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

Title	:	Reporting and Analysis Plan for Study 205687: A randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab)
Compound Number	:	SB240563
Effective Date	:	20-FEB-2020

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Study 205687 (Protocol 2016N294302_04)
- This version of the RAP includes amendments to the originally approved RAP.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Study 205687 (Protocol 2016N294302_04):

Revision Chronology for Protocol:		
Original Protocol (2016N294302_00)	08-Dec-2016	Original
2016N294302_01	15-May-2017	To support country-specific requirements and amendments for South Korea.
2016N294302_02	14-July-2017	To clarify wording, document removal of CT scans and exit interviews, simplifying some of the endpoints
2016N294302_03	20-Feb-2018	To clarify that screen failures can be re-screened, and that the ECG machine does not need to be automated
2016N294302_04	13-Feb-2020	To reflect the feedback received from regulatory authorities regarding 1) analysis methodology for the co-primary endpoints, 2) clarify the definition of surgery to more invasive procedures, 3) assess courses of steroids used rather than total burden. This amendment also reflects two additional secondary endpoints.

1.1. RAP Amendments

Revision chronology:

RAP Section	Amendment Details
Reporting and Analysis Plan _Final: Effective Date 05-SEP-2019	
Reporting and Analysis Plan Amendment 1: Effective Date 20-FEB-2020	
Section 2.1,Section 5.4,Section 7,Section 14.6.5	• To reflect the changes in protocol amendment 4
Section 12	• Updated measures of exposure for the exploratory exposure-efficacy response analysis
Section 14.8.1	• Updated definition for ALT values of potential clinical concern

2. SUMMARY OF KEY PROTOCOL INFORMATION

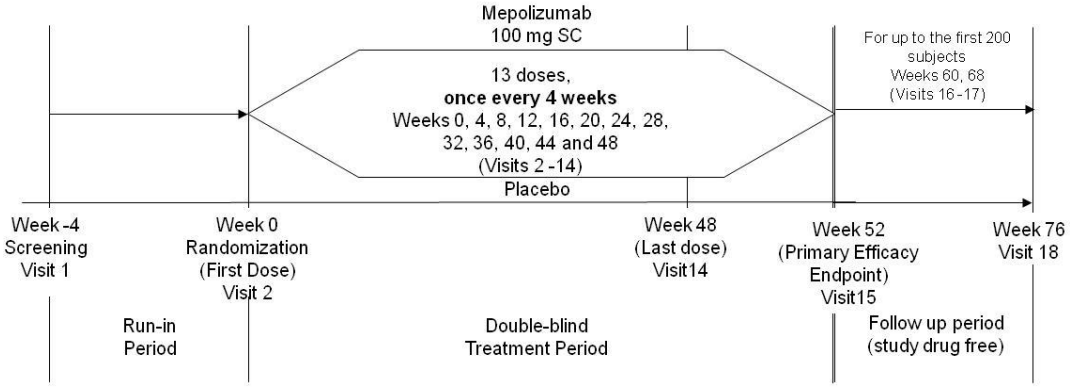
2.1. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary Objectives	**Co-Primary Endpoints**
• To evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in total endoscopic NP score at Week 52 (based on centrally read data). • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the impact on actual nasal surgery of 100mg mepolizumab compared to placebo	• Time to first nasal surgery up to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52.
• To evaluate the impact on quality of life of 100mg mepolizumab compared to placebo	• Change from baseline in SNOT-22 total score at Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Proportion of participants requiring systemic steroids for nasal polyps up to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in the mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) during the 4 weeks prior to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52.
Other Objectives	**Other Endpoints**
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Percentage of participants classified as responders according to a 1 point or greater decrease from baseline in NP Score at Week 52 (based on centrally ready data). • Change from baseline in mean individual VAS symptom scores for nasal discharge, mucus in the throat, and facial pain during the 4 weeks prior to Week 52. • Change from baseline in the mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain) during the 4 weeks prior to Week 52. • Change from baseline in UPSIT at Week 52. • Change from baseline in PnIF at Week 52.
• To evaluate the impact on quality of life of 100mg mepolizumab compared to placebo	• Percentage of participants classified at Week 52 as responders according to an 8.9 point or greater decrease from baseline in SNOT-22 total score. • Change from baseline in SNOT-22 domain scores at Week 52.
• To further evaluate the impact on	• Rate of nasal surgery up to Week 52.

Objectives	Endpoints
requirement for nasal surgery of 100mg mepolizumab compared to placebo	• Time to first inclusion on waiting list for NP surgery up to Week 52. • Percentage of participants who are included on waiting list for NP surgery. • Percentage of participants classified as 'need for surgery' responders according to NP score (based on centrally ready data) and overall VAS symptom score.
• To evaluate exploratory biomarkers of nasal polyposis and response to 100mg mepolizumab compared to placebo	• Evaluate exploratory blood biomarkers (including blood eosinophils) on response to mepolizumab.
• To evaluate the impact on health outcomes of 100mg mepolizumab compared to placebo	• Change from baseline in SF-36 Mental Component Summary (MCS), Physical Component Summary (PCS) and 8 summary scores at Week 52. • Change from baseline in WPAI Questionnaire at Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo on systemic steroid use such as OCS and antibiotic use as part of SoC	• Number of Courses of systemic steroid therapy up to Week 52. • Number of mgs per year of prednisolone-equivalent OCS dose up to Week 52. • Number of days on systemic steroid therapy up to Week 52. • Time to first course of OCS up to Week 52. • Number of courses of antibiotics up to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo in the subgroup of participants with Asthma	In addition to endoscopic NP score, VAS symptoms score, medication and surgery, the following asthma related endpoints will be assessed: • Change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 52. • Number of clinically significant asthma exacerbations defined as worsening of asthma requiring systemic corticosteroids (i.v. or oral steroid) for at least 3 days or a single IM CS dose and/or ED visit and/or hospitalisation for asthma up to Week 52.
• To assess the maintenance of response after cessation of mepolizumab treatment compared to placebo	For all participants who enter post treatment follow-up period, the following will be assessed at Week 76: • Change from baseline in total endoscopic NP score (centrally read data). • Change from baseline in mean nasal obstruction VAS score. • Change from baseline in mean individual VAS symptom score for nasal discharge, mucus in throat, loss of smell, facial pain and overall VAS symptom score during the 4 weeks prior to Week 76. • Number of mgs per year of prednisolone-equivalent OCS dose. • Change from baseline in SNOT-22 total score. • Change from baseline in SF-36 Mental Component Summary (MCS), Physical Component Summary (PCS) and 8 summary scores. • Change from baseline in WPAI Questionnaire.

Objectives	Endpoints
	• Time to first nasal surgery including off treatment period from randomization to Week 76. • Time to first inclusion on waiting list for NP surgery up to Week 76.
Safety Objectives	**Safety Endpoints**
• To evaluate the safety and tolerability of 100mg mepolizumab compared to placebo	• Frequency of adverse events (AEs)/ serious adverse events (SAEs) including systemic and injection site reactions reported throughout the treatment period. • Vital signs (pulse rate, systolic and diastolic blood pressure) throughout the treatment period. • Hematological and clinical chemistry parameters throughout the treatment period. • 12 lead ECG derived endpoints. • Presence of anti-mepolizumab antibodies.
Pharmacokinetics Objectives	**Pharmacokinetics Endpoints**
• To evaluate the pharmacokinetics (PK) of 100mg mepolizumab	• PK concentrations and Population PK parameters • PK/PD (blood eosinophil count) analysis

2.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-centre, randomised, placebo-controlled, double-blind, parallel-group design. • The study will include a 4-week run in period followed by a 52-week randomised treatment period with visits every 4 weeks. • Patients prematurely discontinued from study treatment continue, where possible, being followed up per the protocol schedule • Patients who have surgery for nasal polyps during the study are allowed to continue on study treatment until completion of the 52-week treatment period • Following Week 52, there is a planned study drug free, 6-month, follow-up period for the first 200 randomised participants, to investigate maintenance of response to study treatment.
Main participant entry criteria	• Participants aged ≥18 years with severe bilateral nasal polyps and at least one surgery in the previous 10 years for the removal of nasal polyps (see Section 6 of protocol).
Dosing	• The study treatment period will consist of thirteen, 4-weekly doses with the last dose of interventional product to be administered at Week 48 (Visit 14). • Interventional product is given in addition to standard of care (SoC): daily mometasone furoate nasal spray (MF), saline nasal douching as required and, if required, occasional short courses of high dose oral corticosteroids (OCS) and/or antibiotics.
Schedule of Activities	• See Appendix 2: Schedule of Activities
Treatment Assignment	• 400 participants (planned) will be randomised in a 1:1 ratio to receive mepolizumab or matching placebo (i.e. 200 per treatment group) delivered subcutaneously via a pre-filled safety syringe in addition to SoC. • Randomisation schedule generated using GSK validated randomisation software RandAll NG, stratified by country. • Treatment assigned randomly via an interactive voice response system (IVRS).
Interim Analysis	• No interim analysis of data is planned for this study.

2.3. Statistical Hypotheses

The study is designed to test the superiority of mepolizumab 100mg SC vs. placebo in addition to standard of care. Significance tests will be guided by a two-sided 5% alpha level (one-sided 2.5%).

2.4. Changes to the Protocol Defined Statistical Analysis Plan

Minor changes/deviations from the planned statistical analysis specified in Protocol Amendment 4 (Dated: 13 Feb 2020) are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Co-primary endpoint defined as Change from baseline in total endoscopic nasal polyps (NP) score at Week 52.	Co-primary endpoint defined as Change from baseline in total endoscopic NP score at Week 52 (based on centrally read data).	To clarify the total endoscopic NP score used in the analysis of the co-primary endpoint is based on data from the blinded independent review of endoscopy data (as per Protocol Section 9.2.1).

3. PLANNED ANALYSES

Planned dry run(s) will be performed on a subset of blinded data, with the aim of ensuring the required displays detailed in Appendix 12: List of Data Displays are correctly created and formatted.

3.1. Interim Analyses

No interim analysis of data is planned for this study.

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 database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met, and the randomisation codes have been released.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants enrolled and for whom a record exists on the study database.	Reasons for screen and run-in failures
Randomized	• All randomized participants	Study population
Intent-To-Treat (ITT)	• All randomized participants who take at least 1 dose of study treatment. • Data will be analysed according to randomised treatment arm.	Subject disposition Efficacy endpoints
Safety	• All randomized participants who take at least 1 dose of study treatment. • Data will be analysed according to actual treatment received for more than 50% of treatment administrations (see Section 14.6.2).	Safety endpoints
Per-Protocol (PP) [1]	• All participants in the ITT population who have not been identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. • Protocol deviations that would exclude participants from the PP population are defined in Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population	Supplementary analyses of co-primary endpoints
Pharmacokinetic (PK) [1]	All participants in the ITT population for whom at least one PK sample was obtained, analysed and measurable.	Pharmacokinetic endpoints
Follow-up after	• Participants in the ITT population who participate in the	Efficacy/safety

Population	Definition / Criteria	Analyses Evaluated
Week 52 (FU) [1]	'No treatment follow-up' period after Visit 15. • Data will be summarised according to randomised treatment arm.	endpoints

Refer to Appendix 12: List of Data Displays which details the population used for each display.
[1] Analysis population not defined in protocol, added for clarification of analysis requirements.

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP) dated 10 January 2018 (Version 1.01). Protocol deviations classified as important are detailed in the PDMP and those requiring exclusion from the Per-Protocol (PP) population are detailed in Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population.

A final blinded review of all deviations will take place at the database release stage to ensure all important deviations are identified as well as those leading to exclusion of the participant from the PP population.

Important protocol deviations and deviations which result in exclusion from the PP population will be summarised and listed. A separate listing of all inclusion/ exclusion criteria deviations based on data as recorded on the eligibility page of the eCRF will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF[1]
1	Placebo	Placebo	1
2	Mepolizumab 100mg SC	Mepolizumab 100mg SC	2

[1] TLF=Tables, Listings, Figures (as specified in Appendix 12: List of Data Displays)

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

Mepolizumab 100mg SC vs Placebo

5.2. Baseline Definitions

5.2.1. Visit-based endpoints

The co-primary endpoint of endoscopic NP score (based on centrally read data) is assessed at Screening (Visit 1) and Day 1 (Visit 2), the Screening value is used to confirm if a participant has met the criteria for randomisation. Baseline will be defined as the Day 1 value, if missing the immediately preceding centrally read value prior to Day 1 will be used.

For all other visit-based endpoints, Baseline will be defined as the latest non-missing measurement collected prior to the first dose of interventional product. This will generally be from the Day 1 assessment but may be from an unscheduled assessment.

Where time is collected, an assessment is valid for use as Baseline if the date and time is prior to or the same as the date and time of first dose. Where time is not collected, an assessment is valid for use as Baseline if the date of assessment is on or before the date of first dose.

5.2.2. eDiary Data

Participants report daily on the severity of individual and overall NP symptoms using an eDiary, this includes information for the co-primary endpoint of mean nasal obstruction VAS score. The baseline value for endpoints reported in the eDiary will be determined as the average score from the 7 days of diary data collected prior to Day 1 (using non-missing data recorded between Day -7 and Day -1 inclusive).

5.3. Multicentre Studies

In this multicentre global study, the number of enrolled participants and the number randomised to each treatment arm will be presented by centre, country and region.

Region will be included as a fixed effect covariate in the analysis models for efficacy endpoints (as detailed in Section 5.4). Countries have been grouped into the following regions with consideration for standard of care medical practice, number of participants enrolled and regulatory considerations.

Region	Countries
Europe (EU)	Germany, Netherlands, Romania, Sweden, UK
United States (US)	United States
Rest of World (RoW)	South Korea, Argentina, Australia, Canada, Russia

NOTE: Small numbers of participants in a treatment group within a region may result in model convergence issues, in these cases further combining of regions may be considered or if required exclusion of the region covariate.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

Covariates to be included in the statistical analysis models of the co-primary efficacy endpoints:

- Randomised treatment group
- Region
- Baseline score
- Baseline $\log_e$ blood eosinophil count

Covariates to be included in the statistical analysis model of time to first nasal surgery:

- Randomised treatment group
- Region
- Baseline total NP endoscopic score (based on centrally read data)
- Baseline nasal obstruction VAS
- Baseline $\log_e$ blood eosinophil count
- Number of previous surgeries (1, 2, >2; as an ordinal variable)

Covariates to be included in the statistical analysis model of proportion of subjects with at least one course of systemic steroids for nasal polyps up to Week 52:

- Randomised treatment group
- Region
- Baseline total NP score (based on centrally read data)
- Baseline nasal obstruction VAS
- Baseline $\log_e$ blood eosinophil count
- Number of OCS courses for NP in the previous 12 months (0, 1, >1, as an ordinal variable)

Section 7 provides full details of the analysis methods for each of the efficacy endpoints.

5.4.2. Examination of Subgroups

This section details the subgroups of interest within this study. For each co-primary endpoint, a separate exploratory analysis within each of the subgroup categories will be carried out. Subgroup analyses for all other endpoints are detailed in the statistical methods/analysis sections. Unless otherwise stated no formal hypothesis testing in subgroups of the population will be performed.

Subgroup	Categories
Participants with Asthma	Concurrent asthma, No concurrent asthma
Aspirin Exacerbated Respiratory Disease (AERDS)	Current AERDS, No Current AERDS
Number of previous surgeries	1, 2, >2
Baseline Blood Eosinophil Categories (GI/L)	≤0.3 GI/L; >0.3 to ≤0.5 GI/L; >0.5 to ≤0.7 GI/L; >0.7 GI/L
Region	Europe, United States, Rest of World
Age	18-<40, 40-<65, ≥65 years
Gender	Male, Female
Race	African American/African Heritage, White, Asian, Other

If, following unblinding, the analysis model within a subgroup category fails to converge due to small numbers of participants, the model will be rerun with consideration of further refining regions or if required exclusion of the region covariate. Failing this, subgroup categories may be further refined when possible, otherwise only a descriptive summary of the data will be presented. Footnotes will clearly identify the covariates included in the analysis model.

There is a biological rationale for potentially observing greater efficacy with increasing levels of baseline blood eosinophils. Except for baseline blood eosinophils, differential treatment effects are not expected for any of the other subgroups listed above and therefore any differences in efficacy of mepolizumab compared to placebo observed in subgroup categories will be viewed as exploratory.

5.5. Multiple Comparisons and Multiplicity

The treatment comparison of mepolizumab 100mg SC vs. placebo is of interest for the co-primary and secondary endpoints. Multiplicity arising from the multiple secondary endpoints will be controlled through testing of the secondary endpoints using a closed testing procedure according to the following pre-defined hierarchy:

1. Time to first nasal surgery

2. Change from baseline in overall VAS symptom score

3. Change from baseline in SNOT-22 total score

4. Proportion of subjects requiring systemic steroids for nasal polyps

5. Change from baseline in the mean composite VAS score (nasal obstruction, nasal discharge, mucus in the throat and loss of smell)

6. Change from baseline in mean individual VAS symptom score for loss of smell

For strong control of type I error, statistical significance for the first secondary endpoint in the pre-defined hierarchy will be dependent on statistical significance having been achieved for the two co-primary endpoints. Statistical significance for the subsequent secondary endpoints will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy.

For secondary endpoints, unadjusted p-values and p-values adjusted for multiplicity based on the above hierarchy, will be presented.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

All displays will be based on the ITT population, unless otherwise specified.

Study population displays including summaries of subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications and treatment exposure will be based on GSK Core Data Standards. Additional summary information showing the amount of time within the 52-week treatment period considered as on-treatment, off-treatment and missing will be presented.

A summary of subject disposition and duration of time spent in the no-treatment follow-up will be provided for the subset of participants who participated in the 6-month no-treatment follow-up.

Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. EFFICACY ANALYSES

Data reported up to Week 52 will be included in the analyses described in Section 7.1 to Section 7.4. Details of all planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary treatment effect to be estimated (estimand) will be the comparison of mepolizumab 100mg SC to placebo for the co-primary endpoints of:

- Change from baseline in total endoscopic NP score at Week 52 (based on centrally read data)
- Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52

Independent reviewers blinded to treatment, grade the total endoscopic NP score from image recording of endoscopies. The total score is reported as the sum of the right and left nostril scores and ranges from 0 to 8, with higher scores indicating greater disease severity.

Participants rate individual symptoms including nasal obstruction daily on a visual analogue scale (VAS) using an eDiary, the scale range is 0 (none) to 100 (as bad as you can imagine), with higher scores indicating greater disease severity, for analysis derived scores ranging from 0 to 10 are used (see Section 14.6.5).

Surgery/sinuplasty represents an intercurrent event as any nasal surgical procedure or dilatation of the air passages in the nasal cavity can affect subsequent scores for the co-primary endpoints. For analysis of the co-primary endpoints the intercurrent event of surgery/sinuplasty includes any procedure involving instruments resulting in incision and removal of tissue (e.g. polypectomy) or dilatation of the air passages (e.g. balloon sinuplasty) in the nasal cavity.

A composite strategy will be used for the intercurrent event of surgery/sinuplasty and a treatment policy strategy will be used for the intercurrent event of discontinuation of study medication. The study is designed to continue collecting data for participants who have prematurely discontinued from randomised treatment, off-treatment data collected for these participants will be included in the primary analysis.

Subjects who undergo surgery/sinuplasty prior to Week 52 will be assigned their worst observed NP score prior to the surgery/sinuplasty for the change from baseline value at Week 52 in total endoscopic NP score. Subjects who withdraw from study before Week 52 without having experienced surgery/sinuplasty will be assigned their worst observed NP score prior to study withdrawal.

Similarly, for the mean nasal obstruction VAS, subjects who undergo surgery/sinuplasty will be assigned their worst observed 4-week mean prior to surgery for change from baseline during the 4-weeks prior to Week 52. Subjects who withdraw from the study before Week 52 without having experienced surgery/sinuplasty will be assigned their worst observed 4-week mean prior to study withdrawal.

Sensitivity analyses to examine the impact of handling missing data as described above are detailed in Section 7.1.5.

7.1.2. Summary Measure

The summary measure of treatment effect will be the difference between mepolizumab and placebo in the variable medians.

7.1.3. Population of Interest

The primary population of interest for analysis of the co-primary endpoints is defined by the study inclusion/exclusion and randomisation criteria and is therefore the ITT population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The anticipated intercurrent events occurring prior to Week 52 for the co-primary endpoints are: Surgery/sinuplasty, which includes any procedure involving instruments resulting in incision and removal of tissue (e.g. polypectomy) or dilatation of the air passages (e.g. balloon sinuplasty) in the nasal cavity and premature discontinuation of interventional product.

For each co-primary endpoint, the anticipated intercurrent event of surgery/sinuplasty will be handled using a composite strategy such that the occurrence of the event is incorporated into the definition of the endpoint. In participants who do not experience surgery/sinuplasty, the anticipated intercurrent event of premature discontinuation of interventional product will be handled using a treatment policy strategy, such that in these participants all data reported at week 52 for total endoscopic NP score (or during the 4-week period prior to Week 52 for nasal obstruction VAS) will be included in the analysis, regardless of discontinuation from treatment.

7.1.5. Statistical Analyses / Methods

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in in total endoscopic NP score (based on centrally read data) at Week 52 • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52
Model Specification
• For each co-primary endpoint, the p-value for the difference in median change from baseline

between treatments will be based on the non-parametric Wilcoxon rank-sum test.

- The difference in median change from baseline with 95% confidence intervals will be estimated by quantile regression using a bootstrap approach ([Keene, 2018], [Mehrotra, 2017]). The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- Median change from baseline within each treatment group.
- Estimated difference between treatments in median change from baseline with 95% confidence interval (CI).
- p-value comparing treatments groups from the Wilcoxon rank-sum test.
- A cumulative distribution function (CDF) plot will be provided for the change from baseline in endoscopic NP score at Week 52 by treatment group.

Subgroup Analyses

- Section 5.4.2 identifies the subgroups of interest for the co-primary endpoints.

Sensitivity and Supportive Analyses

For sensitivity and supplementary analyses, the same methodology as for the primary efficacy analysis will be used.

Sensitivity analyses

- For the primary analysis the change from baseline value for participants with surgery/sinuplasty or missing data at Week 52 (due to premature withdrawal from the study or another reason) will be based on the worst observed score prior to surgery/sinuplasty or study withdrawal respectively. The following sensitivity analyses will be carried out to examine the potential impact of choices for the handling of subjects with missing data and for the handling of data for subjects undergoing surgery/sinuplasty. Sensitivity analysis will be performed for each co-primary endpoint where:
  - a) change from baseline for subjects with missing data is based on the worst possible score across all subjects and change from baseline for subjects with surgery/sinuplasty is based on the worst observed score prior to surgery/sinuplasty.
  - b) change from baseline for subjects with surgery/sinuplasty or with missing data is based on the worst possible score across all subjects.

Supplementary analyses

- A supplementary analysis of each co-primary endpoint will be performed on the Per-Protocol (PP) population (see Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population).

7.2. Secondary Efficacy Analyses

For each secondary endpoint the primary treatment effect to be estimated (estimand) will be the comparison of mepolizumab 100mg SC to placebo.

7.2.1. Time to first nasal surgery

Evaluation of the key secondary endpoint of nasal surgery will be based on invasive procedures involving instruments resulting in incision and removal of tissue (polypectomy). Dilatation of the air passages in the nasal cavity (e.g. balloon sinuplasty) will not be included in this endpoint. Procedures occurring on the same date will be considered as part of the same surgery event. A clinical review will be carried out prior to the unblinding of treatment codes to identify all events to be considered as part of this evaluation.

The time to first nasal surgery will be determined as the number of days from the date of first dose of study medication to the date of first nasal surgery (see Section 14.6.5). If a participant withdraws from the study before Week 52 and before experiencing nasal surgery, the nasal surgery event time will be censored at the time of study withdrawal.

7.2.1.1. Summary Measure

The summary measure of treatment effect will be the hazard ratio, the ratio of hazards corresponding to treatment with mepolizumab compared with placebo. For this endpoint the hazard represents the probability of nasal surgery for a participant at a given point in time following first dose of interventional product, given the participant has not experienced the event prior to that time.

7.2.1.2. Population of Interest

The primary population of interest is the ITT population.

7.2.1.3. Strategy for Intercurrent (Post-Randomization) Events

A treatment policy strategy will be used for the intercurrent event of premature discontinuation of interventional product, such that available nasal surgery times will be included in the analysis regardless of whether the surgery occurred before or after discontinuation of interventional product.

7.2.1.4. Statistical Analyses / Methods

Endpoint / Variables

- Time to first nasal surgery

Model Specification

- Cox proportional hazards model with covariates as follows:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline total nasal polyps endoscopic score (centrally read data), Baseline nasal obstruction VAS, Log_e baseline blood eosinophil

	count, Number of previous surgeries (1, 2, >2; ordinal)

- Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- A log(-log(survival)) plot by treatment group will be used to assess the assumption of proportional hazards.

Model Results Presentation

- The number of participants with an event, the number censored due to study withdrawal and at study completion will be presented by treatment arm.
- The hazard ratio with corresponding 95% CI and p-value from the Cox proportional hazards model will be presented.
- A summary and graph of the Kaplan-Meier estimate of the cumulative proportion of participants with nasal surgery within each treatment arm over time will be produced.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses

- Sensitivity analyses will be performed to assess the censoring-at-random assumption of the cox proportional hazards model where participants who withdraw from the study before experiencing surgery have their event times censored at the time of study withdrawal.
- Sensitivity analysis will be carried out where missing event times for participants randomised to mepolizumab who withdraw from the study before experiencing surgery will be imputed using a censoring-not-at-random method as described in [Jackson, 2014]. A step-change in event rate equivalent to a loss of benefit from mepolizumab will be imputed for these participants after their censoring time. This means a reduction in relative event rate equivalent to 1/(estimated treatment effect). Missing event times for placebo will imputed under a censoring-at-random assumption.

7.2.2. Change from Baseline in Mean Overall VAS Symptom Score During the 4 weeks Prior to Week 52, Mean Composite VAS Score and Mean Loss of Smell VAS Score

Change from baseline during the 4-weeks prior to Week 52 in mean overall VAS symptom score, mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) and mean loss of smell score will be analysed as detailed for the co-primary endpoint of change from baseline in mean nasal obstruction VAS score.

7.2.2.1. Details regarding the summary measure, population of interest and the strategy for intercurrent events are provided in Section 7.1.2 to Section 7.1.4.Statistical Analyses / Methods

Endpoint / Variables

- Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52

- Change from baseline in mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) during the 4 weeks prior to Week 52
- Change from baseline in mean loss of smell VAS symptom score during the 4 weeks prior to Week 52

Model Specification

- For each endpoint the p-value for the difference in median change from baseline between treatments will be based on the non-parametric Wilcoxon rank-sum test.
- The difference in median change from baseline with 95% confidence intervals will be estimated by quantile regression using a bootstrap approach.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- Median change from baseline within each treatment group.
- Estimated difference between treatments in median change from baseline with 95% confidence interval (CI).
- p-value comparing treatment groups from the Wilcoxon rank-sum test.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint

Sensitivity and Supportive Analyses

- No sensitivity/supportive analyses are planned for these endpoints

7.2.3. Change from Baseline in Sino-Nasal Outcomes TEST 22 (SNOT-22) Total Score at Week 52

The 22 questions of the SNOT-22 are each graded on a [redacted]

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

Details regarding the summary measure, population of interest and the strategy for intercurrent events are provided in Section 7.1.2 to Section 7.1.4.

7.2.3.1. Statistical Analyses / Methods

Endpoint / Variables

- Change from baseline in SNOT-22 total score at Week 52

Model Specification

- The p-value for the difference in median change from baseline between treatments will be based on the non-parametric Wilcoxon rank-sum test.
- The difference in median change from baseline with 95% confidence intervals will be estimated by quantile regression using a bootstrap approach.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- Median change from baseline within each treatment group.
- Estimated difference between treatments in median change from baseline with 95% confidence interval (CI).
- p-value comparing treatment groups from the Wilcoxon rank-sum test.
-

Subgroup Analyses

- No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses

- No sensitivity/supportive analyses are planned for this endpoint.

7.2.4. Proportion of subjects requiring systemic steroids for nasal polyps up to Week 52

7.2.4.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant requiring at least one course of systemic steroids up to Week 52 in the mepolizumab arm compared with placebo.

7.2.4.2. Population of Interest

The population of interest is the ITT population.

7.2.4.3. Strategy for Intercurrent (Post-Randomization) Events

Data will be included regardless of the occurrence of events such as surgery or treatment discontinuation.

7.2.4.4. Statistical Analyses / Methods

Endpoint / Variables

- The proportion of subjects requiring at least one course of systemic steroids for nasal polyps up to Week 52

Model Specification

- A logistic regression model will be used to compare the proportion of participants requiring a course of systemic steroids up to week 52 in the mepolizumab arm compared to placebo.
- The odds ratio comparing treatment groups will be estimated using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Number of OCS courses for NP in last 12 months (0, 1, >1; ordinal), baseline total endoscopic NP score (based on centrally read data), baseline nasal obstruction VAS score, Log_e baseline blood eosinophil

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence

Model Results Presentation

- The number and percentage of participants identified as requiring at least one course of systemic steroids for nasal polyps will be displayed by treatment group, as will the number of courses of therapy required.
- The estimated odds ratio, 95% CI and p-value comparing treatments from the logistic regression model will be displayed.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses

- No sensitivity/supportive analyses are planned for this endpoint.

7.3. Other Efficacy Analyses

7.3.1. Total Endoscopic Nasal Polyps Score Responders

A responder is defined as a participant achieving a ≥1-point improvement (decrease) from baseline in total endoscopic NP score (based on centrally read data) at Week 52. Participants with missing data at Baseline or Week 52 (due to early study withdrawal or any other reason) will be included in the analysis as a non-responder.

7.3.1.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder in the mepolizumab arm compared with placebo.

7.3.1.2. Population of Interest

The population of interest is the ITT population.

7.3.1.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.1.4. Statistical Analyses / Methods

Endpoint / Variables

- Total endoscopic nasal polyps score responders

  Participants with a ≥ 1-point improvement from baseline in total endoscopic NP at Week 52 (based on centrally read data) will be included in the analysis as a responder.

  The following participants will be included in the analysis as a non-responder:
  - Participants who had actual surgery prior to Week 52
  - Participants who withdrew early from the study or who had missing data at Baseline or Week 52

Model Specification

- A logistic regression model will be used to compare the proportion of responders in the mepolizumab arm compared to placebo.
- The odds ratio comparing treatment groups will be estimated using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of participants identified as responders and non-responders for analysis will be displayed by treatment group, the non-responder group will be further categorized to display the number of participants with actual surgery, the number withdrawn early from the study and the number with missing baseline data.
- The estimated odds ratio, 95% CI and p-value comparing treatments from the logistic regression model will be displayed.
- A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups will be provided by visit.

Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.3.2. Change from Baseline in Mean Individual and Composite VAS Symptom Scores

Participants rate individual symptoms daily on a visual analogue scale using an eDiary, the scale range for each symptom is [redacted]. Change from baseline during the 4-weeks prior to Week 52 in mean individual VAS symptom scores for nasal discharge, mucus in throat and facial pain and the mean composite VAS score (combining nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain), will be analysed as detailed for the co-primary endpoint of change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52.

Details regarding the summary measure, population of interest and the strategy for intercurrent events are provided in Section 7.1.2 to Section 7.1.4.

7.3.2.1. Statistical Analyses / Methods

Endpoint / Variables

- Change from baseline in individual VAS symptom scores of nasal discharge, mucus in throat and facial pain during the 4 weeks prior to Week 52
- Change from baseline in mean composite VAS score (combining nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain) during the 4 weeks prior to Week 52

Model Specification

- For each endpoint the p-value for the difference in median change from baseline between treatments will be based on the non-parametric Wilcoxon rank-sum test.
- The difference in median change from baseline with 95% confidence intervals will be estimated by quantile regression using a bootstrap approach.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- Median change from baseline within each treatment group.
- Estimated difference between treatments in median change from baseline with 95% confidence

interval (CI). • p-value comparing treatment groups from the Wilcoxon rank-sum test. •
Subgroup Analyses
• No subgroup analyses are planned for these endpoints.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for these endpoints.

7.3.3. SNOT-22 Responders

A responder is defined as a participant achieving a ≥8.9-point improvement (decrease) from baseline in SNOT-22 total score at Week 52. Participants with missing data at Baseline or Week 52 (due to early study withdrawal or any other reason) will be included in the analysis as a non-responder.

7.3.3.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder in the mepolizumab arm compared with placebo.

7.3.3.2. Population of Interest

The population of interest is the ITT population.

7.3.3.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.3.4. Statistical Analyses / Methods

Endpoint / Variables
• Participants with a ≥ 8.9-point improvement from baseline in SNOT-22 score at Week 52 will be included in the analysis as a responder. • The following participants will be included in the analysis as a non-responder: o Participants who had actual surgery prior to Week 52 o Participants who withdrew early from the study or who had missing data at Baseline or Week 52
Model Specification
• See Section 7.3.1.4
Model Checking & Diagnostics
• See Section 7.3.1.4
Model Results Presentation
• See Section 7.3.1.4

Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.3.4. SNOT-22 Domain Scores

There are six proposed domain scores for the SNOT-22 (nasal, non-nasal symptoms, ear/facial symptoms, sleep, fatigue, emotional consequences). For each domain the actual and change from baseline score will be summarised by visit. These summaries will be based on datasets where the intercurrent events of actual surgery and treatment discontinuation have been handled as detailed in Section 7.1.4.

7.3.5. Need for Surgery

Participants enter the trial with severity of nasal polyps consistent with the need for surgery (inclusion criteria 8 of study protocol). Participants are identified as no longer having a need for surgery based on improvements in the total nasal polyps endoscopy score (centrally read) and overall VAS score at Week 52 (further details in Section 14.6.5). Participants with missing data at Week 52 (due to early study withdrawal or any other reason) will be identified as still having a need for surgery at Week 52.

7.3.5.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant no longer having a need for surgery at Week 52 in the mepolizumab arm compared with placebo.

7.3.5.2. Population of Interest

The population of interest is the ITT population.

7.3.5.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.5.4. Statistical Analyses / Methods

Endpoint / Variables

• Need for surgery at week 52 will be assessed for each participant as detailed in Section 14.6.5.
• The following participants will be included in the analysis as still having a need for surgery:
  ○ Participants who had surgery prior to Week 52
  ○ Participants who withdrew early from the study or who had missing data at Baseline or Week 52

Model Specification

- A logistic regression model will be used to compare the proportion of participants who no longer have a need for surgery in the mepolizumab arm compared to placebo.
- The odds ratio comparing treatment groups will be estimated using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline total nasal polyps endoscopic score (centrally read data), Baseline overall VAS score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checking for issues with convergence.

Model Results Presentation

- The number and percentage of participants identified as no longer having a need/still having a need for surgery will be displayed by treatment group, the still having a need for surgery group will be further categorized to display the number participants with actual surgery, the number withdrawn early from the study and the number with missing Baseline data.
- The estimated odds ratio, 95% CI and p-value comparing treatments from the logistic regression model will be displayed.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses

- No sensitivity/supportive analyses are planned for this endpoint.

7.3.6. Rate of Nasal Surgery

A summary of the number and percentage of participants who have undergone surgery will be presented, the rate of surgery will also be presented for each treatment arm.

7.3.7. Time to First Inclusion on Waiting List for NP Surgery

A summary and graph of the Kaplan-Meier estimates of the cumulative proportion of participants having been placed on a waiting list for nasal polyps surgery/sinuplasty over time will be provided.

7.3.8. Waiting List for NP surgery

A summary of the number and percentage of participants placed on a waiting list for nasal polyp surgery at each visit and over the whole study will be presented.

7.3.9. Change from baseline in UPSIT (University of Pennsylvania Smell Identification Test)

UPSIT is designed to test the function of an individual's olfactory system. The test is scored out of 40 with a lower score indicating a worse outcome. The test will be performed only by participants at sites in the UK, US and Canada. Details regarding the summary measure, population of interest and the strategy for intercurrent events are provided in Section 7.1.2 to Section 7.1.4.

7.3.9.1. Statistical Analyses / Methods

Endpoint / Variables

- Change from baseline in UPSIT at Week 52

Model Specification

- The p-value for the difference in median change from baseline between treatments will be based on the non-parametric Wilcoxon rank-sum test.
- The difference in median change from baseline with 95% confidence intervals will be estimated by quantile regression using a bootstrap approach.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Country
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- Median change from baseline within each treatment group.
- Estimated difference between treatments in median change from baseline with 95% confidence interval (CI) and p-value comparing treatments from the Wilcoxon rank-sum test.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint.

Sensitivity and Supportive Analyses

- No sensitivity/supportive analyses are planned for this endpoint.

7.3.10. Change from baseline in PnIF (Peak Nasal Inspiratory Flow)

A PnIF meter will be used to derive forced inspiratory peak flow through the nose. A summary of PnIF data and change from baseline at each visit will be presented. These summaries will be based on a dataset where the intercurrent events of surgery/sinuplasty and treatment discontinuation have been handled as detailed in Section 7.1.4.

7.3.11. Health Outcomes

7.3.11.1. SF-36 Mental Component Summary (MCS), Physical Component Summary (PCS) and 8 summary scores

Certified scoring of the SF-36 survey will be performed using OPTUM™ software.

The eight domain scores (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality) as well as the physical and mental component summary scores are provided by the software.

Domain and component summary scores will be summarised by visit, including change from baseline. These summaries will be based on a dataset where the intercurrent events of surgery/sinuplasty and treatment discontinuation have been handled as detailed in Section 7.1.4.

7.3.11.2. Work Productivity and Activity Impairment Questionnaire (WPAI)

The WPAI questionnaire is an instrument to measure impairment in paid and unpaid work. Summary information from the WPAI at each visit will include information on employment status, hours missed from work due to health problems and due to other reasons, hours actually worked, and how much health problems affected productivity and activity.

7.3.12. Systemic Steroid Use

7.3.12.1. Number of mgs per year of prednisolone-equivalent OCS dose for nasal polyps up to Week 52

The total number of milligrams (mgs) of prednisolone-equivalent OCS per year for nasal polyps will be summarised for each treatment arm based on the use reported for each subject up to Week 52, data will be included in the summary regardless of the occurrence of events such as surgery or treatment discontinuation.

7.3.12.2. Days on Therapy

The mean number of days and percentage of days on systemic steroids for nasal polyps will be presented for each treatment arm. Data will be included in the summary regardless of the occurrence of events such as surgery or treatment discontinuation.

7.3.12.3. Time to First Course of Systemic Steroids

A summary and graph of the Kaplan-Meier estimates of the cumulative proportion of participants with a first course of systemic steroids for nasal polyps over time will be provided.

7.3.13. Number of Courses of Antibiotics

A summary of the number of courses of antibiotics will be presented for each treatment arm. Courses of antibiotics which are separated by less than 7 days will be considered a

continuation of the same course. Data will be included in the summary regardless of the occurrence of events such as surgery or treatment discontinuation.

7.3.14. Time to first nasal surgery or course of systemic steroids

The time to first nasal surgery or course of systemic steroids for nasal polyps will be determined as the number of days from the date of first dose of study medication to the date of first nasal surgery or course of systemic steroids for nasal polyps (see Section 14.6.5). If a participant withdraws from the study before experiencing nasal surgery or having a course of systemic steroids for nasal polyps, the event time will be censored at the time of study withdrawal.

7.3.14.1. Summary Measure

The summary measure of treatment effect will be the hazard ratio, the ratio of hazards corresponding to treatment with mepolizumab compared with placebo. For this endpoint the hazard represents the probability of nasal surgery or course of systemic steroids for nasal polyps for a participant at a given point in time following first dose of interventional product, given the participant has not experienced either event prior to that time.

7.3.14.2. Population of Interest

The primary population of interest is the ITT population.

7.3.14.3. Strategy for Intercurrent (Post-Randomisation) Events

A treatment policy strategy will be used for the intercurrent event of premature discontinuation of interventional product, such that available event times will be included in the analysis regardless of whether the event occurred prior to discontinuation of randomised treatment.

7.3.14.4. Statistical Analyses / Methods

Endpoint / Variables
• Time to first nasal surgery or course of systemic steroids for nasal polyps
Model Specification
• Cox proportional hazards model with covariates as follows: Fixed Categorical: Treatment group, Region Fixed Continuous: Baseline total nasal polyps endoscopic score (centrally read data), Baseline nasal obstruction VAS, Log_e baseline blood eosinophil count, Number of previous surgeries (1, 2, >2; ordinal) • Participants with missing covariate information will be excluded from the analysis
Model Checking & Diagnostics
• A log(-log(survival)) plot by treatment group will be used to assess the assumption of proportional hazards.
Model Results Presentation
• The number of participants with an event, the number censored due to study withdrawal and at study completion will be presented by treatment arm. • The hazard ratio with corresponding 95% CI and p-value from the Cox proportional hazards model will be presented. • A summary and graph of the Kaplan-Meier estimate of the cumulative proportion of participants with nasal surgery within each treatment arm over time will be produced.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.4. Participants with Asthma

A subgroup analysis by concurrent asthma will be carried out for each of the following endpoints:

- Total endoscopic nasal polyps score (Centrally Read)
- Nasal obstruction VAS score
- Proportion of subjects requiring systemic steroids for nasal polyps up to Week 52

In addition, for participants with asthma the Asthma Control Questionnaire (ACQ-5) score and number of clinically significant asthma exacerbations will be summarised. These summaries will be based on a dataset where the intercurrent events of surgery/sinuplasty and treatment discontinuation have been handled as detailed in Section 7.1.4.

7.5. Maintenance of response

The following endpoints will be summarised for the subset of participants who entered the no-treatment 6-month follow up period after Week 52. All data reported by these participants for the duration of their time in the study will be included in these summaries, this will include data reported prior to entering the follow-up period (whether or not the subject had prematurely discontinued from interventional product during that time) and data reported after entering the follow-up period.

- Change from baseline in total endoscopic NP score (centrally read)
- Change from baseline in mean nasal obstruction VAS score
- Change from baseline in mean individual VAS symptom score for nasal discharge, mucus in throat, loss of smell and facial
- Change from baseline in mean overall VAS symptom score
- Proportion of subjects requiring systemic steroids for nasal polyps
- Number of mgs per year of prednisolone-equivalent OCS dose
- Change from baseline in SNOT-22 total score
- Time to first nasal surgery
- Time to first inclusion on waiting list for NP surgery

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population. Unless otherwise specified data reported as part of the no-treatment follow-up will not be included in summaries of on-treatment data or post-treatment data. Data reported during the no-treatment follow-up will be summarised separately.

Summaries of adverse events (AEs), serious adverse events (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.

8.1. Adverse Events Analyses

8.2. Adverse Events of Special Interest Analyses

Adverse events of special interest (AESIs) are adverse events which are to be closely monitored as the development of mepolizumab progresses.

Systemic reactions are AESIs which are collected via targeted eCRF and further categorised by the investigator as either an allergic (type I hypersensitivity) or other systemic reaction. These events are required to be assessed against Sampson's diagnostic criteria for anaphylaxis. Local injection site reactions are also collected via targeted eCRF within the study.

AESIs of potential opportunistic infections, malignancies, serious cardiac, vascular and thromboembolic (CVT) events and serious ischemic events will be identified from a list

of relevant preferred terms maintained within a project level reference dataset created based on the MedDRA dictionary available at the time of source data lock for this study. Further details of how relevant preferred terms are identified for the AESIs are given in the Program Safety Analysis Plan (PSAP).

Separate summary tables showing the number and percent of participants with each type of AESI, broken down by preferred term will be created. These summaries will be reported as part of the standard AE/SAE tables for the AESIs of infections, serious infections, neoplasms, cardiac disorders and serious cardiac disorders. The relative risk of each AESI between mepolizumab and placebo will be presented with 95% confidence intervals.

For each AESI a profile summary table will be produced containing information on event characteristics including, but not be limited to, the number of participants with the AESI, the number of occurrences of the AESI, the number of participants with a serious event or a drug related event, summaries by maximum severity and separately by outcome.

Separate listings will be provided of participants with systemic reactions identified by the investigator as meeting the criteria for anaphylaxis, systemic reactions categorised as allergic (type I hypersensitivity), systemic reactions categorised as other, and all other AESIs.

8.3. Clinical Laboratory Analyses

Summaries of laboratory data including chemistry and haematology parameters, and liver function test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

The details of the planned displays are in Appendix 12: List of Data Displays.

8.4. Other Safety Analyses

8.4.1. ECG and Vital Signs

Summaries of ECG and vital signs data will be based on GSK Core Data Standards. The details of the planned displays are presented in Appendix 12: List of Data Displays.

For ECG data, summaries of the maximum post-baseline and change from baseline values for QTc(F), QTc(B) and heart rate will be provided.

Individual maximum and maximum change from baseline QTc(F) and QTc(B) values will be categorised as detailed in Section 14.6.6. The number (percent) of participants in each of the categories will be displayed.

The number of abnormal and clinically significant ECG results post baseline will be produced showing the worst recorded value post baseline.

8.4.2. Immunogenicity Data

An immune response to a therapeutic drug can lead to generation of anti-drug antibodies within the blood. For the immunogenicity assessment, two types of antibody assays will be performed, a binding anti-drug antibody (ADA) assay and a neutralizing antibody (NAb) assay.

For the binding ADA assay, there will be three testing steps: 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. Participants with a positive confirmation result will be positive for the binding ADA assay. Participants who test positive for the binding ADA assay, will be tested for the NAb assay, which also reports results as positive or negative.

Immunogenicity data will be summarised for all subjects in the safety population (excluding data reported during the follow-up period after Week 52), as well as for the subjects entering the follow-up period after Week 52 (using all data). For the binding ADA assay, confirmation results at each visit will be categorised as negative or positive and summarised. NAb assay results will also be summarised.

The highest binding ADA assay confirmatory result obtained for a participant (including any off-treatment data), will be summarised with a positive result being considered higher than a negative one, participants with both positive and negative results being identified in the positive category. Summary statistics for titre results will also be presented. In addition, the highest NAb assay result during the same period will be summarised (again with a positive result being considered higher than a negative one and participants with both positive and negative results will be identified in the positive category).

A summary of treatment emergent positive confirmatory binding ADA assay results in the subset of participants who did not have a positive confirmatory binding ADA assay result prior to the first dose of interventional product will also be presented.

All immunogenicity results (i.e. binding ADA screening and confirmatory assay results, titre values, NAb results and observed mepolizumab concentration) will be listed.

9. PHARMACODYNAMIC ANALYSES

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.

9.1. Pharmacodynamic Analyses

The treatment effect to be estimated (estimand) will be the comparison of mepolizumab 100mg SC to placebo for change from baseline blood eosinophils at Week 52.

9.1.1. Endpoint / Variables

Absolute and ratio to baseline blood eosinophil counts will be summarised at each visit.

9.1.2. Summary Measure

The summary measure of treatment effect will be the ratio of the effect at Week 52 of mepolizumab compared to placebo.

9.1.3. Population of Interest

The population of interest is the Intent to Treat population.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Only data collected while the participant was on-treatment will be used in the analysis ('while on-treatment strategy). Blood eosinophil counts taken more than 28 days following last dose will not be included in the analysis.

Missing data will be assumed to be missing at random.

9.1.5. Statistical Analyses / Methods

9.1.5.1. Statistical Methodology Specification

Endpoint / Variables

- Ratio to baseline blood eosinophils

Model Specification

- Blood eosinophil counts will be log transformed (loge) prior to analysis, transformations for values of 0 GI/L will be based on a value of 0.005 GI/L (see Section 14.6.6).
- This endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis including the following terms:

Fixed Categorical:	Treatment group, Region, Visit
Fixed Continuous:	Baseline $\log_e$ blood eosinophil count,
Repeated:	Visit
Interaction Terms:	Visit by baseline, visit by treatment group.

- Participants with missing covariate information will be excluded from the analysis

• An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line
Model Checking & Diagnostics
The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
Model Results Presentation
• The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • Model-estimates of the absolute mean and mean ratio to baseline will be back-transformed and presented as ratios with corresponding standard errors on the log scale for each treatment group by visit. Estimated treatment differences (Mepolizumab/Placebo) with corresponding 95% CIs and p-values will also be presented.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of mepolizumab administered subcutaneously in participants with severe nasal polyps. The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of mepolizumab in this population will be investigated. The individual subject PK parameters will be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses.

In support of the analysis described below, a dataset will be generated for which specifications will be provided in a separate document.

The 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. Refer to Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic Data).

10.1. Primary Pharmacokinetic Analyses

A population PK analysis of sparse concentration data will be performed on the PK population.

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Based on previous knowledge of mepolizumab 100 mg SC pharmacokinetics, concentrations below the limit of quantification (BLQ) of the assay are not anticipated. Any such results 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.

10.2. Population Pharmacokinetic Methodology

Sparse blood sampling is implemented in this study for determination of mepolizumab plasma concentration and subsequent data analysis by population PK methods using the most recent population pharmacokinetics model (meta-analysis PK model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00). Since mepolizumab PK following intravenous administration in NP subjects has already been established, the main objectives of this population PK analysis are:

- To evaluate mepolizumab pharmacokinetics in subjects with NP following the subcutaneous administration of a 100 mg dose every 4 weeks.
- To investigate the impact of covariates of interest in the studied NP population (such as baseline characteristics, co-medication) on specific parameters (e.g. clearance) to identify potential sources of inter-individual variability in these parameters.
- To obtain individual plasma concentration predictions for the timepoints at which PD is measured to allow the conduct of population PKPD analyses if deemed appropriate.

Further details are provided in Appendix 9: Population Pharmacokinetic (PopPK) Analyses.

10.3. Exploratory Pharmacokinetic Analyses

Complementing the population-PK analysis, a repeated measures linear mixed-effects model of $\log_e$-transformed concentration will be used to analyse the sparse (Weeks 4, 52 and 68) data. All data will be analysed on an ITT basis using planned Visit, irrespective of withdrawal. The model will adjust for Region and Visit number and consider the covariates listed above. Selection of covariates will be based on biological plausibility, parsimony and a significance level of 0.05. Forwards and backwards selection criteria may be applied as per the population PK model.

10.3.1. Summary Measure

Log-transformed mepolizumab plasma concentration.

10.3.2. Population of Interest

The population of interest is the PK population.

10.3.3. Statistical Analyses / Methods

Endpoint / Variables

- Plasma concentration

Model Specification

- Plasma concentration will be log transformed (log_e) prior to analysis, values BQL will be set to missing.
- This endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis including the following terms:

Fixed Categorical:	Region, Visit
Fixed Continuous:	log_e bodyweight, log_e creatinine clearance, log_e serum albumin
Repeated:	Visit
Interaction Terms:	None

  - Participants with missing covariate information will be excluded from the analysis

- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line

Model Checking & Diagnostics

The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Model Results Presentation

- The estimated means for each visit will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement).
- Model-estimates of the absolute mean and mean ratio to Week 4 (accumulation ratio) will be back-transformed and presented as ratios with corresponding standard errors on the log scale by visit. Estimated exposure ratios with corresponding 95% CIs and p-values will also be presented.
- Effects of bodyweight, creatinine clearance and serum albumin will be evaluated as ratio to standard values and back-transformed and presented as ratios with corresponding standard errors on the log scale. Estimated exposure ratios with corresponding 95% CIs and p-values will also be presented.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint

Sensitivity and Supportive Analyses

- No sensitivity/supportive analyses are planned for this endpoint

11. POPULATION PHARMACOKINETIC/ PHARMACODYNAMIC (POPPKPD) ANALYSES

In support of the analysis described below, a specific dataset will be generated for which specifications will be provided in a separate document.

The details of the planned displays are presented in Appendix 12: List of Data Displays.

11.1. Population Pharmacokinetic/Pharmacodynamic Methodology

If deemed appropriate, a population pharmacokinetic/pharmacodynamic analysis will be conducted on the PK population and the ITT population (for blood eosinophils).

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Zero values for the baseline blood eosinophil count as well as for blood eosinophil count during the study will be replaced by 0.005 prior to log transformation (consistent with approaches used in other analyses).

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.

Blood eosinophil counts were measured during the course of the study over the 52 weeks treatment period and will be analysed by population methods using the most recent population PKPD model (meta-analysis PKPD model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00).

The objectives of the population PKPD analysis are:

- To evaluate mepolizumab pharmacodynamics in subjects with NP following subcutaneous administration of a 100 mg dose every 4 weeks;
- To investigate the impact of covariates of interest in the studied NP population (such as baseline characteristics, co-medication) on specific parameters (e.g. maximum blood eosinophil reduction) in order to identify potential sources of inter-individual variability in these parameters.

Further details are provided in Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses.

12. EXPLORATORY EXPOSURE-EFFICACY RESPONSE ANALYSIS

If deemed appropriate an exposure-efficacy response analysis for the change from baseline in total endoscopic NP score and change from baseline in mean nasal obstruction VAS score during the 52-week study treatment period and subsequent 6-month follow-up period will be conducted.

12.1. Population of Interest

The exploratory exposure-efficacy response analysis will be performed on the ITT population.

12.2. Endpoints

Two measures of exposure will be considered for this analysis:

i) Dose/bodyweight (Week 52 endpoints only)

ii) C_{av} = Average concentration defined as 100 mg / (post-hoc apparent individual clearance x 28d)

Summary exposures (i) and (ii) will be categorised by quartiles for categorical analysis.

12.3. Methodology

12.3.1. Statistical analysis using exposure quartiles

12.3.1.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in total endoscopic NP score (based on centrally read data) at Week 52, categorized for analysis as in Section 7.1.5.1. • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52, categorized for analysis as in Section 7.1.5.1.
Model Specification
• Each co-primary endpoint will be analyzed using ordinal logistic regression to compare the odds between treatment exposure quartiles to placebo of being in a more favorable endpoint category. • Odds ratios will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates. • The analysis model will include the following terms:

Fixed Categorical:	Region
Fixed Continuous:	Treatment (placebo and exposure quartiles), Baseline score, Log_e baseline blood eosinophil count

• Participants with missing covariate information will be excluded from the analysis
Model Checking & Diagnostics
• Models will be checked for issues with convergence.
Model Results Presentation
• A forest plot of the estimated odds ratio and 95% CI for the comparison of quartiles will be provided.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint

13. REFERENCES

GlaxoSmithKline Document Number 2015N238436_00 Study ID N/A. A population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 27-MAY-2015.

GlaxoSmithKline Document Number 2015N255079_00 Study ID N/A. Supplementary outputs from a population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 04-OCT-2015.

GlaxoSmithKline Document Number N/A Study ID Health Outcomes Study. Evaluation of the measurement properties of visual analog scales and the SNOT-22 in nasal polyps. Report Date Jan-2018.

Hopkins S., Gillet, S., Slack, R., Lund, V.J., Browne, J.P. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin. Otolaryngol.* 2009;34:447-454.

Jackson D, White, I.R., Seaman, S., Evans, H., Baisley, K., Carpenter, J. Relaxing the independent censoring assumption in the Cox proportional hazards model using multiple imputation. *Statistics in Medicine.* 2014;33:4681-4694.

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Relevant CDISC documentation available on www.cdisk.org

14. APPENDICES

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

14.1.1. Exclusions from Per Protocol Population

Participants with protocol deviations considered to potentially effect efficacy will be excluded from the Per Protocol (PP) population. Determination of exclusion of a participant from the Per Protocol population will be made, where possible, before the database is frozen.

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

Number	Exclusion Description
01	Informed consent never signed
02	Does not meet at least one of the following inclusion criteria (as numbered in the protocol): 1. 18 years of age and older inclusive, at the time of signing the informed consent. 4. Participants who have had at least one previous surgery in the previous 10 years for the removal of NP. 5. Participants with bilateral NP as diagnosed by endoscopy or historical CT scan. 6. Presence of at least two different symptoms for at least 12 weeks prior to screening: nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and at least one of the following: nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell. 7. Participants with severe NP symptoms defined as an obstruction VAS symptom score of >5. 8. Severity consistent with a need for surgery as described by: a) Participants with an overall VAS symptom score >7 b) Participants with an endoscopic bilateral NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) 9. Treatment with INCS (including intranasal liquid steroid wash/douching) for at least 8 weeks prior to screening. 10. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
03	Meets any of the following exclusion criteria (as numbered in the protocol) 1. As a result of medical interview, physical examination, or screening investigation the physician responsible considers the participant unfit for the study. 2. Cystic fibrosis. 3. Eosinophilic granulomatosis with polyangiitis (also known as Churg Strauss syndrome), Young's, Kartagener's or dyskinetic ciliary syndromes. 4. Antrochoanal polyps. 5. Nasal septal deviation occluding one nostril. 6. Acute sinusitis or upper respiratory tract infection (URTI) at screening or in 2 weeks prior to screening. 7. Ongoing rhinitis medicamentosa (rebound or chemical induced rhinitis). 8. Participants who have had an asthma exacerbation requiring admission to hospital within 4 weeks of Screening.

Number	Exclusion Description
	9. Participants who have undergone any intranasal and/or sinus surgery (for example polypectomy, balloon dilatation or nasal stent insertion) within 6 months prior V1. 12. Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1. 13. Participants who are currently receiving or have received within 3 months (or 5 half-lives – whatever is the longest) prior to screening visit, radiotherapy or investigational medications/therapies. 14. Participants with a history of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation. Aspirin-sensitive participants are acceptable. 15. Participants with a history of allergic reaction to anti-IL-5 or another monoclonal antibody therapy. 17. Participants that have taken part in previous mepolizumab, reslizumab, dupilumab or benralizumab studies. 18. Use of systemic corticosteroids (including oral corticosteroids) within 4 weeks prior to screening or planned use of such medications during the double-blind period. 19. INCS dose changes within 1 month prior to screening. 20. Treatments with biological or immunosuppressive treatment (other than Xolair) treatment within 5 terminal phase half-lives of Visit 1. 21. Omalizumab (Xolair) treatment in the 130 days prior to Visit 1. 22. Commencement or change of dose of leukotriene antagonist treatment less than 30 days prior to Visit 1. 23. Commencement or change of dose of allergen immunotherapy within the previous 3 months. 28. Immunocompromised, other than that explained by the use of corticosteroids taken as therapy.
04	Does not meet any of the following randomisation criteria (as numbered in the protocol): 1. Endoscopic NP score of at least 3 in one nostril and 2 in the other as per over read from central lab taken at Visit 1. 2. Mean overall VAS >7 over the last 7 days preceding Visit 2 (excluding Visit 2) (from eDiary). 3. Mean nasal obstruction VAS score >5 over the last 7 days preceding Visit 2 (excluding Visit 2) (from eDiary). 4. Not had any NP surgery or have been included into a waiting list for NP surgery between Visit 1 and Visit 2. 5. eDiary compliance for VAS (4 out of the last 7 days preceding Visit 2). 8. Asthma Exacerbation: No asthma exacerbations during run-in period. An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids (i.v. or oral steroid) for at least 3 days or a single IM CS dose and/or emergency department visit, or hospitalization. 9. Maintenance Therapy: No changes or commencement during the run-in period in the dose or regimen of any regular baseline medication including a) INCS, b) course of systemic corticosteroids, such as OCS, c) leukotriene receptor antagonists, d) allergen immunotherapy. 10. If the participant has a cold during run in then run in should be extended so to have the baseline visit, 2 weeks post the resolution of the cold but no greater than a total of 6 weeks from screening. Colds that are not resolved within the 4th week of the nominal run-in period (28 days after screening) will be ineligible for randomization as they would have exceed this

Number	Exclusion Description
	6 week period.
05	Use of any prohibited medication during the study [1]
06	Received the wrong study treatment at any point during the study
07	Two or more of the following deviations related to wrong study treatment/administration/dose: • Study treatment not administered per protocol • Study treatment administered while contraindication • Expired study treatment administered • Use of study treatment impacted by a temperature excursion which was not reported or approved, or which was disapproved for further use • Study treatment not available at site for administration • Missed dose • Other deviations related to wrong study treatment/administration/dose
08	Patient/Investigator unblinded

NOTES:
[1] See Section 7.6 of protocol for a list of prohibited medications

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

		Pre screen[9]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ± 7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
Screening/ baseline	Informed consent[15]	X							
	Concurrent medication review (including INCS)	X	X						
	Inclusion and exclusion criteria		X						
	Demography	X							
	Full physical exam including height and weight		X						
	Medical history (including past and present medical conditions, substance usage family history of premature CV disease) and asthma exacerbation		X						
	History of HIV and Hep B and Hep C screen		X						
	Parasitic screening[10]		X						
	Medication History including INCS and OCS use for NP		X						
	History of NP surgery		X						
	Screening 12-lead ECG		X						

		Pre screen[9]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ±7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Screening Vital signs		X						
	Dispense "Medical Problems and Medication Taken Worksheet"	X	X						
	Collect "Medical Problems and Medication Taken Worksheet"		X						
	SAE review		X						
	Assessment of endoscopic NP score		X						
	Overall VAS symptom score and VAS for nasal obstruction to be captured on eDiary after training		X						
	Screening Laboratory assessments (include liver chemistries)		X						
	Screening Urinalysis		X						
	Urine pregnancy test (WOCBP only)		X						
	Dispense MF and eDiary		X						
	Register visit	X	X	X	X	X	X	X	X
	Review randomisation criteria			X					

		Pre screen[9]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ± 7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Randomisation (if applicable)			X					
	Genetic sample (PGX)			X					
Efficacy[11]	Assessment of Surgery (actual and waiting list)			X	X	X	X	X	X
	Assessment of OCS dose and duration			X	X	X	X	X	X
	Overall VAS symptom score [1]			X	X	X	X	X	X
	VAS symptom score for nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain [1]			X	X	X	X	X	X
	SNOT-22 [5]			X	X	X	X	X	X
	SF-36 [5, 7]			X	X[7]	X	X	X	X
	PnIF [2]			X	X	X			
	UPSIT [13]			X	X	X			

				Treatment Phase			No treatment Follow[6]		
Visit	Procedure	Pre screen[8]	Screening [8]	2	3 -14	15	16-17	18	EW Visit
Study day **(Visit window ±7 days)**			(28 days prior to Day 1)	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Endoscopic NP score [16, 17]			X	X[16, 17]	X	X	X	X
	WPAI-SHP [5]			X	X	X	X	X	X
	ACQ – 5[3, 5]			X	X	X			X
	Asthma exacerbation			X	X	X			X
	Blood for PK[4]			X	X	X	X[9]		X
	Blood for biomarkers			X		X			
Safety	AE/SAE review			X	X	X	X	X	X
	Dispense "Medical Problems and Medication Taken Worksheet"			X	X	X	X	X	
	Collect "Medical Problems and Medication Taken Worksheet"		X	X	X	X	X	X	X
	Concurrent medication review (including INCS)			X	X	X	X	X	X
	12-lead ECG			X		X			X
	Vital signs (HR and BP)			X	X	X			X
	Laboratory assessment: Haematology			X	X	X	X	X	X
	All other Laboratory assessments (including liver chemistries)			X		X			X
	Blood for immunogenicity			X		X	X[9]		X
	Urinalysis			X		X			X
	Urine pregnancy test (WOCBP)			X	X	X			X
Medication/ supplies	Dispense and train on eDiary for run in and remainder of the study		X						

		Pre screen[8]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ±7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Review and re train on eDiary (if required)			X	X	X	X	X	X
	eDiary completion [12]			X	X	X	X	X	X
	Review compliance and dispense MF			X	X	X[14]	X	X[14]	X[14]
	Dosing with study drug (active/ placebo)			X	X				
	Collect eDiary for the first 200 randomized participants							X	X
	Collect eDiary for remainder of the participants					X			X

1. Performed daily on the electronic Diary.
2. Performed monthly at study visits
3. For asthmatic participants only
4. Blood for PK will be collected at pre dose Visit 2 (baseline) and then pre dose at Visits 3, 15 and 17
5. Performed at site during study visits
6. For approximate up to the first 200 randomized participants
7. SF36 at visits 3, 5, 7, 9, 11, 13, 15, 16, 17 and 18 only
8. Pre screening and screening can be performed on the same day
9. At Visit 17 only
10. Parasitic screening is only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months. Sites should use local laboratories
11. All questionnaires will be performed before any other assessments on each particular visit, VAS scores, SNOT-22, SF-36 and WPAI

12. eDiary completion by participants will be daily every morning between screening visit and Visit 18 (or EW if appropriate) for the first 200 randomized participants or between screening and Visit 15 (or EW if appropriate) for the remainder of the participants.
13. UPSIT performed at Visits 2, 3, 5, 7, 9, 11, 13, 15 NB: UPSIT test will be performed only in selected countries
14. Dispensing of MF is not required if study 15, 18 or EW is the last study visit
15. PGx informed consent can be performed anytime prior sampling
16. The endoscopy assessment may be performed up to 3 days prior to the day of dosing but must not exceed the protocol defined windows of ± 7 days from the nominal study visit.
17. Endoscopy NP score assessment will be performed at visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 17, 18 and EW

- Abbreviations: ACQ, - Asthma Control Questionnaire; ECG – Electrocardiogram; EW- Early Withdrawal ; MF- mometasone furorate; NP- nasal polyps ; OCS- Oral Corticosteroids; PD- Pharmacodynamic ; PK- Pharmacokinetic ; PnIF- Peak Nasal Inspiratory Flow; SNOT- Sino-Nasal Outcome Test; SF-36 - Short Form Health Survey 36; UPSIT - University of Pennsylvania Smell Identification Test; VAS- Visual Analogue Scale; WOCBP -women of child bearing potential ; WPAI- Work Productivity and Activity Impairment
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

14.3. Appendix 3: Assessment Windows

14.3.1. Visit Based Assessments

No assessment windows are defined for visit based assessments. Clinic visits are scheduled to take place as specified in Appendix 2: Schedule of Activities and are subject to a ± 7-day window, however assessments performed outside of these visit windows will still be included in any analyses. Nominal visits will be used for reporting and analysis.

14.3.2. Unscheduled Visits

Data recorded at an unscheduled visit will be re-assigned to the closest nominal visit at which collection of the data was scheduled, unless information already exists at that visit. If an unscheduled visit occurs between two scheduled visits for which data has been reported, the data will remain in the unscheduled visit and will not be included in any by visit summary tables; it will however be included in relevant summaries of any time post-baseline data and listings.

14.3.3. Data from eDiary

The overall severity of nasal polyposis and of individual symptoms of nasal polyposis will be collected daily on a visual analogue scale using an eDiary. For the purposes of analysis, data from the eDiary will be slotted as shown in Table 2.

Table 2 Definition of Baseline and Week 52 Periods for eDiary Data

	Analysis Window	
Analysis Timepoint	**Beginning Timepoint**	**Ending Timepoint**
Baseline	Date of First Dose - 7	Date of First Dose -1
Weeks 1-4	Later of: Date of Visit 3 (Week 4) – 28 Date of First Dose + 1	Date of Visit 3 (Week 4) - 1
Weeks 5-8	Later of: Date of Visit 4 (Week 8) – 28 Date of Visit 3 (Week 4)	Date of Visit 4 (Week 8) - 1
Weeks 9-12	Later of: Date of Visit 5 (Week 12) – 28 Date of Visit 4 (Week 8)	Date of Visit 5 (Week 12) -1
Weeks 13-16	Later of: Date of Visit 6 (Week 16) – 28 Date of Visit 5 (Week 12)	Date of Visit 6 (Week 16) -1
Weeks 17-20	Later of: Date of Visit 7 (Week 20) – 28 Date of Visit 6 (Week 16)	Date of Visit 7 (Week 20) - 1
Weeks 21-24	Later of: Date of Visit 8 (Week 24) – 28 Date of Visit 7 (Week 20)	Date of Visit 8 (Week 24) - 1
Weeks 25-28	Later of:	Date of Visit 9 (Week 28) - 1

	Analysis Window	
Analysis Timepoint	**Beginning Timepoint**	**Ending Timepoint**
	Date of Visit 9 (Week 28) – 28 Date of Visit 8 (Week 24)	
Weeks 29-32	Later of: Date of Visit 10 (Week 32) – 28 Date of Visit 9 (Week 28)	Date of Visit 10 (Week 32) - 1
Weeks 33-36	Later of: Date of Visit 11 (Week 36) – 28 Date of Visit 10 (Week 32)	Date of Visit 11 (Week 36) - 1
Weeks 37-40	Later of: Date of Visit 12 (Week 40) – 28 Date of Visit 11 (Week 36)	Date of Visit 12 (Week 40) - 1
Weeks 41-44	Later of: Date of Visit 13 (Week 44) – 28 Date of Visit 12 (Week 40)	Date of Visit 13 (Week 44) - 1
Weeks 45-48	Later of: Date of Visit 14 (Week 48) – 28 Date of Visit 13 (Week 44)	Date of Visit 14 (Week 48) - 1
Weeks 49-52 (Primary timepoint for analysis)	Later of: Date of Visit 15 (Week 52) – 28 Date of Visit 14 (Week 48)	Date of Visit 15 (Week 52) - 1
Weeks 53-56	Later of: Date of Visit 16 (Week 60) – 56 Date of Visit 15 (Week 52)	Date of Visit 16 (Week 60) - 29
Weeks 57-60	Date of Visit 16 (Week 60) - 28	Date of Visit 16 (Week 60) - 1
Weeks 61-64	Later of: Date of Visit 17 (Week 68) – 56 Date of Visit 16 (Week 60)	Date of Visit 17 (Week 68) - 29
Weeks 65-68	Date of Visit 17 (Week 68) - 28	Date of Visit 17 (Week 68) - 1
Weeks 69-72	Later of: Date of Visit 18 (Week 76) – 56 Date of Visit 17 (Week 68)	Date of Visit 18 (Week 76) - 29
Weeks 73-76	Date of Visit 18 (Week 76) - 28	Date of Visit 18 (Week 76) - 1

NOTES:

- Data collected on Day 1 (Date of first dose) will not be used in analysis/summaries
- Analysis periods will be up to a maximum of 28 days
- Where a missing visit date prevents the start or end of a period from being determined, an imputed date (Date of First Dose + Week of Visit with missing date x 7) will be used.

14.3.4. Premature Withdrawals from Interventional Product or Study

Any data reported at the early withdrawal visit will be re-assigned to the closest available scheduled visit, unless information already exists at that visit. Data reported at the early withdrawal visit which has been re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Data reported at the early withdrawal visit will be included in the assessment of maximum or worst-case post-baseline summaries for any relevant endpoints, and all data will be included in listings.

14.4. Appendix 4: Study Phases

14.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose of interventional product.

14.4.1.1. Phases for Efficacy Assessments

Study Phase	Definition
Pre-Treatment	Assessment Date ≤ Interventional Product Start Date
On-Treatment	Participants who did not withdraw early from Interventional Product: Interventional Product Start Date < Assessment Date ≤ Earlier of Interventional Product Stop Date +28 days / Week 52 Visit Date Participants who withdrew early from Interventional Product: Interventional Product Start Date < Assessment Date ≤ Earlier of Interventional Product Stop Date +28 days/Date of Phase Conclusion
Off-Treatment	Participants who did not withdraw early from Interventional Product: Interventional Product Stop Date +28 days < Assessment Date ≤ Week 52 Visit Date Participants who withdrew early from Interventional Product: Interventional Product Stop Date + 28 days < Assessment Date ≤ Date of Phase Conclusion
Off-Treatment (Follow-up after Week 52)	Participants who enter the follow-up period after Week 52: Week 52 Visit Date < Assessment Date

14.4.1.2. Phases for Safety Assessments

Study Phase	Definition
Pre-Treatment	Assessment Date ≤ Interventional Product Start Date
On-Treatment	Interventional Product Start Date < Assessment Date ≤ Interventional Product Stop Date +28 days
Post -Treatment	Participants who do not enter the follow-up period after Week 52: Interventional Product Stop Date + 28 days < Assessment Date Participants who enter the follow-up period after Week 52: Interventional Product Stop Date + 28 days < Assessment Date ≤Week 52 Visit Date
Post -Treatment (Follow-up after Week 52)	Participants who enter the follow-up period after Week 52: Week 52 Visit Date < Assessment Date

14.4.1.3. Phases for Adverse Events

Study Phase	Definition
Pre-Treatment	Event Start Date < Interventional Product Start Date
On-Treatment	Interventional Product Start Date ≤ Event Start Date ≤ Interventional Product Stop

Study Phase	Definition
	Date + 28 days
Post -Treatment	Participants who do not enter the follow-up period after Week 52: Event Start Date > Interventional Product Stop Date + 28 days Participants who enter the follow-up period after Week 52: Interventional Product Stop Date + 28 days < Event Date ≤Week 52 Visit Date
Post -Treatment (Follow-up after Week 52)	Participants who enter the follow-up period after Week 52: Week 52 Visit Date < Event Date

NOTES: An event will be considered On-treatment if the event start date is missing and/or the interventional product stop date is missing
Where time of event is recorded, the time of event and time of first dose will be considered to differentiate between Pre-treatment and On-treatment events.

14.4.1.4. Phases for Concomitant Medication Start Dates

Study Phase	Definition
Pre-Treatment (Started prior to treatment)	Concomitant medication (CM) start date < IP start date
On-Treatment (Started during Treatment)	If CM start date is on/after IP start date & on/before IP stop date +28 days. (IP Start Date ≤ CM Start Date ≤ IP Stop Date + 28 days)
Post-Treatment (Started post-treatment)	If CM start date is after the IP stop date + 28 days. (CM Start Date > IP Stop Date + 28 days)
Follow-Up After Week 52 (started during the Follow-up period after Week 52)	Participants who enter the follow-up period after Week 52: If CM start date is after the Week 52 Visit date.

NOTES: If the IP stop date is missing and/or the CM start date is missing then the CM is considered to have started on-treatment

14.4.1.5. Phases for Concomitant Medication Usage Dates

Study Phase	Definition
Taken Prior to Treatment	If CM start date < IP Start Date
Taken During Treatment	If CM start date < IP start date and CM stop date ≥ IP start date If IP start date < CM start Date ≤ IP Stop Date + 28 days
Taken Post-Treatment	If CM start date ≤ IP stop date+28 days and CM stop date > IP stop date +28 days If CM start Date > IP stop date + 28 days

NOTES: If the IP stop date is missing and CM start date is on/after IP start date then CM considered taken during treatment

If CM start date is missing, then CM considered to be taken during treatment

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	PPD
HARP Compound	
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards [SDTM IG Version 3.2 & ADaM IG Version 1.1]. • Analysis datasets will include variables to clearly indicate whether each observation was observed while the patient was on randomized treatment, observed after the patient discontinued randomized treatment, or was imputed or is missing.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

14.5.2. Reporting Standards

General

• All data displays (Tables, Figures & Listings) will use the term "Subject" rather than "Participant" which reflects CDISC and GSK Data Display Standards terminology.
• Templates and standards within the current GSK Integrated Data Standards Library (IDSL) will be used for reporting unless otherwise stated.
IDSL standards located at https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx (under supporting documentation/component/statistical displays) will be applied:
  • 4.03 to 4.24: 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

Formats

• GSK IDSL Statistical Principles for the precision to which data and summary statistics are to be presented will in general be adopted, these may be adjusted to a clinically interpretable number of decimal places (d.p.).
  • For Blood Eosinophil Counts displayed as GI/L the following will be applied:
  Geometric Mean, Median, Min and Max (2 d.p.); SD Logs (3 d.p.)

Planned and Actual Time

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

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures, however they will be included in listings. • Data from unscheduled visits may be included in summary tables/figures when the unscheduled visit has been reassigned (Section 14.3.2). • Data from unscheduled visits will be included in any-time post-baseline summaries
Early Withdrawal from Interventional Product or from Study
• Data recorded at the early withdrawal visit will be re-assigned to the next scheduled visit, unless information already exists at that visit. Early withdrawal data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Early withdrawal visit data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. • Data recorded at early withdrawal visits will be included in the assessment of maximum or worst-case post-baseline for relevant endpoints. • Data from all early withdrawal visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	n, mean, standard deviation or standard error, median, minimum, maximum
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals for Graphics	

14.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: BLQ concentration values will be imputed as per GUI_51487 for descriptive summary statistics only.
NONMEM/Pop PK File	Pop-PK file (CSV and SAS format) for the POP-PK and POP-PKPD analyses performed by the Clinical Pharmacology Modelling and Simulation function will be created according to the POP-PKPD Dataset Specification document.
Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Unless otherwise specified, if there are multiple measurements reported under the same nominal visit, the value of the first assessment will be used in any derivation of summary statistics, all individual measurements will be presented in any data listings. • Participants with post-baseline safety data in both High and Low categories with respect to the Normal Range/Potential Clinical Concern will be counted in each of the categories for the "Any visit post-baseline" row of any related summary tables.
Study Day

• Calculated as the number of days from the first dose of study medication (IP start date).
  • If Visit Date = Missing → Study Day = Missing
  • If Visit Date < First Dose Date → Study Day = Visit Date – IP Start Date
  • If Visit Date ≥ First Dose Date → Study Day = Visit Date – (IP Start Date) + 1

14.6.2. Analysis Population

Actual Treatment for Safety Population
• Analysis of safety data will be by actual treatment arm. • For participants identified as having any discrepancies between the treatment group they were randomised to and the treatment received, the actual treatment arm will be derived based on the treatment received for more than 50% of all treatment administrations. For all other participants, actual treatment arm will be the same as the randomised treatment arm.

14.6.3. Study Population

Demographics
Age
• Year of birth is collected as 'YYYY' and will be presented as collected in listings • Date of birth will be imputed as '30th June YYY' • Age is calculated according to GSK standard IDSL algorithms and is based on the imputed date of birth relative to the date of Visit 1 (Screening).
BMI
• BMI will be calculated as Weight (kg) / [Height (m)]^2

Exposure
Extent of Exposure (Therapeutic Coverage)

• IP is administered approximately every 4 weeks and each dose viewed as providing therapeutic coverage for 4 weeks (28 days).
• Duration of exposure is calculated based on the therapeutic coverage as follows:
  ○ Duration of Exposure (days) = (IP Stop Date – IP Start Date + 29)
  ○ Duration of Exposure (months) = (IP Stop Date – IP Start Date + 29) * 12/365.25

Exposure
Extent of Exposure (Therapeutic Coverage)
• Subject Years Exposure is calculated as follows;   ○ Subject Years Exposure = (IP Stop Date – IP Start Date + 29)/365.25 • If the IP start date is missing and there is evidence the participant received at least one dose of IP, the IP start date will be taken to be the date of randomisation, if the IP end date is missing it will be taken to be the last on-treatment visit attended. • Randomised participants with no evidence of receiving at least one dose of IP will be considered as having zero days of exposure.

Exposure for treatment period and no-treatment follow-up
Number of years on and off-treatment or missing

• All participants are expected to participate in the study for at least 52 weeks (±7 days)
• The number of years on-treatment will be calculated as follows:
  ○ (IP Stop Date – IP Start Date + 29)/365.25
• The number of years off-treatment will be calculated as follows:
  ○ Date of Phase Conclusion – (IP stop date +28)/365.25
• The number of years missing will be calculated as follows for subjects who withdrew from study:
  ○ 1 – (number of years on-treatment) – (number of years off-treatment)

Duration of time in no-treatment follow-up
• This will be calculated in months for subjects who enter no-treatment follow-up after Week 52 as follows: ○ (Date of study end – Date of Week 52) * 12/365.25

Concomitant Medications (CM)
Time since first dose (days)
• The time since first dose will be calculated as follows: If CM start date < IP start date = CM start date - IP start date If CM start date ≥ IP start date = CM start date – IP Start Date +1 Missing otherwise. • The duration in days will be calculated as follows: CM end date – CM start date + 1

NOTES: Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates

Subgroups
Participants With Asthma
• Concurrent asthma: Subjects with a response of 'Current' for the medical condition of 'Asthma'. • No concurrent asthma: Subjects with a response of 'Past', 'Not Assessed' or 'No Medical Condition' for the medical condition of 'Asthma'. Subjects with a missing response will also be included in this category.

Subgroups

Aspirin Exacerbated Respiratory Disease (AERDS)

- Current AERDS: Subjects with a response of 'Current' for the medical condition of 'Drug Allergy'.
- No Current AERDS: Subjects with a response of 'Past', 'Not Assessed' or 'No Medical Condition' for the medical condition of 'Drug Allergy'. Subjects with a missing response will also be included in this category.

Number of previous surgeries

- Participants will be categorised as follows based on data collected on the eCRF regarding number of previous surgeries: 1, 2, >2

Baseline Blood Eosinophil Categories

- Categories for baseline blood eosinophils will be:
  - ≤0.3 GI/L; >0.3 to ≤0.5 GI/L; >0.5 to ≤0.7 GI/L; >0.7 GI/L
- Blood eosinophils are reported in GI/L, each category is rounded to 1 d.p. which is equivalent to rounding blood eosinophils to the nearest 100 cells/µL.

Region

- Europe: Participants from sites in Germany, Netherlands, Romania, Sweden, UK
- United States: Participants from sites in US
- Rest of World: Participants from sites in South Korea, Argentina, Australia, Canada, Russia

Age Categories

- Participants will be categorised as follows based on the derived age:
- 18-<40 years, 40 - < 65 years, ≥65 years.

Race Categories

- Subjects will be categorised by Race based on the Geographic Ancestry reported on the eCRF:

Race Category	Geographic Ancestry reported on the eCRF
African American/African Heritage	African American/African Heritage
White	White – Arabic/North African Heritage White – White/Caucasian/European Heritage
Asian	Asian – Central/South Asian Heritage Asian – East Asian Heritage Asian – Japanese Heritage Asian – South East Asian Heritage
Other	American Indian or Alaskan Native Native Hawaiian or Other Pacific Islander Multiple Race

14.6.4. Change from Baseline

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Ratio to Baseline [1]	= Post-Dose Visit Value / Baseline

NOTES: Refer to Section 5.2 for definition of Baseline. Unless otherwise stated, if Baseline or the Post-Dose value is missing the result will be set to missing.
[1] For $\log_e$ transformed data Ratio to Baseline is the back transformed change from baseline value

14.6.5. Efficacy

Assigning the worst score for subjects with surgery or missing data
Relevant efficacy endpoints
• Subjects who undergo surgery/sinuplasty will have their worst observed score (or worst observed 4-week mean) assigned for all subsequent visits (or 4-week periods) following surgery/sinuplasty. The assigned value will be the worst observed value from baseline up to before the surgery/sinuplasty. Assessments taking place on the same day as surgery/sinuplasty are assumed to have been carried out before the surgery/sinuplasty. • Subjects who have not experienced surgery/sinuplasty and have missing values due to study withdrawal, will have their worst observed score (or worst observed 4-week mean) assigned for all missing visits (or 4-week periods) following study withdrawal. The assigned value will be the worst observed value from baseline up until study withdrawal. • Subjects with missing data for other reasons will have their worst observed score (or worst observed 4-week mean) prior to the missing visit (or missing 4-week period) assigned.

Total Endoscopic Nasal Score
Responder
• A responder will be defined as a participant with a ≥1-point improvement from baseline in total endoscopic nasal score (centrally read). • Participants with no improvement/worsening or with missing data will be considered a non-responder for analysis.

VAS scores (individual and composite)
Individual VAS Scores
• VAS scores are captured electronically using an eDiary, participants indicate their response on a line CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. . • The final VAS scores for inclusion in summary and analysis tables will be derived from the electronically captured score by CCI .
Change from baseline categories
• The baseline scores will be calculated as the mean of the scores reported between the 7 days prior to the first dose. • The scores for each 4-week period will be calculated as the mean of the scores reported between timepoints detailed in Section 14.3.3.
Composite VAS scores

VAS scores (individual and composite)

• Two separate composite VAS scores will be derived using the final VAS scores:
• Composite of nasal obstruction, nasal discharge, mucus in the throat and loss of smell
  ○ CCI [redacted]
• Composite of nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain
  ○ CCI [redacted]

Nasal Surgery (reported on the disease related events page of the eCRF)

Time to first nasal surgery

- Calculated as (Date of first nasal surgery – Date of first dose of study treatment) + 1

- Analysis excluding data from the follow-up period after Week 52:
  For participants who withdraw from the study before Week 52 and before experiencing surgery, event times will be censored at the time of study withdrawal
  For participants who complete to Week 52 without experiencing surgery, event times will be censored at the time of the Week 52 visit.

- Analysis including data from the follow-up period after Week 52:
  For participants who withdraw from the follow-up period before completion and before experiencing surgery, event times will be censored at the time of study withdrawal.
  For participants who complete the follow-up period without experiencing surgery, event times will be censored at time of completion of follow-up.

Need for surgery

- Need for surgery at Week 52 is based on the overall VAS symptoms score and the endoscopic NP score (centrally read). Participants will be classified as having a need for surgery if they meet the following:
  - Overall VAS symptoms score >7 (Weeks 49-52) and total endoscopic NP score ≥5 (Week 52, centrally read)
- Participants who have undergone nasal polyps surgery at any time prior to the week 52 visit, or who have a missing endoscopic NP score (centrally read) at Week 52, or missing overall VAS symptom score (Weeks 49-52) will be identified for analysis as still having a need for surgery.

Rate of surgery

- The crude rate of surgery will be presented for each treatment arm, this will be calculated as:

$$\left(\frac{\text{Total number of nasal surgeries}}{\text{Total number of days in the study}}\right)*365.25$$

Systemic steroid use

Conversion of glucocorticoid dose to mgs of prednisolone equivalent OCS use

- The total number of mgs of prednisolone equivalent OCS use per year will be calculated as follows and will be based on systemic steroids taken via the following routes: Oral, Intravenous, Intramuscular:

$$\left(\frac{\text{Total cumulative mgs prednisolone}-\text{equivalent OCS use in period}}{\text{Total number of days in period}}\right)*365.25$$

- The following table from the study reference manual will be used for conversion of intravenous and oral steroid use into prednisolone equivalent OCS use in mgs:

Systemic steroid use

Glucocorticoid	Approximate equivalent dose (mg)
Short-Acting	
Cortisone	25
Hydrocortisone	20
Intermediate-Acting	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
Long- Acting	
Betamethasone	0.6-0.75
Dexamethasone	0.75

- Participants who withdraw early from the study will have yearly use estimated based on use during the study.

Courses of Therapy

- A course of systemic steroid therapy is defined by the start and stop date of therapy.
- If the start date of a course of systemic steroid therapy occurs <7 days from the stop date of the previous course, it will be considered a continuation of the same course.

Days on Therapy

- The duration of a course of systemic steroids will be calculated as the number of days between the start and stop date of the course: stop date – start date +1
- For each participant the total number of days on systemic steroids will be calculated as the sum of the duration of each of their courses of therapy.
- For each participant the percentage of days on systemic steroids will be calculated as follows:

$$\left(\frac{\text{Total number of days on systemic steroids}}{\text{Total number of days in the study}}\right)*100$$

Nasal Surgery or Course of Systemic Steroids

Time to first nasal surgery or course of systemic steroids

- Calculated as (Date of first nasal surgery/course of systemic steroids – Date of first dose of study treatment) + 1
- Analysis excluding data reported in the follow-up period after Week 52:
  For participants who withdraw from the study before Week 52 and before experiencing either event, event times will be censored at the time of study withdrawal
  For participants who complete to Week 52 without experiencing either event, event times will be censored at the time of the Week 52 visit

Antibiotic Use

Courses of Therapy

- A course of antibiotics is defined by the start and stop date of therapy.
- If the start date of a course of antibiotics occurs <7 days from the stop date of the previous course, it will be considered a continuation of the same course.

SNOT-22

SNOT-22 Total Score

- Each question of the SNOT-22 is graded on a CCI [redacted] The scores for each of the questions will be summed to derive CCI [redacted] [Hopkins, 2009].
- CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. [redacted]
- If a participant does not complete any questions at a visit the total score for that visit will be missing.
- If a participant has some (but no more than 50%) missing responses to questions at a visit, then the missing responses will be imputed with the unrounded mean of the non-missing responses at that visit. The SNOT-22 total score for that visit will then be rounded to the nearest integer.

SNOT-22 Responder

- A responder is defined as having a ≥8.9-point improvement (decrease) from baseline in SNOT-22 total score.

SNOT-22 Domain Scores

- The six SNOT-22 domain scores are shown below; the domain scores are derived from the sum of the individual item-scores shown [Health Outcomes Study, 2018]:

Domain	Items/Questions
Nasal	CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. [redacted]
Non-nasal symptoms	
Ear/facial symptoms	
Sleep	
Fatigue	
Emotional consequences	

UPSIT

UPSIT total score

- The total score is calculated as the number of times the correct smell is identified out of a possible 4 choices, for 40 different smells.

Work Productivity and Activity Impairment Questionnaire (WPAI)
• The following summary variables will be derived from the 6 WPAI questions:

Summary variable	Derivation
CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.	

ACQ-5
ACQ-5 Score
• ACQ-5 is a 5-item questionnaire developed as a measure of patient's asthma control. Response options for each question are on CCI
• The questions are equally weighted, and the ACQ-5 score is calculated as the mean of the 5 questions, CCI
• For a given visit, if the response to one of the 5 questions is missing then the ACQ-5 score will be calculated as the mean of the available responses. If the response to more than one question is missing, then the ACQ-5 score will be set to missing.

Asthma exacerbations
Clinically significant asthma exacerbation
• A clinically significant asthma exacerbation is defined as a worsening of asthma requiring systemic steroids (i.v. or oral) for at least 3 days or a single intra-muscular corticosteroid dose, and/or an ED visit and/or hospitalisation.

14.6.6. Safety

Adverse Events
Drug Related AE's
• AEs where the response to "Is there a reasonable possibility that the AE may have been caused by the Study Treatment?" is "Yes" or it is missing
AE's Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study
• AE's leading to permanent discontinuation of study treatment are defined as AEs where the response to "Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the AE" is "Study Treatment(s) Withdrawn".
• AEs leading to withdrawal from study are defined as AEs where the response to "Did the subject withdraw from study as a result of this AE?" is "Yes".

AE's on Day of Dosing

- These are defined as AEs with an onset date on the same day as dosing with interventional product and an onset time on or after the time of dosing with interventional product on the given day.

AE Time Since First Dose

- If AE onset time is missing, calculate in days as follows:
  - If AE start date < Date of first dose of Interventional Product, then
    Time since first dose = AE start date - Date of first dose of Interventional Product
  - If AE start date ≥ Date of first dose of Interventional Product, then
    Time since first dose = AE start date – Date of first dose of Interventional Product +1
  - If AE start date or date of first dose of Interventional Product is missing time since first dose is missing.

- If AE onset time is present, calculate as above but in days, hours, minutes using AE start date/time and date/time of first dose of interventional product

AE Duration in Days

- If AE onset time is missing calculate in days: AE end date - AE start date + 1
- If AE onset time is present calculate in days, hours, minutes as above but using AE end date/time and AE start date/time.
- If AE start/end date is missing duration is missing.

AE's of Special Interest

- Section 8.2 provides a full list of AEs of special interest for this compound.
- AESIs of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF.
- The AESIs of potential opportunistic infections, malignancies, serious CVT events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset; created based on the latest version of the MedDRA dictionary available at the time of database freeze for this study (See Program Safety Analysis Plan for additional details).

ECG

Multiple Assessments

- Where multiple assessments are performed at a given time point, the mean value over the replicate assessments will be used for summary statistics; the highest value amongst the individual replicate assessments will be used in the evaluation of the highest post-baseline value.

QTc values

- A single 12-lead ECG machine will be used to assess heart rate and measure PR, QRS, QT and QTc intervals
- QTc(F) will be derived from QT (uncorrected) and RR interval as: $QTc(F) = \frac{QT}{\sqrt[3]{RR/1000}}$
- QTc(B) will be derived from QT (uncorrected) and RR interval as: $QTc(B) = \frac{QT}{\sqrt{RR/1000}}$
- If present the reported QTc value will be included in any summaries, else the derived QTc value will be included.

Categorised QTc values

Individual maximum QTc(F) and QTc(B) values and maximum change from baseline QTc(F) and QTc(B) will be categorised as follows:

	Lower	Upper
QTc Interval (msec)		≤ 450

		> 450	≤ 480	
		> 480	≤ 500	
		> 500		
	QTc Change from Baseline (msec)		≤ 30	
		> 30	≤ 60	
		> 60		

Laboratory Parameters

Character Values

- If a laboratory value which is expected to have a numeric value for summary purposes has a non-detectable level reported in the database, where the numeric value is missing, but instead a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, a numeric value will be imputed; the number of significant digits in the observed value will be used to determine how much to add or subtract to impute the corresponding numeric value:
  - Example 1: 2 Significant Digits = '< x 'imputed as x – 0.01
  - Example 2: 1 Significant Digit = '> x' imputed as x + 0.1
  - Example 3: 0 Significant Digits = '< x' imputed as x –1
- Laboratory values with missing values due to being below the limit of quantification (BLQ) for that parameter will have a value imputed as half the lower limit of quantification for that measure (i.e. the lowest observed value for that measure within the entire study database).
- Values of potential clinical concern and those outside the ≥2, ≥3 etc. limit of normal will be identified as detailed in Section 14.8.

Blood Eosinophils

- Blood eosinophil counts will be log transformed (loge) prior to analysis. The log transformation for values of 0GI/L will be based on a value of 0.005GI/L.

Biomarkers

- No analyses of additional biomarker will be carried out as part of this RAP.

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail

General	• The protocol objective is to collect data over the full study treatment period (up to Week 52) for all participants, whether they continue on interventional product (IP) and complete Week 52 on-treatment, or whether they withdraw prematurely from IP.
	  ○ For the participants who withdraw prematurely from IP before Week 52 and agree to the continued collection of data off-treatment, data will be collected for up to 52 weeks after randomization (or up to 76 weeks if the participant enters the Follow-up period after Week 52) either through clinic visits or via phone contact, in accordance with the participants existing visit schedule.
	  ○ Where available, off-treatment data will be included in the analysis of the co-primary endpoints and, unless otherwise indicated, in the analysis of other efficacy endpoints.
	• A participant will be considered to have completed study treatment if he/she continues to take study treatment until Visit 14 (Week 48) and completes Visit 15 (week 52).
	• As specified in the protocol participants will be considered to have completed the study upon completion of Visit 15 (Week 52) regardless of whether they continue to take IP.
	• A participant eligible for the no-treatment follow-up will be considered to have completed follow-up if they continue to participate in the study until Visit 18 (Week 76)
	• All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified.
	• Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

Pre-Screen/Screen and Run-in Failures	• Participants are assigned a subject number at the time of signing informed consent. • Pre-Screen Failure: A participant who is assigned a subject number but did not continue through to Visit 1. • Screening Failure: Participant performs a Visit 1 procedure, but does not enter the run-in period • Run-in Failure: Participant enters the run-in period, may perform a Visit 2 procedure, but is not subsequently randomised.

14.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated using a “blank” in data listings. Where all data for a specific visit are missing the visit will be excluded from the listing.
	  ○ Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed.
	Values reported as ‘BLQ’ are not considered as missing data and are handled as detailed in

Element	Reporting Detail
	Section 14.6.6, these values will be displayed in the listings and included in any summary/analysis outputs.
Outliers	• All data will be included in the summaries and analyses of each endpoint. The exclusion of participants or participant data from any supplementary analyses will be documented within footnotes and where required the clinical study report.
Covariate information	• Participants with missing information for a covariate included in the analysis model will be excluded from the analysis.

14.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Start or end dates which are completely missing (i.e. no day, month or year is specified) will remain missing, with no imputation applied. Derivations requiring this information such as time to onset and duration will be set to missing.

14.7.2.2. Handling of Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listings.
Adverse Events	• The eCRF allows for the possibility of partial dates to be recorded for AE start and end dates. • For partial dates the following imputations will be applied: o Partial Start Date: '01' will be used for a missing day and 'Jan' will be used for a missing month. If this results in a date prior to the start of study treatment, then the treatment start date will be used. The event will then be considered 'On-treatment' as per Section 14.4.1.3. o Partial Stop Date: '28/29/30/31' will be used for a missing day (dependent on the month and year) and 'Dec' will be used for a missing month. If this results in a date after the study stop date, then the study stop date will be used. • The above imputations will be applied when calculating the time to onset and duration of the event.
Concomitant Medications	• For concomitant medications partial dates will be imputed as follows: o Partial start date: '01' will be used for a missing day and 'Jan' will be used for a missing month o Partial stop date: '28/29/30/31' will be used for a missing day (dependent on the month and year) and 'Dec' will be used for a missing month.

14.7.2.3. Missing Data for Statistical Analysis

Element	Reporting Detail
General	• The study is designed to collect data for the 52 weeks following randomisation for all participants, including for participants who prematurely withdraw from interventional product. The following scenarios may arise. 1) Participant completes interventional product and study 2) Participant prematurely withdrawn from interventional product and agrees to continued data collection off-treatment for 52 weeks following randomisation 3) Participant prematurely withdrawn from interventional product and initially agrees to continued off-treatment data collection, but subsequently withdraws from the study prior to 52 weeks following randomisation 4) Participant prematurely withdrawn from interventional product and does not agree to continued off-treatment data collection • For participants under any scenario missing data may arise intermittently due to nonattendance at scheduled visits. For participants under scenarios 3 and 4 missing data will arise due to premature withdrawal from the study. • Unless otherwise specified on-treatment data and where available off-treatment data will be included in the analysis of efficacy endpoints.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values of Potential Clinical Concern

Haematology				
Laboratory Parameter	**Units**	**Age Category (years)**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	12+	0.201	0.599
Haemoglobin	G/L	12+	71	199
Platelet Count	GI/L	1+	31	1499
While Blood Cell Count (WBC)	GI/L	12+	1.1	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Age Category (years)**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
ALT	U/L	3-12		>143
	U/L	13+		>239
Calcium	mmol/L	3+	1.50	3.24
Creatinine Phosphokinase	IU/L	12+		>5 x ULN
Glucose	mmol/L	1+	2.2	27.8
Phosphorus, Inorg	mmol/L	3+	0.32	
Potassium	mmol/L	3+	2.8	6.5
Sodium	mmol/L	0+	120	160

Possible Hy's Law Cases			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT, Bilirubin			ALT ≥ 3xULN and Bilirubin ≥ 2xULN (>35% direct)
ALT, INR			ALT ≥ 3xULN and INR > 1.5

NOTES: ULN=Upper Limit of Normal

14.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

14.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

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

14.9.2. Population Pharmacokinetic (PopPK) Methodology

Mepolizumab plasma concentration-time data (samples collected at Weeks 4, 52 and 68; at the Early Withdrawal Visit and the additional follow-up visits (if applicable)) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

14.9.2.1. Base Model

In consideration of the sparse sampling (3 samples post-start of treatment over 68 weeks: Week 4, 52 and 68) and the wealth of mepolizumab PK knowledge, the most recent population PK model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated, against which the model will be validated prospectively using appropriate goodness of fit tests. For example, the Anderson-Darling and Cramér–von Mises tests are accepted methods of comparing Empirical Distribution Functions for model and data (i.e. PK concentrations) to evaluate whether independent observations (i.e. observed PK concentrations from the study) are adequately described by a model (i.e. most recent population PK model).

The following will be obtained:

- A description of the key models tested during the model development will be provided and tabulated;
- Population mepolizumab plasma 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 post-hoc PK parameter estimates (such as area under the plasma concentration-time curve over the dosing interval [AUC (0-τ)], C_{AV} [AUC (0-τ)/τ]) will be summarised descriptively and listed;
- Individual post-hoc predicted plasma concentrations will be summarised descriptively and listed;
- Accumulation ratio estimate will be assessed at Week 52.

The most recent model consists of a two-compartment pharmacokinetic model with first-order absorption and elimination. Bodyweight is incorporated into the model using allometry with fixed physiological allometric exponents of 0.75 and unity for clearance and volumes, respectively. Albumin and creatinine clearance are also included as covariates of mepolizumab clearance on physiological grounds, however their effects are small and not of clinical relevance. Details of the model can be found in report GlaxoSmithKline Document Number 2015N238436_00.

14.9.2.2. Investigation of Covariates

The impact of the following prospectively selected covariates on mepolizumab exposure (e.g. clearance) will be evaluated using the procedures described in Section 14.9.2.3.

Category	Covariates
Demographics	Weight (included in the structural model), age, race, gender, country
Baseline clinical status	Creatinine clearance, albumin (both already included in the current model), serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, total protein
Baseline disease status	Total endoscopic NP score (centrally read), mean nasal obstruction VAS, number of previous surgeries, blood eosinophils and baseline OCS dose
Concomitant medications	If data permits[1], e.g. leukotriene receptor antagonists, proton pump inhibitors, statins, antihistamines, pain relief (e.g. paracetamol, NSAIDs) and antihypertensive drugs
Others	Presence/absence of anti-drug antibodies and previous biologics use (monoclonal antibodies).

[1] Attempt to investigate those classes of drug will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PK parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.4 (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, in line with criteria used in previous analyses. 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 in Section 14.9.2.3. If deemed appropriate box plots of systemic clearance versus covariates of interest (e.g. immunogenicity status) will be provided.

14.9.2.3. 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, in line with criteria used in previous analyses.

- **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 also be supported by examination of the goodness of fit. This will constitute the full model.

- **Backward elimination procedure**

From the full model, the significance of each covariate will be tested individually by removing covariates 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.

Note: centering of continuous covariates may be considered, as appropriate. The mean or median value of the subjects included in the analysis may be used for example.

The impact of the presence of anti-mepolizumab antibodies may not be formally tested as a covariate in the model, considering the low incidence observed in the mepolizumab programme to date. Instead a graphical approach will be used, if deemed appropriate.

14.9.2.4. Model Evaluation

The uncertainty in the parameter estimates will be assessed (e.g. from the standard error estimates provided by NONMEM or from the 95% CI estimates provided by other appropriate analysis conducted using other software). Furthermore, the model performance will be investigated using a set of goodness of fit plots as well as Visual Predictive Check (VPC) method. Other evaluation methods may be used (e.g. bootstrapping) if deemed appropriate.

14.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

14.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

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

14.10.2. Pharmacokinetic / Pharmacodynamic Methodology

Mepolizumab blood eosinophil count-time data (samples collected every 4 weeks from Baseline to Week 52, and at Weeks 60, 68 and 76) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

14.10.3. Base Model

The most recent population PKPD model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated against which the model will be validated prospectively using appropriate goodness of fit tests as described in Section 14.9.2.1 (using the observed data from the study).

The following will be obtained:

- 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.

The most recent population PKPD model consists of 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). Observed baseline blood eosinophil count is included as covariates of both predicted baseline and mepolizumab inhibitory response; and disease for predicted baseline blood eosinophil count. Details of the model can be found in GlaxoSmithKline Document Number 2015N238436_00 and GlaxoSmithKline Document Number 2015N255079_00 (extension of the former report).

14.10.4. Investigation of Covariates

The impact of the following prospectively selected plausible covariates on relevant parameters (i.e., baseline blood eosinophil count and maximum effect) will be evaluated.

Category	Covariates
Demographics	Age, race, gender
Baseline disease status	Total endoscopic NP score (centrally read), mean nasal obstruction VAS, number of previous surgeries, blood eosinophils and baseline OCS dose
Others	If data permits[1], e.g. leukotriene receptor antagonists,

	proton pump inhibitors, statins, antihistamines, pain relief (e.g. paracetamol, NSAIDs) and antihypertensive drugs

[1] Attempt to investigate those covariates will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PD parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.4 (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, in line with criteria used in previous analyses. 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 Section 14.9.2.3 for the population PK model.

Model evaluation will be as described in Section 14.9.2.4 for the population PK model.

14.11. Appendix 11: Abbreviations & Trade Marks

14.11.1. Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
ED	Emergency Department
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IP	Interventional Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
NP	Nasal Polyps
OCS	Oral Corticosteroid
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PnIF	Peak Nasal Inspiratory Flow
PP	Per Protocol
PopPK	Population PK
PopPKPD	Pharmacokinetic / Pharmacodynamic
QC	Quality Control
QTcF	Frederica'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
SC	Subcutaneous
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SF-36	Short Form-36
SNOT-22	Sino-Nasal Outcome Test -22
SoC	Standard of Care
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
UPSIT	University of Pennsylvania Smell Identification Test
VAS	Visual Analogue Scale
WPAI	Work Productivity and Impairment

14.11.2. Trademarks

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

14.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	1.1
Efficacy	2.1 to 2.69	2.1 to 2.25
Safety	3.1 to 3.68	3.1 to 3.3
Population Pharmacokinetic (PopPK)	4.1 to 4.7	4.1 to 4.9
Pharmacokinetic / Pharmacodynamic (PopPKPD)	5.1 to 5.4	5.1 to 5.8
Exposure-Efficacy		6.1 to 6.4
Section	**Listings**	
ICH and Other Listings	1 to 52	

14.12.2. 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
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacokinetic / Pharmacodynamic (PopPKPD)	POPPKPD_Fn	POPPKPD_Tn	POPPKPD_Ln
Efficacy Exposure	EE_Fn	EE_Tn	EE_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL/Shell' or 'Programming Notes' column with an associated reference.'

14.12.3. Deliverables

Delivery Priority [1]	Description
SAC [1]	Headline Results
SAC [2]	Final Statistical Analysis Complete

NOTES:

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

14.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC [1]
1.2.	ITT	SHELL	Summary of Time On- and Off-Treatment by Withdrawal Scenario	Withdrawal scenarios are detailed in Section 14.7.2.3. Add footnote to indicate exclusion of data from the follow-up period after Week 52	SAC [2]
1.3.	ITT	ES1	Summary of Subject Disposition (Week 52)	ICH E3, FDAAA, EudraCT	SAC [1]
1.4.	FU	ES1	Summary of Subject Disposition (Follow-Up Period after Week 52)		SAC [2]
1.5.	FU	SHELL	Summary of Duration of Time in Follow-Up Period after Week 52		SAC [2]
1.6.	ENROLLED	ES6	Summary of Screening and Run-In Status and Reasons for Screen and Run-In Failures	Journal Requirements	SAC [2]
1.7.	ENROLLED	NS1/SHELL	Summary of Number of Subjects by Region, Country and Centre	EudraCT/Clinical Operations Add in column for region, add a total for each region and a total for each country.	SAC [2]
Protocol Deviation					
1.8.	ITT	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [2]
Population Analysed					
1.9.	ENROLLED	SP1	Summary of Study Populations	IDSL	SAC [1]
1.10.	Randomised	SP2A	Summary of Exclusions from the Intent-to-Treat and Safety Populations	IDSL	SAC [2]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.11.	ITT	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC [1]
1.12.	ENROLLED	DM11	Summary of Age Ranges	EudraCT	SAC [2]
1.13.	ITT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC [2]
1.14.	ITT	Shell	Summary of Nasal Polyps Disease History and Characteristics	Include Disease Duration (years/months); Number of previous surgeries; Number of Courses of OCS for NP in previous 12 months. Baseline Nasal Polyps endoscopy score (centrally read and investigator read); Baseline SNOT-22.	SAC [1]
1.15.	ITT	Shell	Summary of Previous Exacerbation History	To include separate summary of information for Asthma and COPD Exacerbation History	SAC [2]
Medical Conditions					
1.16.	ITT	MH4	Summary of Past Medical Conditions	ICH E3	SAC [2]
1.17.	ITT	MH4	Summary of Current Medical Conditions	ICH E3	SAC [2]
Prior and Concomitant Medications					
1.18.	ITT	CM1	Summary of Medications Started Prior to Treatment	ICH E3; ATC classification to be displayed for combination medications (not for individual ingredients)	SAC [2]
1.19.	ITT	CM1	Summary of Concomitant Medications Started During Treatment	ICH E3; ATC classification to be displayed for combination medications (not for individual ingredients). Footnote: Includes medications started after first dose and before last dose + 28 days.	SAC [2]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.20.	ITT	CM1	Summary of Systemic Corticosteroids Started During Treatment	Footnote: Includes medications started after first dose and before last dose + 28 days.	SAC [2]
Exposure					
1.21.	ITT	SHELL	Summary of Exposure (Therapeutic Coverage) to Interventional Product	ICH E3 Range of Exposure (months): 1-<3, 3-<6, 6-<9, 9-<12, >=12Also add subject years exposure	SAC [2]
1.22.	ITT	SHELL	Summary of Number of Treatments Administered		SAC [2]

14.12.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	SHELL	Subject Withdrawal from Interventional Product	Footnote: Kaplan-Meier estimates of time to withdrawal from IP. Subjects are represented from Day 1 to Day of withdrawal from IP	SAC [2]

14.12.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Co-Primary Endpoints					
2.1.	ITT	SHELL	Summary of Total Endoscopic Nasal Polyps Score (Centrally Read)	Footnote: Includes data reported up to Week 52 Include actual scores and change from baseline Based on the primary analysis dataset	SAC [1]
2.2.	ITT	SHELL	Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52		SAC [1]
2.3.	ITT	SHELL	Sensitivity Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Assigned Worst Possible Score Across All Subjects for Missing and Worst Observed Score for Surgery/Sinuplasty		SAC [2]
2.4.	ITT	SHELL	Sensitivity Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Assigned Worst Possible Score Across All Subjects for Missing and Surgery/Sinuplasty		SAC [2]
2.5.	PP	SHELL	Supplementary Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Per-Protocol Population		SAC [2]
2.6.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Participants with Asthma		SAC [2]
2.7.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Aspirin Exacerbated Respiratory Disease (AERDS)		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Number of Previous Surgeries		SAC [2]
2.9.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Baseline Blood Eosinophil Categories		SAC [2]
2.10.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Region		SAC [2]
2.11.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Age		SAC [2]
2.12.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Gender		SAC [2]
2.13.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Race		SAC [2]
2.14.	ITT	SHELL	Summary of Individual VAS Symptom Scores	Footnote: Includes data reported up to Week 52 Subheaders: Nasal Obstruction, Nasal Discharge, Mucus in Throat, Loss of Smell, Facial Pain	SAC [2]
2.15.	ITT	SHELL	Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52)		SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	ITT	SHELL	Sensitivity Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52):- Assigned Worst Possible Mean Across All Subjects for Missing and Worst Observed Mean for Surgery/Sinuplasty		SAC [2]
2.17.	ITT	SHELL	Sensitivity Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52): Assigned Worst Possible Mean Across All Subjects for Missing and Surgery/Sinuplasty		SAC [2]
2.18.	PP	SHELL	Supplementary Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52): Per-Protocol Population		SAC [2]
2.19.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Subjects with Asthma		SAC [2]
2.20.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Aspirin Exacerbated Respiratory Disease (AERDS)		SAC [2]
2.21.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Number of Previous Surgeries		SAC [2]
2.22.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Baseline Blood Eosinophil Categories		SAC [2]
2.23.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Region		SAC [2]
2.24.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Age		SAC [2]
2.25.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Gender		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.26.	ITT	SHELL	Subgroup Analysis of Median Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Race		SAC [2]
Secondary Endpoints					
2.27.	ITT	SHELL	Analysis of Time to First Nasal Surgery	Footnote: Includes data reported up to Week 52	SAC [1]
2.28.	ITT	SHELL	Sensitivity Analysis of Time to First Nasal Surgery: Tipping Point Analysis	Footnote: Includes data reported up to Week 52	SAC [2]
2.29.	ITT	SHELL	Summary of Overall VAS Score	Footnote: Includes data reported up to Week 52	SAC [1]
2.30.	ITT	SHELL	Analysis of Median Change from Baseline Overall VAS Score (Weeks 49-52)		SAC [1]
2.31.	ITT	SHELL	Summary of SNOT-22 Total Score	Footnote: Includes data reported up to Week 52	SAC [1]
2.32.	ITT	SHELL	Analysis of Median Change from Baseline SNOT-22 at Week 52		SAC [1]
2.33.	ITT	SHELL	Summary and Analysis of Proportion of Subjects Requiring Systemic Steroids for Nasal Polyps up to Week 52	Footnote: Courses of systemic steroids separated by <7 days are considered a continuation of the same course Include n (%) with 0 vs ≥1 and 0, 1, 2, etc courses and total number of courses	SAC [1]
2.34.	ITT	SHELL	Subgroup Analysis of Proportion of Subjects Requiring Systemic Steroids for Nasal Polyps up to Week 52 by Participants with Asthma	Footnote: Courses of systemic steroids separated by <7 days are considered a continuation of the same course Include n (%) with 0 vs ≥1 and 0, 1, 2, etc courses and total number of courses	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.35.	ITT	SHELL	Summary of Composite VAS Scores	Footnote: Includes data reported up to Week 52 Subheaders: Composite - Nasal Symptoms [1] and Composite - Nasal Symptoms and Facial Pain [2] Footnote: [1] Composite - Nasal Symptoms includes nasal obstruction, nasal discharge, mucus in the throat and loss of smell [2] Composite - Nasal Symptoms and Facial Pain includes nasal obstruction, nasal discharge, mucus in the throat and loss of smell and facial pain	SAC [1]
2.36.	ITT	SHELL	Analysis of Median Change from Baseline Composite VAS Score - Nasal Symptoms (Weeks 49-52)		SAC [1]
2.37.	ITT	SHELL	Analysis of Median Change from Baseline Loss of Smell VAS Score (Weeks 49-52)		SAC [1]
2.38.	ITT	SHELL	Summary of P-values for Treatment Comparisons Adjusted for Multiplicity According to Hierarchy of Endpoints		SAC [1]
Other Endpoints					
2.39.	ITT	SHELL	Summary of Total Endoscopic Nasal Polyps Score (Investigator Read)	Footnote: Includes data reported up to Week 52 Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]
2.40.	ITT	SHELL	Summary and Analysis of Total Endoscopic Nasal Polyps Score (Centrally Read) Responders	Footnote: Includes data reported up to Week 52	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.41.	ITT	SHELL	Analysis of Median Change from Baseline VAS Scores: Nasal Discharge, Mucus in Throat, Facial Pain (Weeks 49-52)		SAC [2]
2.42.	ITT	SHELL	Analysis of Median Change from Baseline Composite VAS Score - Nasal Symptoms and Facial Pain (Weeks 49-52)		SAC [2]
2.43.	ITT	SHELL	Summary and Analysis of SNOT-22 Responders at Week 52	Footnote: Includes data reported up to Week 52	SAC [2]
2.44.	ITT	SHELL	Summary of SNOT-22 Domain Scores	Footnote: Includes data reported up to Week 52 Subheaders: Nasal, Non-nasal symptoms, Ear/facial symptoms, Sleep, Fatigue, Emotional consequences Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]
2.45.	ITT	SHELL	Summary and Analysis of Need for Surgery to Week 52	Footnote: Includes data reported up to Week 52	SAC [2]
2.46.	ITT	SHELL	Summary of Frequency and Rate of Nasal Surgery	Include n (%) with 0, 1, 2, etc surgeries and crude rate Footnote: Includes data reported up to Week 52	SAC [2]
2.47.	ITT	SHELL	Time to First Inclusion on Waiting List for Nasal Polyps Surgery	Footnote: Includes data reported up to Week 52	SAC [2]
2.48.	ITT	SHELL	Summary of Subjects Placed on Waiting List for Surgery to Week 52	Footnote: Includes data reported up to Week 52	SAC [2]
2.49.	ITT	SHELL	Summary of University of Pennsylvania Smell Identification Test (UPSIT)	Footnote: Includes data reported up to Week 52 Footnote: performed in UK, US and Canada only	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.50.	ITT	SHELL	Analysis of Median Change from Baseline University of Pennsylvania Smell Identification Test (UPSIT)	Footnote: performed in UK, US and Canada only	SAC [2]
2.51.	ITT	SHELL	Summary of Peak Nasal Inspiratory Flow (PNIF)	Include actual and change from baseline Footnote: Includes data reported up to Week 52 Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]
2.52.	ITT	SHELL	Summary of Total Prednisolone-equivalent OCS Use for Nasal Polyps (mgs per year)	Footnote: Includes data reported up to Week 52	SAC [2]
2.53.	ITT	SHELL	Summary of Days on Systemic Steroids for Nasal Polyps	Footnote: Includes data reported up to Week 52 Include days on therapy and percentage of days on therapy	SAC [2]
2.54.	ITT	SHELL	Time to First Course of Systemic Steroids for Nasal Polyps	Footnote: Includes data reported up to Week 52	SAC [2]
2.55.	ITT	SHELL	Analysis of Time to First Nasal Surgery or Course of Systemic Steroids for Nasal Polyps	Footnote: Includes data reported up to Week 52	SAC [2]
2.56.	ITT	SHELL	Summary of Number of Courses of Antibiotics	Footnote: Includes data reported up to Week 52 Footnote: Courses of antibiotics separated by <7 days are considered a continuation of the same course Include n (%) with 0 vs ≥1 and 0, 1, 2, courses and total number of courses	SAC [2]
2.57.	ITT	SHELL	Summary of On-Treatment Blood Eosinophils (GI/L)	Include absolute and ratio to baseline values	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.58.	ITT	SHELL	Analysis of On-Treatment Blood Eosinophils (GI/L) Ratio Compared to Baseline Mixed Model Repeated Measures		SAC [2]
Other Endpoints – Health Economics/Medical Resource Utilisation					
2.59.	ITT	SHELL	Summary of SF-36 Domain Scores and Component Summary Scores	Include 8 domain scores bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality and Mental and Physical Component Summary scores. Include actual and change from baseline [redacted] Footnote: Includes data reported up to Week 52 Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]
2.60.	ITT	SHELL	Summary of Work Productivity and Activity Impairment Questionnaire (WPAI)	Footnote: Includes data reported up to Week 52 Include only summary variables	SAC [2]
Other Endpoints – Participants with Asthma					
2.61.	ITT	SHELL	Summary of ACQ-5 in Participants with Asthma	Include actual and change from baseline Footnote: Includes data reported up to Week 52 Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.62.	ITT	SHELL	Summary of Frequency of Clinically Significant Asthma Exacerbations in Participants with Asthma	Provide n (%) with 0 vs ≥1 and 0, 1, 2 etc exacerbations and total number of exacerbations Footnote: Includes data reported up to Week 52	SAC [2]
Other Endpoints – Maintenance of Response Following Cessation of Interventional Product (Follow-Up Period After Week 52)					
2.63.	FU	SHELL	Summary of Total Endoscopic Nasal Polyps Score (Centrally Read) for Subjects in the Follow-Up Period After Week 52	Include actual and change from baseline Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]
2.64.	FU	SHELL	Summary of Individual VAS Symptom Scores for Subjects in the Follow-Up Period After Week 52	Include actual and change from baseline Include nasal obstruction, nasal discharge, mucus in throat, loss of smell, facial pain, overall VAS score Programming Note: summaries from dataset with assigned values for subjects with surgery/missing data	SAC [2]
2.65.	FU	SHELL	Summary of SNOT-22 for Subjects in the Follow-Up Period After Week 52	Include actual and change from baseline Programming Note: summaries from dataset with assigned values for subjects with surgery/sinuplasty/missing data	SAC [2]
2.66.	FU	SHELL	Time to First Nasal Surgery for Subjects in the Follow-Up Period After Week 52		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.67.	FU	SHELL	Summary of Number of Courses of Systemic Steroids for Subjects in the Follow-Up Period After Week 52	Footnote: Courses of systemic steroids separated by less than 7 days are considered a continuation of the same course	SAC [2]
2.68.	FU	SHELL	Summary of Total Prednisolone-equivalent OCS Use for Nasal Polyps (mgs per year)		SAC [2]
2.69.	FU	SHELL	Summary of Blood Eosinophils (GI/L) for Subjects in the Follow-up Period After Week 52		SAC [2]

14.12.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Co-Primary Endpoints					
2.1.	ITT	SHELL	Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52	Show percentages in each category Programming Note: dataset with assigned values for subjects with surgery/missing data	SAC [1]
2.2.	ITT	SHELL	Figure of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) by Visit	Median and 95%CI Footnote: Includes data reported up to Week 52	SAC [1]
2.3.	ITT	SHELL	Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Cumulative Distribution Function	Programming Note: dataset with assigned values for subjects with surgery/missing data	SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.4.	ITT	SHELL	Figure of Median Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Primary and Sensitivity Analyses	Include primary and sensitivity analyses	SAC [2]
2.5.	ITT	SHELL	Figure of Change from Baseline Nasal Obstruction VAS Score (Week 49-52)	Show percentages in each category Programming Note: dataset with assigned values for subjects with surgery/missing data	SAC [1]
2.6.	ITT	SHELL	Figure of Median Change from Baseline Nasal Obstruction VAS Score in each 4-Weekly Period	Median and 95%CI Footnote: Includes data reported up to Week 52	SAC [1]
2.7.	ITT	SHELL	Figure of Median Change from Baseline Nasal Obstruction VAS Score (Week 49-52): Primary and Sensitivity Analyses	Include primary and sensitivity analyses	SAC [2]
Secondary Endpoints					
2.8.	ITT	SHELL	Kaplan-Meier Time to First Nasal Surgery	Footnote: Includes data reported up to Week 52	SAC [1]
2.9.	ITT	SHELL	Sensitivity Time to First Nasal Surgery: Tipping Point	Heat Map Footnote: Includes data reported up to Week 52	SAC [2]
2.10.	ITT	SHELL	Sensitivity Time to First Nasal Surgery: Tipping Point – MAR Assumption for Placebo	2-dimensional Footnote: Includes data reported up to Week 52	SAC [2]
2.11.	ITT	SHELL	Figure of Median Change from Baseline Overall VAS Score in Each 4-Weekly Period	Median and 95%CIFootnote: Includes data reported up to Week 52	SAC [1]
2.12.	ITT	SHELL	Figure of Median Change from Baseline SNOT-22 by Visit	Median and 95%CI Footnote: Includes data reported up to Week 52	SAC [1]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.13.	ITT	SHELL	Figure of Median Change from Baseline Composite VAS Score - Nasal Symptoms in each 4-Weekly Period	Median and 95%CI Footnote: Includes data reported up to Week 52	SAC [1]
2.14.	ITT	SHELL	Figure of Median Change from Baseline Loss of Smell VAS Score in each 4-Weekly Period	Median and 95%CI Footnote: Includes data reported up to Week 52	SAC [1]
Other Endpoints					
2.15.	ITT	SHELL	Figure of Total Endoscopic Nasal Polyps Score (Centrally Read) Responders by Visit	OR and 95%CI Footnote: Includes data reported up to Week 52	SAC [2]
2.16.	ITT	SHELL	Figure of University of Pennsylvania Smell Identification Test (UPSIT) Change from Baseline by Visit	Median and 95%CI Footnote: Includes data reported up to Week 52	SAC [2]
2.17.	ITT	SHELL	Figure of SNOT-22 Responders by Visit	OR and 95%CI Footnote: Includes data reported up to Week 52	SAC [2]
2.18.	ITT	SHELL	Kaplan-Meier Time to First Inclusion on Waiting List for Nasal Polyps Surgery	Footnote: Includes data reported up to Week 52	SAC [2]
2.19.	ITT	SHELL	Kaplan-Meier Time to First Course of Systemic Steroids	Footnote: Includes data reported up to Week 52	SAC [2]
2.20.	ITT	SHELL	Kaplan-Meier Time to First Nasal Surgery or Course of Systemic Steroids	Footnote: Includes data reported up to Week 52	SAC [2]
2.21.	ITT	SHELL	Figure of On-Treatment Blood Eosinophils Absolute Values	No reference line. Include screening/baseline geometric mean values without 95% CI. Week 4 onwards adjusted estimates from MMRM model with 95% CI.	SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.22.	ITT	SHELL	Figure of On-Treatment Blood Eosinophils Ratio to Baseline	Reference line at 1	SAC [2]
Other Endpoints – Maintenance of Response Following Cessation of Interventional Product (Follow-Up Period After Week 52)					
2.23.	FU	SHELL	Kaplan-Meier Time to First Nasal Surgery for Subjects in the Follow-Up Period After Week 52		SAC [2]
2.24.	FU	SHELL	Kaplan-Meier Time to First Inclusion on Waiting List for Nasal Polyps Surgery for Subjects in the Follow-Up Period After Week 52		SAC [2]
2.25.	FU	SHELL	Figure of Blood Eosinophils for Subjects in the Follow-Up Period After Week 52		SAC [2]

14.12.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE13/SHELL	Adverse Event Overview		SAC [1]
3.2.	Safety	AE1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.3.	Safety	AE1	Summary of Post-Treatment Adverse Events by System Organ Class and Preferred Term	Footnote: Includes data reported up to Week 52	SAC [1]
3.4.	FU	AE1	Summary of Adverse Events Reported During the Follow-Up Period After Week 52 by System Organ Class and Preferred Term		SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.5.	Safety	AE3	Summary of Common (>=3% in Any Treatment Group) On-Treatment Adverse Events by Overall Frequency	ICH E3 ≥3% (prior to rounding to nearest percent)	SAC [2]
3.6.	Safety	AE5a	Summary of On-Treatment Adverse Events by System Organ Class and Maximum Severity	Add a Total column across all severities	SAC [2]
3.7.	Safety	AE1	Summary of Drug-Related On-Treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [2]
3.8.	Safety	AE5a	Summary of Drug Related On-Treatment Adverse Events by System Organ Class and Maximum Severity	Add a Total column across all severities	SAC [2]
3.9.	Safety	AE15	Summary of Common (>=3% In Any Treatment Group) Non-Serious On-Treatment Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT≥3% (prior to rounding to nearest percent)	SAC [2]
3.10.	Safety	AE1	Summary of On-Treatment Adverse Events by Highest Post-Baseline Anti-Drug Antibody Result	Add in row with n in each ADA result category. Footnote: Highest Post-Baseline Anti-Drug Antibody result excluding data from no-treatment follow-up period.	SAC [2]
3.11.	Safety	AE1	Summary of Post-Treatment Adverse Events by Highest Post-Baseline Anti-Drug Antibody Result	Add in row with n in each ADA result category. Footnote: Highest Post-Baseline Anti-Drug Antibody result excluding data from no-treatment follow-up period. Footnote: Includes data reported up to Week 52	SAC [2]
3.12.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class	IDSL; Footnote: Includes data reported up to Week 52	SAC [2]
3.13.	Safety	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class	IDSL; Footnote: Includes data reported up to Week 52	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.14.	Safety	AE1	Summary of Adverse Events Reported on Day of Dosing by System Organ Class	Footnote: Includes data reported up to Week 52	SAC [2]
Serious and Other Significant Adverse Events					
3.15.	Safety	AE3	Summary of Fatal Serious Adverse Events		SAC [1]
3.16.	Safety	AE3	Summary of Fatal Drug-Related Serious Adverse Events		SAC [2]
3.17.	Safety	AE1	Summary of Non-Fatal Serious Adverse Events by System Organ Class	Include on-treatment and post-treatment	SAC [2]
3.18.	Safety	AE1	Summary of Non-Fatal Serious On-Treatment Adverse Events by System Organ Class		SAC [1]
3.19.	Safety	AE1	Summary of Non-Fatal Serious Post-Treatment Adverse Events by System Organ Class	Footnote: Includes data reported up to Week 52	SAC [2]
3.20.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class	Include on-treatment and post-treatment	SAC [1]
3.21.	Safety	AE1	Summary of Serious On-Treatment Adverse Events by System Organ Class		SAC [2]
3.22.	Safety	AE1	Summary of Serious Post-Treatment Adverse Events by System Organ Class	Footnote: Includes data reported up to Week 52	SAC [2]
3.23.	FU	AE1	Summary of Serious Adverse Events Reported During the Follow-Up Period After Week 52 by System Organ Class		SAC [2]
3.24.	Safety	AE1	Summary of Serious Drug-Related On-Treatment Adverse Events by System Organ Class		SAC [2]
3.25.	Safety	AE1	Summary of Pre-Treatment Serious Adverse Events by System Organ Class		SAC [2]
3.26.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.27.	Safety	SHELL	Summary of Deaths	Includes all deaths separating those reported in no-treatment follow-up	SAC [2]
Adverse Events of Special Interest					
3.28.	Safety	SHELL	Summary of On-Treatment Serious AEs and AEs of Special Interest: Incidence, Relative Risk and Risk Difference (Placebo vs 100mg SC)		SAC [2]
3.29.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Systemic Reactions Reported by the Investigator as Meeting the Criteria for Anaphylaxis		SAC [2]
3.30.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity) and Other Reactions		SAC [2]
3.31.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity)		SAC [2]
3.32.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Other Reactions		SAC [2]
3.33.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Local Injection Site Reactions		SAC [2]
3.34.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events		SAC [2]
3.35.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Serious Ischemic Events		SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.36.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Malignancies		SAC [2]
3.37.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Potential Opportunistic Infections		SAC [2]
3.38.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Systemic Reactions Reported by the Investigator as Meeting the Criteria for Anaphylaxis		SAC [2]
3.39.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity) and Other Reactions		SAC [2]
3.40.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity)		SAC [2]
3.41.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions –Other Reactions		SAC [2]
3.42.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Local Injection Site Reactions		SAC [2]
3.43.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events		SAC [2]
3.44.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Serious Ischemic Events		SAC [2]
3.45.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Malignancies		SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.46.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Potential Opportunistic Infections		SAC [2]
Laboratory: Chemistry					
3.47.	Safety	LB1	Summary of On-Treatment Chemistry Changes from Baseline	ICH E3 Includes Baseline values	SAC [2]
3.48.	Safety	LB3	Summary of On-Treatment Chemistry Shifts from Baseline Relative to Normal Range	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
3.49.	Safety	LB3	Summary of On-Treatment Chemistry Shifts from Baseline Relative to PCI Criteria	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
Laboratory: Hematology					
3.50.	Safety	LB1	Summary of On-Treatment Haematology Changes from Baseline	ICH E3 Includes Baseline values	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.51.	Safety	LB3	Summary of On-Treatment Haematology Shifts from Baseline Relative to Normal Range	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
3.52.	Safety	LB3	Summary of On-Treatment Haematology Shifts from Baseline Relative to PCI Criteria	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
Laboratory: Urinalysis					
3.53.	Safety	UR1	Summary of Worst Case On-Treatment Urinalysis Results Post-Baseline Relative to Baseline	ICH E3	SAC [2]
Laboratory: Hepatobiliary (Liver)					
3.54.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC [2]
3.55.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC [2]
ECG					
3.56.	Safety	EG1	Summary of ECG Findings	IDSL	SAC [2]
3.57.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.58.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [2]
3.59.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [2]
Vital Signs					
3.60.	Safety	VS1	Summary Vital Signs		SAC [2]
3.61.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC [2]
Immunogenicity					
3.62.	Safety	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Confirmatory Result	Footnote: Includes data reported up to Week 52	SAC [2]
3.63.	Safety	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Treatment Emergent Confirmatory Result	Footnote: Includes data reported up to Week 52	SAC [2]
3.64.	Safety	SHELL	Summary of Neutralising Antibody Assay: Highest Result	Footnote: Includes data reported up to Week 52	SAC [2]
3.65.	FU	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Confirmatory Result for Subjects in the Follow-up Period After Week 52	Footnote: Includes all available data	SAC [2]
3.66.	FU	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Treatment Emergent Confirmatory Results for Subjects in the Follow-up Period After Week 52	Footnote: Includes all available data	SAC [2]
3.67.	FU	SHELL	Summary of Neutralising Antibody Assay: Highest Result for Subjects in the Follow-up Period After Week 52	Footnote: Includes all available data	SAC [2]
3.68.	Safety	SHELL	Summary of On-Treatment Blood Eosinophils (GI/L) by Anti Drug Antibody Status		SAC [2]

14.12.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE10	Common (>=3% In Any Treatment Group) On-Treatment Adverse Events and Relative Risk	IDSL	SAC [2]
3.2.	Safety	SHELL	On-treatment Serious Adverse Events and Adverse Events of Special Interest (Placebo vs Mepolizumab 100mg SC)	Provide relative risk with 95% CI	SAC [2]
Laboratory					
3.3.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC [2]

14.12.10. Pharmacokinetic Population (PopPK) Tables

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK01	Summary of Plasma Mepolizumab Concentration-Time Data (Observed and Predicted)		SAC [2]
4.2.	PK	PK06	Summary Statistics of Individual Model Predicted Plasma Mepolizumab Pharmacokinetic Parameters (Non-transformed and Log-transformed)		SAC [2]
4.3.	PK	-	Description and Evaluation of Key PK Models Tested	Provided by CPMS	SAC [2]
4.4.	PK	-	Population PK Parameter Estimates with 95% CI of Final PK Model	Provided by CPMS	SAC [2]
4.5.	PK	-	Demographics Summary	Provided by CPMS	SAC [2]

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.6.	PK	-	Samples Summary	Provided by CPMS	SAC [2]
4.7.	PK	-	Accumulation Ratio Estimate at Week 52	Provided by CPMS	SAC [2]

14.12.11. Pharmacokinetic Population (PopPK) Figures

Pharmacokinetic Population (POPPK): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	-	Plasma Mepolizumab Concentration-Time Profiles (by Treatment)	Provided by CPMS	SAC [2]
4.2.	PK	-	Model Goodness of Fit Plots	Provided by CPMS	SAC [2]
4.3.	PK	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC [2]
4.4.	PK	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC [2]
4.5.	PK	-	Automated Covariate Selection	Provided by CPMS	SAC [2]
4.6.	PK	-	Visual Predictive Check	Provided by CPMS	SAC [2]
4.7.	PK	-	Observed Plasma Mepolizumab Concentration-Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC [2]
4.8.	PK	-	Plasma Mepolizumab Observed/Predicted Concentration-Time Profiles (by Subject)	Provided by CPMS	SAC [2]
4.9.	PK	-	Box Plot of Systemic Clearance versus Covariates of Interest	Provided by CPMS	SAC [2]

14.12.12. Pharmacokinetic/Pharmacodynamic Population (PopPK/PD) Tables

Pharmacokinetic/Pharmacodynamic Population (POPPK/PD): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK and PD	-	Description and Evaluation of Key PKPD Models Tested	Provided by CPMS	SAC [2]
5.2.	PK and PD	-	Population PD Parameter Estimates with 95% CI of Final PKPD Model	Provided by CPMS	SAC [2]
5.3.	PK and PD	-	Demographics Summary	Provided by CPMS	SAC [2]
5.4.	PK and PD	-	Samples Summary	Provided by CPMS	SAC [2]

14.12.13. Pharmacokinetic/Pharmacodynamic Population (PopPKPD) Figures

Pharmacokinetic/Pharmacodynamic Population (POPPK/PD): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK and PD	-	Blood Eosinophil Count-Time Profiles	Provided by CPMS	SAC [2]
5.2.	PK and PD	-	Model Goodness of Fit Plots	Provided by CPMS	SAC [2]
5.3.	PK and PD	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC [2]
5.4.	PK and PD	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC [2]
5.5.	PK and PD	-	Automated Covariate Selection	Provided by CPMS	SAC [2]
5.6.	PK and PD	-	Visual Predictive Check	Provided by CPMS	SAC [2]
5.7.	PK and PD	-	Observed Blood Eosinophil Count -Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC [2]
5.8.	PK and PD	-	Observed/Predicted Blood Eosinophil Count-Time Profiles (by Subject)	Provided by CPMS	SAC [2]

14.12.14. Exposure-Efficacy Figures

Exposure-Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 vs Dose/Body Weight	Provided by CPMS	Post-SAC [2]
6.2.	ITT		Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 vs Cav	Provided by CPMS	Post-SAC [2]
6.3.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) vs Dose/Body Weight	Provided by CPMS	Post-SAC [2]
6.4.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) vs Cav	Provided by CPMS	Post-SAC [2]

14.12.15. ICH and Other Listings

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	ENROLLED	ES7	Listing of Reasons for Screen and Run-In Failures	Journal Guidelines	SAC [2]
2.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC [2]
3.	ITT	ES2	Listing of Reasons for Study Withdrawal	ICH E3 Include and identify withdrawals from no-treatment follow-up	SAC [2]
4.	ENROLLED	ES9	Listing of Subjects Who Were Rescreened		SAC [2]
5.	ITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC [2]
6.	ITT	TA1	Listing of Planned and Actual Treatments	IDSL	SAC [2]
Protocol Deviations					
7.	ITT	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [2]
8.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion/Randomisation Criteria Deviations	ICH E3	SAC [2]
Populations Analysed					
9.	Randomised	SP3	Listing of Subjects Excluded from Any Population	ICH E3	SAC [2]
Demographic and Baseline Characteristics					
10.	ITT	DM2	Listing of Demographic Characteristics	ICH E3	SAC [2]
11.	ITT	DM9	Listing of Race	ICH E3	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	ITT	SHELL	Listing of Nasal Polyps Disease History and Baseline Characteristics	Include Disease Duration (years/months); Number of previous surgeries; Number of Courses of OCS for NP in previous 12 months; History of Sinusitis; Baseline Nasal Polyps endoscopy score (centrally read and investigator read); Nasal Obstruction VAS, Overall VAS, Baseline SNOT-22; Baseline SF-36. Include tobacco history.	SAC [2]
Prior and Concomitant Medications					
13.	ITT	CM3	Listing of Concomitant Medications	IDSL Include column to identify entries coming from the systemic corticosteroid eCRF page	SAC [2]
Efficacy					
14.	ITT	SHELL	Listing of Surgical Events	Programming Note: Include indication of surgeries included in evaluation of key secondary endpoint	SAC [2]
Exposure					
15.	Randomised	SHELL/EX3	Listing of Exposure Data	ICH E3	SAC [2]
Adverse Events					
16.	Safety	AE8	Listing of All Adverse Events	ICH E3 add Phase (pre/on/post-trt)	SAC [2]
17.	Safety	AE8	Listing of All Adverse Events on Day of Dosing		SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
18.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3 Split on-treatment, post-treatment, reported during follow-up period after Week 52	SAC [2]
19.	Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	ICH E3 add Phase (pre/on/post-trt)	SAC [2]
20.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC [2]
Serious and Other Significant Adverse Events					
21.	Safety	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC [2]
22.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC [2]
23.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC [2]
24.	Safety	DTH3	Listing of Deaths		SAC [2]
25.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: All Cause Deaths		SAC [2]
26.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Arrhythmias		SAC [2]
27.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Congestive Heart Failure		SAC [2]
28.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke		SAC [2]
29.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/Pulmonary Embolism		SAC [2]
30.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina		SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
31.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism		SAC [2]
32.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Pulmonary Hypertension		SAC [2]
33.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Revascularisation		SAC [2]
34.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Valvulopathy		SAC [2]
Adverse Events of Special Interest					
35.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Meeting the Criteria for Anaphylaxis	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
36.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity)	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
37.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Other Reactions	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
38.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Local Injection Site Reactions	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
39.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events	add Phase(on/post-trt)	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
40.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Serious Ischemic Events	add Phase(on/post-trt)	SAC [2]
41.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Malignancies	add Phase(on/post-trt)	SAC [2]
42.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Potential Opportunistic Infections	add Phase(on/post-trt)	SAC [2]
Hepatobiliary (Liver)					
43.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC [2]
44.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC [2]
45.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC [2]
46.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC [2]
All Laboratory					
47.	Safety	LB5	Listing of Chemistry Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
48.	Safety	LB5	Listing of Haematology Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
49.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC [2]
50.	Safety	UR2A/UR2B	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
ECG					

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
51.	Safety	EG3 / EG4	Listing of All ECG Values for Subjects with Protocol Defined QTc Stopping Criteria	IDSL	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
52.	Safety	IMM2	Listing of Immunogenicity Data	Include column titled: Screening Binding Assay, Confirmation Antibody Assay, Confirmation Assay Titre, Neutralizing Antibody Assay	SAC [2]

14.13. Appendix 13: Example Mock Shells for Data Displays

Shells are available upon request.

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

Title	:	Reporting and Analysis Plan for Study 205687: A randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab)
Compound Number	:	SB240563
Effective Date	:	05-SEP-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Study 205687 (Protocol 2016N294302_03).

RAP Author:

Author	Date
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PPD Senior Director (Clinical Pharmacology)	16-AUG-2019

RAP Team Review Confirmations
(Method: E-mail):

Reviewer	Date
PPD Study Physician Lead (Clinical Development, Respiratory)	20-AUG-2019
PPD Project Physician Lead (Clinical Development, Respiratory)	21-AUG-2019
PPD Clinical Investigation Lead (Clinical Development, Respiratory)	21-AUG-2019
PPD Director (SERM Safety & Medical Governance Pharma)	21-AUG-2019
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(Method: Pharma TMF eSignature):

Approver	Date
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PPD (on behalf of PPD) Programming Director (Biostatistics)	01-SEP-2019

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205687

TABLE OF CONTENTS

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Study 205687 (Protocol 2016N294302_03):

Revision Chronology for Protocol:		
Original Protocol (2016N294302_00)	08-Dec-2016	Original
2016N294302_01	15-May-2017	To support country-specific requirements and amendments for South Korea.
2016N294302_02	14-July-2017	To clarify wording, document removal of CT scans and exit interviews, simplifying some of the endpoints
2016N294302_03	20-Feb-2018	To clarify that screen failures can be re-screened, and that the ECG machine does not need to be automated

2. SUMMARY OF KEY PROTOCOL INFORMATION

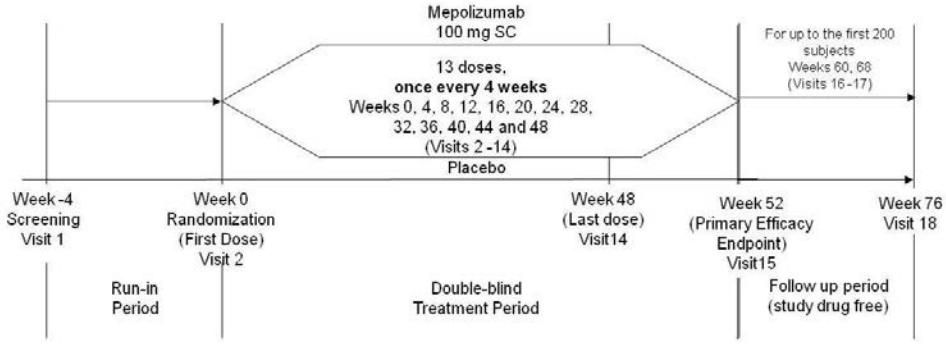
2.1. Study Objective(s) and Endpoint(s)

Objectives	**Endpoints**
Primary Objectives	**Co-Primary Endpoints**
• To evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in total endoscopic NP score at Week 52 (based on centrally read data). • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52.
Secondary Objectives	**Secondary Endpoints**
• To evaluate the impact on actual nasal surgery of 100mg mepolizumab compared to placebo	• Time to first nasal surgery up to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52.
• To evaluate the impact on quality of life of 100mg mepolizumab compared to placebo	• Change from baseline in SNOT-22 total score at Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Number of mgs per year of prednisolone-equivalent OCS dose up to Week 52.
Other Objectives	**Other Endpoints**
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo	• Percentage of participants classified as responders according to a 1 point or greater decrease from baseline in NP Score at Week 52 (based on centrally ready data). • Change from baseline in mean individual VAS symptom scores for nasal discharge, mucus in the throat, loss of smell and facial pain during the 4 weeks prior to Week 52. • Change from baseline in the mean composite VAS score

Objectives	Endpoints
	(combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) during the 4 weeks prior to Week 52. • Change from baseline in the mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain) during the 4 weeks prior to Week 52. • Change from baseline in UPSIT at Week 52. • Change from baseline in PnIF at Week 52.
• To evaluate the impact on quality of life of 100mg mepolizumab compared to placebo	• Percentage of participants classified at Week 52 as responders according to a 9 point or greater decrease from baseline in SNOT-22 total score.
• To further evaluate the impact on requirement for nasal surgery of 100mg mepolizumab compared to placebo	• Rate of nasal surgery up to Week 52. • Time to first inclusion on waiting list for NP surgery up to Week 52. • Percentage of participants who are included on waiting list for NP surgery. • Percentage of participants classified as 'need for surgery' responders according to NP score (based on centrally ready data) and overall VAS symptom score.
• To evaluate exploratory biomarkers of nasal polyposis and response to 100mg mepolizumab compared to placebo	• Evaluate exploratory blood biomarkers (including blood eosinophils) on response to mepolizumab.
• To evaluate the impact on health outcomes of 100mg mepolizumab compared to placebo	• Change from baseline in SF-36 Mental Component Summary (MCS), Physical Component Summary (PCS) and 8 summary scores at Week 52. • Change from baseline in WPAI Questionnaire at Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo on systemic steroid use such as OCS and antibiotic use as part of SoC	• Number of Courses of systemic steroid therapy up to Week 52. • Number of days on systemic steroid therapy up to Week 52. • Time to first course of OCS up to Week 52. • Number of courses of antibiotics up to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared to placebo in the subgroup of participants with Asthma	In addition to endoscopic NP score, VAS symptoms score, medication and surgery, the following asthma related endpoints will be assessed: • Change from baseline in Asthma Control Questionnaire (ACQ-5) score at Week 52. • Number of clinically significant asthma exacerbations defined as worsening of asthma requiring systemic corticosteroids (i.v. or oral steroid) for at least 3 days or a single IM CS dose and/or ED visit and/or hospitalisation for asthma up to Week.
• To assess the maintenance of response after cessation of	For all participants who enter post treatment follow-up period, the following will be assessed at Week 76:

Objectives	Endpoints
mepolizumab treatment compared to placebo	• Change from baseline in total endoscopic NP score (centrally read data). • Change from baseline in mean nasal obstruction VAS score. • Change from baseline in mean individual VAS symptom score for nasal discharge, mucus in throat, loss of smell, facial pain and overall VAS symptom score during the 4 weeks prior to Week 76. • Number of mgs per year of prednisolone-equivalent OCS dose. • Change from baseline in SNOT-22 total score. • Change from baseline in SF-36 Mental Component Summary (MCS), Physical Component Summary (PCS) and 8 summary scores. • Change from baseline in WPAI Questionnaire. • Time to first nasal surgery including off treatment period from randomization to Week 76. • Time to first inclusion on waiting list for NP surgery up to Week 76.
Safety Objectives	**Safety Endpoints**
• To evaluate the safety and tolerability of 100mg mepolizumab compared to placebo	• Frequency of adverse events (AEs)/ serious adverse events (SAEs) including systemic and injection site reactions reported throughout the treatment period. • Vital signs (pulse rate, systolic and diastolic blood pressure) throughout the treatment period. • Hematological and clinical chemistry parameters throughout the treatment period. • 12 lead ECG derived endpoints. • Presence of anti-mepolizumab antibodies.
Pharmacokinetics Objectives	**Pharmacokinetics Endpoints**
• To evaluate the pharmacokinetics (PK) of 100mg mepolizumab	• PK concentrations and Population PK parameters • PK/PD (blood eosinophil count) analysis

2.2. Study Design

Overview of Study Design and Key Features	
	
Design Features	• Multi-centre, randomised, placebo-controlled, double-blind, parallel-group design. • The study will include a 4-week run in period followed by a 52-week randomised treatment period with visits every 4 weeks. • Patients prematurely discontinued from study treatment continue, where possible, being followed up per the protocol schedule • Patients who have surgery for nasal polyps during the study are allowed to continue on study treatment until completion of the 52-week treatment period • Following Week 52, there is a planned study drug free, 6-month, follow-up period for the first 200 randomised participants, to investigate maintenance of response to study treatment.
Main participant entry criteria	• Participants aged ≥18 years with severe bilateral nasal polyps and at least one surgery in the previous 10 years for the removal of nasal polyps (see Section 6 of protocol).
Dosing	• The study treatment period will consist of thirteen, 4-weekly doses with the last dose of interventional product to be administered at Week 48 (Visit 14). • Interventional product is given in addition to standard of care (SoC): daily mometasone furoate nasal spray (MF), saline nasal douching as required and, if required, occasional short courses of high dose oral corticosteroids (OCS) and/or antibiotics.
Schedule of Activities	• See Appendix 2: Schedule of Activities
Treatment Assignment	• 400 participants (planned) will be randomised in a 1:1 ratio to receive mepolizumab or matching placebo (i.e. 200 per treatment group) delivered subcutaneously via a pre-filled safety syringe in addition to SoC. • Randomisation schedule generated using GSK validated randomisation software RandAll NG, stratified by country. • Treatment assigned randomly via an interactive voice response system (IVRS).
Interim Analysis	• No interim analysis of data is planned for this study.

2.3. Statistical Hypotheses

The study is designed to test the superiority of mepolizumab 100mg SC vs. placebo in addition to standard of care. Significance tests will be guided by a two-sided 5% alpha level (one-sided 2.5%).

2.4. Changes to the Protocol Defined Statistical Analysis Plan

Minor changes/deviations from the originally planned statistical analysis specified in Protocol Amendment 3 (Dated: 20 FEB 2018) are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Each co-primary endpoint will be analysed using an ordinal logistic regression model (proportional odds model) with covariates of treatment group, baseline score and region.	Each co-primary endpoint will be analysed using an ordinal logistic regression model (proportional odds model) with covariates of treatment group, baseline score, loge baseline blood eosinophil count and region.	Including a covariate for baseline blood eosinophils to provide an estimate of treatment effect adjusted for differing levels of baseline blood eosinophils.
'All Participants Enrolled' analysis population defined as all participants who sign the ICF.	'All Participants Enrolled' analysis population defined as all participants enrolled and for whom a record exists on the study database.	Clarifying population definition used to report on reasons for screen failure and run-in failure.
Co-primary endpoint defined as Change from baseline in total endoscopic nasal polyps (NP) score at Week 52.	Co-primary endpoint defined as Change from baseline in total endoscopic NP score at Week 52 (based on centrally read data).	To clarify the total endoscopic NP score used in the analysis of the co-primary endpoint is based on data from the blinded independent review of endoscopy data (as per Protocol Section 9.2.1).

3. PLANNED ANALYSES

Planned dry run(s) will be performed on a subset of blinded data, with the aim of ensuring the required displays detailed in Appendix 12: List of Data Displays are correctly created and formatted.

3.1. Interim Analyses

No interim analysis of data is planned for this study

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 database freeze (DBF) has been declared by Data Management.
3. All criteria for unblinding the randomization codes have been met, and the randomisation codes have been released.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Enrolled	• All participants who sign the Informed Consent Form and who have a record on the database	Reasons for screen and run-in failures
Randomized	• All randomized participants	Study population
Intent-To-Treat (ITT)	• All randomized participants who take at least 1 dose of study treatment. • Data will be analysed according to randomised treatment arm.	Subject disposition Efficacy endpoints
Safety	• All randomized participants who take at least 1 dose of study treatment. • Data will be analysed according to actual treatment received for more than 50% of treatment administrations (see Section 14.6.2).	Safety endpoints
Per-Protocol (PP) [1]	• All participants in the ITT population who have not been identified as protocol deviators with respect to criteria that are considered to impact the primary efficacy analysis. • Protocol deviations that would exclude participants from the PP population are defined in Appendix 1: Protocol Deviation Management and Definitions for Per-Protocol Population	Supplementary analyses of co-primary endpoints
Pharmacokinetic (PK) [1]	All participants in the ITT population for whom at least one PK sample was obtained, analysed and measurable.	Pharmacokinetic endpoints
Follow-up after	• Participants in the ITT population who participate in the	Efficacy/safety

Population	Definition / Criteria	Analyses Evaluated
Week 52 (FU) [1]	'No treatment follow-up' period after Visit 15. • Data will be summarised according to randomised treatment arm.	endpoints

Refer to Appendix 12: List of Data Displays which details the population used for each display.
[1] Analysis population not defined in protocol, added for clarification of analysis requirements.

4.1. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP) dated 10 January 2018 (Version 1.01). Protocol deviations classified as important are detailed in the PDMP and those requiring exclusion from the Per-Protocol (PP) population are detailed in Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population.

A final blinded review of all deviations will take place at the database release stage to ensure all important deviations are identified as well as those leading to exclusion of the participant from the PP population.

Important protocol deviations and deviations which result in exclusion from the PP population will be summarised and listed. A separate listing of all inclusion/ exclusion criteria deviations based on data as recorded on the eligibility page of the eCRF will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Descriptions			
RandAll NG		Data Displays for Reporting	
Code	Description	Description	Order in TLF[1]
1	Placebo	Placebo	1
2	Mepolizumab 100mg SC	Mepolizumab 100mg SC	2

[1] TLF=Tables, Listings, Figures (as specified in Appendix 12: List of Data Displays)

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

Mepolizumab 100mg SC vs Placebo

5.2. Baseline Definitions

5.2.1. Visit-based endpoints

The co-primary endpoint of endoscopic NP score (based on centrally read data) is assessed at Screening (Visit 1) and Day 1 (Visit 2), the Screening value is used to confirm if a participant has met the criteria for randomisation. Baseline will be defined as the Day 1 value, if missing the immediately preceding centrally read value prior to Day 1 will be used.

For all other visit-based endpoints, Baseline will be defined as the latest non-missing measurement collected prior to the first dose of interventional product. This will generally be from the Day 1 assessment but may be from an unscheduled assessment.

Where time is collected, an assessment is valid for use as Baseline if the date and time is prior to or the same as the date and time of first dose. Where time is not collected, an assessment is valid for use as Baseline if the date of assessment is on or before the date of first dose.

5.2.2. eDiary Data

Participants report daily on the severity of individual and overall NP symptoms using an eDiary, this includes information for the co-primary endpoint of mean nasal obstruction VAS score. The baseline value for endpoints reported in the eDiary will be determined as the average score from the 7 days of diary data collected prior to Day 1 (using non-missing data recorded between Day -7 and Day -1 inclusive).

5.3. Multicentre Studies

In this multicentre global study, the number of enrolled participants and the number randomised to each treatment arm will be presented by centre, country and region.

Region will be included as a fixed effect covariate in the analysis models for efficacy endpoints (as detailed in Section 5.4). Countries have been grouped into the following regions with consideration for standard of care medical practice, number of participants enrolled and regulatory considerations.

Region	Countries
Europe (EU)	Germany, Netherlands, Romania, Sweden, UK
United States (US)	United States
Rest of World (RoW)	South Korea, Argentina, Australia, Canada, Russia

NOTE: Small numbers of participants in a treatment group within a region may result in model convergence issues, in these cases further combining of regions may be considered or if required exclusion of the region covariate.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

Covariates to be included in the statistical analysis models of the co-primary efficacy endpoints:

- Randomised treatment group
- Region
- Baseline score
- Baseline $\log_e$ blood eosinophil count

Covariates to be included in the statistical analysis model of time to first nasal surgery:

- Randomised treatment group
- Region
- Baseline total NP endoscopic score (based on centrally read data)
- Baseline nasal obstruction VAS
- Baseline $\log_e$ blood eosinophil count
- Number of previous surgeries (1, 2, >2; as an ordinal variable)

Covariates to be included in the statistical analysis model of Number of mgs per year of prednisolone-equivalent OCS:

- Randomised treatment group
- Region
- Baseline total NP score (based on centrally read data)
- Baseline nasal obstruction VAS
- Baseline $\log_e$ blood eosinophil count
- Number of OCS courses for NP in the previous 12 months (0, 1, >1, as an ordinal variable)

Section 7 provides full details of the analysis methods for each of the efficacy endpoints.

5.4.2. Examination of Subgroups

This section details the subgroups of interest within this study. For each co-primary endpoint, a separate exploratory analysis within each of the subgroup categories will be carried out. Subgroup analyses for all other endpoints are detailed in the statistical methods/analyses sections. Unless otherwise stated no formal hypothesis testing in subgroups of the population will be performed.

Subgroup	Categories
Participants with Asthma	Concurrent asthma, No concurrent asthma
Aspirin Exacerbated Respiratory Disease (AERDS)	Current AERDS, No Current AERDS
Number of previous surgeries	1, 2, >2
Baseline Blood Eosinophil Categories (GI/L)	≤0.3 GI/L; >0.3 to ≤0.5 GI/L; >0.5 to ≤0.7 GI/L; >0.7 GI/L
Region	Europe, United States, Rest of World
Age	18-<40, 40-<65, ≥65 years
Gender	Male, Female
Race	African American/African Heritage, White, Asian, Other

If, following unblinding, the analysis model within a subgroup category fails to converge due to small numbers of participants, the model will be rerun with consideration of further refining regions or if required exclusion of the region covariate. Failing this, subgroup categories may be further refined when possible, otherwise only a descriptive summary of the data will be presented. Footnotes will clearly identify the covariates included in the analysis model.

Except for baseline blood eosinophils, differential treatment effects are not expected for any of the other subgroups listed above and therefore any differences in efficacy of mepolizumab compared to placebo observed in subgroup categories will be viewed as exploratory.

5.4.2.1. Baseline Blood Eosinophils as a Predictive Biomarker

There is a biological rationale for potentially observing greater efficacy with increasing levels of baseline blood eosinophils. The role of baseline blood eosinophil counts on the effectiveness of mepolizumab with respect to the co-primary endpoints will be further assessed using a statistical model including terms for baseline blood eosinophil count ($\log_e$) as a continuous variable (as defined in Section 5.2) and its interaction with treatment. The analysis will also be adjusted for region and baseline score, as described in Section 5.4.1. Fractional polynomial transformations of baseline blood eosinophil count may also be explored to find the best fitting model for the relationship.

5.5. Multiple Comparisons and Multiplicity

The treatment comparison of mepolizumab 100mg SC vs. placebo is of interest for the co-primary and secondary endpoints. Multiplicity arising from the multiple secondary endpoints will be controlled through testing of the secondary endpoints using a closed testing procedure according to the following pre-defined hierarchy:

1. Time to first nasal surgery

2. Change from baseline in overall VAS symptom score

3. Change from baseline in SNOT-22 total score

4. Number of mgs per year of prednisolone-equivalent dose

For strong control of type I error, statistical significance for the first secondary endpoint in the pre-defined hierarchy will be dependent on statistical significance having been achieved for the two co-primary endpoints. Statistical significance for the subsequent secondary endpoints will be dependent on statistical significance having been achieved for the previous endpoints in the hierarchy.

For secondary endpoints, unadjusted p-values and p-values adjusted for multiplicity based on the above hierarchy, will be presented.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

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

Section	Component
14.3	Appendix 3: Assessment Windows
14.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
14.5	Appendix 5: Data Display Standards & Handling Conventions
14.6	Appendix 6: Derived and Transformed Data
14.7	Appendix 7: Reporting Standards for Missing Data
14.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

All displays will be based on the ITT population, unless otherwise specified.

Study population displays including summaries of subject disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications and treatment exposure will be based on GSK Core Data Standards. Additional summary information showing the amount of time within the 52-week treatment period considered as on-treatment, off-treatment and missing will be presented.

A summary of subject disposition and duration of time spent in the no-treatment follow-up will be provided for the subset of participants who participated in the 6-month no-treatment follow-up.

Details of the planned displays are presented in Appendix 12: List of Data Displays.

7. EFFICACY ANALYSES

Data reported as part of the follow-up period after Week 52 will be excluded from the analyses described in Section 7.1 to Section 7.4. Details of all planned displays are provided in Appendix 12: List of Data Displays and will be based on GSK data standards and statistical principles.

7.1. Primary Efficacy Analyses

7.1.1. Endpoint / Variables

The primary treatment effect to be estimated (estimand) will be the comparison of mepolizumab 100mg SC to placebo for the co-primary endpoints of:

- Change from baseline in total endoscopic NP score at Week 52 (based on centrally read data)
- Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52

Independent reviewers blinded to treatment, grade the total endoscopic NP score from image recording of endoscopies, the total score is reported as the sum of the right and left nostril scores and ranged from 0 to 8, with higher scores indicating greater disease severity.

Participants rate individual symptoms including nasal obstruction daily on a visual analogue scale using an eDiary, the scale range is 0 (none) to 100 (as bad as you can imagine), with higher scores indicating greater disease severity, for analysis derived scores ranging from 0 to 10 are used (see Section 14.6.5).

A composite strategy will be used for the intercurrent event of actual surgery and a treatment policy strategy for the intercurrent event of discontinuation of study medication. The study is designed to continue collecting data for participants who have prematurely discontinued from randomised treatment, off-treatment data collected for these participants will be included in the primary analysis.

For each co-primary endpoint, change from baseline will be categorised for analysis into varying levels of improvement, no change or worsening, and a least favourable category of actual surgery (Section 7.1.5.1).

Participants with missing data at Baseline will be included in the ‘no change/worsening’ category for analysis. For analysis of total endoscopic NP score, participants with missing visit information (due to early study withdrawal or any other reason) will, in the absence of actual surgery, be included in the ‘no change/worsening’ category for analysis. For analysis of nasal obstruction VAS, participants with missing data for a 4-week period will, in the absence of surgery, be included in the ‘no change/worsening’ category for that 4-week period. Sensitivity analyses to examine the impact of handling missing data as described above are detailed in Section 7.1.5.

Each co-primary endpoint will be analysed as an ordinal categorical variable [Keene, 2018]. NP score and VAS symptom scores have usually been analysed using models which assume the response is normally distributed. Such models do not acknowledge the bounded response for the scales and there is no ideal approach for inclusion of actual surgery as a worst response. For the proportional odds model, it is not necessary to assign scores to the response categories, and if the model holds for a particular set of response categories, it holds with the same effects when the response scale is collapsed in any way [McCullagh, 1980]. In the comparison of two treatments with no adjustment for covariates, this approach becomes equivalent to the Wilcoxon test.

7.1.2. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant achieving a greater improvement by category for mepolizumab compared with placebo.

7.1.3. Population of Interest

The primary population of interest for analysis of the co-primary endpoints is defined by the study inclusion/exclusion and randomisation criteria and is therefore the ITT population.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

The anticipated intercurrent events occurring prior to the week 52 analysis time point for the co-primary endpoints are: Actual surgery for nasal polyps and premature discontinuation of interventional product.

For each co-primary endpoint, the anticipated intercurrent event of actual surgery will be handled using a composite strategy such that the occurrence of the event is incorporated into the definition of the endpoint. In participants who do not experience actual surgery, the anticipated intercurrent event of premature discontinuation of interventional product will be handled using a treatment policy strategy, such that in these participants all data reported at week 52 for total endoscopic NP score (or during the 4-week period prior to Week 52 for nasal obstruction VAS) will be included in the analysis, regardless of discontinuation from treatment.

7.1.5. Statistical Analyses / Methods

Each co-primary endpoint will be analysed using an ordinal logistic regression model (proportional odds model) with covariates as detailed. The treatment effect of mepolizumab compared with placebo will be expressed as an odds ratio with corresponding 95% confidence interval and p-value.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
Change from baseline in total endoscopic NP score (based on centrally read data) at Week 52 and other defined visits, will be categorized for analysis as follows: 1. ≥ 5-point improvement 2. 4-point improvement 3. 3-point improvement 4. 2-point improvement 5. 1-point improvement 6. No change/worsening 7. Nasal surgery prior to visit • For analysis, participants with missing data at Baseline will be included in the 'no change/worsening' category, participants with missing data at a visit will be included in the 'no change/worsening' category for the respective visit. • If a participant had actual surgery prior to a visit, they will be included in the 'Nasal surgery prior to visit' category regardless of whether a score for the respective visit was obtained. Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52, and other defined 4-week periods, will be categorized for analysis as follows: 1. > 5-point improvement 2. >4 to 5-point improvement 3. >3 to 4-point improvement 4. >2 to 3-point improvement 5. >1 to 2-point improvement 6. >0 to 1-point improvement 7. No change/worsening 8. Nasal surgery prior to visit • For analysis, participants with missing data at Baseline will be included in the 'no change/worsening' category, participants with missing data for the 4-week period will be included in the 'no change/worsening' category for the respective period. • If a participant had actual surgery prior to or during a 4-week period, they will be included in the 'Nasal surgery prior to visit' category regardless of whether data for the respective period was obtained.
Model Specification
• Each co-primary endpoint will be analyzed using ordinal logistic regression to compare the odds between treatment groups of being in a more favorable endpoint category. • The odds ratio comparing treatment groups will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates. • The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

- Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of patients in each analysis category will be displayed by treatment group, as will the estimated odds ratio, 95% confidence interval (CI) and p-value comparing treatments from the ordinal logistic regression model.
- A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups at each visit will be provided.
- A cumulative distribution function (CDF) plot will be provided for the change from baseline in endoscopic NP score at Week 52 by treatment group. Participants having had nasal surgery prior to Week 52 will be included as having the worst outcome for the study.

Subgroup Analyses

- Section 5.4.2 identifies the subgroups of interest for the co-primary endpoints.

Sensitivity and Supportive Analyses

For sensitivity and supplementary analyses an ordinal logistic regression model (proportional odds model) with covariates as for the primary efficacy analysis will be used.

Sensitivity analyses

- In the primary analysis participants with missing data at baseline or Week 52 (due to premature withdrawal from the study or another reason) will be included in the 'no change or worsening' category for analysis. Sensitivity analyses will be carried out to examine the potential impact of choices for the handling of missing data. Sensitivity analysis will be performed where the participants with missing data are included in the:
  - a) least favourable category of actual surgery for each co-primary endpoint
  - b) 1-point improvement category for total endoscopic NP score and the 0 to 1-point improvement category for mean nasal obstruction VAS.

Supplementary analyses

- A supplementary analysis will be performed for each co-primary endpoint where the anticipated intercurrent event of premature discontinuation of interventional product will be handled using a composite strategy, such that the event is incorporated into the definition of the endpoint. For this supplementary analysis, all participants in the population of interest will be included in this sensitivity analysis, the co-primary endpoints will be analysed as follows:
  - The least favourable treatment response category will incorporate the intercurrent events of actual surgery and premature discontinuation of interventional product, this will be labelled as 'Nasal surgery prior to visit or premature discontinuation of interventional product'
- A supplementary analysis of each co-primary endpoint will be performed on the Per-Protocol (PP) population (see Appendix 1: Protocol Deviation Management and Definitions for Per Protocol Population)

7.2. Secondary Efficacy Analyses

For each secondary endpoint the primary treatment effect to be estimated (estimand) will be the comparison of mepolizumab 100mg SC to placebo.

7.2.1. Time to first nasal surgery

The time to first nasal surgery will be determined as the number of days from the date of first dose of study medication to the date of first nasal surgery (see Section 14.6.5). If a participant withdraws from the study before Week 52 and before experiencing nasal surgery, the nasal surgery event time will be censored at the time of study withdrawal.

7.2.1.1. Summary Measure

The summary measure of treatment effect will be the hazard ratio, the ratio of hazards corresponding to treatment with mepolizumab compared with placebo. For this endpoint the hazard represents the probability of nasal surgery for a participant at a given point in time following first dose of interventional product, given the participant has not experienced the event prior to that time.

7.2.1.2. Population of Interest

The primary population of interest is the ITT population.

7.2.1.3. Strategy for Intercurrent (Post-Randomization) Events

A treatment policy strategy will be used for the intercurrent event of premature discontinuation of interventional product, such that available nasal surgery times will be included in the analysis regardless of whether the surgery occurred before or after discontinuation of interventional product.

7.2.1.4. Statistical Analyses / Methods

Endpoint / Variables

Time to first nasal surgery

Model Specification

- Cox proportional hazards model with covariates as follows:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline total nasal polyps endoscopic score (centrally read data), Baseline nasal obstruction VAS, Log_e baseline blood eosinophil count, Number of previous surgeries (1, 2, >2; ordinal)

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- A log(-log(survival)) plot by treatment group will be used to assess the assumption of proportional hazards.

Model Results Presentation
• The number of participants with an event, the number censored due to study withdrawal and at study completion will be presented by treatment arm. • The hazard ratio with corresponding 95% CI and p-value from the Cox proportional hazards model will be presented. • A summary and graph of the Kaplan-Meier estimate of the cumulative proportion of participants with nasal surgery within each treatment arm over time will be produced.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• Sensitivity analyses will be performed to assess the censoring-at-random assumption of the cox proportional hazards model where participants who withdraw from the study before experiencing surgery have their event times censored at the time of study withdrawal. • Sensitivity analysis will be carried out where missing event times for participants randomised to mepolizumab who withdraw from the study before experiencing surgery will be imputed using a censoring-not-at-random method as described in [Jackson, 2014]. A step-change in event rate equivalent to a loss of benefit from mepolizumab will be imputed for these participants after their censoring time. This means a reduction in relative event rate equivalent to 1/(estimated treatment effect). Missing event times for placebo will imputed under a censoring-at-random assumption.

7.2.2. Change from Baseline in Mean Overall VAS Symptom Score During the 4 weeks Prior to Week 52

Change from baseline in mean overall VAS symptom score will be categorised for analysis into varying levels of improvement, no change or worsening, and a least favourable category of actual surgery. Participants with missing data at Baseline or at Week 52 (due to study withdrawal or any other reason) will be included in the 'no change/worsening' category for analysis.

7.2.2.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds for a participant achieving a greater improvement by category with mepolizumab compared with placebo.

7.2.2.2. Population of Interest

The primary population of interest is the ITT population.

7.2.2.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.2.2.4. Statistical Analyses / Methods

Endpoint / Variables

Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52, and other defined 4-week periods, will be categorized for analysis as follows:

1. > 5-point improvement
2. >4 to 5-point improvement
3. >3 to 4-point improvement
4. >2 to 3-point improvement
5. >1 to 2-point improvement
6. >0 to 1-point improvement
7. No change/worsening
8. Nasal surgery prior to visit

- For analysis, participants with missing data at Baseline will be included in the 'no change/worsening' category, participants with missing data for the 4-week period will be included in the 'no change/worsening' category for the respective period
- If a participant had actual surgery prior to or during a 4-week period, they will be included in the 'Nasal surgery prior to visit' category regardless of whether data for the respective period was obtained.

Model Specification

- This endpoint will be analyzed using ordinal logistic regression to compare the odds between treatment groups of being in a more favorable endpoint category.
- The odds ratio comparing treatment groups will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of patients in each 'change from baseline' category will be displayed by treatment group, as will the estimated odds ratio, 95% CI and p-value comparing treatments from the ordinal logistic regression model.
- A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups at each visit will be provided.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint

Sensitivity and Supportive Analyses

- No sensitivity analyses are planned for this endpoint

7.2.3. Change from Baseline in Sino-Nasal Outcomes TEST 22 (SNOT-22) Total Score at Week 52

The 22 questions of the SNOT-22 are each graded on CCI [redacted] CCI [redacted] The scores for each of the questions are summed to derive the total score which ranges CCI [redacted] CCI [redacted].

Change from baseline at Week 52 will be categorised for analysis into varying levels of improvement, no change or worsening and a least favourable category of actual surgery. Participants with missing data at Week 52 (due to early study withdrawal or any other reason) will be included for analysis in the 'no change/worsening' category.

7.2.3.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds for a participant achieving a greater improvement by category for mepolizumab compared with placebo.

7.2.3.2. Population of Interest

The primary population of interest is the ITT population.

7.2.3.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.2.3.4. Statistical Analyses / Methods

Endpoint / Variables
Change from baseline in SNOT-22 total score at Week 52, and other defined visits, will be categorized as follows: 1. >45-point improvement 2. >36 to 45-point improvement 3. >27 to 36-point improvement 4. >18 to 27-point improvement 5. >9 to 18-point improvement 6. >0 to 9-point improvement 7. No change/worsening 8. Nasal surgery prior to visit • For analysis, participants with missing data at Baseline will be included in the 'no change/worsening' category, participants with missing data at a visit will be included in the 'no change/worsening' category for the respective visit • If a participant had actual surgery prior to a visit, they will be included in the 'Nasal surgery prior to visit' category regardless of whether a score for the respective visit was obtained.

Model Specification
• This endpoint will be analyzed using ordinal logistic regression to compare the odds between treatment groups of being in a more favorable endpoint category. • The odds ratio comparing treatment groups will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates. • The analysis model will include the following terms: Fixed Categorical: Treatment group, Region Fixed Continuous: Baseline score, Log_e baseline blood eosinophil count • Participants with missing covariate information will be excluded from the analysis
Model Checking & Diagnostics
• Models will be checked for issues with convergence.
Model Results Presentation
• The number and percentage of patients in each 'change from baseline' category will be displayed by treatment group, as will the estimated odds ratio, 95% CI and p-value comparing treatments from the ordinal logistic regression model. • A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups at each visit will be provided.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint
Sensitivity and Supportive Analyses
• No sensitivity analyses are planned for this endpoint

7.2.4. Number of mgs per year of prednisolone-equivalent OCS dose up to Week 52

The total number of milligrams (mgs) of prednisolone-equivalent OCS use per year will be categorised and analysed as an ordinal categorical variable representing a composite of varying levels of prednisolone-equivalent OCS use in mgs per year up to Week 52.

7.2.4.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds for a participant achieving a greater improvement by category for mepolizumab compared with placebo.

7.2.4.2. Population of Interest

The primary population of interest is the ITT population.

7.2.4.3. Strategy for Intercurrent (Post-Randomization) Events

The anticipated intercurrent events for this endpoint are actual surgery and premature discontinuation of interventional product, these will be handled using a treatment policy

strategy such that all data will be included in the analysis, regardless of the occurrence of either intercurrent event.

7.2.4.4. Statistical Analyses / Methods

Endpoint / Variables

The total number of mgs of prednisolone-equivalent OCS use per year (see Section 14.6.5) will be categorized for analysis as follows:

1. 0mg
2. >0 to 100mg
3. >100 to 200mg
4. >200 to 400mg
5. >400mg
6. Nasal Surgery

- If a participant had actual surgery, they will be included in the 'Nasal surgery' category regardless of the total use of prednisolone equivalent OCS.

Model Specification

- This endpoint will be analyzed using ordinal logistic regression to compare the odds between treatment groups of being in a more favorable endpoint category.
- The odds ratio comparing treatment groups will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Number of OCS courses for NP in last 12 months (0, 1, >1; ordinal), baseline total endoscopic NP score (based on centrally read data), baseline nasal obstruction VAS score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of patients in each category will be displayed by treatment group, with the estimated odds ratio, 95% CI and p-value comparing treatments from the ordinal logistic regression model.
- A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups will be provided.

Subgroup Analyses

- Analysis will be carried out of the following subgroups: Participants with asthma. See Section 5.4.2 for further details.

Sensitivity and Supportive Analyses

• No sensitivity analyses are planned for this endpoint

7.3. Other Efficacy Analyses

7.3.1. Total Endoscopic Nasal Polyps Score Responders

A responder is defined as a participant achieving a ≥1-point improvement (decrease) from baseline in total endoscopic NP score (based on centrally read data) at Week 52. Participants with missing data at Baseline or Week 52 (due to early study withdrawal or any other reason) will be included in the analysis as a non-responder.

7.3.1.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder in the mepolizumab arm compared with placebo.

7.3.1.2. Population of Interest

The population of interest is the ITT population.

7.3.1.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.1.4. Statistical Analyses / Methods

Endpoint / Variables

Participants with a ≥ 1-point improvement from baseline in total endoscopic NP at Week 52 (based on centrally read data) will be included in the analysis as a responder.

- The following participants will be included in the analysis as a non-responder:
  - Participants who had actual surgery prior to Week 52
  - Participants who withdrew early from the study or who had missing data at Baseline or Week 52

Model Specification

- A logistic regression model will be used to compare the proportion of responders in the mepolizumab arm compared to placebo.
- The odds ratio comparing treatment groups will be estimated using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

• Models will be checked for issues with convergence.
Model Results Presentation
• The number and percentage of participants identified as responders and non-responders for analysis will be displayed by treatment group, the non-responder group will be further categorized to display the number of participants with actual surgery, the number withdrawn early from the study and the number with missing baseline data. • The estimated odds ratio, 95% CI and p-value comparing treatments from the logistic regression model will be displayed. • A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups will be provided by visit.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.3.2. Change from baseline in individual and composite VAS symptom scores

Participants rate individual symptoms daily on a visual analogue scale using an eDiary, the scale range for each symptom is CCI [redacted]

The following endpoints will be analysed in the same manner and using the same change from baseline categories as the co-primary endpoint of change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52:

- Change from baseline in mean individual VAS symptom scores during the 4 weeks prior to Week 52 for:
  - nasal discharge
  - mucus in the throat
  - loss of smell
  - facial pain

- Change from baseline in the mean composite VAS score during the 4 weeks prior to Week 52 for:
  - Composite of nasal obstruction, nasal discharge, mucus in the throat and loss of smell
  - Composite of nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain

7.3.2.1. Summary Measure

See Section 7.1.2. for details.

7.3.2.2. Population of Interest

See Section 7.1.3. for details.

7.3.2.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.2.4. Statistical Analyses / Methods

Endpoint / Variables

Change from baseline during the 4 weeks prior to Week 52, and other defined 4-week periods, will be categorized for analysis as follows:

1. > 5-point improvement
2. >4 to 5-point improvement
3. >3 to 4-point improvement
4. >2 to 3-point improvement
5. >1 to 2-point improvement
6. >0 to 1-point improvement
7. No change/worsening
8. Nasal surgery prior to visit

- For analysis, participants with missing data at Baseline will be included in the 'no change/worsening' category, participants with missing data for the 4-week period will be included in the 'no change/worsening' category for the respective period.
- If a participant had actual surgery prior to or during a 4-week period, they will be included in the 'Nasal surgery prior to visit' category regardless of whether data for the respective period was obtained.

Model Specification

- For each endpoint an ordinal logistic regression model will be used to compare the odds between treatment groups of being in a more favorable endpoint category.
- The odds ratio comparing treatment groups will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

  - Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of patients in each analysis category will be displayed by treatment group, as will the estimated odds ratio, 95% confidence interval (CI) and p-value comparing treatments from the ordinal logistic regression model.

• A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups at each visit will be provided.
Subgroup Analyses
• No subgroup analyses are planned for these endpoints.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for these endpoints.

7.3.3. SNOT-22 Responders

A responder is defined as a participant achieving a ≥9-point improvement (decrease) from baseline in SNOT-22 total score at Week 52. Participants with missing data at Baseline or Week 52 (due to early study withdrawal or any other reason) will be included in the analysis as a non-responder.

7.3.3.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant being a responder in the mepolizumab arm compared with placebo.

7.3.3.2. Population of Interest

The population of interest is the ITT population.

7.3.3.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.3.4. Statistical Analyses / Methods

Endpoint / Variables

Participants with a ≥ 9-point improvement from baseline in SNOT-22 score at Week 52 will be included in the analysis as a responder.
• The following participants will be included in the analysis as a non-responder:
  ○ Participants who had actual surgery prior to Week 52
  ○ Participants who withdrew early from the study or who had missing data at Baseline or Week 52

Model Specification
• See Section 7.3.1.4
Model Checking & Diagnostics
• See Section 7.3.1.4
Model Results Presentation
• See Section 7.3.1.4
Subgroup Analyses

• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.3.4. Need for Surgery

Participants enter the trial with severity of nasal polyps consistent with the need for surgery (inclusion criteria 8 of study protocol). Participants are identified as no longer having a need for surgery based on improvements in the total nasal polyps endoscopy score (centrally read) and overall VAS score at Week 52 (further details in Section 14.6.5). Participants with missing data at Week 52 (due to early study withdrawal or any other reason) will be identified as still having a need for surgery at Week 52.

7.3.4.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant no longer having a need for surgery at Week 52 in the mepolizumab arm compared with placebo.

7.3.4.2. Population of Interest

The population of interest is the ITT population.

7.3.4.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.4.4. Statistical Analyses / Methods

Endpoint / Variables

Need for surgery at week 52 will be assessed for each participant as detailed in Section 14.6.5.

- The following participants will be included in the analysis as still having a need for surgery:
  - Participants who had actual surgery prior to Week 52
  - Participants who withdrew early from the study or who had missing data at Baseline or Week 52

Model Specification

- A logistic regression model will be used to compare the proportion of participants who no longer have a need for surgery in the mepolizumab arm compared to placebo.
- The odds ratio comparing treatment groups will be estimated using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Region
Fixed Continuous:	Baseline total nasal polyps endoscopic score (centrally read data), Log_e baseline blood eosinophil count

• Participants with missing covariate information will be excluded from the analysis
Model Checking & Diagnostics
• Models will be checking for issues with convergence.
Model Results Presentation
• The number and percentage of participants identified as no longer having a need/still having a need for surgery will be displayed by treatment group, the still having a need for surgery group will be further categorized to display the number participants with actual surgery, the number withdrawn early from the study and the number with missing Baseline data. • The estimated odds ratio, 95% CI and p-value comparing treatments from the logistic regression model will be displayed.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.3.5. Rate of Nasal Surgery

A summary of the number and percentage of participants who have undergone surgery will be presented, the rate of surgery will also be presented for each treatment arm.

7.3.6. Time to First Inclusion on Waiting List for NP Surgery

A summary and graph of the Kaplan-Meier estimates of the cumulative proportion of participants having been placed on a waiting list for nasal polyps surgery over time will be provided.

7.3.7. Waiting List for NP surgery

A summary of the number and percentage of participants placed on a waiting list for nasal polyp surgery at each visit and over the whole study will be presented.

7.3.8. Change from baseline in UPSIT (University of Pennsylvania Smell Identification Test)

UPSIT is designed to test the function of an individual's olfactory system. The test is scored out of 40 with a lower score indicating a worse outcome. The test will be performed only by participants at sites in the UK, US and Canada. Change from baseline in UPSIT total score will be categorised for analysis into varying levels of improvement, no change or worsening, and a least favourable category of actual surgery. Participants with missing data at Baseline or at Week 52 (due to study withdrawal or any other reason) will, in the absence of surgery, be included in the 'no change or worsening category' for analysis.

7.3.8.1. Summary Measure

The summary measure of treatment effect will be the odds ratio which represents the relative odds of a participant achieving a greater improvement by category for mepolizumab compared with placebo.

7.3.8.2. Population of Interest

The population of interest is the ITT population.

7.3.8.3. Strategy for Intercurrent (Post-Randomization) Events

See Section 7.1.4. for details.

7.3.8.4. Statistical Analyses / Methods

Endpoint / Variables

Change from baseline in UPSIT at Week 52 and other defined visits, will be categorized for analysis as follows:

1. > 20-point improvement
2. >10 to 20-point improvement
3. >0 to 10-point improvement
4. No change/worsening
5. Nasal surgery prior to visit

- For analysis, participants with missing data at Baseline will be included in the 'no change/worsening' category, participants with missing data at a visit will be included in the 'no change/worsening' category for the respective visit
- If a participant had actual surgery prior to a visit, they will be included in the 'Nasal surgery prior to visit' category regardless of whether a score for the respective visit was obtained.

Model Specification

- Change from baseline in UPSIT will be analyzed using ordinal logistic regression to compare the odds between treatment groups of being in a more favorable endpoint category.
- The odds ratio comparing treatment groups will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates.
- The analysis model will include the following terms:

Fixed Categorical:	Treatment group, Country
Fixed Continuous:	Baseline score, Log_e baseline blood eosinophil count

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of patients in each analysis category will be displayed by treatment group, as will the estimated odds ratio, 95% CI and p-value comparing treatments from the ordinal logistic regression model.

• A forest plot of the estimated odds ratio and 95% CI for the comparison of treatment groups at each visit will be provided.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.3.9. Change from baseline in PnIF (Peak Nasal Inspiratory Flow)

A PnIF meter will be used to derive forced inspiratory peak flow through the nose. A summary of PnIF data and change from baseline at each visit will be presented.

7.3.10. Health Outcomes

7.3.10.1. SF-36 Mental Component Summary (MCS), Physical Component Summary (PCS) and 8 summary scores

Certified scoring of the SF-36 survey will be performed using OPTUM™ software.

The eight domain scores (bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality) as well as the physical and mental component summary scores are provided by the software.

Domain and component summary scores will be summarised by visit, including change from baseline. Data will be included in these summaries regardless of the occurrence of events such as actual surgery or treatment discontinuation.

7.3.10.2. Work Productivity and Activity Impairment Questionnaire (WPAI)

The WPAI questionnaire is an instrument to measure impairment in paid and unpaid work. Summary information from the WPAI at each visit will include information on employment status, hours missed from work due to health problems and due to other reasons, hours actually worked, and how much health problems affected productivity and activity. Data will be included in these summaries regardless of the occurrence of events such as actual surgery or treatment discontinuation.

7.3.11. Systemic Steroid Use

7.3.11.1. Number of Courses of Therapy

A summary of the number of courses of systemic steroids will be presented for each treatment arm. Courses of systemic steroids which are separated by less than 7 days will be considered a continuation of the same course. Data will be included in the summary regardless of the occurrence of events such as surgery or treatment discontinuation.

7.3.11.2. Days on Therapy

The mean number of days and percentage of days on systemic steroids will be presented for each treatment arm. Data will be included in the summary regardless of the occurrence of events such as surgery or treatment discontinuation.

7.3.11.3. Time to First Course of Systemic Steroids

A summary and graph of the Kaplan-Meier estimates of the cumulative proportion of participants with a first course of systemic steroids over time will be provided.

7.3.12. Antibiotic Use

7.3.12.1. Number of Courses of Therapy

A summary of the number of courses of antibiotics will be presented for each treatment arm. Courses of antibiotics which are separated by less than 7 days will be considered a continuation of the same course. Data will be included in the summary regardless of the occurrence of events such as surgery or treatment discontinuation.

7.3.13. Time to first nasal surgery or course of systemic steroids

The time to first nasal surgery or course of systemic steroids will be determined as the number of days from the date of first dose of study medication to the date of first nasal surgery or course of systemic steroids (see Section 14.6.5). If a participant withdraws from the study before experiencing nasal surgery or course of systemic steroids, the event time will be censored at the time of study withdrawal.

7.3.13.1. Summary Measure

The summary measure of treatment effect will be the hazard ratio, the ratio of hazards corresponding to treatment with mepolizumab compared with placebo. For this endpoint the hazard represents the probability of nasal surgery or course of systemic steroids for a participant at a given point in time following first dose of interventional product, given the participant has not experienced either event prior to that time.

7.3.13.2. Population of Interest

The primary population of interest is the ITT population.

7.3.13.3. Strategy for Intercurrent (Post-Randomisation) Events

A treatment policy strategy will be used for the intercurrent event of premature discontinuation of interventional product, such that available event times will be included in the analysis regardless of whether the event occurred prior to discontinuation of randomised treatment.

7.3.13.4. Statistical Analyses / Methods

Endpoint / Variables
Time to first nasal surgery or course of systemic steroids
Model Specification
• Cox proportional hazards model with covariates as follows: Fixed Categorical: Treatment group, Region Fixed Continuous: Baseline total nasal polyps endoscopic score (centrally read data), Baseline nasal obstruction VAS, Log_e baseline blood eosinophil count, Number of previous surgeries (1, 2, >2; ordinal) • Participants with missing covariate information will be excluded from the analysis
Model Checking & Diagnostics
• A log(-log(survival)) plot by treatment group will be used to assess the assumption of proportional hazards.
Model Results Presentation
• The number of participants with an event, the number censored due to study withdrawal and at study completion will be presented by treatment arm. • The hazard ratio with corresponding 95% CI and p-value from the Cox proportional hazards model will be presented. • A summary and graph of the Kaplan-Meier estimate of the cumulative proportion of participants with nasal surgery within each treatment arm over time will be produced.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint.
Sensitivity and Supportive Analyses
• No sensitivity/supportive analyses are planned for this endpoint.

7.4. Participants with Asthma

A subgroup analysis by concurrent asthma will be carried out for each of the following endpoints:

- Total endoscopic nasal polyps score (Centrally Read)
- Nasal obstruction VAS score
- Total Prednisolone-equivalent OCS Use (mgs per year)

In addition, for participants with asthma the Asthma Control Questionnaire (ACQ-5) score and number of clinically significant asthma exacerbations will be summarised.

7.5. Maintenance of response

The following endpoints will be summarised for the subset of participants who entered the no-treatment 6-month follow up period after Week 52. All data reported by these participants for the duration of their time in the study will be included in these summaries, this will include data reported prior to entering the follow-up period (whether or not the subject had prematurely discontinued from interventional product during that time) and data reported after entering the follow-up period.

- Change from baseline in total endoscopic NP score (centrally read)
- Change from baseline in mean nasal obstruction VAS score
- Change from baseline in mean individual VAS symptom score for nasal discharge, mucus in throat, loss of smell and facial
- Change from baseline in mean overall VAS symptom score
- Number of mgs per year of prednisolone-equivalent OCS dose
- Change from baseline in SNOT-22 total score
- Time to first nasal surgery
- Time to first inclusion on waiting list for NP surgery

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population. Unless otherwise specified data reported as part of the no-treatment follow-up will not be included in summaries of on-treatment data or post-treatment data. Data reported during the no-treatment follow-up will be summarised separately.

Summaries of adverse events (AEs), serious adverse events (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.

8.1. Adverse Events Analyses

8.2. Adverse Events of Special Interest Analyses

Adverse events of special interest (AESIs) are adverse events which are to be closely monitored as the development of mepolizumab progresses.

Systemic reactions are AESIs which are collected via targeted eCRF and further categorised by the investigator as either an allergic (type I hypersensitivity) or other systemic reaction. These events are required to be assessed against Sampson's diagnostic criteria for anaphylaxis. Local injection site reactions are also collected via targeted eCRF within the study.

AESIs of potential opportunistic infections, malignancies, serious cardiac, vascular and thromboembolic (CVT) events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset created

based on the MedDRA dictionary available at the time of source data lock for this study. Further details of how relevant preferred terms are identified for the AESIs are given in the Program Safety Analysis Plan (PSAP).

Separate summary tables showing the number and percent of participants with each type of AESI, broken down by preferred term will be created. These summaries will be reported as part of the standard AE/SAE tables for the AESIs of infections, serious infections, neoplasms, cardiac disorders and serious cardiac disorders. The relative risk of each AESI between mepolizumab and placebo will be presented with 95% confidence intervals.

For each AESI a profile summary table will be produced containing information on event characteristics including, but not be limited to, the number of participants with the AESI, the number of occurrences of the AESI, the number of participants with a serious event or a drug related event, summaries by maximum severity and separately by outcome.

Separate listings will be provided of participants with systemic reactions identified by the investigator as meeting the criteria for anaphylaxis, systemic reactions categorised as allergic (type I hypersensitivity), systemic reactions categorised as other, and all other AESIs.

8.3. Clinical Laboratory Analyses

Summaries of laboratory data including chemistry and haematology parameters, and liver function test data will be based on GSK Core Data Standards and unless otherwise specified will include on-treatment and post-treatment data.

A scatter plot of maximum post-baseline ALT vs maximum post-baseline total bilirubin will be produced. In addition, if any liver stopping or liver monitoring events occur during the study, summaries of liver monitoring/stopping event reporting and hepatobiliary laboratory abnormalities will be produced.

The details of the planned displays are in Appendix 12: List of Data Displays.

8.4. Other Safety Analyses

8.4.1. ECG and Vital Signs

Summaries of ECG and vital signs data will be based on GSK Core Data Standards. The details of the planned displays are presented in Appendix 12: List of Data Displays.

For ECG data, summaries of the maximum post-baseline and change from baseline values for QTc(F), QTc(B) and heart rate will be provided.

Individual maximum and maximum change from baseline QTc(F) and QTc(B) values will be categorised as detailed in Section 14.6.6. The number (percent) of participants in each of the categories will be displayed.

The number of abnormal and clinically significant ECG results post baseline will be produced showing the worst recorded value post baseline.

8.4.2. Immunogenicity Data

An immune response to a therapeutic drug can lead to generation of anti-drug antibodies within the blood. For the immunogenicity assessment, two types of antibody assays will be performed, a binding anti-drug antibody (ADA) assay and a neutralizing antibody (NAb) assay.

For the binding ADA assay, there will be three testing steps: 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. Participants with a positive confirmation result will be positive for the binding ADA assay. Participants who test positive for the binding ADA assay, will be tested for the NAb assay, which also reports results as positive or negative.

Immunogenicity data will be summarised for all subjects in the safety population (excluding data reported during the follow-up period after Week 52), as well as for the subjects entering the follow-up period after Week 52 (using all data). For the binding ADA assay, confirmation results at each visit will be categorised as negative or positive and summarised. NAb assay results will also be summarised.

The highest binding ADA assay confirmatory result obtained for a participant (including any off-treatment data), will be summarised with a positive result being considered higher than a negative one, participants with both positive and negative results being identified in the positive category. Summary statistics for titre results will also be presented. In addition, the highest NAb assay result during the same period will be summarised (again with a positive result being considered higher than a negative one and participants with both positive and negative results will be identified in the positive category).

A summary of treatment emergent positive confirmatory binding ADA assay results in the subset of participants who did not have a positive confirmatory binding ADA assay result prior to the first dose of interventional product will also be presented.

All immunogenicity results (i.e. binding ADA screening and confirmatory assay results, titre values, NAb results and observed mepolizumab concentration) will be listed.

9. PHARMACODYNAMIC ANALYSES

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.

9.1. Pharmacodynamic Analyses

The treatment effect to be estimated (estimand) will be the comparison of mepolizumab 100mg SC to placebo for change from baseline blood eosinophils at Week 52.

9.1.1. Endpoint / Variables

Absolute and ratio to baseline blood eosinophil counts will be summarised at each visit.

9.1.2. Summary Measure

The summary measure of treatment effect will be the ratio of the effect at Week 52 of mepolizumab compared to placebo.

9.1.3. Population of Interest

The population of interest is the Intent to Treat population.

9.1.4. Strategy for Intercurrent (Post-Randomization) Events

Only data collected while the participant was on-treatment will be used in the analysis ('while on-treatment strategy). Blood eosinophil counts taken more than 28 days following last dose will not be included in the analysis.

Missing data will be assumed to be missing at random.

9.1.5. Statistical Analyses / Methods

9.1.5.1. Statistical Methodology Specification

Endpoint / Variables

- Ratio to baseline blood eosinophils

Model Specification

- Blood eosinophil counts will be log transformed (loge) prior to analysis, transformations for values of 0 GI/L will be based on a value of 0.005 GI/L (see Section 14.6.6).
- This endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis including the following terms:

Fixed Categorical:	Treatment group, Region, Visit
Fixed Continuous:	Baseline $\log_e$ blood eosinophil count,
Repeated:	Visit
Interaction Terms:	Visit by baseline, visit by treatment group.

- Participants with missing covariate information will be excluded from the analysis

• An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line
Model Checking & Diagnostics
The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.
Model Results Presentation
• The estimated means for each treatment group will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement). • Model-estimates of the absolute mean and mean ratio to baseline will be back-transformed and presented as ratios with corresponding standard errors on the log scale for each treatment group by visit. Estimated treatment differences (Mepolizumab/Placebo) with corresponding 95% CIs and p-values will also be presented.
Subgroup Analyses
• No subgroup analyses are planned for this endpoint
Sensitivity and Supportive Analyses
• No sensitivity analyses are planned for this endpoint

10. POPULATION PHARMACOKINETIC (POPPK) ANALYSES

The primary goal of this analysis is to characterize the population pharmacokinetics of mepolizumab administered subcutaneously in participants with severe nasal polyps. The influence of subject demographics, baseline characteristics, including disease activity, and co-medication on the pharmacokinetics of mepolizumab in this population will be investigated. The individual subject PK parameters will be estimated and documented for the purposes of any subsequent exposure-response (PK/PD) analyses.

In support of the analysis described below, a dataset will be generated for which specifications will be provided in a separate document.

The 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. Refer to Data Display Standards & Handling Conventions (Section 14.5.3 Reporting Standards for Pharmacokinetic Data).

10.1. Primary Pharmacokinetic Analyses

A population PK analysis of sparse concentration data will be performed on the PK population.

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Based on previous knowledge of mepolizumab 100 mg SC pharmacokinetics, concentrations below the limit of quantification (BLQ) of the assay are not anticipated. Any such results 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.

10.2. Population Pharmacokinetic Methodology

Sparse blood sampling is implemented in this study for determination of mepolizumab plasma concentration and subsequent data analysis by population PK methods using the most recent population pharmacokinetics model (meta-analysis PK model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00). Since mepolizumab PK following intravenous administration in NP subjects has already been established, the main objectives of this population PK analysis are:

- To evaluate mepolizumab pharmacokinetics in subjects with NP following the subcutaneous administration of a 100 mg dose every 4 weeks.
- To investigate the impact of covariates of interest in the studied NP population (such as baseline characteristics, co-medication) on specific parameters (e.g. clearance) to identify potential sources of inter-individual variability in these parameters.
- To obtain individual plasma concentration predictions for the timepoints at which PD is measured to allow the conduct of population PKPD analyses if deemed appropriate.

Further details are provided in Appendix 9: Population Pharmacokinetic (PopPK) Analyses.

10.3. Exploratory Pharmacokinetic Analyses

Complementing the population-PK analysis, a repeated measures linear mixed-effects model of $\log_e$-transformed concentration will be used to analyse the sparse (Weeks 4, 52 and 68) data. All data will be analysed on an ITT basis using planned Visit, irrespective of withdrawal. The model will adjust for Region and Visit number and consider the covariates listed above. Selection of covariates will be based on biological plausibility, parsimony and a significance level of 0.05. Forwards and backwards selection criteria may be applied as per the population PK model.

10.3.1. Summary Measure

Log-transformed mepolizumab plasma concentration.

10.3.2. Population of Interest

The population of interest is the PK population.

10.3.3. Statistical Analyses / Methods

Endpoint / Variables

- Plasma concentration

Model Specification

- Plasma concentration will be log transformed (log_e) prior to analysis, values BQL will be set to missing.
- This endpoint will be analyzed using a mixed model repeated measures (MMRM) analysis including the following terms:

Fixed Categorical:	Region, Visit
Fixed Continuous:	log_e bodyweight, log_e creatinine clearance, log_e serum albumin
Repeated:	Visit
Interaction Terms:	None

  - Participants with missing covariate information will be excluded from the analysis

- An unstructured covariance structure for the R matrix will be used by specifying 'type=UN' on the REPEATED line

Model Checking & Diagnostics

The Kenward and Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects will be used.

Model Results Presentation

- The estimated means for each visit will be calculated from the model using the observed marginal distributions of the sample covariates (OM option in LSMEANS statement).
- Model-estimates of the absolute mean and mean ratio to Week 4 (accumulation ratio) will be back-transformed and presented as ratios with corresponding standard errors on the log scale by visit. Estimated exposure ratios with corresponding 95% CIs and p-values will also be presented.
- Effects of bodyweight, creatinine clearance and serum albumin will be evaluated as ratio to standard values and back-transformed and presented as ratios with corresponding standard errors on the log scale. Estimated exposure ratios with corresponding 95% CIs and p-values will also be presented.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint

Sensitivity and Supportive Analyses

- No sensitivity analyses are planned for this endpoint

11. POPULATION PHARMACOKINETIC/ PHARMACODYNAMIC (POPPKPD) ANALYSES

In support of the analysis described below, a specific dataset will be generated for which specifications will be provided in a separate document.

The details of the planned displays are presented in Appendix 12: List of Data Displays.

11.1. Population Pharmacokinetic/Pharmacodynamic Methodology

If deemed appropriate, a population pharmacokinetic/pharmacodynamic analysis will be conducted on the PK population and the ITT population (for blood eosinophils).

For subjects withdrawing prematurely from study treatment, all available data will be included in the analysis.

Zero values for the baseline blood eosinophil count as well as for blood eosinophil count during the study will be replaced by 0.005 prior to log transformation (consistent with approaches used in other analyses).

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.

Blood eosinophil counts were measured during the course of the study over the 52 weeks treatment period and will be analysed by population methods using the most recent population PKPD model (meta-analysis PKPD model of data across indications described in GlaxoSmithKline Document Number 2015N238436_00).

The objectives of the population PKPD analysis are:

- To evaluate mepolizumab pharmacodynamics in subjects with NP following subcutaneous administration of a 100 mg dose every 4 weeks;
- To investigate the impact of covariates of interest in the studied NP population (such as baseline characteristics, co-medication) on specific parameters (e.g. maximum blood eosinophil reduction) in order to identify potential sources of inter-individual variability in these parameters.

Further details are provided in Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses.

12. EXPLORATORY EXPOSURE-EFFICACY RESPONSE ANALYSIS

If deemed appropriate an exposure-efficacy response analysis for the change from baseline in total endoscopic NP score and change from baseline in mean nasal obstruction VAS score during the 52-week study treatment period and subsequent washout period to Week 60 will be conducted.

12.1. Population of Interest

The exploratory exposure-efficacy response analysis will be performed on the ITT population.

12.2. Endpoints

Three measures of exposure will be considered for this analysis:

i) Dose/bodyweight (Week 52 endpoints only)

ii) C_{52} = week 52 mepolizumab trough concentration (Week 52 endpoints only)

iii) Predicted individual concentration during the treatment and washout phase (all observations)

Summary exposures (i) and (ii) will be categorised by quartiles for categorical analysis.

12.3. Methodology

12.3.1. Statistical analysis using exposure quartiles

12.3.1.1. Statistical Methodology Specification

Endpoint / Variables
• Change from baseline in total endoscopic NP score (based on centrally read data) at Week 52 and other defined visits, categorized for analysis as in Section 7.1.5.1. • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52, and other defined 4-week periods, categorized for analysis as in Section 7.1.5.1.
Model Specification
• Each co-primary endpoint will be analyzed using ordinal logistic regression to compare the odds between treatment exposure quartiles to placebo of being in a more favorable endpoint category. • Odds ratios will be estimated from the ordinal logistic regression model using the observed marginal distribution of the sample covariates. • The analysis model will include the following terms:

Fixed Categorical:	Region

Fixed Continuous:	Treatment (placebo and exposure quartiles), Baseline score, Log_e baseline blood eosinophil count

- Participants with missing covariate information will be excluded from the analysis

Model Checking & Diagnostics

- Models will be checked for issues with convergence.

Model Results Presentation

- The number and percentage of patients in each quartile will be displayed, as will the estimated odds ratio and 95% CI comparing quartiles from the ordinal logistic regression model.
- A forest plot of the estimated odds ratio and 95% CI for the comparison of quartiles will be provided.

Subgroup Analyses

- No subgroup analyses are planned for this endpoint

Sensitivity and Supportive Analyses

- No subgroup analyses are planned for this endpoint

13. REFERENCES

GlaxoSmithKline Document Number 2015N238436_00 Study ID N/A. A population PK and PKPD meta-analysis of combined intravenous and subcutaneous mepolizumab data. Report Date 27-MAY-2015.

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Hopkins S., Gillet, S., Slack, R., Lund, V.J., Browne, J.P. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin. Otolaryngol.* 2009;34:447-454.

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McCullagh P. Regression models for ordinal data. Journal of the Royal Statistical Society, Series B. 1980;43:109-142. Relevant CDISC documentation available on www.cdisk.org

14. APPENDICES

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

14.1.1. Exclusions from Per Protocol Population

Participants with protocol deviations considered to potentially effect efficacy will be excluded from the Per Protocol (PP) population. Determination of exclusion of a participant from the Per Protocol population will be made, where possible, before the database is frozen.

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

Number	Exclusion Description
01	Informed consent never signed
02	Does not meet at least one of the following inclusion criteria (as numbered in the protocol): 1. 18 years of age and older inclusive, at the time of signing the informed consent. 4. Participants who have had at least one previous surgery in the previous 10 years for the removal of NP. 5. Participants with bilateral NP as diagnosed by endoscopy or historical CT scan. 6. Presence of at least two different symptoms for at least 12 weeks prior to screening: nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and at least one of the following: nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell. 7. Participants with severe NP symptoms defined as an obstruction VAS symptom score of >5. 8. Severity consistent with a need for surgery as described by: a) Participants with an overall VAS symptom score >7 b) Participants with an endoscopic bilateral NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) 9. Treatment with INCS (including intranasal liquid steroid wash/douching) for at least 8 weeks prior to screening. 10. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
03	Meets any of the following exclusion criteria (as numbered in the protocol) 1. As a result of medical interview, physical examination, or screening investigation the physician responsible considers the participant unfit for the study. 2. Cystic fibrosis. 3. Eosinophilic granulomatosis with polyangiitis (also known as Churg Strauss syndrome), Young's, Kartagener's or dyskinetic ciliary syndromes. 4. Antrochoanal polyps. 5. Nasal septal deviation occluding one nostril. 6. Acute sinusitis or upper respiratory tract infection (URTI) at screening or in 2 weeks prior to screening. 7. Ongoing rhinitis medicamentosa (rebound or chemical induced rhinitis). 8. Participants who have had an asthma exacerbation requiring admission to hospital within 4 weeks of Screening.

Number	Exclusion Description
	9. Participants who have undergone any intranasal and/or sinus surgery (for example polypectomy, balloon dilatation or nasal stent insertion) within 6 months prior V1. 12. Participants with a known, pre-existing parasitic infestation within 6 months prior to Visit 1. 13. Participants who are currently receiving or have received within 3 months (or 5 half-lives – whatever is the longest) prior to screening visit, radiotherapy or investigational medications/therapies. 14. Participants with a history of sensitivity to any of the study medications, or components thereof or a history of drug or other allergy that, in the opinion of the investigator or GSK Medical Monitor, contraindicates their participation. Aspirin-sensitive participants are acceptable. 15. Participants with a history of allergic reaction to anti-IL-5 or another monoclonal antibody therapy. 17. Participants that have taken part in previous mepolizumab, reslizumab, dupilumab or benralizumab studies. 18. Use of systemic corticosteroids (including oral corticosteroids) within 4 weeks prior to screening or planned use of such medications during the double-blind period. 19. INCS dose changes within 1 month prior to screening. 20. Treatments with biological or immunosuppressive treatment (other than Xolair) treatment within 5 terminal phase half-lives of Visit 1. 21. Omalizumab (Xolair) treatment in the 130 days prior to Visit 1. 22. Commencement or change of dose of leukotriene antagonist treatment less than 30 days prior to Visit 1. 23. Commencement or change of dose of allergen immunotherapy within the previous 3 months. 28. Immunocompromised, other than that explained by the use of corticosteroids taken as therapy.
04	Does not meet any of the following randomisation criteria (as numbered in the protocol): 1. Endoscopic NP score of at least 3 in one nostril and 2 in the other as per over read from central lab taken at Visit 1. 2. Mean overall VAS >7 over the last 7 days preceding Visit 2 (excluding Visit 2) (from eDiary). 3. Mean nasal obstruction VAS score >5 over the last 7 days preceding Visit 2 (excluding Visit 2) (from eDiary). 4. Not had any NP surgery or have been included into a waiting list for NP surgery between Visit 1 and Visit 2. 5. eDiary compliance for VAS (4 out of the last 7 days preceding Visit 2). 8. Asthma Exacerbation: No asthma exacerbations during run-in period. An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids (i.v. or oral steroid) for at least 3 days or a single IM CS dose and/or emergency department visit, or hospitalization. 9. Maintenance Therapy: No changes or commencement during the run-in period in the dose or regimen of any regular baseline medication including a) INCS, b) course of systemic corticosteroids, such as OCS, c) leukotriene receptor antagonists, d) allergen immunotherapy. 10. If the participant has a cold during run in then run in should be extended so to have the baseline visit, 2 weeks post the resolution of the cold but no greater than a total of 6 weeks from screening. Colds that are not resolved within the 4th week of the nominal run-in period (28 days after screening) will be ineligible for randomization as they would have exceed this

Number	Exclusion Description
	6 week period.
05	Use of any prohibited medication during the study [1]
06	Received the wrong study treatment at any point during the study
07	Two or more of the following deviations related to wrong study treatment/administration/dose: • Study treatment not administered per protocol • Study treatment administered while contraindication • Expired study treatment administered • Use of study treatment impacted by a temperature excursion which was not reported or approved, or which was disapproved for further use • Study treatment not available at site for administration • Missed dose • Other deviations related to wrong study treatment/administration/dose
08	Patient/Investigator unblinded

NOTES:
[1] See Section 7.6 of protocol for a list of prohibited medications

14.2. Appendix 2: Schedule of Activities

14.2.1. Protocol Defined Schedule of Events

		Pre screen[9]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ± 7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
Screening/ baseline	Informed consent[15]	X							
	Concurrent medication review (including INCS)	X	X						
	Inclusion and exclusion criteria		X						
	Demography	X							
	Full physical exam including height and weight		X						
	Medical history (including past and present medical conditions, substance usage family history of premature CV disease) and asthma exacerbation		X						
	History of HIV and Hep B and Hep C screen		X						
	Parasitic screening[10]		X						
	Medication History including INCS and OCS use for NP		X						
	History of NP surgery		X						
	Screening 12-lead ECG		X						

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	Procedure	Pre screen[3]	Screening [3]	Treatment Phase			No treatment Follow[6]		
Visit		**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ± 7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Screening Vital signs		X						
	Dispense "Medical Problems and Medication Taken Worksheet'	X	X						
	Collect "Medical Problems and Medication Taken Worksheet'		X						
	SAE review		X						
	Assessment of endoscopic NP score		X						
	Overall VAS symptom score and VAS for nasal obstruction to be captured on eDiary after training		X						
	Screening Laboratory assessments (include liver chemistries)		X						
	Screening Urinalysis		X						
	Urine pregnancy test (WOCBP only)		X						
	Dispense MF and eDiary		X						
	Register visit	X	X	X	X	X	X	X	X
	Review randomisation criteria			X					

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		Pre screen[9]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ± 7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Randomisation (if applicable)			X					
	Genetic sample (PGX)			X					
Efficacy[11]	Assessment of Surgery (actual and waiting list)			X	X	X	X	X	X
	Assessment of OCS dose and duration			X	X	X	X	X	X
	Overall VAS symptom score [1]			X	X	X	X	X	X
	VAS symptom score for nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain [1]			X	X	X	X	X	X
	SNOT-22 [5]			X	X	X	X	X	X
	SF-36 [5, 7]			X	X[7]	X	X	X	X
	PnIF [2]			X	X	X			
	UPSIT [13]			X	X	X			

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		Pre screen[8]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	**0**	**1**	**2**	**3 -14**	**15**	**16-17**	**18**	**EW Visit**
Study day **(Visit window ± 7 days)**			**(28 days prior to Day 1)**	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Endoscopic NP score [16,17]			X	X[16, 17]	X	X	X	X
	WPAI-SHP [3]			X	X	X	X	X	X
	ACQ – 5[3,5]			X	X	X			X
	Asthma exacerbation			X	X	X			X
	Blood for PK[4]			X	X	X	X[9]		X
	Blood for biomarkers			X		X			
Safety	AE/SAE review			X	X	X	X	X	X
	Dispense "Medical Problems and Medication Taken Worksheet"			X	X	X	X	X	
	Collect "Medical Problems and Medication Taken Worksheet"		X	X	X	X	X	X	X
	Concurrent medication review (including INCS)			X	X	X	X	X	X
	12-lead ECG			X		X			X
	Vital signs (HR and BP)			X	X	X			X
	Laboratory assessment: Haematology			X	X	X	X	X	X
	All other Laboratory assessments (including liver chemistries)			X		X			X
	Blood for immunogenicity			X		X	X[9]		X
	Urinalysis			X		X			X
	Urine pregnancy test (WOCBP)			X	X	X			X
Medication/ supplies	Dispense and train on eDiary for run in and remainder of the study		X						

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		Pre screen[8]	Screening [8]	Treatment Phase			No treatment Follow[6]		
Visit	Procedure	0	1	2	3 -14	15	16-17	18	EW Visit
Study day **(Visit window ± 7 days)**			(28 days prior to Day 1)	1	**29, 57, 85, 113, 141, 169, 197, 225, 253, 281, 309, 337**	**365**	**421, 477**	**533**	**28 days post last visit**
Week				0	4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48	52	60, 68	76	
	Review and re train on eDiary (if required)			X	X	X	X	X	X
	eDiary completion [12]			X	X	X	X	X	X
	Review compliance and dispense MF			X	X	X[14]	X	X[14]	X[14]
	Dosing with study drug (active/ placebo)			X	X				
	Collect eDiary for the first 200 randomized participants							X	X
	Collect eDiary for remainder of the participants					X			X

1. Performed daily on the electronic Diary.
2. Performed monthly at study visits
3. For asthmatic participants only
4. Blood for PK will be collected at pre dose Visit 2 (baseline) and then pre dose at Visits 3, 15 and 17
5. Performed at site during study visits
6. For approximate up to the first 200 randomized participants
7. SF36 at visits 3, 5, 7, 9, 11, 13, 15, 16, 17 and 18 only
8. Pre screening and screening can be performed on the same day
9. At Visit 17 only
10. Parasitic screening is only required in countries with high-risk or for participants who have visited high-risk countries in the past 6 months. Sites should use local laboratories
11. All questionnaires will be performed before any other assessments on each particular visit, VAS scores, SNOT-22, SF-36 and WPAI

12. eDiary completion by participants will be daily every morning between screening visit and Visit 18 (or EW if appropriate) for the first 200 randomized participants or between screening and Visit 15 (or EW if appropriate) for the remainder of the participants.
13. UPSIT performed at Visits 2, 3, 5, 7, 9, 11, 13, 15 NB: UPSIT test will be performed only in selected countries
14. Dispensing of MF is not required if study 15, 18 or EW is the last study visit
15. PGx informed consent can be performed anytime prior sampling
16. The endoscopy assessment may be performed up to 3 days prior to the day of dosing but must not exceed the protocol defined windows of ± 7 days from the nominal study visit.
17. Endoscopy NP score assessment will be performed at visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 17, 18 and EW

- Abbreviations: ACQ, - Asthma Control Questionnaire; ECG – Electrocardiogram; EW- Early Withdrawal ; MF- mometasone furorate; NP- nasal polyps ; OCS- Oral Corticosteroids; PD- Pharmacodynamic ; PK- Pharmacokinetic ; PnIF- Peak Nasal Inspiratory Flow; SNOT- Sino-Nasal Outcome Test; SF-36 - Short Form Health Survey 36; UPSIT - University of Pennsylvania Smell Identification Test; VAS- Visual Analogue Scale; WOCBP -women of child bearing potential ; WPAI- Work Productivity and Activity Impairment
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

14.3. Appendix 3: Assessment Windows

14.3.1. Visit Based Assessments

No assessment windows are defined for visit based assessments. Clinic visits are scheduled to take place as specified in Appendix 2: Schedule of Activities and are subject to a ± 7-day window, however assessments performed outside of these visit windows will still be included in any analyses. Nominal visits will be used for reporting and analysis.

14.3.2. Unscheduled Visits

Data recorded at an unscheduled visit will be re-assigned to the closest nominal visit at which collection of the data was scheduled, unless information already exists at that visit. If an unscheduled visit occurs between two scheduled visits for which data has been reported, the data will remain in the unscheduled visit and will not be included in any by visit summary tables; it will however be included in relevant summaries of any time post-baseline data and listings.

14.3.3. Data from eDiary

The overall severity of nasal polyposis and of individual symptoms of nasal polyposis will be collected daily on a visual analogue scale using an eDiary. For the purposes of analysis, data from the eDiary will be slotted as shown in Table 2.

Table 2 Definition of Baseline and Week 52 Periods for eDiary Data

	Analysis Window	
Analysis Timepoint	**Beginning Timepoint**	**Ending Timepoint**
Baseline	Date of First Dose - 7	Date of First Dose -1
Weeks 1-4	Later of: Date of Visit 3 (Week 4) – 28 Date of First Dose + 1	Date of Visit 3 (Week 4) - 1
Weeks 5-8	Later of: Date of Visit 4 (Week 8) – 28 Date of Visit 3 (Week 4)	Date of Visit 4 (Week 8) - 1
Weeks 9-12	Later of: Date of Visit 5 (Week 12) – 28 Date of Visit 4 (Week 8)	Date of Visit 5 (Week 12) -1
Weeks 13-16	Later of: Date of Visit 6 (Week 16) – 28 Date of Visit 5 (Week 12)	Date of Visit 6 (Week 16) -1
Weeks 17-20	Later of: Date of Visit 7 (Week 20) – 28 Date of Visit 6 (Week 16)	Date of Visit 7 (Week 20) - 1
Weeks 21-24	Later of: Date of Visit 8 (Week 24) – 28 Date of Visit 7 (Week 20)	Date of Visit 8 (Week 24) - 1
Weeks 25-28	Later of:	Date of Visit 9 (Week 28) - 1

	Analysis Window	
Analysis Timepoint	**Beginning Timepoint**	**Ending Timepoint**
	Date of Visit 9 (Week 28) – 28 Date of Visit 8 (Week 24)	
Weeks 29-32	Later of: Date of Visit 10 (Week 32) – 28 Date of Visit 9 (Week 28)	Date of Visit 10 (Week 32) - 1
Weeks 33-36	Later of: Date of Visit 11 (Week 36) – 28 Date of Visit 10 (Week 32)	Date of Visit 11 (Week 36) - 1
Weeks 37-40	Later of: Date of Visit 12 (Week 40) – 28 Date of Visit 11 (Week 36)	Date of Visit 12 (Week 40) - 1
Weeks 41-44	Later of: Date of Visit 13 (Week 44) – 28 Date of Visit 12 (Week 40)	Date of Visit 13 (Week 44) - 1
Weeks 45-48	Later of: Date of Visit 14 (Week 48) – 28 Date of Visit 13 (Week 44)	Date of Visit 14 (Week 48) - 1
Weeks 49-52 (Primary timepoint for analysis)	Later of: Date of Visit 15 (Week 52) – 28 Date of Visit 14 (Week 48)	Date of Visit 15 (Week 52) - 1
Weeks 53-56	Later of: Date of Visit 16 (Week 60) – 56 Date of Visit 15 (Week 52)	Date of Visit 16 (Week 60) - 29
Weeks 57-60	Date of Visit 16 (Week 60) - 28	Date of Visit 16 (Week 60) - 1
Weeks 61-64	Later of: Date of Visit 17 (Week 68) – 56 Date of Visit 16 (Week 60)	Date of Visit 17 (Week 68) - 29
Weeks 65-68	Date of Visit 17 (Week 68) - 28	Date of Visit 17 (Week 68) - 1
Weeks 69-72	Later of: Date of Visit 18 (Week 76) – 56 Date of Visit 17 (Week 68)	Date of Visit 18 (Week 76) - 29
Weeks 73-76	Date of Visit 18 (Week 76) - 28	Date of Visit 18 (Week 76) - 1

NOTES:

- Data collected on Day 1 (Date of first dose) will not be used in analysis/summaries
- Analysis periods will be up to a maximum of 28 days
- Where a missing visit date prevents the start or end of a period from being determined, an imputed date (Date of First Dose + Week of Visit with missing date x 7) will be used.

14.3.4. Premature Withdrawals from Interventional Product or Study

Any data reported at the early withdrawal visit will be re-assigned to the closest available scheduled visit, unless information already exists at that visit. Data reported at the early withdrawal visit which has been re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Data reported at the early

withdrawal visit will be included in the assessment of maximum or worst-case post-baseline summaries for any relevant endpoints, and all data will be included in listings.

14.4. Appendix 4: Study Phases

14.4.1. Study Phases

Assessments and events will be classified according to the time of occurrence relative to the first dose of interventional product.

14.4.1.1. Phases for Efficacy Assessments

Study Phase	Definition
Pre-Treatment	Assessment Date ≤ Interventional Product Start Date
On-Treatment	Participants who did not withdraw early from Interventional Product: Interventional Product Start Date < Assessment Date ≤ Earlier of Week 52 Visit Date/Day 372[1] Participants who withdrew early from Interventional Product: Interventional Product Start Date < Assessment Date ≤ Earlier of Interventional Product Stop Date +28 days/Date of Phase Conclusion
Off-Treatment	Participants who did not withdraw early from Interventional Product: Day 372 < Assessment Date ≤ Week 52 Visit Date Participants who withdrew early from Interventional Product: Interventional Product Stop Date + 28 days < Assessment Date ≤ Date of Phase Conclusion
Off-Treatment (Follow-up after Week 52)	Participants who enter the follow-up period after Week 52: Week 52 Visit Date < Assessment Date
[1] Allowing for the ±7-day window in the protocol; Day 372 is defined as 371 days (364+7 days) after the first dose of interventional product	

14.4.1.2. Phases for Safety Assessments

Study Phase	Definition
Pre-Treatment	Assessment Date ≤ Interventional Product Start Date
On-Treatment	Interventional Product Start Date < Assessment Date ≤ Interventional Product Stop Date +28 days
Post -Treatment	Participants who do not enter the follow-up period after Week 52: Interventional Product Stop Date + 28 days < Assessment Date Participants who enter the follow-up period after Week 52: Interventional Product Stop Date + 28 days < Assessment Date ≤Week 52 Visit Date
Post -Treatment (Follow-up after Week 52)	Participants who enter the follow-up period after Week 52: Week 52 Visit Date < Assessment Date

14.4.1.3. Phases for Adverse Events

Study Phase	Definition
Pre-Treatment	Event Start Date < Interventional Product Start Date
On-Treatment	Interventional Product Start Date ≤ Event Start Date ≤ Interventional Product Stop Date + 28 days
Post -Treatment	Participants who do not enter the follow-up period after Week 52: Event Start Date > Interventional Product Stop Date + 28 days Participants who enter the follow-up period after Week 52: Interventional Product Stop Date + 28 days < Event Date ≤Week 52 Visit Date
Post -Treatment (Follow-up after Week 52)	Participants who enter the follow-up period after Week 52: Week 52 Visit Date < Event Date

NOTES: An event will be considered On-treatment if the event start date is missing and/or the interventional product stop date is missing
Where time of event is recorded, the time of event and time of first dose will be considered to differentiate between Pre-treatment and On-treatment events.

14.4.1.4. Phases for Concomitant Medication Start Dates

Study Phase	Definition
Pre-Treatment (Started prior to treatment)	Concomitant medication (CM) start date < IP start date
On-Treatment (Started during Treatment)	If CM start date is on/after IP start date & on/before IP stop date +28 days. (IP Start Date ≤ CM Start Date ≤ IP Stop Date + 28 days)
Post-Treatment (Started post-treatment)	If CM start date is after the IP stop date + 28 days. (CM Start Date > IP Stop Date + 28 days)
Follow-Up After Week 52 (started during the Follow-up period after Week 52)	Participants who enter the follow-up period after Week 52: If CM start date is after the Week 52 Visit date.

NOTES: If the IP stop date is missing and/or the CM start date is missing then the CM is considered to have started on-treatment

14.4.1.5. Phases for Concomitant Medication Usage Dates

Study Phase	Definition
Taken Prior to Treatment	If CM start date < IP Start Date
Taken During Treatment	If CM start date < IP start date and CM stop date ≥ IP start date If IP start date < CM start Date < IP Stop Date + 28 days
Taken Post-Treatment	If CM start date < IP stop date+28 days and CM stop date ≥ IP stop date +28 days If CM start Date > IP stop date + 28 days

NOTES: If the IP stop date is missing and CM start date is on/after IP start date then CM considered taken during treatment

If CM start date is missing, then CM considered to be taken during treatment

14.5. Appendix 5: Data Display Standards & Handling Conventions

14.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	PPD
HARP Compound	
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards [SDTM IG Version 3.2 & ADaM IG Version 1.0]. • Analysis datasets will include variables to clearly indicate whether each observation was observed while the patient was on randomized treatment, observed after the patient discontinued randomized treatment, or was imputed or is missing.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

14.5.2. Reporting Standards

General

• All data displays (Tables, Figures & Listings) will use the term "Subject" rather than "Participant" which reflects CDISC and GSK Data Display Standards terminology.
• Templates and standards within the current GSK Integrated Data Standards Library (IDSL) will be used for reporting unless otherwise stated.
IDSL standards located at https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx (under supporting documentation/component/statistical displays) will be applied:
  • 4.03 to 4.24: 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

Formats

• GSK IDSL Statistical Principles for the precision to which data and summary statistics are to be presented will in general be adopted, these may be adjusted to a clinically interpretable number of decimal places (d.p.).
  • For Blood Eosinophil Counts displayed as GI/L the following will be applied:
  Geometric Mean, Median, Min and Max (2 d.p.); SD Logs (3 d.p.)

Planned and Actual Time

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

Unscheduled Visits
• Unscheduled visits will not be included in summary tables and/or figures, however they will be included in listings. • Data from unscheduled visits may be included in summary tables/figures when the unscheduled visit has been reassigned (Section 14.3.2). • Data from unscheduled visits will be included in any-time post-baseline summaries
Early Withdrawal from Interventional Product or from Study
• Data recorded at the early withdrawal visit will be re-assigned to the next scheduled visit, unless information already exists at that visit. Early withdrawal data re-assigned to a scheduled visit will be included in analyses, summary tables and figures by scheduled visit. Early withdrawal visit data that is not re-assigned to a scheduled visit will not be included in analyses, summary tables or figures by scheduled visit. • Data recorded at early withdrawal visits will be included in the assessment of maximum or worst-case post-baseline for relevant endpoints. • Data from all early withdrawal visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	n, mean, standard deviation or standard error, median, minimum, maximum
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals for Graphics	

14.5.3. Reporting Standards for Pharmacokinetic Data

Pharmacokinetic Concentration Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1. Note: BLQ concentration values will be imputed as per GUI_51487 for descriptive summary statistics only.
NONMEM/Pop PK File	Pop-PK file (CSV and SAS format) for the POP-PK and POP-PKPD analyses performed by the Clinical Pharmacology Modelling and Simulation function will be created according to the POP-PKPD Dataset Specification document.
Pharmacokinetic Parameter Data	
Descriptive Summary Statistics, Graphical Displays and Listings	Refer to IDSL PK Display Standards. Refer to IDSL Statistical Principle 6.06.1.

14.6. Appendix 6: Derived and Transformed Data

14.6.1. General

Multiple Measurements at One Analysis Time Point
• Unless otherwise specified, if there are multiple measurements reported under the same nominal visit, the value of the first assessment will be used in any derivation of summary statistics, all individual measurements will be presented in any data listings. • Participants with post-baseline safety data in both High and Low categories with respect to the Normal Range/Potential Clinical Concern will be counted in each of the categories for the "Any visit post-baseline" row of any related summary tables.
Study Day

• Calculated as the number of days from the first dose of study medication (IP start date).
  • If Visit Date = Missing → Study Day = Missing
  • If Visit Date < First Dose Date → Study Day = Visit Date – IP Start Date
  • If Visit Date ≥ First Dose Date → Study Day = Visit Date – (IP Start Date) + 1

14.6.2. Analysis Population

Actual Treatment for Safety Population
• Analysis of safety data will be by actual treatment arm. • For participants identified as having any discrepancies between the treatment group they were randomised to and the treatment received, the actual treatment arm will be derived based on the treatment received for more than 50% of all treatment administrations. For all other participants, actual treatment arm will be the same as the randomised treatment arm.

14.6.3. Study Population

Demographics
Age
• Year of birth is collected as 'YYYY' and will be presented as collected in listings • Date of birth will be imputed as '30th June YYY' • Age is calculated according to GSK standard IDSL algorithms and is based on the imputed date of birth relative to the date of Visit 1 (Screening).
BMI
• BMI will be calculated as Weight (kg) / [Height (m)]^2

Exposure
Extent of Exposure (Therapeutic Coverage)

• IP is administered approximately every 4 weeks and each dose viewed as providing therapeutic coverage for 4 weeks (28 days).
• Duration of exposure is calculated based on the therapeutic coverage as follows:
  ○ Duration of Exposure (days) = (IP Stop Date – IP Start Date + 29)
  ○ Duration of Exposure (months) = (IP Stop Date – IP Start Date + 29) * 12/365.25

Exposure
Extent of Exposure (Therapeutic Coverage)
• Subject Years Exposure is calculated as follows;   o Subject Years Exposure = (IP Stop Date – IP Start Date + 29)/365.25 • If the IP start date is missing and there is evidence the participant received at least one dose of IP, the IP start date will be taken to be the date of randomisation, if the IP end date is missing it will be taken to be the last on-treatment visit attended. • Randomised participants with no evidence of receiving at least one dose of IP will be considered as having zero days of exposure.

Exposure for treatment period and no-treatment follow-up
Number of years on and off-treatment or missing

• All participants are expected to participate in the study for at least 52 weeks (±7 days)
• The number of years on-treatment will be calculated as follows:
  o (IP Stop Date – IP Start Date + 29)/365.25
• The number of years off-treatment will be calculated as follows:
  o Date of Phase Conclusion – (IP stop date +29)/365.25
• The number of years missing will be calculated as follows:
  o 371/365.25 – (number of years on-treatment) – (number of years off-treatment)

Duration of time in no-treatment follow-up
• This will be calculated in months as follows: o (Date of study end – Date of entering no-treatment follow up)/30.5

Concomitant Medications (CM)
Time since first dose (days)
• The time since first dose will be calculated as follows: If CM start date < IP start date = CM start date - IP start date If CM start date ≥ IP start date = CM start date – IP Start Date +1 Missing otherwise. • The duration in days will be calculated as follows: CM end date – CM start date + 1

NOTES: Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates

Subgroups
Participants With Asthma
• Concurrent asthma: Subjects with a response of 'Current' for the medical condition of 'Asthma'. • No concurrent asthma: Subjects with a response of 'Past', 'Not Assessed' or 'No Medical Condition' for the medical condition of 'Asthma'. Subjects with a missing response will also be included in this category.
Aspirin Exacerbated Respiratory Disease (AERDS)
• Current AERDS: Subjects with a response of 'Current' for the medical condition of 'Drug Allergy'.

Subgroups

- No Current AERDS: Subjects with a response of 'Past', 'Not Assessed' or 'No Medical Condition' for the medical condition of 'Drug Allergy'. Subjects with a missing response will also be included in this category.

Number of previous surgeries

- Participants will be categorised as follows based on data collected on the eCRF regarding number of previous surgeries: 1, 2, >2

Baseline Blood Eosinophil Categories

- Categories for baseline blood eosinophils will be:
    - ≤0.3 GI/L; >0.3 to ≤0.5 GI/L; >0.5 to ≤0.7 GI/L; >0.7 GI/L
- Blood eosinophils are reported in GI/L, each category is rounded to 1 d.p. which is equivalent to rounding blood eosinophils to the nearest 100 cells/µL.

Region

- Europe: Participants from sites in Germany, Netherlands, Romania, Sweden, UK
- United States: Participants from sites in US
- Rest of World: Participants from sites in South Korea, Argentina, Australia, Canada, Russia

Age Categories

- Participants will be categorised as follows based on the derived age:
- 18-<40 years, 40 - < 65 years, ≥65 years.

Race Categories

- Subjects will be categorised by Race based on the Geographic Ancestry reported on the eCRF:

Race Category	Geographic Ancestry reported on the eCRF
African American/African Heritage	African American/African Heritage
White	White – Arabic/North African Heritage White – White/Caucasian/European Heritage
Asian	Asian – Central/South Asian Heritage Asian – East Asian Heritage Asian – Japanese Heritage Asian – South East Asian Heritage
Other	American Indian or Alaskan Native Native Hawaiian or Other Pacific Islander Multiple Race

14.6.4. Change from Baseline

Definition	Reporting Details
Change from Baseline	= Post-Dose Visit Value – Baseline
% Change from Baseline	= 100 x [(Post-Dose Visit Value – Baseline) / Baseline]
Ratio to Baseline [1]	= Post-Dose Visit Value / Baseline

NOTES: Refer to Section 5.2 for definition of Baseline. Unless otherwise stated, if Baseline or the Post-Dose value is missing the result will be set to missing.
[1] For $\log_e$ transformed data Ratio to Baseline is the back transformed change from baseline value

14.6.5. Efficacy

Total Endoscopic Nasal Score
Change from baseline categories
• Categories for the change from baseline total endoscopic nasal score (centrally read) are detailed in Section 7.1.5.1, the same categories will be used for the investigator read scores.
Responder
• A responder will be defined as a participant with a ≥1-point improvement from baseline in total endoscopic nasal score (centrally read). • Participants with no improvement/worsening or with missing data will be considered a non-responder for analysis.

VAS scores (individual and composite)
Individual VAS Scores
• VAS scores are captured electronically using an eDiary, participants indicate their response on a line CCI [redacted] • The final VAS scores for inclusion in summary and analysis tables will be derived from the electronically captured score by CCI [redacted].
Change from baseline categories
• Categories for the change from baseline in individual, overall and composite VAS scores are detailed in Section 7.2.2.4. • The baseline scores will be calculated as the mean of the scores reported between the 7 days prior to the first dose. • The scores for each 4-week period will be calculated as the mean of the scores reported between timepoints detailed in Section 14.3.3.
Composite VAS scores

• Two separate composite VAS scores will be derived using the final VAS scores:
• Composite of nasal obstruction, nasal discharge, mucus in the throat and loss of smell
  ○ CCI [redacted]
• Composite of nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain
  ○ CCI [redacted]

Nasal Surgery (reported on the disease related events page of the eCRF)
Time to first nasal surgery
• Calculated as (Date of first nasal surgery – Date of first dose of study treatment) + 1 • Analysis excluding data from the follow-up period after Week 52: For participants who withdraw from the study before Week 52 and before experiencing surgery, event times will be censored at the time of study withdrawal For participants who complete to Week 52 without experiencing surgery, event times will be censored at the time of the Week 52 visit. • Analysis including data from the follow-up period after Week 52: For participants who withdraw from the follow-up period before completion and before experiencing surgery, event times will be censored at the time of study withdrawal. For participants who complete the follow-up period without experiencing surgery, event times will be censored at time of completion of follow-up.
Need for surgery(responder)
• Need for surgery at Week 52 is based on the overall VAS symptoms score and the endoscopic NP score (centrally read). Participants will be classified as not having a need for surgery if they meet the following: o Overall VAS symptoms score >7 (Weeks 49-52) and total endoscopic NP score ≥5 (Week 52, centrally read) • Participants who have undergone nasal polyps surgery at any time prior to the week 52 visit, or who have a missing endoscopic NP score (centrally read) at Week 52, or missing overall VAS symptom score (Weeks 49-52) will be identified for analysis as still having a need for surgery.
Rate of surgery
• The crude rate of surgery will be presented for each treatment arm, this will be calculated as: $\left(\frac{\text{Total number of nasal surgeries}}{\text{Total number of days in the study}}\right)$*365.25

Systemic steroid use
Conversion of glucocorticoid dose to mgs of prednisolone equivalent OCS use
• The total number of mgs of prednisolone equivalent OCS use per year will be calculated as follows and will be based on systemic steroids taken via the following routes: Oral, Intravenous, Intramuscular: $\left(\frac{\text{Total cumulative mgs prednisolone-equivalent OCS use in period}}{\text{Total number of days in period}}\right)$*365.25

Systemic steroid use

- The following table from the study reference manual will be used for conversion of intravenous and oral steroid use into prednisolone equivalent OCS use in mgs:

Glucocorticoid	Approximate equivalent dose (mg)
Short-Acting	
Cortisone	25
Hydrocortisone	20
Intermediate-Acting	
Methylprednisolone	4
Prednisolone	5
Prednisone	5
Triamcinolone	4
Long- Acting	
Betamethasone	0.6-0.75
Dexamethasone	0.75

- Participants who withdraw early from the study will have yearly use estimated based on use during the study.

Milligrams of use per year

- Categories of total mgs prednisolone equivalent OCS dose used per year are detailed in Section 7.2.4.4.

Courses of Therapy

- A course of systemic steroid therapy is defined by the start and stop date of therapy.
- If the start date of a course of systemic steroid therapy occurs <7 days from the stop date of the previous course, it will be considered a continuation of the same course.

Days on Therapy

- The duration of a course of systemic steroids will be calculated as the number of days between the start and stop date of the course: stop date – start date +1

- For each participant the total number of days on systemic steroids will be calculated as the sum of the duration of each of their courses of therapy.

- For each participant the percentage of days on systemic steroids will be calculated as follows:

$$\left(\frac{\text{Total number of days on systemic steroids}}{\text{Total number of days in the study}}\right)*100$$

Nasal Surgery or Course of Systemic Steroids
Time to first nasal surgery or course of systemic steroids
• Calculated as (Date of first nasal surgery/course of systemic steroids – Date of first dose of study treatment) + 1 • Analysis excluding data reported in the follow-up period after Week 52: For participants who withdraw from the study before Week 52 and before experiencing either event, event times will be censored at the time of study withdrawal For participants who complete to Week 52 without experiencing either event, event times will be censored at the time of the Week 52 visit
Antibiotic Use
Courses of Therapy
• A course of antibiotics is defined by the start and stop date of therapy. • If the start date of a course of antibiotics occurs <7 days from the stop date of the previous course, it will be considered a continuation of the same course.

SNOT-22
SNOT-22 Total Score
• Each question of the SNOT-22 is graded on CCI [redacted] [Hopkins, 2009]. • CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded. [redacted] • If a participant does not complete any questions at a visit the total score for that visit will be missing. • If a participant has some (but no more than 50%) missing responses to questions at a visit, then the missing responses will be imputed with the unrounded mean of the non-missing responses at that visit. The SNOT-22 total score for that visit will then be rounded to the nearest integer.
Change from baseline categories
• Categories for the change from baseline in SNOT-22 total score are detailed in Section 7.2.3.4.
SNOT-22 Responder
• A responder is defined as having a ≥9-point improvement (decrease) from baseline in SNOT-22 total score.

UPSIT
UPSIT total score
• The total score is calculated as the number of times the correct smell is identified out of a possible 4 choices, for 40 different smells.
Change from baseline categories
• Categories for the change from baseline in UPSIT total score are detailed in Section 7.3.8.4.

ACQ-5
ACQ-5 Score
• ACQ-5 is a 5-item questionnaire developed as a measure of patient's asthma control. Response

ACQ-5
options for each question are on CCI [redacted] • The questions are equally weighted, and the ACQ-5 score is calculated as the mean of the 5 questions, CCI [redacted]. • For a given visit, if the response to one of the 5 questions is missing then the ACQ-5 score will be calculated as the mean of the available responses. If the response to more than one question is missing, then the ACQ-5 score will be set to missing.

Asthma exacerbations
Clinically significant asthma exacerbation
• A clinically significant asthma exacerbation is defined as a worsening of asthma requiring systemic steroids (i.v. or oral) for at least 3 days or a single intra-muscular corticosteroid dose, and/or an ED visit and/or hospitalisation.

14.6.6. Safety

Adverse Events
Drug Related AE's
• AEs where the response to "Is there a reasonable possibility that the AE may have been caused by the Study Treatment?" is "Yes" or it is missing
AE's Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study
• AE's leading to permanent discontinuation of study treatment are defined as AEs where the response to "Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the AE" is "Study Treatment(s) Withdrawn". • AEs leading to withdrawal from study are defined as AEs where the response to "Did the subject withdraw from study as a result of this AE?" is "Yes".
AE's on Day of Dosing
• These are defined as AEs with an onset date on the same day as dosing with interventional product and an onset time on or after the time of dosing with interventional product on the given day.
AE Time Since First Dose
• If AE onset time is missing, calculate in days as follows: o If AE start date < Date of first dose of Interventional Product, then Time since first dose = AE start date - Date of first dose of Interventional Product o If AE start date ≥ Date of first dose of Interventional Product, then Time since first dose = AE start date – Date of first dose of Interventional Product +1 o If AE start date or date of first dose of Interventional Product is missing time since first dose is missing. • If AE onset time is present, calculate as above but in days, hours, minutes using AE start date/time and date/time of first dose of interventional product
AE Duration in Days
• If AE onset time is missing calculate in days: AE end date - AE start date + 1 • If AE onset time is present calculate in days, hours, minutes as above but using AE end date/time and AE start date/time. • If AE start/end date is missing duration is missing.

Adverse Events
Drug Related AE's
• AEs where the response to "Is there a reasonable possibility that the AE may have been caused by the Study Treatment?" is "Yes" or it is missing
AE's Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study
• AE's leading to permanent discontinuation of study treatment are defined as AEs where the response to "Most Clinically Significant Action Taken with Study Treatment(s) as a Result of the AE" is "Study Treatment(s) Withdrawn". • AEs leading to withdrawal from study are defined as AEs where the response to "Did the subject withdraw from study as a result of this AE?" is "Yes".
AE's on Day of Dosing
• These are defined as AEs with an onset date on the same day as dosing with interventional product and an onset time on or after the time of dosing with interventional product on the given day.
AE Time Since First Dose
• If AE onset time is missing, calculate in days as follows: o If AE start date < Date of first dose of Interventional Product, then Time since first dose = AE start date - Date of first dose of Interventional Product o If AE start date ≥ Date of first dose of Interventional Product, then Time since first dose = AE start date – Date of first dose of Interventional Product +1 o If AE start date or date of first dose of Interventional Product is missing time since first dose is missing. • If AE onset time is present, calculate as above but in days, hours, minutes using AE start date/time and date/time of first dose of interventional product
AE Duration in Days
• If AE onset time is missing calculate in days: AE end date - AE start date + 1 • If AE onset time is present calculate in days, hours, minutes as above but using AE end date/time and AE start date/time. • If AE start/end date is missing duration is missing.
AE's of Special Interest
• Section 8.2 provides a full list of AEs of special interest for this compound. • AESIs of anaphylaxis reactions, systemic reactions, and local injection site reactions are collected via targeted eCRF. • The AESIs of potential opportunistic infections, malignancies, serious CVT events and serious ischemic events will be identified from a list of relevant preferred terms maintained within a project level reference dataset; created based on the latest version of the MedDRA dictionary available at the time of database freeze for this study (See Program Safety Analysis Plan for additional details).

ECG
Multiple Assessments
• Where multiple assessments are performed at a given time point, the mean value over the replicate assessments will be used for summary statistics; the highest value amongst the individual replicate assessments will be used in the evaluation of the highest post-baseline value.
QTc values
• A single 12-lead ECG machine will be used to assess heart rate and measure PR, QRS, QT and QTc intervals

- QTc(F) will be derived from QT (uncorrected) and RR interval as: $QTc(F) = \frac{QT}{\sqrt[3]{RR/1000}}$
- QTc(B) will be derived from QT (uncorrected) and RR interval as: $QTc(B) = \frac{QT}{\sqrt{RR/1000}}$
- If present the reported QTc value will be included in any summaries, else the derived QTc value will be included.

Categorised QTc values

Individual maximum QTc(F) and QTc(B) values and maximum change from baseline QTc(F) and QTc(B) will be categorised as follows:

	Lower	Upper
QTc Interval (msec)		≤ 450
	> 450	≤ 480
	> 480	≤ 500
	> 500	
QTc Change from Baseline (msec)		≤ 30
	> 30	≤ 60
	> 60	

Laboratory Parameters

Character Values

- If a laboratory value which is expected to have a numeric value for summary purposes has a non-detectable level reported in the database, where the numeric value is missing, but instead a character value starting with '<x' or '>x' (or indicated as less than x or greater than x in the comment field) is present, a numeric value will be imputed; the number of significant digits in the observed value will be used to determine how much to add or subtract to impute the corresponding numeric value:
  - Example 1: 2 Significant Digits = '< x 'imputed as x – 0.01
  - Example 2: 1 Significant Digit = '> x' imputed as x + 0.1
  - Example 3: 0 Significant Digits = '< x' imputed as x –1
- Laboratory values with missing values due to being below the limit of quantification (BLQ) for that parameter will have a value imputed as half the lower limit of quantification for that measure (i.e. the lowest observed value for that measure within the entire study database).
- Values of potential clinical concern and those outside the ≥2, ≥3 etc. limit of normal will be identified as detailed in Section 14.8.

Blood Eosinophils

- Blood eosinophil counts will be log transformed (loge) prior to analysis. The log transformation for values of 0GI/L will be based on a value of 0.005GI/L.

Biomarkers

- No analyses of additional biomarker will be carried out as part of this RAP.

14.7. Appendix 7: Reporting Standards for Missing Data

14.7.1. Premature Withdrawals

Element	Reporting Detail
General	• The protocol objective is to collect data over the full study treatment period (up to Week 52) for all participants, whether they continue on interventional product (IP) and complete Week 52 on-treatment, or whether they withdraw prematurely from IP. o For the participants who withdraw prematurely from IP before Week 52 and agree to the continued collection of data off-treatment, data will be collected for up to 52 weeks after randomization (or up to 76 weeks if the participant enters the Follow-up period after Week 52) either through clinic visits or via phone contact, in accordance with the participants existing visit schedule. o Where available, off-treatment data will be included in the analysis of the co-primary endpoints and, unless otherwise indicated, in the analysis of other efficacy endpoints. • A participant will be considered to have completed study treatment if he/she continues to take study treatment until Visit 14 (Week 48) and completes Visit 15 (week 52). • As specified in the protocol participants will be considered to have completed the study upon completion of Visit 15 (Week 52) regardless of whether they continue to take IP. • A participant eligible for the no-treatment follow-up will be considered to have completed follow-up if they continue to participate in the study until Visit 18 (Week 76) • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified. • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.
Pre-Screen/Screen and Run-in Failures	• Participants are assigned a subject number at the time of signing informed consent. • Pre-Screen Failure: A participant who is assigned a subject number but did not continue through to Visit 1. • Screening Failure: Participant performs a Visit 1 procedure, but does not enter the run-in period • Run-in Failure: Participant enters the run-in period, may perform a Visit 2 procedure, but is not subsequently randomised.

14.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: o These data will be indicated using a “blank” in data listings. Where all data for a specific visit are missing the visit will be excluded from the listing. o Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed. Values reported as ‘BLQ’ are not considered as missing data and are handled as detailed in

Element	Reporting Detail
	Section 14.6.6, these values will be displayed in the listings and included in any summary/analysis outputs.
Outliers	• All data will be included in the summaries and analyses of each endpoint. The exclusion of participants or participant data from any supplementary analyses will be documented within footnotes and where required the clinical study.report.
Covariate information	• Participants with missing information for a covariate included in the analysis model will be excluded from the analysis.

14.7.2.1. Handling of Missing Dates

Element	Reporting Detail
General	Start or end dates which are completely missing (i.e. no day, month or year is specified) will remain missing, with no imputation applied. Derivations requiring this information such as time to onset and duration will be set to missing.

14.7.2.2. Handling of Partial Dates

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

Adverse Events	• The eCRF allows for the possibility of partial dates to be recorded for AE start and end dates.
	• For partial dates the following imputations will be applied:
	  ○ Partial Start Date: '01' will be used for a missing day and 'Jan' will be used for a missing month. If this results in a date prior to the start of study treatment, then the treatment start date will be used. The event will then be considered 'On-treatment' as per Section 14.4.1.3.
	  ○ Partial Stop Date: '28/29/30/31' will be used for a missing day (dependent on the month and year) and 'Dec' will be used for a missing month. If this results in a date after the study stop date, then the study stop date will be used.
	• The above imputations will be applied when calculating the time to onset and duration of the event.

Concomitant Medications	• For concomitant medications partial dates will be imputed as follows:
	  ○ Partial start date: '01' will be used for a missing day and 'Jan' will be used for a missing month
	  ○ Partial stop date: '28/29/30/31' will be used for a missing day (dependent on the month and year) and 'Dec' will be used for a missing month.

14.7.2.3. Missing Data for Statistical Analysis

Element	Reporting Detail
General	• The study is designed to collect data for the 52 weeks following randomisation for all participants, including for participants who prematurely withdraw from interventional product. The following scenarios may arise. 1) Participant completes interventional product and study 2) Participant prematurely withdrawn from interventional product and agrees to continued data collection off-treatment for 52 weeks following randomisation 3) Participant prematurely withdrawn from interventional product and initially agrees to continued off-treatment data collection, but subsequently withdraws from the study prior to 52 weeks following randomisation 4) Participant prematurely withdrawn from interventional product and does not agree to continued off-treatment data collection • For participants under any scenario missing data may arise intermittently due to nonattendance at scheduled visits. For participants under scenarios 3 and 4 missing data will arise due to premature withdrawal from the study. • Unless otherwise specified on-treatment data and where available off-treatment data will be included in the analysis of efficacy endpoints.

14.8. Appendix 8: Values of Potential Clinical Importance

14.8.1. Laboratory Values of Potential Clinical Concern

Haematology				
Laboratory Parameter	**Units**	**Age Category (years)**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
Hematocrit	Ratio of 1	12+	0.201	0.599
Haemoglobin	G/L	12+	71	199
Platelet Count	GI/L	1+	31	1499
While Blood Cell Count (WBC)	GI/L	12+	1.1	

Clinical Chemistry				
Laboratory Parameter	**Units**	**Age Category (years)**	**Clinical Concern Range**	
			Low Flag (< x)	**High Flag (>x)**
ALT	U/L	3-12		>143 (and Total Bilirubin >43)
	U/L	13+		>239 (and Total Bilirubin >43)
Calcium	mmol/L	3+	1.50	3.24
Creatinine Phosphokinase	IU/L	12+		>5 x ULN
Glucose	mmol/L	1+	2.2	27.8
Phosphorus, Inorg	mmol/L	3+	0.32	
Potassium	mmol/L	3+	2.8	6.5
Sodium	mmol/L	0+	120	160

Possible Hy's Law Cases			
Test Analyte	**Units**	**Category**	**Clinical Concern Range**
ALT, Bilirubin			ALT ≥ 3xULN and Bilirubin ≥ 2xULN (>35% direct)
ALT, INR			ALT ≥ 3xULN and INR > 1.5

NOTES: ULN=Upper Limit of Normal

14.9. Appendix 9: Population Pharmacokinetic (PopPK) Analyses

14.9.1. Population Pharmacokinetic (PopPK) Dataset Specification

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

14.9.2. Population Pharmacokinetic (PopPK) Methodology

Mepolizumab plasma concentration-time data (samples collected at Weeks 4, 52 and 68; at the Early Withdrawal Visit and the additional follow-up visits (if applicable)) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

14.9.2.1. Base Model

In consideration of the sparse sampling (3 samples post-start of treatment over 68 weeks: Week 4, 52 and 68) and the wealth of mepolizumab PK knowledge, the most recent population PK model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated, against which the model will be validated prospectively using appropriate goodness of fit tests. For example, the Anderson-Darling and Cramér–von Mises tests are accepted methods of comparing Empirical Distribution Functions for model and data (i.e. PK concentrations) to evaluate whether independent observations (i.e. observed PK concentrations from the study) are adequately described by a model (i.e. most recent population PK model).

The following will be obtained:

- A description of the key models tested during the model development will be provided and tabulated;
- Population mepolizumab plasma 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 post-hoc PK parameter estimates (such as area under the plasma concentration-time curve over the dosing interval [AUC (0-τ)], C_{AV} [AUC (0-τ)/τ]) will be summarised descriptively and listed;
- Individual post-hoc predicted plasma concentrations will be summarised descriptively and listed;
- Accumulation ratio estimate will be assessed at Week 52.

The most recent model consists of a two-compartment pharmacokinetic model with first-order absorption and elimination. Bodyweight is incorporated into the model using allometry with fixed physiological allometric exponents of 0.75 and unity for clearance and volumes, respectively. Albumin and creatinine clearance are also included as covariates of mepolizumab clearance on physiological grounds, however their effects are small and not of clinical relevance. Details of the model can be found in report GlaxoSmithKline Document Number 2015N238436_00.

14.9.2.2. Investigation of Covariates

The impact of the following prospectively selected covariates on mepolizumab exposure (e.g. clearance) will be evaluated using the procedures described in Section 14.9.2.3.

Category	Covariates
Demographics	Weight (included in the structural model), age, race, gender, country
Baseline clinical status	Creatinine clearance, albumin (both already included in the current model), serum creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin, total protein
Baseline disease status	Total endoscopic NP score (centrally read), blood eosinophils and baseline OCS dose
Concomitant medications	If data permits*, e.g. immunosuppressant therapies (e.g. methotrexate, azathioprine and mycophenolate mofetil), proton pump inhibitors, statins, pain relief (e.g. paracetamol, NSAIDs), interferon alfa and antihypertensive drugs
Others	Presence/absence of anti-drug antibodies and previous biologics use (monoclonal antibodies).

*Attempt to investigate those classes of drug will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PK parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.4 (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, in line with criteria used in previous analyses. 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 in Section 14.9.2.3. If deemed appropriate box plots of systemic clearance versus covariates of interest (e.g. immunogenicity status) will be provided.

14.9.2.3. 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, in line with criteria used in previous analyses.

- **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 also be supported by examination of the goodness of fit. This will constitute the full model.

- **Backward elimination procedure**

From the full model, the significance of each covariate will be tested individually by removing covariates 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.

Note: centering of continuous covariates may be considered, as appropriate. The mean or median value of the subjects included in the analysis may be used for example.

The impact of the presence of anti-mepolizumab antibodies may not be formally tested as a covariate in the model, considering the low incidence observed in the mepolizumab programme to date. Instead a graphical approach will be used, if deemed appropriate.

14.9.2.4. Model Evaluation

The uncertainty in the parameter estimates will be assessed (e.g. from the standard error estimates provided by NONMEM or from the 95% CI estimates provided by other appropriate analysis conducted using other software). Furthermore, the model performance will be investigated using a set of goodness of fit plots as well as Visual Predictive Check (VPC) method. Other evaluation methods may be used (e.g. bootstrapping) if deemed appropriate.

14.10. Appendix 10: Pharmacokinetic / Pharmacodynamic Analyses

14.10.1. Pharmacokinetic / Pharmacodynamic Dataset Specification

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

14.10.2. Pharmacokinetic / Pharmacodynamic Methodology

Mepolizumab blood eosinophil count-time data (samples collected every 4 weeks from Baseline to Week 52, and at Weeks 60, 68 and 76) will be analysed by population methods using nonlinear mixed-effects modelling. The analysis will be carried out using appropriate software (e.g., NONMEM or SAS).

14.10.3. Base Model

The most recent population PKPD model will be applied directly to the dataset without estimation (e.g. maxevals=0 in NONMEM) and predictions generated against which the model will be validated prospectively using appropriate goodness of fit tests as described in Section 14.9.2.1 (using the observed data from the study).

The following will be obtained:

- 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.

The most recent population PKPD model consists of 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). Observed baseline blood eosinophil count is included as covariates of both predicted baseline and mepolizumab inhibitory response; and disease for predicted baseline blood eosinophil count. Details of the model can be found in GlaxoSmithKline Document Number 2015N238436_00 and GlaxoSmithKline Document Number 2015N255079_00 (extension of the former report).

14.10.4. Investigation of Covariates

The impact of the following prospectively selected plausible covariates on relevant parameters (i.e., baseline blood eosinophil count and maximum effect) will be evaluated.

Category	Covariates
Demographics	Age, race, gender
Baseline disease status	Total endoscopic NP score (centrally read), blood eosinophils (already included in the current model)
Others	Baseline OCS absolute dose, presence/absence of anti-drug antibodies*, immunosuppressant therapies* (e.g.

	methotrexate, azathioprine and mycophenolate mofetil), interferon alfa*

*Attempt to investigate those covariates will be made providing data permits.

Covariate selection will be based on physiological plausibility, supported by graphical evaluation (PD parameters vs. covariates), and formally by automated linear model fitting using proc glmselect in SAS 9.4 (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, in line with criteria used in previous analyses. 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 Section 14.9.2.3 for the population PK model.

Model evaluation will be as described in Section 14.9.2.4 for the population PK model.

14.11. Appendix 11: Abbreviations & Trade Marks

14.11.1. Abbreviations

Abbreviation	Description
ACQ	Asthma Control Questionnaire
ADaM	Analysis Data Model
AE	Adverse Event
A&R	Analysis and Reporting
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CS	Clinical Statistics
CSR	Clinical Study Report
DBF	Database Freeze
DBR	Database Release
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
ECG	Electrocardiogram
ED	Emergency Department
GSK	GlaxoSmithKline
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IP	Interventional Product
ITT	Intent-To-Treat
MMRM	Mixed Model Repeated Measures
NP	Nasal Polyps
OCS	Oral Corticosteroid
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PnIF	Peak Nasal Inspiratory Flow
PP	Per Protocol
PopPK	Population PK
PopPKPD	Pharmacokinetic / Pharmacodynamic
QC	Quality Control
QTcF	Frederica'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
SC	Subcutaneous
SDSP	Study Data Standardization Plan

Abbreviation	Description
SDTM	Study Data Tabulation Model
SF-36	Short Form-36
SNOT-22	Sino-Nasal Outcome Test -22
SoC	Standard of Care
SOP	Standard Operation Procedure
TA	Therapeutic Area
TFL	Tables, Figures & Listings
UPSIT	University of Pennsylvania Smell Identification Test
VAS	Visual Analogue Scale
WPAI	Work Productivity and Impairment

14.11.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

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

14.12. Appendix 12: List of Data Displays

14.12.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.22	1.1
Efficacy	2.1 to 2.69	2.1 to 2.25
Safety	3.1 to 3.68	3.1 to 3.3
Population Pharmacokinetic (PopPK)	4.1 to 4.7	4.1 to 4.9
Pharmacokinetic / Pharmacodynamic (PopPKPD)	5.1 to 5.6	5.1 to 5.10
Exposure-Efficacy		6.1 to 6.4
Section	**Listings**	
ICH and Other Listings	1 to 51	

14.12.2. 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
Efficacy	EFF_Fn	EFF_Tn	EFF_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Population Pharmacokinetic (PopPK)	POPPK_Fn	POPPK_Tn	POPPK_Ln
Pharmacokinetic / Pharmacodynamic (PopPKPD)	POPPKPD_Fn	POPPKPD_Tn	POPPKPD_Ln
Efficacy Exposure	EE_Fn	EE_Tn	EE_Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL/Shell' or 'Programming Notes' column with an associated reference.'

14.12.3. Deliverables

Delivery Priority [1]	Description
SAC [1]	Headline Results
SAC [2]	Final Statistical Analysis Complete

NOTES:

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

14.12.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment	ICH E3	SAC [1]
1.2.	ITT	SHELL	Summary of Time On- and Off-Treatment by Withdrawal Scenario	Withdrawal scenarios are detailed in Section 14.7.2.3. Add footnote to indicate exclusion of data from the follow-up period after Week 52	SAC [2]
1.3.	ITT	ES1	Summary of Subject Disposition (Week 52)	ICH E3, FDAAA, EudraCT	SAC [1]
1.4.	FU	ES1	Summary of Subject Disposition (Follow-Up Period after Week 52)		SAC [1]
1.5.	FU	SHELL	Summary of Duration of Time in Follow-Up Period after Week 52		SAC [2]
1.6.	ENROLLED	ES6	Summary of Screening and Run-In Status and Reasons for Screen and Run-In Failures	Journal Requirements	SAC [2]
1.7.	ENROLLED	NS1/SHELL	Summary of Number of Subjects by Region, Country and Centre	EudraCT/Clinical Operations Add in column for region, add a total for each region and a total for each country.	SAC [2]
Protocol Deviation					
1.8.	ITT	DV1	Summary of Important Protocol Deviations	ICH E3	SAC [2]
Population Analysed					
1.9.	ENROLLED	SP1	Summary of Study Populations	IDSL	SAC [1]
1.10.	Randomised	SP2A	Summary of Exclusions from the Intent-to-Treat and Safety Populations	IDSL	SAC [2]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.11.	ITT	DM1	Summary of Demographic Characteristics	ICH E3, FDAAA, EudraCT	SAC [1]
1.12.	ENROLLED	DM11	Summary of Age Ranges	EudraCT	SAC [2]
1.13.	ITT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC [2]
1.14.	ITT	Shell	Summary of Nasal Polyps Disease History and Characteristics	Include Disease Duration (years/months); Number of previous surgeries; Number of Courses of OCS for NP in previous 12 months. Baseline Nasal Polyps endoscopy score (centrally read and investigator read); Baseline SNOT-22; Baseline SF-36.	SAC [1]
1.15.	ITT	Shell	Summary of Previous Exacerbation History	To include separate summary of information for Asthma and COPD Exacerbation History	SAC [2]
Medical Conditions					
1.16.	ITT	MH4	Summary of Past Medical Conditions	ICH E3	SAC [2]
1.17.	ITT	MH4	Summary of Current Medical Conditions	ICH E3	SAC [2]
Prior and Concomitant Medications					
1.18.	ITT	CM1	Summary of Medications Started Prior to Treatment	ICH E3; ATC classification to be displayed for combination medications (not for individual ingredients)	SAC [2]
1.19.	ITT	CM1	Summary of Concomitant Medications Started During Treatment	ICH E3; ATC classification to be displayed for combination medications (not for individual ingredients). Footnote: Includes medications started after first dose and before last dose + 28 days.	SAC [2]

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.20.	ITT	CM1	Summary of Systemic Corticosteroids Started During Treatment	Footnote: Includes medications started after first dose and before last dose + 28 days.	SAC [2]
Exposure					
1.21.	ITT	SHELL	Summary of Exposure (Therapeutic Coverage) to Interventional Product	ICH E3 Range of Exposure (months): 1-<3, 3-<6, 6-<9, 9-<12, >=12Also add subject years exposure	SAC [2]
1.22.	ITT	SHELL	Summary of Number of Treatments Administered		SAC [2]

14.12.5. Study Population Figures

Study Population Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	SHELL	Subject Withdrawal from Interventional Product	Footnote: Kaplan-Meier estimates of time to withdrawal from IP. Subjects are represented from Day 1 to Day of withdrawal from IP	SAC [2]

14.12.6. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Co-Primary Endpoints					
2.1.	ITT	SHELL	Summary of Total Endoscopic Nasal Polyps Score (Centrally Read)	Footnote: Excludes data reported during the follow-up period after Week 52 Include actual categories	SAC [1]
2.2.	ITT	SHELL	Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read)		SAC [1]
2.3.	ITT	SHELL	Sensitivity Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Subjects with Missing Data Included in the Actual Surgery Category		SAC [2]
2.4.	ITT	SHELL	Sensitivity Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Subjects with Missing Data Included in the 1-point Improvement Category		SAC [2]
2.5.	ITT	SHELL	Supplementary Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Subjects with Early Withdrawal from Interventional Product Included in the Actual Surgery Category	All intercurrent events in least favourable treatment response category	SAC [2]
2.6.	PP	SHELL	Supplementary Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Per-Protocol Population		SAC [2]
2.7.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Participants with Asthma		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Aspirin Exacerbated Respiratory Disease (AERDS)		SAC [2]
2.9.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Number of Previous Surgeries		SAC [2]
2.10.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Baseline Blood Eosinophil Categories		SAC [2]
2.11.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Region		SAC [2]
2.12.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Age		SAC [2]
2.13.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Gender		SAC [2]
2.14.	ITT	SHELL	Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 by Race		SAC [2]
2.15.	ITT	SHELL	Predicted Change from Baseline Total Endoscopic Nasal Score (Centrally Read) at Week 52 by Baseline Blood Eosinophils		SAC [2]
2.16.	ITT	SHELL	Summary of Nasal Obstruction VAS score	Footnote: Excludes data reported during the follow-up period after Week 52 Include actual categories	SAC [1]
2.17.	ITT	SHELL	Analysis of Change from Baseline Nasal Obstruction VAS Score		SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.18.	ITT	SHELL	Sensitivity Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) - Subjects with Missing Data included in the Actual Surgery Category		SAC [2]
2.19.	ITT	SHELL	Sensitivity Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) – Subjects with Missing Data Included in the >0 to 1-point Improvement Category		SAC [2]
2.20.	ITT	SHELL	Supplementary Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52): Subjects with Early Withdrawal from Interventional Product Included in the Actual Surgery Category		SAC [2]
2.21.	PP	SHELL	Supplementary Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52): Per-Protocol Population		SAC [2]
2.22.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Subjects with Asthma		SAC [2]
2.23.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Aspirin Exacerbated Respiratory Disease (AERDS)		SAC [2]
2.24.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Number of Previous Surgeries		SAC [2]
2.25.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Baseline Blood Eosinophil Categories		SAC [2]
2.26.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Region		SAC [2]
2.27.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Age		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.28.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Gender		SAC [2]
2.29.	ITT	SHELL	Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) by Race		SAC [2]
2.30.	ITT	SHELL	Predicted Change from Baseline Nasal Obstruction VAS (Weeks 49-52) by Baseline Blood Eosinophils		SAC [2]
Secondary Endpoints					
2.31.	ITT	SHELL	Analysis of Time to First Nasal Surgery	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]
2.32.	ITT	SHELL	Sensitivity Analysis of Time to First Nasal Surgery: Tipping Point Analysis	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.33.	ITT	SHELL	Summary of Overall VAS score	Footnote: Excludes data reported during the follow-up period after Week 52 Include actual categories	SAC [1]
2.34.	ITT	SHELL	Analysis of Change from Baseline Overall VAS Score		SAC [1]
2.35.	ITT	SHELL	Summary of SNOT-22 Total Score	Footnote: Excludes data reported during the follow-up period after Week 52 Include actual categories	SAC [1]
2.36.	ITT	SHELL	Analysis of Change from Baseline SNOT-22		SAC [1]
2.37.	ITT	SHELL	Summary and Analysis of Total Prednisolone-equivalent OCS Use (mgs per year)	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.38.	ITT	SHELL	Subgroup Analysis of Total Prednisolone-equivalent OCS Use (mgs per year) by Participants with Asthma	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.39.	ITT	SHELL	Summary of P-values for Treatment Comparisons Adjusted for Multiplicity According to Hierarchy of Endpoints		SAC [1]
Other Endpoints					
2.40.	ITT	SHELL	Summary of Total Endoscopic Nasal Score (Investigator Read)	Footnote: Excludes data reported during the follow-up period after Week 52 Include actual and change from baseline categories	SAC [2]
2.41.	ITT	SHELL	Summary and Analysis of Total Endoscopic Nasal Polyps Score (Centrally Read) Responders	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.42.	ITT	SHELL	Summary and Analysis of SNOT-22 Responders	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.43.	ITT	SHELL	Summary and Analysis of Change from Baseline Individual VAS Symptom Scores	Footnote: Excludes data reported during the follow-up period after Week 52 Include data for nasal discharge, mucus in throat, loss of smell, facial pain	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.44.	ITT	SHELL	Summary and Analysis of Change from Baseline Composite VAS Scores	Footnote: Excludes data reported during the follow-up period after Week 52 Footnote: Composite includes nasal obstruction, nasal discharge, mucus in the throat and loss of smell Include Composite Excluding Facial Pain and Composite Including Facial Pain	SAC [2]
2.45.	ITT	SHELL	Summary of University of Pennsylvania Smell Identification Test (UPSIT)	Footnote: Excludes data reported during the follow-up period after Week 52 Footnote: performed in UK, US and Canada only Include actual categories	SAC [2]
2.46.	ITT	SHELL	Analysis of Change from Baseline University of Pennsylvania Smell Identification Test (UPSIT)	Footnote: performed in UK, US and Canada only	SAC [2]
2.47.	ITT	SHELL	Summary of Peak Nasal Inspiratory Flow (PNIF)	Include actual and change from baseline Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.48.	ITT	SHELL	Summary of Frequency and Rate of Nasal Surgery	Include n (%) with 0, 1, 2, etc surgeries and crude rate Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.49.	ITT	SHELL	Time to First Inclusion on Waiting List for Nasal Polyps Surgery	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.50.	ITT	SHELL	Summary of Subjects Placed on Waiting List for Surgery to Week 52	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.51.	ITT	SHELL	Summary and Analysis of Need for Surgery to Week 52	Footnote: Subjects no longer having a need for surgery based on improvements seen in total endoscopic nasal polyps score and overall VAS score Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.52.	ITT	SHELL	Summary of Number of Courses of Systemic Steroids	Footnote: Excludes data reported during the follow-up period after Week 52 Footnote: Courses of systemic steroids separated by <7 days are considered a continuation of the same course Include n (%) with 0 vs ≥1 and 0, 1, 2, etc courses and total number of courses	SAC [2]
2.53.	ITT	SHELL	Summary of Days on Systemic Steroids	Footnote: excludes data reported during the follow-up period after Week 52 Include days on therapy and percentage of days on therapy	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.54.	ITT	SHELL	Time to First Course of Systemic Steroids	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.55.	ITT	SHELL	Analysis of Time to First Nasal Surgery or Course of Systemic Steroids	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.56.	ITT	SHELL	Summary of Number of Courses of Antibiotics	Footnote: Excludes data reported during the follow-up period after Week 52 Footnote: Courses of antibiotics separated by <7 days are considered a continuation of the same course Include n (%) with 0 vs ≥1 and 0, 1, 2, courses and total number of courses	SAC [2]
2.57.	ITT	SHELL	Summary of On-Treatment Blood Eosinophils (GI/L)	Include absolute and ratio to baseline values	SAC [1]
2.58.	ITT	SHELL	Analysis of On-Treatment Blood Eosinophils (GI/L) Ratio Compared to Baseline Mixed Model Repeated Measures		SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Endpoints – Health Economics/Medical Resource Utilisation					
2.59.	ITT	SHELL	Summary of SF-36 Domain Scores and Component Summary Scores	Include 8 domain scores bodily pain, general health, mental health, physical functioning, role emotional, role physical, social functioning and vitality and Mental and Physical Component Summary scores. Include actual and change from baseline Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.60.	ITT	SHELL	Summary of Work Productivity and Activity Impairment Questionnaire (WPAI)	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
Other Endpoints – Participants with Asthma					
2.61.	ITT	SHELL	Summary of ACQ-5 in Participants with Asthma	Include actual and change from baseline Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.62.	ITT	SHELL	Summary of Frequency of Clinically Significant Asthma Exacerbations in Participants with Asthma	Provide n (%) with 0 vs ≥1 and 0, 1, 2 etc exacerbations and total number of exacerbations Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]

Efficacy: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Other Endpoints – Maintenance of Response Following Cessation of Interventional Product (Follow-Up Period After Week 52)					
2.63.	FU	SHELL	Summary of Total Endoscopic Nasal Polyps Score (Centrally Read) for Subjects in the Follow-Up Period After Week 52	Include actual and change from baseline	SAC [2]
2.64.	FU	SHELL	Summary of Individual VAS Symptom Scores for Subjects in the Follow-Up Period After Week 52	Include actual and change from baseline Include nasal obstruction, nasal discharge, mucus in throat, loss of smell, facial pain, overall VAS score	SAC [2]
2.65.	FU	SHELL	Summary of Total Prednisolone-equivalent OCS Use (mgs per year) for Subjects in the Follow-Up Period After Week 52		SAC [2]
2.66.	FU	SHELL	Summary of SNOT-22 for Subjects in the Follow-Up Period After Week 52	Include actual and change from baseline	SAC [2]
2.67.	FU	SHELL	Time to First Nasal Surgery for Subjects in the Follow-Up Period After Week 52		SAC [2]
2.68.	FU	SHELL	Summary of Number of Courses of Systemic Steroids for Subjects in the Follow-Up Period After Week 52	Footnote: Courses of systemic steroids separated by less than 7 days are considered a continuation of the same course	SAC [2]
2.69.	FU	SHELL	Summary of Blood Eosinophils (GI/L) for Subjects in the Follow-up Period After Week 52		SAC [2]

14.12.7. Efficacy Figures

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Co-Primary Endpoints					
2.1.	ITT	SHELL	Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52	Show percentages in each category	SAC [1]
2.2.	ITT	SHELL	Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) by Visit	OR and 95%CI	SAC [1]
2.3.	ITT	SHELL	Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Cumulative Distribution Function		SAC [2]
2.4.	ITT	SHELL	Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Sensitivity and Supplementary Analyses	Include primary, sensitivity and supplementary analyses	SAC [2]
2.5.	ITT	SHELL	Figure of Predicted Change from Baseline Total Endoscopic Nasal Score (Centrally Read) at Week 52 by Baseline Blood Eosinophils		SAC [2]
2.6.	ITT	SHELL	Figure of Change from Baseline Nasal Obstruction VAS Score (Week 49-52)	Show percentages in each category	SAC [1]
2.7.	ITT	SHELL	Figure of Change from Baseline Nasal Obstruction VAS Score in each 4-Weekly Period	OR and 95%CI Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.8.	ITT	SHELL	Figure of Nasal Obstruction VAS Score (Week 49-52): Sensitivity and Supplementary Analyses	Include primary, sensitivity and supplementary analyses	SAC [2]
2.9.	ITT	SHELL	Figure of Predicted Change from Baseline Nasal Obstruction VAS (Weeks 49-52) by Baseline Blood Eosinophils		SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Secondary Endpoints					
2.10.	ITT	SHELL	Kaplan-Meier Time to First Nasal Surgery	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]
2.11.	ITT	SHELL	Sensitivity Time to First Nasal Surgery: Tipping Point	Heat Map Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.12.	ITT	SHELL	Sensitivity Time to First Nasal Surgery (TBD): Tipping Point – Fixed Assumption for Placebo	2-dimensional Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.13.	ITT	SHELL	Figure of Change from Baseline Overall VAS Score in Each 4-Weekly Period	OR and 95%CI Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]
2.14.	ITT	SHELL	Figure of Change from Baseline SNOT-22 by Visit	OR and 95%CI Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]
Other Endpoints					
2.15.	ITT	SHELL	Figure of Total Endoscopic Nasal Polyps Score (Centrally Read) Responders by Visit	OR and 95%CI Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.16.	ITT	SHELL	Figure of University of Pennsylvania Smell Identification Test (UPSIT) Change from Baseline by Visit	OR and 95%CI Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.17.	ITT	SHELL	Figure of SNOT-22 Responders by Visit	OR and 95%CI Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.18.	ITT	SHELL	Kaplan-Meier Time to First Inclusion on Waiting List for Nasal Polyps Surgery	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.19.	ITT	SHELL	Kaplan-Meier Time to First Course of Systemic Steroids	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.20.	ITT	SHELL	Kaplan-Meier Time to First Nasal Surgery or Course of Systemic Steroids	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
2.21.	ITT	SHELL	Figure of On-Treatment Blood Eosinophils Absolute Values	No reference line. Include screening/baseline geometric mean values without 95% CI. Week 4 onwards adjusted estimates from MMRM model with 95% CI.	SAC [2]
2.22.	ITT	SHELL	Figure of On-Treatment Blood Eosinophils Ratio to Baseline	Reference line at 1	SAC [2]
Other Endpoints – Maintenance of Response Following Cessation of Interventional Product (Follow-Up Period After Week 52)					
2.23.	FU	SHELL	Kaplan-Meier Time to First Nasal Surgery for Subjects in the Follow-Up Period After Week 52		SAC [2]

Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.24.	FU	SHELL	Kaplan-Meier Time to First Inclusion on Waiting List for Nasal Polyps Surgery for Subjects in the Follow-Up Period After Week 52		SAC [2]
2.25.	FU	SHELL	Figure of Blood Eosinophils for Subjects in the Follow-Up Period After Week 52		SAC [2]

14.12.8. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events (AEs)					
3.1.	Safety	AE13/SHELL	Adverse Event Overview		SAC [1]
3.2.	Safety	AE1	Summary of On-Treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [1]
3.3.	Safety	AE1	Summary of Post-Treatment Adverse Events by System Organ Class and Preferred Term	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]
3.4.	FU	AE1	Summary of Adverse Events Reported During the Follow-Up Period After Week 52 by System Organ Class and Preferred Term		SAC [2]
3.5.	Safety	AE3	Summary of Common (>=3% in Any Treatment Group) On-Treatment Adverse Events by Overall Frequency	ICH E3 ≥3% (prior to rounding to nearest percent)	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.6.	Safety	AE5a	Summary of On-Treatment Adverse Events by System Organ Class and Maximum Severity	Add a Total column across all severities	SAC [2]
3.7.	Safety	AE1	Summary of Drug-Related On-Treatment Adverse Events by System Organ Class and Preferred Term	ICH E3	SAC [2]
3.8.	Safety	AE5a	Summary of Drug Related On-Treatment Adverse Events by System Organ Class and Maximum Severity	Add a Total column across all severities	SAC [2]
3.9.	Safety	AE15	Summary of Common (>=3% In Any Treatment Group) Non-Serious On-Treatment Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT≥3% (prior to rounding to nearest percent)	SAC [2]
3.10.	Safety	AE1	Summary of On-Treatment Adverse Events by Highest Post-Baseline Anti-Drug Antibody Result	Add in row with n in each ADA result category. Footnote: Highest Post-Baseline Anti-Drug Antibody result excluding data from no-treatment follow-up period.	SAC [2]
3.11.	Safety	AE1	Summary of Post-Treatment Adverse Events by Highest Post-Baseline Anti-Drug Antibody Result	Add in row with n in each ADA result category. Footnote: Highest Post-Baseline Anti-Drug Antibody result excluding data from no-treatment follow-up period. Footnote: Excludes AEs reported during the follow-up period after Week 52	SAC [2]
3.12.	Safety	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment by System Organ Class	IDSL	SAC [2]
3.13.	Safety	AE1	Summary of Adverse Events Leading to Withdrawal from Study by System Organ Class	IDSL	SAC [2]
3.14.	Safety	AE1	Summary of Adverse Events Reported on Day of Dosing by System Organ Class		SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious and Other Significant Adverse Events					
3.15.	Safety	AE3	Summary of Fatal Serious Adverse Events		SAC [1]
3.16.	Safety	AE3	Summary of Fatal Drug-Related Serious Adverse Events		SAC [2]
3.17.	Safety	AE1	Summary of Non-Fatal Serious Adverse Events by System Organ Class	Include on-treatment and post-treatment	SAC [2]
3.18.	Safety	AE1	Summary of Non-Fatal Serious On-Treatment Adverse Events by System Organ Class		SAC [2]
3.19.	Safety	AE1	Summary of Non-Fatal Serious Post-Treatment Adverse Events by System Organ Class	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [1]
3.20.	Safety	AE1	Summary of Serious Adverse Events by System Organ Class	Include on-treatment and post-treatment	SAC [1]
3.21.	Safety	AE1	Summary of Serious On-Treatment Adverse Events by System Organ Class		SAC [2]
3.22.	Safety	AE1	Summary of Serious Post-Treatment Adverse Events by System Organ Class	Footnote: Excludes data reported during the follow-up period after Week 52	SAC [2]
3.23.	FU	AE1	Summary of Serious Adverse Events Reported During the Follow-Up Period After Week 52 by System Organ Class		SAC [2]
3.24.	Safety	AE1	Summary of Serious Drug-Related On-Treatment Adverse Events by System Organ Class		SAC [2]
3.25.	Safety	AE1	Summary of Pre-Treatment Serious Adverse Events by System Organ Class		SAC [2]
3.26.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.27.	Safety	SHELL	Summary of Deaths	Includes all deaths separating those reported in no-treatment follow-up	SAC [2]
Adverse Events of Special Interest					
3.28.	Safety	SHELL	Summary of On-Treatment Serious AEs and AEs of Special Interest: Incidence, Relative Risk and Risk Difference (Placebo vs 100mg SC)		SAC [2]
3.29.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Systemic Reactions Reported by the Investigator as Meeting the Criteria for Anaphylaxis		SAC [2]
3.30.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity) and Other Reactions		SAC [2]
3.31.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Defined by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity)		SAC [2]
3.32.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Defined by the Investigator as Systemic Reactions – Other Reactions		SAC [2]
3.33.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Local Injection Site Reactions		SAC [2]
3.34.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events		SAC [2]
3.35.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Serious Ischemic Events		SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.36.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Malignancies		SAC [2]
3.37.	Safety	AE1	Summary of On-Treatment Adverse Events of Special Interest: Potential Opportunistic Infections		SAC [2]
3.38.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Systemic Reactions Reported by the Investigator as Meeting the Criteria for Anaphylaxis		SAC [2]
3.39.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity) and Other Reactions		SAC [2]
3.40.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Defined by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity)		SAC [2]
3.41.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Defined by the Investigator as Systemic Reactions –Other Reactions		SAC [2]
3.42.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Local Injection Site Reactions		SAC [2]
3.43.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events		SAC [2]
3.44.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Serious Ischemic Events		SAC [2]
3.45.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Malignancies		SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.46.	Safety	SHELL	Summary Profile of On-Treatment Adverse Events of Special Interest: Potential Opportunistic Infections		SAC [2]
Laboratory: Chemistry					
3.47.	Safety	LB1	Summary of On-Treatment Chemistry Changes from Baseline	ICH E3 Includes Baseline values	SAC [2]
3.48.	Safety	LB3	Summary of On-Treatment Chemistry Shifts from Baseline Relative to Normal Range	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
3.49.	Safety	LB3	Summary of On-Treatment Chemistry Shifts from Baseline Relative to PCI Criteria	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
Laboratory: Hematology					
3.50.	Safety	LB1	Summary of On-Treatment Haematology Changes from Baseline	ICH E3 Includes Baseline values	SAC [2]

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.51.	Safety	LB3	Summary of On-Treatment Haematology Shifts from Baseline Relative to Normal Range	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]
3.52.	Safety	LB3	Summary of On-Treatment Haematology Shifts from Baseline Relative to PCI Criteria	ICH E3 Include Any Time Post Baseline Add footnotes: Note: Any Time Post Baseline – Includes scheduled and any unscheduled assessments Subjects may be counted in more than one category.	SAC [2]

Laboratory: Urinalysis					
3.53.	Safety	UR1	Summary of Worst Case Urinalysis Results Post-Baseline Relative to Baseline	ICH E3	SAC [2]
Laboratory: Hepatobiliary (Liver)					
3.54.	Safety	LIVER1	Summary of Liver Monitoring/Stopping Event Reporting	IDSL	SAC [2]
3.55.	Safety	LIVER10	Summary of Hepatobiliary Laboratory Abnormalities	IDSL	SAC [2]
ECG					
3.56.	Safety	EG1	Summary of ECG Findings	IDSL	SAC [2]
3.57.	Safety	EG2	Summary of Change from Baseline in ECG Values by Visit	IDSL	SAC [2]
3.58.	Safety	EG10	Summary of Maximum QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [2]
3.59.	Safety	EG11	Summary of Maximum Increase in QTc Values Post-Baseline Relative to Baseline by Category	IDSL	SAC [2]
Vital Signs					
3.60.	Safety	VS1	Summary Vital Signs		SAC [2]
3.61.	Safety	VS1	Summary of Change from Baseline in Vital Signs	ICH E3	SAC [2]
Immunogenicity					
3.62.	Safety	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Confirmatory Result	Footnote: Excludes data from no-treatment follow-up period	SAC [2]
3.63.	Safety	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Treatment Emergent Confirmatory Result	Footnote: Excludes data from no-treatment follow-up period	SAC [2]
3.64.	Safety	SHELL	Summary of Neutralising Antibody Assay: Highest Result	Footnote: Excludes data from no-treatment follow-up period	SAC [2]
3.65.	FU	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Confirmatory Result for Subjects in the Follow-up Period After Week 52	Footnote: Includes all available data	SAC [2]

Laboratory: Urinalysis					
3.66.	FU	SHELL	Summary of Binding Anti Drug Antibody Assay: Highest Treatment Emergent Confirmatory Results for Subjects in the Follow-up Period After Week 52	Footnote: Includes all available data	SAC [2]
3.67.	FU	SHELL	Summary of Neutralising Antibody Assay: Highest Result for Subjects in the Follow-up Period After Week 52	Footnote: Includes all available data	SAC [2]
3.68.	Safety	SHELL	Summary of On-Treatment Blood Eosinophils (GI/L) by Anti Drug Antibody Status		SAC [2]

14.12.9. Safety Figures

Safety: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Adverse Events					
3.1.	Safety	AE10	Common (>=3% In Any Treatment Group) On-Treatment Adverse Events and Relative Risk	IDSL	SAC [2]
3.2.	Safety	SHELL	On-treatment Serious Adverse Events and Adverse Events of Special Interest (Placebo vs Mepolizumab 100mg SC)	Provide relative risk with 95% CI	SAC [2]
Laboratory					
3.3.	Safety	LIVER9	Scatter Plot of Maximum ALT vs. Maximum Total Bilirubin	IDSL	SAC [2]

14.12.10. Pharmacokinetic Population (PopPK) Tables

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**

Pharmacokinetic Population (POPPK): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	PK01	Summary of Plasma Mepolizumab Concentration-Time Data (Observed and Predicted)		SAC [2]
4.2.	PK	PK06	Summary Statistics of Individual Model Predicted Plasma Mepolizumab Pharmacokinetic Parameters (Non-transformed and Log-transformed)		SAC [2]
4.3.	PK	-	Description and Evaluation of Key PK Models Tested	Provided by CPMS	SAC [2]
4.4.	PK	-	Population PK Parameter Estimates with 95% CI of Final PK Model	Provided by CPMS	SAC [2]
4.5.	PK	-	Demographics Summary	Provided by CPMS	SAC [2]
4.6.	PK	-	Samples Summary	Provided by CPMS	SAC [2]
4.7.	PK	-	Accumulation Ratio Estimate at Week 52	Provided by CPMS	SAC [2]

14.12.11. Pharmacokinetic Population (PopPK) Figures

Pharmacokinetic Population (POPPK): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.1.	PK	-	Plasma Mepolizumab Concentration-Time Profiles (by Treatment)	Provided by CPMS	SAC [2]
4.2.	PK	-	Model Goodness of Fit Plots	Provided by CPMS	SAC [2]
4.3.	PK	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC [2]
4.4.	PK	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC [2]
4.5.	PK	-	Automated Covariate Selection	Provided by CPMS	SAC [2]
4.6.	PK	-	Visual Predictive Check	Provided by CPMS	SAC [2]

Pharmacokinetic Population (POPPK): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
4.7.	PK	-	Observed Plasma Mepolizumab Concentration-Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC [2]
4.8.	PK	-	Plasma Mepolizumab Observed/Predicted Concentration-Time Profiles (by Subject)	Provided by CPMS	SAC [2]
4.9.	PK	-	Box Plot of Systemic Clearance versus Covariates of Interest	Provided by CPMS	SAC [2]

14.12.12. Pharmacokinetic/Pharmacodynamic Population (PopPK/PD) Tables

Pharmacokinetic/Pharmacodynamic Population (POPPK/PD): Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK and PD	-	Description and Evaluation of Key PKPD Models Tested	Provided by CPMS	SAC [2]
5.2.	PK and PD	-	Population PD Parameter Estimates with 95% CI of Final PKPD Model	Provided by CPMS	SAC [2]
5.3.	PK and PD	-	Demographics Summary	Provided by CPMS	SAC [2]
5.4.	PK and PD	-	Samples Summary	Provided by CPMS	SAC [2]
5.5.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Total Endoscopic NP Score (Centrally Read) at Week 52 vs Dose/Body Weight		Post-SAC [2]
5.6.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Total Endoscopic NP Score (Centrally Read) at Week 52 vs Cav		Post-SAC [2]

14.12.13. Pharmacokinetic/Pharmacodynamic Population (PopPKPD) Figures

Pharmacokinetic/Pharmacodynamic Population (POPPK/PD): Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.1.	PK and PD	-	Blood Eosinophil Count-Time Profiles	Provided by CPMS	SAC [2]
5.2.	PK and PD	-	Model Goodness of Fit Plots	Provided by CPMS	SAC [2]
5.3.	PK and PD	-	Continuous Covariate Correlation Plot	Provided by CPMS	SAC [2]
5.4.	PK and PD	-	Categorical Covariate Correlation Plot	Provided by CPMS	SAC [2]
5.5.	PK and PD	-	Automated Covariate Selection	Provided by CPMS	SAC [2]
5.6.	PK and PD	-	Visual Predictive Check	Provided by CPMS	SAC [2]
5.7.	PK and PD	-	Observed Blood Eosinophil Count -Time Profiles by Anti-Drug Antibody Status	Provided by CPMS	SAC [2]
5.8.	PK and PD	-	Observed/Predicted Blood Eosinophil Count-Time Profiles (by Subject)	Provided by CPMS	SAC [2]
5.9.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 vs Dose/Body Weight		Post-SAC [2]
5.10.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) vs Dose/Body Weight		Post-SAC [2]

14.12.14. Exposure-Efficacy Figures

Exposure-Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**

Exposure-Efficacy: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
6.1.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 vs Dose/Body Weight		Post-SAC [2]
6.2.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) vs Dose/Body Weight		Post-SAC [2]
6.3.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) vs Week 52 Ctau		Post-SAC [2]
6.4.	ITT	-	Exploratory Exposure-Efficacy Response Modelling of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52 vs Week 52 Ctau		Post-SAC [2]

14.12.15. ICH and Other Listings

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	ENROLLED	ES7	Listing of Reasons for Screen and Run-In Failures	Journal Guidelines	SAC [2]
2.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation	ICH E3	SAC [2]
3.	ITT	ES2	Listing of Reasons for Study Withdrawal	ICH E3 Include and identify withdrawals from no-treatment follow-up	SAC [2]
4.	ENROLLED	ES9	Listing of Subjects Who Were Rescreened		SAC [2]
5.	ITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken	ICH E3	SAC [2]
6.	ITT	TA1	Listing of Planned and Actual Treatments	IDSL	SAC [2]
Protocol Deviations					
7.	ITT	DV2	Listing of Important Protocol Deviations	ICH E3	SAC [2]
8.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC [2]
Populations Analysed					
9.	Randomised	SP3	Listing of Subjects Excluded from Any Population	ICH E3	SAC [2]
Demographic and Baseline Characteristics					
10.	ITT	DM2	Listing of Demographic Characteristics	ICH E3	SAC [2]
11.	ITT	DM9	Listing of Race	ICH E3	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
12.	ITT	SHELL	Listing of Nasal Polyps Disease History and Baseline Characteristics	Include Disease Duration (years/months); Number of previous surgeries; Number of Courses of OCS for NP in previous 12 months; History of Sinusitis; Baseline Nasal Polyps endoscopy score (centrally read and investigator read); Nasal Obstruction VAS, Overall VAS, Baseline SNOT-22; Baseline SF-36. Include tobacco history.	SAC [2]
Prior and Concomitant Medications					
13.	ITT	CM3	Listing of Concomitant Medications	IDSL Include column to identify entries coming from the systemic corticosteroid eCRF page	SAC [2]
Exposure					
14.	Randomised	SHELL/EX3	Listing of Exposure Data	ICH E3	SAC [2]
Adverse Events					
15.	Safety	AE8	Listing of All Adverse Events	ICH E3 add Phase (pre/on/post-trt)	SAC [2]
16.	Safety	AE8	Listing of All Adverse Events on Day of Dosing		SAC [2]
17.	Safety	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3 Split on-treatment, post-treatment, reported during follow-up period after Week 52	SAC [2]
18.	Safety	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	ICH E3 add Phase (pre/on/post-trt)	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
19.	Safety	AE2	Listing of Relationship Between Adverse Event System Organ Classes, Preferred Terms, and Verbatim Text	IDSL	SAC [2]
Serious and Other Significant Adverse Events					
20.	Safety	AE8	Listing of Fatal Serious Adverse Events	ICH E3	SAC [2]
21.	Safety	AE8	Listing of Non-Fatal Serious Adverse Events	ICH E3	SAC [2]
22.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC [2]
23.	Safety	DTH3	Listing of Deaths		SAC [2]
24.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: All Cause Deaths		SAC [2]
25.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Arrhythmias		SAC [2]
26.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Congestive Heart Failure		SAC [2]
27.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Cerebrovascular Events/Stroke		SAC [2]
28.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Deep venous Thrombosis/Pulmonary Embolism		SAC [2]
29.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Myocardial Infarction/Unstable Angina		SAC [2]
30.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Peripheral Arterial Thrombosis Embolism		SAC [2]
31.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Pulmonary Hypertension		SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
32.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Revascularisation		SAC [2]
33.	Safety	IDSL	Patient Profiles of Investigator Reported Cardiovascular Events: Valvulopathy		SAC [2]
Adverse Events of Special Interest					
34.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Meeting the Criteria for Anaphylaxis	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
35.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Defined by the Investigator as Systemic Reactions – Allergic (Type I Hypersensitivity)	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
36.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Defined by the Investigator as Systemic Reactions – Other Reactions	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
37.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Events Reported by the Investigator as Local Injection Site Reactions	add Phase(on/post-trt) add number of doses taken prior to the event and symptoms related to the event	SAC [2]
38.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Serious Cardiac, Vascular and Thromboembolic Events	add Phase(on/post-trt)	SAC [2]
39.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Serious Ischemic Events	add Phase(on/post-trt)	SAC [2]
40.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Malignancies	add Phase(on/post-trt)	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
41.	Safety	AE8	Listing of On-Treatment Adverse Events of Special Interest: Potential Opportunistic Infections	add Phase(on/post-trt)	SAC [2]
Hepatobiliary (Liver)					
42.	Safety	MH2	Listing of Medical Conditions for Subjects with Liver Stopping Events	IDSL	SAC [2]
43.	Safety	LIVER13	Listing of Subjects Meeting Hepatobiliary Laboratory Criteria Post-Baseline		SAC [2]
44.	Safety	LIVER5	Listing of Liver Monitoring/Stopping Event Reporting		SAC [2]
45.	Safety	SU2	Listing of Substance Use for Subjects with Liver Stopping Events	IDSL	SAC [2]
All Laboratory					
46.	Safety	LB5	Listing of Chemistry Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
47.	Safety	LB5	Listing of Haematology Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
48.	Safety	LB14	Listing of Laboratory Data with Character Results	ICH E3	SAC [2]
49.	Safety	UR2A/UR2B	Listing of Urinalysis Data for Subjects with Any Value of Potential Clinical Importance	ICH E3	SAC [2]
ECG					
50.	Safety	EG3 / EG4	Listing of All ECG Values for Subjects with Protocol Defined QTc Stopping Criteria	IDSL	SAC [2]

ICH and Other Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Immunogenicity					
51.	Safety	IMM2	Listing of Immunogenicity Data	Include column titled: Screening Binding Assay, Confirmation Antibody Assay, Confirmation Assay Titre, Neutralizing Antibody Assay	SAC [2]

14.13. Appendix 13: Example Mock Shells for Data Displays

Shells are available upon request.