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

Title	:	Reporting and Analysis Plan for a randomised double-blind (sponsor open), placebo-controlled, single ascending dose, First Time in Human study in participants with mild to moderate asthma to assess safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of GSK3511294 administered subcutaneously.
Compound Number	:	GSK3511294
Effective Date	:	23-MAY-2019

Description:

- The purpose of this RAP amendment is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol GSK Document Number 2016N270529_06
- This RAP is intended to describe the safety, tolerability, immunogenicity, pharmacokinetic (PK) and pharmacodynamic (PD) analyses required for the study.
- This RAP will be provided to the study team members to convey the content of the Dose Escalation, Interim Analyses and Statistical Analysis Complete (SAC) deliverables.
- All displays (Tables, Figures & Listings) will use the term 'Subjects'. However, RAP text will refer to "Participants" in-line with the master RAP template and protocol.
- At the time of this RAP amendment, the Dose Escalations and Interim Analysis 1 have taken already place. Following Interim Analysis 1, the protocol was amended to allow additional interim analyses to examine PD and PK data over a longer duration.

RAP Author(s):

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RAP Team Review Confirmations
(Method: E-mail)

Reviewer	Date
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Clinical Statistics and Clinical Programming Line Approvals

(Method: Pharma TMF eSignature)

Approver	Date
PPD Director, Clinical Statistics	23 May 2019
PPD Director, Programming	23 May 2019

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1. INTRODUCTION

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

Revision Chronology:		
2016N270529_00	13-JUN-2013	Original
2016N270529_01	21-JUN-2013	To correct errors in the Secondary Medical Monitor's email address and in the inflammatory marker tests to be performed at screening.
2016N270529_02	04-AUG-2017	To amend the pharmacokinetic stopping criterion and clarify that saline for placebo will be an EU licensed product sourced locally by trial sites, in response to comments from the Medicines and Healthcare Products Regulatory Agency.
2016N270529_03	04-SEP-2017	To correct errors and make minor clarifications.
2016N270529_04	02-FEB-2018	To amend the timeframe for collection of PEF measurements. To clarify that demography, height, weight and BMI will be collected at the pre-screening visit if this visit is required. Alignment of ECG collection timeframe. Clarify timeframe for review of safety data from sentinel participants. Clarify that sentinel participants will be used at each escalating dose level. To remove the necessity for evidence of airway hyperresponsiveness, airflow variation (peak flow rate or FEV1) or reversible airflow obstruction at inclusion. Added live vaccines to prohibited concomitant medications list. Added Right Bundle Branch Block as an exclusion criteria. Clarification of the study halting criteria. Clarification that each participants consent must be available, as well as obtained, before they are entered into the study. Added an exclusion criteria regarding vulnerable participants. Clarify the definition of a pre-screening failure. Added in country specific requirements for Germany, concerning the addition of Hepatitis B core antibody test screening and to increase the in-patient period to 8-days post dosing. Clarified that the PK sample information is located in the appropriate lab manual and not the study reference manual. To ensure there is no un-blinding that can occur for Eosinophil counts due to availability of other components and their contributions to WBC count.
2016N270529_05	18-JUN-2018	A raw QT interval change from baseline as one of the criteria for limiting dose escalation and for increased monitoring of individual participants has been included in error. QTcF has been chosen as the most appropriate corrective measure of QT for this study and this is now reflected throughout. Accordingly, one of the required criteria for limiting further dose escalation and increased monitoring of individuals is now a change in QTcF from baseline of > 60 msec. To remove the requirement for reversibility testing at prescreening/screening,

Revision Chronology:		
		as evidence of reversibility is no longer a requirement for inclusion as per the previous amendment. Consequently, participants who would not be a screen failure under the entry criteria in the current version of the protocol may be rescreened. Furthermore, participants that were not a screen failure but could not be dosed during the screening window due to logistical reasons may also be rescreened. To extend the PK sampling period in the 2 mg and 10 mg cohorts, to better characterise the PK profile of GSK3511294. To clarify that local labs are required for all sentinel participants at the 48 hour time point to enable dosing of the rest of the cohort. As the German in-patient stay is longer than the UK, local labs prior to discharge from the clinical site are required on Day 8 and not at 48 hours post dosing (Day 3). Minor corrections of typos throughout.
2016N270529_06	07-Jan-2019	Inclusion of additional interim analyses to better assess blood eosinophil count return towards baseline profiles at the highest dose levels investigated and better inform dose and dosing regimen to move forward into the next phase of development. The earliest additional interim analysis is planned no earlier than once data is available at the 26-week time point after dosing Cohort 4 (planned 100 mg dose).

1.1. RAP Amendments

The original RAP was finalised prior to the first interim analysis. This RAP amendment was written after the first interim analysis and prior to any subsequent interim analyses, and prior to final DBF.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

There were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 6 (Dated: 07/JAN/2019).

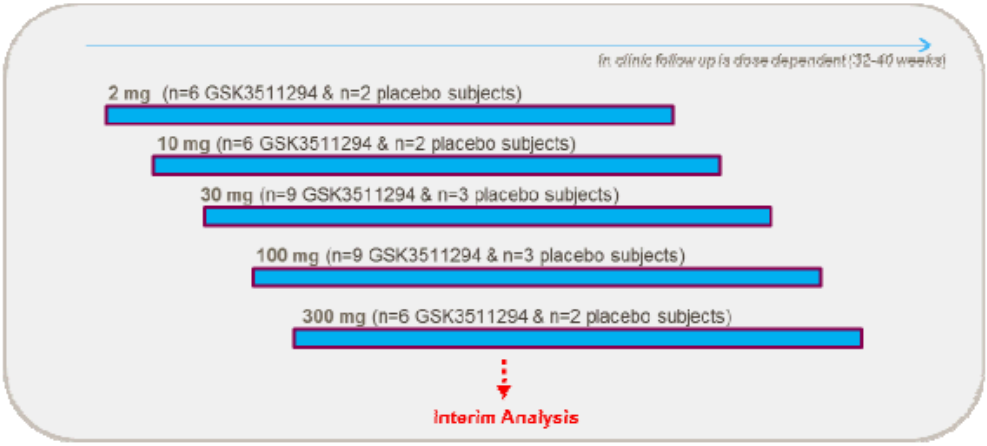
2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To assess the safety and tolerability of ascending single subcutaneous (SC) doses of GSK3511294 in participants with mild to moderate asthma	• Adverse events (AE), serious adverse events (SAE), including systemic reactions and local injection site reactions • Vital signs, electrocardiograms (ECGs), laboratory safety data – including liver and renal chemistry, high sensitivity C-reactive protein

Objectives	Endpoints
	(hsCRP), and complement (C3 and C4)
Secondary Objectives	**Secondary Endpoints**
• To evaluate the plasma pharmacokinetics (PK) of ascending single SC doses of GSK3511294 in participants with mild to moderate asthma	• Plasma PK parameters of GSK3511294 after single SC doses: AUC(0-∞), AUC(0-t), AUC(0-Week4), AUC(0-Week12), AUC(0-Week26), %AUCex, Cmax, tmax, tlast, CL/F, Vd/F, λz and t½ when assessable*
• To evaluate the dose response of blood eosinophil counts after ascending single SC doses of GSK3511294 in participants with mild to moderate asthma	• Ratio to baseline in absolute blood eosinophil count
• To assess the immunogenicity of GSK3511294	• Frequency and titers of binding anti-drug antibodies (ADAs) to GSK3511294, before and after GSK3511294 administration
Exploratory Objectives	**Exploratory Endpoints**
• To assess the effect of single SC doses of GSK3511294 on lung function	• Change from baseline: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), peak expiratory flow (PEF)
• Serum total IL-5 following single SC doses of GSK3511294	• Serum total IL-5 levels
• To explore drug specific circulating immune complexes (CIC) after single SC doses of GSK3511294	• Levels of CICs
• To determine the effect of single SC doses of GSK3511294 on serum markers of asthma	• Change from baseline in asthma biomarkers
• To explore the PK/PD (blood eosinophil count) relationship after single SC doses of GSK3511294, if deemed appropriate	• GSK3511294 plasma concentration and blood eosinophil count for determination of Half maximal effective concentration (EC50) and maximum effect, if deemed appropriate

* PK parameter abbreviations: AUC(0-∞) = area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; AUC(0-t) = area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments; AUC(0-WeekX) = area under the concentration-time curve from time zero to Week X; %AUCex = percentage of AUC(0-∞) obtained by extrapolation; Cmax = maximum observed concentration; tmax = time of occurrence of Cmax; tlast = time of last quantifiable concentration; CL/F = apparent clearance following subcutaneous dosing; Vd/F = apparent volume of distribution after subcutaneous administration; λz = terminal phase elimination rate constant; t½ = terminal phase half-life.

2.3. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Single ascending dose FTIH study to evaluate the safety, tolerability, immunogenicity, PK and pharmacodynamics of subcutaneously administered GSK3511294 in participants with mild to moderate asthma and blood eosinophils ≥ 200 cells/μL at screening. • Multi-centre, randomised, double-blind (sponsor clinical pharmacology modelling and simulation [CPMS] and statistician representatives open), placebo-controlled, parallel-group study.
Dosing	• Each participant will receive a single SC dose of GSK3511294 or placebo • Sentinel participants: In each cohort, one placebo and one GSK3511294 participant will be dosed before the remaining participants. Providing no safety issues are identified in the sentinel participants over an observation period of at least 72 hours, the remaining participants in the cohort may be dosed. The Investigator will discuss any safety concerns with the GlaxoSmithKline (GSK) medical monitor before dosing the remaining participants in a cohort. Sentinel dosing is not required in cohorts investigating a dose lower than or equal to the highest dose tested to date.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Planned single ascending SC doses of GSK3511294 were 2, 10, 30, 100 and 300 mg. • Actual dose levels matched the planned doses. • Planned cohort sizes are shown in the Overview of Study Design and Key Features figure; additional participants may be added to cohorts, if necessary to characterise the PK or pharmacodynamics of GSK3511294. • In each cohort, participants will be randomised 3:1 to receive GSK3511294 or placebo. • Additional cohorts of up to 12 participants may be added to test additional dose levels or to repeat a dose level already tested, if deemed necessary; however, the dose will not exceed 300 mg. The planned sample size is n=48 participants; the maximum sample size is n=72 participants (excluding

Overview of Study Design and Key Features	
	replacements for prematurely withdrawn participants).
Interim Analyses	• In stream data review occurred during the study to support dose escalation decisions. A formal interim analysis (IA1) took place once data were available at the 12-week time point after dosing in Cohort 4 (100 mg dose). The aim of the first interim analysis was to determine the doses and a dosing interval to move forward into the next phase of development. • The primary focus of the first interim analysis was the reduction in blood eosinophil counts. The ratio to baseline was derived for each dose and time point and compared to corresponding data from the placebo arm. Posterior means and corresponding 95% credible intervals were constructed for each of the available doses and time points. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest were constructed. • Following the review of the data from the first interim analysis, the protocol was amended to allow additional interim analyses to further assist the clinical development plan of the asset. None of the interim analyses are expected to affect the progression of this FTIH study. • Subsequent interim analyses will also mainly focus on the reduction in blood eosinophil counts and if deemed appropriate may also review CIC, IL-5, PK and immunogenicity data, as data permit. • In addition, blinded summary tables by cohort may be produced to facilitate review of safety data for Global Safety Board (GSB).

2.4. Statistical Hypotheses / Statistical Analyses

Given this study is the FTIH for GSK3511294, there are no formal statistical hypotheses to be tested. The assessment of safety and tolerability of single SC doses of GSK3511294 in this study will not include any formal comparisons.

For the PK and PD data, where appropriate, an estimation approach will be adopted and point estimates with corresponding confidence intervals will be provided. In addition, for the analysis of blood eosinophils, posterior means and corresponding 95% credible intervals will be constructed for each dose and time point. Furthermore, posterior probabilities that the placebo adjusted ratio is less than various thresholds of interest will be constructed.

3. PLANNED ANALYSES

3.1. Interim Analyses

In Stream Data Review

- In stream data review occurred during the study to support dose escalation decisions.
- Clinical Statistics were responsible for producing summary statistics of blood eosinophil data by dose and timepoint. Participants assigned to placebo were pooled across cohorts. Care was taken to ensure that no outputs were shared with the study team that would have inadvertently disclosed the treatment allocation of individual participants either that had started dosing or who had yet to be dosed. For example, n's were not displayed in the summary statistics of incomplete cohorts where 1 participant had yet to be dosed.
- Blood eosinophil count data were natural log-transformed prior to summarising and back-transformed as appropriate. The following summary statistics were presented: number of participants with available data (n) (if blind could be maintained), geometric mean, 95% CI of geometric mean and Standard Deviation (SD) logs. Blood eosinophil count data and blood eosinophil count ratio to baseline were presented. Outputs were produced using SAS software and independently Quality Controlled (QCed). Cut-off dates for each dose escalation meeting were agreed in advance and all available data for the cohort were included unless the inclusion of partial data for a specific timepoint and individual would have unblinded any participants. Summaries for earlier cohorts were updated if additional data were available for those cohorts.
- Dose escalation was only allowed after review of the following data at the highest dose level tested to date: at least 4 weeks' post-dose safety data and at least 2 weeks' post-dose PK data from at least 4 participants on active treatment; and at least 72 hours' post-dose safety data from the remaining participants in the cohort. In the unlikely event that one or more of the remaining participants discontinued the study within 72 hours after dosing, all available safety data from that/those participants were to have been reviewed. There were no minimum data requirements for blood eosinophil data – all available data were summarised.
- Clinical Pharmacology Modelling & Simulation (CPMS) were responsible for producing summary statistics of available derived PK parameters by cohort. CPMS are unblinded to study treatment. Care was taken to maintain the study blind. Summaries for earlier cohorts were updated if deemed appropriate. The following summary statistics were presented: geometric mean, 95% CI of geometric mean, SD logs, geometric coefficient of variation (CV) (%), median, minimum and maximum. Estimates for C_{max} and AUC(0-∞) with 95% prediction interval at the next dose level were provided.
- The outputs are for study team guidance and will not form part of the Clinical Study Report though formal summaries and plots of the final, complete and cleaned data will form part of the Clinical Study Report.

- In addition, blinded summary tables by cohort may be produced to facilitate review of safety data for GSB. If produced, these will be identical to the SAC outputs except will be presented by cohort rather than by actual treatment. Any AE summaries will have a total column. Possible candidates for blinded safety outputs for GSB are indicated in Appendix 12.

Planned Interim Analyses

- A first formal interim analysis took place once the accumulated safety, PK and PD data were deemed sufficient to determine the doses and a dosing interval to move forward into the next phase of development. This did not affect the progression of this FTIH study.
- The first interim analysis (IA1) occurred once data were available at the 12-week time point after dosing in Cohort 4 (100 mg or placebo).
- A second interim analysis (IA2) will take place after blood eosinophil data are available up to Week 26 for all subjects in Cohorts 1 – 4 and in at least 7 out of the 8 participants in Cohort 5 (300mg or placebo).
- A third interim analysis (IA3) is planned to occur once blood eosinophil data are available at the 32-week timepoint for 7 out of the 8 participants in Cohort 5 (300mg or placebo).
- Currently there are no plans for a fourth interim analysis (IA4), but this might be re-assessed after the results for the third interim analysis have been discussed. If performed, IA4 would be a repeat of a sub-set of the outputs included in IA3 but would include available data at the latest timepoints.
- The aim of the interim analyses is to assist in the clinical development plan of the asset by informing dose and dosing interval recommendations for future GSK3511294 studies.
- IA1 focussed on the reduction in blood eosinophil count data, but also included a review of the PK data. IA2 will only include a review of blood eosinophil data. IA3 in addition to blood eosinophil data will also include CIC, IL-5, Complement, Total IgE, immunogenicity and PK data, as data permit. IA4 (if performed) will be a subset of the outputs produced for IA3.
- The blood eosinophil count, CIC, IL-5 and immunogenicity data included in any interim analyses (where applicable) will not have been fully cleaned by Data Management as they will remain blinded to the results. Nevertheless, haematology and biomarker sample dates and times data will have been cleaned. A list of data required for the interim analyses is provided in the table below:

Form	Source	Reason	Notes	Interim Analysis
LAB	DM dataset	Require clean dataset to merge sample dates and times to enable windowing rules to be applied	Only dates/times corresponding to LBTESTCD=EOS_BLC were required for IA1. In addition, dates/times corresponding to LBTESTCD= IGE_PLC, C3_PLC and C4_PLC are required for IA3 and may also be required for IA4 (if performed). For blood eosinophil counts, this dataset will only contain results for screening values. Post dose results are treated as missing with an original text result of 'BLINDED' for EOS_BLC. Must be a record for each subject for each visit. There shouldn't be any missing records for intermediate visits.	Blood eosinophil count data required for all interim analyses, IgE, C3 and C4 required for IA3 and may be included in IA4 if performed.
Lab test results	Q2	Contain actual blood eosinophil counts as well as IgE, and Complement (C3 and C4) data	Must not be disseminated outside of CS or CPMS. CS will directly query any odd-looking results.	Blood eosinophil count data required for all interim analyses, IgE, C3 and C4 required for IA3 and may be required for IA4 if performed.

Form	Source	Reason	Notes	Interim Analysis
EXPOSURE	DM dataset	Needed so that actual date and time of dosing can be merged in order to apply the windowing rules.		All
RAND	DM dataset	Required to merge on randomisation numbers and subsequently the actual treatment codes.		All
Randomisation	CSV file from RandAll NG Coordinator	Actual treatment allocations are required, though study team members will only review summary information.	This information is already available to CS up to the latest cohort to be reviewed at the dose escalation meetings. Must not be disseminated outside of CS or CPMS.	All
CONMEDS	DM dataset	CS don't require this dataset, but all concomitant medications must be clean and up to date to make decisions on protocol deviations.	Will need to discuss protocol deviations prior to the interim analysis and identify if any subjects need to be excluded or partially excluded from the interim analysis.	All
PK	SMS2000	Required for population PK analysis	Treatment details and body weight need to be merged on to the PK concentration dataset	Required for IA1 and IA3, may be required for IA4 if

Form	Source	Reason	Notes	Interim Analysis
				performed
VITALS	DM dataset	Body weight (latest available Predose) required for population PK analysis		Required for IA1 and IA3, may be required for IA4 if performed
BIOMARK	DM dataset	IL-5 and CIC sample dates and times	DM to reconcile dates and times of collections but will remain blinded to test results.	Required for IA3, may be required for IA4 if performed
IL-5 results	Alliance Pharma	IL-5 data	DM will remain blinded to test results. Test result must not be disseminated outside of CS or CPMS.	Required for IA3, may be required for IA4 if performed
CIC results	BIB	CIC data	DM will remain blinded to test results. Test result must not be disseminated outside of CS or CPMS	Required for IA3, may be required for IA4 if performed
IMGEN	DM dataset	Immunogenicity sample dates and times	DM to reconcile dates and times of collections but will remain blinded to test results.	Required for IA3, may be required for IA4 if performed
Immunogenicity results	GSK Clinical Immunology Lab (US)	Binding antibody and neutralising antibody detection	DM will remain blinded to test results. Test result must not be disseminated outside of CS or CPMS	Required for IA3, may be required for IA4 if performed

- The primary focus of the interim analyses will be reduction in blood eosinophil counts. The ratio to baseline will be derived for each dose and time point and will be

compared to corresponding data from the placebo arm. Posterior means and corresponding 95% credible intervals will be constructed for each of the available doses and time points.

- For each available dose group, the posterior probability that the placebo adjusted ratio to baseline in blood eosinophils is ≤0.16 at the 12-week timepoint will be calculated. This corresponds to the posterior probability that the reduction from baseline in blood eosinophil count is at least 84% compared to placebo at Week 12. If this probability exceeds 80%, the dose will be deemed to have met the pre-defined success criterion.
- The same statistical methods will be applied for the interim analyses as for the SAC analysis.
- For the interim analyses, the posterior probability that the placebo adjusted ratio from baseline in blood eosinophils is less than various thresholds (e.g. ≤0.50, ≤0.30 and ≤0.15) at appropriate timepoints including at least 12, 18, 26 and 32 weeks (if available) will also be calculated, dependent on the previous results. For example, if there is insufficient evidence of a 50% improvement over placebo (corresponding to a ratio of 0.50), then lower ratio thresholds will not be investigated. Later timepoints may also be included if it is considered there are sufficient data.
- The PD interim analysis will be performed by GSK Clinical Statistics and only the responsible statistician (and Quality control [QC] statistician) will have access to individual participant data. However, the findings of the interim analysis will be shared with the entire GSK study team and relevant decision-makers within GSK.
- In support of the blood eosinophil data analysis, an interim population PK analysis will be conducted. The population PK parameters will be estimated using planned sampling times. This analysis will be performed by GSK CPMS who will be unblinded to study treatment.
- Interim analysis outputs may be shared with relevant regulatory authorities to discuss the clinical development plan strategy.

3.2. Final Analyses

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

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final SDL 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.
5. PK data have been uploaded

6. Data Quality Lead (DQL) has declared database freeze (DBF)

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprised of all participants who were screened.	• Listings (unless specified otherwise)
Safety	• Comprised of all randomised participants who receive at least one dose of study treatment. • This population will be based on the treatment the participant actually received rather than their randomised treatment. • Note that any non-randomised participant that received at least one dose of study treatment should be listed.	• Study Population • Safety
Pharmacokinetic (PK)	• Participants in the 'Safety' population for whom a pharmacokinetic sample was obtained and analysed.	• PK
Pharmacodynamic (PD)	• Participants in the 'Safety' population for whom a post-dose pharmacodynamic (ie blood eosinophil) sample was obtained and analysed.	• Blood eosinophils
Enrolled	• All participants who were randomised. Note screening failures (who never passed screening even if rescreened and even if they did pass pre-screening) and participants screened but never enrolled into the study (Reserve, Not Used) are excluded from the Enrolled population if they were not randomised. Participants that were randomised, but not dosed (e.g. because of failing pre-dosing checks) are included in the Enrolled population.	• Study Population

1. Refer to Appendix 12: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

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

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (V1.0/05Oct2017).

- 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.
- Protocol deviations will be assessed prior to unblinding at the interim analyses as well as prior to the final unblinding and freezing of the data. It is likely that participants who were included in the interim analysis will have the same analysis population flag at final analysis that they had at interim analysis. However, it is possible that information may come to light after the interim analyses that hadn't

been considered at the interim analyses, leading to a change in analysis population flag at final analysis for individual subjects.

- 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 at the final analysis. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description[2]	Description	Order [1]
A	GSK3511294 2 mg SC	GSK 2 mg	2
B	GSK3511294 Dose level 2	GSK 10 mg	3
C	GSK3511294 Dose level 3	GSK 30 mg	4
D	GSK3511294 Dose level 4	GSK 100 mg	5
E	GSK3511294 Dose level 5	GSK 300 mg	6
F	GSK3511294 Dose level 6	GSK XX mg	7
G	GSK3511294 Dose level 7	GSK XX mg	8
N/A	GSK3511294 All Active Doses	GSK All Doses	9
N/A	All doses including placebo	Total	10
P	Placebo	Placebo	1

NOTES:

1. Order represents treatments being presented in Tables, Figures and Listings (TFL), as appropriate.
2. Actual dose levels will be confirmed during the study. Dose levels 6 and 7: no current plans but included in case additional doses are to be investigated or doses are to be repeated. Replace X's with actual dose used in the cohort.

Treatment comparisons for each dose group versus placebo will be displayed using the following format, with XX replaced with the actual dose

GSK XX mg vs Placebo

A column denoting all active doses will be displayed for all safety tables. Some population summaries will include an overall total for all subjects in the population. These will be indicated in the programming notes for the relevant table specifications.

5.2. Baseline Definitions

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

Unless otherwise stated, if baseline data are missing no derivation will be performed and baseline will be set to missing.

5.3. Multicentre Studies

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

Centre Number	Name	Country	Status
PPD	PPD -Hannover	Germany	Active
PPD	PPD Berlin	Germany	Active
PPD	PPD -Manchester	United Kingdom	Active
PPD	PPD -London	United Kingdom	Active
PPD	PPD -London	United Kingdom	Active
PPD	PPD -Cambridge	United Kingdom	Active

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	Details
Strata	None
Covariates	Baseline blood eosinophil counts

5.4.2. Examination of Subgroups

- There will be an optional sensitivity analysis to assess the impact of participants in the following subgroups for the primary PD analysis. Although not expected in this patient population, exacerbations and changes in medication could affect the PD results. Other subgroups of interest may be defined prior to unblinding.

Subgroup	Categories
ICS Asthma Medication	Changed
Exacerbations or other events leading to the use of corticosteroids	>=1

5.5. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
17.3	Appendix 3: Assessment Windows
17.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
17.5	Appendix 5: Data Display Standards & Handling Conventions
17.6	Appendix 6: Derived and Transformed Data
17.7	Appendix 7: Reporting Standards for Missing Data
17.8	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, unless otherwise specified.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics and prior and concomitant medications will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. SAFETY ANALYSES

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

7.1. Overview of Planned Analyses

Table 1 provides an overview of the planned analyses, with further details of data displays being presented in Appendix 12: List of Data Displays.

Table 1 Overview of Planned Safety Analyses

Endpoint / Parameter/ Display Type	Absolute				Change from Baseline			
	Summary		Individual		Summary		Individual	
	T	F	F	L	T	F	F	L
Adverse Events								
All AEs	Y			Y				
Drug-related AEs	Y							
Serious AEs	Y			Y				
AEs leading to withdrawal	Y			Y				
Relationship between SOC and verbatim text				Y				
AEs by Preferred Term with Occurrences >=5%	Y							
AEs of Special Interest	Y			Y				
AEs by ADA Assay Result Category	Y							
Laboratory Data								
Liver and renal Chemistry			Y	Y[1]	Y			
Haematology				Y[1]	Y			
Urinalysis Data				Y[1]	Y			
High sensitivity C-reactive protein (hsCRP)				Y	Y			
ECG								
ECG Values	Y			Y[2]	Y			
ECG Findings	Y			Y				
Frequency of Maximum ECG Values by Pre-Specified Categories	Y							
Vital Signs								
Vital Signs Values				Y[3]	Y			

NOTES :

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

[1] Two Listings of chemistry and haematology data will be produced. One will list all abnormalities of PCI and the other will list all chemistry/haematology data for all participants with any chemistry/haematology abnormalities.
[2] Two listings of ECG data will be produced. One will list all ECG abnormalities of PCI and the other will list all ECG data for all participants with any ECG PCI values.
[3] Two listings of vital signs data will be produced. One will list all vital signs abnormalities of PCI and the other will list all vital signs data for all participants with any vital signs PCI values.

7.2. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 12: List of Data Displays.

7.3. Adverse Events of Special Interest Analyses

A summary table showing the number and percent of subjects, broken down by preferred term will be created using Hypersensitivity SMQ (narrow), Anaphylactic Reaction SMQ (narrow) and Vasculitis SMQ (narrow) as well as the number and percent of subjects with events of injection site reaction broken down by preferred term using MedDRA high level term (HLT) "Injection site reactions" under General disorders and administration site conditions SOC.

In addition, a profile summary table will be produced containing information including, but not be limited to, the number of occurrences of the event, event characteristics, time to onset, intensity, outcome and whether it led to withdrawal from the study.

A listing will be produced for subjects reporting events under the specified above SMQs and MedDRA HLT.

7.4. Clinical Laboratory Analyses

Laboratory evaluations including the analyses of Chemistry laboratory tests, Haematology laboratory tests, Urinalysis, and liver function tests will be based on GSK Core Data Standards. The details of the planned displays are in Appendix 12: List of Data Displays.

7.5. Other Safety Analyses

The analyses of non-laboratory safety test results including ECGs and vital signs will be based on GSK Core Data Standards, unless otherwise specified. Test results for hsCRP and Complement (C3 and C4) will be included within the laboratory data transfer and summarised in the same format as the standard haematology and chemistry data. For the purposes of summary statistics, any values <LLQ for hsCRP will be imputed to half the LLQ value (i.e. imputed to 0.075). The details of the planned displays are presented in Appendix 12: List of Data Displays.

8. LUNG FUNCTION TESTS

FEV1, % predicted normal FEV1 and FVC will be summarised at each scheduled timepoint. The details of the planned displays are presented in Appendix 12: List of Data Displays.

9. PHARMACOKINETIC ANALYSES

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

9.1. Primary Pharmacokinetic Analyses

9.1.1. Endpoint / Variables

9.1.1.1. Drug Concentration Measures

Refer to Appendix 5: Data Display Standards & Handling Conventions (Section 17.5.3 Reporting Standards for Pharmacokinetic)

Blood sampling time will be related to the start of dosing. Linear and semi-logarithmic individual plasma concentration-time profiles (by dose and participant) and mean (±SD) and median profiles by GSK3511294 dose will be plotted. Plasma concentrations of GSK3511294 will be listed and summarised by dose and nominal time.

9.1.1.2. Derived Pharmacokinetic Parameters

GSK3511294 Pharmacokinetic parameters will be calculated by standard non-compartmental analysis according to current working practices and using Phoenix.

All calculations of non-compartmental PK parameters will be based on actual sampling times. For each participant and for each dose, pharmacokinetic parameters described in Table 2 will be determined from the GSK3511294 plasma concentration-time data, as data permit.

- All pharmacokinetic parameters will be listed and summarised descriptively by dose.

Table 2 Derived Pharmacokinetic Parameters

Parameter	Parameter Description
AUC(0-t)	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (C(t)) will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.
AUC(0-∞)	Area under the plasma concentration-time curve from time zero extrapolated to infinity will be calculated as: AUC(0-inf) = AUC(0-t) + C(t) / lambda_z
AUC(0-WeekX)	Area under the plasma concentration-time curve from time zero to Week X will be calculated using the linear trapezoidal rule for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid. Planned parameters are AUC(0-Week4), AUC(0-Week12) and AUC(0-Week26).
%AUCex	The percentage of AUC (0-∞) obtained by extrapolation (%AUCex) will be calculated as: [AUC(0-inf) – AUC(0-t)] / AUC(0-inf) x 100
Cmax	Maximum observed plasma concentration, determined directly from the plasma concentration-time data.
λz	Terminal phase elimination rate constant. The number of points used to determine λz will also be reported.

Parameter	Parameter Description
tmax	Time to reach Cmax, determined directly from the plasma concentration-time data.
t½	Apparent terminal phase half-life will be calculated as: t½ = ln2 / lambda_z
tlast	Last time point where the concentration is above the limit of quantification
CL/F	Apparent clearance CL/F=dose / AUC(0-inf)
Vd/F	Apparent volume of distribution Vd/F=dose/ (λz x AUC(0-inf))

NOTES:

- Additional parameters may be included as required.

9.1.2. Summary Measures

- Area under plasma concentration-time curve (AUC (0-∞)) and Cmax following a single dose

9.1.3. Population of Interest

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

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Missing concentrations and concentrations below the limit of quantification of the assay will be handled as described in Guidance Document GUI_51487.

9.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

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

9.1.5.1. Statistical Methodology Specification

The following pharmacokinetic statistical analyses will only be performed if sufficient data are available (i.e. if participants have well defined plasma profiles). Analyses may not be performed on Cmax or AUC if the team considers there are a large amount of data either below the limit of quantification or non-calculable; alternatively, if the dose with limited data is at the lower end of the dose range, the data of this dose will be excluded, and the appropriate analysis conducted on the rest of the data. However, if there are non-calculable PK parameter data at intermittent doses no statistical analyses will be performed. A minimum of 3 doses will be required to assess dose proportionality.

Pharmacokinetic Statistical Analyses for Dose Proportionality: Power Method
Endpoint / Variables
• AUC(0-∞) and Cmax to be separately analysed after loge-transformation.
Model Specification
• Dose proportionality (Power Model) • Fixed effect model with log dose as a covariate
Model Checking & Diagnostics
• Model assumptions will be applied, but appropriate adjustments may be made based on the data. • Normality 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. • If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data
Model Results Presentation
• The coefficient of the slope with 90% confidence intervals, on the log scale, will be calculated, using the pooled estimate of variance, and used to assess dose proportionality. Point estimates and confidence intervals for the slope will be reported to 2 decimal places. • Scatter plots of log PK parameter vs Log (dose) will be produced for AUC(0-inf) and Cmax.

9.2. Secondary Pharmacokinetic Analyses

Dose proportionality will also be assessed using the ANOVA method

Pharmacokinetic Statistical Analyses for Dose Proportionality: ANOVA Method
Endpoint(s)
• AUC(0-∞), Cmax • Each endpoint to be assessed separately.
Model Specification
• The PK parameter will be dose-normalised prior to loge-transformation by multiplying by the reference dose / dose • Dose will be fitted as a fixed effect • To calculate the dose normalised parameters, the derived parameter for each dose will be divided by the relevant dose and multiplied by the chosen nominal dose (10mg).
Model Checking & Diagnostics
• Refer to dose proportionality power method analyses.
Model Results Presentation
• Point estimates for the adjusted means on the $\log_e$ scale, the mean difference between each dose (test) and the reference dose and associated 90% confidence interval will be constructed using the residual variance. These will not be presented. • The point estimate and confidence interval will then be exponentially back-transformed to allow the presentation of the adjusted (least square) geometric means for each treatment (dose) and associated 90% confidence intervals for the ratio test/reference.

Pharmacokinetic Statistical Analyses for Dose Proportionality: ANOVA Method
• Plots will also be provided showing the adjusted geometric mean ratio of test to reference treatment (dose) for AUC(0-∞) and Cmax together with 90% confidence interval. • Boxplots of dose-normalised AUC(0-∞) and Cmax versus dose will also be produced, a separate plot for each PK parameter.

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of GSK3511294 administered subcutaneously in participants with mild to moderate asthma enrolled in this single dose escalation FTIH study. The influence of participant demographics (e.g. weight, Body Mass Index (BMI)), and if deemed appropriate, baseline characteristics on the pharmacokinetics of GSK3511294 in this population will be investigated, as data permit. The individual participant PK parameters and predicted concentrations (post-hoc estimates) will be estimated and may be used to conduct any subsequent exposure and/or concentration-response (PK/PD) analyses (PD=blood eosinophil count), if deemed appropriate.

10.1. Statistical Analyses / Methods

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

- GSK3511294 plasma concentration-time data will be analysed by population methods (non-linear mixed effects modelling) using appropriate software (e.g. NONMEM, SAS).
- A description of the key models tested during the model development will be provided and tabulated.
- The population PK parameter estimates with 95% CI from the final model will be tabulated. Goodness of fit plots for the final model will be presented.
- Individual predicted GSK3511294 plasma concentrations will be listed.
- Individual post-hoc PK parameter estimates will be listed.

In support of the described analysis, a specific dataset will be generated. Further details of the population PK analysis methodology are provided in Appendix 9: Population Pharmacokinetic (PopPK) Analyses.

11. IMMUNOGENICITY ANALYSES

For the immunogenicity assessment, two types of anti-drug antibody (ADA) assays will be performed, a binding antibody assay and a neutralizing antibody assay.

For the binding assay, there will be a three-tiered analysis: screening, confirmation and titration. The screening assay produces a result of positive or negative relative to a screening cut point. Positive samples continue with the confirmation assay, which also produces a result of positive or negative relative to a confirmation cut point. For positive confirmation samples, a titre value will also be obtained to quantify the degree of binding in a titration assay and the sample will be tested with the neutralizing assay, which also reports results as positive or negative.

The binding ADA results at each available timepoint, including Predose as well as at any time post-baseline, will be summarised. Summary statistics for the titre result will also be presented by visit.

The binding ADA results at each visit will be categorised as negative, transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments or a single result at the final study assessment). In addition, the highest post-baseline binding ADA confirmatory result obtained for a subject will be summarised. Subjects with both positive and negative results will be identified in the positive category. Summary statistics for the highest titre result will also be presented.

A summary of adverse events by highest post-baseline binding ADA result will be produced.

A summary of positive confirmation binding ADA assay results in the subset of subjects who did not have a positive confirmation binding ADA assay result prior to the dosing of study treatment will also be presented. Neutralizing antibody assay results will be summarised by visit and will also be summarised by category (positive or negative).

Immunogenicity data will be listed for participants with at least one positive screening binding assay result.

12. CIRCULATING IMMUNE COMPLEXES

The presence of CICs will be determined in serum samples using a validated bioanalytical assay, using immunoglobulin detection. Further characterization with drug specific detection may be performed as needed. Summary statistics will be presented of CIC concentration by visit. A summary figure will also be presented.

13. COMPLEMENT, IgE AND INFLAMMATORY MARKERS

Complement (C3 and C4) and Total IgE will be summarised by parameter and visit and presented as a table and as a figure. The summary table will include baseline concentration, concentrations at each visit and ratio to baseline at each visit. Summary statistics to be presented are n, geometric mean, standard deviation (on log scale), median, minimum and maximum.

Inflammatory markers at screening will comprise Tumour necrosis factor-alpha (TNF-α), IL-2, IL-6, IL-10, Interferon-gamma (IFN-γ) and C3a. A screening serum sample will also be stored for assay of Antinuclear antibodies (ANA), Anti-neutrophil cytoplasmic antibody (ANCA) and anti-DNA antibodies, if required at a later date based on symptoms. After dosing, additional inflammatory markers and tests will be considered on an ad hoc basis should there be clinical concerns regarding an immune mediated AE. Inflammatory marker data will be presented as a listing.

14. PHARMACODYNAMIC AND BIOMARKER ANALYSES

14.1. Primary Pharmacodynamic and Biomarker Analyses

14.1.1. Endpoint / Variables

- Blood eosinophil ratio to baseline (following log-transformation)

14.1.2. Population of Interest

The primary pharmacodynamics and biomarker analyses will be based on the "Pharmacodynamic" population, unless otherwise specified.

14.1.3. Strategy for Intercurrent (Post-Randomization) Events

Missing data will not be imputed. Important events, such as the use of disallowed medication, that could affect the blood eosinophil counts will be considered during the review of protocol deviations prior to unblinding. A decision will be made prior to unblinding as to whether participants are full or partial protocol violators. Full protocol violators will be excluded from the PD population and partial violators will have only assessments included that occurred prior to the violation.

14.1.4. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 14.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

14.1.4.1. Statistical Methodology Specification

Endpoint / Variables
• Blood eosinophil ratio to baseline (following log-transformation)
Model Specification
• Data will be analysed by fitting a Bayesian dose response model. The 4-parameter Emax model will be fitted by first intent: • Log Blood Ratio $=E_0 - E_{max} * (Dose^n / (ED_{50}^n+Dose^n) + E_b$ where E_0 is the basal effect corresponding to the response when the dose is zero, E_{max} is the maximum eosinophil reduction. ED_{50} is the dose achieving half the maximum eosinophil reduction, n is the slope parameter and E_b is the baseline eosinophil count. • However, should the data not allow for a suitable model fit, then other models, such as the 3-parameter Emax model, may be attempted. Alternatively, other endpoints may be investigated if they allow a more suitable model fit. For example, weighted means may be analysed, derived as Area Under Effect Curve up to Week 26 (AUEC(0-Week 26)) divided by the duration. AUEC would be calculated using the linear trapezoidal rule for blood eosinophil counts or ratio to

baseline and will be based on actual sample times.

- This endpoint will be analysed using Bayesian inference assuming non-informative priors of the form;

PRIOR e0~Normal (0,1, sd=1000);
PRIOR E_{max}~Normal(0.1, sd=1000, lower=0);
PRIOR ed50~Beta(0.5, 5);
PRIOR n~Uniform(0.5, 5);

Model Checking & Diagnostics

- Refer to the relevant documentation (Bayesian Statistics Best Practice at GSK – Clinical Trials using Bayesian Inference).

Model Results Presentation

- For each dose and timepoint, blood eosinophil ratios will be summarised with descriptive statistics
- Posterior means and corresponding 95% credible intervals will be constructed for each dose and time point.
- At the interim analysis, for each available dose group, the posterior probability that the placebo adjusted ratio from baseline in blood eosinophils is ≤0.16 at the 12 week timepoint will be calculated. If this probability exceeds 80%, the dose will be deemed to have met the pre-defined success criterion.
- At the final analysis, for each dose group, the posterior probability that the placebo adjusted ratio from baseline in blood eosinophils is ≤0.25 at the 26 week timepoint will be calculated. If this probability exceeds 80%, the dose will be deemed to have met the pre-defined success criterion.
- For both the interim analyses and the final analysis, the posterior probability that the placebo adjusted ratio from baseline in blood eosinophils is less than various thresholds (e.g. ≤0.50,≤ 0.30 and ≤0.15) at appropriate timepoints including at least 12, 18, 26 and 32 week timepoints (data permitting for the interim analysis) will also be calculated, dependent on the previous results. For example, if there is insufficient evidence of a 50% improvement over placebo (corresponding to a ratio of 0.50), then lower ratio thresholds will not be investigated.

Subgroup Analyses

- N/A

Sensitivity and Supportive Analyses

- If the PD and Safety populations differ, the same statistical analysis using the Safety population may also be conducted.
- If any participants experience an exacerbation during the treatment phase and are given systemic steroids, or if they change their ICS asthma medication or if they are prescribed corticosteroids during the treatment phase, then the same statistical analysis may be conducted excluding those participants.
- The primary analysis will be repeated using windowed observations (See Section 17.3.1).
- Ratio to Baseline Blood eosinophils will be loge transformed and compared between

treatments using a mixed model repeated measures analysis, adjusting for baseline blood eosinophil count (loge scale) as a fixed effect. Visit and Treatment will be fitted as categorical fixed effects variables. Treatment by Visit and baseline blood eosinophil count by visit interaction effects will be included in the model as fixed effects. Each dose will be compared to Placebo at each Visit. The following SAS options will be applied:

- REPEATED statement with TYPE=UN to specify an unstructured covariance structure for the R matrix.
- The OBSMARGIN option on the LSMEANS statement in order to compute the adjusted geometric means with weights proportional to the input data set.
- The Kenward and Roger method (DDFM = KR) for approximating the denominator degrees of freedom to correct for bias in the estimated variance-covariance matrix.

14.2. Secondary Pharmacodynamic (and / or Biomarker) Analyses

Absolute blood eosinophil count data will be summarised descriptively by visit.

Serum samples will be collected during this study to measure total IL-5 levels as a marker of target engagement. Serum total IL-5 levels will be summarised descriptively.

Serum samples will also be collected during this study to allow the potential to measure biomarkers to identify factors that may influence the development of asthma and/or medically related conditions or the development of asthma treatments, as well as the biological and clinical responses to GSK3511294. If these samples are analysed for potential biomarkers, then they will be reported as a separate report. They will not form part of the SAC outputs.

14.2.1. Endpoint / Variables

- Blood eosinophil counts
- Serum IL-5, Total

14.2.2. Summary Measure

Both blood eosinophil counts data and Total serum IL-5 data are expected to be log-normally distributed and so will be log-transformed (natural logs) prior to summarisation by endpoint, treatment group and visit. Summary statistics to be presented are: n, geometric mean, SD Log, Median, Min, Max. For Total Serum IL-5 data the number of BLQ results will also be presented. Any values below the Lower Limit of Quantification (LLQ) will be imputed using LLQ/2.

Geometric means (±95% CIs) will be plotted for both endpoints based on absolute values.

14.2.3. Population of Interest

The secondary pharmacodynamics (and / or biomarker) analyses will be based on the 'Pharmacodynamic' population, unless otherwise specified.

14.2.4. Strategy for Intercurrent (Post-Randomization) Events

Missing data will not be imputed.

14.2.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK Data Standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 14.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

15. PHARMACOKINETIC / PHARMACODYNAMIC ANALYSES

The primary goal of this analysis is to investigate the relationship between plasma concentration and blood eosinophil count after single subcutaneous doses of GSK3511294 in participants with mild to moderate asthma enrolled in this FTIH study, if data permits, by population methods using for example an indirect response model. The influence of covariates such as participant baseline characteristics or if appropriate participant demographics on the PK/PD relationship will be investigated, as data permits. These PK/PD outputs will be produced by CPMS.

15.1. Statistical Analyses / Methods

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

- GSK3511294 plasma concentration (or pharmacokinetic parameter) and blood eosinophil count data will be analysed by population methods (non-linear mixed-effects modelling) using appropriate software (e.g., NONMEM, SAS).
- A description of the key models tested during the model development will be provided and tabulated.
- The population PD parameter estimates with 95% CI from the final model will be tabulated. Goodness of fit plots for the final model will be presented.

In support of the described analysis, a specific dataset will be generated. Further details of the population PK/PD analysis methodology are provided in Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses.

16. REFERENCES

GlaxoSmithKline Document No.: 2016N270529_06: A randomised double-blind (sponsor open), placebo-controlled, single ascending dose, First Time in Human study in participants with mild to moderate asthma to assess safety, tolerability, immunogenicity, pharmacokinetics and pharmacodynamics of GSK3511294 administered subcutaneously. Effective date: 07-JAN-2019.

17. APPENDICES

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

17.1.1. Exclusions from Per Protocol Population

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

Number	Exclusion Description
01	Inclusion #2 – Did not have >=200 cells/μL blood eosinophil count at screening
02	Prohibited Medication was taken

17.2. Appendix 2: Schedule of Activities

17.2.1. Protocol Defined Schedule of Events

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
			Day –1	Day 1				Day 2	Day 3	Day 4	Week											
											NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Informed consent	X [6]																					
Pre-screening Blood eosinophils	X[7]																					
Inclusion & exclusion criteria		X	X	X																		
Demography	X																					
Medical history [10]		X																				
Concomitant medication		←																				→
HIV, Hep B and Hep C screen		X																				
FSH and estradiol [8]		X																				
Pregnancy test [9]		X	X											X	X	X	X	X		X [5]	X [5]	X [5]
Drug, alcohol and cotinine screen		X	X																			
Genetic sample					X [11]																	
Administer IP					X																	
ACT [12]		X													X		X			X [5]	X [5]	X [5]
Height, weight and BMI	X [13]		X [13]																	X [5,13]	X [5,13]	X [5,13]
Full phys exam		X																		X [5]	X [5]	X [5]
Brief phys exam			X			X				X		X			X							

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
											Week											
			Day –1	Day 1				Day 2	Day 3	Day 4	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
Dispense rescue SABA		X	Resupply, as required.																			
Haematology (including blood eosinophil count), Clin. Chem., Urinalysis and hsCRP		X	X					X	X	X	X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Serum save (for immunological analysis, if needed)		X				Ad hoc, as required by symptoms – see Appendix 3.																
Inflammatory markers		X				Ad hoc, as required by symptoms – see Appendix 3.																
Complement (C3 & C4)		X	X					X	X	X	X		X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Total IgE			X					X	X	X	X			X	X	X	X	X		X [5]	X [5]	X [5]
PK Blood Samples				See Table 4.																		
Immunogenicity				X									X	X	X	X	X	X	X	X [5]	X [5]	X [5]
CICs				X				X					X	X	X	X	X	X	X	X [5]	X [5]	X [5]
12-lead ECG [14]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Vital signs [15]		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
AE/SAE review (inc local ISR up to 72 h after dosing)	X [16]		← →																			
IL-5 sample			X					X	X			X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]
Exploratory biomarkers of asthma in blood			X											X			X					
Spirometry		X	X			X		X		X		X			X					X [5]	X [5]	X [5]
PEF Training [17]		X																				

Procedure	Pre-Screen [1]	Screen [2]	In-Patient Period [3,4]								Out-patient Visits [4,5]											
											Week											
			Day –1	Day 1				Day 2	Day 3	Day 4	NA	1	2	4	8	12	18	24	26	32 [5]	36 [5]	40 [5]
				Pre-dose	0	2 h	8 h	24 h	48 h	72 h	Day											
											5	8	15	29	57	85	127	169	183	225 [5]	253 [5]	281 [5]
PEF [17]											X [17]											
Diary review [17]											X	X	X	X	X	X	X	X	X	X [5]	X [5]	X [5]

Abbreviations: ACT = Asthma Control Test; AE = adverse event; BMI = body mass index; CICs = circulating immune complexes; CRP = C-reactive protein; ECG = electrocardiogram; FSH = follicle stimulating hormone; h = hour(s); Hep B = Hepatitis B; Hep C = Hepatitis C; HIV = human immunodeficiency virus; IgE = immunoglobulin E; IL-5 = interleukin-5; IP = Investigational Product; ISR = injection site reactions; PEF = peak expiratory flow; PK = pharmacokinetic; SABA = short acting β-agonist; SAE = serious adverse event.

Notes:

1. Pre-screen up to 12 weeks before dosing. Blood eosinophils must be ≥ 200 cells/μL for participants to proceed to screening. Blood eosinophil count may be existing data or obtained at a pre-screen visit.
2. Screening up to 4 weeks before randomisation. Screening procedures may be done at one or more visits, within the screening window.
3. In the UK, all participants will be in-patient for at least 72 h after dosing. In Germany, all participants will be in-patient for at least 8 days after dosing (see Appendix 8 of the protocol for the German-specific time and events table).
4. Allowed time deviations will be documented in the Study Reference Manual.
5. All participants will have all out-patient visits up to Week 26 after dosing. Each cohort will also have out-patient visits after week 26, depending on the dose, as follows:
   - 2 and 10 mg: Week 32 only
   - 30 mg and 100 mg: Week 36 only
   - 300 mg: Weeks 32 and 40

   (For unplanned dose levels, the timing of out-patient visits will be documented in a Note to File.)
6. Informed consent will be taken either at the pre-screen visit, for participants who don't have an existing eosinophil count, or at screening, for those who do.
7. Blood eosinophils will be included in the haematology panel at all time points other than the pre-screen visit.
8. If required to confirm postmenopausal status.
9. Women on hormone replacement therapy, whose post-menopausal status cannot be confirmed, only.
10. Including cardiovascular (CV) disease, asthma exacerbation, and drug, alcohol and smoking history.
11. If the participant consents, an optional, genetic sample will be collected once during the study.
12. At each applicable visit, ACT should be done before any other assessment.
13. Height at pre-screening or screening only.
14. ECGs triplicate at all time points. ECGs should be time-matched to baseline (i.e. pre-dose on Day 1) from Day 2 onwards.
15. Blood pressure and heart rate in triplicate before dosing; single measurements after dosing. Single temperature and respiratory rate measurements at all time points.

16. Only SAEs are collected before dosing (see Section 7.3.1).
17. PEF will be recorded in the evening before bedtime on the day of the screening visit, then **twice** each day **(once in the morning upon waking and once in the evening before bedtime)** from the day after screening until the end of the study. Training of the participant in how to take measurements will occur at screening. PEF measurements will be taken and results will be recorded by the site while the participant is in-patient at the clinical site (ie from the evening of Day –1 until the morning of discharge). At all other time points, the participant will record their PEF as instructed, on their diary card, along with any rescue medication use and adverse events. Site staff will review the diary cards at each out-patient visit.

Note: References to Sections, Appendices and Tables in this Schedule of Activities refer to parts of Protocol amendment 6 (Dated: 07/JAN/2019).

17.3. Appendix 3: Assessment Windows

- All scheduled and unscheduled data will be considered for each assessment window.
- In summary tables, only scheduled timepoints for that cohort and assessment will be displayed. For example, spirometry data are not expected to be collected at all timepoints; if any spirometry data were taken e.g. at Week 4 then they will not be summarised. Similarly, Week 36 is not an expected visit for Cohorts 1 or 2 and so any data for the 2 lowest dose groups should not be displayed for Week 36.
- Only 1 value per participant, assessment and assessment window will be used in the calculation of summary statistics for that assessment; if a participant has more than 1 valid observation within an assessment window then the observation closest to the planned time will be used. If 2 observations are equidistant from the planned timepoint then the mean of the values will be taken.
- The assigned assessment windows will be shown in the listings, together with the planned assessment times.
- For the blood eosinophil data, windows based both on the study day and the dosing time have been agreed for the later timepoints. For example, to be included in the Day 85 (Week 12) window, the blood eosinophil sample must have been taken on Day 83, Day 84, Day 85, Day 86, Day 87 or Day 88 AND the time of the sample must have been within 3h relative to the Day 1 dosing time. If more than 1 sample with valid and non-missing results falls within this window, then only the results for the sample that was taken closest to the target timepoint will be included in the summary table. Both results will be included in the listing.
- All PD and safety summary outputs will be displayed by scheduled timepoint (not applying windowing rules). In addition, the statistical analysis for blood eosinophil data will also be displayed by windowed timepoint. Unwindowed outputs will be considered as the primary outputs, with the windowed output produced as a sensitivity analysis.

17.3.1. Definitions of Assessment Windows for Analyses

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint Label
			Beginning Timepoint	Ending Timepoint	
PD	Blood eosinophil data sensitivity analysis	Day -1	< Day 1 0h (Latest Predose)		Day -1
		Day 2 (24h)	Day 2 (22h)	Day 2 (26h)	Day 2 (24h)
		Day 3 (48h)	Day 3 (46h)	Day 3 (50h)	Day 3 (48h)
		Day 4 (72h)	Day 4 (70h)	Day 4 (74h)	Day 4 (72h)
		Day 5 (96h)	Day 5 (93h)	Day 5 (99h)	Day 5
		Day 8 (Week 1)	±1 Day and ± 3h of dosing time		Day 8 (Week 1)
		Day 15 (Week 2)	± 2 days and ± 3h of dosing time		Day 15 (Week 2)
		Day 29 (Week 4)	±2 days and ± 3h of dosing time		Day 29 (Week 4)
		Day 57 (Week 8)	±2 days and ± 3h of dosing time		Day 57 (Week 8)
		Day 85 (Week 12)	±2 days and ± 3h of dosing time		Day 85 (Week 12)
		Day 127 (Week 18)	±4 days and ± 3h of dosing time		Day 127 (Week 18)
		Day 169 (Week 24)	±4 days and ± 3h of dosing time		Day 169 (Week 24)
		Day 183 (Week 26)	±4 days and ± 3h of dosing time		Day 183 (Week 26)
		Day 225 (Week 32)	±4 days and ± 3h of dosing time		Day 225 (Week 32)
		Day 253 (Week 36)	±4 days and ± 3h of dosing time		Day 253 (Week 36)
		Day 281 (Week 40)	±4 days and ± 3h of dosing time		Day 281 (Week 40)
Safety, Spirometry, Complement, IgE and Il-5 data presented by visit.	ECG, Vital signs, laboratory, Spirometry, C3 and C4, IgE, IL-5	Day -1	Any time on Day -1. Note that if there is no scheduled Predose assessment for the parameter then latest valid result prior to Day 1 dosing should be used.		Day -1
	Immunogenicity, CICs, ECG, Vital signs	Day 1 (Predose)	≤75 m prior to dosing time		Day 1 (Predose)
	ECG, Vital signs	Day 1 (2h)	Day 1 (1.75h)	Day 1 (2.25h)	Day 1 (2h)
	Spirometry	Day 1 (2h)	Day 1 (1.5h)	Day 1 (2.5h)	Day 1 (2h)
	ECG, Vital signs	Day 1 (8h)	Day 1 (7.75h)	Day 1 (8.25h)	Day 1 (8h)

Analysis Set / Domain	Parameter (if applicable)	Target	Analysis Window		Analysis Timepoint Label
			Beginning Timepoint	Ending Timepoint	
	Laboratory, Complement, IgE, CICs, ECG, Vital signs, Spirometry, IL-5	Day 2 (24h)	Day 2 (23.75h)	Day 2 (24.25h)	Day 2 (24h)
	Laboratory, Complement, IgE, ECG, Vital signs, IL-5	Day 3 (48h)	Day 3 (47h)	Day 3 (49h)	Day 3 (48h)
	Laboratory, Complement, IgE, ECG, Vital signs, Spirometry, IL-5	Day 4 (72h)	Day 4 (71h)	Day 4 (73h)	Day 4 (72h)
	Laboratory, Complement, IgE, ECG, Vital signs, IL-5	Day 5	Assessment must have been done on Day 5		Day 5
	Laboratory, ECG, Vital signs, Spirometry, IL-5	Day 8 (Week 1)	±1 day		Day 8 (Week 1)
	Laboratory, Complement, Immunogenicity, CICs, ECG, Vital signs, IL-5	Day 15 (Week 2)	±1 day		Day 15 (Week 2)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, IL-5	Day 29 (Week 4)	±3 days		Day 29 (Week 4)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, Spirometry, IL-5	Day 57 (Week 8)	±3 days		Day 57 (Week 8)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, IL-5	Day 85 (Week 12)	±3 days		Day 85 (Week 12)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, IL-5	Day 127 (Week 18)	±3 days		Day 127 (Week 18)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, IL-5	Day 169 (Week 24)	±3 days		Day 169 (Week 24)
	Laboratory, Complement, Immunogenicity, CICs, ECG, Vital signs, IL-5	Day 183 (Week 26)	±3 days		Day 183 (Week 26)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, Spirometry, IL-5	Day 225 (Week 32)	±3 days		Day 225 (Week 32)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, Spirometry, IL-5	Day 253 (Week 36)	±3 days		Day 253 (Week 36)
	Laboratory, Complement, IgE, Immunogenicity, CICs, ECG, Vital signs, Spirometry, IL-5	Day 281 (Week 40)	±3 days		Day 281 (Week 40)

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

17.4.1. Study Phases

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

17.4.2. Treatment States

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

17.4.2.1. Treatment States for Safety and Pharmacodynamic Data

Treatment State	Definition
Pre-Treatment	Date and Time ≤ Dosing Date and Time
On-Treatment	Date and Time > Dosing Date and Time

17.4.2.2. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If concomitant medication end date is not missing and is before 28 days prior to screening visit
Concomitant	Any medication that is not considered as prior. These will be further split into those that were started prior to dosing and those started after dosing as follows: • Pre-Treatment: Start Date and Time ≤ Dosing Date and Time • On-Treatment: Start Date and Time > Dosing Date and Time

NOTES:

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

17.4.3. Study Phases for Adverse Events

Treatment State	Definition
Pre-Treatment	AE Start Date and time < Study Treatment Start Date and time
On-Treatment	If AE Start date and time ≥Study treatment start date and time
Onset Time Since Dose (Days)	If Dose Date > AE Start Date = AE Start Date - Treatment Start Date If Dose Date ≤ AE Start Date = AE Start Date - Treatment Start Date +1 Missing otherwise.
Duration (Days)	AE End Date – AE Start Date + 1
Drug-related	If relationship is marked 'YES' on Inform/CRF OR value is missing.

17.4.4. Treatment Emergent Flags for Adverse Events

Flag	Definition
Treatment Emergent	• If AE start date is on or after treatment start date

NOTES:

- Time of study treatment dosing and start/stop time of AEs should be considered

17.5. Appendix 5: Data Display Standards & Handling Conventions

All displays (Tables, Figures & Listings) will use the term 'Subjects'. However, RAP text will refer to "Participants" in-line with the master RAP template and protocol.

17.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175.corpnet2.com
HARP Area	SAC: GSK3511294/MID205722/Final_01 Interim 1 (restricted access): GSK3511294/MID205722/Internal_01 Unblinded data review for dose escalations (restricted access): GSK3511294/MID205722/Internal_03 Interim 2 (restricted access): GSK3511294/MID205722/Internal_02 Interim 3 (restricted access): GSK3511294/MID205722/Internal_04 Dry-run: GSK3511294/MID205722/Internal_05 Interim 4 (restricted access): GSK3511294/MID205722/Internal_06 (if performed) GSB: GSK3511294/MID205722/Safety_02 (if performed)
QC Spreadsheet	SAC: ARWORK\GSK3511294\MID205722\Final_01\Documents Interim1: ARWORK\GSK3511294\MID205722\Internal_01\Documents Interim2: ARWORK\GSK3511294\MID205722\Internal_02\Documents Interim3: ARWORK\GSK3511294\MID205722\Internal_04\Documents Interim4: ARWORK\GSK3511294\MID205722\Internal_06\Documents (if performed) Dry-run: ARWORK\GSK3511294\MID205722\Internal_05\Documents Unblinded data review for dose escalations: ARWORK\GSK3511294\MID205722\Internal_03\Documents GSB: ARWORK\GSK3511294\MID205722\Safetyl_02\Documents (if performed)
Analysis Datasets	
• Analysis datasets will be created according to Integrated Data Standards Library (IDSL) dataset standards.	
Generation of RTF Files	
• RTF files will be generated for all SAC and GSB (if performed) tables.	

17.5.2. 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

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

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Actual time relative to dosing will be used for individual participant plasma concentration-time figures and for derivation of PK parameters.
  - Windowed time relative to dosing will be used in all other summary figures, summary tables, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  - The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  - Unscheduled or unplanned readings will be presented within the participant's listings.
  - Visits outside the protocol defined time-windows (i.e. recorded as protocol deviations) will be included in listings but omitted from summary figures and summary tables. The statistical analysis of blood eosinophil data will be performed using planned times and repeated using windowed times.

Unscheduled Visits

- Only planned timepoints will be included in summary tables and/or figures. Results from unscheduled assessments will be included in summaries if they are within the scheduled time window and are closer to the target timepoint than the scheduled assessment.
- All scheduled and unscheduled visits will be included in listings and individual participant figures.
- If there is an 'any time post baseline' category or a 'Worst case' category, then both scheduled and unscheduled results will be considered.

Descriptive Summary Statistics

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

Graphical Displays

- Refer to IDSL Statistical Principles 7.01 to 7.13.

17.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
PC Windows Non-Linear (WNL) File	PC WNL file (CSV format) for the non-compartmental analysis by Clinical Pharmacology Modelling and Simulation function will be created according to the 'Standards for the Transfer and Reporting of PK Data using HARP' guideline. Note: BLQ concentration values will be imputed as per GUI_51487
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Note: BLQ concentration values will be imputed as per GUI_51487 for descriptive summary statistics/analysis and summarized graphical displays only.
NONMEM/Pop PKPD File	Pop-PKPD file (CSV and SAS) for the Pop-PK and Pop PKPD analyses by Clinical Pharmacology Modelling and Simulation function will be created according to the Pop PKPD Dataset Specification document (separate document).
Pharmacokinetic Parameter Data	
Is NQ impacted PK Parameters Rule Being Followed	Yes, refer to Standards for Handling NQ Impacted PK Parameters.
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.
Descriptive Summary Statistics (Log Transformed)	N, n, geometric mean, 95% CI of geometric mean, standard deviation (SD) of logged data and between geometric coefficient of variation (CVb (%)) will be reported. $CVb\ (\%) = \sqrt{(\exp(SD^2) - 1)} * 100$ (SD = SD of log transformed data)
Parameters Not Being Log Transformed	Tmax and tlast
Parameters to be listed only	First point, last point and number of points used to determine λz.

17.6. Appendix 6: Derived and Transformed Data

17.6.1. 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 17.3.1) 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 (including post-baseline unscheduled assessments) for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

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

Baseline
• If the baseline value is missing, then all subsequent derived baseline variables will also be missing. The baseline definition will be footnoted on all change from baseline displays. • Unless otherwise specified, baseline measurements will be derived as follows: Change from Baseline= Post-Dose Visit Value – Baseline % Change from Baseline=100 x [(Post-Dose Visit Value – Baseline) / Baseline] Maximum Change from Baseline= Calculate the change from baseline at each given timepoint and determine the maximum change Ratio to Baseline= Post-Dose Visit Value/Baseline

17.6.2. Safety

Adverse Events
AE'S of Special Interest
• Please refer to Section 7.3.

17.6.3. Pharmacokinetic

PK parameters
• PK concentrations will be handled as described in document GUI_51487. • PK parameters will be derived as described in document GUI_51487.

17.6.4. Population Pharmacokinetic, Pharmacokinetic/ Pharmacodynamic (PopPK, PKPD)

PK concentrations
Blood eosinophil counts
• PK concentrations below the limit of quantification of the assay will be treated as missing. • Zero value blood eosinophil count will be imputed with a value of 0.005.

17.6.5. Pharmacodynamic and Biomarker

Blood eosinophils
Ratio to Baseline
• Blood eosinophil counts will be natural log-transformed prior to analysis. Any zero values will be imputed with a value of 0.005 prior to log transformation. • Missing values e.g. due to missed assessments will not be imputed. This will include values missing at baseline. • Baseline is defined as the latest Predose non-missing blood eosinophil count. • Change from Baseline at time T=log (blood eosinophil count at Time T) – log(Baseline blood eosinophil count). • Ratio to Baseline at time T=exp(Change from Baseline at time T) • If the weighted mean (0-Week 26) is derived, it will be calculated as AUEC(0-Week 26)/duration up to Week 26 visit. If the Week 26 result is missing then AUEC(0-Week 26) will be set to missing. If derived, AUEC will be calculated using the linear trapezoidal rule for blood eosinophil counts or ratio to baseline and will be based on actual sample times.

17.6.6. Other

Asthma Control Test (ACT)
• Total ACT score will be derived for each subject at each ACT assessment visit. • The 5 subscores will be added to create the total ACT score. • Each subscale may have the value 1- 5; Total ACT score may range from 5 – 25. • If any of the subscores are missing then the total score will be set to missing for that subject at that visit.

17.7. Appendix 7: Reporting Standards for Missing Data

17.7.1. Premature Withdrawals

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

17.7.2. 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 tool/eCRF: ○ These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. • Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Outliers	○ Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.
Biomarkers	• Any values below the Lower Limit of Quantification (LLQ) will be assigned a value of ½ LLQ for display purposes in Figures and for computation of summary statistics. Any values above the Upper Limit of Quantification (ULQ) will be assigned to the ULQ for display purposes in Figures and for computation of summary statistics. If multiple LLQ and /or ULQ values are available per assay (for example if multiple runs with different standard curves are utilised) then the LLQ and/or ULQ value used for the above imputation shall be the minimum of the available LLQs and/or the maximum of the ULQs. Where biomarker concentrations are from an assay of an increased dilution factor the LLQ and ULQ will be multiplied by this factor. • If the number of LLQ (and/or ULQ) values is large for an Individual biomarker then alternative analysis methods such as TOBIT analysis may be required. "Large" is hard to define prospectively and may depend upon the dataset in question. Any such methodology will be documented in the statistical contributions to the study report. • Imputed values will be used in tables and figures, unless the proportion of imputed values at a given time point is large, in which case the summary statistics may not be presented for that time point and/or alternative actions will be taken and documented in the study report. • Where values are imputed, the number of such imputations will be included as a summary statistic in the relevant summary tables.

17.7.2.1. Handling of Missing and Partial Dates

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

17.8. Appendix 8: Values of Potential Clinical Importance

17.8.1. Laboratory Values

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	Male		0.54
		Female		0.54
		Δ from BL	↓0.075	
Hemoglobin	g/L	Male		180
		Female		180
		Δ from BL	↓25	
Lymphocytes	$x10^9$/ L		0.8	
Neutrophil Count	$x10^9$/ L		1.5	
Platelet Count	$x10^9$/ L		130	550
While Blood Cell Count (WBC)	$x10^9$/ L		3	15

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Albumin	mmol/L		30	
Calcium	mmol/L		2	2.75
Creatinine	mmol/L	Δ from BL		↑ 44.2
Glucose	mmol/L		3	9
Magnesium	mmol/L		0.5	1.23
Phosphorus	mmol/L		0.8	1.6
Potassium	mmol/L		3	5.5
Sodium	mmol/L		130	150
Total CO2	mmol/L		18	32

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

Laboratory Parameter	Units	Category	Clinical Concern Range	
			Low Flag (< x)	High Flag (>x)
hsCRP				10

17.8.2. ECG

ECG Parameter	Units	Clinical Concern Range	
		Lower	Upper
Absolute			
Absolute QTcF Interval	msec	> 450 [1]	
Absolute PR Interval	msec	< 110 [1]	> 220 [1]
Absolute QRS Interval	msec	< 75 [1]	> 110 [1]
Absolute QT	msec	>600	
Change from Baseline			
Increase from Baseline QTcF	msec	> 60 [1]	

NOTES: [1] Represent standard ECG values of PCI for HV studies

17.8.3. Vital Signs

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

17.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

17.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

Specifications for the generation of the dataset will be provided in a separate document.

17.9.2. Population Pharmacokinetic (PopPK) Methodology

GSK3511294 plasma concentration-time data collected in this single ascending dose FTIH study will be analysed by population methods (non-linear mixed-effects modelling), using appropriate software (e.g., NONMEM or SAS), and based on the PK population. GSK3511294 plasma concentrations below the limit of quantification of the assay will be treated as missing. Outlier data will be assessed for plausibility; however, the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

Data will be analysed by fitting a one-compartment pharmacokinetic model with first-order absorption and elimination. Since bodyweight is a known determinant of monoclonal antibodies exposure, the inclusion of bodyweight into the model using allometry with fixed physiological allometric exponents of 0.75 and unity for clearance and volume, respectively, will be tested. If deemed appropriate and if data permits, the effect of other covariates may be investigated.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PK parameters vs. covariates), and formally by automated linear model fitting using for example proc glmselect in SAS 9.2 (or higher). Individual PK parameters and covariates will be log-transformed and standardized before analysis. For forward and backward selections, significance levels of 0.1 and 0.05 will be applied, respectively. Co-linearity between covariates will be carefully considered.

Identified covariates will then be subjected to traditional covariate analysis (with estimation step) and will follow the procedures described below. If deemed appropriate box plots of apparent systemic clearance versus covariates of interest (e.g. immunogenicity status) will be provided.

A description of the key models tested during the model development and the population PK parameter estimates with 95% CI from the final model will be provided and tabulated. Individual predicted GSK3511294 plasma concentrations and individual post-hoc PK parameter estimates will be listed.

Covariate Model Selection Procedures

The covariate model building will follow a step-wise process consisting of a forward and backward selection procedure. The likelihood ratio test will be used to evaluate the significance of incorporating or removing covariates into the population model based on alpha levels set *a priori*. For forward and backward selections, a significance level of

0.05 and 0.01 for first order conditional estimation with interaction (FOCE-I) will be used, respectively.

- **Step-wise forward addition procedure**

Each covariate will be included individually in the 'base model' to identify covariates resulting in a decrease in the objective function value (OFV) of > 3.84, $\chi 2 < 0.05$ for 1 degree of freedom (*df*) using FOCE-I. The retained covariates will then be added to the base model one by one, starting with the most significant ones until all covariates have been tested. Note, if a covariate exponent estimate is numerically small, the covariate will not be retained; irrespective of objective function. This will constitute the full model.

- **Backward elimination procedure**

From the full model, the significance of each covariate will be tested individually by removing covariate one by one until all non-significant covariates have been excluded. A covariate will be retained if upon removal, the OFV increase by more than 6.64 points ($\chi 2< 0.01$ for 1 *df)* using FOCE-I. Note, a covariate may be retained in the model despite being found non-statistically significant, if there is a strong rationale for its inclusion. This will constitute the final model. Centering of continuous covariates may be considered, as appropriate. The mean or median value of the participants included in the study may be used for example.

Model Evaluation

The uncertainty in the parameter estimates will be assessed. Furthermore, the model performance will be investigated using a set of goodness of fit plots and if deemed necessary, by Visual Predictive Check (VPC) method. Other evaluation methods may be used (e.g., bootstrapping) if deemed appropriate.

17.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

17.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

Specifications for the generation of the dataset will be provided in a separate document.

17.10.2. Pharmacokinetic / Pharmacodynamic Methodology

GSK3511294 plasma concentration (or pharmacokinetic parameter) and blood eosinophil count data collected in this single ascending dose FTIH study will be analysed by population methods (non-linear mixed-effects modelling), using appropriate software (e.g., NONMEM, SAS). Zero values for the baseline blood eosinophil count as well as for blood eosinophil count post-dosing will be imputed a value of 0.005. Outlier data will be assessed for plausibility; however, the aim is to use all available data whenever possible. Any decision to exclude data will be fully documented and specified in the clinical study report.

A two-stage approach will be employed whereby post-hoc individual predicted GSK3511294 plasma concentrations will be merged with blood eosinophil data before model fitting. Data will be analysed by fitting an indirect response model parameterised in term of baseline blood eosinophil count (KRO), rate of elimination of eosinophils in the blood (Kout), concentration resulting in 50% of maximum drug effect (IC_{50}) and maximum effect (Imax).

If deemed appropriate and if data permits, the effect of covariates (e.g., baseline blood eosinophil count) may be investigated.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PD parameters vs. covariates), and formally by automated linear model fitting using for example proc glmselect in SAS 9.2 (or higher). Individual PD parameters and covariates will be log-transformed and standardized before analysis. For forward and backward selections, significance levels of 0.1 and 0.05 will be applied, respectively. Co-linearity between covariates will be carefully considered. Identified covariates will then be subjected to traditional covariate analysis (with estimation step) and will follow the same procedures as described in Appendix 9.

A description of the key models tested during the model development and the population PD parameter estimates with 95% CI from the final model will be provided and tabulated.

Model evaluation will be as described in Appendix 9.

17.11. Appendix 11: Abbreviations & Trade Marks

17.11.1. Abbreviations

Abbreviation	Description
ACT	Asthma Control Test
ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIC	Akaike's Information Criteria
ANOVA	Analysis of Variance
AUC	Area under concentration-time curve
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a participant across all treatments
AUC(0-Week x)	Area under the concentration-time curve from time zero to Week x
AUEC(0-Week x)	Area under the PD effect-time curve from time zero to Week x
BLQ	Below limit of Quantification
BMI	Body Mass Index
C	Complement
CI	Confidence Interval
CIC	Circulating immune complex
CL	Clearance
CL/F	Apparent clearance following subcutaneous dosing
Cmax	Maximum observed concentration
CPMS	Clinical Pharmacology Modelling & Simulation
CPSSO	Clinical Pharmacology Science & Study Operations
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
Df	Degrees of Freedom
DOB	Date of Birth
DP	Decimal Places
DQL	Data Quality Lead
EC50	Half maximal effective concentration
ECG	Electrocardiogram
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration

Abbreviation	Description
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
FEV1	Forced expiratory volume in 1 second
FOCE-I	First order conditional estimation with interaction
FTIH	First Time in Humans
FVC	Forced vital capacity
GSB	Global Safety Board
GSK	GlaxoSmithKline
hsCRP	High Sensitivity C-reactive Protein
IA	Interim Analysis
IC50	Concentration resulting in 50% of maximum drug effect
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IgE	Immunoglobulin E
IL	Interleukin
Imax	Maximum effect
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
KOUT	Rate of elimination of eosinophils in the blood
KRO	Baseline blood eosinophil count
λz	Terminal phase elimination rate constant
LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
n	Number of participants with available data
NONMEM	Non-linear mixed-effects modelling
OFV	Objective function value
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PEF	Peak expiratory flow
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
PSAP	Program Safety Analysis Plan
QC	Quality Control
QTcF	Fridericia's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SC	Subcutaneous
SD	Standard Deviation

Abbreviation	Description
SDL	Source Data Lock
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SOP	Standard Operation Procedure
t½	Terminal phase half-life
TA	Therapeutic Area
TFL	Tables, Figures & Listings
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
Vd/F	Apparent volume of distribution after subcutaneous Administration
VPC	Visual Predictive Check

17.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
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17.12. Appendix 12: List of Data Displays

17.12.1. 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
Safety	2.1 to 2.n	2.1 to 2.n
Pharmacokinetic	3.1 to 3.n	3.1 to 3.n
Population Pharmacokinetic (PopPK)	4.1 to 4.n	4.1 to 4.n
Pharmacodynamic and Exploratory Markers	5.1 to 5.n	5.1 to 5.n
Pharmacokinetic / Pharmacodynamic	6.1 to 6.n	6.1 to 6.n
Other	7.1 to 7.n	7.1 to 7.n
Section	**Listings**	
Listings	1 to x	

17.12.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 13: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacokinetic	PK_Fn	PK_Tn	PK_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacodynamic and Exploratory Markers	PD_Fn	PD_Tn	PD_Ln
Pharmacokinetic / Pharmacodynamic	PKPD_Fn	PKPD_Tn	PK/PD_Ln
Other	OTH_Fn	OTH_Tn	OTH_Ln

NOTES:

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

17.12.3. Deliverables

Delivery	Description
IAn	Interim Analysis n
GSB	Global Safety Board
SAC	Final Statistical Analysis Complete

17.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Participant Disposition					
1.1.	Safety	ES1	Summary of Participant Disposition for the Participant Conclusion Record	ICH E3, FDAAA, EudraCT	SAC
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC
1.3.	Enrolled	NS1	Summary of Number of Participant by Country and Site ID	EudraCT/Clinical Operations	SAC
Protocol Deviation					
1.4.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3 Include total column	SAC
Population Analysed					
1.5.	All subjects	SP1	Summary of Study Populations	IDSL	SAC
Demographic and Baseline Characteristics					
1.6.	Safety	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT Include BMI Include an overall total group.	SAC
1.7.	Enrolled	DM11	Summary of Age Ranges	EudraCT	SAC
1.8.	Safety	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.9.	Safety	FH1	Summary of Family History of Cardiovascular Risk Factors		SAC

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
1.10.	Safety	MH1	Summary of Current Medical Conditions	ICH E3	SAC
1.11.	Safety	MH1	Summary of Past Medical Conditions	ICH E3 Separate summaries for Current & Past conditions, if collected.	SAC
1.12.	Safety	CM1	Summary of Prior Medications by Asthma Medication Status	ICH E3 Split by Asthma medication and non-asthma medication.	SAC
1.13.	Safety	CM1	Summary of Concomitant Medications by Asthma Medication Status – Pre-Treatment	ICH E3 Split by Asthma medication and non-asthma medication. Only present if at least 5 medications were started within 28 days before screening visit and if the start date of medication is prior to dosing.	SAC
1.14.	Safety	CM1	Summary of Concomitant Medications by Asthma Medication Status – On Treatment	ICH E3 Split by Asthma medication and non-asthma medication.	SAC

17.12.5. Safety Tables

Note that a column denoting all active doses will be displayed for all safety summary tables.

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
2.1.	Safety	CP_AE1p	Summary of All Adverse Events by System Organ Class and Preferred Term	ICH E3 Include a total column Post dose AEs only	GSB (if required) / SAC
2.2.	Safety	AE5A	Summary of Adverse Events by System Organ Class and Preferred Term and Maximum Intensity	ICH E3	SAC
2.3.	Safety	CP_AE1p	Summary All Drug-Related Adverse Events by System Organ Class and Preferred Term	ICH E3 .	SAC
2.4.	Safety	CP_AE1p	Summary of All Adverse events leading to study withdrawal by System Organ Class and Preferred Term	Only produce if at least 5 participants have an AE that leads to study withdrawal.	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.5.	Safety	AE15	Summary of Common (>=5%) Non-serious Adverse Events by System Organ Class and Preferred Term (Number of Participant and Occurrences)	FDAAA, EudraCT Note that due to the low numbers in each treatment group, all AEs will be included. If 1 subject has a particular AE then this will automatically result in more than 5% of that treatment group having that AE.	SAC
Serious and Other Significant Adverse Events					
2.6.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT If required	SAC
2.7.	Safety	SAF_T2	Summary of AEs of Special Interest (On-treatment)		GSB (if required) / SAC
2.8.	Safety	SAF_T3	Summary Profile of On-Treatment Adverse Events of Special Interest	Present by event of special interest. If no subjects experience a particular AE of special interest, then no need to summarise for that special interest AE.	SAC
2.9.	Safety	Similar to Table 3.43 in sb240563/mid200862/final/	Summary of Adverse Events, by ADA Assay Result Category (On-Treatment)	AE table should be based on the highest post-baseline binding antibody result Present postdose AEs only	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.10.	Safety	AE3	Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency	This is a required input to the Plain Language Summary (PLS) requirements.	SAC
2.11.	Safety	SAF_T1	Adverse Event Overview	Include rows for: Any AEs On-treatment AEs AEs related to study treatment AEs leading to study withdrawal Any SAEs On-treatment SAEs SAEs relating to study treatment Fatal SAEs Fatal SAEs related to study treatment Retain rows even if zero counts in all treatment columns.	GSB (if required) / SAC
Laboratory: Chemistry					
2.12.	Safety	LB1	Summary of Chemistry Changes from Baseline	ICH E3 Include hsCRP	SAC
2.13.	Safety	LB17	Summary of Worst Case Chemistry Relative to Potential Clinical Importance (PCI Criteria) Post-Baseline Relative to Baseline	ICH E3	GSB (if required) / SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.14.	Safety	LB15	Summary of Worst Case Chemistry Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC
Laboratory: Haematology					
2.15.	Safety	LB1	Summary of Haematology Changes from Baseline	ICH E3	SAC
2.16.	Safety	LB17	Summary of Worst Case Haematology Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	ICH E3	GSB (if required) / SAC
2.17.	Safety	LB15	Summary of Worst Case Haematology Results Relative to Normal Range Post-Baseline Relative to Baseline		SAC
Laboratory: Urinalysis					
2.18.	Safety	UR1	Summary of Urinalysis Results	ICH E3	SAC
Laboratory: Hepatobiliary (Liver)					
2.19.	Safety	SAF_T4	Summary of Hepatobiliary Laboratory Abnormalities	Based on Liver10 standard shell.	SAC
ECG					
2.20.	Safety	EG1	Summary of ECG Findings	IDSL	SAC
2.21.	Safety	EG10	Summary of Maximum QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	GSB (if required) / SAC
2.22.	Safety	LAB17	Summary of Worst Case ECG Results Relative to Potential Clinical Importance (PCI) Criteria Post-Baseline Relative to Baseline	Include each of the ECG PCI criteria	SAC
2.23.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.24.	Safety	EG11	Summary of Maximum Increase in QTcF Values Post-Baseline Relative to Baseline by Category	IDSL	SAC
Vital Signs					
2.25.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	GSB (if required) / SAC
2.26.	Safety	VS7	Summary of Worst Case Vital Signs Results Relative to Potential Clinical Importance (PCI Criteria) Post-Baseline Relative to Baseline	IDSL	SAC

17.12.6. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Laboratory: Hepatobiliary (Liver)					
2.1.	Safety	sb240563/mid205050/final_02	Scatter Plot of Maximum vs Baseline for ALT	Use a different colour and symbol for each dose group.	SAC
2.2.	Safety	sb240563/mid205050/final_02 Figure 3.2	Scatter Plot of Maximum ALT vs Maximum Total Bilirubin	Use a different colour and symbol for each dose group.	SAC

17.12.7. Pharmacokinetic Tables

Pharmacokinetic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations and Parameters					
3.1.	PK	PKCT1	Summary of Plasma GSK3511294 Pharmacokinetic Concentration-Time Data		SAC
3.2.	PK	PKPT1	Summary of Derived Plasma GSK3511294 Pharmacokinetic Parameters	Cmax, AUC(0-∞), AUC(0-t), AUC(0-WeekX), CL/F, Vd/F, λz, t½, %AUCextrapolated, tmax, tlast.	SAC
3.3.	PK	PKPT3	Summary of Derived Plasma GSK3511294 Pharmacokinetic Parameters (log transformed)	Cmax, AUC(0-∞), AUC(0-t), AUC(0-WeekX), CL/F, Vd/F, λz, t½, %AUCextrapolated.	SAC
Dose Proportionality					
3.4.	PK	See Table 3.8 in /arenv/arprod/gsk226955 7/pii116617/parts_cb/driv ers/t_pkpower_partcb.sa s	Summary of Results of Statistical Analysis of Plasma GSK3511294 Cmax and AUC(0-∞) to Assess Dose Proportionality, Power Model		SAC
3.5.	PK	Table 3.10 in /arenv/arprod/gsk226955 7/pii116617/parts_cb/driv ers/t_pkaccum_stat_part cb.sas	Summary of Results of Statistical Analysis of Plasma GSK3511294 Cmax and AUC(0-∞) to Assess Dose Proportionality, ANOVA Model		SAC

17.12.8. Pharmacokinetic Figures

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Concentrations					
3.1.	PK	PKCF1x	Individual Participant Plasma GSK3511294 Concentration-Time Plots (Linear and Semi-log) by Treatment	One treatment per page (all participants within a treatment group on one plot). Add a horizontal line at y-axis = 20 pg/mL and footnote: LLQ = 20 pg/mL,Set pre-dose NQs to missing.	SAC
3.2.	PK	PKCF1x	Individual Participant Plasma GSK3511294 Concentration-Time Plots (Linear and Semi-log) by Participant		SAC
3.3.	PK	PKCF2	Mean (±SD) Plasma GSK3511294 Concentration-Time Plot (Linear and Semi-Log)		SAC
3.4.	PK	PKCF3	Median Plasma GSK3511294 Concentration-Time Plot (Linear and Semi-Log)		SAC
Dose Proportionality					
3.5.	PK	PK28	Plot of Individual (+ Geometric Mean and 90% CIs) for Plasma GSK3511294 PK Parameters versus Dose	AUC(0-∞) and Cmax	SAC
3.6.	PK	Fig 3.9 in /arenv/arprod/gsk2269557/pii116617/parts_cb/drivers/f_pkcmax_dosenorm_partcb.sas	Box Plot of Dose Normalised Plasma GSK3511294 PK Parameters against Dose	Separate plots for AUC(0-∞) and Cmax	SAC

Pharmacokinetic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.7.	PK	PK28	Plot of Individual (+ Geometric Mean and 95% CIs) Log GSK3511294 PK parameter vs Log (dose)	Separate plots for AUC(0-∞) and Cmax	SAC

17.12.9. Pharmacokinetic Population (PopPK) Tables

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Insert Endpoint Category					
4.1.	PK		Description and Evaluation of Key PK Models Tested	Provided by CPMS	SAC
4.2.	PK		Population PK Parameter Estimates with 95% CI of Final PK Model	Provided by CPMS	IA1, IA3, IA4 (if performed and required), SAC
4.3.	PK		Demographics Summary	Provided by CPMS	SAC
4.4.	PK		Samples Summary	Provided by CPMS	SAC

17.12.10. Pharmacokinetic Population (PopPK) Figures

Pharmacokinetic Population (POPPK): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Insert Endpoint Category					
4.1.	PK		Plasma GSK3511294 concentration-time profiles (by treatment)	Provided by CPMS	IA1, IA3, IA4 (if performed and required), SAC
4.2.	PK		Model goodness of fit plots	Provided by CPMS	IA1, IA3, IA4 (if performed and required), SAC
4.3.	PK		Continuous covariate correlation plot	Provided by CPMS	SAC
4.4.	PK		Categorical covariate correlation plot	Provided by CPMS	SAC
4.5.	PK		Automated covariate selection	Provided by CPMS	SAC
4.6.	PK		Visual predictive check	Provided by CPMS	SAC
4.7.	PK		Observed plasma GSK3511294 concentration-time profiles by anti-drug antibody status	Provided by CPMS	SAC
4.8.	PK		Plasma GSK3511294 observed/predicted concentration-time profiles (by participant)	Provided by CPMS	IA1, IA3, IA4 (if performed and required), SAC
4.9.	PK		Box plot of apparent systemic clearance versus covariates of interest (if necessary)	Provided by CPMS	SAC

17.12.11. Pharmacodynamic and Exploratory Markers

Pharmacodynamic and Exploratory Markers: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Blood Eosinophils					
5.1.	PD	PD_T1: Same format as Table 2.73 in /arenv/arprod/sb240563 /mid200862/final	Summary of Blood Eosinophil Data	Extract from haematology panel of lab dataset. Treat as log-normal data SAC output will supersede IA output, IA output will have 'at Interim' in the title. Will need to be careful not to unblind for interim output.	IA1 and subsequent IAs, SAC
5.2.	PD	PD_T2	Statistical Analysis of Change from Baseline Blood Eosinophil Data	SAC output will supersede IA output, IA output will have 'at Interim' in the title. Will need to be careful not to unblind for interim output.	IA1 and subsequent IAs, SAC
5.3.	PD	PD_T2	Statistical Analysis of Change from Baseline Blood Eosinophil Data (Windowing Sensitivity Analysis)	Apply time window rules	SAC

Pharmacodynamic and Exploratory Markers: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.4.	PD	Similar format to /sb240563/mid205050/final_02/ Table 5.2	Statistical Analysis of Ratio to Baseline Blood Eosinophil Data (MMRM Sensitivity Analysis)	Will need to split treatments across 2 pages.	SAC
5.5.	Safety	PD_T2	Statistical Analysis of Change from Baseline Blood Eosinophil Data	If Safety population and PD population are different	SAC
5.6.	PD	PD_T2	Statistical Analysis of Change from Baseline Blood Eosinophil Data Excluding Subjects with Use of Corticosteroids or Change in ICS Asthma Medication	If applicable	SAC
IL-5					
5.7.	PD	See Table 6.75 in sb240563/mea112997/final	Summary of Serum Total IL-5 [units] Over Time	Add a footnote if any BLQ values are imputed. Total only (no free)	IA3 and subsequent IAs if performed and required, SAC

17.12.12. Pharmacodynamic and Exploratory Markers Figures

Pharmacodynamic and Exploratory Markers: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Blood eosinophils					
5.1.	PD	PD_F1	Geometric means (and 95% CIs) of Ratio to Baseline Blood Eosinophils	SAC output will supersede IA output, IA output will have 'at Interim' in the title. Will need to be careful not to unblind for interim output.	IA1 and subsequent IAs, SAC
5.2.	PD	PD_F1	Geometric Means (and 95% CIs) of Blood Eosinophil Count Data (<units>)	SAC output will supersede IA output, IA output will have 'at Interim' in the title. Will need to be careful not to unblind for interim output.	IA1 and subsequent IAs, SAC
5.3.	PD	PD_F2	Predicted and Observed Blood Eosinophil Ratios to Baseline	By treatment group	IA1 and subsequent IAs, SAC
Serum IL-5					
5.4.	PD	PD_F1	Geometric Means (and 95% CIs) of Total Serum IL-5 Data (<units>)	Plot absolute values rather than ratios to baseline. Include a reference line for the LOQ	IA3 and subsequent IAs if performed and required, SAC

17.12.13. Pharmacokinetic / PharmacodynamicTables

Pharmacokinetic / Pharmacodynamic: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Insert Endpoint Category					
6.1.	PD		Description and Evaluation of Key PKPD Models Tested	Provided by CPMS	SAC
6.2.	PD		Population PD Parameter Estimates with 95% CI of Final PKPD Model	Provided by CPMS	SAC
6.3.	PD		Demographics summary (only if different from study population)	Provided by CPMS	SAC
6.4.	PD		Samples summary	Provided by CPMS	SAC

17.12.14. Pharmacokinetic / Pharmacodynamic Figures

Pharmacokinetic / Pharmacodynamic: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Insert Endpoint Category					
6.1.	PD		Blood eosinophil count-time profiles	Provided by CPMS	SAC
6.2.	PD		Model goodness of fit plots	Provided by CPMS	SAC
6.3.	PD		Continuous covariate correlation plot	Provided by CPMS	SAC
6.4.	PD		Categorical covariate correlation plot	Provided by CPMS	SAC
6.5.	PD		Automated covariate selection	Provided by CPMS	SAC
6.6.	PD		Visual predictive check	Provided by CPMS	SAC
6.7.	PD		Observed blood eosinophil count -time profiles by anti-drug antibody status	Provided by CPMS	SAC
6.8.	PD		Observed/predicted blood eosinophil count-time profiles (by participant)	Provided by CPMS	SAC

17.12.15. Other Tables

Other: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Lung Function Tests					
7.1.	Safety	Similar format to Table 3.11 in /arenv/arprod/sb240563/mid201312/final/	Summary of Spirometry Data	Summarise FEV1, FVC and %Predicted Normal FEV1	SAC
7.2.	Safety	PFT3	Summary of Changes from Baseline Spirometry Data		SAC
Immunogenicity					
7.3.	Safety	SAF_T5	Summary of Binding Antibody by Visit	Positive/Negative at each visit as well as transient positive and transient positive at post dose visits. Separate column for each dose. Include the titre value (min, median and max) when available for participants with a positive result	IA3 and subsequent IAs if performed and required, SAC
7.4.	Safety	sb240563/mid204958/final_01 Table 9.2	Summary of Binding Antibody by Visit – Subjects Without Positive Result Prior to Dosing	Positive/Negative at each visit. Separate column for each dose. Include the titre value (min, median and max) when available for participants with a positive result	SAC
7.5.	Safety	sb240563/mid204958/final_01 Table 9.3	Summary of Neutralising Antibody by Visit		SAC

Other: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
CICs					
7.6.	Safety		Summary of Circulating Immune Complexes	Data from Biomark dataset	IA3 and subsequent IAs if performed and required, SAC
Complement, IgE and Inflammatory Markers					
7.7.	Safety	See sb240563/mea115588/final Table 6.71	Summary of Complement (C3 and C4) and IgE	C3, C4 and IgE from LAB dataset Present by parameter and visit	IA3 and subsequent IAs if performed and required, SAC
Exacerbations					
7.8.	Safety	sb240563/mea112997/final/t_eff_6_01.sas	Summary of Frequency of All Exacerbations	Only present If at least 5 exacerbations reported.	SAC
7.9.	Safety	Similar to sb240563/mea115575/final/drivers/Table 6.19	Overview of Exacerbations	Do not split into different treatment phases. All post dose exacerbations to be displayed on the same page. Include all exacerbation data categories that are collected e.g. hospitalisation, clinical significance, etc. Only summarise exacerbations if reported by >= 5 participants.	SAC

Other: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Asthma Control Test (ACT)					
7.10.	Safety	Similar to Table 6.56 in sb240563/mea 115588/final	Summary of Asthma Control Test (ACT) Total Scores	Note that the example is for ACQ rather than ACT. Total ACT score can range from 5 – 25.	SAC

17.12.16. Other Figures

Other: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
CICs					
7.1.	Safety	PD_F1	Geometric Means (and 95% CIs) of CICs (<units>)	Plot absolute values rather than ratios to baseline. Include a reference line for the LOQ	IA3 and subsequent IAs if performed and required, SAC
Complement, IgE and Inflammatory Markers					
7.2.	Safety	PD_F1	Geometric Means (and 95% CIs) of Complement and IgE Data	Plot absolute values rather than ratios to baseline. Include a reference line for the LOQ if applicable	IA3 and subsequent IAs if performed and required, SAC

17.12.17. ICH and Other Listings

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Participant Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC
3.	Safety	BL1	Listing of Participants for Whom the Treatment Blind was Broken	ICH E3	SAC
4.	Safety	TA1	Listing of Planned and Actual Treatments	IDSL	SAC
Protocol Deviations					
5.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC
6.	Safety	IE3	Listing of Participants with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC
Populations Analysed					
7.	Enrolled	SP3	Listing of Participants Excluded from Any Population	ICH E3	SAC
Demographic and Baseline Characteristics					
8.	Screened	DM2	Listing of Demographic Characteristics	ICH E3 Include all parameters in demography summary table	SAC
9.	Screened	DM9	Listing of Race	ICH E3	SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Prior and Concomitant Medications					
10.	Screened	CP_CM3	Listing of Concomitant Medications	IDSL	SAC
Exposure and Treatment Compliance					
11.	Safety	EX3	Listing of Exposure Data	ICH E3	SAC
Adverse Events					
12.	Screened	CP_AE8	Listing of All Adverse Events	ICH E3	GSB (if required) / SAC
13.	Screened	AE7	Listing of Participant Numbers for Individual Adverse Events	ICH E3	SAC
14.	Screened	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC
Serious and Other Significant Adverse Events					
15.	Screened	CP_AE8a	Listing of Serious Adverse Events	ICH E3	SAC
16.	Screened	CP_AE8	Listing of Adverse Events Leading to Withdrawal from Study	ICH E3	SAC
17.	Safety	CP_AE8a	Listing of Adverse Events of Special Interest	ICH E3 Order by each category of AE of SI.	SAC
18.	Safety		Listing of Cardiovascular Events	If applicable	SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
19.	Safety	CP_AE8	Listing of Adverse Events for Participants with at least One Positive Predose Binding Assay		SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Hepatobiliary (Liver)					
20.	Safety	MH2	Listing of Medical Conditions for Participants with Liver Stopping Events	IDSL	SAC
21.	Safety	SU2	Listing of Substance Use for Participants with Liver Stopping Events	IDSL	SAC
All Laboratory					
22.	Safety	CP_LB5	Listing of All Clinical Chemistry Laboratory Data for Participants with PCI Abnormalities	ICH E3 Will include hsCRP data.	SAC
23.	Safety	CP_LB5	Listing of All Haematology Laboratory Data for Participants with PCI Abnormalities	ICH E3	SAC
24.	Safety	CP_LB5	Listing of Clinical Chemistry Abnormalities of Potential Clinical Importance	Subset of 'Listing of All Clinical Chemistry Laboratory Data for Participants with PCI Abnormalities'.	SAC
25.	Safety	CP_LB5	Listing of Haematology Abnormalities of Potential Clinical Importance	Subset of 'Listing of All Hematology Laboratory Data for Participants with PCI Abnormalities'	SAC
26.	Safety	UR2A/UR2B	Listing of All Urinalysis Data	ICH E3	SAC
27.	Safety	CP_LB5	Listing of Liver Chemistry Data for Subjects with ALT at Least 3xULN	Include ALT, bilirubin and INR only	SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
ECG					
28.	Safety	CP_EG3	Listing of All ECG Values for Participants with Any Value of Potential Clinical Importance	IDSL Based on means of triplicate values	SAC
29.	Safety	CP_EG4	Listing of ECG Values of Potential Clinical Importance	IDSL Based on means of triplicate values	SAC
30.	Safety	CP_EG5	Listing of All ECG Findings for Participants with an Abnormal ECG Finding	IDSL	SAC
31.	Safety	EG5	Listing of Abnormal ECG Findings	IDSL	SAC
Vital Signs					
32.	Safety	CP_VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL	SAC
33.	Safety	CP_VS4	Listing of Vital Signs of Potential Clinical Importance	IDSL Subset of above listing.	SAC
Lung Function Tests					
34.	Screened	PFT8	Listing of Spirometry Data	FEV1, FVC and %predicted normal FEV1. Individual readings are not databased, only max of the 3 readings.	SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacokinetic Data					
35.	PK		Listing of Plasma GSK3511294 Pharmacokinetic Concentration-Time Data (Observed)		SAC
36.	PK		Listing of Plasma GSK3511294 Pharmacokinetic Parameters	From noncompartmental analysis	SAC
37.	PK		Listing of Plasma GSK3511294 Pharmacokinetic Concentration-Time Data (Predicted)	From popPK analysis Data provided by CPMS to CS for listing generation	SAC
38.	PK		Listing of Model Predicted Plasma GSK3511294 Pharmacokinetic Parameters	From popPK analysis Data provided by CPMS to CS for listing generation	SAC
39.	PK		Listing of Data and Participants Excluded from Analysis	From popPK analysis Provided by CPMS	SAC
40.	PK		Final PK Model Listings	From popPK analysis Provided by CPMS	SAC
Immunogenicity					
41.	Safety	IMM2	Listing of Immunogenicity Data for Participants with at Least One Positive Screening Binding Assay	Include columns for Screening Binding Assay, Confirmation Binding Assay, Confirmation Binding Assay Titre, Transient/Persistent, Neutralizing Antibody Assay	SAC
Exacerbations					
42.	Screened	Similar to sb240563/mea115575/final/Listing 6.02	Listing of Exacerbations	If applicable	SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Asthma Control Test (ACT)					
43.	Screened	Similar format to EQ5	Listing of Asthma Control Test (ACT) Data	Include all subscores and total score. Present codes and decodes in a similar way to EQ5. Replace 'Utility/ Thermometer Score' with 'Total Score'.	SAC
CICs					
44.	Screened		Listing of Circulating Immune Complexes Data		SAC
Complement, IgE Data and Inflammatory Markers					
45.	Screened	See Listing 6.04 in /arenv/arprod/sb240563 /mea115588/final	Listing of Complement (C3 and C4) and IgE		SAC
46.	Screened	Similar to gsk2269557/pii115117/part_c_cohort_4 Listing 33	Listing of Inflammatory Markers		SAC
Pharmacodynamic and Exploratory Markers					
47.	Screened	See Listing 18 in /arenv/arprod/sb240563 /mid200862/final	Listing of Blood Eosinophil Data	Blood eosinophil counts and ratios to baseline. Include windowed time column.	SAC
48.	Screened	Similar to sb240563/mid205050/final_02/ Listing 38	Listing of Serum IL-5 Data	Total IL-5 only	SAC
PK/PD					
49.	PD		Listing of Data and Participants Excluded from Analysis	From popPKPD analysis Provided by CPMS	SAC

Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
50.	PD		Final PKPD Model Listings	From popPKPD analysis Provided by CPMS	SAC

17.13. Appendix 13: Example Mock Shells for Data Displays

Example SAF_T1
Protocol: GSK123456 Page 1 of n
Population: Safety

Table X
Adverse Event Overview

	Treatment A (N=100)	Treatment B (N=100)
Any AE	50 (50%)	50 (50%)
On-treatment AEs	20 (10%)	20 (10%)
AEs related to study treatment	XX (XX%)	XX (XX%)
AEs leading to study withdrawal	5 (5%)	5 (5%)
Any SAE	10 (10%)	10 (10%)
On-treatment SAEs	20 (10%)	20 (10%)
SAEs related to study treatment	XX (XX%)	XX (XX%)
Fatal SAEs	2 (2%)	2 (2%)
Fatal SAEs related to study treatment	1 (1%)	1 (1%)

Note to programmer: List placebo, each individual dose group on order of ascending dose and then all active doses column.

Based on Standard Shell AE13. Note that some categories have been deleted/ modified.

Example SAF_T2
Protocol: 205722
Population: Safety

Table X.XX
Summary of AEs of Special Interest (On-treatment)

	Placebo (N=12)	GSK 2mg (N=6)	GSK 10mg (N=6)	GSK 30mg (N=9)	GSK 100mg (N=9)	GSK 300mg (N=6)	GSK All Active (N=36)
Special Interest Adverse Events							
Hypersensitivity SMQ (narrow)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 1>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 2>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 3>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Anaphylactic Reaction SMQ (narrow)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 1>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 2>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 3>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Vasculitis SMQ (narrow)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 1>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 2>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 3>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
Injection Site Reactions [1]	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 1>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 2>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)
<Preferred Term 3>	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)	X (XX%)

[1] Injection site reactions obtained via the General disorders and administration site conditions SOC under the Injection site reactions MedDRA high level term.
Note to programmer: Table based on simplification of Table 7.32 from sb240563/MEA115588/Final. If there are no qualifying events for a particular AE of special interest, then present 0's for the event row.

Example: SAF_T3
Protocol: MEA115921
Population: Safety

Table 3.37
Summary Profile of On-Treatment Adverse Events of Special Interest

AE of special interest: <Anaphylactic Reaction SMQ>

	Placebo (N=68)	Mepolizumab 300 mg SC (N=68)
All Events		
>=1 event [1]	3/2 (3%)	5/5 (7%)
1 event	1 (1%)	5 (7%)
2 events	1 (1%)	0
3 events	0	0
>=4 events	0	0
Serious Events		
>=1 event [1]	1/1 (1%)	0
Events considered related to investigational product		
>=1 event [1]	1/1 (1%)	1/1 (1%)
Intensity [1]		
Mild	0	4/4 (6%)
Moderate	2/2 (3%)	1/1 (1%)
Severe	1/1 (1%)	0
Outcome [1]		
Recovered/Resolved	3/2 (3%)	5/5 (7%)
Recovering/Resolving	0	0
Not Recovered/Not Resolved	0	0
Recovered/Resolved With Sequelae	0	0
Fatal	0	0
Action Taken [1]		
Withdrawn from study	0	0

[1] Information presented as number of events / number (%) subjects with at least one event.

Note to programmer: Replace the currently displayed treatment headings with Placebo, each individual dose group in order of ascending dose and then all active doses column.

Example: SAF_T4

Protocol: XYZ100001

Population: Safety/Other study specific

Table X

Summary of Hepatobiliary Laboratory Abnormalities

Laboratory Criteria [1][2]	Treatment A (N=123)	Treatment B (N=240)
n	122	237
ALT ≥3xULN and BIL ≥2xULN [3]	1 (<1%)	2 (<1%)
n	81	182
ALT ≥3xULN and INR >1.5 [4]	1 (1%)	1 (<1%)
n	80	180
ALT ≥3xULN and BIL ≥2xULN [3] and (ALP <2xULN)	1 (1%)	1 (<1%)
n	123	237
ALT ≥3xULN	6 (5%)	42 (18%)
ALT ≥5xULN	4 (3%)	23 (10%)
ALT ≥8xULN	2 (2%)	13 (5%)
ALT ≥10xULN	2 (2%)	13 (5%)
ALT ≥20xULN	1 (<1%)	5 (2%)

[1] Subjects may be counted in more than one category.

[2] ALT: alanine aminotransferase; ALP: alkaline phosphatase; BIL: total bilirubin; INR: International Normalized Ratio; ULN=upper limit of normal.

[3] If direct bilirubin is available, then direct bilirubin as a portion of total bilirubin must be ≥35% when total bilirubin is ≥2xULN, in order to satisfy the criteria. Bilirubin value is on or up to 28 days after ALT value.

[4] INR value is on or up to 28 days after ALT value.

Example: SAF_T4 (continued)

Protocol: XYZ100001

Population: Safety/Other study specific

Table X

Summary of Hepatobiliary Laboratory Abnormalities

Laboratory Criteria [1][2]	Treatment A (N=123)	Treatment B (N=240)
n	122	237
BIL ≥2xULN [3]	3 (2%)	12 (5%)
n	123	237
ALP ≥2xULN and Baseline ALP <2xULN or Baseline ALP missing	2 (2%)	10 (4%)
Time from Dose to First ALT Elevation ≥3xULN (days)		
n	6 (5%)	42 (18%)
Mean	33.7	30.1
SD	21.13	15.61
Median	31.0	21.2
Min.	14	9
Max.	56	48

[1] Subjects may be counted in more than one category.
[2] ALT: alanine aminotransferase; ALP: alkaline phosphatase; BIL: total bilirubin; INR: International Normalized Ratio; ULN=upper limit of normal.
[3] If direct bilirubin is available, then direct bilirubin as a portion of total bilirubin must be ≥35% when total bilirubin is ≥2xULN, in order to satisfy the criteria. Bilirubin value is on or up to 28 days after ALT value.
[4] INR value is on or up to 28 days after ALT value.
[5] Hepatocellular injury is defined as ((ALT/ALT ULN)/(ALP/ALP ULN)) ≥ 5 and ALT ≥3xULN. ALT and ALP values must occur on the same day.

Example: SAF_T5

Protocol: 204958
Population: All Treated Subjects (Safety)

Table 9.1
Summary of Binding Antibody by Visit

Visit	Assay Result	Lyophilised Vial (N=85)	Liquid Autoinjector (N=79)	Liquid Safety Syringe (N=80)	Total Liquid (N=159)	Total (N=244)
SCREENING	n	85	79	80	159	244
	NEGATIVE	83 (98%)	79 (100%)	79 (99%)	158 (>99%)	241 (99%)
	POSITIVE	2 (2%)	0	1 (1%)	1 (<1%)	3 (1%)
DAY 1	n	85	79	80	159	244
	NEGATIVE	83 (98%)	79 (100%)	80 (100%)	159 (100%)	242 (>99%)
	POSITIVE	2 (2%)	0	0	0	2 (<1%)
DAY 43	n	84	79	80	159	243
	NEGATIVE	82 (98%)	77 (97%)	77 (96%)	154 (97%)	236 (97%)
	POSITIVE	2 (2%)	2 (3%)	3 (4%)	5 (3%)	7 (3%)
	TRANSIENT POSITIVE	1 (1%)	0	0	0	1 (<1%)
	PERSISTENT POSITIVE	1 (1%)	2 (3%)	3 (4%)	5 (3%)	6 (2%)
FOLLOW UP	n	84	79	80	159	243
	NEGATIVE	82 (98%)	75 (95%)	77 (96%)	152 (96%)	234 (96%)
	POSITIVE	2 (2%)	4 (5%)	3 (4%)	7 (4%)	9 (4%)
	PERSISTENT POSITIVE	2 (2%)	4 (5%)	3 (4%)	7 (4%)	9 (4%)

[1] A subject is considered positive if they have at least one positive post-baseline anti-drug antibody (ADA) result.
[2] Highest post-baseline titre.

PPD

Example: SAF_T5 (continued)

Protocol: 204958
Population: All Treated Subjects (Safety)

Table 9.1
Summary of Binding Antibody by Visit

Visit	Assay Result		Lyophilised Vial (N=85)	Liquid Autoinjector (N=79)	Liquid Safety Syringe (N=80)	Total Liquid (N=159)	Total (N=244)
ANY POST-BASELINE	n		84	79	80	159	243
	NEGATIVE		81 (96%)	74 (94%)	77 (96%)	151 (95%)	232 (95%)
	POSITIVE [1]		3 (4%)	5 (6%)	3 (4%)	8 (5%)	11 (5%)
	TRANSIENT POSITIVE		1 (1%)	1 (1%)	0	1 (<1%)	2 (<1%)
	PERSISTENT POSITIVE		2 (2%)	4 (5%)	3 (4%)	7 (4%)	9 (4%)
	Titre value [2]	Min.	16	8	32	8	8
		Median	16.0	32.0	256.0	32.0	32.0
		Max.	32	32	320	320	320

[1] A subject is considered positive if they have at least one positive post-baseline anti-drug antibody (ADA) result.
[2] Highest post-baseline titre.

PPD

Protocol: 205722
Population: PD

Table Insert Table Number
Summary of Blood Eosinophils (10^9/L)

Time Point			Placebo (N=XX)	GSK 2mg (N=8)	GSK 10mg (N=8)
Baseline	Blood Eosinophils (10^9/L)	n	XX	X	X
		Geo. Mean	0.35	0.30	X.XX
		Std Logs	0.922	1.107	X.XXX
		Median	0.35	0.34	X.XX
		Min.	0.0	0.0	X.X
		Max.	3.7	14.0	XX.X
Day 2 (24h)	Blood Eosinophils (10^9/L)	n	XX	X	X
		Geo. Mean	0.30	0.06	X.XX
		Std Logs	1.129	0.855	X.XXX
		Median	0.35	0.06	X.XX
		Min.	0.0	0.0	X.X
		Max.	2.4	0.9	XX.X
	Blood Eosinophils Ratio to Baseline	n	XX	X	X
		Geo. Mean	0.86	0.20	X.XX
		Std Logs	1.000	1.099	X.XXX
		Median	0.94	0.17	X.XX
		Min.	0.0	0.0	X.X
		Max.	23.3	20.0	XX.X

Note: Where a result of zero was recorded, a small value (0.005) was added prior to log transformation.
[Note to programmer: Will need to add columns for other dose groups on another page, repeat Day 2 (24h) format for all scheduled visits]

Example: PD_T2
Protocol: 200862
Page 1 of 2
Population: PD

Table X.XX
Statistical Analysis of Change from Baseline Blood Eosinophil Data

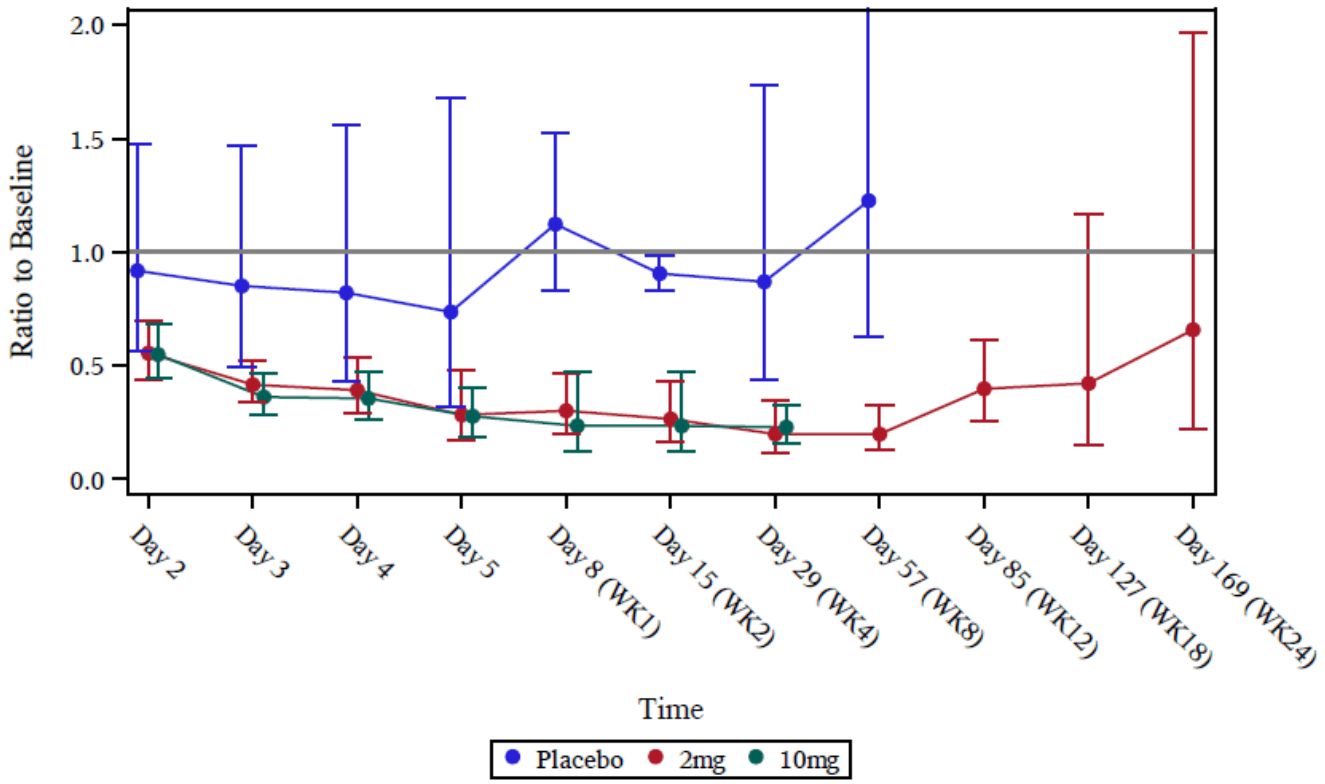
Treatment	N	Visit	Ratio to Baseline	95% CI of Ratio to Baseline		Prob (Ratio < X.X) 0.3	0.5	0.75	1.0
GSK 2mg	X	Day 2 (24h)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
		Day 3 (48h)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
		Day 4 (72h)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
	0.XX								
.....									
		Week 32 (Day 225)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
GSK 10mg	X	Day 2 (24h)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
		Day 3 (48h)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
		Day 4 (72h)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX
	0.XX								
.....									
		Week 32 (Day 225)	X.XX	X.XX	X.XX	0.XX	0.XX	0.XX	0.XX

etc.

Note: Prob ratios displayed will be dependent on the data and the time of analysis. For the interim, prob (ratio < 0.84) will be displayed and for the final analysis, prob (ratio <0.75) will be displayed.

Example: PD_F1
Protocol: 205722
Population: PD

Figure X.XX
Geometric means (and 95% CIs) of Ratio to Baseline Blood Eosinophils



Include all available groups, will need to be careful about unblinding at later timepoints for the Interim analysis.

Example PD_F2
Protocol: 205722
Population: PD