects	CP_AE1p	Summary of All Drug-Related Adverse Events by System Organ Class	GSK CTR	FSP: SAC 1
3.3.	All Subjects	AE5	Summary of All Adverse Events by System Organ Class and Maximum Grade / Severity	ICH E3	FSP: SAC 1
3.4.	All Subjects	AE5	Summary of All Drug-Related Adverse Events by System Organ Class and Maximum Grade / Severity	GSK CTR	FSP: SAC 1
3.5.	All Subjects	AE15	Summary of Common (>=10%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	FSP: SAC 1
Cytokine Release Syndrome (CRS) Events					
3.6.	All Subjects	SAFE_T2 (Also see GSK2245035 TL7116958 idslfinal Table 10.104)	Summary of Cytokine Release Syndrome Events	Create two versions of the Table within the output. The 1st uses the Main Treatment descriptors and the 2nd uses the Alternative Treatment descriptors (Pbo P, Pbo U, 20ng P, 20ng U).	SAC 1

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.	All Subjects	SAFE_T3 (Also see GSK2245035 TL7116958 idslfinal Table 10.105)	Summary of the Consistency of Cytokine Release Syndrome Events Reporting by Individuals over Dosing Visits	Create two versions of the Table within the output. The 1st uses the Main Treatment descriptors and the 2nd uses the Alternative Treatment descriptors (Pbo P, Pbo U, 20ng P, 20ng U). Sort by CRS Category, Treatment Add footnotes about set interval notation for category boundaries	SAC 1
Serious and Other Significant Adverse Events					
3.8.	All Subjects	CP_AE1p	Summary of Serious Adverse Events by System Organ Class	Only produce if more than 5 events IDSL / GSK CTR	FSP: SAC 1
3.9.	All Subjects	CP_AE1p	Summary of Drug-Related Serious Adverse Events by System Organ Class	Only produce if more than 5 events GSK CTR	FSP: SAC 1
Laboratory: Chemistry					
3.10.	All Subjects	LB1	Summary of Chemistry Changes from Baseline	ICH E3 Include (absolute) Baseline values summarised as a row in the table and then the change from baseline for each visit below. Do not include Screening visit 1 values	FSP: SAC 2
3.11.	All Subjects	LB4	Summary of Emergent Chemistry Results by Normal Range Criteria	ICH E3 Planned times should be each post-visit timepoint (e.g. DV1 24h, DV8 pre-dose, DV8 24h). Do not include screening visit 1 values. Use Normal Ranges for Lab tests rather than PCI ranges to determine criteria.	FSP: SAC 2

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Haematology					
3.12.	All Subjects	LB1	Summary of Haematology Changes From Baseline	ICH E3 As per Lab Chemistry equivalent	FSP: SAC 2
3.13.	All Subjects	LB4	Summary of Emergent Haematology Results by Normal Range Criteria	ICH E3 As per Lab Chemistry equivalent	FSP: SAC 2
Laboratory: Hepatobiliary (Liver)					
3.14.	All Subjects	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	FSP: SAC 2
ECG					
3.15.	All Subjects	EG1	Summary of ECG Findings	IDSL	FSP: SAC 2
3.16.	All Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL Include (absolute) Baseline values as the first record. Do not include Screening visit 1 values	FSP: SAC 2
Vital Signs					
3.17.	All Subjects	VS1	Summary of Change From Baseline in Vital Signs by Visit	ICH E3 Include (absolute) Baseline values as the first record. Do not include Screening visit 1 values	FSP: SAC 2
Medications					
3.18.	All Subjects	CP_CM1	Summary of Concomitant Medications by Generic Term		FSP: SAC 2
Rescue Medication					
3.19.	All Subjects	Table 10.112 TL7116958	Summary of Rescue Medication Usage	Include reasons (if easily condensed to a handful of terms). Exclude any rescue medication given as part of the BAC procedure(s) and add this as an explanatory footnote.	FSP: SAC 2

Safety: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PEF					
3.20.	All Subjects	EFF_T1	Summary of Weekly Maximum PEF by Visit	Calculate the maximum PEF for the week per subject Add Appropriate Visit Column to Shell	FSP: SAC 2
3.21.	All Subjects	EFF_T1	Summary of Weekly Weighted Mean PEF by Visit	Add Appropriate Visit Column to Shell	FSP: SAC 2
Nasal Examination					
3.22.	All Subjects	SAFE_T1	Summary of Nasal Examination Data by Visit	Count as yes any entries in the free text field for Signs of Bleeding.	FSP: SAC 2
3.23.	All Subjects	SAFE_T4	Shift Tables of Nasal Examination Status from Pre-Dose DV1 to 24h Post Dose DV8	Count as yes any entries in the free text field for Signs of Bleeding. Separate page per category/domain	FSP: SAC 2

11.13.8 Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PEF					
3.1.	All Subjects	Figure 10.107 TL7116958	Unadjusted Mean Peak Expiratory Flow vs Time Profiles by Treatment (with approx 95% CI Bands)	Display the raw Treatment means for each day and connect each (1st page uses main treatment descriptors and 2nd page uses Alternative descriptors). Do not add individual CIs for each day, but instead display them as a band plot. X-axis is continuous (Week) with tick marks every 7 days (1st Dose is Week 0) Add vertical reference lines for the 1st and 8th planned dose	FSP: SAC [2]
3.2.	All Subjects	Figure 10.107 TL7116958	Unadjusted Mean AM Peak Expiratory Flow vs Time Profiles by Treatment (with approx 95% CI Bands)	As per Mean PEF Figure	FSP: SAC [2]
3.3.	All Subjects	Figure 10.107 TL7116958	Unadjusted Mean PM Peak Expiratory Flow vs Time Profiles by Treatment (with approx 95% CI Bands)	As per Mean PEF Figure	FSP: SAC [2]

Safety: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4.	All Subjects	SAFE_F1	Frequency of Cytokine Release Syndrome Events (within individuals) over the Eight Planned Dosing Visits	Try to get all CRS events on one page. Do not distinguish between CRS severity grades in this display. 1st Page should be Placebo and 20ng treatments (two bars per CRS category) 2nd Page should use Placebo/Allergen stratum combinations (four bars per CRS category) Footnote each subsection of each bar when individuals did not complete all 8 visits fall. If possible consider patterns/fill types that can display in black and white (but revert to example shell (colours only) if patterns result in confusing figure details)	SAC [1]

11.13.9 Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentrations					
4.1.	PK	pkct1	Summary of GSK2245035 Plasma Concentration-time Data by Dose	Only to be produced if at least 20% quantifiable values at any time point.	SAC [3]

11.13.10 Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentrations					
4.1.	PK	pkcf1	Individual Subject GSK2245035 Concentration-time Plot (Linear and Semi-log) by Subject	Only to be produced if at least 20% quantifiable values at any time point.	SAC [3]
4.2.	PK	pkcf2	Mean GSK2245035 Concentration-time Plot (Linear and Semi-log)	Only to be produced if at least 20% quantifiable values at any time point.	SAC [3]

11.13.11 Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarkers supporting the BAC related exploratory objective(s)					
5.1.	Sputum Producers	PD_T1	Sputum Cell Pellet: Summary of data availability by Treatment and selected visits	Little n's relate to the number of subjects with evaluable samples satisfying the header criteria. The % relate to the big N of the corresponding treatment/strata combination. "Overall" displays the treatment arms ignoring strata. Complete profile represents all eight planned timepoints.	SAC [2]
5.2.	Sputum Producers	PD_T2	Sputum Cell Pellet: Summary of Absolute Cell Counts	Absolute relates to the derived Total cells/g values and not the raw counts provided by the vendor. Cells/g sputum	SAC [2]
5.3.	Sputum Producers	PD_T2	Sputum Cell Pellet: Summary of Percentage Cell Counts		SAC [2]
5.4.	Sputum Producers	EFF_T2	Sputum Cell Pellet: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Absolute Cell Count Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC [2]
5.5.	Sputum Producers	EFF_T2	Sputum Cell Pellet: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of all Absolute Cell Count Samples	Conditional on sufficient evaluable data points.	SAC [2]
5.6.	Sputum Producers	EFF_T2	Sputum Cell Pellet: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Percentage Cell Counts Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC [2]
5.7.	Sputum Producers	EFF_T2	Sputum Cell Pellet: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of all Percentage Cell Counts Samples	Conditional on sufficient evaluable data points.	SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.8.	All Subjects	PD_T2	PBS Wash: Summary of Concentration data		SAC [2]
5.9.	All Subjects	EFF_T2	PBS Wash: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Pre-BAC Samples		SAC [2]
5.10.	All Subjects	EFF_T2	PBS Wash: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of all Samples		SAC [2]
5.11.	All Subjects	PD_T2	Blood Differentials: Summary of Absolute Counts		SAC [2]
5.12.	All Subjects	PD_T2	Blood Differentials: Summary of Percentages		SAC [2]
5.13.	All Subjects	EFF_T2	Blood Differentials: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Absolute Count Pre-BAC Samples		SAC [2]
5.14.	All Subjects	EFF_T2	Blood Differentials: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of all Absolute Count Samples		SAC [2]
5.15.	All Subjects	EFF_T2	Blood Differentials: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Percentages Pre-BAC Samples		SAC [2]
5.16.	All Subjects	EFF_T2	Blood Differentials: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of all Percentages Samples		SAC [2]
5.17.	All Subjects	PD_T2	FeNO: Summary of All FeNO Data	Include BAC and Dosing Visit samples in the same table.	SAC [2]
5.18.	All Subjects	EFF_T2	FeNO: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of BAC Visit FeNO data		SAC [2]
Biomarkers supporting the NAC related exploratory objective(s)					
5.19.	All Subjects	PD_T2	Nasal Lavage: Summary of Fluid and Filter Concentration data (All NAC associated Timepoints)	Include all data from all NAC visit planned timepoints in this listing (i.e. Background, Pre-NAC, 5m Post NAC and 6h Post NAC for SV, FUV1, FUV2)	SAC [2]

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.20.	All Subjects	EFF_T2	Nasal Lavage: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of NAC Background Samples		SAC [2]
5.21.	All Subjects	EFF_T2	Nasal Lavage: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Direct NAC Samples		SAC [2]
Biomarkers supporting the Induction of TLR7 (target engagement) exploratory objective(s)					
5.22.	All Subjects	PD_T2	Nasal Lavage: Summary of Fluid and Filter Concentration data (All Dosing Visit associated Timepoints)	Include all data from all Dosing Visit planned timepoints in this listing (i.e. Pre-Dose and 24h Post Dose for DV1, DV4 and DV8)	SAC [2]
5.23.	All Subjects	EFF_T2	Nasal Lavage: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Dosing Visit Samples		SAC [2]
5.24.	All Subjects	PD_T2	Serum: Summary of Concentration data		SAC [2]
5.25.	All Subjects	EFF_T2	Serum: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Dosing Visit Samples		SAC [2]
5.26.	All Subjects	EFF_T2	FeNO: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Dosing Visit FeNO data		SAC [2]
Multivariate / Composite					
5.27.	All Subjects	n/a	Multivariate Approach 1 - Profile Regression Summary Tables		SAC [2]
5.28.	All Subjects	n/a	Multivariate Approach 2 – Summary Tables		SAC [2]

11.13.12 Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Biomarkers supporting the BAC related exploratory objective(s)					
5.1.	Sputum Producers	PD_F1	Sputum Cell Pellet: By Subject profiles of Absolute Cell Counts		SAC 2
5.2.	Sputum Producers	PD_F2	Sputum Cell Pellet: Summary profiles of Absolute Cell Counts by Visit		SAC 2
5.3.	Sputum Producers	PD_F3	Sputum Cell Pellet: Summary profiles of Absolute Cell Counts by Planned Sampling Time		SAC 2
5.4.	Sputum Producers	PD_F6	Sputum Cell Pellet: Point estimates and 95% Credible Intervals from the Analysis of Absolute Cell Count Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC 2
5.5.	Sputum Producers	EFF_F6	Sputum Cell Pellet: Posterior Distribution Density Plots from the Analysis of Absolute Cell Count Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC 2
5.6.	Sputum Producers	PD_F4	Sputum Cell Pellet: Summary profiles of Fold Changes in Absolute Cell Counts (24h Post BAC /Pre-BAC)		SAC 2
5.7.	Sputum Producers	PD_F7	Sputum Cell Pellet: Point estimates and 95% Credible Intervals from the Analysis of all Absolute Cell Count Samples	Conditional on sufficient evaluable data points.	SAC 2
5.8.	Sputum Producers	EFF_F6	Sputum Cell Pellet: Posterior Distribution Density Plots from the Analysis of all Absolute Cell Count Samples	Conditional on sufficient evaluable data points.	SAC 2
5.9.	Sputum Producers	PD_F1	Sputum Cell Pellet: By Subject profiles of Percentage Cell Counts		SAC 2
5.10.	Sputum Producers	PD_F2	Sputum Cell Pellet: Summary profiles of Percentage Cell Counts by Visit		SAC 2
5.11.	Sputum Producers	PD_F3	Sputum Cell Pellet: Summary profiles of Percentage Cell Counts by Planned Sampling Time		SAC 2

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.12.	Sputum Producers	PD_F6	Sputum Cell Pellet: Point estimates and 95% Credible Intervals from the Analysis of Percentage Cell Counts Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC 2
5.13.	Sputum Producers	EFF_F6	Sputum Cell Pellet: Posterior Distribution Density Plots from the Analysis of Percentage Cell Counts Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC 2
5.14.	Sputum Producers	PD_F4	Sputum Cell Pellet: Summary profiles of Fold Changes in Percentage Cell Counts (24h Post BAC /Pre-BAC)		SAC 2
5.15.	Sputum Producers	PD_F7	Sputum Cell Pellet: Point estimates and 95% Credible Intervals from the Analysis of all Percentage Cell Counts Samples	Conditional on sufficient evaluable data points.	SAC 2
5.16.	Sputum Producers	EFF_F6	Sputum Cell Pellet: Posterior Distribution Density Plots from the Analysis of all Percentage Cell Counts Samples	Conditional on sufficient evaluable data points.	SAC 2
5.17.	All Subjects	PD_F1	PBS Wash: By Subject profiles of Concentration data		SAC 2
5.18.	All Subjects	PD_F2	PBS Wash: Summary profiles of Concentration data by Visit		SAC 2
5.19.	All Subjects	PD_F3	PBS Wash: Summary profiles of Concentration data by Planned Sampling Time		SAC 2
5.20.	All Subjects	PD_F6	PBS Wash: Point estimates and 95% Credible Intervals from the Analysis of Pre-BAC Samples		SAC 2
5.21.	All Subjects	EFF_F6	PBS Wash: Posterior Distribution Density Plots from the Analysis of Pre-BAC Samples		SAC 2
5.22.	All Subjects	PD_F4	PBS Wash: Summary profiles of Fold Changes (24h Post BAC /Pre-BAC)		SAC 2
5.23.	All Subjects	PD_F7	PBS Wash: Point estimates and 95% Credible Intervals from the Analysis of all Samples		SAC 2
5.24.	All Subjects	EFF_F6	PBS Wash: Posterior Distribution Density Plots from the Analysis of all Samples		SAC 2
5.25.	All Subjects	PD_F1	Blood Differentials: By Subject profiles of Absolute Counts		SAC 2

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.26.	All Subjects	PD_F2	Blood Differentials: Summary profiles of Absolute Counts by Visit		SAC 2
5.27.	All Subjects	PD_F3	Blood Differentials: Summary profiles of Absolute Counts by Planned Sampling Time		SAC 2
5.28.	All Subjects	PD_F6	Blood Differentials: Point estimates and 95% Credible Intervals from the Analysis of Absolute Count Pre-BAC Samples		SAC 2
5.29.	All Subjects	EFF_F6	Blood Differentials: Posterior Distribution Density Plots from the Analysis of Absolute Count Pre-BAC Samples		SAC 2
5.30.	All Subjects	PD_F4	Blood Differentials: Summary profiles of Fold Changes in Absolute Counts (24h Post BAC /Pre-BAC)		SAC 2
5.31.	All Subjects	PD_F7	Blood Differentials: Point estimates and 95% Credible Intervals from the Analysis of all Absolute Count Samples		SAC 2
5.32.	All Subjects	EFF_F6	Blood Differentials: Posterior Distribution Density Plots from the Analysis of all Absolute Count Samples		SAC 2
5.33.	All Subjects	PD_F1	Blood Differentials: By Subject profiles of Percentages		SAC 2
5.34.	All Subjects	PD_F2	Blood Differentials: Summary profiles of Percentages by Visit		SAC 2
5.35.	All Subjects	PD_F3	Blood Differentials: Summary profiles of Percentages by Planned Sampling Time		SAC 2
5.36.	All Subjects	PD_F6	Blood Differentials: Point estimates and 95% Credible Intervals from the Analysis of Percentages Pre-BAC Samples		SAC 2
5.37.	All Subjects	EFF_F6	Blood Differentials: Posterior Distribution Density Plots from the Analysis of Percentages Pre-BAC Samples		SAC 2
5.38.	All Subjects	PD_F4	Blood Differentials: Summary profiles of Fold Changes in Percentages (24h Post BAC /Pre-BAC)		SAC 2

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.39.	All Subjects	PD_F7	Blood Differentials: Point estimates and 95% Credible Intervals from the Analysis of all Percentages Samples		SAC 2
5.40.	All Subjects	EFF_F6	Blood Differentials: Posterior Distribution Density Plots from the Analysis of all Percentages Samples		SAC 2
5.41.	All Subjects	PD_F1	FeNO: By Subject profiles of BAC Visit FeNO data		SAC 2
5.42.	All Subjects	PD_F2	FeNO: Summary profiles of BAC Visit FeNO data by Visit		SAC 2
5.43.	All Subjects	PD_F4	FeNO: Summary profiles of Fold Changes in BAC Visit FeNO data (24h Post BAC /Pre-BAC)		SAC 2
5.44.	All Subjects	PD_F7	FeNO: Point estimates and 95% Credible Intervals from the Analysis of BAC Visit FeNO data		SAC 2
5.45.	All Subjects	EFF_F6	FeNO: Posterior Distribution Density Plots from the Analysis of BAC Visit FeNO data		SAC 2
Biomarkers supporting the NAC related exploratory objective(s)					
5.46.	All Subjects	PD_F1	Nasal Lavage: By Subject profiles of NAC associated Fluid and Filter Concentration data		SAC 2
5.47.	All Subjects	PD_F3	Nasal Lavage: Summary profiles of NAC associated Background Samples		SAC 2
5.48.	All Subjects	PD_F6	Nasal Lavage: Point estimates and 95% Credible Intervals from the Analysis of NAC associated Background Samples		SAC 2
5.49.	All Subjects	EFF_F6	Nasal Lavage: Posterior Distribution Density Plots from the Analysis of NAC associated Background Samples		SAC 2
5.50.	All Subjects	PD_F2	Nasal Lavage: Summary profiles of Direct NAC Samples by Visit	Do not include Background timepoints from each visit	SAC 2

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.51.	All Subjects	PD_F4	Nasal Lavage: Summary profiles of Fold Changes in Direct NAC Samples (relative to the respective visits Pre-NAC)	Do not include Background timepoints. Panel structure/layout can change across biomarkers (e.g. If a biomarker has data at both the 5m and 6h timepoints then there should be two columns per visit). However most biomarkers are only expected to have either the 5m or the 6h timepoint so there would only be one column per visit.	SAC 2
5.52.	All Subjects	PD_F7	Nasal Lavage: Point estimates and 95% Credible Intervals from the Analysis of Direct NAC Samples		SAC 2
5.53.	All Subjects	EFF_F6	Nasal Lavage: Posterior Distribution Density Plots from the Analysis of Direct NAC Samples		SAC 2
Biomarkers supporting the Induction of TLR7 (target engagement) exploratory objective(s)					
5.54.	All Subjects	PD_F1	Nasal Lavage: By Subject profiles of Dosing Visit associated Fluid and Filter Concentration data		SAC 2
5.55.	All Subjects	PD_F2	Nasal Lavage: Summary profiles of Dosing Visit associated Fluid and Filter Concentration data by Visit		SAC 2
5.56.	All Subjects	PD_F5	Nasal Lavage: Summary profiles of Fold Changes in Dosing Visit associated Fluid and Filter Concentration data		SAC 2
5.57.	All Subjects	PD_F8	Nasal Lavage: Point estimates and 95% Credible Intervals from the Analysis of Dosing Visit Samples		SAC 2
5.58.	All Subjects	EFF_F6	Nasal Lavage: Posterior Distribution Density Plots from the Analysis of Dosing Visit Samples		SAC 2
5.59.	All Subjects	PD_F1	Serum: By Subject profiles of Dosing Visit associated Concentration data		SAC 2

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.60.	All Subjects	PD_F2	Serum: Summary profiles of Dosing Visit associated Concentration data by Visit		SAC 2
5.61.	All Subjects	PD_F5	Serum: Summary profiles of Fold Changes in Dosing Visit associated Concentration data		SAC 2
5.62.	All Subjects	PD_F8	Serum: Point estimates and 95% Credible Intervals from the Analysis of Dosing Visit Samples		SAC 2
5.63.	All Subjects	EFF_F6	Serum: Posterior Distribution Density Plots from the Analysis of Dosing Visit Samples		SAC 2
5.64.	All Subjects	PD_F1	FeNO: By Subject profiles of Dosing Visit FeNO data	Modify PD_F1 structure to use PD_F3 axis layouts (i.e. one panel per subject with visit as x-axis category and points joined)	SAC 2
5.65.	All Subjects	PD_F3	FeNO: Summary profiles of Dosing Visit FeNO data by Visit	Only require one column (Pre-Dose)	SAC 2
5.66.	All Subjects	PD_F6	FeNO: Point estimates and 95% Credible Intervals from the Analysis of Dosing Visit FeNO data		SAC 2
5.67.	All Subjects	EFF_F6	FeNO: Posterior Distribution Density Plots from the Analysis of Dosing Visit FeNO data		SAC 2

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Multivariate / Composite					
5.68.	Sputum Producers	n/a	Exploratory: Scatterplots of Sputum and WBC Cell Differentials	One page per figure. Order pages by the display orders in Table 13 for variables common to each sampling method. Present absolute variable 1st (then percentage). Suggestion to use the SAS SGxxx procedures so that the derivation and display of the required regression line(s) is one step; and display the resulting parameters and goodness of fit (r squared) next to their corresponding line X axis: WBC, Y axis Sputum Use Main treatment descriptor colours for plotting symbols and regression lines and a contrasting colour for the overall regression line (e.g. solid black)	SAC [2]
5.69.	All Subjects	n/a	Multivariable responder/non-responders: Starcharts of the Proportion of responders for each Question ID by Treatment	To Save space use the abbreviated question IDs (e.g. A1, B1, N1p etc) and add footnote referring the reader to the Output with the link to the full text/criteria (i.e. the listing number that is used at time of reporting) Produce versions using the main and alternate sets of treatment descriptors and see Section 8.4.3.2 for more details.	SAC [2]
5.70.	All Subjects	n/a	Multivariate Approach 1 - Profile Regression Summary Figures		SAC [2]
5.71.	All Subjects	n/a	Multivariate Approach 2 – Summary Figures		SAC [2]

11.13.13 Exploratory Tables

Exploratory: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
TNSS					
6.1.	All Subjects	EFF_T1	Summary Statistics of Weighted Mean TNSS by Week	Separate Tables within the output for Overall TNSS and the AM and PM WM endpoints	FSP: SAC 2
6.2.	All Subjects	EFF_T2	WM TNSS: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Weekly WM TNSS data		FSP: SAC [2]
6.3.	All Subjects	EFF_T1	Summary Statistics of TNSS component Weighted Means by Week	Conditional	FSP: SAC 2
6.4.	All Subjects	EFF_T2	WM TNSS: Summary of Posterior Distributions and Posterior Probability statements from the Analysis of Weekly WM TNSS component data	Conditional	FSP: SAC [2]

Exploratory: Tables					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Intradermal Allergen Challenge					
6.5.	All Subjects	EFF_T1	Intradermal Allergen Challenge: Summary Statistics of Mean Diameter Early/Late Phase Wheal/Flare Response by Visit and Treatment/Allergen Strata Combinations	Include an additional column for Visit (SV, FUV1 and FUV2) between the Shell columns "Treatment" & "N" (group items by treatment then visit) and modify Parameter names as appropriate to the information being displayed; namely "Challenge" and "Negative control" and have additional columns "Item" to capture if its Wheal or Flare and "Phase" to capture Early (15m) or Late (6h) Create two versions of the Table within the output. The 1st uses the Main Treatment descriptors and the 2nd uses the Alternative Treatment descriptors (Pbo P, Pbo U, 20ng P, 20ng U).	FSP: SAC [2]
6.6.	All Subjects	EFF_T1	Intradermal Allergen Challenge: Summary Statistics of Mean Change from Baseline Diameter Early/Late Phase Wheal/Flare Response by Visit and Treatment/Allergen Strata Combinations	As per main summary table except SV (baseline) visit not included.	FSP: SAC [2]

11.13.14 Exploratory Figures

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Intradermal Allergen Challenge					
6.1.	All Subjects	EFF_F2	Intradermal Allergen Challenge: Boxplots of derived Change from Baseline in Mean Diameter Early/Late Phase Wheal/Flare By Visit and Treatment/Allergen Strata Combinations	Overlay individual data points next to boxes (but do not obscure key features such as mean/median symbols and whiskers/outliers) Use default SAS boxplot type Deviate from treatment/strata colour schemes if necessary to display all information types (e.g. use different box fill colours/patterns for presumed and unknown allergen strata) Response variable is the derived change from baseline (SV) Separate page for Wheal and Flare responses Row categories are Early phase (15m timepoint) and Late phase (6h timepoint) Columns are Visits (FUV1 and FUV2) Add horizontal ref line(s) at zero	FSP: SAC 2

Exploratory: Figures					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Weighted Mean Total Nasal Symptom Score (TNSS)					
6.2.	All Subjects	PD_F3	WM TNSS: Summary profiles of Weekly WM TNSS data by Week	Separate Figure/Page for Overall TNSS and the AM and PM versions. Do not include the mean and 95% CI profiles for the allergen exposure strata (grey lines in shell) If necessary to improve clarity/readability of figure display CIs for a subset of the timepoints (e.g. Week 1, 4, 8, FUV1, FUV2)	FSP: SAC [2]
6.3.	All Subjects	PD_F6	WM TNSS: Point estimates and 95% Credible Intervals from the Analysis of Weekly WM TNSS data		FSP: SAC 2
6.4.	All Subjects	EFF_F6	WM TNSS: Posterior Distribution Density Plots from the Analysis of Weekly WM TNSS data		FSP: SAC 2
6.5.	All Subjects	PD_F3	WM TNSS: Summary profiles of Weekly WM TNSS component data by Week	Conditional. As per TNSS equivalent	FSP: SAC [2]
6.6.	All Subjects	PD_F6	WM TNSS: Point estimates and 95% Credible Intervals from the Analysis of Weekly WM TNSS component data	Conditional. As per TNSS equivalent	FSP: SAC 2
6.7.	All Subjects	EFF_F6	WM TNSS: Posterior Distribution Density Plots from the Analysis of Weekly WM TNSS component data	Conditional. As per TNSS equivalent	FSP: SAC 2

11.13.15 ICH Listings

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines Only include failures	FSP: SAC 1
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal	ICH E3	IA 1, HR 1, SAC 1
3.	All Subjects	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	IA 1, HR 1, SAC 1
4.	All Subjects	TA1 / CP_RD1x	Listing of Planned and Actual Treatments	IDSL Also include Allergen Strata as an additional column	IA 1, HR 1, SAC 1
Protocol Deviations					
5.	All Subjects	DV2	Listing of Important Protocol Deviations	ICH E3	IA 1, HR 1, SAC 1
6.	All Subjects	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	IA 1, HR 1, SAC 1
Populations Analysed					
7.	Enrolled	SP3	Listing of Subjects Excluded from All Subjects, mITT, PP, PK, Sputum Populations	ICH E3 Include subjects who are randomised. If 'Enrolled' and 'All Subjects' Populations are the same, use population 'All Subjects' label and change title to 'Listing of Subjects Excluded from mITT, PP, PK, Sputum Populations.'	IA 1, HR 1, SAC 1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
8.	All Subjects	DM2	Listing of Demographic Characteristics	ICH E3	IA 1, HR 1, SAC 1
9.	All Subjects	DM9	Listing of Race	ICH E3	IA 1, HR 1, SAC 1
Medical Conditions and Prior and Concomitant Medications					
10.	All Subjects	MH2	Listing of Past and Current Medical History		FSP: SAC 2
11.	All Subjects	CP_CM3	Listing of Concomitant Medications	IDSL	FSP: SAC 2
Exposure and Treatment Compliance					
12.	All Subjects	EX3	Listing of Exposure Data	ICH E3 GSK may have coded AR Exposure dataset to support IA	FSP: SAC 2
Adverse Events					
13.	All Subjects	CP_AE8 (Also see GSK2245035 TL7116958 idslfinal Listing 111)	Listing of All Adverse Events	ICH E3 Add columns for the CRS Category and CRS Grading	FSP: SAC 1
14.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	FSP: SAC 1
15.	All Subjects	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	FSP: SAC 1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Cytokine Release Syndrome (CRS) Events					
16.	All Subjects	CP_AE8 (Also see GSK2245035 TL7116958 idslfinal Listing 113)	Listing of Cytokine Release Syndrome Events	List all CRS events (even ones that map to the same CRS category but a lower grade)	SAC 1
17.	All Subjects	SAFE_L2 (Also see GSK2245035 TL7116958 idslfinal Listing 115)	Listing of worst case Cytokine Release Syndrome (CRS) Score by subject and dosing visit	Also add the allergen stratum to the Treatment when setting the page by line. Handle subjects who withdraw early like Subject PP in the example shell	SAC 1
18.	All Subjects	AE7 (Also see GSK2245035 TL7116958 idslfinal Listing 114)	Listing of Subject Numbers for Individual Cytokine Release Syndrome Events	ICH E3	SAC 1
19.	All Subjects	AE2	Listing of Relationship Between Cytokine Release Syndrome Event and associated AE System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC 1
Serious and Other Significant Adverse Events					
20.	All Subjects	CP_AE8a	Listing of Serious Adverse Events	ICH E3	FSP: SAC 1
21.	All Subjects	SAE Reasons	Listing of Reasons for Considering as a Serious Adverse Event	FDA Note: IDSL shell in development.	FSP: SAC 1

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
22.	All Subjects	CP_AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	FSP: SAC 1
Hepatobiliary (Liver)					
23.	All Subjects	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	FSP: SAC 2
24.	All Subjects	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	FSP: SAC 2
Laboratory – Haematology					
25.	All Subjects	LB5	Listing of All Haematology Laboratory Data for Subjects with Values of Potential Clinical Importance	ICH E3	FSP: SAC 2
26.	All Subjects	CP_LB5	Listing of Haematology Laboratory Data Values of Potential Clinical Importance		FSP: SAC 2
Laboratory – Chemistry					
27.	All Subjects	LB5	Listing of All Chemistry Laboratory Data for Subjects with Values of Potential Clinical Importance	ICH E3	FSP: SAC 2
28.	All Subjects	CP_LB5	Listing of Chemistry Laboratory Data Values of Potential Clinical Importance		FSP: SAC 2
Laboratory – Urinalysis					
29.	All Subjects	UR2a	Listing of All Urinalysis Laboratory Data for Subjects with Abnormal Values of Potential Clinical Concern	ICH E3 Abnormal values are any Positive dipstick result and/or greater than or equal to 1+ in the urine blood test and/or greater than equal to 1+ in the urine protein test	FSP: SAC 2
30.	All Subjects	UR2a	Listing of Urinalysis Laboratory Data Abnormal Values	Only include abnormal values (see above)	FSP: SAC 2

ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
All Laboratory					
31.	All Subjects	LB13	Listing of Laboratory Tests and Associated Reference Ranges	Split into separate listings by chemistry, hematology, urinalysis, etc.	FSP: SAC 2
ECG					
32.	All Subjects	CP_EG3	Listing of ECG Values for Subjects with Values of Potential Clinical Importance	IDSL	FSP: SAC 2
33.	All Subjects	CP_EG3	Listing of ECG Values of Potential Clinical Importance	IDSL	FSP: SAC 2
34.	All Subjects	CP_EG5	Listing of Abnormal ECG Findings	IDSL	FSP: SAC 2
Vital Signs					
35.	All Subjects	CP_VS4	Listing of Vital Signs for Subjects with Values of Potential Clinical Importance	IDSL	FSP: SAC 2
36.	All Subjects	CP_LB5	Listing of Vital Sign Values of Potential Clinical Importance	IDSL	FSP: SAC 2

11.13.16 Non-ICH Listings

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
37.	All Subjects	See GW685968_GW642444 HZA113126 final Listing 4	Listing of Skin Prick Test at Screening	Modify Example Shell Columns for Parallel group design	FSP: SAC 2
38.	All Subjects	PFT10	Listing of FEV1 and Percent Predicted FEV1 Data at Screening	Modify Shell for Parallel group design Include columns for site Footnote [1] Values have been recalculated from raw data using equations in Quanjer, 2012	FSP: SAC 2
Allergen Challenge					
39.	All Subjects	See GW685968_GW642444 HZA113126 final Listing 6	Listing of Allergen Challenge FEV_1	Modify Example Shell Columns for Parallel group design	IA 1, HR 1, SAC 1
LAR/EAR					
40.	All Subjects	EFF_L1	Listing of Subjects Treated with Placebo Who Did Not Experience a Late Asthmatic Response at Week 9 (LAR Non-Responder at FUV1)		SAC 1

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
41.	All Subjects	See GSK2190915 LPA111834 final Listing 8	Bronchial Allergen Challenge Listing of Minimum and Weighted Mean LAR and EAR absolute Change from Saline	Modify Example Shell Columns for Parallel group design Omit the Placebo Difference column Have Absolute (L), Change (L) and Change (%) columns for each Derived endpoint (Min and WM) Make "Treatment" the leftmost column. Period column becomes Visit.	IA 1, HR 1, SAC 1
42.	PP	n/a	Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Primary Analysis Minimum LAR Absolute Change from Saline at Week 9 (FUV1)		IA 1, HR 1, SAC 1
43.	PP	n/a	Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Primary Analysis Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1)		IA 1, HR 1, SAC 1
44.	mITT	n/a	Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Minimum LAR Absolute Change from Saline at Week 9 (FUV1)	Conditional on PP and mITT populations differing.	IA 1, HR 1, SAC 1
45.	mITT	n/a	Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1)	Conditional on PP and mITT populations differing.	IA 1, HR 1, SAC 1
46.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Minimum LAR Absolute Change from Saline at Week 9 (FUV1) using Informative Priors	Sensitivity analysis: Display priors as footnotes / or as appropriate in the output	HR 2, SAC 2
47.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1) using Informative Priors	Sensitivity analysis: Display priors as footnotes / or as appropriate in the output	HR 2, SAC 2

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
48.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Minimum LAR Absolute Change from Saline at Week 9 (FUV1) using Blood Eosinophil level as a covariate		SAC 2
49.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Weighted Mean LAR Absolute Change from Saline at Week 9 (FUV1) using Blood Eosinophil level as a covariate		SAC 2
50.	PP	n/a	Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Minimum LAR Absolute Change from Saline		SAC 2
51.	PP	n/a	Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Weighted Mean LAR Absolute Change from Saline		SAC 2
52.	mITT	n/a	Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Minimum LAR Absolute Change from Saline	Conditional on PP and mITT populations differing.	SAC 2
53.	mITT	n/a	Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Weighted Mean LAR Absolute Change from Saline	Conditional on PP and mITT populations differing.	SAC 2
54.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Minimum LAR Absolute Change from Saline using Blood Eosinophil level as a covariate		SAC 2

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
55.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Weighted Mean LAR Absolute Change from Saline using Blood Eosinophil level as a covariate		SAC 2
56.	PP	n/a	Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Minimum EAR Absolute Change from Saline at Week 9 (FUV1)		SAC 1
57.	PP	n/a	Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Weighted Mean EAR Absolute Change from Saline at Week 9 (FUV1)		SAC 1
58.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Minimum EAR Absolute Change from Saline at Week 9 (FUV1) using Blood Eosinophil level as a covariate		SAC 2
59.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Statistical Analysis - Bronchial Allergen Challenge Weighted Mean EAR Absolute Change from Saline at Week 9 (FUV1) using Blood Eosinophil level as a covariate		SAC 2
60.	PP	n/a	Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Minimum EAR Absolute Change from Saline		SAC 2
61.	PP	n/a	Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Weighted Mean EAR Absolute Change from Saline		SAC 2

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
62.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Minimum EAR Absolute Change from Saline using Blood Eosinophil level as a covariate		SAC 2
63.	PP	n/a	Sensitivity Analysis: Raw SAS Output for the Repeated Measures Statistical Analysis - Bronchial Allergen Challenge Weighted Mean EAR Absolute Change from Saline using Blood Eosinophil level as a covariate		SAC 2
Other Safety Parameters					
64.	All Subjects	CP_CM3	Listing of Rescue Medication (excluding that given as part of BAC procedures)	Rescue medications include Salbutamol (review with medical monitor prior to DBF the conmeds and/or any diary card data to determine if any other rescue medications exist)	FSP: SAC 2
65.	All Subjects	n/a	Listing of Disease Related Events	By Subject listing of the information collected and the derived time since 1st dose and time since most recent dose	FSP: SAC 2
66.	All Subjects	SAFE_L3	Listing of Peak Expiratory Flow (PEF)	Also display the Max and WM summary measure. Study day does not reset when it gets to a new week.	FSP: SAC 2
67.	All Subjects	SAFE_L1	Listing of Nasal Examination Data	Use "-" when the item was normal / not present. Wrap free text from Signs of bleeding field. Slot in any unscheduled data using the date/time of observations.	FSP: SAC 2
Pharmacokinetic					
68.	PK	pkcl1p	Listing of GSK2245035 Plasma Concentration-time Data		SAC [3]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic and Biomarker					
	Biomarkers supporting the BAC related exploratory objective(s)				
69.	Sputum Producers	PD_L1	Sputum Cell Pellet: Listing of evaluable data by Subject	For a sample to be evaluable it must have been both sent and viable (read without any quality issues) Order to display individuals (within each treatment): Complete profiles at top of list, then subjects with Pre-BAC SV timepoint missing, then 24h Post-BAC SV timepoint missing and finish by displaying remaining subjects by the (ascending) number of missing timepoints. In the event of identical profiles order by Allergen Strata and then subject ID.	SAC [2]
70.	Sputum Producers	PD_L2	Sputum Cell Pellet: Listing of Collection information	CONDITIONAL: Content may need revising when the precise nature of the sputum data transfer is agreed. The intent of this display is to provide the eCRF data, and whether sample sent for processing and whether it was subsequently rejected (non-viable)	SAC [2]
71.	Sputum Producers	PD_L3	Sputum Cell Pellet: Listing of Absolute Counts from each Slide Reader provided by the Vendor	CONDITIONAL: Content may need revising when the precise nature of the sputum data transfer is agreed. The intent of this display is to show the vendor provided “raw data”. It may not be required	SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
72.	Sputum Producers	PD_L4	Sputum Cell Pellet: Listing of Sputum Percentage data	CONDITIONAL: Content may need revising when the precise nature of the sputum data transfer is agreed. The intent of this display is to provide the raw data used in subsequent stats analyses	SAC [2]
73.	Sputum Producers	PD_L5	Sputum Cell Pellet: Listing of Absolute Cell Counts/g sputum data	CONDITIONAL: Content may need revising when the precise nature of the sputum data transfer is agreed. The intent of this display is to provide the raw data used in subsequent stats analyses	SAC [2]
74.	Sputum Producers	n/a	Sputum Cell Pellet: Raw SAS Output for the Statistical Analysis of Absolute Cell Count Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC [2]
75.	Sputum Producers	n/a	Sputum Cell Pellet: Raw SAS Output for the Statistical Analysis of all Absolute Cell Count Samples	Conditional on sufficient evaluable data points.	SAC [2]
76.	Sputum Producers	n/a	Sputum Cell Pellet: Raw SAS Output for the Statistical Analysis of Percentage Cell Counts Pre-BAC Samples	Conditional on sufficient evaluable data points.	SAC [2]
77.	Sputum Producers	n/a	Sputum Cell Pellet: Raw SAS Output for the Statistical Analysis of all Percentage Cell Counts Samples	Conditional on sufficient evaluable data points.	SAC [2]
78.	All Subjects	PD_L6	PBS Wash: Listing of concentration data		SAC [2]
79.	All Subjects	n/a	PBS Wash: Raw SAS Output for the Statistical Analysis of Pre-BAC Samples	Separate analysis for each inflammatory mediator	SAC [2]
80.	All Subjects	n/a	PBS Wash: Raw SAS Output for the Statistical Analysis of all Samples	Separate analysis for each inflammatory mediator	SAC [2]
81.	All Subjects	PD_L6	Blood Differentials: Listing of Absolute count data		SAC [2]
82.	All Subjects	PD_L6	Blood Differentials: Listing of Percentages data		SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
83.	All Subjects	n/a	Blood Differentials: Raw SAS Output for the Statistical Analysis of Absolute Count Pre-BAC Samples		SAC [2]
84.	All Subjects	n/a	Blood Differentials: Raw SAS Output for the Statistical Analysis of all Absolute Count Samples		SAC [2]
85.	All Subjects	n/a	Blood Differentials: Raw SAS Output for the Statistical Analysis of Percentages Pre-BAC Samples		SAC [2]
86.	All Subjects	n/a	Blood Differentials: Raw SAS Output for the Statistical Analysis of all Percentages Samples		SAC [2]
87.	All Subjects	PD_L7	FeNO: Listing of All FeNO data	Include BAC and Dosing Visit samples in the same listing.	SAC [2]
88.	All Subjects	n/a	FeNO: Raw SAS Output for the Statistical Analysis of BAC Visit FeNO data		SAC [2]
	Biomarkers supporting the NAC related exploratory objective(s)				
89.	All Subjects	PD_L8	Nasal Lavage: Listing of Fluid and Filter Concentration data (All NAC associated Timepoints)	Include all data from all NAC visit planned timepoints in this listing (i.e. Background, Pre-NAC, 5m Post NAC and 6h Post NAC for SV, FUV1, FUV2)	SAC [2]
90.	All Subjects	n/a	Nasal Lavage: Raw SAS Output for the Statistical Analysis of NAC Background Samples	Separate analysis for each biomarker (Fluid and Filters)	SAC [2]
91.	All Subjects	n/a	Nasal Lavage: Raw SAS Output for the Statistical Analysis of Direct NAC Samples	Separate analysis for each biomarker (Fluid and Filters)	SAC [2]
	Biomarkers supporting the Induction of TLR7 (target engagement) exploratory objective(s)				
92.	All Subjects	PD_L8	Nasal Lavage: Listing of Fluid and Filter Concentration data (All Dosing Visit associated Timepoints)	Include all data from all Dosing Visit planned timepoints in this listing (i.e. Pre-Dose and 24h Post Dose for DV1, DV4 and DV8)	SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
93.	All Subjects	n/a	Nasal Lavage: Raw SAS Output for the Statistical Analysis of Dosing Visit Samples	Separate analysis for each biomarker	SAC [2]
94.	All Subjects	PD_L8	Serum: Listing of Concentration data	Drop the volume of sample column.	SAC [2]
95.	All Subjects	n/a	Serum: Raw SAS Output for the Statistical Analysis of Dosing Visit Samples	Separate analysis for each biomarker	SAC [2]
96.	All Subjects	n/a	FeNO: Raw SAS Output for the Statistical Analysis of Dosing Visit FeNO data		SAC [2]
Multivariate / Composite					
97.	All Subjects	n/a	Multivariable responder/non-responders: Listing of Question IDs and their associated text / criteria	Note: Data may drive the addition or removal of questions/criteria. Any new post hoc additions (but not counting re-ordering of items in Table 15) should be indicated using a lowercase p as a suffix, e.g. N1p, N2p	SAC [2]
98.	All Subjects	n/a	Multivariable responder/non-responders: Listing of Individual subjects responder status to each Question ID	To Save space use the abbreviated question IDs (e.g. A1, B1, N1p etc) and add footnote referring the reader to the Output with the link to the full text/criteria (i.e. the listing number that is used at time of reporting) Note: Individual questions may use different analysis populations and the All Subjects has been specified here because it should encompass all of them.	SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
99.	All Subjects	n/a	Multivariable responder/non-responders: Listing of the Proportion of responders for each Question ID by Treatment	To Save space use the abbreviated question IDs (e.g. A1, B1, N1p etc) and add footnote referring the reader to the Output with the link to the full text/criteria (i.e. the listing number that is used at time of reporting) Derive separate proportions for the main and alternate sets of treatment descriptors.	SAC [2]
100.	All Subjects	n/a	Multivariate Approach 1 - Profile Regression Raw Output		SAC [2]
101.	All Subjects	n/a	Multivariate Approach 2 – Raw Output		SAC [2]
Exploratory					
102.	All Subjects	Base around principles of gsk2245035 mid204540 final listing 13	Listing of Total Nasal Symptom Score (TNSS)	Include individual components and total. Include column for the overall daily score (akin to the BAC FEV1 repeat measures from a timepoint being modelled using their max value)	FSP: SAC [2]
103.	All Subjects	Base around principles of gsk2245035 mid204540 final listing 14 & 15	Listing of Weighted Mean Total Nasal Symptom Score (TNSS)	Include WMs derived for individual components and total for each study week	FSP: SAC [2]
104.	All Subjects	EXP_L1	Listing of Intradermal Allergy Testing – Wheal/Flare data	List Negative control and Challenge (Allergen) data on same row if possible.	FSP: SAC [2]

Non-ICH : Listings					
No.	**Population**	**IDSL / TST ID / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
105.	All Subjects	EXP_L2	Listing of Intradermal Allergy Testing – Change from Baseline Mean Diameter Wheal/Flare data	List Negative control and Challenge (Allergen) data on same row if possible. Include SV2 absolute value (baseline) as a row and then the change from baselines as record per visit underneath	FSP: SAC [2]
Interim Analysis Specific					
106.	All Subjects (at the time of IA1)	EFF_L1	Interim Analysis: Listing of Subjects Treated with Placebo Who Did Not Experience a Late Asthmatic Response at Week 9 (LAR Non-Responder at FUV1)	1st Section: Table of how many non-LAR responders there were on Placebo at FUV1 2nd Section: Lists the non-LAR responders (if any) and which item(s) they failed on	IA [1]
107.	All Subjects (at the time of IA1)	EFF_L2	Interim Analysis: Raw SAS output from predicting the probability of achieving end of study success	Conditional on observed data at time of interim (Consult GSK Study statistician to determine whether to produce)	IA [1]

11.14 Appendix 14: Example Mock Shells for Data Displays

See separate document: RAP-Mock Tables-205540.doc