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

Title	:	Reporting and Analysis Plan for a randomised, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma
Compound Number	:	GSK3772847
Effective Date	:	27-MAR-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 2017N311825_02.
- This RAP is intended to describe the Efficacy, Safety, PK, PD and Biomarker analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the End of Treatment Phase (ETP) and Statistical Analysis Complete (SAC) deliverable.
- This study does have an internal safety review committee (iSRC) and all details of iSRC deliverable are documented in a separate iSRC RAP.

Author's Name and Functional Area:

Approver	Date
PPD Principal Statistician (Respiratory, Clinical Statistics)	20-MAR-2019

RAP Team Review Confirmations
(Method: E-mail)

Reviewer	Date
PPD Clinical Investigation Lead (Respiratory, HUP Clinical Development)	20-MAR-2019
PPD Principal Programmer (Respiratory, Clinical Programming)	22-MAR-2019
PPD Clinical Development Physician (Respiratory, MDC Global Clinical)	25-MAR-2019
PPD Scientist (Respiratory, Patient Centred Outcomes, Value Evidence and Outcomes)	22-MAR-2019
PPD Director (Respiratory, Value Evidence and Outcomes)	20-MAR-2019
PPD Senior Director (Respiratory, Clinical Pharmacology Modelling and Simulation)	22-MAR-2019
PPD Director of Clinical Development (Respiratory, MDC Global Clinical)	26-MAR-2019
PPD Senior Scientific Director (Respiratory, RD AI DPU Head)	25-MAR-2019

Clinical Statistics & Clinical Programming Line Approvals
(Method: Pharma TMF eSignature)

Approver	Date
PPD Senior Statistics Director (Respiratory, Clinical Statistics)	27-MAR-2019
PPD Programming Manager (Respiratory, Clinical Programming)	27-MAR-2019

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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 207597:

Protocol Revision Chronology:		
2017N311825_00	2017-MAR-06	Original
2017N311825_01	2017-JUN-02	To address clarifications regarding the aim of the study, the eligibility criteria, the schedule of activities, the clinical assessments, and the recording of lab data and adverse events. The benefit: risk section was also updated based on the Part 2 results from study CNTO7160ASH1001. Also, a few typographical errors were corrected.
2017N311825_02	2017-SEP-13	To add more information on the risk: benefit section and the study design justification sections. To address clarifications regarding the unblinding of treatment in case of emergency. To clarify that rechallenge is not allowed once the treatment discontinuation criteria are met. Also, a few typographical errors were corrected.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Modified Intent to Treat population.	Modified Intent to Treat (Loss of Control), Modified Intent to Treat and Safety excluding GCP non-compliant subjects populations.	The Modified Intent to Treat (Loss of Control) was added to account for the intercurrent event when participants receive the wrong study treatment. Whilst the data from GCP non-compliant participants should not be used in the efficacy analysis, the participants were dosed with GSK3772847 or Placebo so all safety data (AEs, SAEs, ECGs etc.) should be reported.
Section 10.4.1 of the protocol describes a sensitivity analysis where data is analysed as missing and worst case (loss of control) for participants who withdraw from the study for reasons other than loss of asthma control.	A primary and secondary estimand have been defined to capture where data is analysed as missing and worst case (loss of control) for various intercurrent events where participants withdraw from the study for reasons other than loss of asthma control.	The protocol was approved before the ICH E9 addendum on estimands. The RAP is performing the same planned analysis as detailed in the Protocol however the terminology has been updated in accordance with ICH E9.
Statistical analysis would be performed for each screening eosinophil strata separately.	Bayesian analysis will include screening eosinophil strata as a covariate instead of performing split analysis models. In addition, an exploratory analysis using fractional polynomials was added to examine the relationship between loss of control and screening eosinophils (continuous), IgE and FeNO.	Bayesian analysis will now include the same covariates as the frequentist analysis. By modelling eosinophils as a continuous endpoint, it will provide more information on the impact of varying screening eosinophil levels on the treatment effect. It will also provide additional information on the role of IgE and FeNO on loss of asthma control.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Mixed model repeated measures will be used to analyse the following endpoints. The baseline value of each endpoint will be included along with baseline*visit and treatment*visit interactions. Treatment differences, 95% confidence intervals and p-values will be presented. • Change from baseline in ACQ-5 absolute score • Change from baseline in SGRQ total score • Change from baseline in Pre-bronchodilator FEV_1 • Change from baseline in FeNO	FEV_1 and FeNO will only be analysed up until Week 4 (down titration of ICS), all data post Week 4 will be summarised descriptively only. In addition, an exploratory analysis using fractional polynomials was added to examine the relationship between FEV_1 at Week 4 with screening eosinophils (continuous), IgE and FeNO. Continuous ACQ-5 and SGRQ will only be summarised and will not be analysed.	FEV_1 and FeNO are impacted by ICS, so including change from baseline post-down titration of ICS would be confounding change due to study treatment with change due to ICS. To better explore the data prior to down titration, the fractional polynomial analysis has been added to examine the relationship between FEV_1 at Week 4 with screening eosinophils (continuous), IgE and FeNO. FEV1, FeNO, ACQ-5 and SGRQ analysed using an MMRM would be assuming that data is missing at random. In fact, participants could have withdrawn due to loss of asthma control which is related to study treatment, so the analysis assumptions would not have been valid.
Secondary endpoints listed as: • Serum concentrations of GSK3772847 at weeks 2, 4, 8, 12, 16, 20, 24 and 28. • Free and total soluble ST2 levels at weeks 2, 4, 8, 12, 16, 20, 24 and 28.	Secondary endpoints listed as: • Serum concentrations of GSK3772847 by nominal time. • Free and total soluble ST2 levels in serum by nominal time.	Endpoint updated to use nominal time so that all data collected is summarised.
Proportion of participants with loss of asthma control assessed over Weeks 0-16 only.	Proportion of participants with loss of asthma control assessed over Weeks 0-16 and over Weeks 0-6.	An additional endpoint assessing loss of control between Weeks 0 and 6 was added to help support the time to loss of asthma control analysis.
The posterior probabilities that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.5 and 0.2 (i.e. more than a 0%, 25%, 50% and 80% reduction) will be produced.	The posterior probabilities that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.7, 0.5 and 0.2 (i.e. more than a 0%, 25%, 30%, 50% and 80% reduction), and greater than 0.6 (i.e. less than a 40% reduction) will be produced.	The additional posterior probabilities of the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo being <0.70 (more than a 30% reduction) and >0.60 (less that a 40% reduction) were added to assist internal decision making.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Endpoints included: • Proportion of participants with a ≥0.5 point ACQ-5 score increase from baseline. • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16.	Endpoints to be summarised and not analysed.	Due to participants being withdrawn after they reach one component of loss of control, there is no information available for the other components/ ACQ-5 /SGRQ after this date. As a result the numbers of the subjects who have useable data are very small, and any estimates will be biased, so informative decisions can't be made. The data must still be summarised to comply with disclosure rules for pre-specified secondary endpoints.
The minimum detectable effect for the sample size calculations is reported as 31% corresponding to a proportion with loss of control on GSK3772847 of 28%.	The minimum detectable effect for the sample size calculations is reported as 36% corresponding to a proportion with loss of control on GSK3772847 of 28%.	A typographical error in the protocol which meant that minimum detectable effect was incorrectly reported as 31%, this has been corrected in the RAP.

2.2. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan_207597_Final_V01 [20-DEC-2018]	
Reporting and Analysis Plan_207597_Amendment_Final_V01	
Analysis of components of loss of asthma control and responder analysis	• Analysis of components of loss of asthma control and responder analysis were removed as explained in Section 2.1.
Bayesian Analysis	• Additional information provided on the Bayesian logistic regression including starting values, set seeds and thinning options. • The posterior probabilities of the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo being <0.70 (more than a 30% reduction) and >0.40 (less that a 40% reduction) were added to assist internal decision making.
Repeated Measures Analysis	• Information on the variance-covariance matrix and use of the OM option added.
Treatment Discontinuation Date	• Derivation added for treatment discontinuation date
Sample Size	• A typographical error in the protocol which meant that minimum detectable effect was incorrectly reported as 31%, this has been corrected in the RAP amendment.
Tables, Listings and Figures	• Minor clarification/typographical errors in output titles and associated RAP text were added.

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

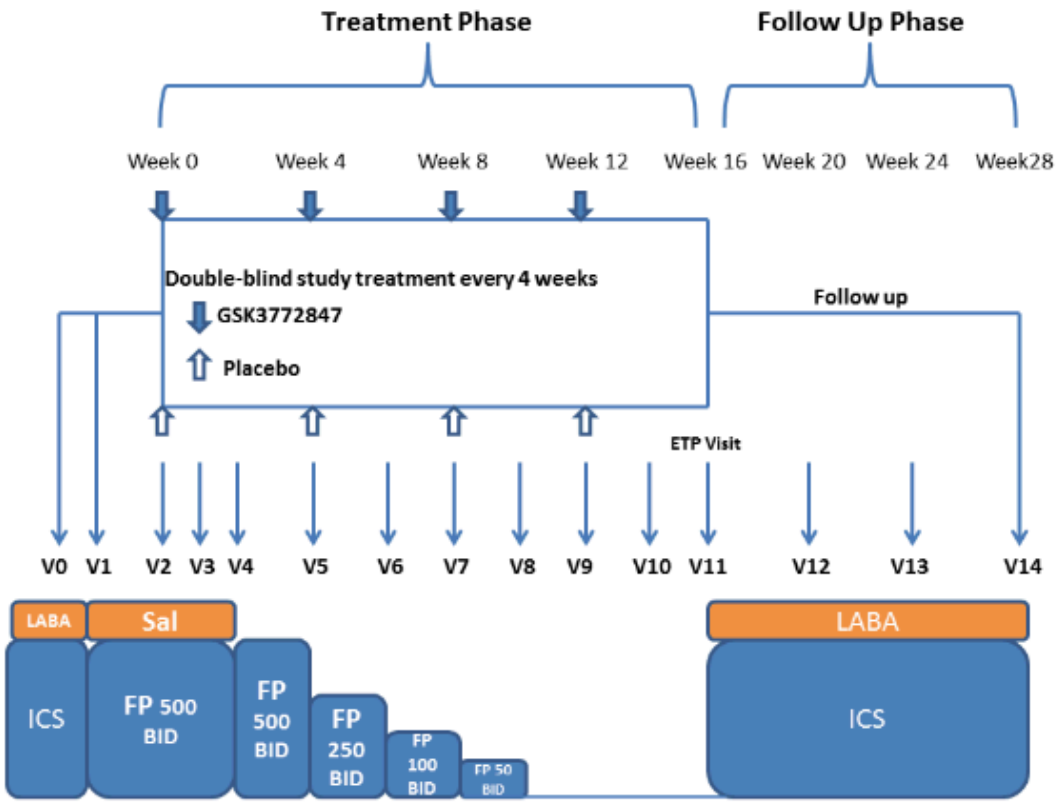
Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3772847, compared with placebo, administered intravenously every 4 weeks for 12 weeks (Week 0 – Week 12, 4 doses in total) in participants with moderately severe asthma.	Primary – Proportion of participants with loss of asthma control over Weeks 0-16 where 'loss of asthma control' is defined as at least one of the following: • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥ 0.5 point or • Pre-bronchodilator Forced expiratory volume in 1 second (FEV1) decrease from baseline (measured at the end of Run-in) >7.5 % or • Inability to titrate inhaled corticosteroid according to the pre-defined schedule or • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation).
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with moderately severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants with a ≥0.5 point ACQ-5 score increase from baseline. • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • Proportion of participants with loss of asthma control over Weeks 0-6 • Time to loss of asthma control. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule • The incidence, mean rate, and total number per participant of hospitalisations or Emergency Room (ER) visits during the study treatment period. • Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16. • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to

Objectives	Endpoints
	Week 16. • Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16. • Change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16. • Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF over each four weeks of the 16 week treatment period. • Change from baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period. • Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period. • Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the16 week treatment period. • Change from baseline in fractional exhaled nitric oxide (FeNO) at each week measured.
• To evaluate the safety and tolerability of GSK3772847, compared with placebo administered intravenously every 4 weeks for 12 weeks (Week 0-12, 4 doses in total) in participants with moderately severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28. • Change between post-dose and pre-dose in vital signs at weeks 0, 4, 8 and 12. • Change from baseline in 12-lead electrocardiogram (ECG) measurements at weeks 4, 8, 12 and 16. • Change between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12. • Change from baseline in 24 hours Holter measurements at weeks 4 and 12. • Change from baseline in clinical chemistry at weeks 2, 4, 8, 12, 16 and 28. • Change from baseline in haematology and cardiac markers at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28. • Incidence of and titres of anti- GSK3772847 antibodies at weeks 2, 4, 8, 12, 16, 20, 24 and 28.

Objectives	Endpoints
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with moderately severe asthma.	• Serum concentrations of GSK3772847 by nominal time.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with moderately severe asthma.	• Free and total soluble ST2 levels in serum by nominal time.
Exploratory	
• To compare the effect of GSK3772847 with placebo on biomarkers in serum and sputum.	• Changes from baseline in induced sputum biomarkers (subset) at weeks 8 and 16. • Changes from baseline in exploratory serum markers at weeks 8 and 16.

2.4. Study Design

Overview of Study Design and Key Features



Design Features	• The study is a Phase IIa, multicenter, randomised, placebo-controlled, double-blind, stratified, parallel group study.
Dosing	• Participants will have a two-week Run-in period in which they take a background therapy of fluticasone propionate (FP)/salmeterol 500/50 mcg BID. • Following run-in they will be randomised to receive four doses of either GSK3772847 or Placebo intravenously (Week 0, 4, 8 and 12) whilst initially still receiving background FP/Salmeterol 500/50 mcg BID. • At Week 2 background therapy will be changed to FP 500 mcg BID only. This will then be reduced by approximately 50 % every two weeks until complete FP discontinuation at Week 10.
Treatment Assignment	• Participants will be randomised in a 1:1 ratio to receive four doses of either GSK3772847 or Placebo administered intravenously every 4 weeks. • Randomisation will be stratified based on participants' baseline peripheral blood eosinophil count which is measured at screening (<150 cells/µL, >=150 cells/µL), Randomisation will also be stratified according to whether participants consent to the sputum sub study.

Overview of Study Design and Key Features	
Interim Analysis	• The End of Treatment Phase Analysis will take place after all subjects have completed the week 16 visit, and will be considered an interim analysis for both efficacy and safety. There will be no modifications to dosing regimens, sample size or any other aspects of the trial based on this data, as all study assessments, apart from follow-up, will have already been completed.

2.5. Statistical Hypotheses

The primary null hypothesis (H_0) for this study is that the ratio of the proportions of subjects with loss of asthma control from randomisation to Week 16 between GSK3772847 and placebo is unity.

$$H_0: \frac{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ GSK3772847}{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ Placebo} = 1$$

The alternative hypothesis (H_1) for this study is that the ratio of the proportions of subjects with loss of asthma control from randomisation to Week 16 between GSK3772847 and placebo is not unity.

$$H_1: \frac{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ GSK3772847}{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ Placebo} \neq 1$$

2.6. Sample Size Calculations

With 70 evaluable participants per arm and assuming the true proportion with loss of control on placebo is 44%, the smallest observed difference that would lead to rejection of the null hypothesis (minimum detectable effect) is 36% corresponding to a proportion with loss of control on GSK3772847 of 28%.

As detailed in Section 2.1, there was a typographical error in the protocol which meant that minimum detectable effect was incorrectly reported as 31%, this has been corrected above.

3. PLANNED ANALYSES

3.1. End of Treatment Phase Analyses

The End of Treatment Phase Analysis will be performed after the completion of the following sequential steps:

1. All subjects have completed the Week 16 visit or the Early Withdrawal visit
2. All required database cleaning activities have been completed and database release has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

Due to an inability to lock log forms used for collection of exacerbation data, the end of treatment phase analysis will be considered an interim analysis for both efficacy and safety. Any safety data collected for participants who have completed clinic visits after Week 16 will also be cleaned and included in the analysis.

All participants will have completed the active treatment phase of the study by the time of the interim, so no modifications will be made to the study as a result of the End of Treatment Phase Analysis. The Final Analysis is intended to be an analysis of safety data collected in the Post-treatment Follow-Up phase.

The sponsor will be unblinded to the results of the analysis.

3.2. Final Analyses

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

- All subjects have completed the study.
- All required database cleaning activities for data after Week 16/ Early Withdrawal as well as data collected on log pages have been completed.
- Final database release and database freeze has been declared by Data Management.

No unblinding will take place as part of the final analysis as all participants will have already been unblinded during the End of Treatment Phase Analysis.

4. ANALYSIS POPULATIONS

Some participants are being excluded from the efficacy analyses due to a failure at their site to follow GCP. As these participants received GSK3772847 or placebo during their period of participation, all safety data will be reported.

Population	Definition / Criteria	Analyses Evaluated
Enrolled	• The All Subjects Enrolled (ASE) population will consist of all participants who sign the ICF.	•Study population •Reason for withdrawal prior to randomisation
Randomised	• The randomised population will consist of all participants who were randomised. A participant who is recorded as a screen or run-in failure and also randomised will be considered to be randomised in error provided they have not performed any study assessments.	•No formal analysis will be performed on this population
Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control)	• The Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control) (mITT_LoC) will consist of all randomised participants who take at least 1 dose of study treatment, excluding participants where an investigation by GSK has shown that good clinical practice has not been followed. Any participants excluded from this population will be identified as protocol deviations and listed in a separate output. Participants will be analysed according to the treatment they receive >=50% of the time. If the participant receives 50% of each treatment they will be analysed according to the randomised treatment. For loss of asthma control, participants will be analysed according to the treatment they were receiving at the time of loss of control.	•Efficacy (loss of control)
Modified Intent-to-Treat excluding GCP non-compliant subjects	• The Modified Intent-to-Treat excluding GCP non-compliant subjects (mITT) population will consist of all randomised participants who take at least 1 dose of study treatment, excluding participants where an investigation by GSK has shown that good clinical practice has not been followed. Any participants excluded from this population will be identified as protocol deviations and listed in a separate output. Participants will be analysed according to the treatment they receive	•Efficacy (all except loss of control)

Population	Definition / Criteria	Analyses Evaluated
	>=50% of the time. If the participant receives 50% of each treatment they will be analysed according to the randomised treatment.	
Safety including GCP non-compliant subjects	• The Safety (SAFF_ALL) population will consist of all randomised participants who take at least 1 dose of study treatment. Participant will be analysed according to the treatment they receive >=50% of the time. If the participant receives 50% of each treatment they will be analysed according to the randomised treatment.	•Study population •Inclusion, exclusion and randomisation criteria deviations •Participant disposition •Safety
Pharmacokinetic	• The PK population will consist of all randomised participants who received at least one dose of study medication, and for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	•PK

NOTES :

1. Please refer to Appendix 10: List of Data Displays which details the population to be used for each display being generated.
2. If a participant is inadvertently given both study treatments they will be analysed according to the treatment that they received the more frequently.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [21-Aug-2017 (Version 1) or later].

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

Note: Inclusion and exclusion criteria deviations are always reported as important.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
G	GSK3772847 10 mg/kg	GSK3772847	2
P	Placebo	Placebo	1

NOTES:

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

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

- GSK3772847 vs Placebo

There were four strata used for the randomisation depending on the participants baseline blood eosinophil count and whether they consented to the sputum sub-study:

- Sputum sub-study and screening blood eosinophils < 150 cells/µL
- Sputum sub-study and screening blood eosinophils >=150 cells/µL
- Not sputum sub-study and screening blood eosinophils < 150 cells/µL
- Not sputum sub-study and screening blood eosinophils >=150 cells/µL

Displays will be presented by combining data across all four strata to give the overall estimate of GSK3772847 versus placebo.

Sputum sub-study will not be accounted for within the statistical analysis as the sputum sub-study strata was for monitoring recruitment only.

An additional exploratory analysis using fractional polynomials has been added to further investigate the relationship between loss of control and screening eosinophils and summary statistics on eosinophils will also be provided.

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.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Pre-Screening	Screen Run-in	Day 1 (Pre-Dose)	
Loss of Asthma Control				
Pre-bronchodilator Forced expiratory volume in 1 second (FEV_1)		X	X	Day 1
Asthma Control Questionnaire (ACQ-5) score		X	X	Day 1
Other Patient Reported Outcomes				
St. George's Respiratory Questionnaire (SGRQ)			X	Day 1
Peak Expiratory Flow (PEF)				
Mean morning peak expiratory flow (PEF)		X	X	Run-in [1]
Mean evening peak expiratory flow (PEF)		X	X	Run-in [1]
Fractional Exhaled Nitric Oxide (FeNO)				
Fractional Exhaled Nitric Oxide (FeNO)			X	Day 1
Symptom Scores				
Mean daytime asthma symptom score		X	X	Run-in [1]
Night-time awakenings due to asthma symptoms requiring rescue medication		X	X	Run-in [1]

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Pre-Screening	Screen Run-in	Day 1 (Pre-Dose)	
Rescue Medication				
Rescue medication use		X	X	Run-in [1]
Mean number of inhalations per day over each four weeks		X	X	Run-in [1]
Safety				
Vital Signs		X	X	Day 1
12-lead Electrocardiogram (ECG) measurements		X	X	Day 1
24 hours Holter measurements		X		Screen/Run in
Clinical laboratory tests (haematology and chemistry)		X	X	Day 1
Biomarkers				
Induced sputum biomarkers			X	Day 1
Serum biomarkers			X	Day 1
Exploratory serum markers			X	Day 1

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1] Mean over the last 7 days of the run-in period prior to V2. Participants must have at least 4 full days of data (morning and evening) in the last 7 days of run-in to be eligible.

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by investigative site, country, and regions.

Region	Countries
North America	United States, Canada
Latin America	Mexico
Eastern Europe	Ukraine, Russian Federation
Oceania	Australia

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

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

Category	Covariates
Screening eosinophils	At randomisation participants are stratified according to their screening peripheral blood eosinophil count. Screening eosinophils will be included in both primary and secondary analysis as a categorical variable (<150 cells/µL, >=150 cells/µL). If the analysis models are unable to converge due to low number of participants with screening blood eosinophils <150 cells/µL, then screening eosinophil will be re-categorised according to a cut point of 300 cells/µL instead i.e. <300 cells/µL and >=300 cells/µL

5.5. Multiple Comparisons and Multiplicity

As there is a single primary treatment comparison, no adjustment is required for primary comparisons. No adjustments will be made for multiplicity for other endpoints.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety Population including GCP non-compliant subjects population (SAFF_ALL), unless specified to be on the All Subjects Enrolled (ASE) population.

Study population analyses including analyses of subject'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 10: List of Data Displays.

6.2. Disposition

The study population summary will use the All Subjects Enrolled (ASE) population and show the number of subjects overall who were enrolled, the number of screen failures and the number with each reason for screen failure. It will also show the number of subjects who were randomised and who were in the modified Intent-to-treat (Loss of Control), modified Intent-to-treat, Safety including GCP non-compliant subjects, and PK populations.

For the Safety including GCP non-compliant subjects, reasons for withdrawal summary will show the number and percentage of subjects who completed the study, who withdrew prematurely from the study and who reported each primary and sub-reason for withdrawal.

6.3. Medical Conditions

The number and percentage of subjects reporting each current medical condition will be presented. This table will include a subheading of 'Cardiovascular Disorders,' which will summarise the information taken from the cardiac disorders page in the eCRF. All medical conditions must be summarised on this table regardless of frequency. This will be repeated for past medical conditions.

6.4. Concomitant Medications

Non-Asthma medications will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. Asthma medications will be summarised by the latest version of the Respiratory Medication Class (RMC), and will be derived for each asthma concomitant medication. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients.

Asthma and non-asthma medications will be listed separately. A listing of the relationship between ATC Level 1, ingredient and verbatim text will be produced for non-asthma medications only.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint

- Proportion of participants with loss of asthma control over Weeks 0-16
- Proportion of participants with loss of asthma control over Weeks 0-6 (Secondary)

7.1.2. Summary Measure

Bayesian Method (Primary): The posterior median and 95% credible interval. In addition, the posterior probabilities that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.7, 0.5 and 0.2 (i.e. more than a 0%, 25%, 30%, 50% and 80% reduction), and greater than 0.6 (i.e. less than a 40% reduction).

Frequentist Method (Supportive): Odds Ratio. The odds of having experienced loss of asthma control on GSK3772847 compared to the odds of having experienced loss of asthma control on placebo.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the modified Intent to Treat (Loss of Control) population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent Event	Primary Estimand	Secondary Estimand
Study treatment discontinuation due to an AE/SAE	Excluded from analysis	Set as loss of asthma control (i.e. worst case scenario).
Death	Excluded from analysis	Set as loss of asthma control (i.e. worst case scenario).
Prohibited/ Concomitant medications that could impact patients' asthma control	Use data as is.	Set as loss of asthma control (i.e. worst case scenario).
Non-compliance with FP/SAL, FP or study titration	Use data as is.	Set as loss of asthma control (i.e. worst case scenario).
Missing data *	Excluded from analysis	Set as loss of asthma control (i.e. worst case scenario).

Notes:

- * Missing data is not an intercurrent event, however missing values will be imputed according to the estimand under investigation.

• If the intercurrent event occurs after loss of asthma control then all information on loss of asthma control will be used. • Prohibited/ concomitant medications will be identified as protocol deviations within the prohibited/ concomitant medications category and will have text that start with "LoAC" • Non-compliance FP/SAL, FP or study titration will be identified as compliance <80%, compliance ≥ 120% or protocol deviations within the other deviations related to wrong study treatment/administration/dose sub-category and will have text that starts with "TIT"

If any of the following intercurrent events occurs, then all data will be accepted:

- Pregnancy
  Accidental unblinding

Whilst it's possible that site staff were unable to administer study drug as they were unable to find a suitable vein, the team felt this would not be caused by the randomised study treatment and the visit would be rescheduled. Therefore, if this occurs all data will be accepted and treated as any other out of window assessment.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: 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
• Proportion of participants with loss of asthma control over Weeks 0-16 • Proportion of participants with loss of asthma control over Weeks 0-6 (Secondary)
Model Specification
• The primary endpoint proportion of subjects with loss of asthma control will be analysed for the Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control) population using both Bayesian (primary) and Frequentist (supportive) methods. Bayesian Method (Primary): • A logistic regression model within proc MCMC will be used to generate the posterior distribution of the ratio of GSK/Placebo. • The analysis model will include categorical variables for treatment and screening eosinophil strata, with each coefficient (including the intercept) having a non-informative normal(mean=0,var=$1x10^6$) prior. • Odds ratios generated from the model will be back-transform to produce the probability of experiencing loss of asthma control on both GSK3772847 and Placebo. From these estimates the ratio of loss of asthma control on GSK/Placebo will be calculated within the proc MCMC call.

- Three Markov chain Monte Carlo (MCMC) chains will be run, with all parameters in the model being assessed for convergence. This is done to ensure that the results are not sensitive to the initial values selected. The chain with the lowest deviance information criteria (DIC) will be used for the analysis output. Each chain will have 100,000 simulations, with a thinning of 10 and a burn-in of 500, in order to generate 10,000 samples per chain. This may be adjusted if the chains fail to converge. The starting seeds and initial values for all three chains are given below:

	Set Seed	Starting Value
Chain 1	2075971	-2
Chain 2	2075972	0
Chain 3	2075973	2

- The posterior probabilities that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.7, 0.5 and 0.2 (i.e. more than a 0%, 25%, 30%, 50% and 80% reduction), and greater than 0.6 (i.e. less than a 40% reduction) will be calculated, along with the estimated median ratio and associated 95% credible interval. The 95% credible interval will use the highest posterior density where possible, and if this isn't possible then the 2.5% and 97.5% credible intervals will be reported.
- In addition to summary tables a plot of the cumulative probabilities from the posterior distribution for the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo will be generated.
- This analysis will be repeated for loss of asthma control between Weeks 0 and 6.

Frequentist Method (Supportive):

- The proportion of participants with loss of asthma control will be analysed using logistic regression allowing for screening eosinophils strata. It will include fixed effects terms for treatment and screening eosinophil strata.

Fractional Polynomials (Exploratory Analysis for Loss of Control Over Weeks 0-16):

- Screening blood eosinophil count will be transformed using a first order fractional polynomial term, and then a second order fractional polynomial term which will be included in the model as a continuous covariate. A treatment group by transformed eosinophil covariate interaction will also be included in the model to allow the magnitude of the treatment difference to differ by screening eosinophil count.

- The impact of extreme observations are a well-known problem with fraction polynomial modelling. To address this a two-step transformation to "pull-in" extremes and shift the origin away from zero will be used (Royston and Sauerbrei, 2007). The formula to achieve this is given below:

$$g\delta(x) = \delta + (1-\delta)\frac{g(x)-g(x_{(1)})}{g(x_{(n)})-g(x_{(1)})}$$

where $g(x) = \left[\ln\left(\frac{\emptyset\left(\frac{(x-\bar{x})}{s}\right)+\varepsilon}{1-\emptyset\left(\frac{(x-\bar{x})}{s}\right)+\varepsilon}\right) + \varepsilon^*\right] / (2\varepsilon^*)$

with: $0 < \delta < 1$

$\varepsilon = 0.01$

$\varepsilon^* = -\ln[\varepsilon/(1+\varepsilon)]$

$\bar{x} = n^{-1}\sum x_i$

$s = (n-1)^{-1}\sum (x_{(i)} - \bar{x})^2$

As recommended we shall use $\varepsilon = 0.01$ and $\delta = 0.2$.

- All models (first and second order) will be evaluated and the best fitting model will be selected based on the Akaike information criterion (AIC).
- The selected best fitting model will be used to predict the probability of loss of control by treatment arm along with the corresponding predicted odds ratio by screening eosinophil count. This model will include the observed margins (OM) option which will use the analysis dataset.
- The fit of the model to the raw data will be assessed visually by overlaying a plot of the treatment estimates and differences estimated in groups defined by quartiles of screening eosinophil counts. Estimates will be plotted against the mean eosinophil count within each subgroup.
- The role of baseline immunoglobulin E (IgE) and baseline FeNO (separately) on the effectiveness of GSK3772847 with respect to loss of asthma control will be investigated in a similar way.

Model Checking & Diagnostics

Bayesian Method (Primary):

- The Markov chain standard error (MCSE) should be compared to the standard deviation of the distribution (SD) to make sure that MCSE/SD ≤ 0.01 for all parameters in the mode.
- The Geweke diagnostic test will be used to check whether the mean estimates have converged by comparing means from the early and later part of the Markov chain using a z-score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.
- Gelman & Rubin diagnostic checks should be used to assess if the Markov chains have mixed.
- Visual checks on diagnostic plots will be performed to assess:

- Has the Markov chain settled down?
- Are sufficient simulations being run?
- Is there sufficient burn-in?
- Is the effective sample size large enough?

Frequentist Method (Supportive):

- None.

Model Results Presentation

Bayesian Method (Primary):

- The proportions of participants experience loss of asthma control on GSK3772847, Placebo and the ratio of GSK3772847/Placebo will be presented along with their 95% credible interval.

Frequentist Method (Supportive):

- The proportion of participants experiencing loss of asthma control on GSK3772847, Placebo and the odds ratio will be presented along with the 95% confidence intervals and p-value. This will be presented for all participants combined.

Fractional Polynomials (Exploratory Analysis):

- A plot of the relationship between the probability of experiencing loss of control on each treatment as well as the odds ratio versus continuous eosinophils will be produced.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint and Summary Measure

Endpoint	Summary Measure
Individual Components of Loss of Asthma Control: • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule	Number and percentage of participants experiencing each component of loss of asthma control (summary statistics only).
Time to loss of asthma control.	Mean, median, lower and upper quartiles of time to loss of asthma control, along with probability of experiencing loss of asthma control at each dosing visit.
The incidence, mean rate, and total number per participant of Asthma Related hospitalisations or Emergency Room (ER) visits during the study treatment period.	Summary statistics and study treatment exposure (no statistical analysis required).
Responders: • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16.	Number and percentage of participants (summary statistics only)
Change from Baseline Analysis: • Change from baseline in pre-bronchodilator FEV1 • Change from baseline in fractional exhaled nitric oxide (FeNO)	Mean change from baseline (summary statistics only)

Endpoint	Summary Measure
Change from Baseline: • Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16. • Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16.	Mean change from baseline (summary statistics only)
• Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF for each four week period of the overall 16 week treatment period. • Change from baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period. • Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the 16 week treatment period. • Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period.	Change from baseline (summary statistics only)

7.2.2. Population of Interest

The secondary efficacy analyses will be based on the modified Intent to Treat population, unless otherwise specified.

7.2.3. Strategy for Intercurrent (Post-Randomisation) Events

For the analysis of time to loss of asthma control, both primary and secondary estimands (Section 7.1.4) will be examined. It is important to assess both estimands as data is missing after withdrawal or loss of asthma control. This could produce biased estimates, as loss of control and therefore missing data is related to study treatment, and so the secondary estimand where missing data is set as non-responders must also be considered.

For all other endpoints, only the primary estimand will be examined. This estimand uses all data as collected, except for data collected after the date of loss of asthma control or early withdrawal from study treatment.

Once participants experience loss of asthma control and/or withdraw from study treatment they immediately restart their standard of care medication (ICS/LABA). As a

result, any data collected past this point will have been impacted by the standard of care medications and any estimates produced biased by the additional use of ICS/LABA. For this reason, data post withdrawal from study treatment is not included in the on-treatment efficacy analysis.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: 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.

7.2.4.1. Statistical Methodology Specification

Endpoint / Variables
• Time to loss of asthma control.
Strategy for Intercurrent (Post-Randomisation) Events
• Both primary and secondary estimands (Section 7.1.4) will be examined. It is important to assess both estimands as data is missing after withdrawal or loss of asthma control. This could produce biased estimates, as loss of control and therefore missing data is related to study treatment, and so the secondary estimand where missing data is set as non-responders must also be considered.
Model Specification
• Time to loss of asthma control will be analysed on the Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control) population using Kaplan-Meier analysis (Proc lifetest). Within the Kaplan Meier plot participants will either be counted as an event or they will be censored. • A log rank test will be performed to test for difference between the time to loss of asthma control on Placebo compared with GSK3772847 Primary Estimand: • Events: Participants who experience loss of asthma control during the study • Censoring: Participants who discontinue investigational product for reasons other than loss of asthma control will be censored at the date of early withdrawal from study treatment. Participants who successfully complete the 16 week treatment period will be censored at 113 days (16 weeks + 1 day). Secondary Estimand: • Events: Participants who experience loss of asthma control during the study or who discontinue investigational product for reasons other than loss of asthma control (date of event will be set to date of early withdrawal from study treatment). • Censoring: Participants who successfully complete the 16 week treatment period will be censored at 113 days (16 weeks + 1 day).

Time to event/censoring = Date of event/censoring– Treatment start date + 1. If participants experience multiple reasons for loss of control then the earliest date will be used as described in Section 0.

Model Checking & Diagnostics

- None

Model Results Presentation

- Kaplan-Meier plots of the probability of a participant experiencing loss of asthma control by treatment will be produced.
- In addition, a summary table will be produced showing the probability of experiencing loss of asthma control by 4, 8, 12 and 16 weeks along with the median, upper and lower quartiles of time to loss of asthma control on both treatment arms (this will be NA if <50% of participants on a treatment lose control).

Endpoint / Variables

- Change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16.

Strategy for Intercurrent (Post-Randomisation) Events

Primary estimand only.

Model Specification

Only data until Week 4 (down titration of ICS) will be analysed, all data post Week 4 will be summarised descriptively only.

Data up to and include Week 4 (down titration of ICS):
A repeated measures model with terms for baseline FEV_1, treatment, visit and screening eosinophil strata. The model will also include baseline FEV_1 by visit, visit by treatment and screening eosinophil strata by visit interactions.

Model Structure:

- The variance-covariance matrix will be assumed unstructured.
- Kenward Roger (KR) method will be used for calculating degrees of freedom. If the analysis does not run using the KR method then the residual method will be used instead.
- An observed margins (OM) dataset will be used to derive the LS means using coefficients which are based on the subjects used in the analysis. This is a dataset with a row for every subject-visit combination that contains all of the covariates. The OM will be at the average baseline FEV_1.

FEV_1 at Weeks 4 Only - Fractional Polynomials (Exploratory Analysis):

- Screening blood eosinophil count will be transformed using a first order fractional polynomial term, and then a second order fractional polynomial term which will be included in the model as a continuous covariate. A treatment group by transformed eosinophil covariate interaction will also be included in the model to allow the magnitude of the treatment difference to differ by

screening eosinophil count.

- The impact of extreme observations are a well-known problem with fraction polynomial modelling. To address this a two-step transformation to "pull-in" extremes and shift the origin away from zero will be used (Royston and Sauerbrei, 2007). The formula to achieve this is given below:

$$g\delta(x) = \delta + (1-\delta)\frac{g(x) - g(x_{(1)})}{g(x_{(n)}) - g(x_{(1)})}$$

where $g(x) = \left[\ln\left(\frac{\emptyset\left(\frac{(x-\bar{x})}{s}\right)+\varepsilon}{1-\emptyset\left(\frac{(x-\bar{x})}{s}\right)+\varepsilon}\right) + \varepsilon^*\right] / (2\varepsilon^*)$

with: $0 < \delta < 1$

$\varepsilon = 0.01$

$\varepsilon^* = -\ln[\varepsilon/(1+\varepsilon)]$

$\bar{x} = n^{-1}\sum x_i$

$s = (n-1)^{-1}\sum (x_{(i)} - \bar{x})^2$

As recommended we shall use $\varepsilon = 0.01$ and $\delta = 0.2$.

- All models (first and second order) will be evaluated and the best fitting model will be selected based on the AIC.
- The selected best fitting model will be used to predict FEV_1 by treatment arm along with the corresponding predicted difference in FEV_1 by screening eosinophil count. This model will include the OM option which will use the analysis dataset.
- The fit of the model to the raw data will be assessed visually by overlaying a plot of the treatment estimates and differences estimated in groups defined by quartiles of screening eosinophil counts. Estimates will be plotted against the mean eosinophil count within each subgroup.

Model Checking & Diagnostics

- Distributional assumptions underlying the model used for analysis will be examined by

obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The estimates of the mean and difference for each treatment group from the model will be produced, along with 95% confidence intervals and p-values for treatment comparisons.

Endpoint / Variables
• Change from baseline in fractional exhaled nitric oxide (FeNO). • Change from baseline in blood eosinophils
Strategy for Intercurrent (Post-Randomisation) Events
Primary estimand only.
Model Specification
Only data until Week 4 (down titration of ICS) will be analysed, all data post Week 4 will be summarised descriptively only. Both FeNO and eosinophils have the ratio of post-baseline values to baseline values log transformed prior to analysis. For FeNO where multiple measurements can be taken at a visit, the data will be log transformed (using the natural logarithm (ln) hereby referred to as log) and the average log transformed value used as the visit value. FeNO Analysis Model: A repeated measures model with terms for log(baseline FeNO), treatment, visit, screening eosinophil strata and interaction terms for log(baseline FeNO) by visit, treatment by visit and screening eosinophil strata by visit. Eosinophil Analysis Model: A repeated measures model with terms log(baseline eosinophils), treatment, visit and interaction terms for log(baseline eosinophils) by visit and treatment by visit. Model Structure: • The variance-covariance matrix will be assumed unstructured. • Kenward Roger (KR) method will be used for calculating degrees of freedom. If the analysis does not run using the KR method then the residual method will be used instead. • An observed margins (OM) dataset will be used to derive the LS means using coefficients which are based on the subjects used in the analysis. This is a dataset with a row for every subject-visit combination that contains all of the covariates. The OM will be at the average logarithm of baseline FeNO or average logarithm of baseline eosinophils dependent on the model. Due to a large amount of FeNO data being outside the normal range, further analysis of FeNO may be explored.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model

respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The estimated treatment ratios together with 95% CIs (back-transformed from the differences on the log-scale) will be produced for each treatment group along with the treatment comparisons and p-values. • In addition the percentage change from baseline will also be presented where this is calculated as: % change from baseline = (ratio-1)*100

The following endpoints will be summarised descriptively only. No analysis will be performed and all data will be reported as collected excluding data after which participants had reached loss of asthma control/withdrawn early from study treatment and restarted their standard of care medication (Primary Estimand only), using the modified Intent to Treat population:

- Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16.
- Participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16.
- Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16.
- St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16.
- Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF over each four weeks of the 16 week treatment period. Note: Each PEF is taken in triplicate with the maximum value being used.
- Change from baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period.
- Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the16 week treatment period. Note: This is the change from baseline in the average number of nights a participant woke up at least once and had to use their rescue medication.
- Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety including GCP non-compliant subjects population, unless otherwise specified. The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and Adverse Events of Special Interest (AESIs) will be based on GSK Core Data Standards.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

8.3. Vital Signs, Electrocardiogram (ECG) and Holter

Summary statistics for vital signs at baseline, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28 will be produced along with change from baseline summaries for each post baseline timepoint. In addition, the change between post-dose and pre-dose vital signs measurements will be summarised at weeks 0, 4, 8 and 12.

Similar 12-lead electrocardiogram (ECG) measurements at baseline, weeks 4, 8, 12 and 16 will be produced along with change from baseline summaries for each post baseline timepoint, and changes between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12.

24 hour Holter measurements collected at baseline, weeks 0, 4 and 12 will be summarised along with change from baseline at weeks 0, 4 and 12. Only participants with at least 16hrs worth of data will be included in any tables however all data will be listed.

8.4. Clinical Chemistry, Haematology and Cardiac Markers

Summaries of clinical chemistry results at baseline, weeks 2, 4, 8, 12, 16 and 28 along with change from baseline for all post-baseline measurements will be produced.

Similarly, haematology and cardiac markers at baseline, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28 along with change from baseline for all post-baseline measurements will also be produced.

8.5. Antibodies

Summaries of the incidence of and titres of anti- GSK3772847 antibodies at weeks 0*, 2, 4*, 8*, 12*, 16, 20, 24 and 28.

* = Pre-dose only

8.6. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of liver function tests will be based on GSK Core Data Standards.

9. PHARMACOKINETIC ANALYSES

Due to the time required to analyse PK samples, no PK outputs will be included in the end of treatment phases analysis.

9.1. Secondary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

Serum concentrations of GSK3772847 by nominal time.

9.1.2. Population of Interest

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

9.1.3. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

9.1.4. Statistical Analyses / Methods

- No statistical analysis will be performed.
- Serum concentration will be summarised descriptively with summary figures being produced.
- Scatter plots of trough serum concentration vs FeNO, trough serum concentration vs blood eosinophils, and trough serum concentration vs IgE at Week 4 only will also be produced.

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

10.1. Secondary Pharmacodynamic Analyses

10.1.1. Endpoint / Variables

Free and total soluble ST2 levels in serum

10.1.2. Summary Measure

Free soluble ST2: Summary statistics and percentage change from baseline
Total soluble ST2: Summary statistics and percentage change from baseline

Only pre-dose trough sST2 will be used for analysis. Post-dose trough sST2 will be summarised only.

10.1.3. Population of Interest

The secondary pharmacodynamics analyses will be based on the modified Intent to Treat population, unless otherwise specified.

10.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

10.1.5. Statistical Analyses / Methods

Endpoint / Variables
• Percentage change from baseline in free sST2 (On-treatment) • Percentage change from baseline in free sST2 (Post-treatment) • Percentage change from baseline in total sST2 (On-treatment) • Percentage change from baseline in total sST2 (Post-treatment)
Strategy for Intercurrent (Post-Randomisation) Events
No intercurrent events are considered for this endpoint. All data will be used as collected.
Model Specification
• The ratio of post-baseline sST2 values to baseline sST2 values will be log transformed prior to analysis. Note: Log(post baseline sST2 /baseline sST2) is equivalent to log(post baseline sST2) – log(baseline sST2). • A repeated measures model with terms for treatment, visit, visit by treatment, the logarithm of baseline sST2, the logarithm of baseline sST2 by visit and screening eosinophil strata will be fitted. Model Structure: • The variance-covariance matrix will be assumed unstructured. • Kenward Roger (KR) method will be used for calculating degrees of freedom. If the analysis does not run using the KR method then the residual method will be used instead.

• An observed margins (OM) dataset will be used to derive the LS means using coefficients which are based on the subjects used in the analysis. This is a dataset with a row for every subject-visit combination that contains all of the covariates. The OM will be at the average baseline of free sST2 (either On-treatment or Post-treatment according to the model).
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The estimated treatment ratios together with 95% CIs (back-transformed from the differences on the log-scale).

Fractional Polynomials (Exploratory Analysis)

The role of free sST2 on the effectiveness of GSK3772847 with respect to loss of asthma control will be investigated, using the modified intent to treat (loss of control) population. The number of participants experiencing loss of control will be predicted at each level of baseline free sST2 based on a model including a free sST2 main effect term and an interaction with treatment term.

Baseline free sST2 will be transformed using a first order fractional polynomial term, and then a second order fractional polynomial term which will be included in the model as a continuous covariate. A treatment group by transformed free sST2 covariate interaction will also be included in the model to allow the magnitude of the treatment difference to differ by baseline free sST2.

The impact of extreme observations are a well-known problem with fraction polynomial modelling. To address this a two-step transformation to "pull-in" extremes and shift the origin away from zero will be used (Royston and Sauerbrei, 2007). The formula to achieve this is given below:

$$g\delta(x) = \delta + (1-\delta)\frac{g(x)-g(x_{(1)})}{g(x_{(n)})-g(x_{(1)})}$$

where $g(x) = \left[\ln\left(\frac{\emptyset\left(\frac{(x-\bar{x})}{s}\right)+\varepsilon}{1-\emptyset\left(\frac{(x-\bar{x})}{s}\right)+\varepsilon}\right) + \varepsilon^*\right] / (2\varepsilon^*)$

with: $0 < \delta < 1$

$\varepsilon = 0.01$

$\varepsilon^* = -\ln[\varepsilon/(1+\varepsilon)]$

$$\bar{x} = n^{-1} \sum x_i$$

$$s = (n-1)^{-1} \sum (x_{(i)} - \bar{x})^2$$

As recommended we shall use $\varepsilon = 0.01$ and $\delta = 0.2$.

All models (first and second order) will be evaluated and the best fitting model will be selected based on the AIC.

The selected best fitting model will be used to predict the probability of loss of control by treatment arm along with the corresponding predicted odds ratio by baseline free sST2. This model will include the OM option which will use the analysis dataset.

The fit of the model to the raw data will be assessed visually by overlaying a plot of the treatment estimates and differences estimated in groups defined by quartiles of baseline free sST2 counts. Estimates will be plotted against the mean baseline free sST2 count within each subgroup.

10.2. Exploratory Biomarker Analyses

10.2.1. Endpoint / Variables

- Changes from baseline in induced sputum biomarkers (subset) at weeks 8 and 16.
- Changes from baseline in exploratory serum markers at weeks 8 and 16.

10.2.2. Summary Measure

Change from baseline

10.2.3. Population of Interest

The exploratory biomarker analyses will be based on the modified Intent to Treat population, unless otherwise specified.

10.2.4. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

10.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Induced sputum biomarkers and exploratory serum markers at weeks 8 and 16 will be summarised using descriptive statistics, including the geometric mean and CV as well as listed.

No statistical analysis will be performed on this data.

11. REFERENCES

Charter for the Internal Safety Review Commitee (iSRC), Protocol 207597 Title: A randomised, double-blind, parallel group, multicenter, stratified study assessing the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with severe asthma, 26 June 2017

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Internal Safety Review Commitee (iSRC) Reporting and Analysis Plan for a randomised, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma, 20 July 2018

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Royston and Sauerbrei, Improving the robustness of fractional polynomial models by preliminary covariate transformation: A pragmatic approach, Computational Statistics & Data Analysis , Volume 51, Issue 9, 15 May 2007, Pages 4240-4253 doi.org/10.1016/j.csda.2006.05.006

Winthrop et al, 2015, Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance, Annals of the Rheumatoid Arthritis Disease, doi: 10.1136/annrheumdis-2015-207841. Epub 2015 Sep 22

12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management

The full list of protocol deviations collected on the eCRF is in the PDMP. Please refer to this document for current guidance.

There is no per protocol population in this study.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Informed consent (ICF)	X															
Genetic ICF	X															
ICF for sputum	X															
Inclusion and exclusion criteria		X														
Randomisation Criteria			X													
Demography	X															
Full physical exam including height and weight		X														
Medical history (includes substance abuse)		X														Substances [Drugs, Alcohol, tobacco] and family history of premature CV disease]): [including cardiovascular medical history]
Laboratory																

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Laboratory assessments		X[1,2]	X[1]	X	X[1]	X[1]	X	X[1]	X	X[1]	X	X[1]			X[1]	Haematology (including eosinophil count) and cardiac markers measured at all clinic visits. 1. Clinical chemistry (including liver chemistry). 2. Routine urinalysis at screening (Visit 1)
Pregnancy test[1]	X[2]		X[3]			X[3]		X[3]		X[3]		X	X	X	X	1. Test for women with child bearing potential. 2. Serum pregnancy test at V0/V1. 3. Test to be performed pre-dose during the treatment period.
[HIV, Hep B and Hep C screen]		X														A confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. If test has been performed within 3 months prior to first dose of study treatment, testing at screening is not required.

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Genetic blood sample – Pre dose			X													Pharmacogenetic sample may be drawn any time from Visit 2 onwards. Informed consent for optional substudies e.g. genetics must be obtained before collecting a sample
Sputum sample collection			X					X				X				Pre-dose collection and in a sub-set of participants (~50 %) at selected sites; also collected for EW participants
PK, target engagement and immunogenicity assessments			X	X	X	X		X		X		X	X	X	X	See SoA Table 2 for details
Exploratory Biomarkers			X					X				X				Pre dose collection
Efficacy																
Spirometry		X	X		X	X	X	X	X	X	X	X				Test to be performed pre-dose during the Treatment period
Reversibility		X														
FeNO			X	X	X	X	X	X	X	X	X	X				Test to be performed pre-dose
Review loss of asthma control criteria				X	X	X	X	X	X	X	X	X				It will include review of data to determine loss of asthma control. See Section 9.1.5.
Dispense eDiary		X														

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Collect eDiary												X				
Review eDiary			X	X	X	X	X	X	X	X	X	X				
Safety																
12-lead ECG		X	X[1]			X[1]		X[1]		X[1]		X				1. Test to be performed pre-dose and post-dose within 30 mins after end of infusion.
24 hrs Holter		X	X[1]			X[1]				X[1]						Holter monitor needs to be returned to clinic at end of 24-hour recording (i.e. the next day). 1. Place the Holter 30-60 mins prior to dosing.
Vital signs		X	X[1]	X	X	X[1]	X	X[1]	X	X[1]	X	X	X	X	X	1. Test to be performed pre-dose prior to spirometry and post-dose prior the 12 –lead ECG.
Dispense paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X		
Review paper Medical Problems/Medications Taken worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
AE/SAE review	X[1]	X[1]	←==========									==========→	X	X	X	1. At V0 and V1 collect only SAEs considered as related to study participation.
Concomitant medication review	X	X	←==========									==========→	X	X	X	
Questionnaires																
ACQ-5		X	X													After randomization, ACQ5 will be completed by the participants every 7 days.
SGRQ			X			X		X		X		X				
Study Treatment																
Double blind Study Treatment (IP)			X			X		X		X						Patients will remain in the clinic for monitoring for at least 2 hours after the end of infusion.
FP/Sal (500/50) dispensing		X	X													
FP (mcg) dispensing					500	250	100	50								
Dispense albuterol (as needed)		X	X	X	X	X	X	X	X	X	X	X				

Procedure	Treatment Period										Follow-up[2] (± 3 days)			Notes
	± 2 days			± 3 days										
Visit	2[1]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1. Visit 2 = Day 1 (first dose of IP). 2. FU period to start 4 weeks after ETP or EW visit.
Week	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	1	8	15	29	43	49	71	85	99	113				
Double blind Study Treatment (IP)	X			X		X		X						
PK sample	X[2]	X	X	X[3]		X[3]		X[1]		X	X	X	X	1. Pre dose and post dose. 2. Post dose only. 3. Pre dose only. Pre-dose samples within 2 hours from the planned dosing time. Post-dose samples as soon as possible after end of infusion but must be taken within 4 hours.
Free and total sST2	X[1]	X	X	X[3]		X[3]		X[1]		X	X	X	X	
Immunogenicity sample	X[3]		X	X[3]		X[3]		X[3]		X	X	X	X	

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

Nominal visits will be used and no windowing will be applied for analysis.

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

12.4.1. Study Phases

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

Study Phase for all data except efficacy	Definition
Pre-treatment	Date ≤ Study Treatment Start Date
On-treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 28 days
Post-treatment	Date > Study Treatment Stop Date + 28 days

Study Phase for efficacy	Definition
Pre-treatment	Date ≤ Study Treatment Start Date
On-treatment	Study Treatment Start Date < Date ≤ Date of discontinuation from study treatment Or if the participant did not discontinue early from study treatment Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 28 days
Post-treatment	Date > Study Treatment Stop Date + 28 days

Once participants withdraw from study treatment they immediately restart their standard of care medication (ICS/LABA). As a result, any data collected past this point will have been impacted by the standard of care medications and any estimates produced biased by the additional use of ICS/LABA. For this reason, data post withdrawal from study treatment is not included in the on-treatment efficacy analysis.

The post treatment definition is the same for efficacy and safety analysis.

Completion of study epoch's will be defined as the following:

Study Phase	Definition of Completion
Run-in	Randomised into study and received first dose of study treatment
Treatment	Completed Week 16 visit or withdrew from treatment phase due to loss of asthma control
Follow up	Completed 12 week follow-up period

12.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition **Note: All programming should use start and end dates where available, CMSTRF and CMENRF are only to be used where dates are unavailable to help determine the correct study phase.**
Pre-treatment	• Conmed Start Date < Study Treatment First Dose Date • Conmed End Date < Study Treatment First Dose Date • CMSTRF = ”BEFORE” • Randomisation date is missing i.e. subject was not randomised
On-treatment	• Study Treatment First Dose Date <= Conmed Start Date <= Study Treatment Last Dose Date + 28 • Study Treatment First Dose Date <= Conmed End Date <= Study Treatment Last Dose Date + 28 • (Conmed Start Date <= Study Treatment Last Dose Date + 28) and (Conmed End Date >= Study Treatment First Dose Date) • (Conmed Start Date <= Study Treatment Last Dose Date + 28) and (CMENRF =”DURING/AFTER” or CMENRF =”AFTER” or CMSTRF = “DURING”) • (CMSTRF = ”BEFORE” or CMSTRF = ”DURING” or CMENRF =”DURING/AFTER”) and (Conmed End Date >= Study Treatment First Dose Date) • (CMSTRF = ”BEFORE” or CMSTRF =”DURING”) and (CMENRF =”DURING/AFTER” or CMENRF =”AFTER”) • CMSTRF = ”DURING” • CMENRF = ”DURING/AFTER”
Post-treatment	• Conmed Start Date > Study Treatment Last Dose Date + 28 • Conmed End Date > Study Treatment Last Dose Date + 28 • CMENRF = ”AFTER” • CMENRF = ”DURING/AFTER”
All phases	• Conmed start date is missing and CMSTRF is missing and conmed end date is missing and CMENRF is missing

1. **NOTES:**

- The duration of a single concomitant medication can extend over multiple study phases
- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

12.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	If AE onset date is on or after treatment start date & on or before treatment stop date + 28 days. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 28 days

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-treatment.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: /arenv/arprod/gsk3772847/mid207597/
Additional information of reporting areas: data_look_01 This is where the blinded dry run will take place. final_01: This is where the end of treatment phase analysis will take place. final_02: This is where the end of study analysis will take place. Details of the reporting efforts used for the iSRC analysis are detailed in the separate iSRC RAP.	
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards	
Generation of RTF Files	
• RTF files will be generated for all reporting efforts	

12.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include 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 Principals 7.01 to 7.13.

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • 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.
Study Day

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

12.6.2. Study Population

Age
Date of birth will be set as PPD YYYY where YYYY is the year of birth taken from the CRF. For participants who attended a screening visit, age will be calculated at the screening visit date. For pre-screen failures, age will be calculated at the pre-screening visit date.
Body Mass Index (BMI)
BMI = Weight (kg) / Height(m)^2
Treatment Misallocations
To allocate treatment, the number of doses of GSK3772847 and Placebo that were given will be calculated, and the subject will be assigned to whichever treatment has the higher number. The only exception will be when both treatments were given equally, in which case the subject will be assigned their randomised treatment.
Early Withdrawal from Study Treatment Date
The eCRF captures the study treatment start and end, however this is the physical time and date of the infusion. The date of early withdrawal from study treatment is not captured and should therefore be calculated as follows: • If the participant withdrew from treatment due to loss of asthma control then the date of early withdrawal from study treatment is set to the date of loss of asthma control. • If the participant withdrew due to an AE/SAE/Death then withdrawal date is set to the AE/SAE onset date (all deaths should be reported as serious adverse events) • If the participant withdrew from study treatment (for a reason other than those above) during the first 10 weeks of the study i.e. during the down titration of the background medications, then the FP/SAL or FP discontinuation date should be used as the date of withdrawal from study treatment. • For participants who withdraw from study treatment (for a reason other than those above) between Week 10 and Week 16, there is no information on when they withdrew as they are no longer taking background medications. The date of early withdrawal from study treatment should therefore be set to the maximum of date of last dose of FP and date of last dose +1. This is because no more information is available other than the fact that they had not lost control prior to completing the down titration or prior to receiving their final dose of IP.

Treatment Compliance for Fluticasone Propionate (FP) and Salmeterol (SAL)
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)*100** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) by each background therapy will be calculated. • Planned Treatment Duration is defined according to the schedule of activities. • Compliance will be summarized by the following categories: <80%, ≥ 80% to < 95%, ≥95% to <105%, ≥ 105% to <120% and ≥120%
Extent of Exposure (Therapeutic Coverage)
• IP is administered approximately every 4 weeks and each dose viewed as providing therapeutic coverage for 4 weeks (28 days). • Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Study Treatment Last Dose Date – (Study Treatment First Dose Date) + 29** • The only exception to this will be when a participant dies in which case **Duration of Exposure in Days = Death Date – (Study Treatment First Dose Date) + 1**

12.6.3. Efficacy

Loss of Asthma Control
Multiple Loss of Asthma Control
• If a participant reaches loss of control for multiple reasons then all reasons will be reported. For any time to loss of asthma control analysis, the time of the earliest component of loss of control will be used.
Date of Loss of Asthma Control
Date of loss of control will be taken from the loss of control log page.

Diary Data
The vendor data captures the date on which the subject completes the diary (actual date of collection) rather than the date to which the questions relate. For example, in the morning diary subjects are asked 'Did you wake up due to asthma symptoms' and 'when you woke up due to your asthma symptoms did you use any rescue bronchodilator?' In the evening diaries subjects answer a question on daytime asthma symptoms and record the number of puffs of rescue medication used during the day. This means that the morning diary date in the raw data refers to the events during the previous night and that the evening diary relates to the events during the day time. In order to ensure that correct observations are assigned to each four-week time period, measurements recorded in the morning diary will have 1 day removed in the analysis dataset to ensure that the date reflects the time period that the information related to. This adjustment is not required for evening diary as these are collected in the evening of the day to which they relate. Questions which this affects are those where the timepoint reference is MORNING: • Was evening dose taken? • Did you wake up due to asthma symptoms? • When you woke up due to your asthma symptoms did you use any rescue bronchodilator? • Number of puffs – night time PEF assessments will not have the adjustment made as these reflect the PEF as assessed (so the PEF recorded in the morning diary is the PEF at that time).

12.6.4. Safety

Adverse Events
Adverse Events of Special Interest (AESI)
Systemic Allergic/Hypersensitivity and Non-allergic Reactions: • Hypersensitivity (SMQ) [narrow] • Anaphylactic reaction (SMQ) [narrow] • Angioedema (SMQ) [narrow] Alterations in immune response (infections) All infections and serious infections reported under the MedDRA system organ class of 'Infections and Infestations'. Specific events of interest are opportunistic infections with preferred terms matching identified/pre-determined terms based on a published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]. Alterations in immune response (malignancies): All neoplasms reported under the MedDRA system organ class of 'Neoplasms, benign, malignant and unspecified (including cysts and polyps)'. Specific events of interest are malignancies which will be identified through matching of collected preferred terms with those from the following: Sub-SMQs under the Malignancies SMQ: • Malignant tumours sub-SMQ (narrow terms) • Tumours of unspecified malignancy sub-SMQ (narrow terms) Alterations in cardiovascular safety: Cardiac disorders and serious cardiac disorders reported under the MedDRA system organ class of 'Cardiac Disorders'. Serious cardiac, vascular and thromboembolic (CVT) events, identified as all serious events classified under the MedDRA system organ classes of 'Cardiac Disorders' and of 'Vascular Disorders', and thromboembolic events identified through matching of collected preferred terms with those from the following: Sub-SMQs under the Embolic and thrombotic events SMQ: • Embolic and thrombotic events, arterial sub-SMQ (narrow terms) • Embolic and thrombotic events, venous sub-SMQ (narrow terms) • Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous sub-SMQ (narrow terms) Sub-SMQs under the Ischaemic Heart Disease SMQ • Myocardial infarction sub-SMQ (narrow terms) • Other Ischaemic heart disease sub-SMQ (narrow terms) Sub-SMQs under the Central Nervous System Vascular Disorders SMQ • Ischaemic central nervous system vascular conditions sub-SMQ (narrow terms) • Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic sub-SMQ (narrow terms) • Serious ischemic adverse events, a subset of the serious CVT events identified through matching of collected preferred terms with those from the following: Local Injection Site Reactions Local injection site reactions are identifying through preferred terms which had been selected by medical review of the MedDRA dictionary and are provided in a separate spreadsheet.

Rate of Events per 1000 Treatment Years
Rate of events per 1000 treatment years will be calculated using: Rate = number of events * 1000 / total treatment exposure in years where subjects can contribute more than one event. This is equivalent to: Rate = number of events * 1000 / (number of subjects in treatment group * mean treatment exposure in years).

Maximum/Minimum Definitions for Vital Signs Data
Maximum and Minimum**:** Maximum and Minimum post-randomisation value over all time-points (including scheduled and unscheduled assessments) will be presented.

FEV_1
Absolute Reversibility
Absolute reversibility (mL) = (post-bronchodilator FEV_1 – pre-bronchodilator FEV_1)
Percent Reversibility
Definition of Percentage Reversibility as a percentage of predicted FEV_1 = ((post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / predicted FEV_1) x 100% Definition of Percentage Reversibility as a percentage of pre-bronchodilator FEV_1 = ((post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / pre-bronchodilator FEV_1) x 100%

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as either completing the 16 week treatment period and three month safety follow up, or withdrawing from the treatment period early due to loss of asthma control and completing the three month safety follow up period. • Withdrawn participants were not replaced in the study, unless the participants were withdrawn due to sites failing to comply with GCP. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

12.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a "blank" in 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.

Analysis	• All missing data will be handled according to estimand of interest as described within the main body of the RAP.
ACQ	• If one of the five items in the ACQ is missing then the response from the four remaining items will be interpolated (pro-rata) to gain the overall response for the participant. • If more than one item is missing then the ACQ will be considered missing.
SGRQ	The SGRQ questionnaire has three components; symptoms, activity and impact. **Symptoms** • The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (662.5) and from the Total weight (3989.4) **Activity** • The Activity component will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity component (1209.1) and from the Total weight (3989.4) **Impacts** • The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (2117.8) and from the Total weight (3989.4) If any component has more missing items then mentioned above then the SGRQ will be considered missing.

12.7.2.1. Handling of Missing and Partial Dates

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

12.8. Appendix 8: Values of Potential Clinical Importance

Values of potential clinical importance will not be used in this study, instead normal reference ranges of “Low”, “Normal” and “High” will be used.

12.9. Appendix 9: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IgE	Immunoglobulin E
IMMS	International Modules Management System
IP	Investigational Product
mIT	Modified Intent-to-Treat excluding GCP non-compliant subjects
mITT_LoC	Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control)
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomisation & Medication Ordering System
SAC	Statistical Analysis Complete
SAFF_ALL	Safety including site including GCP non-compliant subjects
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS

12.10. Appendix 10: List of Data Displays

All displays (Tables, Figures & Listings) will use the term 'Subjects' instead of "Participants".

12.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

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

12.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

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

NOTES:

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

12.10.3. Deliverables

Delivery [Priority] [1]	Description
ETP [1]	End of Treatment Phase Statistical Analysis Complete
SAC [1]	Final Statistical Analysis Complete

NOTES:

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

12.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	SAFF_ALL	ES8	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT	ETP, SAC
1.2.	SAFF_ALL	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	ETP, SAC
1.3.	SAFF_ALL	ES4	Summary of Subject Disposition at Each Study Epoch	ICH E3	ETP, SAC
1.4.	ASE	ES6	Summary of Screening/Run-in Status and Reasons for Screen/Run-in Failure	Journal Requirements	ETP, SAC
1.5.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	ETP, SAC
1.6.	SAFF_ALL	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	ETP, SAC
Protocol Deviation					
1.7.	SAFF_ALL	DV1	Summary of Important Protocol Deviations	ICH E3	ETP, SAC
1.8.	SAFF_ALL	IE1	Summary of Inclusion/ Exclusion Deviations	ICH E3	ETP, SAC
Population Analysed					
1.9.	Enrolled	SP1	Summary of Study Populations	IDSL	ETP, SAC
Demographic and Baseline Characteristics					
1.10.	SAFF_ALL	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	ETP, SAC
1.11.	Enrolled	DM11	Summary of Age Ranges	EudraCT	ETP, SAC
1.12.	SAFF_ALL	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	ETP, SAC
Prior and Concomitant Medications					
1.13.	SAFF_ALL	MH4	Summary of Current Medical Conditions	ICH E3	ETP, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.14.	SAFF_ALL	MH4	Summary of Past Medical Conditions	ICH E3	ETP, SAC
1.15.	SAFF_ALL	SP07	Summary of Family History of Cardiovascular Disorders at Screening		ETP, SAC
1.16.	SAFF_ALL	POP_T01	Summary of Disease Duration and Exacerbation History		ETP, SAC
1.17.	SAFF_ALL	SU1	Summary of Smoking History at Screening		ETP, SAC
1.18.	SAFF_ALL	CM1	Summary of Pre-treatment Non-Asthma Concomitant Medications	ICH E3	ETP, SAC
1.19.	SAFF_ALL	CM1	Summary of On-treatment Non-Asthma Concomitant Medications	ICH E3	ETP, SAC
1.20.	SAFF_ALL	CM1	Summary of Post-treatment Non-Asthma Concomitant Medications	ICH E3	ETP, SAC
1.21.	SAFF_ALL	CM1	Summary of On-treatment Asthma Concomitant Medications	ICH E3	ETP, SAC
1.22.	SAFF_ALL	CM1	Summary of Post-treatment Asthma Concomitant Medications	ICH E3	ETP, SAC
Pre-treatment Lung Function					
1.23.	SAFF_ALL	POP_T02	Summary of Screening Lung Function	Include Pre- and Post- albuterol (salbutamol) FEV_1, FVC, FEV_1/FVC and % Predicted Normal and post-BD at screening %predicted. Include overall and by treatment group.	ETP, SAC
1.24.	SAFF_ALL	POP_T03	Summary of Baseline Lung Function	FEV_1, FVC, FEV_1/FVC and % Predicted Normal. Include overall and by treatment group.	ETP, SAC
Exposure and Treatment Compliance					
1.25.	SAFF_ALL	EX1	Summary of Exposure and Compliance to Background Therapy (FP and SAL)	ICH E3	ETP, SAC

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
2.1.	SAFF_ALL	EX1	Summary of Exposure to Study Treatment	ICH E3	ETP, SAC
Primary Endpoint: Loss of Asthma Control Weeks 0-16					
2.2.	mITT_LoC	EFF_T01	Summary of Loss of Asthma Control	Include overall loss of control, each component and the combination of exacerbation or inability to titrate.	ETP, SAC
2.3.	mITT_LoC	EFF_T02	Summary of On-treatment Intercurrent Events		ETP, SAC
2.4.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-16 (Primary Estimand)		ETP, SAC
2.5.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-16 (Primary Estimand)		ETP, SAC
2.6.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-16 (Secondary Estimand)		ETP, SAC
2.7.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-16 (Secondary Estimand)		ETP, SAC
Secondary Endpoint: Loss of Asthma Control Weeks 0-6					
2.8.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-6 (Primary Estimand)		ETP, SAC
2.9.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-6 (Primary Estimand)		ETP, SAC
2.10.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-6 (Secondary Estimand)		ETP, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-6 (Secondary Estimand)		ETP, SAC
Secondary Endpoints: Time to Loss of Asthma Control					
2.12.	mITT_LoC	EFF_T05	Summary and Analysis of Time to Loss of Asthma Control (Primary Estimand)		ETP, SAC
2.13.	mITT_LoC	EFF_T05	Summary and Analysis of Time to Loss of Asthma Control (Secondary Estimand)		ETP, SAC
Secondary Endpoints: Hospitalisation and Emergency Room Visits					
2.14.	mITT	EFF_T06	Summary and Rate of Asthma-Related On-treatment Hospitalisations and Emergency Room Visits (Primary Estimand)		ETP, SAC
Secondary Endpoint: ACQ-5 and SGRQ					
2.15.	mITT	EFF_T07	Summary of Raw and Change from Baseline in ACQ-5 Total Score (Primary Estimand)		ETP, SAC
2.16.	mITT	EFF_T07	Summary of ACQ-5 Responders (Primary Estimand)		ETP, SAC
2.17.	mITT	EFF_T07	Summary of Raw and Change from Baseline in SGRQ Total Score (Primary Estimand)		ETP, SAC
2.18.	mITT	EFF_T07	Summary of SGRQ-Responders (Primary Estimand)		ETP, SAC
Secondary Endpoint: FEV1 and PEF					
2.19.	mITT	EFF_T07	Summary of Raw and Change from Baseline FEV_1 (Primary Estimand)		ETP, SAC
2.20.	mITT	EFF_T08	Analysis of Change from Baseline in FEV_1 up to Week 4(Primary Estimand)		ETP, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.21.	mITT	EFF_T07	Summary of Raw and Change from Baseline Fractional Exhaled Nitric Oxide (FeNO) (Primary Estimand)		ETP, SAC
2.22.	mITT	EFF_T08	Analysis of Change from Baseline in Fractional Exhaled Nitric Oxide (FeNO) up to Week 4 (Primary Estimand)		ETP, SAC
Secondary Endpoint: Exacerbations					
2.23.	mITT	EFF_T09	Summary of On-treatment Asthma Exacerbations		ETP, SAC
Secondary Endpoint: Eosinophils					
2.24.	mITT	EFF_T07	Summary of Raw and Change from Baseline in Eosinophils (Primary Estimand)		ETP, SAC
2.25.	mITT	EFF_T08	Analysis of Eosinophils up to Week 4 (Primary Estimand)		ETP, SAC
Secondary Endpoint: PEF, Daytime Symptom Score, Night-time Symptom Score and Rescue Medication					
2.26.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Morning Peak Expiratory Flow (PEF)		ETP, SAC
2.27.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Evening Peak Expiratory Flow (PEF)		ETP, SAC
2.28.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Daytime Asthma Symptom Score		ETP, SAC
2.29.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Night-Time Awakenings Due to Asthma Symptoms		ETP, SAC
2.30.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Rescue Medication use (Albuterol/Salbutamol)		ETP, SAC

12.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Endpoint: Loss of Asthma Control					
2.1.	mITT_LoC		Plot of Loss of Asthma Control Over Weeks 0-16 (Primary Estimand)	Include overall and components of loss on control	ETP, SAC
2.2.	mITT_LoC		Plot of Loss of Asthma Control Over Weeks 0-16 (Secondary Estimand)	Include overall and components of loss on control	ETP, SAC
2.3.	mITT_LoC		Cumulative Density Plot of the Posterior Distribution for Loss of Asthma Control Over Weeks 0-16 (Primary Estimand)		ETP, SAC
2.4.	mITT_LoC		Cumulative Density Plot of the Posterior Distribution for Loss of Asthma Control Over Weeks 0-16 (Secondary Estimand)		ETP, SAC
2.5.	mITT_LoC		Plot of Loss of Asthma Control Over Weeks 0-6 (Primary Estimand)	Include overall and components of loss on control	ETP, SAC
2.6.	mITT_LoC		Plot of Loss of Asthma Control Over Weeks 0-6 (Secondary Estimand)	Include overall and components of loss on control	ETP, SAC
2.7.	mITT_LoC		Cumulative Density Plot of the Posterior Distribution for Loss of Asthma Control Over Weeks 0-6 (Primary Estimand)		ETP, SAC
2.8.	mITT_LoC		Cumulative Density Plot of the Posterior Distribution for Loss of Asthma Control Over Weeks 0-6 (Secondary Estimand)		ETP, SAC
Secondary Endpoint: Time to Loss of Control					
2.9.	mITT_LoC		Kaplan-Meir Plot of Time to Loss of Asthma Control (Primary Estimand)		ETP, SAC
2.10.	mITT_LoC		Kaplan-Meir Plot of Time to Loss of Asthma Control (Secondary Estimand)		ETP, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Endpoint: Secondary Analysis of Loss of Asthma Control					
2.11.	mITT_LoC		Cumulative Density Plot of Eosinophils		ETP, SAC
2.12.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.13.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.14.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
2.15.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
2.16.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.17.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.18.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
2.19.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
2.20.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE by Treatment - Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.21.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.22.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
2.24.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.25.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.26.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
2.27.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
Secondary Endpoint: Exploratory Analysis of FEV1					
2.28.	mITT		FEV1 at Week 4 vs Eosinophils by Treatment – Fractional Polynomial Model		ETP, SAC
2.29.	mITT		FEV1 at Week 4 vs Eosinophils – Fractional Polynomial Treatment Difference		ETP, SAC
2.30.	mITT		FEV1 at Week 4 vs IgE by Treatment – Fractional Polynomial Model		ETP, SAC
2.31.	mITT		FEV1 at Week 4 vs IgE – Fractional Polynomial Treatment Difference		ETP, SAC
2.32.	mITT		FEV1 at Week 4 vs FeNO by Treatment – Fractional Polynomial Model		ETP, SAC
2.33.	mITT		FEV1 at Week 4 vs FeNO – Fractional Polynomial Treatment Difference		ETP, SAC

12.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	SAFF_ALL	SAFE_T01	Overview of On-treatment Adverse Events During the Study		ETP, SAC
3.2.	SAFF_ALL	AE1	Summary of All On-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.3.	SAFF_ALL	AE1	Summary of All Post-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.4.	SAFF_ALL	AE1	Summary of All On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.5.	SAFF_ALL	AE1	Summary of All On-treatment Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.6.	SAFF_ALL	AE1	Summary of All On-treatment Fatal Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.7.	SAFF_ALL	AE3	Summary of All On-treatment Common (>=3%) Adverse Events by Overall Frequency	ICH E3	ETP, SAC
3.8.	SAFF_ALL	AE1	Summary of All On-treatment Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.9.	SAFF_ALL	AE15	Summary of All On-treatment Common (>=3%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT	ETP, SAC
3.10.	SAFF_ALL	AE1	Summary of All Pre-treatment Serious Adverse Events by System Organ Class and Preferred Term		ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.11.	SAFF_ALL	AE1	Summary of All On-treatment Serious Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.12.	SAFF_ALL	AE1	Summary of All Post-treatment Serious Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.13.	SAFF_ALL	AE16	Summary of All On-treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	ETP, SAC
3.14.	SAFF_ALL	AE1	Summary of All On-treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	IDSL	ETP, SAC
3.15.	SAFF_ALL	AE1	Summary of All On-treatment Serious Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term	IDSL	ETP, SAC
Adverse Events of Special Interest (AESIs)					
3.16.	SAFF_ALL	AE1	Summary of On-treatment Adverse Events of Special Interest	IDSL	ETP, SAC
3.17.	SAFF_ALL	AE1	Summary of On-treatment Serious Adverse Events of Special Interest	IDSL	ETP, SAC
3.18.	SAFF_ALL	AE1	Summary of Post-treatment Adverse Events of Special Interest	IDSL	ETP, SAC
3.19.	SAFF_ALL	AE1	Summary of Post-treatment Serious Adverse Events of Special Interest	IDSL	ETP, SAC
Mexico Specific Tables					
3.20.	SAFF_ALL		Summary of Suspected Investigational Product Adverse Reaction (Mexican Participants Only)		ETP, SAC
3.21.	SAFF_ALL		Summary of Suspected Investigational Product Adverse Reaction (Non-Mexican Participants)		ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Chemistry					
3.22.	SAFF_ALL	LB1	Summary of Clinical Chemistry	ICH E3	ETP, SAC
3.23.	SAFF_ALL	LB1	Summary of Change from Baseline in Clinical Chemistry	ICH E3	ETP, SAC
3.24.	SAFF_ALL	LB16	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	ETP, SAC
Laboratory: Hematology and Cardiac Markers					
3.25.	SAFF_ALL	LB1	Summary of Hematology and Cardiac Markers	ICH E3	ETP, SAC
3.26.	SAFF_ALL	LB1	Summary of Changes from Baseline in Hematology and Cardiac Markers	ICH E3	ETP, SAC
3.27.	SAFF_ALL	LB16	Summary of Worst Case Hematology and Cardiac Markers Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	ETP, SAC
Laboratory: Hepatobiliary (Liver)					
3.28.	SAFF_ALL	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	ETP, SAC
3.29.	SAFF_ALL	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	ETP, SAC
ECG					
3.30.	SAFF_ALL		Summary of Antihistamine, Decongestant and Caffeine Use Prior to ECG assessments		ETP, SAC
3.31.	SAFF_ALL	EG1	Summary of ECG Findings	IDSL	ETP, SAC
3.32.	SAFF_ALL	EG2	Summary of ECG Values by Visit	IDSL	ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.33.	SAFF_ALL	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	ETP, SAC
3.34.	SAFF_ALL	EG10	Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	ETP, SAC
3.35.	SAFF_ALL	EG11	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	ETP, SAC
Holter					
3.36.	SAFF_ALL	HM1	Summary of Holter Interpretations	IDSL	ETP, SAC
3.37.	SAFF_ALL	HM2	Summary of Holter Abnormalities	IDSL	ETP, SAC
3.38.	SAFF_ALL	HM3	Summary of Holter Values	IDSL	ETP, SAC
3.39.	SAFF_ALL	HM3	Summary of Change from Baseline in Holter Values	IDSL	ETP, SAC
3.40.	SAFF_ALL	HM4	Summary of Subjects with R-on-T Beats	IDSL	ETP, SAC
Vital Signs					
3.41.	SAFF_ALL	VS1	Summary of Vital Signs	ICH E3	ETP, SAC
3.42.	SAFF_ALL	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	ETP, SAC
3.43.	SAFF_ALL	VS1	Summary of Change from Pre-dose to Post-dose in Vital Signs	ICH E3	ETP, SAC

12.10.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacokinetic					
4.1.	PK		Summary of PK Serum Concentrations of GSK3772847		SAC only
4.2.	PK		Summary of Incidence and Titres of Anti-GSK3772847 Antibodies		SAC only

12.10.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacodynamic					
6.1.	mITT		Summary of Raw and Percentage Change from Baseline in Free Soluble ST2 concentration (ug/L) (On-treatment)	Pre and Post dose.	ETP, SAC
6.2.	mITT		Analysis of Percentage Change from Baseline in Free Soluble ST2 concentration (ug/mL) (On-treatment)	Pre dose only.	ETP, SAC
6.3.	mITT		Summary of Raw and Percentage Change from Baseline in Free soluble ST2 concentration (ug/L) (Post-treatment)		ETP, SAC
6.4.	mITT		Analysis of Percentage Change from Baseline in Free soluble ST2 concentration (ug/mL) (Post-treatment)		ETP, SAC
6.5.	mITT		Summary of Raw and Percentage Change from Baseline in Total Soluble ST2 concentration (ug/L) (On-treatment)	Pre and Post dose.	ETP, SAC
6.6.	mITT		Analysis of Percentage Change from Baseline in Total Soluble ST2 concentration (ug/L) (On-treatment)	Pre dose only.	ETP, SAC
6.7.	mITT		Summary of Raw and Percentage Change from Baseline in Total Soluble ST2 concentration (ug/L) (Post-treatment)		ETP, SAC
6.8.	mITT		Analysis of Percentage Change from Baseline in Total Soluble ST2 concentration (ug/L) (Post-treatment)		ETP, SAC
Exploratory: Biomarkers					
6.9.	mITT		Summary and Change from Baseline in Induced Sputum Biomarkers (subset) at Weeks 8 and 16	Include geometric mean and %CV	ETP, SAC
6.10.	mITT		Summary and Change from Baseline in Exploratory Serum Markers at Weeks 8 and 16	Include geometric mean and %CV	ETP, SAC

12.10.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacokinetic					
6.1.	PK		Plot of Serum Concentrations of GSK3772847 over Time		ETP, SAC
6.2.	PK		Pre-dose Trough Concentration of GSK3772847 vs Eosinophils at Week 4		ETP, SAC
6.3.	PK		Pre-dose Trough Concentration of GSK3772847 vs FeNO at Week 4		ETP, SAC
6.4.	PK		Pre-dose Trough Concentration of GSK3772847 vs IgE at Week 4		ETP, SAC

12.10.11. Pharmacodynamic and Biomarker Figures

Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacodynamic					
6.5.	mITT		Plot of Percentage Change from Baseline in Free Soluble ST2 levels (On-treatment)		ETP, SAC
6.6.	mITT		Plot of Percentage Change from Baseline in Free soluble ST2 levels (Post-treatment)		ETP, SAC
6.7.	mITT		Plot of Percentage Change from Baseline in Total Soluble ST2 levels (On-treatment)		ETP, SAC
6.8.	mITT		Plot of Percentage Change from Baseline in Total Soluble ST2 levels (Post-treatment)		ETP, SAC
6.9.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Free soluble ST2 by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
6.10.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Free soluble ST2 Treatment Difference – Fractional Polynomial (Primary Estimand)		ETP, SAC
6.11.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Free soluble ST2 by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
6.12.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Free soluble ST2 Treatment Difference – Fractional Polynomial (Secondary Estimand)		ETP, SAC

12.10.12. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen and Run-in Failure	Journal Guidelines	ETP, SAC
2.	SAFF_ALL	ES2 / ES3	Listing of Reasons for Study Withdrawal	ICH E3	ETP, SAC
3.	SAFF_ALL	SD2/SD3	Listing of Reasons for Study Treatment Discontinuation	ICH E3	ETP, SAC
4.	SAFF_ALL	BL1 / BL2	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	ETP, SAC
5.	SAFF_ALL	TA1 / CP_RD1x	Listing of Planned and Actual Treatments	IDSL	ETP, SAC
Protocol Deviations					
6.	SAFF_ALL	DV2	Listing of Important Protocol Deviations	ICH E3	ETP, SAC
7.	SAFF_ALL	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	ETP, SAC
Populations Analysed					
8.	SAFF_ALL		Listing of Participants Excluded from Any Population (GCP non compliance)	ICH E3.	ETP, SAC
Demographic and Baseline Characteristics					
9.	SAFF_ALL	DM2	Listing of Demographic Characteristics	ICH E3	ETP, SAC
10.	SAFF_ALL	DM9	Listing of Race	ICH E3	ETP, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
11.	SAFF_ALL	CP_CM3	Listing of Concomitant Medications	IDSL	ETP, SAC
Exposure and Treatment Compliance					
12.	SAFF_ALL	EX3	Listing of Exposure Data	ICH E3	ETP, SAC
Adverse Events					
13.	SAFF_ALL	AE8	Listing of All Adverse Events	ICH E3	ETP, SAC
14.	SAFF_ALL	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	ETP, SAC
15.	SAFF_ALL	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	ETP, SAC
16.	SAFF_ALL	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	ETP, SAC
Serious and Other Significant Adverse Events					
17.	SAFF_ALL	AE8	Listing of Fatal Serious Adverse Events	ICH E3	ETP, SAC
18.	SAFF_ALL	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	ETP, SAC
19.	SAFF_ALL	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	ETP, SAC
20.	SAFF_ALL	AE8	Listing of Serious Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	ETP, SAC
21.	SAFF_ALL	AE8	Listing of Adverse Events of Special Interest	ICH E3	ETP, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hepatobiliary (Liver)					
22.	SAFF_ALL	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	ETP, SAC
23.	SAFF_ALL	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	ETP, SAC
All Laboratory					
24.	SAFF_ALL	LB5 / LB6	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3	ETP, SAC
25.	SAFF_ALL	LB14	Listing of Laboratory Data with Character Results	ICH E3	ETP, SAC
ECG					
26.	SAFF_ALL	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	ETP, SAC
27.	SAFF_ALL	EG5	Listing of Abnormal ECG Findings	IDSL	ETP, SAC
Holter					
28.	SAFF_ALL	MH6	Listing of Holter R-on-T Beat Data	IDSL	ETP, SAC
29.	SAFF_ALL	MH7	Listing of Holter {Supraventricular} {Ventricular} Event Data	IDSL, Update title as appropriate based on data	ETP, SAC
30.	SAFF_ALL	MH8	Listing of Holter {Sustained} {Non-sustained} {Supraventricular} {Ventricular} Run	IDSL, Update title as appropriate based on data	ETP, SAC
31.	SAFF_ALL	MH9	Listing of Holter Atrial {Fibrillation} {Flutter} Data	IDSL, Update title as appropriate based on data	ETP, SAC
32.	SAFF_ALL	MH10	Listing of Holter Abnormalities	IDSL	ETP, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
33.	SAFF_ALL	VS4	Listing of All Vital Signs Data	IDSL	ETP, SAC
Primary Analysis Data: Loss of Asthma Control and Intercurrent Events					
34.	mITT_LoC		Listing of Loss of Asthma Control	Include all reasons for loss of control and time to loss of asthma control	ETP, SAC
35.	mITT_LoC		Listing of Intercurrent Events	Include treatment subject was analysed as taking and treatment at time of loss of control	ETP, SAC

12.10.13. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
36.	SAFF_ALL	SP2	Listing of the Follow-up Contact		ETP, SAC
37.	SAFF_ALL	TA1	Listing of Treatment Misallocations	Change Centre ID to Investigator ID: xxxxxx and also Investigator at Centre: xxxxxx	ETP, SAC
38.	SAFF_ALL	SP4	Listing of Overall Percentage Treatment Compliance		ETP, SAC
Secondary Efficacy					
39.	mITT		Listing of Eosinophils	Include randomisation and analysis strata	ETP, SAC
40.	mITT	SP10	Listing of Lung Function Results at Screening		ETP, SAC
41.	mITT	SP10	Listing of Lung Function Results post-Screening		ETP, SAC
42.	mITT	S3	Listing of Asthma Exacerbations	Include a column for severity	ETP, SAC
43.	mITT		Listing of Asthma Control Questionnaire (ACQ-5)		ETP, SAC
44.	mITT		Listing of St George's Respiratory Questionnaire (SGRQ)		ETP, SAC
45.	mITT		Listing of Peak Exploratory Flow (PEF)		ETP, SAC
46.	mITT		Listing of Fractional Exhaled Nitric Oxide (FeNO)		ETP, SAC
47.	mITT		Listing of Daytime and Night-time Asthma Symptoms		ETP, SAC
48.	mITT		Listing of Rescue Medication Use		ETP, SAC
49.	mITT		Listing of Hospitalisations and Emergency Room Visits		ETP, SAC
50.	PK		Listing of Serum GSK3772847 Concentration		SAC Only

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
51.	mITT		List of Free and Total Soluble ST2 Concentrations		
Adverse Events					
52.	SAFF_ALL		Listing of Clinical Chemistry		ETP, SAC
53.	SAFF_ALL		Listing of Haematology and Cardiac Markers		ETP, SAC
54.	SAFF_ALL		Listing of Anti-GSK3772847 Antibodies		ETP, SAC
55.	SAFF_ALL	ESI8	Listing of AE Terms of Special Interest	IDSL	ETP, SAC
Exploratory Biomarker					
56.	mITT		Listing of Induced Sputum and Exploratory Serum Biomarkers		ETP, SAC
Medical History					
57.	SAFF_ALL	MH2	Listing of Medical Conditions at Screening		ETP, SAC
58.	SAFF_ALL	SP5	Listing of Family History of Cardiovascular Disorders		ETP, SAC
59.	SAFF_ALL	SP6	Listing of Asthma History		ETP, SAC
60.	SAFF_ALL	SP7	Listing of Smoking History and Smoking Status		ETP, SAC
61.	SAFF_ALL	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text		ETP, SAC
Liver Events: Note only produced if there is a Liver Event					
62.	SAFF_ALL	LIVER5	Listing of Liver Events		ETP, SAC
63.	SAFF_ALL	LIVER6	Listing of Liver Event Information for RUCAM Score		ETP, SAC
64.	SAFF_ALL	LIVER7	Listing of Liver Biopsy		ETP, SAC

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
65.	SAFF_ALL	LIVER8	Listing of Liver Imaging Details		ETP, SAC
Cardiovascular Events: Note only produced if there is a Cardiovascular Event					
66.	SAFF_ALL	Patient Profile	Listing of Myocardial infarction/unstable angina		ETP, SAC
67.	SAFF_ALL	Patient Profile	Listing of Congestive heart failure		ETP, SAC
68.	SAFF_ALL	Patient Profile	Listing of Arrhythmias		ETP, SAC
69.	SAFF_ALL	Patient Profile	Listing of Valvulopathy		ETP, SAC
70.	SAFF_ALL	Patient Profile	Listing of Pulmonary hypertension		ETP, SAC
71.	SAFF_ALL	Patient Profile	Listing of Cerebrovascular events/stroke and transient ischemic attack		
72.	SAFF_ALL	Patient Profile	Listing of Peripheral arterial thromboembolism		
73.	SAFF_ALL	Patient Profile	Listing of Deep venous thrombosis/pulmonary embolism		
74.	SAFF_ALL	Patient Profile	Listing of Revascularisation		
75.	SAFF_ALL	Patient Profile	Listing of Deaths		

12.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request.

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

Title	:	GSK3772847
Compound Number	:	Reporting and Analysis Plan for a randomised, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma.
Effective Date	:	20-DEC-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 2017N311825_02.
- This RAP is intended to describe the Efficacy, Safety, PK, PD and Biomarker analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the End of Treatment Phase (ETP) and Statistical Analysis Complete (SAC) deliverable.
- This study does have an internal safety review committee (iSRC) and all details of iSRC deliverable are documented in a separate iSRC RAP.

Author's Name and Functional Area:

Approver	Date
PPD Principal Statistician (Respiratory, Clinical Statistics)	27-NOV-2018

RAP Team Review Confirmations
(Method: E-mail)

Reviewer	Date
PPD Clinical Investigation Lead (Respiratory, HUP Clinical Development)	27-NOV-2018
PPD Principal Programmer (Respiratory, Clinical Programming)	27-NOV-2018
PPD Clinical Development Physician (Respiratory, MDC Global Clinical)	27-NOV-2018
PPD Scientist (Respiratory, Value Evidence and Outcomes)	19-DEC-2018
PPD Director (Respiratory, Value Evidence and Outcomes)	29-NOV-2018
PPD Senior Director (Respiratory, Clinical Pharmacology Modelling and Simulation)	27-NOV-2018
PPD Director of Clinical Development (Respiratory, MDC Global Clinical)	18-DEC-2018
PPD Senior Scientific Director (Respiratory, RD AI DPU Head)	18-DEC-2018

Clinical Statistics & Clinical Programming Line Approvals
(Method: Pharma TMF eSignature)

Approver	Date
PPD Senior Statistics Director (Respiratory, Clinical Statistics)	20-DEC-2018
PPD Programming Manger (Respiratory, Clinical Programming)	20-DEC-2018

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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 207597:

Protocol Revision Chronology:		
2017N311825_00	2017-MAR-06	Original
2017N311825_01	2017-JUN-02	To address clarifications regarding the aim of the study, the eligibility criteria, the schedule of activities, the clinical assessments, and the recording of lab data and adverse events. The benefit: risk section was also updated based on the Part 2 results from study CNTO7160ASH1001. Also, a few typographical errors were corrected.
2017N311825_02	2017-SEP-13	To add more information on the risk: benefit section and the study design justification sections. To address clarifications regarding the unblinding of treatment in case of emergency. To clarify that rechallenge is not allowed once the treatment discontinuation criteria are met. Also, a few typographical errors were corrected.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	**Reporting & Analysis Plan**	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Modified Intent to Treat population.	Modified Intent to Treat (Loss of Control), Modified Intent to Treat and Safety excluding GCP non-compliant subjects populations.	The Modified Intent to Treat (Loss of Control) was added to account for the intercurrent event when participants receive the wrong study treatment. Whilst the data from GCP non-compliant participants should not be used in the efficacy analysis, the participants were dosed with GSK3772847 or Placebo so all safety data (AEs, SAEs, ECGs etc.) should be reported.
Section 10.4.1 of the protocol describes a sensitivity analysis	A primary and secondary estimand have been defined to	The protocol was approved before the ICH E9 addendum on

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
where data is analysed as missing and worst case (loss of control) for participants who withdraw from the study for reasons other than loss of asthma control.	capture where data is analysed as missing and worst case (loss of control) for various intercurrent events where participants withdraw from the study for reasons other than loss of asthma control.	estimands. The RAP is performing the same planned analysis as detailed in the Protocol however the terminology has been updated in accordance with ICH E9.
Statistical analysis would be performed for each screening eosinophil strata separately.	Bayesian analysis will include screening eosinophil strata as a covariate instead of performing split analysis models. In addition, an exploratory analysis using fractional polynomials was added to examine the relationship between loss of control and screening eosinophils (continuous), IgE and FeNO.	Bayesian analysis will now include the same covariates as the frequentist analysis. By modelling eosinophils as a continuous endpoint, it will provide more information on the impact of varying screening eosinophil levels on the treatment effect. It will also provide additional information on the role of IgE and FeNO on loss of asthma control.
Mixed model repeated measures will be used to analyse the following endpoints. The baseline value of each endpoint will be included along with baseline*visit and treatment*visit interactions. Treatment differences, 95% confidence intervals and p-values will be presented. • Change from baseline in ACQ-5 absolute score • Change from baseline in SGRQ total score • Change from baseline in Pre-bronchodilator FEV_1 • Change from baseline in FeNO	FEV_1 and FeNO will only be analysed up until Week 4 (down titration of ICS), all data post Week 4 will be summarised descriptively only. In addition, an exploratory analysis using fractional polynomials was added to examine the relationship between FEV_1 at Week 4 with screening eosinophils (continuous), IgE and FeNO. Continuous ACQ-5 and SGRQ will only be summarised and will not be analysed. Responder analysis will still be performed. This will not impact any of the responder analysis in the primary or secondary endpoints.	FEV_1 and FeNO are impacted by ICS, so including change from baseline post-down titration of ICS would be confounding change due to study treatment with change due to ICS. To better explore the data prior to down titration, the fractional polynomial analysis has been added to examine the relationship between FEV_1 at Week 4 with screening eosinophils (continuous), IgE and FeNO. FEV1, FeNO, ACQ-5 and SGRQ analysed using an MMRM would be assuming that data is missing at random. In fact, participants could have withdrawn due to loss of asthma control which is related to study treatment, so the analysis assumptions would not have been valid.
Secondary endpoints listed as: • Serum concentrations of GSK3772847 at weeks 2, 4, 8, 12, 16, 20, 24 and 28. • Free and total soluble ST2 levels	Secondary endpoints listed as: • Serum concentrations of GSK3772847 by nominal time. • Free and total soluble ST2	Endpoint updated to use nominal time so that all data collected is summarised.

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
at weeks 2, 4, 8, 12, 16, 20, 24 and 28.	levels in serum by nominal time.	
Proportion of participants with loss of asthma control assessed over Weeks 0-16 only.	Proportion of participants with loss of asthma control assessed over Weeks 0-16 and over Weeks 0-6.	An additional endpoint assessing loss of control between Weeks 0 and 6 was added to help support the time to loss of asthma control analysis.

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

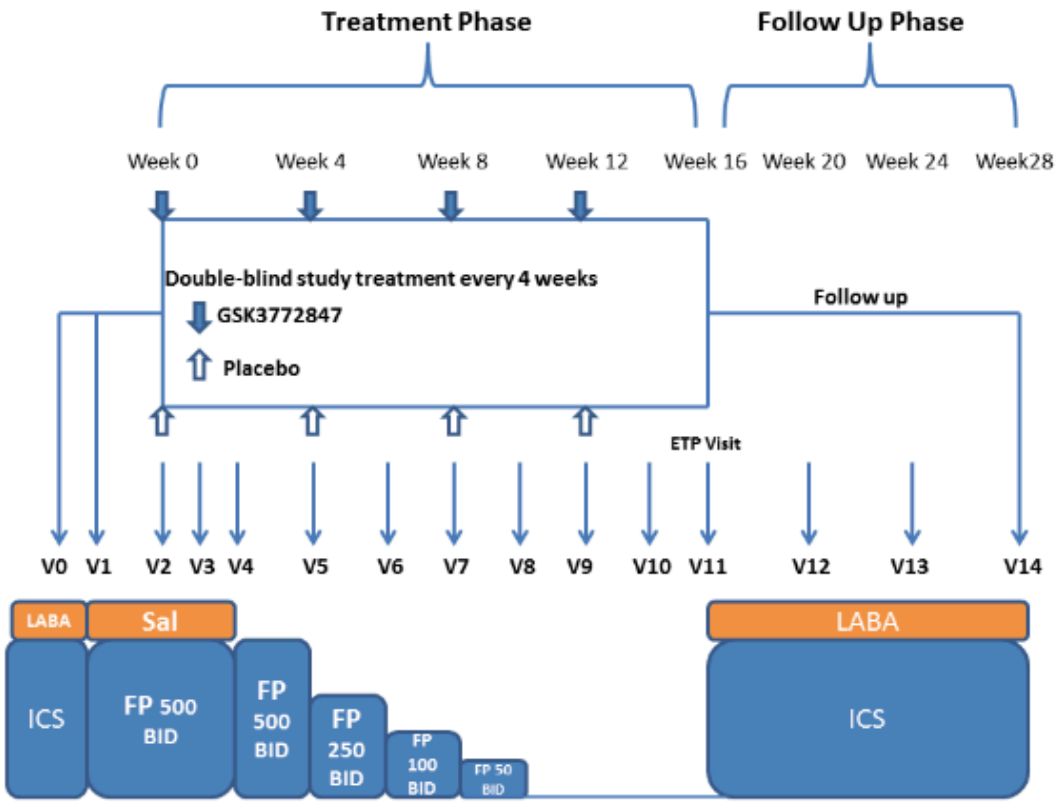
Objectives	Endpoints
Primary	
• To evaluate the efficacy of GSK3772847, compared with placebo, administered intravenously every 4 weeks for 12 weeks (Week 0 – Week 12, 4 doses in total) in participants with moderately severe asthma.	Primary – Proportion of participants with loss of asthma control over Weeks 0-16 where 'loss of asthma control' is defined as at least one of the following: • Asthma Control Questionnaire (ACQ-5) score increase from baseline (measured at the end of Run-in) ≥ 0.5 point or • Pre-bronchodilator Forced expiratory volume in 1 second (FEV1) decrease from baseline (measured at the end of Run-in) >7.5 % or • Inability to titrate inhaled corticosteroid according to the pre-defined schedule or • A clinically significant asthma exacerbation (requiring oral corticosteroid [OCS] and/or hospitalisation).
Secondary	
• To evaluate other aspects of efficacy of GSK3772847 compared with placebo in participants with moderately severe asthma.	Other efficacy endpoints (at or by Week 16): • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • Proportion of participants with loss of asthma control over Weeks 0-6 • Time to loss of asthma control. • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule • The incidence, mean rate, and total number per participant of hospitalisations or Emergency Room (ER) visits during the study treatment period.

Objectives	Endpoints
	• Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16. • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16. • Change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16. • Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF over each four weeks of the 16 week treatment period. • Change from baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period. • Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period. • Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the16 week treatment period. • Change from baseline in fractional exhaled nitric oxide (FeNO) at each week measured.
• To evaluate the safety and tolerability of GSK3772847, compared with placebo administered intravenously every 4 weeks for 12 weeks (Week 0-12, 4 doses in total) in participants with moderately severe asthma.	• Incidence and frequency of adverse events (AEs) and serious adverse events (SAEs). • Change from baseline in vital signs at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28. • Change between post-dose and pre-dose in vital signs at weeks 0, 4, 8 and 12. • Change from baseline in 12-lead electrocardiogram (ECG) measurements at weeks 4, 8, 12 and 16. • Change between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12. • Change from baseline in 24 hours Holter

Objectives	Endpoints
	measurements at weeks 4 and 12. • Change from baseline in clinical chemistry at weeks 2, 4, 8, 12, 16 and 28. • Change from baseline in haematology and cardiac markers at weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28. • Incidence of and titres of anti- GSK3772847 antibodies at weeks 2, 4, 8, 12, 16, 20, 24 and 28.
• To evaluate the pharmacokinetics (PK) of GSK3772847 in participants with moderately severe asthma.	• Serum concentrations of GSK3772847 by nominal time.
• To evaluate the pharmacodynamics (PD) of GSK3772847 in participants with moderately severe asthma.	• Free and total soluble ST2 levels in serum by nominal time.
Exploratory	
• To compare the effect of GSK3772847 with placebo on biomarkers in serum and sputum.	• Changes from baseline in induced sputum biomarkers (subset) at weeks 8 and 16. • Changes from baseline in exploratory serum markers at weeks 8 and 16.

2.3. Study Design

Overview of Study Design and Key Features



Design Features	• The study is a Phase IIa, multicenter, randomised, placebo-controlled, double-blind, stratified, parallel group study.
Dosing	• Participants will have a two-week Run-in period in which they take a background therapy of fluticasone propionate (FP)/salmeterol 500/50 mcg BID. • Following run-in they will be randomised to receive four doses of either GSK3772847 or Placebo intravenously (Week 0, 4, 8 and 12) whilst initially still receiving background FP/Salmeterol 500/50 mcg BID. • At Week 2 background therapy will be changed to FP 500 mcg BID only. This will then be reduced by approximately 50 % every two weeks until complete FP discontinuation at Week 10.
Treatment Assignment	• Participants will be randomised in a 1:1 ratio to receive four doses of either GSK3772847 or Placebo administered intravenously every 4 weeks. • Randomisation will be stratified based on participants' baseline peripheral blood eosinophil count which is measured at screening (<150 cells/µL, >=150 cells/µL), Randomisation will also be stratified according to whether participants consent to the sputum sub study.

Overview of Study Design and Key Features	
Interim Analysis	• The End of Treatment Phase Analysis will take place after all subjects have completed the week 16 visit, and will be considered an interim analysis for both efficacy and safety. There will be no modifications to dosing regimens, sample size or any other aspects of the trial based on this data, as all study assessments, apart from follow-up, will have already been completed.

2.4. Statistical Hypotheses

The primary null hypothesis (H_0) for this study is that the ratio of the proportions of subjects with loss of asthma control from randomisation to Week 16 between GSK3772847 and placebo is unity.

$$H_0: \frac{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ on\ GSK3772847}{Proportion\ with\ loss\ of\ asthma\ control\ \ at\ Week\ 16\ on\ Placebo} = 1$$

The alternative hypothesis (H_1) for this study is that the ratio of the proportions of subjects with loss of asthma control from randomisation to Week 16 between GSK3772847 and placebo is not unity.

$$H_1: \frac{Proportion\ with\ loss\ of\ asthma\ control\ at\ Week\ 16\ \ on\ GSK3772847}{Proportion\ with\ loss\ of\ asthma\ control\ \ at\ Week\ 16\ on\ Placebo} \neq 1$$

3. PLANNED ANALYSES

3.1. End of Treatment Phase Analyses

The End of Treatment Phase Analysis will be performed after the completion of the following sequential steps:

1. All subjects have completed the Week 16 visit or the Early Withdrawal visit
2. All required database cleaning activities have been completed and database release has been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to RandAll NG procedures.

Due to an inability to lock log forms used for collection of exacerbation data, the end of treatment phase analysis will be considered an interim analysis for both efficacy and safety. Any safety data collected for participants who have completed clinic visits after Week 16 will also be cleaned and included in the analysis.

All participants will have completed the active treatment phase of the study by the time of the interim, so no modifications will be made to the study as a result of the End of Treatment Phase Analysis. The Final Analysis is intended to be an analysis of safety data collected in the Post-Treatment Follow-Up phase.

The sponsor will be unblinded to the results of the analysis.

3.2. Final Analyses

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

- All subjects have completed the study.
- All required database cleaning activities for data after Week 16/ Early Withdrawal as well as data collected on log pages have been completed.
- Final database release and database freeze has been declared by Data Management.

No unblinding will take place as part of the final analysis as all participants will have already been unblinded during the End of Treatment Phase Analysis.

4. ANALYSIS POPULATIONS

Some participants are being excluded from the efficacy analyses due to a failure at their site to follow GCP. As these participants received GSK3772847 or placebo during their period of participation, all safety data will be reported.

Population	Definition / Criteria	Analyses Evaluated
Enrolled	• The All Subjects Enrolled (ASE) population will consist of all participants who sign the ICF.	•Study population •Reason for withdrawal prior to randomisation
Randomised	• The randomised population will consist of all participants who were randomised. A participant who is recorded as a screen or run-in failure and also randomised will be considered to be randomised in error provided they have not performed any study assessments.	•No formal analysis will be performed on this population
Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control)	• The Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control) (mITT_LoC) will consist of all randomised participants who take at least 1 dose of study treatment, excluding participants where an investigation by GSK has shown that good clinical practice has not been followed. Any participants excluded from this population will	•Efficacy (loss of control)

Population	Definition / Criteria	Analyses Evaluated
	be identified as protocol deviations and listed in a separate output. Participants will be analysed according to the treatment they receive >=50% of the time. If the participant receives 50% of each treatment they will be analysed according to the randomised treatment. For loss of asthma control, participants will be analysed according to the treatment they were receiving at the time of loss of control.	
Modified Intent-to-Treat excluding GCP non-compliant subjects	• The Modified Intent-to-Treat excluding GCP non-compliant subjects (mITT) population will consist of all randomised participants who take at least 1 dose of study treatment, excluding participants where an investigation by GSK has shown that good clinical practice has not been followed. Any participants excluded from this population will be identified as protocol deviations and listed in a separate output. Participants will be analysed according to the treatment they receive >=50% of the time. If the participant receives 50% of each treatment they will be analysed according to the randomised treatment.	•Efficacy (all except loss of control)
Safety including GCP non-compliant subjects	• The Safety (SAFF_ALL) population will consist of all randomised participants who take at least 1 dose of study treatment. Participant will be analysed according to the treatment they receive >=50% of the time. If the participant receives 50% of each treatment they will be analysed according to the randomised treatment.	•Study population •Inclusion, exclusion and randomisation criteria deviations •Participant disposition •Safety
Pharmacokinetic	• The PK population will consist of all randomised participants who received at least one dose of study medication, and for whom at least one pharmacokinetic sample was obtained, analysed and was measurable.	•PK

NOTES :

1. Please refer to Appendix 10: List of Data Displays which details the population to be used for each display being generated.
2. If a participant is inadvertently given both study treatments they will be analysed according to the treatment that they received the more frequently.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan [21-Aug-2017 (Version 1) or later].

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

Note: Inclusion and exclusion criteria deviations are always reported as important.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order [1]
G	GSK3772847 10 mg/kg	GSK3772847	2
P	Placebo	Placebo	1

NOTES:

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

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

- GSK3772847 vs Placebo

There were four strata used for the randomisation depending on the participants baseline blood eosinophil count and whether they consented to the sputum sub-study:

- Sputum sub-study and baseline blood eosinophils < 150 cells/µL
- Sputum sub-study and baseline blood eosinophils >=150 cells/µL
- Not sputum sub-study and baseline blood eosinophils < 150 cells/µL
- Not sputum sub-study and baseline blood eosinophils >=150 cells/µL

Displays will be presented by combining data across all four strata to give the overall estimate of GSK3772847 versus placebo.

Sputum sub-study will not be accounted for within the statistical analysis as the sputum sub-study strata was for monitoring recruitment only.
An additional exploratory analysis using fractional polynomials has been added to further investigate the relationship between loss of control and screening eosinophils and summary statistics on eosinophils will also be provided.

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.

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Pre-Screening	Screen Run-in	Day 1 (Pre-Dose)	
Loss of Asthma Control				
Pre-bronchodilator Forced expiratory volume in 1 second (FEV_1)		X	X	Day 1
Asthma Control Questionnaire (ACQ-5) score		X	X	Day 1
Other Patient Reported Outcomes				
St. George's Respiratory Questionnaire (SGRQ)			X	Day 1
Peak Expiratory Flow (PEF)				
Mean morning peak expiratory flow (PEF)		X	X	Run-in [1]
Mean evening peak expiratory flow (PEF)		X	X	Run-in [1]
Fractional Exhaled Nitric Oxide (FeNO)				
Fractional Exhaled Nitric Oxide (FeNO)			X	Day 1
Symptom Scores				
Mean daytime asthma symptom score		X	X	Run-in [1]
Night-time awakenings due to asthma symptoms requiring rescue medication		X	X	Run-in [1]

Parameter	Study Assessments Considered As Baseline			Baseline Used in Data Display
	Pre-Screening	Screen Run-in	Day 1 (Pre-Dose)	
Rescue Medication				
Rescue medication use		X	X	Run-in [1]
Mean number of inhalations per day over each four weeks		X	X	Run-in [1]
Safety				
Vital Signs		X	X	Day 1
12-lead Electrocardiogram (ECG) measurements		X	X	Day 1
24 hours Holter measurements		X		Screen/Run in
Clinical laboratory tests (haematology and chemistry)		X	X	Day 1
Biomarkers				
Induced sputum biomarkers			X	Day 1
Serum biomarkers			X	Day 1
Exploratory serum markers			X	Day 1

NOTES :

- Unless otherwise stated, the mean of replicate assessments at any given time point will be used as the value for that time point.
- [1] Mean over the last 7 days of the run-in period prior to V2. Participants must have at least 4 full days of data (morning and evening) in the last 7 days of run-in to be eligible.

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by investigative site, country, and regions.

Region	Countries
North America	United States, Canada
Latin America	Mexico
Eastern Europe	Ukraine, Russian Federation
Oceania	Australia

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

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

Category	Covariates
Screening eosinophils	At randomisation participants are stratified according to their baseline peripheral blood eosinophil. Screening eosinophils will be included in both primary and secondary analysis as a categorical variable (<150 cells/µL, >=150 cells/µL). An additional exploratory analysis of the primary endpoint using continuous eosinophils will also be examined. If the analysis models are unable to converge due to low number of participants with baseline blood eosinophils <150 cells/µL, then screening eosinophil will be re-categorised according to a cut point of 300 cells/µL instead i.e. <300 cells/µL and >=300 cells/µL

5.5. Multiple Comparisons and Multiplicity

As there is a single primary treatment comparison, no adjustment is required for primary comparisons. No adjustments will be made for multiplicity for other endpoints.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

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

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Safety Population including GCP non-compliant subjects population (SAFF_ALL), unless specified to be on the All Subjects Enrolled (ASE) population.

Study population analyses including analyses of subject'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 10: List of Data Displays.

6.2. Disposition

The study population summary will use the All Subjects Enrolled (ASE) population and show the number of subjects overall who were enrolled, the number of screen failures and the number with each reason for screen failure. It will also show the number of subjects who were randomised and who were in the modified Intent-to-treat (Loss of Control), modified Intent-to-treat, Safety including GCP non-compliant subjects, and PK populations.

For the Safety including GCP non-compliant subjects, reasons for withdrawal summary will show the number and percentage of subjects who completed the study, who withdrew prematurely from the study and who reported each primary and sub-reason for withdrawal.

6.3. Medical Conditions

The number and percentage of subjects reporting each current medical condition will be presented. This table will include a subheading of 'Cardiovascular Risk Factors,' which will summarise the information taken from the cardiac disorders page in the eCRF. All medical conditions must be summarised on this table regardless of frequency. This will be repeated for past medical conditions.

6.4. Concomitant Medications

Non-Asthma medications will be summarised by Anatomical-Therapeutic-Chemical (ATC) level 1 and ingredient. Asthma medications will be summarised by the latest version of the Respiratory Medication Class (RMC), and will be derived for each asthma concomitant medication. Multi-ingredient medications will be presented according to their combination ATC classification rather than the classifications of the ingredients.

Asthma and non-asthma medications will be listed separately. A listing of the relationship between ATC Level 1, ingredient and verbatim text will be produced for non-asthma medications only.

7. EFFICACY ANALYSES

7.1. Primary Efficacy Analyses

7.1.1. Endpoint

- Proportion of participants with loss of asthma control over Weeks 0-16
- Proportion of participants with loss of asthma control over Weeks 0-6 (Secondary)

7.1.2. Summary Measure

Bayesian Method (Primary): The posterior probabilities that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.5 and 0.2 (i.e. a 0%, 25%, 50% and 80% reduction).

Frequentist Method (Supportive): Odds Ratio. The odds of having experienced loss of asthma control on GSK3772847 compared to the odds of having experienced loss of asthma control on placebo.

7.1.3. Population of Interest

The primary efficacy analyses will be based on the modified Intent to Treat (Loss of Control) population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Intercurrent Event	Primary Estimand	Secondary Estimand
Treatment discontinuation due to AE/SAE (not related to loss of asthma control)	Set to missing.	●If the AE/SAE was deemed related to IP then set as an event (i.e. worst case scenario). ●If the AE/SAE was not deemed related to IP then set to missing.
Death	Set to missing.	●If the death was deemed related to IP then set as an event (i.e. worst case scenario). ●If the death was not deemed related to IP then set to missing.
Prohibited/ Concomitant medications that could impact patients' asthma control	Use data as is.	Set as an event (i.e. worst case scenario).
Non-compliance with FP/SAL, FP or study titration	Use data as is.	Set as an event (i.e. worst case scenario).
Continuation in the study after LOC criteria met	Use information from first loss of asthma control.	Use information from first loss of asthma control.

Note:
- Identification of whether an event (AE/SAE/Death) is considered related to IP will be identified

using the investigator tick box collected on the eCRF. • If the intercurrent event occurs after loss of asthma control then all information on loss of asthma control will be used. • Prohibited/ concomitant medications will be identified as protocol deviations within the prohibited/ concomitant medications category and will have text that start with "LoAC" • Non-compliance FP/SAL, FP or study titration will be identified as compliance <80%, compliance ≥ 120% or not changing from FP/SAL or FP doses according to the predetermined schedule.

If any of the following intercurrent events occurs, then all data will be accepted:

- Pregnancy
  Accidental unblinding

Whilst it's possible that site staff were unable to administer study drug as they were unable to find a suitable vein, the team felt this would not be caused by the randomised study treatment and the visit would be rescheduled. Therefore, if this occurs all data will be accepted and treated as any other out of window assessment.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: 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
• Proportion of participants with loss of asthma control over Weeks 0-16 • Proportion of participants with loss of asthma control over Weeks 0-6 (Secondary)
Model Specification
• The primary endpoint proportion of subjects with loss of asthma control will be analysed for the Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control) population using both Bayesian (primary) and Frequentist (supportive) methods. Bayesian Method (Primary): • Proc MCMC will be used in order to gain the posterior distribution of the study data combined with a non-information beta(1,1) prior, and screening eosinophil strata included as a covariate. Note: This prior is equivalent to one event on both GSK3772847 and Placebo treatment arms. • Three MCMC chains should be run, with all parameters in the model being assessed for convergence. Each chain will have 10,000 simulations (using a burn-in of 500) and will start with a set seed of 207597 to enable comparison between the main and qc. • The posterior probabilities that the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo is less than 1.0, 0.75, 0.5 and 0.2 (i.e. a 0%, 25%, 50% and 80% reduction) will be calculated along with the estimated ratio and associated 95%

credible interval. The 95% credible interval will use the highest posterior density where possible, and if this isn't possible then the 2.5% and 97.5% credible intervals will be reported.
- The posterior median and standard deviation will also be reported together with a 95% credible interval.
- In addition to summary tables a plot of the posterior distribution for the ratio of the proportion of subjects with loss of asthma control on GSK3772847 compared with placebo, along with the proportion of subjects with loss of asthma control on GSK3772847 and placebo separately will be generated.
- This analysis will be repeated for loss of asthma control between Weeks 0 and 6.

Frequentist Method (Supportive):
- The proportion of participants with loss of asthma control will be analysed using logistic regression allowing for screening eosinophils strata. It will include fixed effects terms for treatment and screening eosinophil strata.

Fractional Polynomials (Exploratory Analysis for Loss of Control Over Weeks 0-16):
- Screening blood eosinophil count will be transformed using a fractional polynomial term which will be included in the model as a continuous covariate. A treatment group by eosinophil covariate interaction will also be included in the model to allow the magnitude of the interaction (but not the order of the fractional polynomial transformation) to differ with each treatment group). The best fitting model will be selected based on likelihood. The selected best fitting model will be plotted as continuous eosinophil count versus loss of asthma control in each treatment arm. The fit of the model to the raw data will be assessed visually.

- The role of baseline IgE and baseline FeNO (separately) on the effectiveness of GSK3772847 with respect to loss of asthma control will be investigated in a similar way.

Model Checking & Diagnostics

Bayesian Method (Primary):
- The Markov chain standard error (MCSE) should be compared to the standard deviation of the distribution (SD) to make sure that MCSE/SD ≤ 0.01 for all parameters in the mode.
- The Geweke diagnostic test will be used to check whether the mean estimates have converged by comparing means from the early and later part of the Markov chain using a z-score t-test. Large absolute values of the z-score statistic indicate rejection of the null hypothesis of no difference between the mean estimates obtained from the early and latter parts of the chain.
- Gelman & Rubin diagnostic checks should be used to assess if the Markov chains have mixed.
- Visual checks on diagnostic plots will be performed to assess:
    - Has the Markov chain settled down?
    - Are sufficient simulations being run?
    - Is there sufficient burn-in?
    - Is the effective sample size large enough?

Frequentist Method (Supportive):
- None.

Model Results Presentation

Bayesian Method (Primary):

- The proportions of participants experience loss of asthma control on GSK3772847, Placebo and the ratio of GSK3882747/Placebo will be presented along with their 95% credible interval for all participants combined.

Frequentist Method (Supportive):

- The odds of experiencing loss of asthma control on GSK3772947, Placebo and the odds ratio will be presented along with the 95% confidence intervals and p-value. This will be presented for all participants combined.

Fractional Polynomials (Exploratory Analysis):

- A plot of the relationship between the probability of experiencing loss of control on each treatment as well as the odds ratio versus continuous eosinophils will be produced.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint and Summary Measure

Endpoint	Summary Measure
Individual Components of Loss of Asthma Control: • Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline. • Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %. • Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule. • Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation). • Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule	Frequentist Method (Supportive): Odds Ratio. For each endpoint listed, the odds of having experienced loss of asthma control on GSK3772847 compared to the odds of having experienced loss of asthma control on placebo will be produced.
Time to loss of asthma control.	Median and lower and upper quartiles (only calculable if>= 50%, 25%, 75% subjects lose control for each treatment respectively) for time to loss of asthma control
The incidence, mean rate, and total number per participant of hospitalisations or Emergency Room (ER) visits during the study treatment period.	Summary statistics and study treatment exposure (no statistical analysis required).
Responder Analysis: • Proportion of participants with ≥0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16.	Odds Ratio. The odds of being a responder on GSK3772847 compared to the odds of being a responder on placebo.
Change from Baseline Analysis: • Change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16. • Change from baseline in fractional	Mean change from baseline

Endpoint	Summary Measure
exhaled nitric oxide (FeNO) at each week measured.	
Change from Baseline Analysis: • Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16. • Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16.	Mean change from baseline
• Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF for each four week period of the overall 16 week treatment period. • Change from baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period. • Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the 16 week treatment period. • Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period.	Change from baseline (summary statistics only)

7.2.2. Population of Interest

The secondary efficacy analyses will be based on the modified Intent to Treat population, unless otherwise specified.

7.2.3. Strategy for Intercurrent (Post-Randomisation) Events

For components of Loss of Asthma Control see Section 7.1.4.

For SGRQ and ACQ Responders primary and secondary estimands as table below:

Intercurrent Event	Primary Estimand	Secondary Estimand
Treatment discontinuation due to AE/SAE (not related to loss of asthma control)	Set to missing.	•If the AE/SAE was deemed related to IP then set as non-responder. •If the AE/SAE was not deemed related to IP then set to missing.

Intercurrent Event	Primary Estimand	Secondary Estimand
Death	Set to missing.	•If the death was deemed related to IP then set as non-responder. •If the death was not deemed related to IP then set to missing.
Prohibited/ Concomitant medications that could impact patients' asthma control	Use data as is.	Set as non-responder.
Non-compliance with FP/SAL, FP or study titration	Use data as is.	Set as non-responder.

Note:

- Identification of whether an event (AE/SAE/Death) is considered related to IP will be identified using the investigator tick box collected on the eCRF.
- If the intercurrent event occurs after loss of asthma control then all information on loss of asthma control will be used.
- Prohibited/ concomitant medications will be identified as protocol deviations within the prohibited/ concomitant medications category and will have text that start with "LoAC"
- Non-compliance FP/SAL, FP or study titration will be identified as compliance <80%, compliance ≥ 120% or not changing from FP/SAL or FP doses according to the predetermined schedule.

7.2.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: 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.

7.2.4.1. Statistical Methodology Specification

Endpoint / Variables

- Proportion of participants with a ≥0.5 point. ACQ-5 score increase from baseline.
- Proportion of participants who have pre-bronchodilator FEV1 decrease from baseline (measured at the end of Run-in) >7.5 %.
- Proportion of participants where inhaled corticosteroids (ICS) cannot be titrated in accordance with the pre-defined schedule.
- Proportion of participants who have a significant asthma exacerbation (requiring OCS and/or hospitalisation).
- Proportion of participants with a clinically significant asthma exacerbation or inability to titrate ICS according to the pre-defined schedule

Strategy for Intercurrent (Post-Randomisation) Events

Both primary and secondary estimands (Section 7.1.4) will be examined. It is important to assess both estimands as data is set to missing after withdrawal or loss of asthma control. This could produce biased estimands, as loss of control and therefore missing data is related to study treatment, and so the secondary estimand where missing data is set as non-responders must also be considered.

Model Specification
• See Section 7.1.5.1.
Model Checking & Diagnostics
• See Section 7.1.5.1
Model Results Presentation
• See Section 7.1.5.1

Endpoint / Variables
• Proportion of participants with ≥ 0.5 point ACQ-5 score decrease from baseline (responder) at each week from Week 1 to Week 16. • Proportion of St. George's Respiratory Questionnaire (SGRQ) responders (at least a 4 unit improvement from baseline) at Weeks 4, 8, 12 and 16.
Strategy for Intercurrent (Post-Randomisation) Events
Both primary and secondary estimands (Section 7.2.3) will be examined. It is important to assess both estimands as data is missing after withdrawal or loss of asthma control. This could produce biased estimands, as loss of control and therefore missing data is related to study treatment, and so the secondary estimand where missing data is set as non-responders must also be considered.
Model Specification
• The proportion of participants who were responders will be analysed using logistic regression allowing for screening eosinophils strata. • A responder on ACQ-5 is defined as participants with a ≥ 0.5 point decrease from baseline whilst a responder on SGRQ is defined as a ≥ 4 point decrease from baseline. • This endpoint will be analysed using logistic regression. Treatment, eosinophil strata will be fixed effects.
Model Checking & Diagnostics
• None
Model Results Presentation
• The odds of being a responder (as defined above) on GSK3772947, Placebo and the odds ratio will be presented along with the 95% confidence intervals and p-value.

Endpoint / Variables
• Time to loss of asthma control.
Strategy for Intercurrent (Post-Randomisation) Events
• Both primary and secondary estimands (Section 7.1.4) will be examined. It is important to assess both estimands as data is missing after withdrawal or loss of asthma control. This could produce biased estimands, as loss of control and therefore missing data is related to study treatment, and so the secondary estimand where missing data is set as non-responders must also be considered.
Model Specification
• Time to loss of asthma control will be analysed on the Modified Intent-to-Treat excluding GCP

non-compliant subjects (Loss of Control) population using Kaplan-Meier analysis (Proc lifetest). Within the Kaplan Meier plot participants will either be counted as an event or they will be censored.

Events:

- Participants who experience loss of asthma control during the study.

Censoring:

- Participants who discontinue investigational product for reasons other than loss of asthma control.
- Participants who successfully complete the 16 week treatment period will be censored at 113 days (16 weeks + 1 day).

Time to loss of asthma control = Date of loss of asthma control – Treatment start date + 1. If participants experience multiple reasons for loss of control then the earliest date will be used as described in Section 12.6.3.

Model Checking & Diagnostics

- None

Model Results Presentation

- Kaplan-Meier plots of the probability of a participant experiencing loss of asthma control by treatment will be produced.
- In addition, a summary table will be produced showing the probability of experiencing loss of asthma control after 4, 8, 12 and 16 weeks along with the median time (this will be NA if <50% of participants on a treatment lose control) to loss of asthma control on both treatment arms.

Endpoint / Variables

- Change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 6, 8, 10, 12, 14, 16.
- Change from baseline in fractional exhaled nitric oxide (FeNO) at each week measured.
- Change from baseline in blood eosinophils

Strategy for Intercurrent (Post-Randomisation) Events

No intercurrent events are considered for this endpoint. All data will be used as collected.

Model Specification

Only data until Week 4 (down titration of ICS) will be analysed, all data post Week 4 will be summarised descriptively only.

Data up to and include Week 4 (down titration of ICS):
A repeated measures model with terms for treatment, visit, visit by treatment and screening eosinophil strata will be included along with the screening eosinophil strata*visit and treatment*visit interactions.

FEV_1 at Weeks 4 Only - Fractional Polynomials (Exploratory Analysis):

- Screening blood eosinophil count will be transformed using a fractional polynomial term which will be included in the model as a continuous covariate. A treatment group by eosinophil

covariate interaction will also be included in the model to allow the magnitude of the interaction (but not the order of the fractional polynomial transformation) to differ with each treatment group). The best fitting model will be selected based on likelihood. The selected best fitting model will be plotted as continuous eosinophil count versus loss of asthma control in each treatment arm. The fit of the model to the raw data will be assessed visually. • The role of baseline IgE and baseline FeNO (separately) on the effectiveness of GSK3772847 with respect to FEV_1 at Weeks 4 will be investigated in a similar way.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The estimates of the mean and difference for each treatment group from the model will be produced, along with 95% confidence intervals and p-values for treatment comparisons.

The following endpoints will be summarised descriptively only. No analysis will be performed and all data will be reported as collected (no intercurrent events will be considered) using the modified Intent to Treat population:

- Change from baseline in ACQ-5 absolute score at each week from Week 1 to Week 16.
- Change from baseline in SGRQ total score at Weeks 4, 8, 12 and 16.
- Change from baseline in mean morning peak expiratory flow (PEF) and mean evening PEF over each four weeks of the 16 week treatment period.
- Change from baseline in mean daytime asthma symptom score over each four weeks of the 16 week treatment period.
- Changes from baseline in night-time awakenings due to asthma symptoms requiring rescue medication use over each four weeks of the16 week treatment period.
- Change from baseline in rescue medication use (albuterol/salbutamol): mean number of inhalations per day over each four weeks of the 16 week treatment period.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety including GCP non-compliant subjects population, unless otherwise specified. The details of the planned displays are provided in Appendix 10: List of Data Displays.

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.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting.

8.3. Vital Signs, Electrocardiogram (ECG) and Holter

Summary statistics for vital signs at baseline, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24 and 28 will be produced along with change from baseline summaries for each post baseline timepoint. In addition, the change between post-dose and pre-dose vital signs measurements will be summarised at weeks 0, 4, 8 and 12.

Similar 12-lead electrocardiogram (ECG) measurements at baseline, weeks 4, 8, 12 and 16 will be produced along with change from baseline summaries for each post baseline timepoint, and changes between post-dose and pre-dose in 12-lead ECG measurements at weeks 0, 4, 8 and 12.

24 hour Holter measurements collected at baseline, weeks 4 and 12 will be summarised along with change from baseline at weeks 4 and 12. Only participants with at least 16hrs worth of data will be included in any tables however all data will be listed.

8.4. Clinical Chemistry, Haematology and Cardiac Markers

Summaries of clinical chemistry results at baseline, weeks 2, 4, 8, 12, 16 and 28 along with change from baseline for all post-baseline measurements will be produced.

Similarly, haematology and cardiac markers at baseline, weeks 1, 2, 4, 6, 8, 10, 12, 14, 16 and 28 along with change from baseline for all post-baseline measurements will also be produced.

8.5. Antibodies

Summaries of the incidence of and titres of anti- GSK3772847 antibodies at weeks 0*, 2, 4*, 8*, 12*, 16, 20, 24 and 26.

* = Pre-dose only

8.6. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of liver function tests will be based on GSK Core Data Standards.

9. PHARMACOKINETIC ANALYSES

Due to the time required to analyse PK samples, no PK outputs will be included in the end of treatment phases analysis.

9.1. Secondary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

Serum concentrations of GSK3772847 by nominal time.

9.1.2. Population of Interest

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

9.1.3. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

9.1.4. Statistical Analyses / Methods

- No statistical analysis will be performed.
- Serum concentration will be summarised descriptively with summary figures being produced.
- Scatter plots of trough serum concentration vs FeNO, trough serum concentration vs blood eosinophils, and trough serum concentration vs IgE at Week 4 only will also be produced.

10. PHARMACODYNAMIC AND BIOMARKER ANALYSES

10.1. Secondary Pharmacodynamic Analyses

10.1.1. Endpoint / Variables

Free and total soluble ST2 levels in serum

10.1.2. Summary Measure

Free soluble ST2: Summary statistics and percentage change from baseline

Total soluble ST2: Summary statistics and change from baseline

Only pre-dose trough sST2 will be used for analysis. Post-dose trough sST2 will be summarised only.

10.1.3. Population of Interest

The secondary pharmacodynamics analyses will be based on the modified Intent to Treat population, unless otherwise specified.

10.1.4. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

10.1.5. Statistical Analyses / Methods

Endpoint / Variables
• Percentage change from baseline in free sST2 (On-treatment) • Percentage change from baseline in free sST2 (Post-treatment)
Strategy for Intercurrent (Post-Randomisation) Events
No intercurrent events are considered for this endpoint. All data will be used as collected.
Model Specification
• The ratio of post-baseline sST2 values to baseline sST2 values will be log transformed prior to analysis. Note: Log(post baseline sST2 /baseline sST2) is equivalent to log(post baseline sST2) – log(baseline sST2). • A repeated measures model with terms for treatment, visit, visit by treatment, the logarithm of baseline sST2, the logarithm of baseline sST2 by visit and screening eosinophil strata will be fitted.
Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The estimated treatment ratios together with 95% CIs (back-transformed from the differences on the log-scale).

Endpoint / Variables
• Change from baseline in free sST2 (On-treatment) • Change from baseline in free sST2 (Post-treatment)
Strategy for Intercurrent (Post-Randomisation) Events
No intercurrent events are considered for this endpoint. All data will be used as collected.
Model Specification
• A repeated measures model with terms for treatment, visit, visit by treatment, baseline sST2, baseline sST2 by visit and screening eosinophil strata will be fitted.

Model Checking & Diagnostics
• Distributional assumptions underlying the model used for analysis will be examined by obtaining a normal probability plot of the residuals and a plot of the residuals versus the fitted values (i.e. checking the normality assumption and constant variance assumption of the model respectively) to gain confidence that the model assumptions are reasonable.
Model Results Presentation
• The estimates of the mean and difference for each treatment group from the model will be produced, along with 95% confidence intervals and p-values for treatment comparisons.

Fractional Polynomials (Exploratory Analysis)

The role of free sST2 on the effectiveness of GSK3772847 with respect to loss of asthma control will be investigated, using the modified intent to treat population. The number of participants experiencing loss of control will be predicted at each level of baseline free sST2 based on a model including a free sST2 main effect term and an interaction with treatment term.

Baseline free sST2 will be transformed using a fractional polynomial term which will be included in the model as a continuous covariate. A treatment group by free sST2 covariate interaction will also be included in the model to allow the magnitude of the interaction (but not the order of the fractional polynomial transformation) to differ with each treatment group. The best fitting model will be selected based on likelihood. The selected best fitting model will be plotted as continuous free sST2 versus loss of asthma control in each treatment arm. The fit of the model to the raw data will be assessed visually.

10.2. Exploratory Biomarker Analyses

10.2.1. Endpoint / Variables

- Changes from baseline in induced sputum biomarkers (subset) at weeks 8 and 16.
- Changes from baseline in exploratory serum markers at weeks 8 and 16.

10.2.2. Summary Measure

Change from baseline

10.2.3. Population of Interest

The exploratory biomarker analyses will be based on the modified Intent to Treat population, unless otherwise specified.

10.2.4. Strategy for Intercurrent (Post-Randomisation) Events

Not applicable.

10.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Induced sputum biomarkers and exploratory serum markers at weeks 8 and 16 will be summarised using descriptive statistics, including the geometric mean and CV as well as listed.

No statistical analysis will be performed on this data.

11. REFERENCES

Charter for the Internal Safety Review Commitee (iSRC), Protocol 207597 Title: A randomised, double-blind, parallel group, multicenter, stratified study assessing the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with severe asthma, 26 June 2017

GlaxoSmithKline Document Number 2017N311825_02, Protocol: A randomised, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma, 13 September 2017

Internal Safety Review Commitee (iSRC) Reporting and Analysis Plan for a randomised, double-blind, parallel group, multicenter, stratified study evaluating the efficacy and safety of repeat doses of GSK3772847 compared with placebo in participants with moderately severe asthma, 20 July 2018

Protocol Deviation Management Plan (PDMP), Version 01, 21 August 2017

Winthrop et al, 2015, Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance, Annals of the Rheumatoid Arthritis Disease, doi: 10.1136/annrheumdis-2015-207841. Epub 2015 Sep 22

12. APPENDICES

12.1. Appendix 1: Protocol Deviation Management

The full list of protocol deviations collected on the eCRF is in the PDMP. Please refer to this document for current guidance.

There is no per protocol population in this study.

12.2. Appendix 2: Schedule of Activities

12.2.1. Protocol Defined Schedule of Events

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Informed consent (ICF)	X															
Genetic ICF	X															
ICF for sputum	X															
Inclusion and exclusion criteria		X														
Randomisation Criteria			X													
Demography	X															
Full physical exam including height and weight		X														
Medical history (includes substance abuse)		X														Substances [Drugs, Alcohol, tobacco] and family history of premature CV disease]): [including cardiovascular medical history]
Laboratory																

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Laboratory assessments		X[1,2]	X[1]	X	X[1]	X[1]	X	X[1]	X	X[1]	X	X[1]			X[1]	Haematology (including eosinophil count) and cardiac markers measured at all clinic visits. 1. Clinical chemistry (including liver chemistry). 2. Routine urinalysis at screening (Visit 1)
Pregnancy test[1]	X[2]		X[3]			X[3]		X[3]		X[3]		X	X	X	X	1. Test for women with child bearing potential. 2. Serum pregnancy test at V0/V1. 3. Test to be performed pre-dose during the treatment period.
[HIV, Hep B and Hep C screen]		X														A confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. If test has been performed within 3 months prior to first dose of study treatment, testing at screening is not required.

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Genetic blood sample – Pre dose			X													Pharmacogenetic sample may be drawn any time from Visit 2 onwards. Informed consent for optional substudies e.g. genetics must be obtained before collecting a sample
Sputum sample collection			X					X				X				Pre-dose collection and in a sub-set of participants (~50 %) at selected sites; also collected for EW participants
PK, target engagement and immunogenicity assessments			X	X	X	X		X		X		X	X	X	X	See SoA Table 2 for details
Exploratory Biomarkers			X					X				X				Pre dose collection
Efficacy																
Spirometry		X	X		X	X	X	X	X	X	X	X				Test to be performed pre-dose during the Treatment period
Reversibility		X														
FeNO			X	X	X	X	X	X	X	X	X	X				Test to be performed pre-dose
Review loss of asthma control criteria				X	X	X	X	X	X	X	X	X				It will include review of data to determine loss of asthma control. See Section 9.1.5.
Dispense eDiary		X														

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
Collect eDiary												X				
Review eDiary			X	X	X	X	X	X	X	X	X	X				
Safety																
12-lead ECG		X	X[1]			X[1]		X[1]		X[1]		X				1. Test to be performed pre-dose and post-dose within 30 mins after end of infusion.
24 hrs Holter		X	X[1]			X[1]				X[1]						Holter monitor needs to be returned to clinic at end of 24-hour recording (i.e. the next day). 1. Place the Holter 30-60 mins prior to dosing.
Vital signs		X	X[1]	X	X	X[1]	X	X[1]	X	X[1]	X	X	X	X	X	1. Test to be performed pre-dose prior to spirometry and post-dose prior the 12 –lead ECG.
Dispense paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	X	X	X	X	X	X	X		
Review paper Medical Problems/Medications Taken worksheet			X	X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Pre-Screening[1]	Screen Run-in	Treatment Period										Follow-up Period[2] (± 3 days)			Notes
			± 2 days			± 3 days										
Visit	0	1	2[3]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1.Pre-screening and screening can occur on the same day 2. FU period to start 4 weeks after ETP or EW visit. 3. Visit 2 = Day 1 (first dose of IP).
Week	-4~-2	-2	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	-28~-14	-14	1	8	15	29	43	57	71	85	99	113				
AE/SAE review	X[1]	X[1]	←==========									==========→	X	X	X	1. At V0 and V1 collect only SAEs considered as related to study participation.
Concomitant medication review	X	X	←==========									==========→	X	X	X	
Questionnaires																
ACQ-5		X	X													After randomization, ACQ5 will be completed by the participants every 7 days.
SGRQ			X			X		X		X		X				
Study Treatment																
Double blind Study Treatment (IP)			X			X		X		X						Patients will remain in the clinic for monitoring for at least 2 hours after the end of infusion.
FP/Sal (500/50) dispensing		X	X													
FP (mcg) dispensing					500	250	100	50								
Dispense albuterol (as needed)		X	X	X	X	X	X	X	X	X	X	X				

Procedure	Treatment Period										Follow-up[2] (± 3 days)			Notes
	± 2 days			± 3 days										
Visit	2[1]	3	4	5	6	7	8	9	10	11 (ETP or EW)	12	13	14	1. Visit 2 = Day 1 (first dose of IP). 2. FU period to start 4 weeks after ETP or EW visit.
Week	0	1	2	4	6	8	10	12	14	16	20	24	28	
Study Day	1	8	15	29	43	49	71	85	99	113				
Double blind Study Treatment (IP)	X			X		X		X						
PK sample	X[2]	X	X	X[3]		X[3]		X[1]		X	X	X	X	1. Pre dose and post dose. 2. Post dose only. 3. Pre dose only. Pre-dose samples within 2 hours from the planned dosing time. Post-dose samples as soon as possible after end of infusion but must be taken within 4 hours.
Free and total sST2	X[1]	X	X	X[3]		X[3]		X[1]		X	X	X	X	
Immunogenicity sample	X[3]		X	X[3]		X[3]		X[3]		X	X	X	X	

12.3. Appendix 3: Assessment Windows

12.3.1. Definitions of Assessment Windows for Analyses

Nominal visits will be used and no windowing will be applied for analysis.

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

12.4.1. Study Phases

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

Study Phase	Definition
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 28 days
Post-Treatment	Date > Study Treatment Stop Date + 28 days

Completion of study epoch's will be defined as the following:

Study Phase	Definition of Completion
Run-in	Randomised into study and received first dose of study treatment
Treatment	Completed Week 16 visit or withdrew from treatment phase due to loss of asthma control
Follow up	Completed 12 week follow-up period

12.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition **Note: All programming should use start and end dates where available, CMSTRF and CMENRF are only to be used where dates are unavailable to help determine the correct study phase.**
Pre-Treatment	• Conmed Start Date < Study Treatment First Dose Date • Conmed End Date < Study Treatment First Dose Date • CMSTRF = "BEFORE" • Randomisation date is missing i.e. subject was not randomised
On-Treatment	• Study Treatment First Dose Date <= Conmed Start Date <= Study Treatment Last Dose Date + 28 • Study Treatment First Dose Date <= Conmed End Date <= Study Treatment Last Dose Date + 28 • (Conmed Start Date <= Study Treatment Last Dose Date + 28) and (Conmed End Date >= Study Treatment First Dose Date) • (Conmed Start Date <= Study Treatment Last Dose Date + 28) and (CMENRF ="DURING/AFTER" or CMENRF ="AFTER" or CMSTRF = "DURING") • (CMSTRF = "BEFORE" or CMSTRF = "DURING" or CMENRF ="DURING/AFTER") and (Conmed End Date >= Study Treatment First Dose Date) • (CMSTRF = "BEFORE" or CMSTRF ="DURING") and (CMENRF ="DURING/AFTER" or CMENRF ="AFTER") • CMSTRF = "DURING" • CMENRF = "DURING/AFTER"

Study Phase	Definition **Note: All programming should use start and end dates where available, CMSTRF and CMENRF are only to be used where dates are unavailable to help determine the correct study phase.**
Post-Treatment	• Conmed Start Date > Study Treatment Last Dose Date + 28 • Conmed End Date > Study Treatment Last Dose Date + 28 • CMENRF = ”AFTER” • CMENRF = ”DURING/AFTER”
All phases	• Conmed start date is missing and CMSTRF is missing and conmed end date is missing and CMENRF is missing

NOTES:

- The duration of a single concomitant medication can extend over multiple study phases
- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

12.4.2. Treatment Emergent Flag for Adverse Events

Flag	Definition
Treatment Emergent	If AE onset date is on or after treatment start date & on or before treatment stop date + 28 days. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date + 28 days

NOTES:

- If the study treatment stop date is missing then the AE will be considered to be On-Treatment.

12.5. Appendix 5: Data Display Standards & Handling Conventions

12.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: uk1salx00175
HARP Compound	: /arenv/arprod/gsk3772847/mid207597/
Additional information of reporting areas: data_look_01 This is where the blinded dry run will take place. final_01: This is where the end of treatment phase analysis will take place. final_02: This is where the end of study analysis will take place. Details of the reporting efforts used for the iSRC analysis are detailed in the separate iSRC RAP.	
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards	
Generation of RTF Files	
• RTF files will be generated for all reporting efforts	

12.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include 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 Principals 7.01 to 7.13.	

12.6. Appendix 6: Derived and Transformed Data

12.6.1. General

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

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

12.6.2. Study Population

Age
Date of birth will be set as PPD YYYY where YYYY is the year of birth taken from the CRF. For participants who attended a screening visit, age will be calculated at the screening visit date. For pre-screen failures, age will be calculated at the pre-screening visit date.
Body Mass Index (BMI)
BMI = Weight (kg) / Height(m)^2
Treatment Misallocations
To allocate treatment, the number of doses of GSK3772847 and Placebo that were given will be calculated, and the subject will be assigned to whichever treatment has the higher number. The only exception will be when both treatments were given equally, in which case the subject will be assigned their randomised treatment.
Treatment Compliance for Fluticasone Propionate (FP) and Salmeterol (SAL)
• Treatment compliance will be calculated based on the formula: **Treatment Compliance = Number of Actual Doses / (Planned Treatment Duration in Days * Frequency)*100** • Frequency is 2 for BID and 1 for QD. Treatment compliance could be greater than 100% if there are events of overdose. Cumulative compliance (since Day 1) by each background therapy will be calculated. • Planned Treatment Duration is defined according to the schedule of activities. • Compliance will be summarized by the following categories: <80%, ≥ 80% to < 95%, ≥95% to <105%, ≥ 105% to <120% and ≥120%

Extent of Exposure (Therapeutic Coverage)
• IP is administered approximately every 4 weeks and each dose viewed as providing therapeutic coverage for 4 weeks (28 days). • Number of days of exposure to study drug will be calculated based on the formula: **Duration of Exposure in Days = Study Treatment Last Dose Date – (Study Treatment First Dose Date) + 29** • The only exception to this will be when a participant dies in which case **Duration of Exposure in Days = Death Date – (Study Treatment First Dose Date) + 1**

12.6.3. Efficacy

Loss of Asthma Control
Multiple Loss of Asthma Control
• If a participant reaches loss of control for multiple reasons then all reasons will be reported. For any time to loss of asthma control analysis, the time of the earliest component of loss of control will be used.
Time of Loss of Asthma Control
Time to loss of control will be taken from the loss of control log page.

12.6.4. Safety

Adverse Events
Adverse Events of Special Interest (AESI)
Systemic Allergic/Hypersensitivity and Non-allergic Reactions: Systemic allergic/hypersensitivity and non-allergic reactions are identifying through preferred terms which had been selected by medical review of the MedDRA dictionary and are provided in a separate spreadsheet. Alterations in immune response (infections) All infections and serious infections reported under the MedDRA system organ class of 'Infections and Infestations'. Specific events of interest are opportunistic infections with preferred terms matching identified/pre-determined terms based on a published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015]. Alterations in immune response (malignancies): All neoplasms reported under the MedDRA system organ class of 'Neoplasms, benign, malignant and unspecified (including cysts and polyps)'. Specific events of interest are malignancies which will be identified through matching of collected preferred terms with those from the following: Sub-SMQs under the Malignancies SMQ: • Malignant tumours sub-SMQ (narrow terms) • Tumours of unspecified malignancy sub-SMQ (narrow terms) Alterations in cardiovascular safety: Cardiac disorders and serious cardiac disorders reported under the MedDRA system organ class of 'Cardiac Disorders'. Serious cardiac, vascular and thromboembolic (CVT) events, identified as all serious events classified under the MedDRA system organ classes of 'Cardiac Disorders' and of 'Vascular Disorders', and thromboembolic events identified through matching of collected preferred terms with those from the following: Sub-SMQs under the Embolic and thrombotic events SMQ: • Embolic and thrombotic events, arterial sub-SMQ (narrow terms) • Embolic and thrombotic events, venous sub-SMQ (narrow terms) • Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous sub-SMQ (narrow terms) Sub-SMQs under the Ischaemic Heart Disease SMQ • Myocardial infarction sub-SMQ (narrow terms) • Other Ischaemic heart disease sub-SMQ (narrow terms) Sub-SMQs under the Central Nervous System Vascular Disorders SMQ • Ischaemic central nervous system vascular conditions sub-SMQ (narrow terms) • Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic sub-SMQ (narrow terms) • Serious ischemic adverse events, a subset of the serious CVT events identified through matching of collected preferred terms with those from the following: Local Injection Site Reactions Local injection site reactions are identifying through preferred terms which had been selected by medical review of the MedDRA dictionary and are provided in a separate spreadsheet.

Rate of Events per 1000 Treatment Years
Rate of events per 1000 treatment years will be calculated using: Rate = number of events * 1000 / total treatment exposure in years where subjects can contribute more than one event. This is equivalent to: Rate = number of events * 1000 / (number of subjects in treatment group * mean treatment exposure in years).

Maximum/Minimum On-Treatment Definitions for Vital Signs Data
Maximum and Minimum on-treatment**:** Maximum and Minimum on-treatment value over all time-points (including scheduled and unscheduled assessments) will be presented.

FEV_1
Absolute Reversibility
Absolute reversibility (mL) = (post-bronchodilator FEV_1 – pre-bronchodilator FEV_1)
Percent Reversibility
Definition of Percentage Reversibility as a percentage of predicted FEV_1 = ((post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / predicted FEV_1) x 100% Definition of Percentage Reversibility as a percentage of pre-bronchodilator FEV_1 = ((post-bronchodilator FEV_1– pre-bronchodilator FEV_1) / pre-bronchodilator FEV_1) x 100%

12.7. Appendix 7: Reporting Standards for Missing Data

12.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as either completing the 16 week treatment period and three month safety follow up, or withdrawing from the treatment period early due to loss of asthma control and completing the three month safety follow up period. • Withdrawn participants were not replaced in the study, unless the participants were withdrawn due to sites failing to comply with GCP. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

12.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in 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.
Analysis	• All missing data will be handled according to estimand of interest as described within the main body of the RAP.
ACQ	• If one of the five items in the ACQ is missing then the response from the four remaining items will be interpolated (pro-rata) to gain the overall response for the participant. • If more than one item is missing then the ACQ will be considered missing.
SGRQ	The SGRQ questionnaire has three components; symptoms, activity and impact. **Symptoms** • The Symptoms component will tolerate a maximum of 2 missed items. The weight for the missed item is subtracted from the total possible weight for the Symptoms component (662.5) and from the Total weight (3989.4) **Activity** • The Activity component will tolerate a maximum of 4 missed items. The weight for the missed item is subtracted from the total possible weight for the Activity component (1209.1) and from the Total weight (3989.4) **Impacts** • The Impacts component will tolerate a maximum of 6 missed items. The weight for the missed item is subtracted from the total possible weight for the Impacts component (2117.8) and from the Total weight (3989.4) If any component has more missing items then mentioned above then the SGRQ will be considered missing.

12.7.2.1. Handling of Missing and Partial Dates

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

Element	Reporting Detail

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.

12.8. Appendix 8: Values of Potential Clinical Importance

Values of potential clinical importance will not be used in this study, instead normal reference ranges of “Low”, “Normal” and “High” will be used.

12.9. Appendix 9: Abbreviations & Trade Marks

12.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CS	Clinical Statistics
CSR	Clinical Study Report
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
mIT	Modified Intent-to-Treat excluding GCP non-compliant subjects
mITT_LoC	Modified Intent-to-Treat excluding GCP non-compliant subjects (Loss of Control)
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
QC	Quality Control
QTcF	Frederica's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomisation & Medication Ordering System
SAC	Statistical Analysis Complete
SAFF_ALL	Safety including site including GCP non-compliant subjects
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings

12.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
None

Trademarks not owned by the GlaxoSmithKline Group of Companies
NONMEM
SAS

12.10. Appendix 10: List of Data Displays

All displays (Tables, Figures & Listings) will use the term 'Subjects' instead of "Participants".

12.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

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

12.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

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

NOTES:

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

12.10.3. Deliverables

Delivery [Priority] [1]	Description
ETP [1]	End of Treatment Phase Statistical Analysis Complete
SAC [1]	Final Statistical Analysis Complete

NOTES:

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

12.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	SAFF_ALL	ES8	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT	ETP, SAC
1.2.	SAFF_ALL	SD4	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	ETP, SAC
1.3.	SAFF_ALL	ES4	Summary of Subject Disposition at Each Study Epoch	ICH E3	ETP, SAC
1.4.	ASE	ES6	Summary of Screening/Run-in Status and Reasons for Screen/Run-in Failure	Journal Requirements	ETP, SAC
1.5.	Enrolled	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	ETP, SAC
1.6.	SAFF_ALL	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	ETP, SAC
Protocol Deviation					
1.7.	SAFF_ALL	DV1	Summary of Important Protocol Deviations	ICH E3	ETP, SAC
1.8.	SAFF_ALL	IE1	Summary of Inclusion/ Exclusion Deviations	ICH E3	ETP, SAC
Population Analysed					
1.9.	Enrolled	SP1	Summary of Study Populations	IDSL	ETP, SAC
Demographic and Baseline Characteristics					
1.10.	SAFF_ALL	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	ETP, SAC
1.11.	Enrolled	DM11	Summary of Age Ranges	EudraCT	ETP, SAC
1.12.	SAFF_ALL	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	ETP, SAC
Prior and Concomitant Medications					
1.13.	SAFF_ALL	MH4	Summary of Current Medical Conditions	ICH E3	ETP, SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.14.	SAFF_ALL	MH4	Summary of Past Medical Conditions	ICH E3	ETP, SAC
1.15.	SAFF_ALL	SP07	Summary of Family History of Cardiovascular Risk Factors at Screening		ETP, SAC
1.16.	SAFF_ALL	POP_T01	Summary of Disease Duration and Exacerbation History		ETP, SAC
1.17.	SAFF_ALL	SU1	Summary of Smoking History at Screening		ETP, SAC
1.18.	SAFF_ALL	CM1	Summary of Pre-Treatment Concomitant Medications	ICH E3	ETP, SAC
1.19.	SAFF_ALL	CM1	Summary of On-Treatment Concomitant Medications	ICH E3	ETP, SAC
1.20.	SAFF_ALL	CM1	Summary of Post-Treatment Concomitant Medications	ICH E3	ETP, SAC
1.21.	SAFF_ALL	CM1	Summary of On-Treatment Asthma Concomitant Medications	ICH E3	ETP, SAC
1.22.	SAFF_ALL	CM1	Summary of Post-Treatment Asthma Concomitant Medications	ICH E3	ETP, SAC
Pre-Treatment Lung Function					
1.23.	SAFF_ALL	POP_T02	Summary of Screening Lung Function	Include Pre- and Post- albuterol (salbutamol) FEV_1, FVC, FEV_1/FVC and % Predicted Normal and post-BD at screening %predicted. Include overall and by treatment group.	ETP, SAC
1.24.	SAFF_ALL	POP_T03	Summary of Baseline Lung Function	FEV_1, FVC, FEV_1/FVC and % Predicted Normal. Include overall and by treatment group.	ETP, SAC
Exposure and Treatment Compliance					
1.25.	SAFF_ALL	EX1	Summary of Exposure and Compliance to Background Therapy (FP and SAL)	ICH E3	ETP, SAC

12.10.5. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure					
2.1.	SAFF_ALL	EX1	Summary of Exposure to Study Treatment	ICH E3	ETP, SAC
Primary Endpoint: Loss of Asthma Control Weeks 0-16					
2.2.	mITT_LoC	EFF_T01	Summary of Loss of Asthma Control	Include overall loss of control, each component and the combination of exacerbation or inability to titrate.	ETP, SAC
2.3.	mITT_LoC	EFF_T02	Summary of Intercurrent Events		ETP, SAC
2.4.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-16 (Primary Estimand)		ETP, SAC
2.5.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-16 (Primary Estimand)		ETP, SAC
2.6.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-16 (Secondary Estimand)		ETP, SAC
2.7.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-16 (Secondary Estimand)		ETP, SAC
Secondary Endpoint: Loss of Asthma Control Weeks 0-6					
2.8.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-6 (Primary Estimand)		ETP, SAC
2.9.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-6 (Primary Estimand)		ETP, SAC
2.10.	mITT_LoC	EFF_T03	Bayesian Analysis of Loss of Asthma Control Over Weeks 0-6 (Secondary Estimand)		ETP, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.11.	mITT_LoC	EFF_T04	Frequentist Analysis of Loss of Asthma Control Over Weeks 0-6 (Secondary Estimand)		ETP, SAC
Secondary Endpoints: Components of Loss of Asthma Control					
2.12.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with an ACQ increase from Baseline >= 0.5 (Primary Estimand)		ETP, SAC
2.13.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with an ACQ increase from Baseline >= 0.5 (Secondary Estimand)		ETP, SAC
2.14.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with an FEV1 decrease from Baseline > 7.5% (Primary Estimand)		ETP, SAC
2.15.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with an FEV1 decrease from Baseline > 7.5% (Secondary Estimand)		ETP, SAC
2.16.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with an Inability to Titrate According to the Pre-Defined Schedule (Primary Estimand)		ETP, SAC
2.17.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with an Inability to Titrate According to the Pre-Defined Schedule (Secondary Estimand)		ETP, SAC
2.18.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with a Significant Asthma Exacerbation (Primary Estimand)		ETP, SAC
2.19.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with a Significant Asthma Exacerbation (Secondary Estimand)		ETP, SAC
2.20.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with a Significant Asthma Exacerbation or Inability to Titrate According to the Pre-Defined Schedule (Primary Estimand)		ETP, SAC
2.21.	mITT_LoC	EFF_T03	Analysis of Proportion of Subjects with a Significant Asthma Exacerbation or Inability to Titrate According to the Pre-Defined Schedule (Secondary Estimand)		ETP, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Endpoints: Time to Loss of Asthma Control					
2.22.	mITT_LoC	EFF_T05	Summary and Analysis of Time to Loss of Asthma Control (Primary Estimand)		ETP, SAC
2.23.	mITT_LoC	EFF_T05	Summary and Analysis of Time to Loss of Asthma Control (Secondary Estimand)		ETP, SAC
Secondary Endpoints: Hospitalisation and Emergency Room Visits					
2.24.	mITT	EFF_T06	Summary and Rate of Asthma-Related On-Treatment Hospitalisations and Emergency Room Visits (Primary Estimand)		ETP, SAC
Secondary Endpoint: ACQ-5					
2.25.	mITT	EFF_T07	Summary of Raw and Change from Baseline in ACQ-5 Total Score (Primary Estimand)		ETP, SAC
2.26.	mITT	EFF_T04	Analysis of Proportion of Subjects with an ACQ-5 Total Score increase from Baseline >= 0.5 (Primary Estimand)		ETP, SAC
2.27.	mITT	EFF_T04	Analysis of Proportion of Subjects with an ACQ-5 Total Score increase from Baseline >= 0.5 (Secondary Estimand)		ETP, SAC
Secondary Endpoint: SGRQ					
2.28.	mITT	EFF_T07	Summary of Raw and Change from Baseline in SGRQ Total Score (Primary Estimand)		ETP, SAC
2.29.	mITT	EFF_T04	Analysis of Proportion of Subjects with an SGRQ Total Score increase from Baseline >= 4 (Primary Estimand)		ETP, SAC
2.30.	mITT	EFF_T04	Analysis of Proportion of Subjects with an SGRQ Total Score decrease from Baseline >= 4 (Secondary Estimand)		ETP, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Endpoint: FEV_1 and PEF					
2.31.	mITT	EFF_T07	Summary of Raw and Change from Baseline FEV_1 (Primary Estimand)		ETP, SAC
2.32.	mITT	EFF_T08	Analysis of Change from Baseline in FEV_1 up to Week 4(Primary Estimand)		ETP, SAC
2.33.	mITT	EFF_T07	Summary of Raw and Change from Baseline Fractional Exhaled Nitric Oxide (FeNO) (Primary Estimand)		ETP, SAC
2.34.	mITT	EFF_T08	Analysis of Change from Baseline in Fractional Exhaled Nitric Oxide (FeNO) up to Week 4 (Primary Estimand)		ETP, SAC
Secondary Endpoint: Exacerbations					
2.35.	mITT	EFF_T09	Summary of On-Treatment Asthma Exacerbations		ETP, SAC
Secondary Endpoint: Eosinophils					
2.36.	mITT	EFF_T07	Summary of Raw and Change from Baseline in Eosinophils (Primary Estimand)		ETP, SAC
2.37.	mITT	EFF_T08	Analysis of Eosinophils (Primary Estimand)		ETP, SAC
Secondary Endpoint: PEF, Daytime Symptom Score, Night-time Symptom Score and Rescue Medication					
2.38.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Morning Peak Expiratory Flow (PEF)		ETP, SAC
2.39.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Evening Peak Expiratory Flow (PEF)		ETP, SAC
2.40.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Daytime Asthma Symptom Score		ETP, SAC
2.41.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Night-Time Awakenings Due to Asthma Symptoms		ETP, SAC

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.42.	mITT	EFF_T010	Summary of Raw and Change from Baseline in Mean Rescue Medication use (Albuterol/Salbutamol)		ETP, SAC

12.10.6. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Primary Endpoint: Loss of Asthma Control					
2.1	mITT_LoC		Plot of Loss of Asthma Control (Primary Estimand)	Include Show overall and components of loss on control	ETP, SAC
2.2	mITT_LoC		Plot of Loss of Asthma Control (Secondary Estimand)	Include Show overall and components of loss on control	ETP, SAC
Secondary Endpoint: Time to Loss of Control					
2.1.	mITT_LoC		Kaplan-Meir Plot of Time to Loss of Asthma Control (Primary Estimand)		ETP, SAC
2.2.	mITT_LoC		Kaplan-Meir Plot of Time to Loss of Asthma Control (Secondary Estimand)		ETP, SAC
Secondary Endpoint: Eosinophils					
2.3.	mITT_LoC		Cumulative Density Plot of Eosinophils		ETP, SAC
2.4.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.5.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.6.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.7.	mITT_LoC		Loss of Control Over Weeks 0-16 vs Eosinophils – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
2.8.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.9.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.10.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
2.11.	mITT_LoC		Loss of Control Over Weeks 0-6 vs Eosinophils – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
Secondary Endpoints: IgE and FeNO Over Weeks 0-16					
2.12.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE by Treatment - Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.13.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.14.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
2.15.	mITT_LoC		Loss of Control Over Weeks 0-16 vs IgE – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
2.16.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
2.17.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO – Fractional Polynomial Treatment Difference (Primary Estimand)		ETP, SAC
2.18.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.19.	mITT_LoC		Loss of Control Over Weeks 0-16 vs FeNO – Fractional Polynomial Treatment Difference (Secondary Estimand)		ETP, SAC
2.20.	mITT		FEV1 at Week 4 vs Eosinophils by Treatment – Fractional Polynomial Model		ETP, SAC
2.21.	mITT		FEV1 at Week vs Eosinophils – Fractional Polynomial Treatment Difference		ETP, SAC
2.22.	mITT		FEV1 at Week 4 vs IgE by Treatment – Fractional Polynomial Model		ETP, SAC
2.23.	mITT		FEV1 at Week vs IgE – Fractional Polynomial Treatment Difference		ETP, SAC
2.24.	mITT		FEV1 at Week 4 vs FeNO by Treatment – Fractional Polynomial Model		ETP, SAC
2.25.	mITT		FEV1 at Week vs FeNO – Fractional Polynomial Treatment Difference		ETP, SAC

12.10.7. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	SAFF_ALL	SAFE_T01	Overview of On-treatment Adverse Events During the Study		ETP, SAC
3.2.	SAFF_ALL	AE1	Summary of All Pre-treatment Adverse Events by System Organ Class and Preferred Term		ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.3.	SAFF_ALL	AE1	Summary of All On-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.4.	SAFF_ALL	AE1	Summary of All Post-treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.5.	SAFF_ALL	AE1	Summary of All On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.6.	SAFF_ALL	AE1	Summary of All On-treatment Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.7.	SAFF_ALL	AE1	Summary of All On-treatment Fatal Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.8.	SAFF_ALL	AE3	Summary of All On-treatment Common (>=3%) Adverse Events by Overall Frequency	ICH E3	ETP, SAC
3.9.	SAFF_ALL	AE1	Summary of All On-treatment Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.10.	SAFF_ALL	AE15	Summary of All On-treatment Common (>=3%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT	ETP, SAC
3.11.	SAFF_ALL	AE1	Summary of All Pre-treatment Serious Adverse Events by System Organ Class and Preferred Term		ETP, SAC
3.12.	SAFF_ALL	AE1	Summary of All On-treatment Serious Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC
3.13.	SAFF_ALL	AE1	Summary of All Post-treatment Serious Adverse Events by System Organ Class and Preferred Term	ICH E3	ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.14.	SAFF_ALL	AE16	Summary of All On-treatment Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT	ETP, SAC
3.15.	SAFF_ALL	AE1	Summary of All On-treatment Serious Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class and Preferred Term	IDSL	ETP, SAC
3.16.	SAFF_ALL	AE1	Summary of All On-treatment Serious Adverse Events Leading to Withdrawal from Study by System Organ Class and Preferred Term	IDSL	ETP, SAC
Adverse Events of Special Interest (AESIs)					
3.17.	SAFF_ALL	AE1	Summary of On-treatment Adverse Events of Special Interest	IDSL	ETP, SAC
3.18.	SAFF_ALL	AE1	Summary of On-treatment Serious Adverse Events of Special Interest	IDSL	ETP, SAC
3.19.	SAFF_ALL	AE1	Summary of Post-treatment Adverse Events of Special Interest	IDSL	ETP, SAC
3.20.	SAFF_ALL	AE1	Summary of Post-treatment Serious Adverse Events of Special Interest	IDSL	ETP, SAC
Mexico Specific Tables					
3.21.	SAFF_ALL		Summary of Suspected Investigational Product Adverse Reaction (Mexican Participants Only)		ETP, SAC
3.22.	SAFF_ALL		Summary of Suspected Investigational Product Adverse Reaction (Non-Mexican Participants)		ETP, SAC
Laboratory: Chemistry					
3.23.	SAFF_ALL	LB1	Summary of Clinical Chemistry	ICH E3	ETP, SAC
3.24.	SAFF_ALL	LB1	Summary of Change from Baseline in Clinical Chemistry	ICH E3	ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.25.	SAFF_ALL	LB16	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	ETP, SAC
Laboratory: Hematology and Cardiac Markers					
3.26.	SAFF_ALL	LB1	Summary of Hematology and Cardiac Markers	ICH E3	ETP, SAC
3.27.	SAFF_ALL	LB1	Summary of Changes from Baseline in Hematology and Cardiac Markers	ICH E3	ETP, SAC
3.28.	SAFF_ALL	LB16	Summary of Worst Case Hematology and Cardiac Markers Results Relative to Normal Range Post-Baseline Relative to Baseline	ICH E3	ETP, SAC
Laboratory: Hepatobiliary (Liver)					
3.29.	SAFF_ALL	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	ETP, SAC
3.30.	SAFF_ALL	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	ETP, SAC
ECG					
3.31.	SAFF_ALL		Summary of Antihistamine, Decongestant and Caffeine Use Prior to ECG assessments		ETP, SAC
3.32.	SAFF_ALL	EG1	Summary of ECG Findings	IDSL	ETP, SAC
3.33.	SAFF_ALL	EG2	Summary of ECG Values by Visit	IDSL	ETP, SAC
3.34.	SAFF_ALL	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	ETP, SAC
3.35.	SAFF_ALL	EG10	Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	ETP, SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.36.	SAFF_ALL	EG11	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	ETP, SAC
Holter					
3.37.	SAFF_ALL	HM1	Summary of Holter Interpretations	IDSL	ETP, SAC
3.38.	SAFF_ALL	HM2	Summary of Holter Abnormalities	IDSL	ETP, SAC
3.39.	SAFF_ALL	HM3	Summary of Holter Values	IDSL	ETP, SAC
3.40.	SAFF_ALL	HM3	Summary of Change from Baseline in Holter Values	IDSL	ETP, SAC
3.41.	SAFF_ALL	HM4	Summary of Subjects with R-on-T Beats	IDSL	ETP, SAC
Vital Signs					
3.42.	SAFF_ALL	VS1	Summary of Vital Signs	ICH E3	ETP, SAC
3.43.	SAFF_ALL	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	ETP, SAC
3.44.	SAFF_ALL	VS1	Summary of Change from Pre-dose to Post-dose in Vital Signs	ICH E3	ETP, SAC

12.10.8. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacokinetic					
4.1.	PK		Summary of PK Serum Concentrations		SAC only

12.10.9. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacodynamic					
6.1.	mITT		Summary of Raw and Percentage Change from Baseline in Free Soluble ST2 concentration (ng/mL) (On-treatment)	Pre and Post dose.	ETP, SAC
6.2.	mITT		Analysis of Percentage Change from Baseline in Free Soluble ST2 concentration (ng/mL) (On-treatment)	Pre dose only.	ETP, SAC
6.3.	mITT		Summary of Raw and Percentage Change from Baseline in Free soluble ST2 concentration (ng/mL) (Post-treatment)		ETP, SAC
6.4.	mITT		Analysis of Percentage Change from Baseline in Free soluble ST2 concentration (ng/mL) (Post-treatment)		ETP, SAC
6.5.	mITT		Summary of Raw and Change from Baseline in Total Soluble ST2 concentration (ng/mL) (On-treatment)	Pre and Post dose.	ETP, SAC
6.6.	mITT		Analysis of Change from Baseline in Total Soluble ST2 concentration (ng/mL) (On-treatment)	Pre dose only.	ETP, SAC
6.7.	mITT		Summary of Raw and Change from Baseline in Total Soluble ST2 concentration (ng/mL) (Post-treatment)		ETP, SAC
6.8.	mITT		Analysis of Change from Baseline in Total Soluble ST2 concentration (ng/mL) (Post-treatment)		ETP, SAC
Exploratory: Biomarkers					
6.9.	mITT		Summary and Change from Baseline in Induced Sputum Biomarkers (subset) at Weeks 8 and 16	Include geometric mean and %CV	ETP, SAC
6.10.	mITT		Summary and Change from Baseline in Exploratory Serum Markers at Weeks 8 and 16	Include geometric mean and %CV	ETP, SAC

12.10.10. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacokinetic					
6.1.	PK		Plot of Serum Concentrations		ETP, SAC
6.2.	PK		Pre-dose Trough Concentration vs Eosinophils at Week 4		ETP, SAC
6.3.	PK		Pre-dose Trough Concentration vs FeNO at Week 4		ETP, SAC
6.4.	PK		Pre-dose Trough Concentration vs IgE at Week 4		ETP, SAC

12.10.11. Pharmacodynamic and Biomarker Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary: Pharmacokinetic					
6.5.	mITT		Plot of Percentage Change from Baseline in Free Soluble ST2 levels (On-treatment)		ETP, SAC
6.6.	mITT		Plot of Percentage Change from Baseline in Free soluble ST2 levels (Post-treatment)		ETP, SAC
6.7.	mITT		Plot of Change from Baseline in Total Soluble ST2 levels (On-treatment)		ETP, SAC
6.8.	mITT		Plot of Change from Baseline in Total Soluble ST2 levels (Post-treatment)		ETP, SAC
6.9.	mITT_LoC		Loss of Control vs Free soluble ST2 by Treatment – Fractional Polynomial Model (Primary Estimand)		ETP, SAC
6.10.	mITT_LoC		Loss of Control vs Free soluble ST2 Treatment Difference – Fractional Polynomial (Primary Estimand)		ETP, SAC
6.11.	mITT_LoC		Loss of Control vs Free soluble ST2 by Treatment – Fractional Polynomial Model (Secondary Estimand)		ETP, SAC
6.12.	mITT_LoC		Loss of Control vs Free soluble ST2 Treatment Difference – Fractional Polynomial (Secondary Estimand)		ETP, SAC

12.10.12. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen and Run-in Failure	Journal Guidelines	ETP, SAC
2.	SAFF_ALL	ES2 / ES3	Listing of Reasons for Study Withdrawal	ICH E3	ETP, SAC
3.	SAFF_ALL	SD2/SD3	Listing of Reasons for Study Treatment Discontinuation	ICH E3	ETP, SAC
4.	SAFF_ALL	BL1 / BL2	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	ETP, SAC
5.	SAFF_ALL	TA1 / CP_RD1x	Listing of Planned and Actual Treatments	IDSL	ETP, SAC
Protocol Deviations					
6.	SAFF_ALL	DV2	Listing of Important Protocol Deviations	ICH E3	ETP, SAC
7.	SAFF_ALL	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	ETP, SAC
8.	SAFF_ALL		Listing of Subjects excluded for GCP non-compliance		
Populations Analysed					
9.	SAFF_ALL	SP3	Listing of Participants Excluded from Any Population	ICH E3.	ETP, SAC
Demographic and Baseline Characteristics					
10.	SAFF_ALL	DM2	Listing of Demographic Characteristics	ICH E3	ETP, SAC
11.	SAFF_ALL	DM9	Listing of Race	ICH E3	ETP, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
12.	SAFF_ALL	CP_CM3	Listing of Concomitant Medications	IDSL	ETP, SAC
Exposure and Treatment Compliance					
13.	SAFF_ALL	EX3	Listing of Exposure Data	ICH E3	ETP, SAC
Adverse Events					
14.	SAFF_ALL	AE8	Listing of All Adverse Events	ICH E3	ETP, SAC
15.	SAFF_ALL	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	ETP, SAC
16.	SAFF_ALL	AE8	Listing of Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	ETP, SAC
17.	SAFF_ALL	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	ETP, SAC
Serious and Other Significant Adverse Events					
18.	SAFF_ALL	AE8	Listing of Fatal Serious Adverse Events	ICH E3	ETP, SAC
19.	SAFF_ALL	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	ETP, SAC
20.	SAFF_ALL	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	ETP, SAC
21.	SAFF_ALL	AE8	Listing of Serious Adverse Events Leading to Withdrawal from Study / Permanent Discontinuation of Study Treatment	ICH E3	ETP, SAC
22.	SAFF_ALL	AE8	Listing of Other Significant Adverse Events	ICH E3	ETP, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hepatobiliary (Liver)					
23.	SAFF_ALL	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	ETP, SAC
24.	SAFF_ALL	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	ETP, SAC
All Laboratory					
25.	SAFF_ALL	LB5 / LB6	Listing of All Laboratory Data for Participants with Any Value Outside Normal Range	ICH E3	ETP, SAC
26.	SAFF_ALL	LB14	Listing of Laboratory Data with Character Results	ICH E3	ETP, SAC
ECG					
27.	SAFF_ALL	EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	ETP, SAC
28.	SAFF_ALL	EG5	Listing of Abnormal ECG Findings	IDSL	ETP, SAC
Holter					
29.	SAFF_ALL	MH6	Listing of Holter R-on-T Beat Data	IDSL	ETP, SAC
30.	SAFF_ALL	MH7	Listing of Holter {Supraventricular} {Ventricular} Event Data	IDSL, Update title as appropriate based on data	ETP, SAC
31.	SAFF_ALL	MH8	Listing of Holter {Sustained} {Non-sustained} {Supraventricular} {Ventricular} Run	IDSL, Update title as appropriate based on data	ETP, SAC
32.	SAFF_ALL	MH9	Listing of Holter Atrial {Fibrillation} {Flutter} Data	IDSL, Update title as appropriate based on data	ETP, SAC
33.	SAFF_ALL	MH10	Listing of Holter Abnormalities	IDSL	ETP, SAC

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Vital Signs					
34.	SAFF_ALL	VS4	Listing of All Vital Signs Data	IDSL	ETP, SAC
Primary Analysis Data: Loss of Asthma Control and Intercurrent Events					
35.	mITT_LoC		Listing of Loss of Asthma Control	Include all reasons for loss of control and time to loss of asthma control	ETP, SAC
36.	mITT_LoC		Listing of Intercurrent Events	Include treatment subject was analysed as taking and treatment at time of loss of control	ETP, SAC

12.10.13. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
37.	SAFF_ALL	SP2	Listing of the Follow-up Contact		ETP, SAC
38.	SAFF_ALL	TA1	Listing of Treatment Misallocations	Change Centre ID to Investigator ID: xxxxxx and also Investigator at Centre: xxxxxx	ETP, SAC
39.	SAFF_ALL	SP4	Listing of Overall Percentage Treatment Compliance		ETP, SAC
Secondary Efficacy					
40.	mITT		Listing of Eosinophils	Include randomisation and analysis strata	ETP, SAC
41.	mITT	SP10	Listing of Lung Function Results including FEV_1		ETP, SAC
42.	mITT	S3	Listing of Asthma Exacerbations	Include a column for severity	ETP, SAC
43.	mITT		Listing of Asthma Control Questionnaire (ACQ-5)		ETP, SAC
44.	mITT		Listing of St George's Respiratory Questionnaire (SGRQ)		ETP, SAC
45.	mITT		Listing of Peak Exploratory Flow (PEF)		ETP, SAC
46.	mITT		Listing of Fractional Exhaled Nitric Oxide (FeNO)		ETP, SAC
47.	mITT		Listing of Daytime and Night-time Asthma Symptoms		ETP, SAC
48.	mITT		Listing of Rescue Medication Use		ETP, SAC
49.	mITT		Listing of Hospitalisations and Emergency Room Visits		ETP, SAC
50.	PK		Listing of Serum Concentration		SAC Only
51.	PD		List of Free and Total Soluble ST2 Levels		

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
52.	SAFF_ALL		Listing of Clinical Chemistry		ETP, SAC
53.	SAFF_ALL		Listing of Haematology and Cardiac Markers		ETP, SAC
54.	SAFF_ALL		Listing of Anti-GSK3772847 Antibodies		ETP, SAC
55.	SAFF_ALL	ESI8	Listing of AE Terms of Special Interest	IDSL	ETP, SAC
Exploratory Biomarker					
56.	mITT		Listing of Induced Sputum and Exploratory Serum Biomarkers		ETP, SAC
Medical History					
57.	SAFF_ALL	MH2	Listing of Medical Conditions at Screening		ETP, SAC
58.	SAFF_ALL	SP5	Listing of Family History of Cardiovascular Risk Factors		ETP, SAC
59.	SAFF_ALL	SP6	Listing of Asthma History		ETP, SAC
60.	SAFF_ALL	SP7	Listing of Smoking History and Smoking Status		ETP, SAC
61.	SAFF_ALL	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Bone Mineral Density and Other Medications		ETP, SAC
Liver Events: Note only produced if there is a Liver Event					
62.	SAFF_ALL	VS4	Listing of Liver Events		ETP, SAC
63.	SAFF_ALL	VS4	Listing of Liver Event Information for RUCAM Score		ETP, SAC
64.	SAFF_ALL	VS4	Listing of Liver Biopsy		ETP, SAC
65.	SAFF_ALL	VS4	Listing of Liver Imaging Details		ETP, SAC
Cardiovascular Events: Note only produced if there is a Cardiovascular Event					
66.	SAFF_ALL	VS4	Listing of Myocardial infarction/unstable angina		ETP, SAC
67.	SAFF_ALL	VS4	Listing of Congestive heart failure		ETP, SAC

mITT

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
68.	SAFF_ALL	VS4	Listing of Arrhythmias		ETP, SAC
69.	SAFF_ALL	VS4	Listing of Valvulopathy		ETP, SAC
70.	SAFF_ALL	VS4	Listing of Pulmonary hypertension		ETP, SAC
71.	SAFF_ALL	VS4	Listing of Cerebrovascular events/stroke and transient ischemic attack		
72.	SAFF_ALL	VS4	Listing of Peripheral arterial thromboembolism		
73.	SAFF_ALL	VS4	Listing of Deep venous thrombosis/pulmonary embolism		
74.	SAFF_ALL	VS4	Listing of Revascularisation		
75.	SAFF_ALL	VS4	Listing of Deaths		

12.11. Appendix 11: Example Mock Shells for Data Displays

Available upon request