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

Title	:	Reporting and Analysis Plan for a placebo-controlled, double-blind (sponsor open), randomised, crossover study to assess the efficacy, safety, and tolerability of GSK2798745 in participants with chronic cough
Compound Number	:	GSK2798745
Effective Date	:	07-SEP-2018

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 207702
- This RAP is intended to describe the efficacy, safety and pharmacokinetic analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Interim Analysis (IA) and Statistical Analysis Complete (SAC) deliverables.

RAP Author(s):

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PPD Principal Statistician (Respiratory, Clinical Statistics)	Not Applicable	Not Applicable
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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 207702:

Revision Chronology:		
2017N319286_00	31-MAY-2017	Original
2017N319286_01	09-OCT-2017	Removal of Simplified Nutritional Appetite Questionnaire (SNAQ).
2017N319286_02	22-NOV-2017	Addition of CSSRS at follow-up and updates to emergency unblinding text on request of MHRA.
2017N319286_03	25-JUN-2018	Increasing the upper BMI limit and removing the upper limit for FEV1

2. SUMMARY OF KEY PROTOCOL INFORMATION

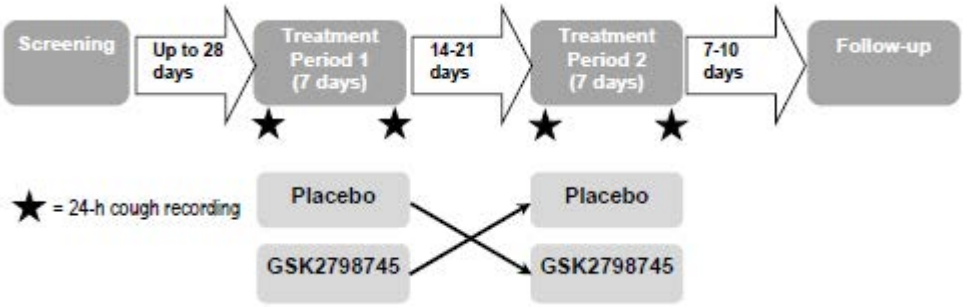
2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol (Dated: 31/MAY/2017), amendment 01 (Dated: 09/OCT/2017), amendment 02 (Dated: 22/NOV/2017) and amendment 03 (Dated: 25/JUN/2018)

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

Objectives	**Endpoints**
Primary Objectives	**Primary Endpoints**
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts during day-time hours following 7 days of dosing
Secondary Objectives	**Secondary Endpoints**
• To compare the safety of GSK2798745 with placebo in participants with idiopathic or treatment-resistant chronic cough	• Adverse events (AE), clinical laboratory values, vital signs, electrocardiogram (ECG), and other safety biomarkers
Exploratory Objectives	**Exploratory Endpoints**
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo in participants with idiopathic or treatment resistant chronic cough	• Total cough counts over 24 hours following 7 days of dosing
• To compare the efficacy of 7 days dosing of GSK2798745 with placebo at improving patient reported outcomes in participants with idiopathic or treatment-resistant chronic cough	• Change from baseline cough severity and urge to cough visual analogue scale (VAS) • Change from baseline Leicester Cough Questionnaire (LCQ) score
• To evaluate the pharmacokinetics (PK) of GSK2798745 and its M1 metabolite in participants with idiopathic or treatment resistant chronic cough	• Plasma concentrations of GSK2798745 and derived PK parameters, as data permit

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-centre • Randomised • Double-blind (sponsor open) • Placebo-controlled • Two-period crossover, each period 7 days with 14-21 day washout between periods • Study duration maximum of 10.5 weeks • Coughs recorded using VitaloJAK cough monitor for 24 hours before dosing in each treatment period (baseline) and for 24 hours after dosing on Day 7 of each treatment period
Dosing	• 4.8 mg GSK2798745 on Day 1, followed by 2.4 mg GSK2798745 once daily for 6 days • Matching placebo once daily for 7 days
Time & Events	• Appendix 2: Schedule of Activities
Treatment Assignment	• Treatment A: Placebo tablets for 7 days • Treatment B: GSK2798745 tablets for 7 days • Participants will be randomised to one of two treatment sequences AB or BA
Interim Analysis	• Planned after at least 12 participants have completed both dosing periods. Following the results of the interim analysis, the study may be stopped for futility, or a re-estimation of the sample size will take place

2.4. Statistical Analyses

The study is designed to estimate the effect of GSK2798745 relative to placebo on day-time cough counts following seven days of dosing. Day-time cough count totals will be

derived from the total number of coughs during the first 10 hours following dosing, during which the participant is expected to be awake.

The inference to be carried out will be with respect to the following hypothesis:

- Treatment with GSK2798745 leads to a reduction in day-time 10-hour cough count totals compared with placebo.

The above hypothesis will be investigated in this study by means of a Bayesian approach, which will assume a non-informative prior distribution. It is anticipated that the day-time 10-hour cough count totals will be log-transformed before statistical analysis, and hence the treatment effect will be evaluated in terms of a ratio of day-time cough count totals (GSK2798745 / placebo), with corresponding 90% credible interval. A day-time cough count total of at least 30% less for GSK2798745 than for placebo is of interest. The posterior probability that the true ratio is less than 0.7 will be obtained and will be referred to as PP (ratio<0.7).

3. PLANNED ANALYSES

3.1. Interim Analyses

An interim analysis is planned after at least 12 participants have completed both dosing periods and will be based on day-time 10h total cough count data, as well as supporting PK data, if required. PK data will remain blinded if assessed as part of any interim analyses.

An ongoing review will take place to ensure that compliance to study drug and validity of cough data are acceptable for the interim analysis. For cough data to be valid, at least 60% of the recording time during the first 10 hours must be available, See Section 7.1.2. If compliance or cough data are deemed to be invalid for the first 12 participants who have completed both dosing periods, then consideration will be given to waiting for additional participants to meet the minimum of 12 participants with valid data for analysis.

The primary objectives of the interim analysis are to:

i) Stop the study on the grounds of futility
ii) Re-estimate the sample size based on the treatment effect and variability observed at the time of the interim.

As the study is double blind (sponsor-open), the results will be made available to a core subset of the GSK study team, who will review the data (treatment level only), before making a decision on whether to stop the study for futility or adjust the sample size. Decisions from the interim analyses and details of members of the GSK study team who reviewed the results, will be documented in the interim results meeting minutes. Any adjustment to the sample size will be communicated to the sites.

The sample size re-estimation will be supplemented by deriving conditional probabilities. As a result of this supportive information, the sample size could be revised either upwards or downwards from the planned sample size of 24 evaluable participants, but the target number of evaluable participants will not exceed 40 participants.

The interim analysis will be performed by GSK Clinical Statistics and only the responsible statistician(s) (including QC statistician(s)) and programmers will have access to the study reporting area where the individual participant data which will be unblinded for the interim analyses. Unblinded treatment sequences will only be made available for participants who will be included in the interim analysis. A list of randomisation numbers of those who have completed the relevant treatment periods for the interim analysis will need to be provided by the study manager or designee, to release the treatment sequence codes.

The interim analysis will use clean efficacy data (cough count data provided by Vitalograph and subject to QC and cleaning processes) and will be supplemented by the following in stream data from the eCRF for use in standard HARP programs; cough dates and times, exposure and compliance information, demography data and stratification responses. SI datasets for the specified eCRF data will be provided by Data Management

to a level as clean as possible at the time of the interim, with data as complete as possible (up to Period 2 Day 8) for the randomised participants who will be included in the interim analysis. Statistics and programming will cut the data (subset) based on the list of randomised participants available for the interim analysis.

It is expected that outputs from the Interim Analysis will not be required for the Clinical Pharmacology Study Report (CPSR) as only final data will be formally reported. The CPSR will provide brief details that an interim analysis was performed and sample size subsequently increased or decreased.

Details for the statistical analysis of total 10h day-time cough counts are provided in Section 7.1.5. The proposed outputs to be provided for the interim analysis are as follows, refer to Section 12.11 for further details and examples:

- Summary of statistical analysis (including treatment ratio and 90% credible intervals along with posterior probabilities of interest, see example EF_T1). A preliminary assessment of carry-over and/or period by treatment interaction will be investigated as part of this analysis. The analysis will be based on imputed 10h totals (see Section 7.1.2).
- Figure of treatment group geometric means and 95% CIs for both baseline and Day 7 10h day-time cough counts (see example EF_F1)
- Figure as above split by treatment period to assist with assessment of carryover and/or period by treatment interaction
- Figure of overall hourly profiles (0-10h), geometric (or arithmetic dependent on data) means ± 95% CIs for GSK2798745 vs Placebo at each hourly timepoint (see example EF_F2).

3.1.1. Review of the Interim Analysis Results

Once the interim results are available, the following steps will be taken to support decision making moving forward.

1. Assessment of results

The results from the interim analysis (as well as final analysis) will be compared with pre-defined criteria for a positive and negative study as follows:

The pre-defined criterion for a **positive study** is a posterior probability of more than 70% that the true treatment ratio (GSK2798745 / placebo) is less than 0.7, i.e. PP(ratio<0.7)>70%.

The pre-defined criterion for a **negative study** is a posterior probability of less than 30% that the true treatment ratio (GSK2798745 / placebo) is less than 0.7, i.e. PP(ratio<0.7)<30%.

There is a grey area in which neither criterion is satisfied.

2. Sample Size Re-estimation

A graphic will be produced displaying the conditional probability of achieving various sample sizes (see Section 3.1.2) under positive and negative scenarios. From these estimates, an initial re-estimated sample size will be identified.

3. Supportive Information

Further information to be considered, which may influence what the final sample size will be:

- The change in conditional probability achieved vs. the change in the number of participants required to achieve it, e.g. increasing the sample size by 10 participants to achieve an extra 2% of conditional probability might not be deemed worthwhile
- The results of the Bayesian mixed model analysis of the interim data, i.e. the treatment ratio and variability observed in the interim data, and the probabilities that the true treatment ratio is less than 0.5, 0.7 and 1 based on the interim data
- Information on the profile of coughing over time as provided by the figure of geometric means and 95% CI for cough counts at each hourly interval
- Results of any further exploratory analyses of the cough count data dependent on the interim analysis results

4. Final Sample Size Decision

The estimate of sample size in the protocol is 24. The maximum revised sample size can be up to 40 evaluable participants (maximum 48 randomised). Factors as described in #1, #2 and #3 above will be reviewed to support a decision on increasing or decreasing the sample size from the planned 24 participants.

Based on the results of the interim analyses, if there is strong evidence of a **positive** outcome based on conditional probabilities then this may, once other factors as described above have been considered, lead to a reduction in sample size equal to **the total number of participants who have completed the study together with those who are currently in the study**.

If there is strong evidence of a **negative** outcome based on conditional probabilities and there are no further factors which suggest that more information is needed, then the sample size may be reduced, again to equal **the total number of participants who have completed the study together with those who are currently in the study.**

In both cases, the total sample size will be estimated closer to the interim based on recruitment at the time and all ongoing participants will complete the study. Strong evidence would include results from the interim that meet our pre-defined criteria and the supporting conditional probabilities indicating a reduction in sample size to close to the interim N.

The full rationale for the decision on the final sample size, incorporating any considerations beyond the primary conditional probabilities, will be documented in the interim analysis meeting minutes.

3.1.2. Conditional Probabilities to Support Sample Size Re-estimations

Sample size re-estimation will be supported by conditional probabilities of meeting the pre-defined positive and negative criteria for the study. This method utilises the data we have from the interim, but makes assumptions on the future data based on different scenarios. When calculating conditional probabilities, scenarios as detailed below will be considered.

The sample size giving a 90% conditional probability of meeting the **positive** criterion at the end of the study, based on the variability observed in the interim sample and based on the variability assumed for the protocol, conditioning on:

- a treatment ratio of 0.5 for the post-interim data
- the treatment ratio observed in the interim sample for the post-interim data

The sample size giving approximately 90% conditional probability of meeting the **negative** criterion at the end of the study, based on the variability observed in the interim sample and based on the variability assumed for the protocol, conditioning using:

- a treatment ratio of 0.95 for the post-interim data
- the treatment ratio observed in the interim sample for the post-interim data

All scenarios will be evaluated as part of the interim results review, however, the positive and negative study scenarios that utilise the interim observed variability and condition on the treatment ratio observed in the interim sample would be the key focus for decision making (yellow and brown dotted lines in the example graphic below).

Example of Graphic to illustrate Conditional Probabilities at the Interim

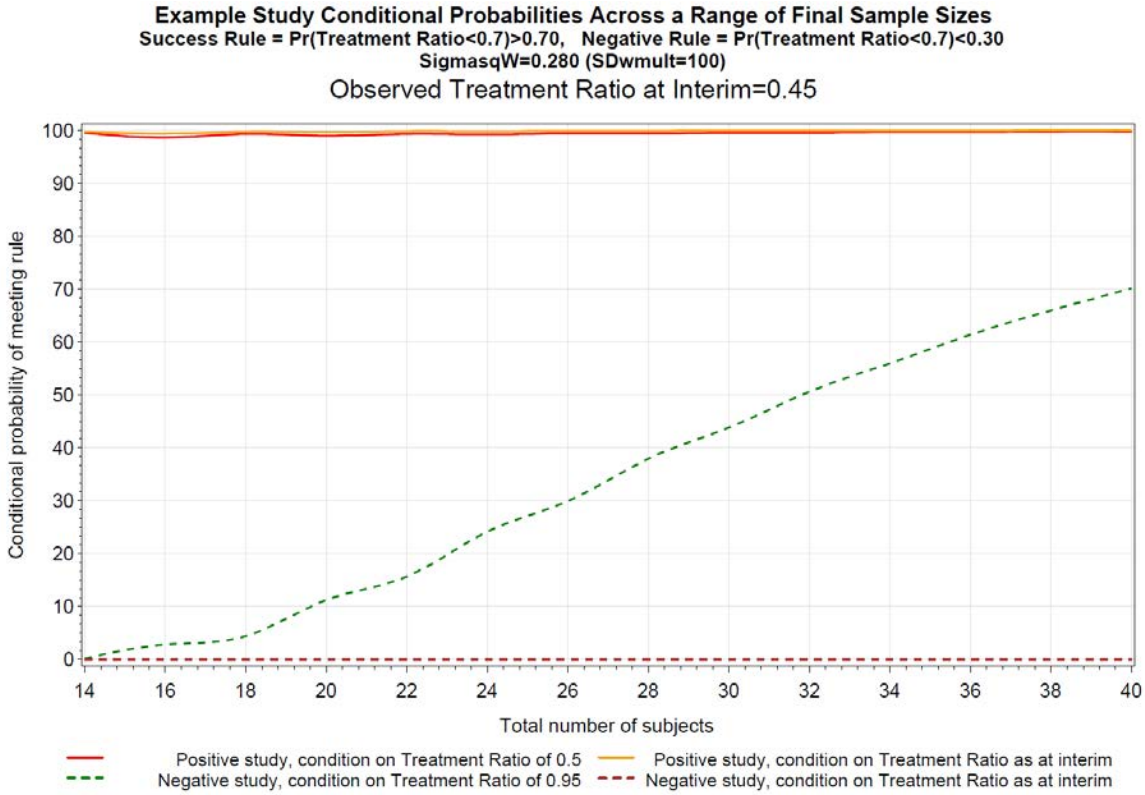
The graphic below shows an example of a 'conditional probabilities' graphic. In this example, it is based on overwhelming success at the interim, a ratio of 0.45 observed. If we assume that effect continues in the study (i.e., yellow line, conditioning on the interim ratio of 0.45) then there is no impact on the probability of meeting the success rule as the sample size increases, this is maintained at ~100% as we have already reached our success criteria. *In this instance, we may continue the study until the currently randomised participants could complete the study, without randomising further participants.*

Similarly, there is no impact on the probability of meeting the negative rule, brown dotted line, conditioning on the interim ratio of 0.45. This stays at ~0% (again as we have already met the success criteria).

The green line shows the impact of observing a very good drug effect at the interim but the probability of declaring a negative study if we still believe our true effect may be 'no/little effect', i.e. conditioning on a ratio of 0.95. In this case, we would have ~25%

probability of declaring a negative study with N=24 patients if we continued this study, when the true effect was in fact 'no effect'.

For the current study, if at the interim we have observed a good effect (ratio close to 0.70) then this graphic will help determine the sample size to continue with based on the variability observed at the interim. If the interim variability is lower than originally predicted, as defined in the protocol, then we may meet our success criteria at that point with a ratio of 0.7 or less. If the variability is as expected or higher, we may need to continue the study to reach our success probability and this graphic will guide us to the sample size most likely to achieve success.



Example operating characteristics for the above scenarios are presented in Section 12.5.6.

3.2. Final Analyses

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

1. All participants have completed the study as defined in the protocol (and subject to decisions made based on the interim analyses).
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met. Note that the study is being run as sponsor open, however for the interim analyses, only a partial randomisation schedule will be made available to GSK Clinical Statistics, applicable

to those participants who completed two dosing periods and for whom cough data will be transferred.

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

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• All participants screened and for whom a record exists on the study database	• Disposition (including reasons for screening failures)
All Subjects	• All randomized participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received	• Study Population • Efficacy • Safety
Pharmacokinetic (PK)	• All randomized participants who take at least 1 dose of study treatment and for whom a pharmacokinetic sample[a] was obtained and analysed	• PK

Refer to Appendix 11: List of Data Displays which details the population used for each display.
[a] refers to sample taken for the analysis of GSK2798745 and metabolite OR sample taken for analysis of Atorvastatin.

4.1. Protocol Deviations

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

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

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

A separate listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the eligibility page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

Note that all displays (Tables, Figures & Listings) will use the term 'Subjects'.

5.1. Study Treatment & Sub-group Display Descriptors

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

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

GSK2798745 vs Placebo

5.2. Baseline Definitions

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

Parameter	Study Assessments Considered as Baseline			Baseline Used in Data Display
	Screening	Day -1	Day 1 (Pre-Dose)	
Efficacy				
Total day-time cough count		X		Day -1
Total 24 hour cough count		X		Day -1
Cough Severity (VAS)	X	X		Day -1
Urge to Cough (VAS)		X		Day -1
Leicester Cough Questionnaire (LCQ)		X		Day -1
Columbia Suicidality Severity Rating Scale (CSSRS)	X	X		Day -1
Safety				
Labs	X		X[a]	Day 1 (Pre-Dose)
ECGs	X[b]		X	Day 1 (Pre-Dose)
Vital Signs	X[b]		X	Day 1 (Pre-Dose)
Audiometry		X		Day -1

[a] Can be completed on Day 1 (pre-dose) or Day -1

[b] Performed in triplicate

Unless otherwise stated, if baseline data is missing no derivation (e.g., change from baseline) will be performed and baseline will be set to missing.

For statistical analyses (for example, Bayesian mixed model) in a crossover design the following baseline derivations may apply:

- Baseline is defined as the 10h daytime cough count total observed pre-dose (Day -1) of each treatment period. This can also be referred to as '**period-specific baseline**'.
- **Subject-level baseline** is defined as the mean of the two period-specific baseline readings (the Day -1 10h cough count total from each of the two treatment periods) for each participant.
- **Period-level baseline** (or '**adjusted period-specific baseline**') is defined as the difference between the baseline ('period-specific baseline') and 'subject-level baseline' for each period and each participant (i.e., the 'period-specific baseline' minus 'subject-level baseline' in each period).

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

5.3. Multicentre Studies

In this multicentre study (UK), enrolment will be presented by investigative site in listings. Data will be summarised for all sites combined. A treatment-by-centre interaction may be investigated in the statistical analysis if sufficient data is available.

5.4. Examination of Covariates, Other Strata and Subgroups

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

Category	Details
Strata	**Prior cough study stratification**: Participants who did/did not take part in previous cough studies in the last 12 months. This is a stratification factor within the randomisation and will also be included in the database. The effect of this will be investigated as part of the statistical analysis.
Covariates	**Centre** If sufficient data is available, the effect of centre on the primary endpoint will be investigated. For data displays, data from centres will be combined unless otherwise specified in the list of outputs.
Subgroups	No subgroups are pre-specified, will be considered on an adhoc basis if required.

5.5. Other Considerations for Data Analyses and Data Handling Conventions

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

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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

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

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

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary efficacy endpoint is the total day-time cough count (10 hours).

This will be calculated from the time of the monitor being attached i.e., immediately after dosing on Day 7 to 10h past the start time of monitoring. The participant is expected to be awake during this period.

In addition, hourly total cough counts will be calculated for descriptive purposes. These will be measured in 60 minute intervals post the start time of the device monitoring.

A dataset of cough events (one row per cough) will be provided by Vitalograph. Four 24 hour sessions of data are expected for each participant (Period 1 Day -1, Period 1 Day 7, Period 2 Day -1 and Period 2 Day 7). This data will be made available to S&P via Data Management. Vitalograph will also provide an additional file (SAS format) containing information related to each session with regards to removal and re-attachment of the cough monitor as well as clearly defined sleep periods within each session. Further details on the cough count data to be transferred is provided in a Cough Analysis Plan written by Vitalograph.

Further details of the file structure for the cough count totals and additional session information are provided in Section 12.5.3.

7.1.2. Missing Data Imputation (0-10h)

In the unlikely event that a participant removes the cough monitor, turns off the device, has a period of data that cannot be analysed (flagged area) or other reasons for potential missing cough monitoring during the 10h from the start of the monitoring period, then the participant's cough profiles will be assessed to determine whether it is best to pro-rata the results based on the full 10h period, or to calculate the day-time 10h cough count total as missing. Should any data be pro-rated the resulting number of coughs will be rounded to the nearest integer value. As a rule of thumb, allowance for pro-rated data can be made if **at least 60%** of the first 10 hours of monitoring includes valid cough monitoring data (e.g., the monitor is attached and working for at least 6 out of the first 10 hours).

For example, if a participant recorded 200 coughs between 0 and 8 hours but the monitor was removed for the next 2 hours, we could estimate the 2 hour cough count as 50, with a resulting imputed 10h total of 250 coughs.

Pro-rated missing data rules as above will also be applied separately to hourly cough count totals, where at least 60% of the hourly interval has valid cough monitoring recorded.

Note that the rules applied to hourly intervals vs the 10h total, could result in the sum of the imputed hourly interval cough totals not being equal to the 10h total. For example, if a participant had an error with the device during the first hour resulting in no cough data then this hourly interval could not be imputed (as > 60% missing). However, if further monitoring was complete then the 10h total could use data from the remaining 9 hours to impute a cough count for the first hour. Hence in this example, the 10h total would be slightly higher than the sum of individual hourly totals.

Information regarding removal and re-attachment, late attachment, early termination/stoppage, sleep periods and flagged periods during the cough monitoring will be provided by Vitalograph in a separate information file (see Section 7.1.1). Dates and times of the events within this file will be merged with the databased cough data to assess the extent of missing time periods. Sleep periods will also be identified and will be classed as missing data, if the sleep period is within the first 10 hours of monitoring.

Further details of the file structure for the cough count totals and additional session information, plus further examples of missing data imputation and associated algorithms are provided in Section 12.5.3.

Details of any imputation will be fully documented and highlighted in participant listings.

7.1.3. Summary Measure

The summary measure for the primary analysis is the adjusted median posterior difference and 90% credible interval for GSK2798745 vs Placebo at Day 7 for total day-time cough counts (10 hours). A log-transformation of the cough count data is expected prior to analysis, in which case, the treatment effect will be evaluated in terms of a ratio of total day-time cough counts (GSK2798745/Placebo).

The primary analysis will be performed on pro-rated/imputed 10h cough count totals.

A sensitivity analysis will be conducted for the final analysis based on raw unimputed data.

7.1.4. Population of Interest

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

7.1.5. Statistical Analyses / Methods

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

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

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Total day-time cough counts (10 hours)
Model Specification
• The description below describes the current thinking of how to analyse these endpoints. The proposed model will be assessed, and if not appropriate alternative models could be used. • The data will be inspected prior to analysis to determine whether a data transformation is required. A log-transformation is expected for the total cough count data. Any data transformations will be applied to observed individual daytime 10h total cough counts prior to any modeling or derivations (e.g. prior to deriving subject baseline or period-adjusted baseline) • A Bayesian mixed effects model (fitted using SAS PROC MCMC), will be used to model the total day-time cough counts (10 hours) after 7 days of dosing. • Covariates for period, treatment, centre and previous cough study participation (stratification factor in the randomisation) will be included as fixed effects. Adjusted period-specific baseline and subject-level baseline will be included as continuous parameters. Subject will be included as a random effect. A treatment by period interaction will be included to investigate preliminary carry-over effects and/or a period by treatment interaction and if deemed appropriate an analysis by period may be performed. The assessment of the interaction will be performed using the equivalent PROC MIXED model and graphical representation. • An unstructured variance-covariance matrix will be fitted. A non-informative prior distribution will be assumed for posterior probabilities. • Examination of additional covariates (for example Age group) may take place, if data permit. In this case, the equivalent model may be fitted in PROC MIXED and the covariate assessed at a 10% alpha level. The final Bayesian model would then be fitted based upon the final model (after covariate examination) obtained using PROC MIXED. • Appropriate combinations of the model parameters will be used to obtain the posterior distribution for the GSK2798745 vs placebo on Day 7. Total 10h day-time cough counts will be represented via adjusted posterior medians for GSK2798745 and placebo, as well as associated 95% equi-tailed credible intervals. These results will be presented within tabular and graphical form after data has been back transformed. • The difference in total day-time cough counts between GSK2798745 and placebo, will be represented via an adjusted median, as well as associated 90% equi-tailed credible interval. These results will be presented within tabular form after data has been back transformed, hence representing the ratio of GSK2798745/placebo. • The posterior distributions will also be used to produce several posterior probability statements, presented in tabular format; the most important being the probability that the true ratio (GSK2798745/placebo) is less than 0.7, representing a 30% reduction in total day-time cough counts on GSK2798745. Probabilities that the true ratio is less than 1 (any effect) and less than 0.5 (excellent effect) will also be constructed.
Model Checking & Diagnostics
• Fixed effects will be assigned a non-informative prior of N(0, Var=1E6) and may be entered as separate univariate priors or as part of a multivariate distribution (variance covariance structure with zeros for off diagonals) in model hyperpriors. • The non-informative UN priors should be an inverse Wishart distribution. If the equivalent of

an unstructured variance covariance matrix does not fit then an AR(1) w/Random Effect structure may be considered, with non-informative priors ϕ~U[-1,1] for the off diagonal elements and σ^2 ~ invGamma(0.0001, scale=0.0001). Example, for N=2:

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

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

-
- Centring of any continuous covariates will take place at the input dataset stage: (valuei – average) for each subject i.
- Examination of trace plots to assess convergence. Autocorrelation plots and lag summary table to assess the degree of autocorrelation. Monte Carlo standard errors compared to posterior standard deviations (target would be MCSE/SD<0.01).
- Number of burn ins, thinning, starting points, number of posterior draws to take (10,000 may be a suitable starting default) will be customised to each model and may not be possible to specify in advance but will be modified to ensure satisfactory diagnostics are produced.
- For robustness, where non-informative priors are used the equivalent PROC MIXED model may be fitted (no output from this would be reported) and LS Means and estimates of treatment differences/ratios compared to the results obtained from the PROC MCMC analysis.
- Model assumptions will be applied, but appropriate adjustments may be made based on the data. A log-transformation is expected to total day-time 10h cough counts.

Model Results Presentation

- Summary table for total 10h day-time cough counts
- Listing of total hourly cough counts and 10h day-time cough counts by timepoint (baseline and Day 7) and treatment
- Individual hourly subject profiles (4 subjects per page) of day-time cough counts by treatment group and timepoint (0-10h)
- Boxplots of cough counts by treatment group and hourly timepoint (0-10h)
- (A) (*) Figure of geometric means ± 95% CIs of cough counts by treatment group and hourly timepoint (0-10h) (data permitting, arithmetic means may be presented)
- (B) (*) Figure of geometric means ±
- 95% CIs by treatment for Day -1 vs Day 7 10h day-time cough count totals
- Figure of subject by total 10h day-time cough counts and treatment
- Figure of individual changes from baseline for 10h cough counts (Day -1) to Day 7 by treatment group
- (*) Summary table of statistical analysis of total 10h day-time cough counts including: adjusted posterior medians and 95% credible intervals by treatment, estimated posterior median treatment effect (ratio GSK2798745/placebo) and 90% credible interval, posterior probabilities of interest (ratio<1, ratio<0.7 and ratio<0.5) – based on imputed data
- Summary table of statistical analysis of total 10h day-time cough counts including: adjusted posterior medians and 95% credible intervals by treatment, estimated posterior median treatment effect (ratio GSK2798745/placebo) and 90% credible interval, posterior probabilities of interest (ratio<1, ratio<0.7 and ratio<0.5) – sensitivity analysis not accounting for missing

data • Figure of statistical analysis adjusted medians and 95% credible intervals by treatment group • Figures (A) and (B) above may also be reproduced split by stratification factor (prior study participation) (*) To be produced for the interim analysis
Sensitivity and Supportive Analyses
• Period 1 analysis: Should the interim analysis or final analysis provide evidence of a possible carryover effect from the treatment of GSK2798745 from period 1 into period 2 and/or period by treatment interaction, then an analysis of period 1 data only may take place. • In this case, a Bayesian model will be fitted including terms for treatment, stratification factor, centre and period 1 baseline. An equivalent PROC MIXED model will be fitted for robustness or as an alternative method. Adjusted posterior medians will be provided as described previously.

7.2. Exploratory Efficacy Analyses

7.2.1. Endpoint / Variables

7.2.1.1. Total Cough Counts over 24 Hours

The endpoint is total cough counts over 24 hours. This will be calculated from the time of the monitor being attached i.e., immediately after dosing on Day 7 to 24h past the start time of monitoring.

In addition, hourly total cough counts will be calculated for descriptive purposes. These will be measured in 60 minute intervals post the start time of the device monitoring.

7.2.1.2. Cough Severity and Urge (VAS)

The endpoints are:

- Change from baseline in cough severity
- Change from baseline in urge to cough

Both will be measured on a 0-100mm visual analogue scale, where 0 represents a good response (no severity or urge to cough) and 100 represents a poor response (extremely severe cough or severe urge to cough).

7.2.1.3. Leicester Cough Questionnaire (LCQ)

The endpoint is change from baseline in Leicester Cough Questionnaire total and domain scores (LCQ).

The Leicester Cough Questionnaire consists of 19 questions, each with a 7 point Likert response scale., where 1 represents a poor response (affecting quality of life) and 7 represents a good response. The 19 questions fall into 3 domains as follows:

Physical: 1, 2, 3, 9, 10, 11, 14, 15

Psychological: 4, 5, 6, 12, 13, 16, 17

Social: 7, 8, 18, 19

For each of the above domains, the domain score will be calculated as the sum of the scores for the questions in that domain, divided by the number of items in the domain. The LCQ Total Score is then calculated as the sum of the three domain scores, and ranges from 3 to 21. A higher score indicates a better health status.

7.2.2. Missing Data Imputation

Total cough counts 24h

Please refer to Section 7.1.2 detailing that at least 60% of cough monitoring data must be available. The 60% cut-off will apply to data over 24 hours, but will apply to intervals within the 24 hours as detailed below. The totals from these intervals will be summed to provide a 24 hour total.

Two methods of determining intervals within the 24h will be used:

1. Where only one sleep period is recorded (will be for the majority of participants), then the 24h data will be split into 'awake' and 'asleep' intervals as determined by the sleep start/stop times provided by Vitalograph. Within each 'awake' and 'asleep' interval if at least 60% of the monitoring data is available, then missing data will be imputed from the remaining data within that interval.

2. If there is more than one sleep period, or where there is no information on sleep times, then the 24 hour data will be split into three distinct intervals: 0-12h (12h) representing an awake period, 12-20h (8h) representing most likely sleep interval and 20-24h (4h) representing the last 4 hours of monitoring on the second day of wearing the device (morning). Missing data, based on the 60% rule, will then be imputed within each of these intervals.

Each interval as described above will be assessed against the 60% criteria. However, in the event that one or more intervals cannot be imputed (as less than 60% of data is available), the following will apply:

- If the overall amount of data available over the 24h period is still at least 60%, then an individual interval can be imputed (regardless of 60% rule within that interval), provided the monitor was switched on and recording for some part of the interval of interest.
- If an interval is completely missing, but the full 24h period still has at least 60% of data, then the imputed 24h total will be calculated based on the full 24h period of data available, ignoring sleep/awake intervals.

If there is no missing data, then the imputed variable will be set to the raw cough total. If there is less than 60% of data available over the 24h period then the imputed variable will be set to missing.

Pro-rated missing data rules as above will also be applied separately to hourly cough count totals over the 24h period, where at least 60% of the hourly interval has valid cough monitoring recorded. For hourly intervals, awake and asleep times will not be evaluated.

On review of the data and potential for scenarios outside of those described above, the most appropriate method of imputation will be used. Any changes to the above methods will be described in the CSR.

Details of any imputation will be fully documented and highlighted in participant listings. Please refer to Section 12.5.3 with regards to further details on variable naming and the proposed structure of an A&R dataset for cough counts.

Severity and Urge to Cough (VAS)

Data will not be imputed.

Leicester Cough Questionnaire (LCQ)

Data for the individual responses that contribute to the domain and total scores will not be imputed. Missing data is unlikely as the questionnaires are completed at clinic visits. In the event of a missing individual question, the domain scores will still be calculated, with the number of questions answered modified in the calculation, see Section 7.2.1.3.

7.2.3. Summary Measure

The summary measure for total 24h cough counts is the adjusted median posterior difference and 90% credible interval for GSK2798745 vs Placebo at Day 7.

The analysis will be performed on pro-rated/imputed 24h cough count totals and a sensitivity analysis will be conducted for the final analysis based on raw unimputed data.

The summary measure for change from baseline in cough severity and urge to cough (VAS) is the adjusted median posterior difference and 90% credible interval for GSK2798745 vs Placebo at Day 7 (pre-dose).

The summary measure for change from baseline in total and domain LCQ scores is the adjusted median posterior difference and 90% credible interval for GSK2798745 vs Placebo at Day 7 (pre-dose).

7.2.4. Population of Interest

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

7.2.5. Statistical Analyses / Methods

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

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

7.2.5.1. Statistical Methodology Specification

Endpoint / Variables
• **Total cough counts over 24 hours**
Model Specification
• Data for this endpoint will be analysed in the same way as for the primary endpoint, see Section 7.1.5.1
Model Checking & Diagnostics
• Refer to Section 7.1.5.1
Model Results Presentation
• Summary table for total 24h day-time cough counts • Listing of total hourly cough counts and 24h day-time cough counts by timepoint (baseline and Day 7) and treatment • Individual hourly subject profiles (4 subjects per page) of day-time cough counts by treatment group and timepoint (0-24h) • Boxplots of cough counts by treatment group and hourly timepoint (0-24h) • (A) Figure of geometric means ± 95% CIs of cough counts by treatment group and hourly timepoint (0-24h) (data permitting, arithmetic means may be presented) • (B) Figure of geometric means ± 95% CIs by treatment for Day -1 vs Day 7 24h cough count totals • Figure of subject by total 24h cough counts and treatment • Figure of individual changes from baseline for 24h cough counts (Day -1) to Day 7 by subject and treatment group • Summary table of statistical analysis of 24h day-time cough counts including: adjusted posterior medians and 95% credible intervals by treatment, estimated posterior median treatment effect (ratio GSK2798745/placebo) and 90% credible interval, posterior probabilities of interest (ratio<1, ratio<0.7 and ratio<0.5) – based on imputed data • Summary table of statistical analysis of 24h day-time cough counts including: adjusted posterior medians and 95% credible intervals by treatment, estimated posterior median treatment effect (ratio GSK2798745/placebo) and 90% credible interval, posterior probabilities of interest (ratio<1, ratio<0.7 and ratio<0.5) – sensitivity analysis not accounting for missing data • Figure of statistical analysis adjusted medians and 95% credible intervals by treatment group • Figure (A) and Figure (B) above may also be reproduced split by stratification factor (prior study participation)

Subgroup Analyses
• Refer to Section 7.1.5.1
Sensitivity and Supportive Analyses
• Refer to Section 7.1.5.1

Endpoint / Variables
• **Change from baseline to Day 7 (pre-dose) in cough severity and urge to cough (VAS)**
Model Specification
• VAS is measured on a 0 to 100mm scale. • The description below describes the current thinking of how to analyse these endpoints. The proposed model will be assessed, and if not appropriate alternative models could be used. • The data will be inspected prior to analysis to determine whether a data transformation is required. • A Bayesian mixed effects model (fitted using SAS PROC MCMC), will be used to model the change from baseline to Day 7 (pre-dose) VAS endpoints as detailed above. • Covariates for period, treatment, centre and previous cough study participation (stratification factor in the randomisation) will be included as fixed effects. Adjusted period-specific baseline and subject-level baseline will be included as continuous parameters. Subject will be included as a random effect. A treatment by period interaction will be included to investigate preliminary carry-over effects and/or a period by treatment interaction and if deemed appropriate an analysis by period may be performed. • An unstructured variance-covariance matrix will be fitted. A non-informative prior distribution will be assumed for posterior probabilities. • Examination of additional covariates (for example Age group) may take place, if data permit. In this case, the equivalent model may be fitted in PROC MIXED and the covariate assessed at a 10% alpha level. The final Bayesian model would then be fitted based upon the final model (after covariate examination) obtained using PROC MIXED. • Appropriate combinations of the model parameters will be used to obtain the posterior distribution for the GSK2798745 vs placebo. • Change from baseline to Day 7 (pre-dose) VAS endpoints will be represented via adjusted posterior medians for GSK2798745 and placebo, as well as associated 95% equi-tailed credible intervals. These results will be presented within tabular and graphical form after data has been back transformed (if necessary). • The difference in change from baseline to Day (pre-dose) VAS endpoints between GSK2798745 and placebo, will be represented via an adjusted median, as well as associated 90% equi-tailed credible interval. These results will be presented within tabular form after data has been back transformed to represent a ratio (if necessary). • The posterior distributions will also be used to produce posterior probability statements, presented in tabular format; for example, the probability that the true difference (GSK2798745-placebo) in change from baseline in VAS is less than 0, less than -17mm or less than -30 mm, i.e. any treatment difference in favour of GSK2798745, a difference of 17 mm in favour of GSK2798745 or a difference of 30 mm in favour of GSK2798745.

Model Checking & Diagnostics
• Refer to Section 7.1.5.1
Model Results Presentation
• Summary table by visit and treatment group (separate outputs for severity and urge) • Summary table of change from baseline by treatment group (separate outputs for severity and urge) • Listing of severity and urge to cough VAS by timepoint (baseline and Day 7) and period (endpoints in one listing) • Figure of absolute mean VAS ± 95% CI by timepoint and treatment group (separate graphic for severity and urge) • Summary table of statistical analysis of change from baseline to Day 7 (pre-dose): adjusted posterior medians and 95% credible intervals by treatment, estimated posterior median treatment effect and 90% credible interval, posterior probabilities of interest (difference <0, difference <-17 mm and difference <-30 mm on VAS scale) (separate outputs for severity and urge) • Figure of statistical analysis adjusted medians and 95% credible intervals by treatment group (separate outputs for severity and urge)
Subgroup Analyses
• Refer to Section 7.1.5.1
Sensitivity and Supportive Analyses
• Refer to Section 7.1.5.1

Endpoint / Variables
• **Change from baseline to Day 7 (pre-dose) in LCQ domain mean scores and total score**
Model Specification
• LCQ is on a 1 to 7-point scale • The description below describes the current thinking of how to analyse these endpoints. The proposed model will be assessed, and if not appropriate alternative models could be used. • The data will be inspected prior to analysis to determine whether a data transformation is required. • A Bayesian mixed effects model (fitted using SAS PROC MCMC), will be used to model the change from baseline to Day 7 (pre-dose) LCQ endpoints as detailed above. • Covariates for period, treatment, centre and previous cough study participation (stratification factor in the randomisation) will be included as fixed effects. Adjusted period-specific baseline and subject-level baseline will be included as continuous parameters. Subject will be included as a random effect. A treatment by period interaction will be included to investigate preliminary carry-over effects and/or a period by treatment interaction and if deemed appropriate an analysis by period may be performed. • An unstructured variance-covariance matrix will be fitted. A non-informative prior distribution will be assumed for posterior probabilities. • Examination of additional covariates (for example Age group) may take place, if data permit. In this case, the equivalent model may be fitted in PROC MIXED and the covariate assessed at a 10% alpha level. The final Bayesian model would then be fitted based upon the final

model (after covariate examination) obtained using PROC MIXED. • Appropriate combinations of the model parameters will be used to obtain the posterior distribution for the GSK2798745 vs placebo. • Change from baseline to Day 7 (pre-dose) LCQ endpoints will be represented via adjusted posterior medians for GSK2798745 and placebo, as well as associated 95% equi-tailed credible intervals. These results will be presented within tabular and graphical form after data has been back transformed (if necessary). • The difference in change from baseline to Day 7 (pre-dose) LCQ endpoints between GSK2798745 and placebo, will be represented via an adjusted median, as well as associated 90% equi-tailed credible interval. These results will be presented within tabular form after data has been back transformed to represent a ratio (if necessary). • The posterior distributions will also be used to produce several posterior probability statements, presented in tabular format; the most important being the probability that the true difference (GSK2798745-placebo) is > 0, > 1 and > 1.3, i.e., any treatment difference or a difference of 1 or 1.3 points on the LCQ domain/total score in favour of GSK2798745.
Model Checking & Diagnostics
• Refer to Section 7.1.5.1
Model Results Presentation
• Summary table by visit and treatment group (domain scores and total in one output) • Summary table of change from baseline by treatment group (domain scores and total in one output) • Listing of LCQ scores by timepoint (baseline and Day 7) and period • Plot of absolute mean LCQ ±- 95% CI by timepoint and treatment group (4 graphics one for each domain and total score, page by endpoint) • Summary table of statistical analysis of change from baseline to Day 7 (pre-dose): adjusted posterior medians and 95% credible intervals by treatment, estimated posterior median treatment effect and 90% credible interval, posterior probabilities of interest (difference >0, >1 and >1.3 points on LCQ scale) (page by LCQ endpoint). A difference of 1.3 points is considered to be a minimally important difference. • Figure of statistical analysis adjusted medians and 95% credible intervals by treatment group (page by LCQ endpoint)
Subgroup Analyses
• Refer to Section 7.1.5.1
Sensitivity and Supportive Analyses
• Refer to Section 7.1.5.1

8. SAFETY ANALYSES

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

8.1. Adverse Events Analyses

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

8.2. Clinical Laboratory Analyses

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

8.3. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. The details of the planned displays are presented in Appendix 11: List of Data Displays.

The CSSRS questionnaire will be summarised by the use of a listing, to present data by participant, treatment group and timepoint.

Weight measured during the study will be summarised with standard vitals signs data.

A listing of audiometry changes from baseline will be produced.

9. PHARMACOKINETIC ANALYSES

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 12.4.3 Reporting Standards for Pharmacokinetic Data).

9.1.1.2. Derived Pharmacokinetic Parameters

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

Parameter	Parameter Description
Cmax	GSK2798745 for Day 1 and Day 7
Tmax	GSK2798745 for Day 1 and Day 7
AUC(0-3.5)	GSK2798745 for Day 1 and Day 7
C24	GSK2798745 for Day 8

NOTES: Additional parameters may be included as required.

9.1.2. Population of Interest

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

9.1.3. Statistical Analyses / Methods

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

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

9.2. Secondary Pharmacokinetic Analyses

9.2.1. Endpoint / Variables

9.2.1.1. Drug Concentration Measures

Refer to Appendix 4: Data Display Standards & Handling Conventions (Section 12.4.3 Reporting Standards for Pharmacokinetic Data).

For atorvastatin, it is expected that patients are on a stable daily dose. Dosing date and time of atorvastatin for Day -1, Day 1, Day 6 and Day 7 will be recorded separately for applicable participants. Therefore, the PKCNC dataset created for atorvastatin will require some non-standard programming to ensure the last dose prior to PK sampling on Day 1 and Day 7 is selected to derive actual sampling times. Time from last dose will therefore vary across participants dependent on when their last dose of atorvastatin was taken.

9.2.1.2. Derived Pharmacokinetic Parameters

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

Parameter	Parameter Description
Cmax	M1 metabolite for GSK2798745 Day 1 and Day 7 Atorvastatin and metabolite in available participants Day 1 and Day 7
Tmax	M1 metabolite for GSK2798745 Day 1 and Day 7 Atorvastatin and metabolite in available participants Day 1 and Day 7
AUC(0-3.5)	M1 metabolite for GSK2798745 Day 1 and Day 7 Atorvastatin and metabolite in available participants Day 1 and Day 7
C24	M1 metabolite for Day 8 Atorvastatin and metabolite in available participants for Day 8

NOTES: Additional parameters may be included as required.

9.2.2. Population of Interest

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

9.2.3. Statistical Analyses / Methods

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

Unless otherwise specified, endpoints / variables defined in Section 9.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

10. POPULATION PHARMACOKINETIC (POPPK) AND PHARMACODYNAMIC ANALYSES

Given the sparse plasma sampling scheme for GSK2798745, a non-linear mixed effects methodology will be applied to characterise the population PK of GSK2798745 allowing for the relatively few number of participants. This poppk model will be adapted from a previous model characterised for GSK2798745 in healthy participants [report in progress] to derive some key PK parameter estimates including Cmax, AUC and average concentration of drug over dosing interval (Cav). The influence of participant demographics, baseline characteristics, including baseline disease activity (cough counts), and co-medication on the pharmacokinetics of GSK2798745 in this population will be investigated. The individual participant PK parameters will be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses.

A population systemic exposure-efficacy model will be developed if data permit. Individual PK metrics such as trough concentration observed on Day 8 as well as the estimated average concentration over the dosing interval (Cav) will be used to derive a parametric model quantifying relationship between drug levels and the primary efficacy endpoint (total day-time cough count (10 hours)).

10.1. Statistical Analyses / Methods

A summary of the planned population pharmacokinetic analyses are outlined below:

- Drug plasma concentration-time data will be subjected to nonlinear mixed effects modelling using the program NONMEM to develop a population PK model or apply a previous pop pk model developed in healthy participants receiving GSK2798745.
- Individual post-hoc estimated PK parameters will be summarised descriptively.
- To support this analysis PopPK and population PK-PD datasets will be generated.

The timeline for these analyses will be independent of statistical analysis complete (SAC). Further details will be documented in a separate CPMS RAP.

The details for the dataset specifications are provided in Appendix 8: Population Pharmacokinetic (PopPK) Analyses.

Detailed Population PK-PD methodology and dataset specifications are presented in Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses.

11. REFERENCES

GlaxoSmithKline Document Number. : 2017N31986_00, A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough; 31-MAY-2017.

GlaxoSmithKline Document Number. : 2017N31986_01, A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough; 09-OCT-2017.

GlaxoSmithKline Document Number. : 2017N31986_02, A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough; 22-NOV-2017.

GlaxoSmithKline Document Number. : 2017N31986_03, A study to assess the effectiveness and side effects of GSK2798745 in participants with chronic cough; 25-JUN-2018.

12. APPENDICES

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

A Per Protocol Population is not defined for the study. Important protocol deviations will be summarised and listed.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Screening and Follow-up Schedule of Activities

Procedure	Screening[1] (up to 28 days before Treatment Period 1, Day -1)	Follow up/Early Withdrawal (7-10 days post last dose)	Notes
Informed consent	X		
Inclusion and exclusion criteria	X		
Demography	X		
Medical history (includes substance usage [and family history of premature CV disease])	X		Substances: Drugs, Alcohol, tobacco
Full physical exam, including height and weight	X	X	Height to be measured at screening only.
Chest imaging [CXR]	X		Not required if chest imaging has been conducted within 12 months of screening with no significant findings.
Columbia Suicidality Severity Rating Scale (CSSRS)	X	X	Use 'Baseline' CSSRS at Screening. Use the 'Since Last Visit' CSSRS at Follow-up.
Human immunodeficiency virus (HIV), hepatitis B (Hep B) and Hepatitis C (Hep C) screen	X		
Clinical chemistry, haematology and urinalysis (including cardiac troponin)	X	X	Non Fasting
Follicle-stimulating hormone and estradiol	X		As needed in women of non-childbearing potential only.
Faecal Occult Blood Test (FOBT)	X		FOBT cards will be provided at screening and must be returned to the laboratory and analysed before Day -1.
Vital signs (blood pressure, heart rate and temperature)	X	X	Triplicate vital signs required at screening.
12-lead ECG	X	X	Triplicate ECG required at screening.
Forced Expiratory Volume in One Second (FEV1)	X		Not required if documented evidence of FEV1 ≥ 80% within the 6 months before screening.

Procedure	Screening[1] (up to 28 days before Treatment Period 1, Day -1)	Follow up/Early Withdrawal (7-10 days post last dose)	Notes
Cough Severity & Urge to Cough Visual Analogue Scale (VAS)	X (Severity only)	X (Severity & Urgency)	Urge to cough VAS will not be completed at screening.
Audiometry		X	Audiometry to be done anytime between end of Treatment Period 2 and Follow-up.
Concomitant Medication review	X	X	
Adverse event (AE)/serious adverse event (SAE) review	X	X	SAEs collected from the time of consent. AEs collected from the time of first dose.

1. Screening assessments may be conducted at multiple visits, if required, but all samples for laboratory safety tests to be collected at one visit (unless repeats).

Treatment Period 1 and 2 Schedule of Activities

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Study Treatment						
Randomisation		X (TP1 only)				Can be done on Day –1 or Pre-dose Day 1. Participants will be stratified based on inclusion in a cough study within the last 12 months (defined as taking an investigational product in a cough study within the last 12 months).
Study Treatment dispensed		X				
Study Treatment dosing		X	X	X		Home dosing on Days 2-6. Dosing to be at about the same time each day ($\pm$ 2 hours relative to dosing on Day 1).
Diary Card dispensed		X		X (TP1 only)		Diary card used to collect dosing information, AEs and concomitant medications. Diary card dispensed on Day 7 in Treatment Period 1 only (to collect AEs and concomitant medications during washout period).

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Efficacy Assessments						
24- hour Cough Counting Starts	X			X		On Day 7, the cough counter must be attached immediately after dosing. Participant to be advised to avoid noisy environments whilst wearing the counter, and to stay awake for 10 h after attachment of cough monitor.
24- hour Cough Counting Ends		X			X	On Day 1, the cough counter must be removed before dosing.
Cough Severity & Urge to Cough VAS	X			X (pre-dose)		To be completed before other assessments
Leicester Cough Questionnaire (LCQ)	X			X (pre-dose)		To be completed before other assessments
Safety Assessments						
Brief physical exam	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Weight	X				X	Baseline can be done on Day –1 or Pre-dose Day 1
Vital signs (blood pressure, heart rate and temperature)		X (pre-dose)			X	Single measurements
12-lead ECG		X (pre-dose)			X	Single measurements
Clinical chemistry, haematology and urinalysis (including cardiac troponin)		X (pre-dose)			X	Non-fasting.
FOBT				X		FOBT cards will be provided on Day 1 and returned on Day 7 or 8, if possible (or returned by post).
CSSRS	X				X	Use the 'Since Last Visit' CSSRS questionnaire. The pre-dose CSSRS in each Treatment Period can be done on Day –1 or Pre-dose Day 1.

Procedure	Treatment Period 1 and 2 (Washout 14-21 days)					Notes
	Day –1	Day 1	Day 2–6	Day 7	Day 8	
Audiometry	X					Pre-Treatment Period 1 audiometry can be done anytime between Screening and Treatment Period 1, Day 1, pre-dose. Pre-Treatment Period 2 audiometry can be done any time during the washout period (up to Treatment Period 2, Day 1 pre-dose).
Concomitant Medication review	X	X	X	X	X	Concomitant medications collected in Diary Card during washout period.
SAE/AE review	X	X	X	X	X	AEs collected in Diary Card during washout period.
Other Assessments						
PK blood samples		X		X	X	**Day 1 and Day 7:** predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5 h post dose **Day 8:** 24 h post dose For participants taking atorvastatin, an extra sample will be taken at each time-point.
Optional Genetic Sample		X				Can be taken any time after consent has been signed and the participant has been randomised.

- The Cough Severity & Urge to Cough VAS should be completed before the LCQ, and both questionnaires should be completed before any other assessments.
- When scheduled at the same time-points, 12-lead ECGs and vital signs should be completed before any blood draws.
- The timing of assessments should allow PK samples to be taken as close as possible to the nominal time-point.
- The timing and number of planned study assessments, including: safety and pharmacokinetic assessments may be altered during the course of the study based on newly available data (e.g. to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

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

12.3.1. Study Phases and Treatment Emergent Rules for AEs

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

Study Phase	Definition
Pre-Treatment	**AE Start Date < Study Treatment Start Date (Period 1)**
On-Treatment (Period 1)	If AE Start Date is on or after Study Treatment Start Date (Period 1) & before Study Treatment Start Date (Period 2). **Study Treatment Start Date (Period 1) ≤ AE Start Date < Study Treatment Start Date (Period 2)**
On-Treatment (Period 2)	If AE Start Date is on or after Study Treatment Start Date (Period 2) & before Follow-Up. **Study Treatment Start Date (Period 2) ≤ AE Start Date ≤ Follow-Up Date**
Post-Treatment	If AE Start Date is on or after Follow-Up. **AE Start Date > Follow-Up Date**

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered, if collected.

12.3.1.1. Study Phases for Concomitant Medication

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

Study Phase	Definition
Pre-Treatment	**CM Start Date < Study Treatment Start Date (Period 1)**
On-Treatment (Period 1)	If CM Start Date is on or after Study Treatment Start Date (Period 1) & before Study Treatment Start Date (Period 2). **Study Treatment Start Date (Period 1) ≤ CM Start Date < Study Treatment Start Date (Period 2)**
On-Treatment (Period 2)	If CM Start Date is on or after Study Treatment Start Date (Period 2) & before Follow-Up. **Study Treatment Start Date (Period 2) ≤ CM Start Date ≤ Follow-Up Date**

12.4. Appendix 4: Data Display Standards & Handling Conventions

12.4.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Compound	: \ARPROD\GSK2798745\207702\Internal_01 : \ARPROD\ GSK2798745\207702\Final_01
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards (Integrated Data Standards Library).	
Generation of RTF Files	
• RTF files will be generated for the Final reporting effort.	

12.4.2. Reporting Standards

General

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

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

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

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures.

• All unscheduled visits will be included in listings.	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principles 7.01 to 7.13.	

12.4.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to GUI_51487. Note: Concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: Concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PK File	Pop-PK file (CSV format) for the POP-PK analysis by CPMS will be created by S&P according to the data specification detailed in Section 12.8.2 Population Pharmacokinetic (PopPK) Dataset Specification.
NONMEM/PK/PD File	PK/PD file (CSV format) for the PK/PD analysis by CPMS will be created by S&P according to the data specification detailed in Section 12.9.2 Pharmacokinetic/Pharmacodynamic Dataset Specification.
Pharmacokinetic Parameter Derivation	
PK Parameters to be Derived	The following PK parameters will be derived by CPMS: Non Compartmental (to be forwarded to Statistics and Programming) : Cmax, Tmax and AUC(0-3.5), C24 on Day 8 PopPK parameters include CL/F, AUC(0-24), Cav and Cmax
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters, December 2009.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards.

12.5. Appendix 5: Derived and Transformed Data

12.5.1. General

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

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

12.5.2. Study Population

Treatment Compliance
• In this study, participants take 2 tablets on Day 1 (2 x 2.4 mg) and 1 tablet (1 x 2.4 mg) on Days 2 through to 7, therefore treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / Planned Number of Doses,** which will be calculated as, **[No. of tablets taken / (No. of days in period + 1)] * 100,** where No. of days in period = (Date of last dose- Date of first Dose) +1 in each period. The denominator has 1 added to it to account for the fact that 2 tablets are taken on Day 1 and 1 tablet is taken on all other days. • Treatment compliance could be greater than 100% if there are events of overdose as recorded for 'tablets taken'. • Reasons for treatment not being returned will be recorded (tick box on eCRF). • Compliance during each study period will be calculated. • For each study period, a bottle containing 15 tablets is dispensed. At the end of each period, 7 tablets should remain if a participant has taken all medication correctly and returned unused tablets correctly.
Extent of Exposure
• Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Treatment Stop Date – (Treatment Start Date) + 1** • Participants who were randomized but did not report a treatment start date will be categorised as having zero days of exposure. • The cumulative dose will be based on the formula: **Cumulative Dose = Sum of (Number of Days on 4.2 mg x Total Daily Dose (for 4.2 mg)) + Sum of (Number of Days on 2.4 mg x Total Daily Dose (for 2.4 mg))**

Treatment Compliance
• If there are any treatment breaks during the study, exposure data will be adjusted accordingly.

12.5.3. Efficacy

Total Cough Counts at 10h and 24h
• Variance stabilising transformations (e.g. taking natural logarithms of the observed responses) may be implemented, if deemed necessary by the study statistician. If transformations are used the results will be reported on the back-transformed response scales. • Other efficacy endpoints to be statistically analysed will also be assessed for data transformation

12.5.3.1. Cough Count SI and A&R Dataset Specifications

SI Dataset COUGH

Provided by Data Management, this is based on data provided by Vitalograph in file 2**07702_cough_YYYYMMDD.csv**

Column Name	Data Type/Format	Label (*additional detail from transfer agreement*)
STUDYID	Char 10	Unique identifier for the study
SUBJID	Num 10.	Subject ID
VISIT	Char 40	Visit description
VISITNUM	Num 7.2	Visit sequence number
PTM	Char 40	Planned timepoint description
PTMNUM	Num 7.2	Planned timepoint sequence number
CENTREID	$45	Centre ID
ACTDT	Date9.	Actual date of assessment *(Start date of cough monitoring)*
ACTSTTM	Time8.	Actual start time of assessment *(Start time of the Cough Monitoring in 24 hour format)*
ENTM	Time5.	Stop time *(Stop time of the Cough Monitoring in 24 hour format)*
COVEID	$80	Cough vendor ID
COVEIDC	$8	Cough vendor ID code
EVNTDT	Date9.	Event date *(Event date in DDMMMYYYY format)*
EVNTTM	Time5.	Event time *(Event time in 24 hour format displayed as HH:MM. This is the time with the seconds and milliseconds removed)*
PRREFID	Char 20	Procedures reference ID *(Sample ID (unique ID) – The serial number from CF Card)*
ELTIMES	Num 8.3	Elapsed time, in seconds *(The seconds and milliseconds portion of the event time displayed as SS.MMM. This combined with EVTDT and EVNTTM will provide the full date and time of the cough event)*

External Dataset g207702_session_YYYYMMDD.sas7bdat

Provided by Vitalograph directly to Statistics and Programming. To be merged with SI COUGH dataset to derive missing data periods.

Column Name	Data Type / Format	Description / Notes
STUDYID	CHAR 6	Study Protocol ID – 207702
SUBJID	CHAR 6	The 6 digit Subject ID.
VISIT	CHAR 23	The name of the visit.
VISITNUM	CHAR 7	Visit sequence number.
CENTREID	CHAR 6	The 6 digit Site ID.
ACTDT	CHAR 9	Start date of the Cough Monitoring in the format DDMMMYYYY.
ACTSTTM	CHAR 5	Start time of the Cough Monitoring in 24 hour format displayed as HH:MM.
ENTM	CHAR 5	Stop time of the Cough Monitoring in 24 hour format displayed as HH:MM.
COVEID	CHAR 80	To be populated with 'Vitalograph Business Park, Maids Moreton, BUCKINGHAM, MK18 1SW'
COVEIDCD	CHAR 8	To be populated with 0001
PRREFID	CHAR 6	The Card Serial Number
FIELD_NAME	CHAR 100	"Session Status" for the status of the session row, each session will display this row e.g. Accepted. The following event rows will only appear for sessions that have these events recorded. The label associated to the non-cough event will be displayed using: "Sleep" – Sleep start event type "Wake" – Wake event type, will be set to the end of the recording if the subject did not wake during the session "Removal" – Removed device event type "Restore" – Restored device event type, will be set to the end of the recording if the device is never restored "Early termination" – The session is terminated early, possibly due to a CF card or battery failure. "Early Stoppage" – The session is stopped when the clinic or subject stops the device manually. "Late Attachment" – The device is attached late. "Flagged Area Start" – Flagged area start event type "Flagged Area End" – Flagged area end event type See cough analysis plan (Vitalograph) for further details.
NCEVNTDT	CHAR 30	Date of the non-cough event. For sessions that have been rejected, 'Rejected' will be displayed. For sessions that have been accepted with no events, 'Accepted with no events' will be displayed. For sessions that have been accepted with events, the full date and time of the event will be displayed including milliseconds, e.g. 10JUL2017 01:17:00:410.

A&R dataset COUGHALL

This derived dataset will include the original SI COUGH data merged together with the session data (transposed event dates/times) to provide all event dates/times in a format suitable for calculation of time periods. This dataset will not need to be formally QCd, but will be available as an intermediate dataset. QC of the dataset COUGHTOT will provide a QC that the non cough-events have merged and been used correctly.

Column Name	**Data Type / Format**	**Label (*additional detail from data transfer agreement*)**
STUDYID	Char 10	Unique identifier for the study
SUBJID	Num 10.	Subject ID
VISIT	Char 40	Visit description
VISITNUM	Num 7.2	Visit sequence number
PTM	Char 40	Planned timepoint description
PTMNUM	Num 7.2	Planned timepoint sequence number
CENTREID	$45	Centre ID
ACTDT	Date9.	Actual date of assessment *(Start date of cough monitoring)*
ACTSTTM	Time8.	Actual start time of assessment *(Start time of the Cough Monitoring in 24 hour format)*
ENTM	Time5.	Stop time *(Stop time of the Cough Monitoring in 24 hour format)*
COVEID	$80	Cough vendor ID
COVEIDCD	$8	Cough vendor ID code
EVNTDT	Date9.	Event date *(Event date in DDMMMYYYY format)*
EVNTTM	Time5.	Event time *(Event time in 24 hour format displayed as HH:MM. This is the time with the seconds and milliseconds removed)*
PRREFID	Char 20	Procedures reference ID *(Sample ID (unique ID) – The serial number from CF Card)*
ELTIMES	Num 8.3	Elapsed time, in seconds *(The seconds and milliseconds portion of the event time displayed as SS.MMM. This combined with EVTDT and EVNTTM will provide the full date and time of the cough event)*
STOPDT	Date9.	Event stop date (**DERIVED VARIABLE** – merge on last cough event and select date of event, should be the next calendar day if 24 hour monitoring achieved)
EVNDTTM	Datetime20.	Cough event date and time (**DERIVED VARIABLE** – merge together each cough date, time and seconds and apply format)
STADTTM	Datetime20.	Cough monitoring start date and time (**DERIVED VARIABLE** – merge together start date, time and seconds and apply format)
STODTTM	Datetime20.	Cough monitoring stop date and time (**DERIVED VARIABLE** – merge together stop date, time and seconds and apply format)

Column Name	Data Type / Format	Label (*additional detail from data transfer agreement*)
FAREAS	Datetime20.	Flagged area start date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
FAREAE	Datetime20.	Flagged area stop date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
ASLEEP	Datetime20.	Sleep period start date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
AWAKE	Datetime20.	Sleep period stop date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
EARLYTRM	Datetime20.	Early termination date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
REMOVE	Datetime20.	Removal date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
RESTOR	Datetime20.	Restore date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
EARLYSTO	Datetime20.	Early stoppage date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
LATEATT	Datetime20.	Late attachment date and time (**DERIVED VARIABLE** – convert character date variable provided to numeric date format)
STATUS	Char 120.	Status of cough recording
TRTCD	Num 8	Randomised Treatment Code (Seq)
TRTGRP	Char 120.	Randomised Treatment Group (Seq)
ATRTCD	Num 8	Actual Treatment Code (Seq)
ATRTGRP	Char 120.	Actual Treatment Group (Seq)
PTRTCD	Num 8	Period Treatment Code
PTRTGRP	Char 120.	Period Treatment Group
PATRTCD	Num 8	Period Actual Treatment Code
PATRTGRP	Char 120.	Period Actual Treatment Group

Note: If there is more than one sleep period, then name subsequent sleep and awake events as ASLEEP1, ASLEEP2, AWAKE1, AWAKE2 etc. The same logic would apply to more than one removal/restore or flagged area.

A&R dataset COUGHTOT

This dataset will use A&R dataset COUGHALL and create hourly, 10h and 24h counts with missing data periods imputed where appropriate. Log transformed variables to be included for use in the analysis.

Column Name	Data Type / Format	Label (*additional detail from data transfer agreement*)
STUDYID	Char 10	Unique identifier for the study

Column Name	Data Type / Format	Label (*additional detail from data transfer agreement*)
SUBJID	Num 10.	Subject ID
VISIT	Char 40	Visit description
VISITNUM	Num 7.2	Visit sequence number
PTM	Char 40	Planned timepoint description
PTMNUM	Num 7.2	Planned timepoint sequence number
CENTREID	$45	Centre ID
Hourly, 10h and 24h timepoint variables		
FLAGHR	Datetime20.	Timepoint Flag (**DERIVED VARIABLE** – one row per hourly interval, 10h, overall 24 period, plus one row for each of the 3 intervals within the 24h period) Values are: 1 2 … 23 24 100 /*for 10h*/ 240 /*for 24h*/ 499 /*for awake period 1*/ 500 /*for sleep period*/ 501 /*for awake period 2*/) 1120 /*for first 12h*/ 1080 /*for next 8h*/ 1040 /*for next 4h*/
FLAGHRC	Char 10	Timepoint Flag Description (**DERIVED VARIABLE** – as above, one row per hourly interval, 10h, overall 24 period, plus one row for each of the 3 intervals within the 24h period) Character values are: 0-1h 1-2h … 22-23h 23-24h 10h 24h 24h Awake1 24h Sleep1 24h Awake2 24h 0-12h 24h 12-20h 24h 20-24h
Imputation derivation variables		
FLAGIMP	Char 2	Flag Imputed (**DERIVED VARIABLE)** Values are: Y /*Yes imputed value*/ YR /*Yes imputed but based on full 24h as an individual interval does not meet 60% criteria, but full 24h does */

Column Name	Data Type / Format	Label (*additional detail from data transfer agreement*)
		NA /*Not applicable – cannot be imputed due to 60% rule */ ' ' data complete and not imputed
Stratification variables		
PRIOR	Char 1	Prior cough study participation (***Renamed*** *SCHORSCD variable in SC dataset)* *Y=Yes, N=No for answer to stratification question*
PRIORCD	Num 8	Numeric code for prior study participation (***Derived****, if PRIOR=Y then PRIORCD=1 else if PRIOR=N then PRIORCD=2*)
Date/time event variables from COUGHALL		
STADTTM	Datetime20.	Cough monitoring start date and time (**from COUGHALL**)
STODTTM	Datetime20.	Cough monitoring stop date and time (**from COUGHALL**)
FAREAS	Datetime20.	Flagged area start date and time (**from COUGHALL**)
FAREAE	Datetime20.	Flagged area stop date and time (**from COUGHALL**)
ASLEEP	Datetime20.	Sleep period start date and time (**from COUGHALL**)
AWAKE	Datetime20.	Sleep period stop date and time (**from COUGHALL**)
EARLYTRM	Datetime20.	Early termination date and time (**from COUGHALL**)
REMOVE	Datetime20.	Removal date and time (**from COUGHALL**)
RESTOR	Datetime20.	Restore date and time (**from COUGHALL**)
EARLYSTO	Datetime20.	Early stoppage date and time (**from COUGHALL**)
LATEATT	Datetime20.	Late attachment date and time (**from COUGHALL**)
Cough count total variables		
COUGHTOT	Num 8	Cough Count Total Raw (**DERIVED VARIABLE** – create for each hourly interval and for 10h and 24h period)
COUGHIMP	Num 8	Cough Count Total Imputed (**DERIVED VARIABLE** – create for each hourly interval and for 10h and 24h period, imputation based on rules as per RAP)
Log transformed cough count total variables		
LOGCTOT	Num 8	Log transformed cough total
LOGCIMP	Num 8	Log transformed imputed cough total
Subject baseline derivation variables		
CTOTBS	Num 8	Subject baseline
CIMPBS	Num 8	Imputed subject baseline
CTOTBP1	Num 8	Baseline period 1
CTOTBP2	Num 8	Baseline period 2

Column Name	Data Type / Format	Label (*additional detail from data transfer agreement*)
CIMPBP1	Num 8	Imputed baseline period 1
CIMPBP2	Num 8	Imputed baseline period 2
Period adjusted baseline derivation variables		
CTOTPA	Num 8	Period adjusted baseline
CIMPPA	Num 8	Period adjusted imputed baseline
Log transformed subject baseline derivation variables		
LCTOTBS	Num 8	Log transformed subject baseline
LCIMPBS	Num 8	Log transformed imputed subject baseline
Log transformed period adjusted baseline derivation variables		
LCTOTPA	Num 8	Log transformed period adjusted baseline
LCIMPPA	Num 8	Log transformed period adjusted imputed baseline
Standard treatment group variables		
TRTCD	Num 8	Randomised Treatment Code (Seq)
TRTGRP	Char 120.	Randomised Treatment Group (Seq)
ATRTCD	Num 8	Actual Treatment Code (Seq)
ATRTGRP	Char 120.	Actual Treatment Group (Seq)
PTRTCD	Num 8	Period Treatment Code
PTRTGRP	Char 120.	Period Treatment Group
PATRTCD	Num 8	Period Actual Treatment Code
PATRTGRP	Char 120.	Period Actual Treatment Group

12.5.3.2. Cough Count Missing Data Period Algorithms

Codes:

L	=	Low hour, H=High hour, M=missing time period
X	=	Start of missing period (e.g. removal),
Y	=	End of missing period (e.g. restore)
LA	=	Late attachment
ET	=	Early Termination
ES	=	Early Stoppage
S	=	Beginning of sleep period
A	=	End of sleep period (awakening)

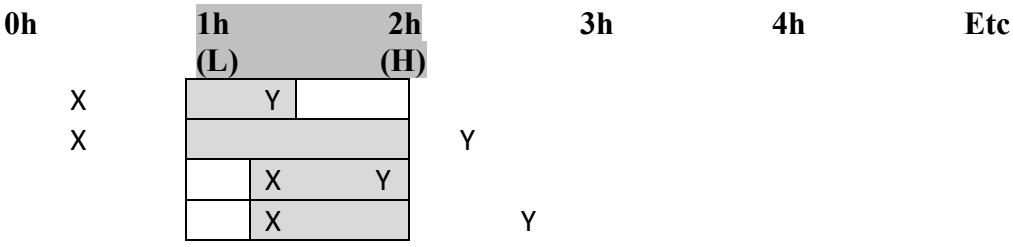
All measured in seconds e.g. 1h = 3600 seconds

X, Y, S, A, LA, ET and ES represent time from start of cough monitoring in seconds
Shaded areas represent potential missing data time intervals

A1 = first awake interval, S1 = sleep interval, A2 = second awake interval

1. HOURLY COUGH COUNT TOTALS

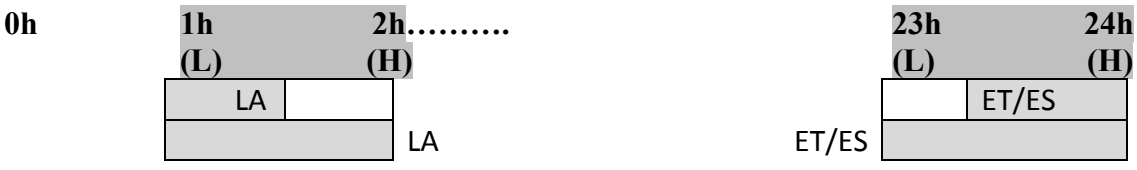
a. Missing periods with a start and end (removal/restore, flagged start/flagged stop)



If X < L then do; If Y <= H then M = Y – L
Else if Y > H then M = H – L (should be 3600 secs)

If L <= X < H then do; If Y <= H then M = Y - X
Else if Y > H then M = H – X

b. Late attachment, early termination or early stoppage

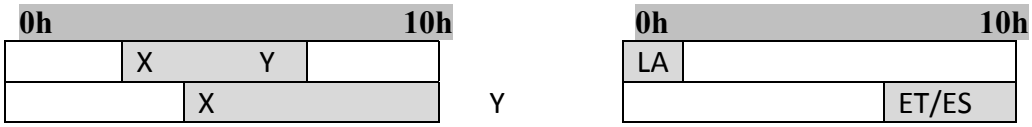


If L <= LA <= H then M = (H – L) – (H – LA),
Else if LA > H then M=H-L

If L <= ET <= H then M = H – ET (same for ES),
Else if ET < L then M=H-L

2. 10H DAYTIME COUGH COUNT TOTALS

a. Missing periods with a start and end (removal/restore, flagged start/flagged stop, sleep/awake)

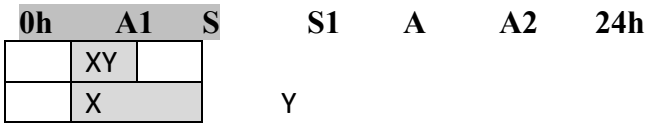


If X < 36000 then do; If Y <= 36000 then M = Y – X
Else if Y > H then M = 36000 - X

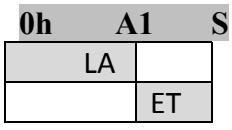
If LA < 36000 then M = LA
If ET < 36000 then M = 36000 – ET (same for ES)

3. 24H COUGH COUNT TOTALS

a. Awake Period 1 (A1) {*or first 12h (0-12h) if applicable*}

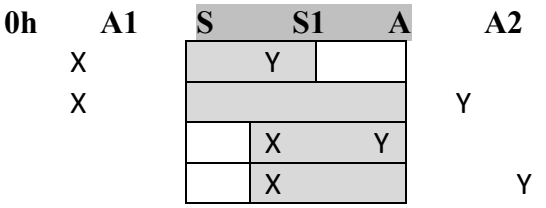


If X < S then do; If Y <= S then M = Y – X
Else if Y > S then M = S – X



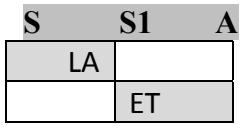
If LA < S then M = LA
If ET/ES < S then M = S – ET/ES

b. Sleep Period (S1) {*or next 8h (12-20h) if applicable*}



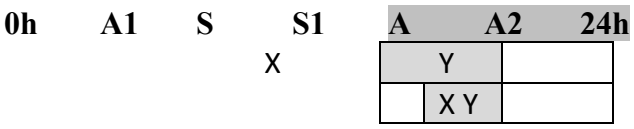
If X < S then do;
If S <= X < A then do;

If S <= Y <= A then M = Y – S
Else if Y > A then M = A – S (sleep period)
If Y <= A then M = Y – X
Else if Y > A then M = A – X

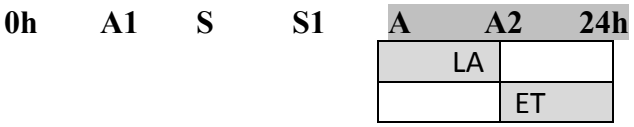


If S <= LA < A then M = LA - S
If S <= ET/ES < A then M = A – ET/ES

c. Awake Period 2 (A2) {*or last 4h (20-24h) if applicable*}



If X < A and Y > A then M = Y – A
Else if X >= A then M = Y – X



If A <= LA < 24h then M = LA – A
If A <= ET/ES < 24h then M = 86460 – ET/ES

Note: Value in seconds for 24 hours has 60 seconds added to allow for discrepancies between date/time variables that do/do not include seconds.

12.5.3.3. Cough Count Imputation Derivations

Imputation of cough counts will be applied when at least 60% of the cough monitoring time is present. If less than 60% of data is available then the missing time period will not be imputed (**with the exception of the overall 24h scenario described in Section 7.2.2**). Imputed cough counts within each time period of interest (hourly, 10h, 24h) will be calculated as follows:

$$\begin{aligned} &imputed\ cough\ count\ (COUGHIMP) \\ &\quad = integer\ \left[cough\ count\ (COUGHTOT)\right. \\ &\quad \left. + \left(missing\ proportion * \left\{\frac{cough\ count\ (COUGHTOT)}{1 - missing\ proportion}\right\}\right)\right] \end{aligned}$$

For example during the 10h period, if we have 3 hours of missing cough monitoring and the databased cough count for the remaining 7 hours is 500 then the imputed cough count would be:

$$imputed\ cough\ count = integer\ \left[500 + \left(0.3 * \left\{\frac{500}{1 - 0.3}\right\}\right)\right]$$

$$imputed\ cough\ count = integer\ [500 + 214.29] = \mathbf{714}$$

12.5.4. Pharmacokinetic

Pharamacokinetic Parameters
• Observed Cmax • Observed AUC(0-3.5) • Observed C24 Day 8 • Observed Tmax

12.5.5. Population Pharmacokinetic (PopPK)

Estimated PK Parameters from PopPK Analyses
• Model-based Cav (Average conc over 24h) • Model-based AUC(0-24) • Model-based Cmax • Model-based CL/F

Note: produced as part of the PopPK analyses and independent of SAC

12.5.6. Operating Characteristics of Decision Criteria Based on Conditional Probabilities

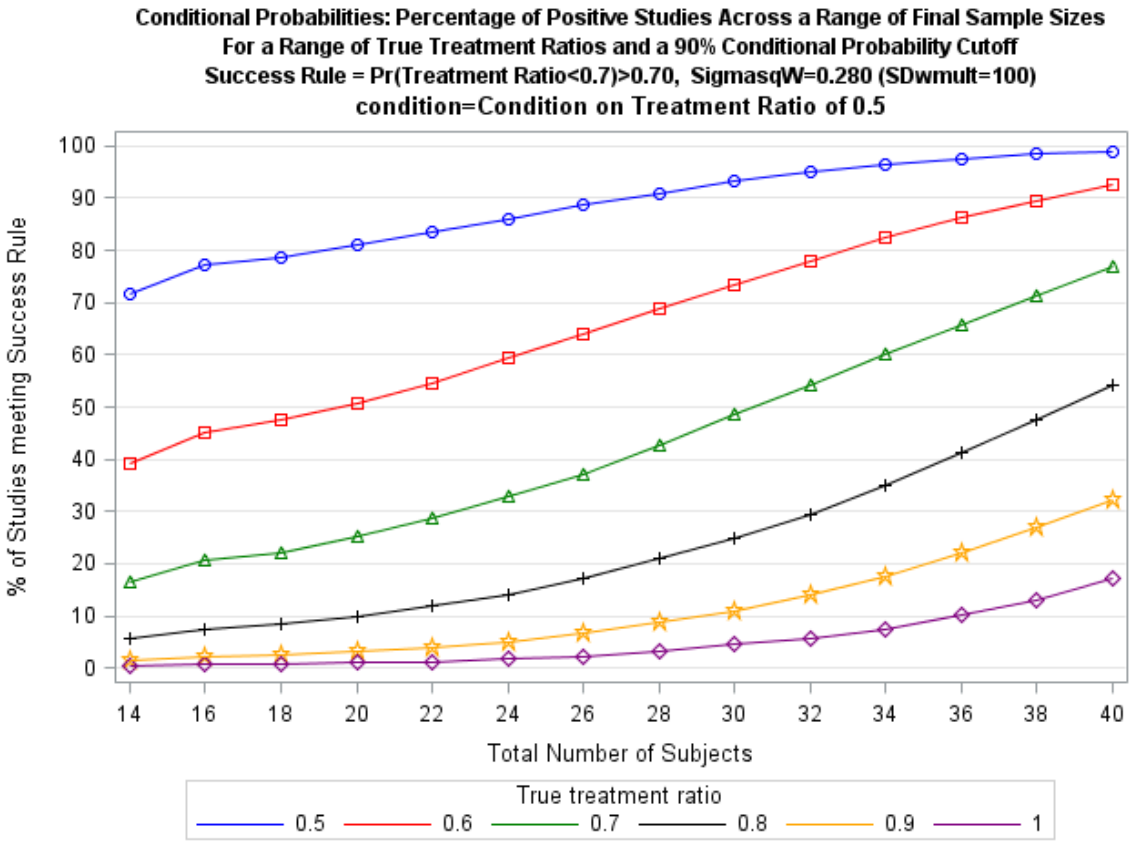
Operating characteristics for the decision criteria were produced based on 10000 simulations to show the long-run properties of the decision rules for a variety of assumptions. For the positive criterion the operating characteristics answer the question "if we ran the study 10000 times, what percentage of those studies would declare a

positive result for the specified set of assumptions?". For the negative criterion the operating characteristics answer the question "if we ran the study 10000 times, what percentage of those studies would declare a negative result for the specified set of assumptions?".

Positive Criterion

The figure below shows operating characteristics for a range of true treatment ratios and final sample sizes, using the variability assumed for the protocol (0.280). This figure shows the percentage of studies giving a 90% conditional probability of a positive study at the final analysis, conditioning on a treatment ratio of 0.5 (very good effect) for the post-interim data.

The **blue/circle** line shows the operating charateristics if the true treatment ratio was 0.5. If the assumptions are true, a final sample size of 24 would give **86.04%** of studies having at least 90% conditional probability of declaring a positive result when the variability from the protocol is assumed. If the true treatment ratio is 1 (**purple/diamond** line) only **1.78%** of studies would have at-least 90% conditional probability of declaring a postive result.



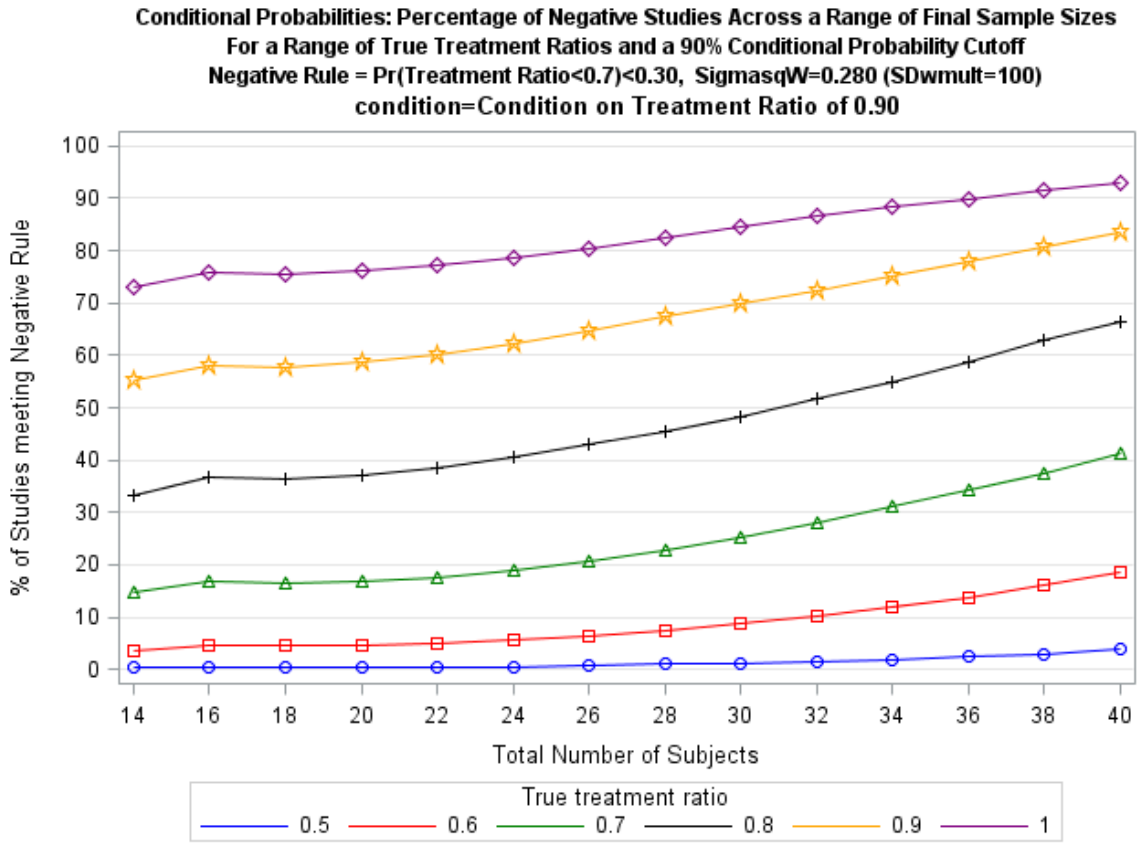
Similar plots were produced based on variability 80% and 120% of that assumed for the protocol and showed changes to these results as expected (data not shown). For example, assuming a smaller variance of 0.179 and larger variance of 0.403 and a true treatment ratio of 0.5, a final sample size of 24 would give **97.05%** and **71.45%** of studies,

respectively, having at least 90% conditional probability of declaring a positive result. Assuming a smaller variance of 0.179 and larger variance of 0.403 and a true treatment ratio of 1, a final sample size of 24 would give **1.63%** and **1.82%** of studies, respectively, having at least 90% conditional probability of declaring a positive result.

Negative Criterion

The figure below shows operating characteristics for a range of true treatment ratios and final sample sizes, using the variability assumed for the protocol (0.280). This figure shows the percentage of studies giving a 90% conditional probability of a negative study at the final analysis, conditioning on a treatment ratio of 0.90 (minimal effect) for the post-interim data.

The **purple/diamond** line shows the operating charateristics if the true treatment ratio was 1.0. If the assumptions are true, a final sample size of 24 would give **78.68%** of studies having at least 90% conditional probability of declaring a negative result when the variability from the protocol is assumed. However, if the true treatment ratio is 0.5 (**blue/circle** line) only **0.57%** of studies would have at-least 90% conditional probability of declaring a negative result.



Similar plots were produced based on variability 80% and 120% of that assumed for the protocol and showed changes to these results as expected (data not shown). For example, assuming a smaller variance of 0.179 and larger variance of 0.403 and a true treatment ratio of 1.0, a final sample size of 24 would give **93.44%** and **62.44%** of studies,

respectively, having at least 90% conditional probability of declaring a negative result. Assuming a smaller variance of 0.179 and larger variance of 0.403 and a true treatment ratio of 0.5, a final sample size of 24 would give **0.45%** and **0.75%** of studies, respectively, having at least 90% conditional probability of declaring a negative result.

12.6. Appendix 6: Reporting Standards for Missing Data

12.6.1. Premature Withdrawals

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

12.6.2. 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 participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Total cough counts (10h, 24h, hourly)	• Consideration will be given to instances where the monitor is turned off unexpectedly, or where a participant has a sleep period recorded during the primary day-time hours 10h period. • Vitalograph will provide a session acceptance file that will details removal and restore dates/times of the monitor for each session (e.g. period 1 day -1) • See Section 7.1.1 for further details on pro-rated data imputation.
Severity and Urge to Cough (VAS)	• Missing data will not be replaced
LCQ	• Missing data will not be replaced

12.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays.
Adverse Events	• Start and End dates for adverse events must be complete in the eCRF.

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

12.7. Appendix 7: Values of Potential Clinical Importance

12.7.1. Laboratory Values

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

Chemistry			
Analyte	**Effect**	**Relative – Low (Multipliers of LLN)**	**Relative – High (Multipliers of ULN)**
Calcium (mmol/L)		0.91	1.06
Glucose (mmol/L)		0.71	1.41
Potassium (mmol/L)		0.86	1.10
Sodium (mmol/L)		0.96	1.03
Blood Urea Nitrogen (mmol/L)		0.7	1.5
Total Protein (mg/dL)		0.6	1.7
Creatinine phosphokinase (IU/L)		0	1.8
Direct Bilirubin (umol/L)		0	1.6
Analyte	**Effect**	**Relative – Low (Absolute Value)**	**Relative – High (Absolute Value)**
Creatinine (umol/L)	Chg from Baseline		> 44 umol/L
Cardiac Troponin I (ug/L)			0.09 ug/L
FOBT		Positive	Positive

Urinalysis: During the study, a dipstick result (positive or negative) will be recorded for each participant at each relevant timepoint. If the dipstick result is positive, a microscopy will be performed. The urinalysis dipstick result at Day 8 will be compared with Day 1

(Pre Dose) and data of PCI will be flagged where a result changes from negative to positive and/or a microscopy is performed.

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

12.7.2. ECG

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

12.7.3. Vital Signs

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

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

12.8. Appendix 8: Population Pharmacokinetic (PopPK) Analyses

12.8.1. Population Pharmacokinetic (PopPK) Methodology

12.8.1.1. Software

All analysis will be performed in the validated Modelling and Analysis Platform (MAP). MAP consists of a Linux desktop containing various modelling applications, including NONMEM, PsN, Pirana, R and RStudio. All software versions used will be documented.

12.8.1.2. Outline

The population PK analysis will be performed in the following sequence of steps:

1. Exploratory data analysis/data check out.
2. Base structural model development.
3. Covariate analysis.
4. Model refinement.
5. Model evaluation.
6. Model application using simulation

The above analysis and reporting steps follow EMEA (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003067.pdf) and FDA population PK guidances (https://www.fda.gov/downloads/drugs/guidances/UCM072137.pdf)

Key components of these regulatory guidelines on population PK are also included in the Global CPMS guidance for pop pk RAP
https://connect.gsk.com/sites/cpms/TandD/Guidances

The analyses described above will be the responsibility of CPMS and will be independent of SAC. Further details will be provided in a separate RAP.

12.8.2. Population Pharmacokinetic (PopPK) Dataset Specification

12.8.2.1. Data Specification

12.8.2.2. Dataset Variable Conventions

Column headings in NONMEM-ready datasets and specifications should be consistent to minimise the programming process, and facilitate a smooth transfer of projects between users as needed. IDSL standards will be followed where possible.

A list of most common standardised variable names for NONMEM datasets can be found in Table below.

File to be produced for Analyte=GSK2798745 only.

List of Variable Names for NONMEM-Ready Datasets for PopPK Analysis

Variable	Label (Variable description)
C	NONMEM line exclusion identifier
ID	NONMEM subject identifier
STUD	Study ID
SUBJID	Subject identifier for study
SITEID	Unique identifier for a study site
AMT	NONMEM Amount of drug administered then EVID =1- dose event record
UAMT	Unit of AMT (mg)
ADDL	NONMEM Additional dose
CONC	Drug Concentration
UCONC	Unit of CONC (ng/mL)
LNCONC	Natural log of CONC column
ANALYTE	Drug label e.g 745
LLQ	Lower Limit of quantification
LNLLQ	Natural log of LLQ column
DAY	Study day number of record or of dosing
TIME	Plasma sample time after last dose (actual time)
UTIME	Unit of TIME (h)
DOSE	Dose amount
EVID	NONMEM Event ID If row has dose then EVID=1 else EVID =0 If EVID=1 then this is a dose event record If EVID = 0 then this is an observation record
II	NONMEM Inter-dose interval II=24 – dose every day
MDV	NONMEM Missing data value then MDV=1 else MDV=0
AGE	Subject Age (yrs)
SEX	Subject gender 0 = Male 1 =Female
SEXTEXT	Subject gender text Male or Female
BMI	Baseline Body Mass Index
WT	Baseline Subject weight
CONMED1*	Identifier for inhibitor CYP3A4 1 =Yes, 0 = No
CONMED1TXT*	Inhibitor Name
CONMED2*	Identifier for inducer CYP3A4 1 =Yes, 0 = No
CONMED2TXT*	Inducer Name
CONMED3*	Identifier for co-admin of ANY statin 1 =Yes, 0 = No
CONMED3TXT*	Statin name
CONMED4*	Identifier for co-admin of Atorvastatin 1 =Yes, 0 = No
CONMED4TXT*	ATORVASTATIN

If observation record e.g CONC has “NA” or “NS” then assign CONC cell as “.”
If observation record e.g CONC has “NQ” or “BQL” then assign CONC cell as “.” and MDV = 1 -this means value can be estimated by model
Missing covariate data should be imputed as “-99.

Statistics & Programming in discussion with CPMS to provide dataset as specified in Table below based on column variables described above. Fields marked with a '*' above will need discussion between S&P and CPMS prior to generating the dataset, to identify concomitant medication data applicable to each column.

Population Pharmacokinetic (PopPK) Dataset Specification   Excel .csv file

C	ID	STUD	SUBJID	SITEID	DAY	TIME	UTIME	AMT	UAMT	ADDL	II	CONC	UCONC	LNCONC	ANALYTE	LLQ	LNLLQ	MDV	EVID	AGE	WT	BMI	SEX	SEXTEXT
.	PPD	207702	PPD		1	0	h	4.8	mg	0	24	.	ng/mL	.	745	5	1.6	1	1	50	70	24	0	M
.		207702			1	0	h	.	.	0	.	.	ng/mL	.	745	5	1.6	0	0	50	70	24	0	M
.		207702			1	0.5	h	.	.	0	.	10	ng/mL	2.30	745	5	1.6	0	0	50	70	24	0	M
.		207702			1	1	h	.	.	0	.	50	ng/mL	3.91	745	5	1.6	0	0	50	70	24	0	M
.		207702			1	1.5	h	.	.	0	.	150	ng/mL	5.01	745	5	1.6	0	0	50	70	24	0	M
.		207702			1	2	h	.	.	0	.	200	ng/mL	5.30	745	5	1.6	0	0	50	70	24	0	M
.		207702			1	3.5	h	.	.	0	.	175	ng/mL	5.16	745	5	1.6	0	0	50	70	24	0	M
.		207702			7	0	h	2.4	mg	6	24	.	ng/mL	.	745	5	1.6	1	1	50	70	24	0	M
.		207702			7	0.5	h	.	.	0	.	10	ng/mL	2.30	745	5	1.6	0	0	50	70	24	0	M
.		207702			7	1	h	.	.	0	.	50	ng/mL	3.91	745	5	1.6	0	0	50	70	24	0	M
.		207702			7	1.5	h	.	.	0	.	150	ng/mL	5.01	745	5	1.6	0	0	50	70	24	0	M
.		207702			7	2	h	.	.	0	.	200	ng/mL	5.30	745	5	1.6	0	0	50	70	24	0	M
.		207702			7	3.5	h	.	.	0	.	175	ng/mL	5.16	745	5	1.6	0	0	50	70	24	0	M
.		207702			7	24	h	.	.	0	.	175	ng/mL	5.16	745	5	1.6	0	0	50	70	24	0	M

CONMED1	CONMED1TXT	CONMED2	CONMED2TXT	CONMED3	CONMED3TXT	CONMED4	CONMED4TXT
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN
1	INH	0	INDU	1	STATIN	1	ATORVASTATIN

Notes: TIME will be actual time from dose. File to be produced just for GSK2798745. In example, CONMED3 represents 1 for a subject taking ANY statin and CONMED4 is applicable to just atorvastatin.

12.9. Appendix 9: Pharmacokinetic / Pharmacodynamic Analyses

12.9.1. Pharmacokinetic / Pharmacodynamic Methodology

12.9.1.1. Exposure-Response Relationship

Graphical exploration of individual predicted steady state PK exposure metric versus cough response (10-hour daily awake cough) on day 7 will be undertaken using both placebo and treatment groups. PK exposure metric for placebo group will be assigned a value of 0. If there is evidence of any trend, various PK-PD models will be explored including linear, Emax, sigmoidal Emax relationships.

PK exposure metrics include: Day 7 Cmax (predicted), Cav (predicted) and C24 (observed) on day 8
Clinical endpoint: Baseline: Day -1 & Day 7 total day-time cough count (10 hours)

Using Monte-Carlo simulations, the optimal PK-PD model for cough count will be applied to provide estimate of systemic exposure range associated with significant clinical response (10h awake cough count) from which optimal dose of GSK2798745 can be estimated for future studies, taking into account estimate of PK variability of parent drug.

The analyses described above will be the responsibility of CPMS and will be independent of SAC. Further details will be provided in a separate RAP.

12.9.2. Pharmacokinetic / Pharmacodynamic Dataset Specification

12.9.2.1. Data Specification

12.9.2.2. Dataset Variable Conventions

Column headings in NONMEM-ready datasets and specifications should be consistent to minimise the programming process, and facilitate a smooth transfer of projects between users as needed. IDSL standards will be followed where possible.

A list of most common standardised variable names for NONMEM datasets can be found in Table below.

File to be produced for Analyte=GSK2798745 only.

List of Variable Names for NONMEM-Ready Datasets for Pop PK-PD Analysis

Variable	Label (Variable description)	Source (other sources may be used)
C	NONMEM line exclusion identifier	Derived as '.' – see example, required for software
ID	NONMEM subject identifier	Derived – set to PPD etc & linked to SUBJID – see example
STUD	Study ID	ARDATA.POP (STUDYID)

Variable	Label (Variable description)	Source (other sources may be used)
SUBJID	Subject identifier for study	ARDATA.POP (SUBJID)
SITEID	Unique identifier for a study site	ARDATA.POP (CENTREID)
DAY	Study day Day -1 10h cough count before dosing. Day 7 10h cough count after day 7 dose	PKCNC (derive from VISIT)
PK1	Predicted Cmax on day 7 – Provided by POPPK analysis*	Create variable but leave blank
PK2	Predicted Cav on day 7 - Provided by POPPK analysis*	Create variable but leave blank
PK3	Predicted C24 on day 8 - Provided by POPPK analysis*	Create variable but leave blank
Analyte	GSK2798745	ARDATA.PKCNC
R10BASE1	Raw baseline 10h cough count before period 1	ARDATA.COUGHTOT (see notes)
R10BASE2	Raw baseline 10h cough count before period 2	As above
RPD10	Raw 10h awake cough count [primary endpoint]	As above
R24BASE1	Raw baseline 24h cough count before period 1	As above
R24BASE2	Raw baseline 24h cough count before period 2	As above
RPD24	Raw 24h cough count total	As above
I10BASE1	Imputed baseline 10h cough count before period 1	As above
I10BASE2	Imputed baseline 10h cough count before period 2	As above
IPD10	Imputed 10h awake cough count [primary endpoint]	As above
I24BASE1	Imputed baseline 24h cough count before period 1	As above
I24BASE2	Imputed baseline 24h cough count before period 2	As above
IPD24	Imputed 24h cough count total	As above
F10BASE1	Flag for imputed baseline 10h cough count before period 1	As above
F10BASE2	Flag for imputed baseline 10h cough count before period 2	As above
FPD10	Flag for imputed 10h awake cough count [primary endpoint]	As above
F24BASE1	Flag for imputed baseline 24h cough count before period 1	As above
F24BASE2	Flag for imputed baseline 24h cough count before period 2	As above
FPD24	Flag for imputed 24h cough count total	As above
AGE	Subject Age (yrs)	ARDATA.DEMO
SEX	Subject gender 0 = Male 1 =Female	ARDATA.DEMO
SEXTEXT	Subject gender text Male or Female	ARDATA.DEMO
BMI	Baseline Body Mass Index	ARDATA.DEMO
WT	Baseline Subject weight	ARDATA.DEMO
TMT	1 = Placebo ; 2 = Drug	ARDATA.TRT
TMTTEXT	Treatment text Placebo or GSK2798745	ARDATA.TRT

Variable	Label (Variable description)	Source (other sources may be used)
PERIOD	1 = Period 1 ; 2 = Period 2	ARDATA.TRT

Statistics & Programming in discussion with CPMS to provide dataset as specified in Table below based on column variables described above.

*The predicted POPPK parameters detailed above will be generated by CPMS. The Pop PK-PD dataset above will be generated by programming with these variables included as blank, for CPMS to populate at a later date.

Note to programmers for cough data:
Variables, R*, I* and F* can be obtained from A&R dataset COUGHTOT.
Cough totals are COUGHTOT (raw totals) and COUGHIMP (imputed totals)
Select where FLAGHR=100 and FLAGHR=240 to get 10h and 24h totals.
Select where VISITNUM in (20, 60) to get Day -1 totals for Period 1 and 2.
Select where VISITNUM in (40, 80) to get Day 7 totals for Period 1 and 2.
FLAGIMP will indicate if imputation occurred at timepoint of interest.

Population Pharmacokinetic-Pharmacodynamic (Pop PK-PD) Dataset Specification Excel .csv file

C	ID	STUD	SITEID	SUBJID	DAY	PK1	PK2	PK3	ANALYTE	R10BASE1	R10BASE2	RPD10	R24BASE1	R24BASE2	RPD24	I10BASE1	I10BASE2	IPD10	I24BASE1	I24BASE2	IPD24	AGE	WT	BMI	SEX	SEXTXT	TMT	TMTTEXT	PERIOD
.	PPD	207702		PPD	-1				GSK2798745	25	23	25	80	75	80	25	23	25	80	75	80	50	70	24	0	M	1	Placebo	1
.		207702			7				GSK2798745	25	23	23	80	75	60	25	23	23	80	75	60	50	70	24	0	M	1	Placebo	1
.		207702			-1				GSK2798745	25	23	23	80	75	75	25	23	23	80	75	75	50	70	24	0	M	2	GSK2798745	2
.		207702			7				GSK2798745	25	23	10	80	75	55	25	23	10	80	75	60	50	70	24	0	M	2	GSK2798745	2
.		207702			-1				GSK2798745	30	28	30	55	57	55	30	28	30	55	57	55	60	75	24	1	F	2	GSK2798745	1
.		207702			7				GSK2798745	30	28	12	55	57	40	30	28	12	55	57	40	60	75	24	1	F	2	GSK2798745	1
.		207702			-1				GSK2798745	30	28	28	55	57	57	30	28	28	55	57	57	60	75	24	1	F	1	Placebo	2
.		207702			7				GSK2798745	30	28	25	55	57	50	30	28	25	55	57	60	60	75	24	1	F	1	Placebo	2

12.10. Appendix 10: Abbreviations & Trade Marks

12.10.1. Abbreviations

Abbreviation	Description
AE	Adverse Event
ALT	Alanine aminotranferase
A&R	Analysis and Reporting
AST	Aspartate aminotransferase
AUC	Area under the concentration time curve
BMI	Body mass index
BUN	Blood urea nitrogen
Cav	Average concentration of drug over the dosing interval
CI	Confidence Interval
Cmax	Maximum observed plasma concentration
CPK	Creatinine phosphokinase
CPMS	Clinical Pharmacology Modelling & Simulation
CPSR	Clinical Pharmacology Study Report
CSSRS	Columbia Suicidality Severity Rating Scale
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DP	Decimal Places
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FOBT	Faecal Occult Blood Test
GSK	GlaxoSmithKline
h	Hours
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
LCQ	Leicester Cough Questionnaire
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular volume
mg	Milligrams
MHRA	Medicine and Healthcare Products Regulatory Agency
mm	Millimetres
MMRM	Mixed Model Repeated Measures
N	Number

Abbreviation	Description
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
RBC	Red blood cells
S&P	Statistics and Programming
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event(s)
SI	System Independent
SOP	Standard Operation Procedure
TFL	Tables, Figures & Listings
Tmax	Time to maximum observed concentration
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WBC	White blood cells

12.10.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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12.11. Appendix 11: List of Data Displays

12.11.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

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

Note that all displays (Tables, Figures & Listings) will use the term 'Subjects'.

12.11.2. Mock Example Shell Referencing

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

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

NOTES:

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

12.11.3. Deliverables

Delivery [Priority] [1]	Description
IA GSK [X]	Interim Analysis Statistical Analysis Complete – Outputs to be generated by **GSK**
SAC [X]	Final Statistical Analysis Complete – Outputs to be generated by **FSP**
SAC GSK [X]	Final Statistical Analysis Complete – Outputs to be generated by **GSK**

NOTES:

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

12.11.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	All Subjects	ES1A	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC [2]
1.2.	All Subjects	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC [2]
1.3.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC [2]
Protocol Deviation					
1.4.	All Subjects	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [2]
Population Analysed					
1.5.	All Subjects	SP1A	Summary of Study Populations	IDSL	SAC [2]
Demographic and Baseline Characteristics					
1.6.	All Subjects	DM3	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC [2]
1.7.	All Subjects	DM11	Summary of Age Ranges	EudraCT	SAC [2]
1.8.	All Subjects	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC [2]
Prior and Concomitant Medications					
1.9.	All Subjects	MH1	Summary of Past Medical Conditions	ICH E3	SAC [2]
1.10.	All Subjects	MH1	Summary of Current Medical Conditions	ICH E3	SAC [2]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.11.	All Subjects	CM1	Summary of Concomitant Medications	ICH E3 See IDSL for options related to ATC groupings and multi-ingredient medications.	SAC [2]
Exposure and Treatment Compliance					
1.12.	All Subjects	EX1	Summary of Exposure to Study Treatment	ICH E3 Dose and/or time on treatment, as applicable. Many possible considerations; defer to therapy area standards where available.	SAC [2]
1.13.	All Subjects	POP_L1	Listing of Compliance		SAC [2]

12.11.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
10H Total Cough Count					
2.1.	All Subjects	**EF_T2**	Summary of Day-Time 10h Total Cough Counts	Include raw cough counts and imputed cough counts as per mock-up, geometric means for log-transformed data on second page	**SAC GSK [1]**
2.2.	All Subjects	**EF_T1**	Summary of Statistical Analysis of Day-Time 10h Total Cough Counts at Day 7	Statistical analysis to be based on **imputed** cough counts	**IA GSK**, **SAC GSK [1]**
2.3.	All Subjects	**EF_T1**	Summary of Statistical Analysis of Day-Time 10h Total Cough Counts at Day 7 (Sensitivity)	Statistical analysis to be based on **non-imputed** cough counts	**SAC GSK [1]**
24H Total Cough Count					
2.4.	All Subjects	**EF_T2**	Summary of 24h Total Cough Counts	Include raw cough counts and imputed cough counts as per mock-up, geometric means for log-transformed data on second page	**SAC GSK [1]**
2.5.	All Subjects	**EF_T1**	Summary of Statistical Analysis of 24h Total Cough Counts at Day 7	Statistical analysis to be based on **imputed** cough counts	**SAC GSK [1]**
2.6.	All Subjects	**EF_T1**	Summary of Statistical Analysis of 24h Total Cough Counts atDay 7 (Sensitivity)	Statistical analysis to be based on **non-imputed** cough counts	**SAC GSK [1]**
Severity of Cough (VAS)					
2.7.	All Subjects	**EF_T3**	Summary of Severity of Cough (VAS)	Collected at Screening, D1(Pre-Dose), D7(Pre-Dose) and FU	SAC [2]
2.8.	All Subjects	**EF_T4**	Summary of Change From Baseline in Severity of Cough (VAS)	Include change from baseline to D7(Pre-Dose) only	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.9.	All Subjects	**EF_T5**	Summary of Statistical Analysis of Change From Baseline in Severity of Cough (VAS) at Day 7	Analysis of change from baseline D1(Pre-Dose) to D7(Pre-Dose)	SAC [2]
Urge to Cough (VAS)					
2.10.	All Subjects	**EF_T3**	Summary of Urge to Cough (VAS)	Collected at D1(Pre-Dose), D7(Pre-Dose) and FU	SAC [2]
2.11.	All Subjects	**EF_T4**	Summary of Change From Baseline in Urge to Cough (VAS)	Include change from baseline to D7(Pre-Dose) only	SAC [2]
2.12.	All Subjects	**EF_T5**	Summary of Statistical Analysis of Change From Baseline in Urge to Cough (VAS) at Day 7	Analysis of change from baseline D1(Pre-Dose) to D7(Pre-Dose)	SAC [2]
Leicester Cough Questionnaire (LCQ)					
2.13.	All Subjects	**EF_T6**	Summary of the Leicester Cough Questionnaire (LCQ)	Summarise each of the 3 domains and an overall total score. Collected at D1(Pre-Dose) and D7(Pre-Dose)	SAC [2]
2.14.	All Subjects	**EF_T7**	Summary of Change From Baseline in the Leicester Cough Questionnaire (LCQ)	Include change from baseline to D7(Pre-Dose) for domain scores and total	SAC [2]
2.15.	All Subjects	**EF_T8**	Statistical Analysis of Change From Baseline in the Leicester Cough Questionnaire (LCQ) at Day 7	4 x analyses, one for each domain and overall score	SAC [2]

12.11.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
10H Total Cough Count and 24 Total Cough Count					
2.1.	All Subjects	**EF_F1**	Summary of Geometric Means and 95% CI for Baseline and Day 7 10h Day-time Cough Counts, by Treatment Group	Footnote to include 'Note: Imputed data is presented, where cough counts are pro-rated based on a minimum of 60% of data being available'	**IA GSK**, **SAC GSK [1]**
2.2.	All Subjects	**EF_F1**	Summary of Geometric Means and 95% CI for Baseline and Day 7 24h Day-time Cough Counts, by Treatment Group	Follow example EF_F1 but use 24 hour totals (imputed). Footnote as above.	**SAC GSK [1]**
2.3.	All Subjects	**EF_F2**	Summary of Geometric Means and 95% CI by Hourly Intervals (0-10h) for Day 7 Cough Counts	If zero counts are present and log-transformation of hourly totals not possible, then this figure will present arithmetic means and 95% CI instead. Footnote as above.	**IA GSK**, **SAC GSK [1]**
2.4.	All Subjects	**EF_F2**	Summary of Geometric Means and 95% CI by Hourly Intervals (0-24h) for Day 7 Cough Counts	If zero counts are present and log-transformation of hourly totals not possible, then this figure will present arithmetic means and 95% CI instead. Footnote as above.	**SAC GSK [1]**
2.5.	All Subjects	**EF_F3**	Individual Subject Profiles of Cough Count Totals by 1 Hour Intervals (0-10h) Day 7	4 subjects per page, hourly timepoint e.g 0-1h, 1-2h etc on the x-axis, cough total on the y-axis, treatment group in a legend. Display imputed hourly data (pro-rated) for this plot. Footnote as above.	**SAC GSK [1]**

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	All Subjects	**EF_F3**	Individual Subject Profiles of Cough Count Totals by 1 Hour Intervals (0-24h) Day 7	4 subjects per page, hourly timepoint e.g 0-1h, 1-2h etc on the x-axis, cough total on the y-axis, treatment group in a legend. Extend to 24h. Display imputed hourly data (pro-rated) for this plot. Footnote as above.	**SAC GSK [1]**
2.7.	All Subjects	**EF_F4**	Boxplots of Cough Count Totals by 1 Hour Intervals (0-10h) Day 7	Hourly timepoint e.g 0-1h, 1-2h etc on the x-axis. Cough count total on the y-axis. Treatment group in a legend. Display imputed hourly data (pro-rated) for this plot. Footnote as above.	**SAC GSK [1]**
2.8.	All Subjects	**EF_F4**	Boxplots of Cough Count Totals by 1 Hour Intervals (0-24h) Day 7	Hourly timepoint e.g 0-1h, 1-2h etc on the x-axis. Cough count total on the y-axis. Treatment group in a legend. Display imputed hourly data (pro-rated) for this plot. Extend to 24h. Footnote as above.	**SAC GSK [1]**
2.9.	All Subjects	**EF_F5**	Individual 10h Cough Counts Day 7	Subject on the x-axis and 10h totals by treatment on the y-axis, with a legend for treatment group. Display imputed 10h data (pro-rated). Footnote as above.	**SAC GSK [1]**

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	All Subjects	**EF_F5**	Individual 24h Cough Counts Day 7	Subject on the x-axis and 24h totals by treatment on the y-axis, with a legend for treatment group. Display imputed 24h data (pro-rated). Follow example EF_F5 but extend to 24h. Footnote as above.	**SAC GSK [1]**
2.11.	All Subjects	**EF_F6**	Individual Changes From Baseline in 10h Day-time Cough Counts	Individual subjects changes from baseline (Day -1) to Day 7 by treatment. 10h totals. Footnote as above.	**SAC GSK [1]**
2.12.	All Subjects	**EF_F6**	Individual Changes From Baseline in 24h Day-time Cough Counts	Individual subjects changes from baseline (Day -1) to Day 7 by treatment. 24h totals. Footnote as above.	**SAC GSK [1]**
2.13.	All Subjects	**EF_F7**	Adjusted Median Responses and 95% Cr. Intervals for 10h Total Cough Counts on Day 7	X-axis can say 'Day 7'. Y-axis will be median cough counts with 95% CrIs (back-transformed estimates). Treatment group in a legend. Footnote as per mock example.	**SAC GSK [1]**
2.14.	All Subjects	**EF_F7**	Adjusted Median Responses and 95% Cr. Intervals for 24h Total Cough Counts on Day 7	X-axis can say 'Day 7'. Y-axis will be median cough counts and 95% CrIs (back-transformed estimates). Treatment group in a legend. Footnote as per mock example.	**SAC GSK [1]**
2.15.	All Subjects	**EF_F1**	Summary of Geometric Means and 95% CI for Baseline and Day 7 10h Day-time Cough Counts, by Treatment Group by Prior Cough Study Participation	Footnote to include 'Note: Imputed data is presented, where cough counts are pro-rated based on a minimum of 60% of data being available'	**SAC GSK [2]**

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	All Subjects	**EF_F1**	Summary of Geometric Means and 95% CI for Baseline and Day 7 24h Day-time Cough Counts, by Treatment Group by Prior Cough Study Participation	Follow example EF_F1 but use 24 hour totals (imputed). Footnote as above.	**SAC GSK [2]**
2.17.	All Subjects	**EF_F2**	Summary of Geometric Means and 95% CI by Hourly Intervals (0-10h) for Day 7 Cough Counts by Prior Cough Study Participation	If zero counts are present and log-transformation of hourly totals not possible, then this figure will present arithmetic means and 95% CI instead. Footnote as above.	**SAC GSK [2]**
2.18.	All Subjects	**EF_F2**	Summary of Geometric Means and 95% CI by Hourly Intervals (0-24h) for Day 7Cough Counts by Prior Cough Study Participation	If zero counts are present and log-transformation of hourly totals not possible, then this figure will present arithmetic means and 95% CI instead. Footnote as above.	**SAC GSK [2]**
2.19.	All Subjects	**EF_F6**	Individual Changes From Baseline in 10h Day-time Cough Counts by Period	Individual subjects changes from baseline (Day -1) to Day 7 by treatment and period. 10h totals. Footnote as above.	**SAC GSK [1]**
2.20.	All Subjects	**EF_F6**	Individual Changes From Baseline in 24h Day-time Cough Counts by Period	Individual subjects changes from baseline (Day -1) to Day 7 by treatment and period. 24h totals. Footnote as above.	**SAC GSK [1]**
2.21.	All Subjects	**EF_F1**	Summary of Geometric Means and 95% CI for Baseline and Day 7 10h Day-time Cough Counts, by Treatment Group and Period	Footnote as above.	**IA GSK**, **SAC GSK [1]**
2.22.	All Subjects	**EF_F1**	Summary of Geometric Means and 95% CI for Baseline and Day 7 24h Day-time Cough Counts, by Treatment Group and Period	Footnote as above.	**SAC GSK [1]**

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Severity of Cough (VAS)					
2.23.	All Subjects	**EF_F1**	Summary of Severity of Cough (VAS) (Means ± 95% CI) by Visit	X-axis will be Day -1 and Day 7. Y-axis will be mean cough severity ± 95% CI. Similar to example EF_F1 but with arithmetic means.	SAC [2]
2.24.	All Subjects	**EF_F7**	Adjusted Median Responses and 95% Cr. Intervals for Change From Baseline in Severity of Cough (VAS)	X-axis can say 'Day 7 (PD)'. Y-axis will be median CFB cough severity and 95% CrIs. Treatment group in a legend or on x-axis.	SAC [2]
Urge to Cough (VAS)					
2.25.	All Subjects	**EF_F1**	Summary of Urge to Cough (VAS) (Means ± 95% CI) by Visit	X-axis will be Day -1 and Day 7. Y-axis will be mean urge to cough ± 95% CI. Similar to example EF_F1 but with arithmetic means.	SAC [2]
2.26.	All Subjects	**EF_F7**	Adjusted Median Responses and 95% Cr. Intervals for Change From Baseline in Urge to Cough (VAS)	X-axis can say 'Day 7 (PD)'. Y-axis will be median CFB urge to cough and 95% CrIs. Treatment group in a legend or on x-axis.	SAC [2]
Leicester Cough Questionnaire (LCQ)					
2.27.	All Subjects	**EF_F1**	Summary of Leicester Cough Questionnaire (LCQ) (Means ± 95% CI) by Visit	X-axis will be Day -1 and Day 7. Y-axis will be mean score ± 95% CI. 4 pages one for each of the 3 domains and one for total score. Similar to example EF_F1 but with arithmetic means.	SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.28.	All Subjects	**EF_F7**	Adjusted Median Responses and 95% Cr. Intervals for Change From Baseline in Leicester Cough Questionniare (LCQ)	X-axis can say 'Day 7 (PD)'. Y-axis will be median CFB LCQ score and 95% CrIs. Treatment group in a legend or on x-axis. 4 pages one for each of the 3 domains and one for total score	SAC [2]

12.11.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	All Subjects	AE1CP	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [2]
3.2.	All Subjects	AE1CP	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term/by Overall Frequency	ICH E3 .	SAC [2]
Serious and Other Significant Adverse Events					
3.3.	All Subjects	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	SAC [2]
Laboratory: Chemistry					
3.4.	All Subjects	LB1	Summary of Chemistry Changes from Baseline	ICH E3	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hematology					
3.5.	All Subjects	LB1	Summary of Hematology Changes from Baseline	ICH E3	SAC [2]
ECG					
3.6.	All Subjects	EG1	Summary of ECG Findings	IDSL	SAC [2]
3.7.	All Subjects	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC [2]
Vital Signs					
3.8.	All Subjects	VS1	Summary of Change from Baseline in Vital Signs	ICH E3 Include Weight as well as Blood Pressure, HR and Temperature	SAC [2]
CSSRS					
3.9.	All Subjects	CSSRS4	Listing of C-SSRS Suicidal Ideation and Behaviour Data	Refer to IDSL guidance and example CSSRS4. For studies with very few suicical events expected, this listing can substitute the summary table.	SAC [2]
Audiometry					
3.10.	All Subjects	SAF_L1	Listing of Audiometry	Add footnote: Pre-Treatment Period 1 audiometry can be done anytime between Screening and Treatment Period 1, Day 1, pre-dose. Pre-Treatment Period 2 audiometry can be done any time during the washout period (up to Treatment Period 2, Day 1 pre-dose).	SAC [2]

12.11.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK	PKCT1 (PK01)	Summary of **GSK2798745** Pharmacokinetic Concentration-Time Data (ng/mL)		SAC [2]
4.2.	PK	PKCT1 (PK01)	Summary of **GSK2798745 M1 Metabolite** Pharmacokinetic Concentration-Time Data (ng/mL)		SAC [2]
4.3.	PK	PKCT1 (PK01)	Summary of **Atorvastatin** Pharmacokinetic Concentration-Time Data (ng/mL)	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.4.	PK	PKCT1 (PK01)	Summary of **Atorvastatin Metabolite** Pharmacokinetic Concentration-Time Data (ng/mL)	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Parameter					
4.5.	PK	PKPT1 (PK03)	Summary Statistics of Derived Plasma **GSK2798745** Pharmacokinetic Parameters		SAC [2]
4.6.	PK	PKPT1 (PK03)	Summary Statistics of Derived Plasma **GSK2798745 M1 Metabolite** Pharmacokinetic Parameters		SAC [2]
4.7.	PK	PKPT1 (PK03)	Summary Statistics of Derived Plasma **Atorvastatin** Pharmacokinetic Parameters		SAC [2]
4.8.	PK	PKPT1 (PK03)	Summary Statistics of Derived Plasma **Atorvastatin Metabolite** Pharmacokinetic Parameters		SAC [2]
4.9.	PK	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma **GSK2798745** Pharmacokinetic Parameters		SAC [2]
4.10.	PK	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma **GSK2798745 M1 Metabolite** Pharmacokinetic Parameters		SAC [2]
4.11.	PK	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma **Atorvastatin** Pharmacokinetic Parameters		SAC [2]
4.12.	PK	PKPT3 (PK05)	Summary Statistics of Log-Transformed Derived Plasma **Atorvastatin Metabolite** Pharmacokinetic Parameters		SAC [2]

12.11.9. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
PK Concentration					
4.1.	PK	PKCF1X (PK16b)	Individual **GSK2798745** Plasma Concentration–Time Plots (Linear and Semi-log)	By Subject plots – by visit (Day 1 pre-dose to 3.5h profile and Day 7 pre-dose to 24h profile)	SAC [2]
4.2.	PK	PKCF6 (PK24)	Individual **GSK2798745** Plasma Concentration–Time Plot (Linear and Semi-log)	Limit to 12 subjects per graphic split over pages (e.g. 2 pages for N=24, 3 pages for N=36)	SAC [2]
4.3.	PK	PKCF2 (PK17)	Mean Plasma **GSK2798745** Concentration-Time Plot (Linear and Semi-Log)		SAC [2]
4.4.	PK	PKCF3 (PK18)	Median Plasma **GSK2798745** Concentration-Time Plot (Linear and Semi-Log)		SAC [2]
4.5.	PK	PKCF1X (PK16b)	Individual **GSK2798745 Metabolite M1** Plasma Concentration–Time Plots (Linear and Semi-log)	By Subject plots – by visit (Day 1 pre-dose to 3.5h profile and Day 7 pre-dose to 24h profile)	SAC [2]
4.6.	PK	PKCF6 (PK24)	Individual **GSK2798745 Metabolite M1** Plasma Concentration–Time Plot (Linear and Semi-log)	Limit to 12 subjects per graphic split over pages (e.g. 2 pages for N=24, 3 pages for N=36)	SAC [2]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.7.	PK	PKCF2 (PK17)	Mean Plasma **GSK2798745 Metabolite M1** Concentration-Time Plot (Linear and Semi-Log)		SAC [2]
4.8.	PK	PKCF3 (PK18)	Median Plasma **GSK2798745 Metabolite M1** Concentration-Time Plot (Linear and Semi-Log)		SAC [2]
4.9.	PK	PKCF1X (PK16b)	Individual **Atorvastatin** Plasma Concentration–Time Plots (Linear and Semi-log)	By Subject plots – by visit (Day 1 pre-dose to 3.5h profile and Day 7 pre-dose to 24h profile) Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.10.	PK	PKCF6 (PK24)	Individual **Atorvastatin** Plasma Concentration–Time Plot (Linear and Semi-log)	Limit to 12 subjects per graphic split over pages (e.g. 2 pages for N=24, 3 pages for N=36) Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.11.	PK	PKCF2 (PK17)	Mean Plasma **Atorvastatin** Concentration-Time Plot (Linear and Semi-Log)	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.12.	PK	PKCF3 (PK18)	Median Plasma **Atorvastatin** Concentration-Time Plot (Linear and Semi-Log)	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.13.	PK	PKCF1X (PK16b)	Individual **Atorvastatin Metabolite** Plasma Concentration–Time Plots (Linear and Semi-log)	By Subject plots – by visit (Day 1 pre-dose to 3.5h profile and Day 7 pre-dose to 24h profile) Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.14.	PK	PKCF6 (PK24)	Individual **Atorvastatin Metabolite** Plasma Concentration–Time Plot (Linear and Semi-log)	Limit to 12 subjects per graphic split over pages (e.g. 2 pages for N=24, 3 pages for N=36) Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.15.	PK	PKCF2 (PK17)	Mean Plasma **Atorvastatin Metabolite** Concentration-Time Plot (Linear and Semi-Log)	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
4.16.	PK	PKCF3 (PK18)	Median Plasma **Atorvastatin Metabolite** Concentration-Time Plot (Linear and Semi-Log)	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]

12.11.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC [2]
2.	All Subjects	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC [2]
3.	All Subjects	SD3	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC [2]
4.	All Subjects	BL2	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC [2]
5.	All Subjects	CP_RA1x	Listing of Planned and Actual Treatments	IDSL	SAC [2]
Protocol Deviations					
6.	All Subjects	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [2]
7.	All Subjects	IE4	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [2]
Populations Analysed					
8.	All Subjects	SP3a	Listing of Participants Excluded from Any Population	ICH E3	SAC [2]
Demographic and Baseline Characteristics					
9.	All Subjects	DM4	Listing of Demographic Characteristics	ICH E3	SAC [2]
10.	All Subjects	DM10	Listing of Race	ICH E3	SAC [2]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
11.	All Subjects	CP_CM4	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
12.	All Subjects	EX4	Listing of Exposure Data	ICH E3	SAC [2]
Adverse Events					
13.	All Subjects	AE9CP	Listing of All Adverse Events	ICH E3	SAC [2]
14.	All Subjects	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC [2]
Serious and Other Significant Adverse Events					
15.	All Subjects	AE9CPa	Listing of Serious Adverse Events	ICH E3	SAC [2]
16.	All Subjects	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3. Provides additional detail from SAE form e.g hospitalisation (Y/N) etc	SAC [2]
17.	All Subjects	AE9CP	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	SAC [2]
All Laboratory					
18.	All Subjects	LB6	Listing of All Clinical Chemistry Data for Participants with Any Value of Potential Clinical Importance/Outside Normal Range	ICH E3	SAC [2]
19.	All Subjects	LB6	Listing of Clinical Chemistry Values of Potential Clinical Importance		SAC [2]
20.	All Subjects	LB6	Listing of All Hematology Data for Participants with Any Value of Potential Clinical Importance/Outside Normal Range		SAC [2]
21.	All Subjects	LB6	Listing of Hematology Values of Potential Clinical Importance		SAC [2]
22.	All Subjects	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC [2]

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
23.	All Subjects	UR2B	Listing of Urinalysis Data for Participants with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
ECGs					
24.	All Subjects	EG4	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL	SAC [2]
25.	All Subjects	EG4	Listing of ECG Values of Potential Clinical Importance	IDSL	SAC [2]
26.	All Subjects	EG6	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC [2]
27.	All Subjects	EG6	Listing of Abnormal ECG Findings	IDSL	SAC [2]
Vital Signs					
28.	All Subjects	VS5	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC [2]
29.	All Subjects	VS5	Listing of Vital Signs of Potential Clinical Importance	IDSL	SAC [2]

12.11.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
30.	All Subjects	**EF_L1**	Listing of Hourly and Total Cough Counts		**SAC GSK [1]**
31.	All Subjects	**EF_L2**	Listing of Severity and Urge to Cough (VAS)		SAC [2]
32.	All Subjects	**EF_L3**	Listing of Leicester Cough Questionnaire (LCQ)		SAC [2]
33.	All Subjects	**-**	Listing of SAS Output for 10h Total Cough Count Analysis		**SAC GSK [1]**
34.	All Subjects	**-**	Listing of SAS Output for 24h Total Cough Count Analysis		**SAC GSK [1]**
35.	All Subjects	**-**	Listing of SAS Output for CFB Severity to Cough Analysis		SAC [2]
36.	All Subjects	**-**	Listing of SAS Output for CFB Urge to Cough Analysis		SAC [2]
37.	All Subjects	**-**	Listing of SAS Output for CFB Leicester Cough Questionnaire Analysis		SAC [2]
38.	PK	PKCL1X (PK08)	Listing of **GSK2798745** Plasma Pharmacokinetic Concentration–Time Data		SAC [2]
39.	PK	PKPL1X (PK14)	Listing of Derived **GSK2798745** Plasma Pharmacokinetic Parameters		SAC [2]
40.	PK	PKCL1X (PK08)	Listing of **GSK2798745 Metabolite M1** Plasma Pharmacokinetic Concentration–Time Data		SAC [2]
41.	PK	PKPL1X (PK14)	Listing of Derived **GSK2798745 Metabolite M1** Plasma Pharmacokinetic Parameters		SAC [2]
42.	PK	PKCL1X (PK08)	Listing of **Atorvastatin** Plasma Pharmacokinetic Concentration–Time Data		SAC [2]
43.	PK	PKPL1X (PK14)	Listing of Derived **Atorvastatin** Plasma Pharmacokinetic Parameters		SAC [2]

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
44.	PK	PKCL1X (PK08)	Listing of **Atorvastatin Metabolite** Plasma Pharmacokinetic Concentration–Time Data	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]
45.	PK	PKPL1X (PK14)	Listing of Derived **Atorvastatin Metabolite** Plasma Pharmacokinetic Parameters	Add footnote 'Planned Relative Time is based on last dose of GSK2798745 but the timing of the last dose of Atorvastatin may vary.'	SAC [2]

12.12. Appendix 12: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request