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Protocol Title: 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)

Protocol Number: 205687 /04

Short Title: Effect of Mepolizumab in severe bilateral nasal polyps

Compound Number: SB240563

Sponsor Name and Legal Registered Address:

GlaxoSmithKline Research & Development Limited
980 Great West Road
Brentford
Middlesex, TW8 9GS
UK

Medical Monitor Name and Contact Information will be provided separately in the SPM

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SPONSOR SIGNATORY:

PPD

13/2/2020

Robert Chan, MD **Date**

Project Physician Lead, Clinical Development Group
Director, Respiratory TAU

SPONSOR SIGNATORY:

PPD

Eric Bradford, MD

February 13, 2020
Date

Physician Project Lead, Medicines Development Center, Global Clinical Development, US Respiratory R&D

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
2016N294302_04	*13-FEB-2020*
2016N294302_03	*20-Feb-2018*
2016N294302_02	*14-July-2017*
2016N294302_01	*15-May-2017*
Original Protocol (2016N294302_00)	*08-Dec-2016*

Amendment 01 15-May-2017

Overall Rationale for the Amendment: The purpose of this amendment is to support country-specific requirements and amendments for South Korea.

Section # and Name	**Description of Change**	**Brief Rationale**
Appendix 10	Include IP label, provide additional clarification about the inclusion criteria age as per local regulations, provide details of OCS supplied for South Korea	Country specific requirement for South Korea

Amendment 02 14-JUL-2017

Overall Rationale for the Amendment: The main purpose of this amendment is to reflect comments from investigators to clarify points in the protocol that might be confusing or inconsistent. In addition it also reflects the removal of CT scans and exit interviews as well as simplifying some of the endpoints such as reduction of endoscopic NP endpoints.

Section # and Name	Description of Change	Brief Rationale
Title	Added the following to the title 'SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab)'	For clarification
Throughout the protocol	The word 'subject' was changed to 'participant'	For consistency
Overall design at synopsis and Section 5.1	Deleted the following: For Japanese and Korean participants CT scans will be included as "other" endpoints as CT scans are part of the diagnostic algorithm in Japan and provide important information for the East Asian population.	Deleted because CT scans are no longer required
Section 2 SOA	**The following amendments or additions were carried out for clarification:** • Treatment day was changed to study day • First day of dosing is Day 1 and visit days are changed to reflect this • Concurrent medication review (including INCS) row added at Pre screen • Added asthma exacerbation as an example in medical history • Row added: Dispense "Medical Problems and Medication Taken Worksheet" every visit from V1-V17 • Row added: Collect "Medical Problems and Medication Taken Worksheet" from V2-V18 and EW visit • NP endoscopy assessment removed from visits 9, 11 and 13 • CT scans assessments were removed • Exit interview was removed • Nasal secretion for biomarkers collection removed • Updated Medication history wording to include INCS • Clarified that Genetic sample is the same as PGX • The following was removed from footnote 1 'Baseline value is calculated	For clarification

Section # and Name	Description of Change	Brief Rationale
	as the average score in the last 7 days before Visit 2. The value at all other treatment phase visits is calculated as the average score in the previous 28 days.' • Added to clarify that UPSIT test will be performed only in selected countries • A new row was added for SAE review from V1 while AEs are only reviewed and collected from V2 • Foot note 4 for PK was changed to reflect that PK at visits 5 and 8 will no longer be performed • Foot note on exit interviews was removed. Foot note numbers were changes to reflect this • Foot note added to clarify that dispensing of MF is not required if study visit 15, 18 or EW is the last study visit • Foot note added to clarify that PGx informed consent can be taken at any time prior PGx sampling • Foot note added to allow a window of 3 days pre dosing to perform the endoscopies but must not exceed the protocol defined windows of ± 7 days from the nominal study visit • Foot note added to clarify that nasal endoscopy score assessment will be performed at visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 15, 16, 17, 18 and EW	To reduce participant burden To improve flexibility To reduce participant burden
Section 4. Objectives and Endpoints	Added to clarify '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, Removed the following: •Change from baseline in Lund-Mackay computed tomography (CT) scan opacification score of the sinuses at Week 52 (Japan and Korea only)	For clarification

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Inclusion Criteria 3 and **Section 9.3.7** Pregnancy and **Section 12.5** Contraceptive Guidance and Collection of Pregnancy Information	Changed 105 Days and 16 weeks to 4 months after the last drug administration as the time frame the WOCBP must commit to the contraception guidance	For consistency
Section 6.1 Inclusion Criteria 5	The word 'historical' was added to CT scan for clarification	For clarification
Section 6.1 Inclusion Criteria 6	**Reworded the inclusion criteria to the following:** Presence of two different symptoms for at least 12 weeks prior to screening of either: ❖ 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	For clarification
Section 6.1 Inclusion Criteria 9	Added 'including intranasal liquid steroid wash/ douching'	For clarification
Section 6.1 Exclusion Criteria 13	Changed 'prior to first mepolizumab dose' to 'prior to screening visit' Deleted chemotherapy	For clarification
Section 6.2 Exclusion Criteria 16	Change 'while at screening' to 'Not willing to be removed from a waiting list for NP surgery (if on one) or have pre-planned surgery date cancelled if randomized A waiting list is a list of patients waiting for a non-emergency or elective surgical procedure.'	For flexibility
Section 6.2 Exclusion Criteria 18	Deleted 'or corticosteroid nasal solution (intranasal corticosteroid is excepted),	For clarification
Section 6.2 Exclusion Criteria 22	Added 'change of dose' to the leukotriene antagonist treatment	For clarification
Section 6.2 Exclusion Criteria 23	Added 'commencement or change of dose' added to allergen immunotherapy	For clarification
Section 6.2 Exclusion Criteria 28	Deleted	Duplication of exclusion criteria 12

Section # and Name	Description of Change	Brief Rationale
Section 6.2 Exclusion Criteria 31	Added 'selected by the site'	For clarification
Section 6.3 randomisation criteria 11	**Added the following:** • 'Agree to be removed from the waiting list for NP surgery or have pre-planned surgery date cancelled' • '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 emergency department visit, or hospitalization ' • No changes in allergen immunotherapy allowed **Deleted the following:** Have been included into a waiting list for NP surgery	For clarification
Section 7.1 treatments administered Study treatment Table for placebo	Changed mepolizumab for placebo and changed the description of placebo from 'colourless' to 'colourless to pale yellow / pale brown '	Correction of transcription error
Section 7.6 Concomitant therapy	Added 'Initiation or changes in the doses of leukotriene receptor antagonist or allergen immunotherapy from screening to end of the study are not allowed.' Added 'or methy-prednisolone for Korea only)	For clarification
Section 7.6 Concomitant therapy; medication table	Clarified that 'Initiation or changes in the dosing regimen of leukotriene receptor antagonist or immunotherapy from screening to end of the study are not allowed.' On the table 'Prohibited' was added to medication 'washout' was replaced by 'time period' 'intranasal liquid steroid wash/douching (intranasal corticosteroid spray excepted)' was deleted	For clarification
Section 8.12 Early Withdrawal Visit	'as soon as possible' was changed to '28 days after the last dose'	For consistency
Section 9.1.1 Pre screening	Changed '2 weeks' to 2 weeks prior (unless specifically authorised by the medical monitor)	For clarification

Section # and Name	Description of Change	Brief Rationale
	Removed "including informed consent for the optional pharmacogenetics part of the study, as applicable)"	
Section 9.1.5 Critical procedures performed throughout treatment period (Visits 2 - 15) and Section 9.2.7. Olfaction testing: University of Pennsylvania Smell Identification Test (UPSIT)	Clarified that UPSIT test will be performed only in selected countries	For clarification and flexibility
Section 9.1.5.Critical procedures performed throughout treatment period (Visits 2 - 15)	Clarified that 12-lead ECG only to be performed at V2 and V15 Clarified Lab assessments are Haematology at all visits and biochemistry (including liver chemistries) at visits 2 and 15 only. Clarified that nasal endoscopy assessment will be performed at visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15 Removed CT scans Removed Nasal secretions for biomarkers Removed exit interview	For clarification
Section 9.2.1 endoscopy NP score	Added nasal endoscopy assessments can be carried out within a 3 day window prior to dosing for each study visit (apart from visit 2) but must not exceed the protocol defined windows of ± 7 days from the nominal study visit.	Allow flexibility in assessments
Section 9.2.3. Computed tomography (CT) scan	Removed this section as CT scans no longer performed	For clarification
Section 9.3.8.3. Prompt Reporting of Medical Device Incidents to Sponsor	Deleted 'The same individual will be the contact for the receipt of medical device reports and SAE.'	Duplication
Section.9.4.3. electrocardiograms	Clarified that the order of assessments is in the SPM	Clarification

Section # and Name	Description of Change	Brief Rationale
Section 9.4.4. Clinical Safety Laboratory Assessments	Added that the lab assessments are defined in Appendix 2	Clarification
Section 9.5 Pharmacokinetics	Removed collection of samples at visits 5 and 8	Reduce burden of assessments
Section 9.7 Genetics	Adjusted the blood volume to up to 6 ml	Allow flexibility
Section 9.8 Exploratory Biomarkers	Removed nasal secretions	Reduce burden of assessments
Section 9.11. exit interviews	Removed	Not required
Section 10.3 Statistical Analysis	Removed reference to analysis of exit interviews	To reflect removal of exit interviews from protocol
Section 12.2. Appendix 2: Clinical Laboratory Tests; Table 1	Removed % Reticulocytes Added Hepatitis B and C testing	Rectify that Reticulocytes will not be specifically measured Clarify that Hep B and C testing will be performed
Section 12.3. Appendix 3: Study Governance Considerations	Added 'the Directive 2001/20/EC'	This Directive might still be active at study start
Section 12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	The following was deleted: 'The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.'	It was part of the hidden text/ protocol template instructions and should have been deleted as it contradicts the bullet just before
Section .12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information	Deleted the following "Male participants with partners who become pregnant • Investigator will attempt to collect pregnancy information on any male participant's female partner of a male study participant who becomes pregnant while participating in this study. This applies only to participants who receive study treatment. • After obtaining the necessary signed informed consent from the pregnant	For consistency with the main body of the protocol

Section # and Name	Description of Change	Brief Rationale
	female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the partner's pregnancy. • Partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to GSK • Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure." Changed the following '24 hrs 'to '2 weeks' for the time when the pregnancy needs to be reported	
Section 12.12. Appendix 12: Assessment of nasal polyposis	Changed the diagram of Nasal polyps score	For clarification
Section 12.12 Appendix 13: CT scans	Removed this section	For clarification as no longer performed
References	Removed Lund 1993 and Bhattacharyya 1999	No longer required

Amendment 03 20-Feb-2018

Overall Rationale for the Amendment: The purpose of this amendment is to clarify that screen failures can also be re screened (not just run in failures) and that the ECG machine does not need to be automated.

Section # and Name	Description of Change	Brief Rationale
6.5 Screen/ Baseline/Run-in Failures	Change from: Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened. Re screening of participants that failed run-in will be permitted, however, advanced approval to proceed with re screen the participant must be obtained from the Medical Monitor (for contact details, see SPM). Change to: Re screening of participants will be permitted, however, advanced approval to proceed with re screening the participant must be obtained from the Medical Monitor (for contact details, see SPM).	To clarify that re screening is allowed not only for run-in failures but also screen failures
9.4.3 Electrocardiograms	Change from: A single 12-lead ECG will be obtained at each timepoint specified in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Change to: A single 12-lead ECG will be obtained at each timepoint specified in the SoA using an ECG machine to assess heart rate and measures PR, QRS, QT, and QTc intervals. (for further details refer to SPM).	To clarify that ECG machines with no automatic facility to calculate heart rate and measures PR, QRS, QT, and QTc intervals can be used.

Amendment 04 13-FEB-2020

Overall Rationale for the Amendment:

In order to reflect regulatory authority feedback, the following changes were made 1) updated analysis methodology for the co-primary endpoints, 2) clarification of the definition of surgery to include more invasive procedures for the secondary endpoint, 3) assess the proportion of patients requiring systemic steroids for nasal polyps instead of the total burden of systemic steroids. This amendment also includes two additional secondary endpoints of composite nasal symptoms score and loss of smell symptom score that were previously included as 'other' endpoints.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 4: objectives and endpoints	Moved the following endpoints from 'other' to secondary endpoints: • Proportion of participants requiring systemic steroids for nasal polyps up to Week 52. • 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. • Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52. Moved the following endpoint from secondary to 'other': • Number of milligrams (mgs) per year of prednisolone-equivalent OCS dose up to Week 52.	To reflect the movement of "other endpoints" to secondary endpoints following regulatory authority feedback
Clarify endpoints Synopsis, Section 5.1: Overall design	Change from: Other secondary endpoints are overall exposure to systemic steroids, expressed as mgs/year of prednisolone-equivalent oral corticosteroids (OCS), change from baseline in overall VAS symptom score, QoL (SNOT-22) at Week 52, with other time points being captured as "other" endpoints. Change to: secondary endpoints are the proportion of participants requiring systemic steroids for	To clarify endpoints following regulatory authority feedback

Section # and Name	Description of Change	Brief Rationale
	nasal polyps, change from baseline in overall VAS symptom score, composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) and loss of smell VAS score, QoL (SNOT-22) at Week 52, with other time points being captured as "other" endpoints.	
'Other' endpoints Section 4: objectives and endpoints	Change from: • 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 to: • 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: • Percentage of participants classified at Week 52 as responders according to a 9 point or greater decrease from baseline in SNOT-22 total score. Change to • Percentage of participants classified at Week 52 as responders according to a 8.9 point or greater decrease from baseline in SNOT-22 total score. The following was added: • Change from baseline in SNOT-22 domain scores at Week 52.	To reflect changes in 'other' endpoints following regulatory authority feedback and to correct a typographical error
Section 5.1: Overall design	Change from: As stated above, actual surgery is an important secondary efficacy endpoint. Given any surgical procedure can influence the co-primary endpoint, after randomization NP surgery is defined as any procedure involving instruments resulting in incision and removal of tissue (eg polypectomy) or dilatation of the air passages (eg balloon sinuplasty) in the nasal cavity.	To refine the definition of surgery following regulatory authority feedback

Section # and Name	Description of Change	Brief Rationale
	Change to: Any nasal surgical procedures can influence the co-primary endpoints, as can dilatation of the air passages (eg balloon sinuplasty) in the nasal cavity, therefore the impact of occurrence of either surgery or sinuplasty will be taken into consideration when assessing efficacy endpoints. As stated above, actual surgery is an important secondary efficacy endpoint. Evaluation of this key secondary endpoint will be based only on invasive procedures involving instruments resulting in incision and removal of tissue (eg polypectomy).	
Definition of surgery Section 9.2.3.: NP surgery	Change from: At each visit it will be recorded whether the participant is on a waiting list for NP surgery and whether the participant has received actual documented surgery. As an endpoint, for the purpose of this study, NP surgery is defined as any procedure involving instruments resulting in incision and removal of tissue (polypectomy) or dilatation of the air passages (e.g. balloon sinuplasty) in the nasal cavity Change to: At each visit it will be recorded whether the participant is on a waiting list for NP surgery and whether the participant has received actual documented surgery and/or sinuplasty. As an endpoint, for the purpose of this study, NP surgery is defined as any procedure involving instruments resulting in incision and removal of tissue (polypectomy) in the nasal cavity	To refine the definition of surgery following regulatory authority feedback
Section 10.2: Population Analyses	Changed from: All participants who sign the ICF Change to: All participants enrolled and for whom a record exists on the study database	To clarify the definition of the All Participants Enrolled population
Section 10.3: statistical analyses	Changed from: 4. Number of mgs per year of prednisolone-equivalent dose	To reflect the change in secondary endpoints following regulatory authority feedback

Section # and Name	Description of Change	Brief Rationale
	Changed to: 4. Proportion of participants 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	
Section 10.3.1: efficacy analyses	Change from: Total endoscopic nasal polyp score is collected at each clinical visit, the primary assessment will be at week 52. Nasal obstruction is collected daily throughout the study via eDiary. Nasal obstruction at Week 52 will be calculated as the mean of all measurements made in the 4 weeks prior to the visit (excluding the day of the visit). The mean VAS score over the last 7 days before Visit 2 will be used to determine the baseline value. Each primary endpoint will be analysed using a categorical approach. The change from baseline in each endpoint at Week 52 will categorised by various levels of improvement (e.g. 1 point decrease, 2 point decrease, 3 point decrease, 4 point or greater decrease), no change or worsening in score, and a least favourable category of actual surgery by Week 52. Participants who withdraw prematurely from the study will be included in the lowest efficacy category (actual surgery). 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. The comparison of mepolizumab with placebo will be expressed as an odds ratio and presented with corresponding 95% confidence interval and p-value. NP score and symptom scores have usually been analysed using models based on a normal distribution assumption for the response. Such models do not	To reflect the change in analysis following regulatory authority feedback

Section # and Name	Description of Change	Brief Rationale
	acknowledge the bounded response for the scales and there is no ideal approach to inclusion of surgery as a worst response. For the proportional odds model, it is unnecessary 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 comparisons of two treatments with no adjustment for covariates, this approach becomes equivalent to the Wilcoxon test. Change to: Total endoscopic nasal polyp score is collected at each clinical visit, the primary assessment will be at week 52 (centrally read data). Nasal obstruction is collected daily throughout the study via eDiary. Nasal obstruction at Week 52 will be calculated as the mean of all measurements made in the 4 weeks prior to the visit (excluding the day of the visit). The mean VAS score over the last 7 days before Visit 2 will be used to determine the baseline value. Participants who undergo surgery/sinuplasty prior to Week 52 will be assigned their worst observed value prior to surgery/sinuplasty. Participants who withdraw from the study without having experienced surgery/sinuplasty will be assigned their worst observed score prior to study withdrawal. The comparison of mepolizumab with placebo will be expressed as a difference in median change from baseline presented with corresponding 95% confidence intervals, the p-value for the difference between treatment groups will be based on the non-parametric Wilcoxon rank-sum test. The difference in median change between placebo and mepolizumab with associated 95% confidence intervals will be assessed by quantile regression using a bootstrap approach (Mehrotra DV 2017; Keene ON 2018), with covariates of treatment group, baseline score, baseline blood eosinophil count and region.	

Section # and Name	Description of Change	Brief Rationale
	Change from: Change from baseline in mean overall VAS symptom score at Week 52 (calculated as the mean of all measurements made in the 4 weeks prior to the visit (excluding the day of the visit)), change from baseline in SNOT-22 total score at Week 52 and number of mgs per year of prednisolone-equivalent OCS steroid dose will be analysed using a categorical approach as for the primary endpoint Change to: Change from baseline 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 VAS loss of smell score at Week 52 (calculated as the mean of all measurements made in the 4 weeks prior to Week 52), and change from baseline in SNOT-22 total score at Week 52 will be analysed in a similar manner to the co-primary endpoints. The proportion of participants requiring systemic steroids for nasal polyps will be analysed using a logistic regression model	
References	Added: Mehrotra DV, Liu F, Permutt T. Missing data in clinical trials: control-based mean imputation and sensitivity analysis. Pharmaceutical Statistics 2017; 16: 378-392. Keene O.N. Strategies for composite estimands in confirmatory clinical trials: Examples from trials in nasal polyps and steroid reduction. Pharmaceutical Statistics. 2018;18:78-84	To support changes following regulatory authority feedback

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1. SYNOPSIS

Protocol Title: 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)

Short Title: Effect of Mepolizumab in severe bilateral nasal polyps

Rationale:

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signaling. Neutralization of IL-5 with mepolizumab has been shown to reduce blood, sputum and tissue eosinophils and this has led GSK to develop mepolizumab as a treatment option in a number of eosinophilic diseases including nasal polyps (NP).

NUCALA (mepolizumab) is currently approved in countries such as the United States (US), Europe, Japan, Canada, Australia, South Korea, Switzerland and Taiwan as an add-on maintenance treatment (100 mg subcutaneously [SC] once every 4 weeks [Q4W]) for patients with severe asthma, and with an eosinophilic phenotype. NUCALA is currently provided as a lyophilized powder in a vial requiring reconstitution with sterile water for injection, however development of a liquid formulation is also underway.

As of September 2016, approximately 3744 participants have been exposed to at least one dose of mepolizumab in clinical studies across various eosinophilic-mediated indications. In addition, there are currently over 300 participants receiving mepolizumab as part of three long term access and compassionate use programs. All studies have shown that mepolizumab is well tolerated when administered by SC, intravenous (IV), or intramuscular (IM) routes. The highest dose administered in these studies was 750 mg IV.

A total of 74 participants with NP have been treated with mepolizumab 750 mg IV every 4 weeks for up to 6 months in two Phase II clinical studies (CRT110178 and MPP111782). Both studies provided information to suggest potential for efficacy and that the overall safety profile of mepolizumab in NP was similar to that observed in the mepolizumab clinical program in severe asthma and there were no known safety concerns that would preclude developing mepolizumab in NP.

Study CRT110178 was an investigator-led, collaborative research study of randomised, double-blind, placebo-controlled design of mepolizumab versus placebo in participants with severe primary NPs (Grade 3 or 4) or NPs that were recurrent after surgery (Grade 1 to 4). Participants were randomized to receive two single IV injections (28 days apart) of mepolizumab 750 mg IV (n=20) or placebo (n=10). The study was double blind up to 48 weeks. The primary endpoint was the change from baseline in total endoscopic NP score (sum of left and right nostril scores) assessed by endoscopy at Week 8. There was a statistically significant difference between mepolizumab 750 mg IV compared to placebo at Week 8 (-1.22, 90% CI: -2.28, -0.17; one –sided p=0.0258).

In the responder analysis (last observation carried forward - LOCF), mepolizumab produced a significant reduction in NP score in 60% of participants versus 10% of participants who received placebo. These effects were confirmed by changes on computed tomography (CT) scans. There were also significant improvements in symptoms such as loss of smell, postnasal drip, and obstruction at Week 8 with mepolizumab, but not in rhinorrhoea.

Study MPP111782 was originally designed as a two-part (Part A and Part B) randomized, double-blind, placebo controlled, multi-centre study to investigate the use of mepolizumab 750 mg IV versus placebo in reducing the need for surgery in participants with severe bilateral NP refractory to current standard of care (SoC). All participants were in need of surgery at the start of the study and had at least one prior surgery. One hundred and five participants were randomized to receive either six 750 mg IV injections of mepolizumab (54 participants) or placebo (51 participants), every 4 weeks. Participants who no longer required surgery at the end of Part A had the option to enter Part B where they were followed up for a further 6 months with no treatment. Limited data are available for Part B of the study as only 7 participants in the placebo group and 14 participants in the mepolizumab group entered before Part B was discontinued.

The primary endpoint was reduction in the need for surgery at the end of Part A (4 weeks post last dose, Week 25), defined as both an improvement in overall visual analogue scale (VAS) symptom score and reduction in the endoscopic NP score. A significantly greater proportion of participants in the mepolizumab group no longer required surgery at the end of Part A (p=0.003). A difference in mean change from baseline in total endoscopic NP score was observed between placebo and mepolizumab as early as Week 5, with a clear difference by Week 9. The overall patient-reported VAS symptom scores also supported the efficacy of mepolizumab, with a treatment difference from placebo at Week 25 of -1.78 (95% CI: -2.88, -0.68; p=0.002, PP Population). Statistically significant differences in favour of mepolizumab compared to placebo were also observed in Week 25 for individual VAS symptom scores and Sino-Nasal Outcome Test (SNOT)-22 questionnaire.

Taken together, the integrated evidence supports the proposition that mepolizumab may be effective in improving symptoms, reducing NP size and reducing the need for surgery in patients with recurrent disease despite current optimal medical management.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 100mg mepolizumab compared to placebo	• Change from baseline in total endoscopic NP score at Week 52. • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52.
Secondary	
• 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.

Overall Design:

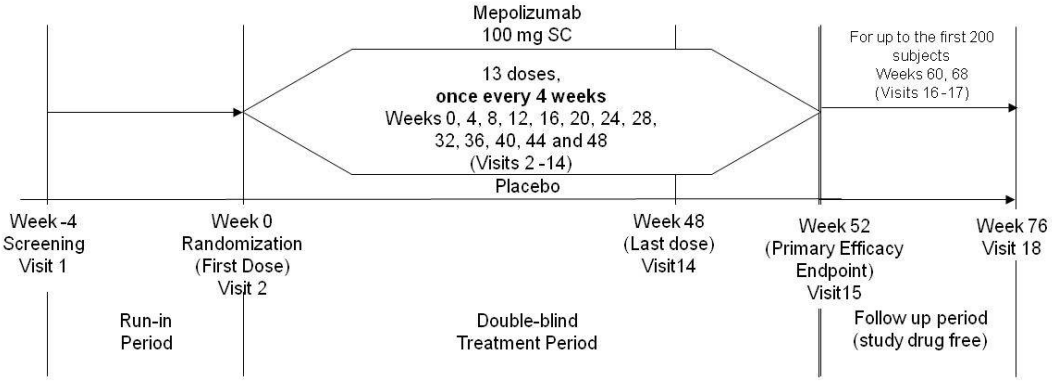
This is a randomized, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral NP.

The objective is to evaluate the safety and efficacy of mepolizumab 100 mg, administered SC by the Investigator or delegate via a pre-filled safety syringe every 4 weeks for 52 weeks. Efficacy of mepolizumab will be assessed using co-primary endpoints of change from baseline in endoscopic NP score (0-8) at Week 52 and nasal obstruction VAS symptom score during the 4 weeks prior to Week 52. Measurement of the co-primary endpoints will also be assessed throughout the study.

The key secondary endpoint is time to first actual surgery for NP by Week 52. Other secondary endpoints are the proportion of participants requiring systemic steroids for nasal polyps, change from baseline in overall VAS symptom score, composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) and loss of smell VAS score, QoL (SNOT-22) at Week 52, with other time points being captured as "other" endpoints.

The study population will consist of adult participants (≥18 years of age) with recurrent severe bilateral NP (defined as an average nasal obstruction VAS symptom score of >5 and an endoscopic NP score of at least 5 out of a maximum score of 8, with a minimum score of 2 in each nasal cavity). Participants must also have a history of at least one prior surgery for NP, have recurrent NP despite treatment with current SoC and in need for NP surgery. The need for current NP surgery is defined when the participant has an overall VAS symptom score greater than 7 in addition to a NP score ≥3 in at least one nostril.

Study Schematic



The study will include a 4 week run in period followed by randomisation to a 52-week treatment period. Throughout the entire study period (run in + treatment period + follow up), participants will be on the SoC for NP which consists of daily mometasone furorate nasal spray (MF), and if required, saline nasal douching, occasional short courses of high dose OCS and/or antibiotics. At the start of run in and throughout the study, participants will be placed on MF at the maximum prescribed dose (if not already) according to local label, if available, or in line with local SoC. The maximum dose is 2 actuations (50 micrograms (µg)/actuation) in each nostril twice daily which equals a total daily dose of 400 µg. For participants intolerant to this dose, the lower dose of 200µg can be used (2 actuations (50 µg /actuation) in each nostril once daily. The treatment period will consist of thirteen, 4-weekly doses of mepolizumab or placebo, delivered by SC injection. In addition, up to the first 200 randomized participants will be followed up every other month for up to a further 6 months after the Visit 15 (7 months post last dose) in order to assess maintenance of response and to validate a physiological model derived from the previous PhII study.

Number of Participants:

Assuming a screen fail rate of 30%, approximately 570 participants will need to be screened in order to allow for approximately 400 participants randomized (200 participants per arm).

Treatment Groups and Duration:

The currently marketed drug product, Nucala (mepolizumab), is supplied as a 100 mg single-dose vial containing a sterile, preservative-free, lyophilized powder for reconstitution and SC injection.

A liquid formulation of mepolizumab is under development which will be provided as pre-filled syringes in a safety syringe device for this study. The liquid formulation in a safety syringe device must be administered by a health care professional in this study. There will also be a matched safety syringe with placebo.

Participants who are successfully enrolled into the study will be randomized into one of two treatment groups, receiving a total of thirteen doses (one every four weeks):

• Group 1: 100 mg SC of mepolizumab on top of SoC which includes intranasal MF

• Group 2: Placebo SC on top of SoC which includes intranasal MF

A participant is considered to have completed study treatment if he/she attends study Visit 15 (Week 52).

For up to the first 200 randomized participants, the final study visit will be Week 76 (Visit 18). For the remainder of participants who are not participating in the 6 months no treatment follow up, the final study visit will be Week 52 (Visit 15).

The end of the whole study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

2. SCHEDULE OF ACTIVITIES (SOA)

	Procedure	Pre scree[9]	Screening [8]	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/ 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			

		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	
	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						

	Procedure	Pre scree[9]	Screening [8]	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	
	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.

3. INTRODUCTION

3.1. Study Rationale

Background on Nasal Polyposis

Nasal polyps (NP) is a chronic inflammatory disease of the nasal mucosa, characterized by soft tissue growth in the upper nasal cavity. The presence of polyps can cause long term symptoms of chronic rhinosinusitis (CRS) such as prominent nasal obstruction, post-nasal drip, loss of smell, facial pain /pressure and nasal discharge. These symptoms can greatly impact a patient's HR QoL. The European Position Paper on Rhinosinusitis and NP [EPOS, 2012] defines the severity of disease using a total severity visual analog scale (VAS) in which a patient is asked to indicate on a 10 cm VAS how troublesome they consider their symptoms. An overall VAS symptom score of 0-3 is defined as mild disease, >3-7 as moderate and >7-10 as severe [Lim, 2007]. Symptoms are invariably accompanied with findings of inflammation of the nasal mucosa and the presence of a polyp seen through nasal endoscopy or positive imaging findings, for example using computerized tomography (CT). The etiology of NP is currently unknown.

Current standard of care for patients with NP is treatment with intranasal corticosteroids (INCS) followed by short courses of oral corticosteroids (OCS) in severe cases when short term relief is required [EPOS, 2012]. Antibiotic courses may also be required for intercurrent sinus infection, which often complicates severe NP. Although many patients with NP can be adequately controlled with simple medical care (INCS and OCS, occasional nasal douching and antibiotic courses) [Alobid, 2012; Newton, 2008], progression to surgery as a result of severe symptoms and disruption to quality of life is common. Surgery, when ultimately indicated, involves the removal of the polyp tissue and diseased mucosa, restoring aeration of the nasal passage and sinuses. Over 250,000 NP surgeries are performed in the US annually (Bhattacharyya, 2010). However, polyps have a strong tendency to recur, often requiring repeat surgery [Levine, 1990; Larsen, 1997; Rucci, 2003; *Wynn*, 2004; Jankowski, 2006, Philpott, 2015] with a timescale that can vary from a few months to years. Data suggests patients with NP associated with tissue eosinophilia constitute the majority of those who have a recurrence after surgery [Brescia, 2015]. Repeat (revision) surgery is associated with diminishing success and a higher potential for adverse effects [Bhattacharyya, 2004; Chu, 1997], hence alternative treatment options are needed for this patient group.

IL-5 is the predominant cytokine in NP associated with tissue eosinophilia, promoting the activation and prolonged survival of eosinophils [Bachert, 1997; Bachert, 1998]. IL-5 is increased in NP tissue compared with that in healthy controls, and correlates with the degree of tissue eosinophilia, strongly suggesting a rationale for anti-IL-5 therapy in this condition [Bachert, 1997].

While the recurrence of bilateral NP despite surgery is common and known to be associated with the IL-5/eosinophilic pathway in adults, this is less so for children [Jones, 1999; EPOS, 2012]. The number of eosinophils and cells expressing messenger RNA for IL-4, IL-5 and IL-10 is higher in patients with CRS excluding cystic fibrosis (CF) versus those with CF and controls [EPOS, 2012]. Antrochoanal polyps are also another form of

NP more common in children that are usually unilateral and associated with low eosinophil tissue levels [EPOS, 2012].

The role of mepolizumab in NP

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa, mAb) that blocks human interleukin-5 (hIL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signaling. Neutralization of IL-5 with mepolizumab has been shown to reduce blood, sputum and tissue eosinophils and this has led GSK to develop mepolizumab as a treatment option in a number of eosinophilic diseases including NP.

NUCALA (mepolizumab) is currently approved in countries such as the United States (US), Europe, Japan, Canada, Australia, South Korea, Switzerland and Taiwan as an add-on maintenance treatment (100 mg subcutaneously [SC] once every 4 weeks [Q4W]) for patients with severe asthma, and with an eosinophilic phenotype. NUCALA is currently provided as a lyophilized powder in a vial requiring reconstitution with sterile water for injection, however development of a liquid formulation is also underway.

As of September 2016, approximately 3744 participants have been exposed to at least one dose of mepolizumab in clinical studies across various eosinophilic-mediated indications. In addition, there are currently over 300 participants receiving mepolizumab as part of three long term access and compassionate use programs. All studies have shown that mepolizumab is well tolerated when administered by SC, IV, or intramuscular (IM) routes. The highest dose administered in these studies was 750 mg IV.

A total of 74 participants with NP have been treated with mepolizumab 750 mg IV every 4 weeks for up to 6 months in two Phase II clinical studies (CRT110178 and MPP111782). Both studies provided information to suggest some efficacy and that the overall safety profile of mepolizumab in NP was similar to that observed in the mepolizumab clinical program in severe asthma and there were no known safety concerns that would preclude developing mepolizumab in NP.

Study CRT110178 was an investigator-led, collaborative research study of randomized, double-blind, placebo-controlled design of mepolizumab versus placebo in participants with severe primary NPs (Grade 3 or 4) or NPs that were recurrent after surgery (Grade 1 to 4). Participants were randomized to receive two single intravenous (IV) injections (28 days apart) of mepolizumab 750 mg IV (n=20) or placebo (n=10). The study was double blind up to 48 weeks. The primary endpoint was the difference in total endoscopic NP score which was the sum of left and right nostril scores assessed by endoscopy at Week 8 versus baseline. Given the grading of each nostril ranged from 0 (no polyp) to 4 (large polyp causing complete obstruction of the inferior meatus), a total score of up to 8 was possible. A statistically significant difference from placebo was observed for the treatment comparison of mepolizumab 750 mg IV versus placebo at Week 8 (-1.22, 90% CI: -2.28, -0.17; one –sided p=0.0258). These effects were confirmed by changes on CT scans. There were also significant improvements in symptoms such as loss of smell, postnasal drip, and obstruction at Week 8 with mepolizumab, but not in rhinorrhoea. A significant decrease in blood eosinophil counts (BEC) in the mepolizumab group compared with the placebo group was also observed.

Study MPP111782 was originally designed as a two-part (Part A and Part B) randomized, double-blind, placebo controlled, multi-centre study to investigate the use of mepolizumab 750 mg IV versus placebo in reducing the need for surgery in participants with severe bilateral NP refractory to current SoC. All participants were in need of surgery at the start of the study and had had at least one prior surgery. Participants were considered in need of surgery if they had an overall VAS symptom score of >7 and an endoscopic NP score of ≥3 in at least one nostril. One hundred and five participants were randomized to receive either six 750 mg IV injections of mepolizumab (54 participants) or placebo (51 participants), one injection every four weeks for up to a total of 6 doses in Part A. Participants who no longer required surgery at the end of Part A were given the chance to enter Part B where they were followed up for a further 6 months with no treatment.

The primary endpoint was a reduction in the need for surgery at the end of Part A (4 weeks post last dose, Week 25). This was taken as a combination of reduced severity of the NP condition as defined by an improvement in overall VAS symptom score (a score of 7 or below) with at least a reduction in endoscopic NP score to less than 3 or if the overall VAS symptom score is still greater than 7 then an endoscopic NP score to 1 or less for the nostril which has the highest score at baseline. Investigators agreed that these thresholds would clearly indicate that a participant had dropped below the threshold at which surgery would normally be indicated. By these criteria, a significantly greater proportion of participants in the mepolizumab group no longer required surgery at the end of Part A (p=0.003). A difference in the mean change from baseline in total endoscopic NP score between mepolizumab and placebo at Week 25 of -1.21 was demonstrated (95% CI: -1.92 to -0.50; p=0.001; ITT Population, LOCF).

The overall patient-reported VAS symptom scores also supported the efficacy of mepolizumab, with a treatment difference from placebo at Week 25 of -1.78 (95% CI: -2.88, -0.68; p=0.002, PP Population).

For individual VAS symptom scores including rhinorrhoea, mucus in the throat, nasal obstruction and loss of smell, the treatment differences were statistically significant in favor of mepolizumab compared with placebo at Week 25 (p≤0.002), and treatment differences could be observed as early as Week 9.

Participants in the mepolizumab group had a greater clinical and statistical improvement in the SNOT-22 questionnaire, a measure of HR QoL associated with CRS and NP, at Week 25, compared with participants who received placebo.

There were 14 participants in the mepolizumab group and 7 participants in the placebo group that entered Part B before this part of the study was discontinued. Data from these participants suggest the beneficial effects of mepolizumab treatment on NP score and symptoms may persist after cessation of treatment.

Taken together, the integrated evidence supports the proposition that mepolizumab may be effective in improving symptoms, reducing NP size and reducing the need for surgery in patients with recurrent disease despite current optimal medical management.

3.2. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) lyophilised drug product can be found in the Investigator's Brochure [GSK Document Number CM2003/00010/10].

3.2.1. Risk Assessment

The following section outlines the key risks, risk assessment and mitigation strategy for this protocol based on mepolizumab lyophilised formulation. The safety profile of the mepolizumab liquid formulation is anticipated to be similar to the lyophilised formulation.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Risk of Systemic Reactions including allergic reactions	Biopharmaceutical products - may elicit systemic (e.g. hypersensitivity) reactions. In the placebo controlled severe asthma (PCSA) studies both acute and delayed systemic reactions including hypersensitivity have been reported following administration of mepolizumab with incidence rates similar between mepolizumab and placebo-treated participants: • 54/915 participants or 6% in the mepolizumab [all doses combined] group • 7/263 participants or 3% in the mepolizumab 100 mg SC group • 12/344 participants or 3% in the mepolizumab 75 mg IV group • 20/412 participants or 5% in the placebo group. The most common symptoms reported with any systemic reaction included headache, rash, pruritus, fatigue, and dizziness. While rare, serious systemic reactions have been reported. Events of anaphylaxis attributed to mepolizumab have been reported post-marketing. Systemic reactions reported to date across the mepolizumab programme are summarized in the IB "Adverse Events of Special Interest" section; see also	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by the GSK study team and/or safety review team. Customised AE and SAE case report form (CRF) utilised for targeted collection of information for systemic reaction adverse events. Use of Joint NIAID/FAAN 2nd Symposium on Anaphylaxis to collect data on reports of anaphylaxis (see Appendix 11: Anaphylaxis Criteria). Participants are monitored in clinic for at least 1 hour following administration of IP for the first 3 doses then per institutional guidelines.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	'Special Warnings and Special Precautions for Use' section located in Section 6 titled 'Summary of Data and Guidance for the Investigator'[GSK Document Number **CM2003/00010/10**].	
Injection site reactions	In the PCSA studies the incidence of local site reactions with SC administration of mepolizumab was higher on mepolizumab 100 mg SC group (21/263 or 8%) compared to mepolizumab 75mg IV (10/344 or 3%) or placebo (13/412 or 3%). Symptoms included pain, erythema, swelling, itching, and burning sensation. Local injection site reactions reported to date across the mepolizumab program are summarized in the IB "Adverse Events of Special Interest" section; see also Section 6 titled 'Summary of Data and Guidance for the Investigator'[GSK Document Number **CM2003/00010/10**].	Daily monitoring of serious adverse events (SAEs) by medical monitor; regular systematic review of adverse event (AE)/SAE data from ongoing studies by GSK study team and/or safety review team. Customised AE and SAE case report form (CRF) utilised for targeted collection of information for local injection site reaction adverse events.
Potential risk of immunogenicity	Biopharmaceutical products may elicit anti-drug antibody (ADA) and neutralising antibody (NAB), which have the potential to modulate pharmacokinetic (PK), pharmacodynamic (PD) or produce adverse reactions. Mepolizumab has low immunogenic potential. Both incidence and titer data from completed studies demonstrate a low risk for loss of efficacy associated with AEs and/or altered PK/PD. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4'Clinical Immunogenicity' and a summary of immunogenicity findings in Section 6 'Other Potentially Clinically Relevant Information for the Investigator'[GSK Document Number **CM2003/00010/10**].	Blood samples will be collected for detection of both ADA and Nab.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Potential risk for injury with phlebotomy	Risks with phlebotomy include bruising, bleeding, infection, nerve damage.	Procedures to be performed by trained personnel (i.e., study nurse)

As of September 2016, approximately 3744 participants have been exposed to at least one dose of mepolizumab in clinical studies across various eosinophilic-mediated indications. In addition, there are currently over 300 participants receiving mepolizumab as part of three long term access and compassionate use programs. All studies have shown that mepolizumab is well tolerated when administered by SC, IV, or intramuscular (IM) routes. The highest dose administered in these studies was 750 mg IV.

Mepolizumab is currently approved for severe asthma with an eosinophilic phenotype at a dose of 100 mg SC every 4 weeks. In this population, over 1200 participants with severe asthma that have received at least one dose of mepolizumab, of which approximately 1000 have received mepolizumab at 100 mg SC, either as part of a randomized placebo-controlled study or in open-label extensions studies. The total treatment exposure for the approximate 1000 participants who received mepolizumab 100 mg SC was equivalent to over 1000 participant years. In addition, over 914 participants have been treated with mepolizumab 100 mg SC up to 12 months and over 340 participants for approximately 3.5 years.

In studies of patients with severe asthma, 177 participants had concomitant diagnosis of NP and received mepolizumab with 143 participants receiving mepolizumab for ≥1 year. Given patients with severe asthma in general have higher morbidity and mortality than those with severe NP, the substantial long-term safety information already collected in severe asthma could be considered relevant and informative for patients with NP.

A total of 74 participants with NP have been treated with mepolizumab 750 mg IV every 4 weeks for up to 6 months in two Phase II clinical studies (CRT110178 and MPP111782). Both studies provided information to suggest that the overall safety profile of mepolizumab in NP was similar to that observed in the mepolizumab clinical program in severe asthma and there were no known safety concerns that would preclude developing mepolizumab in NP. Of note, the dose of 750 mg IV every 4 weeks used in the two Phase II studies was significantly higher than the 100 mg SC every 4 weeks that is proposed for the two Phase III studies.

3.2.2. Benefit Assessment

In addition to asthma and NP, Mepolizumab has demonstrated clinical benefit in other conditions where eosinophilia is considered to play an important part in the pathology, e.g., HES [Rothenberg, 2008] and EGPA [Kim, 2010; Moosig, 2011].

In the proposed study, benefit considerations for a participant may include:

- Potential to receive active drug during study conduct that may have clinical utility
- Contributing to the process of developing new therapies in an area of unmet need
- Medical evaluations/assessments associated with study procedures

3.2.3. Overall Benefit: Risk Conclusion

Current data from mepolizumab preclinical and clinical development indicate the ability of mepolizumab to inhibit IL-5 leading to consistent reduction in blood eosinophils, with demonstration of clinical benefit in the treatment of conditions associated with eosinophilic inflammation. Data from Phase II studies in NP have shown efficacy in both NP score and symptoms as well as impact on the need for surgery. In addition, data from the Phase III asthma programme with mepolizumab demonstrate, compared to placebo, a reduction in asthma exacerbations, improvements in asthma control and quality of life (as measured by the ACQ-5 and SGRQ, respectively), improvements in lung function and a reduction in OCS use in those participants on chronic OCS treatment.

The higher morbidity and mortality in severe asthma compared with NP and the substantial long-term safety information already collected in severe asthma, suggest that to date, the safety profile of mepolizumab has been favourable and the benefit/risk profile supports ongoing development in patients with bilateral severe NP.

The change in drug product presentation from a lyophilised drug product to a liquid drug product in a safety syringe is not anticipated to alter the overall benefit: risk. Treatment will be administered by a trained health care professional at the clinic and participants will be closely observed for at least 1 hr following administration of IP for the first 3 doses then per institutional guidelines.

4. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of 100 mg mepolizumab compared to placebo	• Change from baseline in total endoscopic NP score at Week 52 • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52.
Secondary	
• 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.

Objectives	Endpoints
• 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.

Objectives	Endpoints
"Other"	
• 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. • 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 a 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 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 and overall VAS symptom score.
• To evaluate exploratory biomarker of nasal polyposis and response to 100mg mepolizumab compared to placebo	• Evaluate exploratory blood biomarkers (including blood eosinophils) on response to mepolizumab.

Objectives	Endpoints
• 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 antibiotic up to Week 52.
• To further evaluate the efficacy of 100mg mepolizumab compared placebo in the sub-group 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. • 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.

Objectives	Endpoints
Safety	
• 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	
• To evaluate the pharmacokinetics of 100mg mepolizumab	• PK concentrations and Population PK parameters • PK/PD (blood eosinophil count) analysis

5. STUDY DESIGN

5.1. Overall Design

This is a randomized, 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 NP.

The objective is to evaluate the safety and efficacy of mepolizumab 100 mg, administered SC by the Investigator or delegate via a pre-filled safety syringe every 4 weeks of a 52week treatment period. Efficacy of mepolizumab will be assessed using a co-primary endpoints of change from baseline in endoscopic NP score (0-8) and nasal obstruction VAS symptom score during the 4 weeks prior to Week 52. Measurement of the co-primary endpoints will also be assessed at all other time points through the study.

The key secondary endpoint is time to first actual surgery for NP by Week 52. Other secondary endpoints are the proportion of participants requiring systemic steroids for nasal polyps, change from baseline in overall VAS symptom score, composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) and loss of smell VAS score, QoL (SNOT-22) at Week 52, with other time points being captured as "other" endpoints.

For those participants who have a concomitant diagnosis of asthma, the level of asthma control as assessed by Asthma Control Questionnaire (ACQ-5) and the number of clinically significant asthma exacerbation will also be measured as "other" endpoint.

The population will consist of adult participants (≥18 years of age) with recurrent severe bilateral NP (defined as an average obstruction VAS symptom score of >5 and an endoscopic NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). They must also have a history of at least one prior surgery for NP

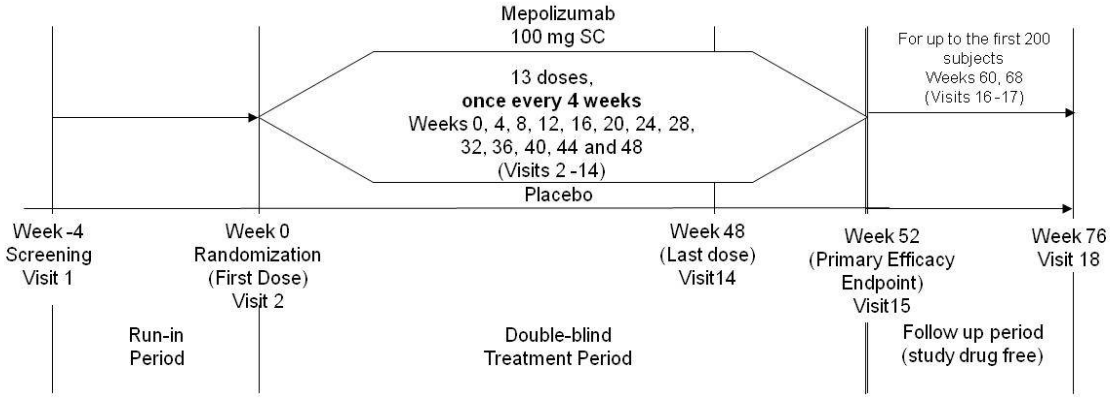
and recurrent NP despite treatment with current standard of care. Participants must be in current need for NP surgery as defined by an overall VAS symptom score greater than 7 in addition to a NP score ≥3 in at least one nostril.

For the purpose of inclusion into this study, NP surgery is defined as any procedure involving instruments with resulting incision (cutting open) and removal of the polyp tissue from the nasal cavity (polypectomy). Any procedure involving instrumentation in the nasal cavity resulting in dilatation of the nasal passage such as balloon sinuplasty, insertion of coated stents or direct injection of steroids or other medication without any removal of NP tissue does not fulfil this criterion. This is because there is no significant reduction in overall eosinophilic load in the nasal cavity. Consequently, it is difficult to discern whether any recurrence of NP disease after such procedures is actually driven by eosinophilia or not.

Any nasal surgical procedures can influence the co-primary endpoints, as can dilatation of the air passages (eg balloon sinuplasty) in the nasal cavity, therefore the impact of occurrence of either surgery or sinuplasty will be taken into consideration when assessing efficacy endpoints. As stated above, actual surgery is an important secondary efficacy endpoint. Evaluation of this key secondary endpoint will be based only on invasive procedures involving instruments resulting in incision and removal of tissue (eg polypectomy). Diagnostic or investigative procedures such as nasal endoscopy would not be considered as surgery.

To ensure that this study can detect a difference in surgical outcome between the two treatment arms, participants, whom in the opinion of the investigator are contraindicated for NP surgery, will be excluded.

Figure 1 Study Schematic



The study will include a 4-week run in period followed by randomization to a 52-week treatment period. Throughout the entire study period (run in + treatment period + follow up), participants will be on the SoC for NP which consists of daily MF, saline nasal douching as required and, if required, occasional short courses of high dose OCS and/or antibiotics. Patients who have NP surgery during the study are allowed to continue on study treatment till completion of the 52-week treatment period. This is to reflect the real

life circumstances in which mepolizumab is intended to be used as a concomitant therapy on top of SoC. During the run-in period, participants will complete baseline safety evaluations, measures of NP status and be educated in the completion of participant eDiary. At the start of run in and throughout the study, participants will be placed on MF at the maximum prescribed dose (if not already) according to local label, if available, or in line with local SoC. The treatment period will consist of thirteen, 4-weekly doses of mepolizumab or placebo, delivered by SC injection on top of SoC. The previous phase II study suggests persistence of beneficial effects after cessation of mepolizumab treatment. A physiological model linking mepolizumab binding to IL-5, IL-5 to blood eosinophil count, and blood eosinophil count to endoscopic NP score was used to describe the wash-out phase of the previous Phase II studies. This model was then used to predict the current proposed dose of 100 mg SC of mepolizumab. To validate this physiological model, the first 200 randomized participants will be followed up every other month for up to a further 6 months after the Week 52 visit (7 months post last dose). This number of participants is also thought to be sufficient to inform on the maintenance of response after cessation of treatment.

5.2. Number of Participants

This study will investigate NP participants most likely to benefit from mepolizumab treatment. GSK believes that a patient population with severe NP (as defined by an obstruction VAS assessment of symptoms >5 with recurrent bilateral NP, despite current SoC) is most likely to be associated with nasal tissue eosinophilia and therefore has the potential to benefit from treatment with anti-IL5 monoclonal antibody treatment.

Assuming a screen fail rate of 30%, approximately 570 participants will need to be screened in order to allow for 400 participants randomized (200 participants per arm).

5.3. Participant and Study Completion

Final treatment visit: For all participants this will be Week 52 (Visit 15), 4 weeks after the last expected injection at Visit 14.

Final study visit: for up to the first 200 randomized participants this will be Week 76 (Visit 18) and for the remainder will be Week 52 (Visit 15).

The end of the whole study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

GSK propose to assess the efficacy of mepolizumab by objectively measuring its ability to reduce the NP size and the effects of this reduction in improving the typical symptoms associated with NP. This study will use centrally read total endoscopic NP score by assessing the change from baseline at Week 52 as well as the patient assessed nasal obstruction VAS symptom score as the co primary outcome measures. In addition, the key secondary endpoint of actual surgery will be assessed at 52 weeks as surgery is also of great importance to patients and physicians.

This study will recruit patients who have severe NP that are refractory to SoC medical treatment. In most cases these patients are at the stage of needing surgical intervention [EPOS, 2012]. By deactivating and reducing the survival time of eosinophils in NP through IL-5 inhibition, mepolizumab can potentially reduce inflammation of the mucosa, and restore aeration of the nasal passage and sinuses through polyp volume reduction.

Therefore, assessment of NP size based on endoscopic NP score as a measure of efficacy is objective and reasonable when supported with data from a symptomatic endpoint such as nasal obstruction VAS score.

The proposal is to have the co primaries of endoscopic score and nasal obstruction VAS score so as to capture both objective assessment of obstruction and symptoms.

Other NP symptoms consisting of nasal discharge, mucus in the throat, loss of smell, facial pain and overall VAS symptom score will be assessed throughout the duration of this Phase III study, including follow up.

The severe symptoms of NP can result in significant disruption to quality of life and productivity of patients. This Phase III study will utilize SNOT-22 and SF-36 questionnaires as measures of QoL. The WPAI questionnaire is also included to assess the impact of treatment on absenteeism, presenteeism, productivity loss, and activity impairment of participants in this study.

Participants are treated with mepolizumab for 13 doses at 28 day intervals. Therefore, assessment of the primary endpoint will be conducted 52 weeks after initiation of therapy.

Two Phase II studies conducted with mepolizumab in severe NP suggest that although treatment with up to 6, 4-weekly doses, are sufficient to demonstrate efficacy of mepolizumab compared to placebo, the maximal effect may not have been achieved. Extending the exploration to thirteen 4 weekly doses will therefore increase the knowledge on the time to potential maximal effect.

In Study CRT110178 significant clinical improvement in NP score was observed after two doses of mepolizumab. The second study, MPP111782, also demonstrated a reduction in the need for surgery, as assessed by a pre-defined composite endpoint based on endoscopic NP score and overall VAS symptom score after 6 doses. A reduction in the number of participants undergoing surgery was also observed. Surgery is an important endpoint for patients and physicians as well as payors as it shows a direct cost burden. Given there is a potential for delay between the decision to have surgery and the actual surgical event, this study will also measure time to admission to a waiting list for NP surgery, a potential surrogate for actual surgery.

Short courses of OCS are part of SoC for severe NP and are known to provide significant improvements in symptoms and reduction in NP size. However, this form of treatment strategy is limited by the short-lived beneficial effects and the significant systemic adverse events, which prevent prolonged and/or frequent use. If mepolizumab is

effective, it has the potential to reduce the overall exposure of patients to systemic steroid therapy, and this will be measured in the study.

The target population for mepolizumab in NP is patients who are refractory to current SoC and highly symptomatic as a consequence. Mepolizumab is intended to be administered chronically on a background of INCS, and other medical therapy usually given as short courses as required (OCS, occasional nasal douching, antibiotic courses) before surgery is considered. There is currently no other chronic treatment that can be added to INCS that can be considered appropriate for an active control in this population. As such, placebo added to SoC will be utilized as the appropriate control.

Mometasone furoate (MF) is the only INCS currently approved for the treatment for NP both in Europe and US and will be part of the SoC in this study. All participants will be provided and are required to take MF at the maximum prescribable dose according to local label, if available, or as per local SoC. This is usually 400 micrograms (μg) which equals 2 actuations (50 μg/actuation) in each nostril twice daily. For participants that are intolerant to this dose, the lower dose of 200μg can be used (2 actuations (50 μg /actuation) in each nostril once daily).

All participants randomized to IP will have their co-primary endpoint and NP surgical status tracked for the duration of the study. Participants may choose to discontinue use of IP at any time but full accountability of IP at the end of the study is required for all participants. To provide information on the durability and maintenance of mepolizumab effect after cessation of treatment, up to the first 200 participants randomized will be followed for a further 6 months without treatment with IP.

5.5. Dose Justification

To date the clinical pharmacology of mepolizumab, an IgG1 mAb, is wholly consistent with other mAbs targeting soluble ligands: the pharmacokinetics are linear, dose-proportional, and time-independent after both IV and SC administration. Of note, a population PK meta-analysis across studies and indications has not identified any covariates of particular clinical interest, mitigating the need for further investigations and dose adjustment in special populations. Mepolizumab's potential for drug-drug interaction is deemed low in light of its elimination pathways and because IL-5 does not signal via hepatocytes. Based on these clinical pharmacology findings and the results of study MPP111782, the clinical pharmacology of mepolizumab administered to participants with NP is considered similar to those with severe asthma.

The proposed dose of 100 mg SC in NP in this study is supported by data from several studies:

- Clinical efficacy of mepolizumab in participants with NP has only been investigated at a supra-pharmacological dose of 750 mg IV Q4W to date, although participants were followed for six months of washout.
- Two studies in participants with severe asthma MEA112997 and MEA114092 provided evidence of a dose response to suppression of blood eosinophil count.

- In study MEA112997, the lowest dose of 75 mg IV (equivalent to the proposed 100 mg SC dose) gave 78% inhibition.
- Higher doses of 250 mg IV and 750 mg IV provided only modest increases in suppression (86% and 88%, respectively) indicating that the lowest dose provides approximately 90% of maximal pharmacological response attributable to drug.
- A subsequent clinical pharmacology study MEA114092 confirmed equivalence of the SC route of administration and identified the half-maximal pharmacological dose of 11 mg SC, consistent with study MEA112997.
- The approved severe asthma dosing regimen of 100 mg SC dose Q4W provides 55% overlap with 750 mg IV data when given 4-weekly.

Since initiation of the NP Phase II program, a meta-analysis of mepolizumab blood eosinophil exposure and dose response across all indications has been conducted to investigate the role disease plays in mepolizumab response. When examined, the distribution of baseline eosinophil count (BEC) in participants enrolled in the Phase II NP studies was broadly similar to that seen in the severe asthma program after adjustment for inhaled and oral corticosteroid usage, and hence the exposure and dose responses for other diseases are predictive of NP. This finding was confirmed using BEC data from the Phase II NP study MPP111782. These data were predicted independently using a physiological exposure-response model of mepolizumab binding to IL-5, coupled to IL-5 action on BEC. After validation, the model was used to simulate alternative dosing regimens of interest in patients with NP, and then estimate the degree of pharmacological overlap 100 mg and 300 mg SC doses have with the tested 750 mg IV Q4W regimen for a range of dosing frequencies. Results show considerable overlap between monthly doses of 100 mg and 300 mg SC and the tested 750 mg IV Q4W.

In addition, the Phase II studies assessing mepolizumab safety and efficacy in NP CRT110178 and MPP111782 both followed participants for periods beyond treatment with mepolizumab 750 mg IV. During the six-month period following mepolizumab treatment, there was evidence of sustained treatment effect. The BEC suppression continues to correlate with a reduced clinical score until NP participants show evidence of blood eosinophil return to baseline after approximately three months (three mepolizumab half-lives). Although numbers are small in both studies, these consistent observations provide a qualitative guide to the degree of blood eosinophil suppression necessary for sustained chronic dosing. Simulations of blood eosinophil count for the two studies suggest that 100 mg Q4W will provide consistent blood eosinophil suppression to levels that were seen during the period of washout where efficacy was sustained.

Given the considerable human safety data in severe asthma, it would therefore seem reasonable to assess this dose for potential efficacy in the target population of patients with NP. Considering the observed IV similarity of clinical pharmacology between patients with severe asthma and NP, overlapping pharmacological response predicted from a model validated in participants with NP, and experiential safety data for the range of doses of mepolizumab in participants from a host of diseases, the assessment of 100 mg SC to provide safety and efficacy information in this study is warranted.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. 18 years of age and older inclusive, at the time of signing the informed consent.

WEIGHT
2. Body weight greater or equal to 40kg.

Gender
3. Male or female participants (with appropriate contraceptive methods) to be eligible for entry into the study; i. To be eligible for entry into the study Woman of Childbearing Potential (WOCBP; see Appendix 5 for definition) must commit to consistent and correct use of an acceptable method of birth control from the time of consent, for the duration of the trial, and for 4 months after last study drug administration. See Appendix 5 for a listing of acceptable methods of birth control.
Previous polyps surgery
4. Participants who have had at least one previous surgery in the previous 10 years for the removal of NP. NP Surgery is defined as any procedure involving instruments with resulting incision (cutting open) and removal of polyp tissue from the nasal cavity (polypectomy). For the purpose of inclusion into this study any procedure involving instrumentation in the nasal cavity resulting in dilatation of the nasal passage such as balloon sinuplasty, insertion of coated stents or direct injection of steroids or other medication without any removal of NP tissue is not accepted.

Current polyps diagnosis medication and need for surgery
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

INFORMED CONSENT
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.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

CONCURRENT CONDITIONS/MEDICAL HISTORY
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.
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
10. Participants where NP surgery is contraindicated in the opinion of the Investigator
11. Participants with a known medical history of HIV infection.
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 other monoclonal antibody therapy.
16. Not willing to be removed from a waiting list for NP surgery (if on one) or have pre-planned surgery date cancelled if randomized A waiting list is a list of patients waiting for a non-emergency or elective surgical procedure.
17. Participants that have taken part in previous mepolizumab, reslizumab, dupilumab or benralizumab studies

CONCOMITANT MEDICATIONS
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.

Pregnancy:
24. Women who are pregnant or lactating or are planning on becoming pregnant during the study.
Smoking History:
25. Participants who currently smoke (including e-cigarettes) or have smoked in the last 6 months

Other Diseases/Abnormalities:
26. Any participant who is considered unlikely to survive the duration of the study period or has any rapidly progressing disease or immediate life-threatening illness (e.g. cancer). In addition, any participant who has any other condition (e.g. neurological condition) that is likely to affect respiratory function should not be included in the study.
27. **Other Concurrent Medical Conditions:** Participants who have known, pre-existing, clinically significant endocrine, autoimmune, cardiovascular, metabolic, neurological, renal, gastrointestinal, hepatic, haematological or any other system abnormalities that are uncontrolled with standard treatment.
28. Immunocompromised, other than that explained by the use of corticosteroids taken as therapy
29. A current malignancy or previous history of cancer in remission for less than 12 months prior to screening. **Note**: Participants with successfully treated basal cell carcinoma, squamous cell carcinoma of the skin, or cervical carcinoma in situ, with no evidence of recurrence may participate in the study.

Severe Hepatic Impairment:
30. **Unstable liver disease:** Current active liver or biliary disease (with the exception of Gilbert's syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment). *Notes:* *Stable chronic liver disease should generally be defined by the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.* *Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if participant otherwise meets entry criteria* ALT >2xULN Bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%). Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, persistent jaundice, or cirrhosis

12-Lead ECG:
31. QTc >450 msec or QTc > 480 msec in participants with bundle branch block at visit 1 NOTES: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF). It is either machine-read or manually over-read The specific formula used to determine eligibility and discontinuation for an individual participant should be selected by the site prior to initiation of the study and the same method should be utilized throughout the study for the individual.

Drug or Alcohol Abuse:
32. A known or suspected history of alcohol or drug abuse within 2 years prior to Screening (Visit 1) that in the opinion of the investigator would prevent the participant from completing the study procedures.

Affiliation with Investigator Site:
33. Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the afore mentioned that is involved in this study.

Inability to Read:
34. In the opinion of the investigator, any participant who is unable to read and/or would not be able to complete a questionnaire.

6.3. Randomisation Criteria

Those participants who meet the randomization criteria below will be randomized into the study until the target of approximately 400 randomized participants is reached.

At the end of the run-in period, study participants must fulfil the following additional criteria in order to be randomized to study treatment:

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).
6. Laboratory abnormality: No evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
7. Liver Function Tests: obtained at Visit 1:
    a. ALT<2x ULN (upper limit of normal)
    b. AST<2x ULN
    c. Alk Phos ≤ 2.0x ULN
    d. Bilirubin ≤ 1.5x ULN (isolated bilirubin>1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)
8. Asthma Exacerbation: No asthma exacerbations during run-in period. An asthma exacerbation is 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 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. a 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 exceeded this 6 week period
11. Agree to be removed from a waiting list for NP surgery, if on one, or have pre-planned NP surgery date cancelled

6.4. Participant and Study Completion

For determination of participant disposition, participants will be considered to have completed the study upon completion of Visit 15 (Week 52).

The end of the study is defined as the last participant's last visit.

6.5. Screen/Baseline/Run-in Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study (fail screening). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

For the purposes of this study, screening failures will be sub-divided as follows:

- Participants will be assigned a study number at the time of signing the informed consent (Pre-screen Visit). Participants who do not progress to the Screening Visit will be deemed a pre-screen failure.
- Those participants that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period will be designated as screen failures.
- Those participants that enter the run-in period, but are not randomized, will be designated as run-in failures.

Re screening of participants will be permitted, however, advanced approval to proceed with re screening the participant must be obtained from the Medical Monitor (for contact details, see SPM).

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The currently marketed drug product, Nucala (mepolizumab), is supplied as a 100 mg single-dose vial containing a sterile, preservative-free, lyophilized powder for reconstitution and subcutaneous injection.

A liquid formulation of mepolizumab is under development which will be provided as pre-filled syringes in a safety syringe device for this study. The liquid formulation has a distinct advantage over the lyophilized product as it does not require reconstitution, and the devices (upon commercial registration) will simplify and facilitate administration. The liquid formulation in a safety syringe device must be administered by a health care professional in this study.

There will also be a matched safety syringe with placebo. Both active and placebo drug products are stored at 2-8°C condition, protected from light.

The study treatment consists of up to 18 visits with a maximal total treatment duration of the study of approximately 52 weeks and maximum study duration of approximately 82 weeks. Screened participants will enter a 4 week run in period, followed by up to 52 week treatment period. Up to the first 200 randomized participants will be further followed up for a drug free period of up to 28 weeks with no injections.

Participants who are successfully enrolled into the study will be randomized into one of two treatment groups, receiving a total of thirteen doses (one every four weeks):

- Group 1: 100 mg SC of mepolizumab on top of SoC which includes intranasal mometasone furorate (MF)
- Group 2: Placebo SC on top of SoC which includes intranasal MF

All participants will be provided and are required to take MF at the maximum prescribable dose according to local label, if available, or as per local SoC. This is usually 400 micrograms (µg), 2 actuations (50 µg/actuation) in each nostril twice daily. For participants that are intolerant to this dose, the lower dose of 200µg can be used (2 actuations (50 µg /actuation) in each nostril once daily).

Study treatment completion is taken as Visit 15 which is Week 52 of the study for each individual participant.

7.1. Treatments Administered

	Study Treatment
Product name:	Mepolizumab Injection, 100 mg/mL
Device:	Safety syringe
Formulation description:	100 mg/mL mepolizumab with sodium phosphate, citric acid, sucrose, Disodium EDTA, Water for Injection and polysorbate 80
Dosage form:	Sterile, liquid formulation
Unit dose strength(s)/Dosage level(s):	100 mg/mL; 1.0 mL (deliverable)
Route of Administration	SC injection
Dosing instructions:	SC dose in thigh, abdomen or upper arm every 4 weeks
Physical description: mepolizumab	Clear to opalescent, colourless to pale yellow to pale brown sterile solution for SC injection in a single-use, safety syringe
Physical description of injection device:	Single use, disposable safety syringe device assembled with a pre-filled syringe containing mepolizumab solution. A plastic needle cover shields the needle before and after injection to minimise the potential for needle stick injuries.
Manufacturer/source of procurement:	Pre-filled syringe is filled with mepolizumab solution and assembled into a safety syringe device at GSK, Barnard Castle, UK.

	Study Treatment
Product name:	Placebo to match Mepolizumab Injection
Device:	Safety syringe
Formulation description:	sodium phosphate, citric acid, sucrose, Disodium EDTA, Water for injection and polysorbate 80
Dosage form:	Sterile, liquid formulation
Unit dose strength(s)/Dosage level(s):	1.0 mL (deliverable)
Route of Administration	SC injection
Dosing instructions:	SC dose in thigh, abdomen or upper arm every 4 weeks
Physical description: placebo	Clear to opalescent, colourless to pale yellow / pale brown sterile solution for SC injection in a single-use, safety syringe
Physical description of injection device:	Single use, disposable safety syringe device assembled with a pre-filled syringe containing placebo solution. A plastic needle cover shields the needle before and after injection to minimise the potential for needle stick injuries.
Manufacturer/source of procurement:	Pre-filled syringe is filled with placebo solution and assembled into a safety syringe device at GSK, Barnard Castle, UK.

7.1.1. Medical Devices

Mepolizumab Injection, 100 mg/mL or Placebo to match Mepolizumab Injection, are provided for use in this study as a prefilled syringe contained within a safety syringe.

The components that comprise the prefilled syringe, including glass barrel with pre staked needle and stopper are sourced from Becton Dickinson. The prefilled syringe is filled and assembled at GSK Barnard Castle. The prefilled syringe is assembled with safety syringe device components at GSK Barnard Castle. The safety syringe components are also sourced from Becton Dickinson. The devices used in the study are representative of the devices planned to be marketed for the product.

The instructions for use (IFU) of these injection devices are provided in the SPM. The instructions were developed and optimized as a result of formative human factors studies.

GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 9.3).

7.2. Method of Treatment Assignment

Participants eligible to enter the study will be assigned to treatment randomly via an interactive response technology (IRT) system. The randomization schedule will be generated using the GSK validated randomization software RandAll NG. The study will be randomized separately for each country. Participants will be assigned to study treatment in accordance with the randomisation schedule. Once a randomization number has been assigned to a participant, it cannot be reassigned to any other participant in the study.

Study treatment will be dispensed at the study visits summarized in SoA

Returned study treatment should not be re-dispensed to the participants.

7.3. Blinding

The site staff and central study team will be blinded to each participant's eosinophil count (including white blood count differential).

RAMOS NG will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. GSK must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote is available). In this case, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

In the case of a **medical emergency or in the event of a serious medical condition**, when knowledge of the investigational product is essential for the clinical management or welfare of the participant, **an investigator or other physician managing the participant may decide to un-blind that participant's treatment code**. The investigator will make every effort to contact the GSK Medical Monitor or appropriate GSK study personnel before un-blinding to discuss options. If the blind is broken for any reason and the investigator is unable to contact GSK prior to un-blinding, the investigator must notify GSK **as soon as possible following** the un-blinding incident **without revealing the participant's study treatment assignment,** unless the information is important to the safety of participants remaining in the study. In addition, the investigator will record the date and reason for revealing the blinded treatment assignment for that participant in the appropriate data collection tool.

A participant may continue in the study if that participant's treatment assignment is unblinded. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required.

Study treatment must be dispensed or administered according to procedures described herein. Only participants enrolled in the study may receive study treatment. Only authorised site staff may supply study treatment. All study treatment must be stored in a secure area with access limited to the investigator and authorised site staff.

Mepolizumab Injection, 100 mg/mL or Placebo to match Mepolizumab injection, will be supplied in a single use prefilled syringe in a safety syringe devise and should be stored in a refrigerator at 2-8°C with protection from light. Each injection device will contain 100 mg mepolizumab or placebo as a single 1.0 mL injection of the liquid drug product. Maintenance of a temperature log at the clinical dispensing sites (manual or automated) is required.

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SPM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff.
- A Material Safety Data Sheet/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.

7.5. Treatment Compliance

- Participants will receive study treatment directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment.
- Participants will be monitored for 1 hour after IP administrations in the clinic following the first three injections. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there are personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the participant including administration of medications (e.g., epinephrine), and have access to a system that can promptly transport the patient to another facility for additional care if appropriate.
- Administration will be documented in the source documents and reported in the CRF.

7.6. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The study site will supply INCS (MF) and oral OCS (prednisolone, prednisone or methy-prednisolone for Korea only) as part of SoC medication that will be provided by the sponsor detailed in the SPM.

Initiation or changes in the dosing regimen of leukotriene receptor antagonist or allergen immunotherapy from screening to end of the study are not allowed. Changes in the dosing regimen of INCS from screening to end of the study are not allowed.

The following medications may be used for all participants:

1. Short courses of high doses of OCS (dose and duration as per SoC for NP). The dose and duration will be recorded in the eCRF.
2. Throughout the study, asthmatic participants are to be maintained on their baseline SoC asthma treatment.
3. Although the use of rescue medications such as OCS is allowable at any time during the study, the date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.
4. For antibiotic treatment for NP, the type, dose and duration must also be recorded.

The following medications are not allowed prior to screening (Visit 1) and throughout the study, according to the following schedule, or during the study:

Prohibited Medication	Time Period Prior to Screening Visit
Investigational	3 months or 5 half-lives whichever is Longer
Omalizumab [Xolair]	130 days
Other monoclonal antibodies	5 half-lives
Experimental anti-inflammatory drugs (non biologicals)	3 months
Immunosuppressive medications such as those listed below (not all inclusive)	
Regular systemic corticosteroids including oral, intramuscular, long-acting depot	1 month
Methotrexate, troleandomycin, cyclosporin, Azathioprine	1 month
Oral gold	3 months
Chemotherapy used for conditions other than asthma	12 months
Changes in intranasal corticosteroid treatment	1 month
Insertion of any non-drug or drug eluting nasal stents such as Propel stents	6 months
Direct steroid injections into NP	6 months

7.7. Treatment after the End of the Study

The investigator is responsible for ensuring that consideration has been given to the post-study care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

There are no plans to provide mepolizumab following study completion.

8. STUDY WITHDRAWAL AND IP DISCONTINUATION CRITERIA

At the point of informed consent prior to screening, participants will be requested to provide permission and agree to be contacted even after study withdrawal/ IP discontinuation to collect information relating to any surgical intervention to the NP. Every effort will be made to have all participants attend study visits even if they discontinue study treatment in order to capture NP size scores, symptom score, any subsequent entry into a surgical waiting list for NP surgery and actual surgical procedures.

The following actions must be taken in relation to a participant who fails to attend the clinic for a required study visit:

- The site must attempt to contact the participant and re-schedule the missed visit as soon as possible.
- The site must counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- In cases where the participant is deemed 'lost to follow up', the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of "Lost to Follow-up".

8.1. Withdrawal from Study

- A participant may withdraw from the study at any time at his/her own request, or if they are lost to follow-up.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- Refer to the SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

8.1.1. Primary reasons for withdrawal from the study

The primary reason for study withdrawal (and sub-reason, if applicable) will be categorized as:

- Withdrew consent
  - participant relocated
  - frequency of visits
  - burden of procedures
  - other (specify)
- Study closed/terminated
- Lost to follow-up

8.1.2. Early Withdrawal Visit

The definition of an early participant withdrawal from the study will be any participant who is randomized to blinded medication and, for any reason, is withdrawn prior to completion of the Visit 15 procedures.

A participant may voluntarily discontinue participation in the study at any time.

Participants that withdraw from the study should return to the clinic return to the clinic 28 days after the last dose for an Early Withdrawal Visit. If possible, at the Early Withdrawal Visit, the following evaluations and procedures should be completed and recorded in the eCRF as required:

- Concomitant medication assessment
- Adverse event assessment
- 12 –lead ECG
- Physical examination (recorded in source documents only)
- Collect/review electronic diary
- Urine pregnancy test for females of childbearing potential
- Assessment of endoscopic nasal polyp score
- Assessment of surgery
- Assessment of OCS use
- Assessment of INCS use
- Assessments of symptoms
- Assessment of QoL
- WPAI
- PK

- Lab assessments including liver chemistry and immunogenicity

Access the RAMOS NG to report participant's early withdrawal from the study

8.2. Premature Discontinuation of Study Treatment (investigational product - IP)

8.2.1. Discontinuation Criteria for IP

A participant may discontinue from study treatment at any time at his/her own request, or at the discretion of the investigator. Participants who discontinue from study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the follow-up Visit assessments. The participant's NP surgical status will be tracked for the duration of the study. Participants may choose to discontinue use of IP at any time but full accountability of IP at the end of the study is required for all participants.

All participants will be followed up for the study duration. However, given that actual NP surgery can distort the anatomical architecture of the nasal cavity nullifying the NP size score and VAS, participants who have had NP surgery prior to Week 52 will be considered as treatment failures in the analysis of the primary endpoints.

Unlike the Phase II study, participants in the Phase III program will be allowed short courses of systemic OCS to control their NP symptoms during the study and as a consequence will help to minimize the overall withdrawal rates.

8.2.2. Study Specific IP Discontinuation Criteria

A participant must have IP discontinued if any of the following criteria are met:

- **Pregnancy:** Positive pregnancy test
- **Liver Chemistry:** Meets any of the protocol-defined liver chemistry stopping criteria.
- **ECG:** If a participant's QTc interval extends beyond 500msec or uncorrected QT interval is > 600 msec or QTc is increased more than 60msec compared to baseline on two or more ECG tracings separated by at least 5 minutes

NB: Courses of OCS or Surgery are not a reason for Study withdrawal or IP discontinuation.

8.2.3. Primary reasons for IP discontinuation

The primary reason for discontinuation of IP (and sub-reason, if applicable) will be categorized as:

- Adverse event
- Lost to follow-up
- Withdrew consent

- participant relocated
- frequency of visits
- burden of procedures
- other (specify)

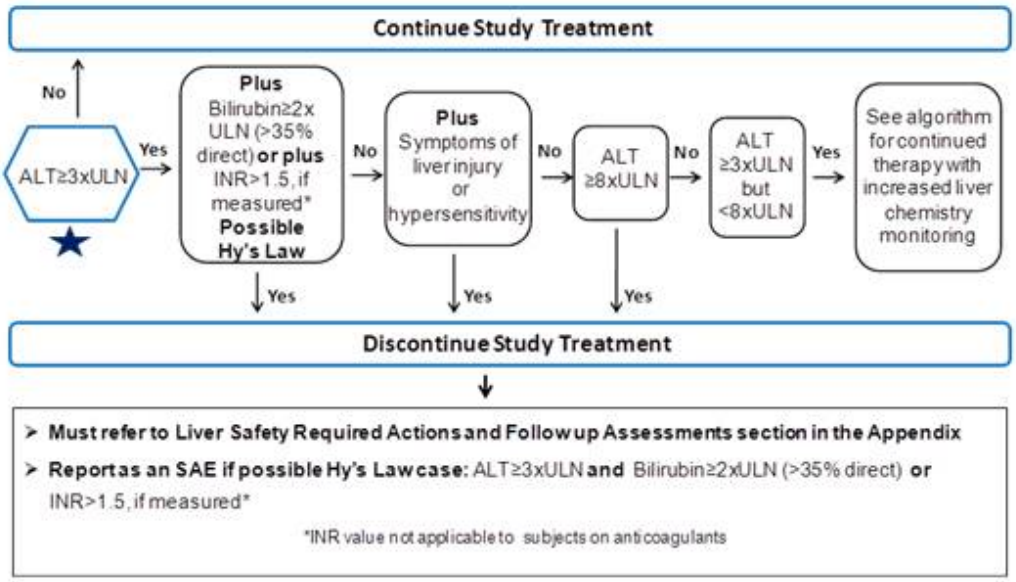
- Protocol deviation
- Lack of efficacy
- Study closed/terminated
- Participant reached protocol-defined stopping criteria
  - Liver event
  - Pregnancy
  - QTc
- Investigator discretion

8.2.3.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). These protocol guidelines are in alignment with FDA premarketing clinical liver safety guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

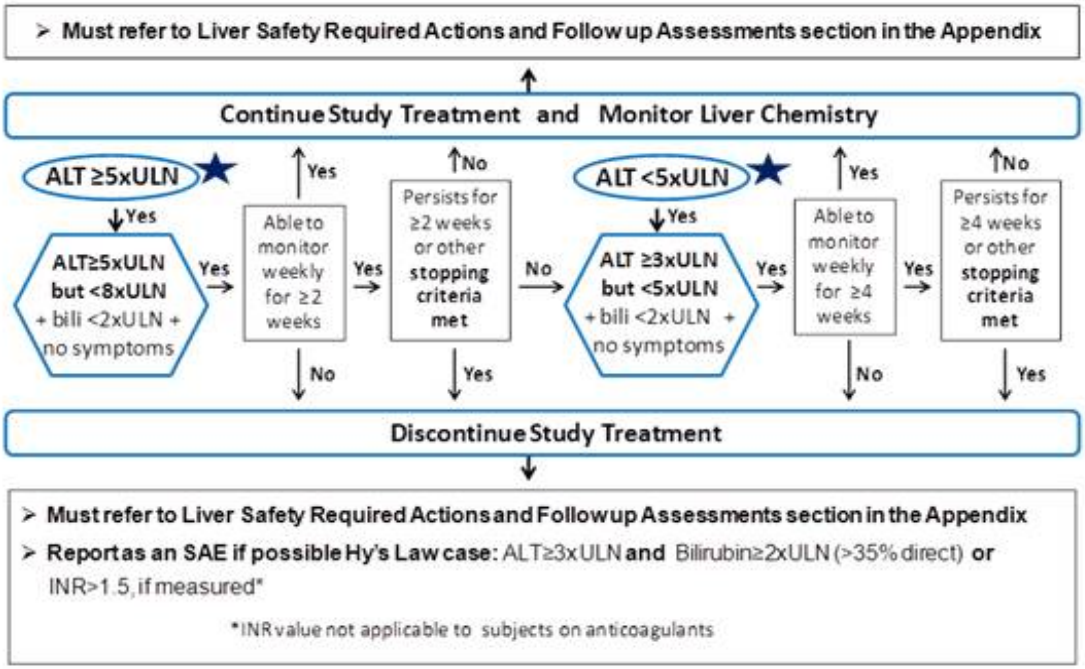
Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7

Algorithm B: Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥3xULN but <8xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 7

8.2.3.2. QTc Stopping Criteria

- The same QT correction formula must be used for each individual participant to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
- For example, if a participant is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

A participant who meets either bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTc > 60 msec

For participants with underlying bundle branch block, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	**Discontinuation QTc with Bundle Branch Block**
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

9. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the SoA Table, are essential and required for study conduct.

- This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the SoA.

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1. Critical pre-Screening, Screening and Baseline Assessments

9.1.1. Pre screening

Participants can perform the pre-screening Visit (Visit 0) up to 2 weeks prior (unless specifically authorised by the medical monitor) to or on the same day as the Screening Visit (Visit 1). A participant number will be assigned at the time the ICF is signed. During the Pre-screening Visit, study designated personnel must provide informed consent to study participants.

Once the informed consent document has been signed, pre-screening assessments can be conducted. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported.

9.1.2. Screening

At the screening visit NP and asthma therapy, NP surgery history, asthma and exacerbation history and concomitant medications will be assessed. Endoscopic NP score as well as VAS score for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, facial pain and overall VAS symptom score will be captured.

9.1.3. Critical procedures performed at Screening (Visit 1)

- Medical history including smoking status, history of sinusitis, NP history (including NP surgery), aspirin sensitivity, history of asthma, courses of rescue corticosteroids in the past 12 months, asthma exacerbation history in the previous 12 months, smoking history.
- Therapy/Concomitant medication history, including use of mepolizumab, omalizumab or previous biologics in the past 12 months.

- Cardiovascular medical history/risk factors (as detailed in the eCRF). This assessment must include a review of the participant responses to the cardiovascular assessment questions and height, weight, blood pressure, smoking history, medical conditions, and family history of premature cardiovascular disease.
- Physical exam
- Vital signs
- Dispensing and training of eDiary
- Nasal obstruction VAS symptom score
- Overall VAS symptom score
- Resting 12-lead ECG
- Laboratory tests. These should include:
  - Chemistry
  - Haematology with differential count
  - Hepatitis B Surface Antigen and hepatitis C antibody
  - Urinalysis
  - Urine pregnancy test- for all WOCBP
  - FSH will be assessed to confirm child-bearing status (if applicable)
  - Parasitic screening (only in countries with a high-risk or in participants who have visited a high-risk country)
- Endoscopic NP score
- Review of Inclusion/Exclusion criteria
- Review of exacerbations, SAEs

Procedures conducted as part of the participant's routine clinical management [e.g. blood eosinophil counts] and obtained prior to signing of informed consent may be utilised for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the timeframe defined in the SoA.

9.1.4. Critical procedures performed at first treatment Visit (Baseline Visit 2)

- Review eDiary and re train if required
- Review randomisation criteria
- Review the Endoscopic NP score recorded during V1 as rated by the core lab
- Vital signs
- Blood for biomarker
- Laboratory tests. This should include
  - Clinical Chemistry

- Haematology with differential
- Blood for baseline immunogenicity
- Blood for PK assessment
- Urine pregnancy test for WOCBP

9.1.5. Critical procedures performed throughout treatment period (Visits 2 - 15)

- SNOT-22 questionnaire
- SF-36 (Visits 2, 3, 5, 7, 9, 11, 13, 15 only)
- WPAI
- ACQ-5 (for asthmatics)
- Review eDiary and re train if required
- Overall VAS symptom score
- VAS for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, facial pain (daily in eDiary)
- Assessment of Surgery (actual and waiting list)
- Assessment of OCS dose and duration
- Endoscopic NP score (be performed at visits 2, 3, 4, 5, 6, 7, 8, 10, 12, 14 and 15)
- PnIF
- UPSIT (Visits 2, 3, 5, 7, 9, 11, 13, 15 only). UPSIT test will be performed only in selected countries
- Blood for PK (to be done only in visits indicated in the SoA)
- Genetic sample (to be done one time only in any of the visits)
- Blood for biomarker (Visit 15)
- AE/SAE review
- Concurrent medication review
- 12-lead ECG (Visits 2 and 15 only)
- Vital signs
- Laboratory assessments (Haematology at all visits and biochemistry, (including liver chemistries) at visits 2 and 15 only.
- Blood for immunogenicity
- Urinalysis
- Urine pregnancy test (for WOCBP)

9.1.6. Critical procedures performed throughout follow up period (Visits 16 - 18)

- Review eDiary and re train if required
- Overall VAS symptom score
- VAS for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, facial pain (Daily on eDiary)
- SNOT-22 questionnaire
- SF-36 (at Visits 16, 17 and 18)
- Assessment of Surgery (actual and waiting list)
- Assessment of OCS dose and duration
- Endoscopic NP score
- WPAI
- Blood for PK (at Visit 17 only)
- AE/SAE review
- Concurrent medication review
- Blood for immunogenicity

9.2. Efficacy Assessments

9.2.1. Endoscopic NP score

Endoscopic NP score will be performed at study visits as described in the SoA. This score is graded based on NP size Appendix 12 (recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status).

Image recordings of endoscopies will be sent to an independent reviewer for centralized blinded data assessment.

Endoscopic NP score will be performed at the site by trained heath care staff (usually ENT surgeon). The images of the assessment will be sent to central labs where there will be central scoring of the NP. The output from the central labs is considered final for the purpose of this study.

Nasal endoscopy assessment can be carried out within a 3 day window prior to dosing for each study visit (apart from visit 2) but must not exceed the protocol defined windows of ± 7 days from the nominal study visit.

9.2.2. Individual Symptoms Visual Analogue Scale (VAS)

All scales to be used in the study will be on the eDiary and will be collected daily in the morning from screening to the end of the study period.

Every day, the participant will be asked to indicate on a VAS the severity of 5 nasal polyposis symptoms (one VAS for each symptom) and symptoms overall:

Please rate your "_____ "at its worst over the previous 24 hours

1. nasal obstruction; 2. nasal discharge; 3. mucus in the throat; 4. loss of smell; 5. facial pain; 6. overall VAS symptoms score.

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. Participants will be instructed on how to use the scale prior to using the scale.

VAS is an instrument that measures a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. CCI
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.
CCI In this study patient reported symptom VAS will be collected using an eDiary. Given that there is no direct relationship between pixel size and mm, on electronic systems the key is that the line must (just like the paper version), have 101 individually selectable points. There are a number of publications which shows the applicability of VAS electronically and its comparability to traditional paper [Hollen, 2013, Reips, 2008, Cook, 2004, Jamison, 2002]. In summary, the length of the VAS doesn't matter, and participant's responses are not altered by implementing the VAS electronically. For the purpose of this protocol a VAS score of 7 in the overall symptom score and 5 in NP obstruction symptoms score are equivalent to 70 units and 50 units in the electronic VAS as measured using the eDiary.

9.2.3. NP surgery

At each visit it will be recorded whether the participant is on a waiting list for NP surgery and whether the participant has received actual documented surgery and/or sinuplasty. As an endpoint, for the purpose of this study, NP surgery is defined as any procedure involving instruments resulting in incision and removal of tissue (polypectomy) in the nasal cavity.

9.2.4. Medication

The number of courses of systemic steroids and OCS as well as the dose and duration of the courses will be recorded in the CRF. The dose for a course of OCS will be according to the participants SoC for OCS use for its NP condition. The dose and duration of the OCS taken will be recorded in the eCRF. For the purpose of this study a course of

systemic corticosteroid is considered continuous if treatment is separated by less than 7 days. The methodology to convert various doses of intravenous and oral steroids to prednisolone-equivalent OCS will be provided in the SPM.

9.2.5. Peak Nasal Inspiratory Flow (PnIF)

A PnIF Meter will be used to derive forced inspiratory peak flow through the nose during the study according to the SoA (Section 2). Please refer to the Study Procedures Manual for further details.

PnIF will be measured using an IN-CHECK flow meter. After blowing their nose, participants inspired forcefully from the residual volume to total lung capacity with their mouth closed. All measurements were made in the sitting position and a good seal around the face mask was ensured. The highest value of three consecutive (maximal) readings was recorded.

9.2.6. Olfaction testing: University of Pennsylvania Smell Identification Test (UPSIT)

UPSIT will be used at the time points indicated in the SoA (Section 2) to assess each participant's sense of smell.

UPSIT test will be performed only in selected countries.

UPSIT is a test that is commercially available for smell identification to test the function of an individual's olfactory system. It is the gold standard of smell identification tests for its reliability and practicality (Doty, 1989).

This test is a measurement of the individual's ability to detect odours at a suprathreshold level. The test is usually administered in a waiting room and takes only a few minutes. The test consists of 4 different 10 page booklets, with a total of 40 questions (Doty, 2007). On each page, there is a different "scratch and sniff" strip which are embedded with a microencapsulated odorant. There is also a four choice multiple choice question on each page. The scents are released using a pencil. After each scent is released, the patient smells the level and detects the odour from the four choices. There is an answer column on the back of the test booklet, and the test is scored out of 40 items. The score is compared to scores in a normative database from 4000 normal individuals, this tells the level of absolute smell function. The score also indicates how the patient does in accordance to their age group and gender. Please refer to the SPM for further details.

9.2.7. Health Related Quality of Life (HR QoL) assessments

9.2.7.1. Sino-Nasal Outcome Test (SNOT-22) questionnaire

SNOT-22 will be completed by the participant monthly at study visits according to the SoA (Section 2) under the supervision of the health care professional. The SNOT-22 will be completed electronically at study visits. Patients are to be provided with a quiet location, free from distraction and instructed that to select the single response option fro each question that most closely reflects their health.

Participants will be asked to rate the severity of their condition on each of the 22 items over the previous 2 weeks using a CCI
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.
CCI [Hopkins, 2009].

The SNOT-22 has been shown to be a reliable outcome measure for successful septal surgery [Buckland, 2003]. It is also recommended as a very suitable questionnaire in chronic rhinosinusitis (CRS) management [Morley, 2006] and its routine use is recommended as a tool to evaluate outcomes in nasal polyposis [Browne, 2006].

9.2.8. Assessments for asthmatic participants only

9.2.8.1. Asthma Control Questionnaire (ACQ-5)

ACQ-5 will be assessed at clinic visits under the supervision of the health care professional, during the study according to the SoA (Section 2). The ACQ-5 is a five-item questionnaire, which has been developed as a measure of patients' asthma control that can be quickly and easily completed (Juniper, 1999) [Juniper, 2005]. The questions are designed to be self-completed by the participant. The five questions enquire about the frequency and/or severity of symptoms over the previous week CCI
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.
CCI scale. Please refer to the SPM for further details.

9.3. Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

The following adverse events of special interest will have a customized AE and SAE pages in the eCRF:

- Local injection site reactions
- Systemic reactions

In addition, the information whether an event met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 11 will be collected on the AE and SAE CRF pages.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment (see Section 8).

9.3.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signing of the ICF until the end of the study at the time points specified in the SoA (Section 2).

- All AEs will be collected from the start of treatment until [the end of the study at the time points specified in the SoA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

9.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non serious AEs of special interest will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up. Further information on follow-up procedures is given in Appendix 4.

9.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will

review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.3.5. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

9.3.6. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

The following disease related events (DREs) are common in participants with Nasal Polyposis and can be serious/life threatening:

- Nasal polyp surgery including sinuplasty

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of SAEs to GSK (even though the event may meet the definition of a SAE). These events will be recorded on the DRE page in the participant's CRF within 2 months. These DREs will be monitored by a SCT on a routine basis.

NOTE: However, if either of the following conditions apply, then the event must be recorded and reported as an SAE (instead of a DRE):

- *The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant, or*
- *The investigator considers that there is a reasonable possibility that the event was related to treatment with the investigational product*

9.3.7. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until 4 months post last dose.
- If a pregnancy is reported, the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Appendix 5.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3.8. Medical Device Incidents (Including Malfunctions)

GSK Medical devices are being provided for use in this study. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices (as defined in Section 7.1.1).

The definition of a Medical Device Incident can be found in Appendix 8.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 4 of the protocol.

9.3.8.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the GSK medical devices are available for use.
- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a GSK medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 8.

9.3.8.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE, will be followed until resolution of the event, until the condition stabilizes, until the condition is otherwise explained, or until the participant is lost to follow-up (as defined in Section 5.5). The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.3.8.3. Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours once the investigator determines that the event meets the protocol definition of a medical device incident.
- Facsimile transmission of the "Medical Device Incident Report Form" is the preferred method to transmit this information to the Medical Monitor.
- In the absence of facsimile equipment, notification by telephone is acceptable for incidents, with a copy of the "Medical Device Incident Report Form" sent by overnight mail.
- The same individual will be the contact for the receipt of medical device reports and SAE.

9.3.8.4. Safety syringe functionality assessment

During administration of the safety syringe the HCP will be asked to inspect the medical device and complete the inspection questions in Appendix 13.

If there is an error with the medical device then refer to the Safety syringe Error / Failure Reporting Form in Appendix 9.

9.3.8.5. Returning defective Medical Devices to GSK

All defective devices will be returned to GSK

- Please refer to the SPM for all details

9.3.8.6. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.3.9. Treatment of Overdose

The dose of mepolizumab considered to be an overdose has not been defined. There are no known antidotes and GSK does not recommend a specific treatment in the event of a suspected overdose. The investigator will use clinical judgment in treating the symptoms of a suspected overdose.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

9.4.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded at Visit 1.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

- As detailed in the SoA vital signs will be measured in semi-supine position after 5 minutes rest and will include systolic and diastolic blood pressure and pulse rate.
- Vital signs assessments will be taken before measurement of any ECGs at the specified time point.

9.4.3. Electrocardiograms

- A single 12-lead ECG will be obtained at each timepoint specified in the SoA using an ECG machine to assess heart rate and measures PR, QRS, QT, and QTc intervals. (for further details refer to SPM).
- If a routine single ECG after randomisation demonstrates a prolonged QT interval, obtain two more ECGs over a brief period, and then use the averaged QTc values of the three ECGs to determine whether the patient should be discontinued from the study.
- ECG measurements will be made after the participant has rested in the supine position for 5 minutes. The ECG should be obtained after the vital signs assessments and followed by other study procedures as described in the SPM.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 , must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

9.5. Pharmacokinetics

- Blood samples for analysis of mepolizumab plasma concentration will be obtained as per the SoA. Samples obtained at Visits 2, 3, and 15 should be drawn prior to dosing. Participants going into no treatment follow up will have additional sample at Visit 17. The date and exact time of collection for each sample will be documented in the eCRF.

- Details for collection and processing of samples may be found in the SPM.

9.6. Pharmacodynamics

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the SoA. From Visit 2 onwards, blood eosinophil counts will not be communicated to investigators, in order to maintain the blind.

9.7. Genetics

Up to 6 mL blood sample for DNA isolation will be collected from CRF participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 6 for Information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SPM.

9.8. Exploratory Biomarkers

Blood samples will be collected during this study and may be used for the purposes of measuring novel biomarkers to identify factors that may influence severe NP, and/or medically related conditions, as well as the biological and clinical responses to mepolizumab. If relevant, this approach will be extended to include the identification of biomarkers associated with adverse events. Samples will be collected at the time points indicated in SoA.

9.9. Immunogenicity Assessments

Blood samples will be collected for the determination of anti-mepolizumab antibodies, prior to dosing, as detailed in the SoA.

Details for sample collection and processing may be found in the SPM.

9.10. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are evaluated in this study by means of the Short Form-36 (SF-36) and the Work Productivity and Activity Impairment Questionnaire (WPAI) questionnaires.

9.10.1. Short Form-36 (SF-36) questionnaire

SF-36 will be performed monthly by the participant at study visits (Section 2) under the supervision of the health care professional.

SF-36 is one of the most widely used generic questionnaires. It consists of 36 self-administered questions that cover eight health domains: physical functioning (PF), role physical (RP), bodily pain (BP), and general health (GH), vitality (VT), role emotional (RE), social functioning (SF), and mental health (MH) with a recall of 4 weeks. Scale CCI In addition, the Physical Component Score (PCS) and the Mental Component Score (MCS) scores can be derived following the original authors' recommendations [Ware, 1994].

Radenne et al. [Radenne, 1999] reported the unique study that has investigated the impact of NP demonstrating that NP impair QoL in all SF-36 domains. Using the SF-36 and compared with a healthy population, other studies has also demonstrated that chronic rhinosinusitis has a considerable impact on all SF-36 domains except for physical functioning [Gliklich, 1997; Winstead, 1998; Durr, 1999; Wang, 2003].

Participants with NP had lower scores in all SF-36 domains except for physical functioning and general health than participants with chronic obstructive pulmonary disease [Alonso, 1998], coronary artery disease [Failde, 2000], and asthma [Espinosa, 2002].

Alobid, 2005 showed that a significant improvement was observed in all domains of SF-36 after medical and surgical treatment. Both mental and physical health reached population levels. Combined steroid treatment and ESS had similar long-term outcomes on QoL. Radenne et al. [Radenne, 1999] showed that steroids and ESS improved the symptoms and the QoL in patients with NP especially in body pain, general health, vitality, social functioning, and mental health domains with no significant differences between both treatment regimes.

9.10.2. Work Productivity and Activity Impairment Questionnaire (WPAI)

WPAI will be assessed by the participant at study visits described in the SoA (Section 2) under the supervision of the health care professional.

The WPAI questionnaire is an instrument to measure impairments in both paid work and unpaid work [Reilly, 1993; Reilly Associates]. It measures absenteeism, presenteeism as well as the impairments in unpaid activity because of health problem during the past seven days. It has been validated to quantify work impairments for numerous diseases such as asthma, psoriasis, irritable bowel syndrome (IBS), ankylosing spondylitis and Crohn's disease [Reilly Associates; Reilly, 2004; Reilly, 2010; Reilly, 2008]. In addition, the WPAI questionnaire has been used to compare work impairments between treatment groups in clinical studies and trials or between participants with different disease severity levels [Reilly, 2004; Reilly, 2010; Reilly, 2008; Revicki, 2007; Pearce, 2006; Chen, 2008).

The WPAI-GH consists of six questions: CCI

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.

CCI [Reilly, 1993; Reilly Associates]. The recall period for the questions 2 to 6 is seven days. Four main outcomes can be generated from the WPAI: 1) percent work time missed due to health for those

who were currently employed; 2) percent impairment while working due to health for those who were currently employed and actually worked in the past seven days; 3) percent overall work impairment due to health for those who were currently employed; 4) percent activity impairment due to health for all respondents [Reilly, 1993; Reilly Associates]. For those who missed work and did not actually work in the past seven days, the percent overall work impairment due to health will be equal to the percent work time missed due to health.

10. STATISTICAL CONSIDERATIONS

The study is designed to test the superiority of mepolizumab 100mg SC vs. placebo. Significance tests will be performed at the two-sided 5% alpha level (one-sided 2.5%).

10.1. Sample Size Determination

The sample size is based on the co-primary efficacy endpoints of total endoscopic nasal polyp score and nasal obstruction VAS score at Week 52 and the key secondary endpoint of time to actual surgery. A trial of 200 participants per treatment group is estimated to have over 90% power to observe statistical significance at the two sided 5% level for both co-primary endpoints and for the key secondary endpoint of time to actual surgery.

The calculation for the co-primary endpoints is based on analysis of study MPP111782. This analysis showed 27% of placebo participants with a one-point improvement in NP score compared to 52% of mepolizumab participants. For nasal blockage, 39% of placebo participants showed a one-point improvement in NP score compared to 70% of mepolizumab participants.

For surgery, 90% power to observe statistical significance at the two sided 5% level is based on a true reduction in the proportion of participants receiving surgery from 40% on placebo to 25% on mepolizumab. In the six month study MPP111782, 20% of participants on placebo and 9% of participants on mepolizumab received surgery; a greater proportion of participants receiving surgery is expected in this twelve month study.

The smallest observed effect predicted to result in a statistically significant difference between treatment groups is a reduction in the proportion of participants receiving surgery from 40% on placebo to 30% on mepolizumab.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Participants Enrolled	All participants enrolled and for whom a record exists on the study database
Randomized	All randomized participants

Intent-to-Treat	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they are allocated at randomisation.
Safety	All randomized participants who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment they actually received for more than 50% of treatment administrations.

10.3. Statistical Analyses

To strongly control the type I error rate for the primary and secondary outcomes, adjustment for multiplicity will be performed based on a hierarchical testing of endpoints in a pre-defined order. The co-primary endpoints will be tested first and if these comparisons are both significant at the two-sided 5% level, the first of the secondary endpoints will be tested. Testing will continue in a similar manner for the remaining secondary endpoints dependent on statistical significance having been achieved for the previous endpoint in the hierarchy.

The secondary endpoints will be tested in the following pre-defined order:

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 participants 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

10.3.1. Efficacy Analyses

Endpoint	**Statistical Analysis Methods**
Co-Primaries	Total endoscopic nasal polyp score is collected at each clinical visit, the primary assessment will be at week 52 (centrally read data). Nasal obstruction is collected daily throughout the study via eDiary. Nasal obstruction at Week 52 will be calculated as the mean of all measurements made in the 4 weeks prior to the visit (excluding the day of the visit). The mean VAS score over the last 7 days before Visit 2 will be used to determine the baseline value. Participants who undergo surgery/sinuplasty prior to Week 52 will be assigned their worst observed value prior to surgery/sinuplasty. Participants who withdraw from study without having experienced surgery/sinuplasty will be assigned their

Endpoint	Statistical Analysis Methods
	worst observed score prior to study withdrawal. The comparison of mepolizumab with placebo will be expressed as a difference in median change from baseline presented with corresponding 95% confidence intervals, the p-value for the difference between treatment groups will be based on the non-parametric Wilcoxon rank-sum test. The difference in median change between placebo and mepolizumab with associated 95% confidence intervals will be assessed by quantile regression using a bootstrap approach (Mehrotra DV 2017; Keene O.N 2018), with covariates of treatment group, baseline score, baseline blood eosinophil count and region.
Secondary	Time to actual NP surgery will be compared between treatment groups using a Cox's proportional hazards model with covariates of treatment group, baseline NP score, baseline nasal obstruction score and region. Graphs of the Kaplan-Meir estimates of the proportion of participants with events over time will be produced by treatment group. Change from baseline 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 VAS loss of smell score at Week 52 (calculated as the mean of all measurements made in the 4 weeks prior to Week 52), and change from baseline in SNOT-22 total score at Week 52 will be analysed in a similar manner to the co-primary endpoints. The proportion of participants requiring systemic steroids for nasal polyps will be analysed using a logistic regression model.
"other"	Will be described in the reporting and analysis plan

10.3.2. Safety Analyses

All safety analyses will be performed on the Safety Population and will be described in the reporting and analysis plan.

10.3.3. Other Analyses

PK, pharmacodynamic, and biomarker exploratory analyses will be described in the reporting and analysis plan. The population PK analysis and pharmacodynamic analyses will be presented separately from the main clinical study report (CSR).

10.3.4. Interim Analyses

No interim analysis of data is planned for this study.

11. REFERENCES

Alobid I, Benítez P, Bernal-Sprekelsen M, Roca J, Alonso J, Picado C, Mullol J. Nasal polyposis and its impact on quality of life: comparison between the effects of medical and surgical treatments. Allergy. 2005 Apr;60(4):452-8.

Alobid I, Mullol J. Role of medical therapy in the management of nasal polyps. Curr Allergy Asthma Rep. 2012;12(2):144-153.

Alonso J, Prieto L, Ferrer M, Vilagut G, Broquetas JM, Roca J et al. Testing the measurement properties of the Spanish version of the SF-36 Health Survey among male patients with chronic obstructive pulmonary disease. Quality of life in COPD study group. J Clin Epidemiol 1998*;*51*:* 1087–1094.

Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 is upregulated in human nasal polyp tissue. J Allergy Clin Immunol 1997; 99:837-842

Bachert C, Wagenmann M, Rudack C, Höpken K, Hillebrandt M, Wang D, van Cauwenberge P. The role of cytokines in infectious sinusitis and nasal polyposis. Allergy 1998; 53:2-13

Bhattacharyya N. Ambulatory sinus and nasal surgery in the United States: demographics and perioperative outcomes. Laryngoscope. 2010;120(3):635-8

Bhattacharyya N. Clinical outcomes after revision endoscopic sinus surgery. Archives of otolaryngology--head & neck surgery. 2004;130 (8):975-8.

Brescia G, Marioni G, Franchella S, Ramacciotti G, Velardita C, Giacomelli L, Marino F, Martini A. Can a panel of clinical, laboratory, and pathological variables pinpoint patients with sinonasal polyposis at higher risk of recurrence after surgery? Am J Otolaryngol. 2015;36(4):554-558

Browne JP, Hopkins C, Slack R, Topham J, Reeves B, Brown P et al. Health-related quality of life after polypectomy with and without additional surgery. Laryngoscope 2006; 116:297-302.

Buckland JR, Thomas S, Harries PG. Can the sinonasal outcome test (SNOT-22) be used as a reliable outcome measure for successful septal surgery? Clin Otolaryngol. 2003; 28:43-7.

Chen H, Blanc PD, Hayden ML, Bleecker ER, Chawla A, Lee JH. TENOR Study Group. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. Value Health. 2008;11:231–239.

Chu CT, Lebowitz RA, Jacobs JB. An analysis of sites of disease in revision endoscopic sinus surgery. American journal of rhinology. 1997;11(4):287-91.

Claeys S, Van Hoecke H, Holtappels G, Gevaert P, De Belder T, Verhasselt B, Van Cauwenberge P, Bachert C. Nasal polyps in patients with and without cystic fibrosis: a

differentiation by innate markers and inflammatory mediators. Clin Exp Allergy. 2005;35(4):467-472.

Cook AJ, Roberts DA, Henderson MD, Van Winkle LC, Chastain DC, Hamill-Ruth RJ. Electronic pain questionnaires: a randomized, crossover comparison with paper questionnaires for chronic pain assessment. Pain. 2004 Jul; 110(1-2):310-7.

Doty, R (2007). "Office procedures for quantitative assessment of olfactory function". American Journal of Rhinology. 24 (4): 460–473.

Doty, RL; Frye RE; Agrawal U (1989). "Internal consistency reliability of the fractionated and whole University of Pennsylvania Semll Identification Test.". Precept Psychophs. 45: 381–384.

Durr DG, Desrosiers MY, Dassa C. Quality of life in patients with rhinosinusitis. J Otolaryngol 1999;28: 108–111.

Espinosa De Los Monteros MJ, Alonso J, Ancochea J, Gonzalez A. Quality of life in asthma: reliability and validity of the short form generic questionnaire (SF-36) applied to the population of asthmatics in a public health area. Arch Bronconeumol 2002;38: 4–9.

Failde I, Ramos I. Validity and reliability of the SF-36 health survey questionnaire in patients with coronary artery disease. J Clin Epidemiol 2000;53: 359–365.

Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012. Rhinol Suppl. 2012 (23):1-298.

Gliklich RE, Metson R. Effect of sinus surgery on quality of life. Otolaryngol Head Neck Surg 1997;117: 12–17.

GSK Document Number CM2003/00010/10, Investigator Brochure (IB) Date 03 DEC 2015.

Hollen PJ, Gralla RJ, Stewart JA, Meharchand JM, Wierzbicki R, Leighl N. Can a computerized format replace a paper form in PRO and HRQL evaluation? Psychometric testing of the computer-assisted LCSS instrument (eLCSS-QL). Support Care Cancer. 2013 Jan;21(1):165-72.

Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22 item Sinonasal Outcome Test. Clin Otolaryngol. 2009; 34:447-54.

Jamison RN, Gracely RH, Raymond SA, Levine JG, Marino B, Herrmann TJ, Daly M, Fram D, Katz NP. Comparative study of electronic vs. paper VAS ratings: a randomized, crossover trial using healthy volunteers. Pain. 2002 Sep;99(1-2):341-7.

Jankowski R, Pirgret D, Decroocq F, Blum A, Gillet P. Comparison of radical (nasalization) and functional ethmoidectomy in patients with severe nasal polyposis. A retrospective study. Rev Laryngol Otol Rhinol (Bord) 2006; 127:131-140

Jones NS. Current concepts in the management of paediatric rhinosinusitis. J Laryngol Otol. 1999; 113(1):1-9.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999; 14: 902–907.

Juniper EF1, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005 May;99(5):553-8.

Keene O.N. Strategies for composite estimands in confirmatory clinical trials: Examples from trials in nasal polyps and steroid reduction. Pharmaceutical Statistics. 2018;18:78-84

Kim S, Marigowda G, Oren E, Israel E, Wechsler M,. Mepolizumab as a steroid sparing treatment option in patients with Churg-Strauss Syndrome. J Allergy Clin Immunol 2010; 125:1336-43.

Larsen K, Toss M. A long-term follow-up study of nasal polyp patients after simple polypectomies. Eur Arch Otorhinolaryngol 1997; 245:85-88

Levine HL. Functional endoscopic sinus surgery: evaluation surgery and follow-up of 250 patients. The Laryngoscope 1990; 100:79-84

Lim M, Lew-Gor S, Darby Y, Brookes N, Scadding G, Lund VJ. The relationship between subjective assessment instruments in chronic rhinosinusitis. Rhinology. 2007 Jun;45(2):144-7.

McCullagh, P. Regression models for ordinal data' (with discussion), Journal of the Royal Statistical Society, Series, B, 1980; 42: 142.

Mehrotra DV, Liu F, Permutt T. Missing data in clinical trials: control-based mean imputation and sensitivity analysis. Pharmaceutical Statistics 2017; 16: 378-392.

Moosig F, Gross WL, Herrmann K, Bremer JP. Targeting interleukin-5 in refractory and relapsing Churg-Strauss Syndrome. Ann Int Med 2011; 155:341-343.

Morley AD, Sharp HR. A review of sinonasal outcome scoring systems - Which is best? Clinical Otolaryngology 2006; 31:103-9.

Newton JR, Ah-See KW. A review of nasal polyposis. Ther Clin Risk Manag. 2008;4(2):507-512.

Pearce DJ, Singh S, Balkrishnan R, Kulkarni A, Fleischer AB, Feldman SR. The negative impact of psoriasis on the workplace. J Dermatolog Treat. 2006;17:24–28.

Philpott C, Hopkins C, Erskine S, et al. The burden of revision sinonasal surgery in the UK —data from the Chronic Rhinosinusitis Epidemiology Study (CRES): a crosssectional study. BMJ Open 2015;5:e006680. doi:10.1136/bmjopen-2014-006680

Radenne F, Lamblin C, Vandezande LM, Tillie-Leblond I, Darras J, Tonnel AB et al. Quality of life in nasal polyposis. J Allergy Clin Immunol 1999;104: 79–84.

Reilly Associates Health Outcomes Research. http://www.reillyassociates.net

Reilly MC, Bracco A, Ricci J, Santoro J, Stevens T. The validity and accuracy of the Work Productivity and Activity Impairment questionnaire - Irritable bowel syndrome version (WPAI:IBS) Alimentary Pharmacology and Therapeutics. 2004;20:459–467.

Reilly MC, Gerlier L, Brabant Y, Brown M. Validity, reliability, and responsiveness of the work productivity and activity impairment questionnaire in Crohn's disease. Clin Ther. 2008;30:393–404.

Reilly MC, Gooch KL, Wong RL, Kupper H, van der Heijde D. Validity, reliability and responsiveness of the Work Productivity and Activity Impairment Questionnaire in ankylosing spondylitis. Rheumatology (Oxford) 2010;49:812–819.

Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. Pharmacoeconomics. 1993;4:353–365.

Reips UD, Funke F. Interval-level measurement with visual analogue scales in Internet-based research: VAS Generator. Behav Res Methods. 2008 Aug;40(3):699-704.

Revicki DA, Willian MK, Menter A, Gordon KB, Kimball AB, Leonardi CL, Langley RG, Kimel M, Okun M. Impact of adalimumab treatment on patient-reported outcomes: results from a Phase III clinical trial in patients with moderate to severe plaque psoriasis. J Dermatolog Treat. 2007;18:341–350.

Rothenberg ME, Klion AD, Roufosse FE, et al Treatment of patients with hypereosinophilic syndrome with mepolizumab. N Engl J Med 2008; 358:1215-1228.

Rucci L, Bocciolini C, Casucci A. Nasal polyposis: microsurgical ethmoidectomy and interruption of autonomic innervation vs conventional surgery. ACTA Otorhinolaryngol Ital 2003; 23:26-32

Sampson HA, Munoz-Furlong A, Campbell RL, *et. Al*. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol* 2006;117:391-397.

Schramm VL Jr, Effron MZ. Nasal polyps in children. Laryngoscope. 1980;90(9):1488-1495.

Wang PC, Tai CJ, Lin MS, Chu CC, Liang SC. Quality of life in Taiwanese adults with chronic rhino-sinusitis. Qual Life Res 2003;12: 443–448.

Ware JE, Konsinski M, Keller SD. SF-36 physical and mental health summary scales: a user's manual. Boston, Massachusetts: The Health Institute New England Medical Center, 1994.

Winstead W, Barnett S. Impact of endoscopic sinus surgery on global health perception: an outcomes study. Otolaryngol Head Neck Surg 1998;119: 486–491.

Wynn R, Har-El G. Recurrence rates after endoscopic sinus surgery for massive sinus polyposis. Laryngoscope 2004; 114:811-813

12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ-5	Asthma Control Questionnaire
AE	Adverse Event
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BEC	blood eosinophil counts
BMI	Body mass index
BP	bodily pain
CRF	Case Report Form
CRS	chronic rhinosinusitis
CT	Computed tomography
CV	Cardiovascular
DNA	Deoxyribonucleic acid
DRE	disease related events
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EW	Early Withdrawal
eDiary	Electronic Diary
ESS	Endoscopic sinus surgery
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance

GH	general health
GSK	GlaxoSmithKline
HBsAg	presence of hepatitis B surface antigen
HCP	Health care practitioner
HIV	Human Immunodeficiency Virus
h/hr	Hour(s)
HR QoL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
IBS	irritable bowel syndrome
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
IEC	Independent Ethics Committee
IL-5	Interleukin-5
IL-5Ra	Interleukin-5 receptor alpha
IM	intramuscular
INCS	Intranasal Corticosteroids
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU	International Unit
IV	Intravenous
kg	Kilogram
L	Litre

LOCF	Last observation carried forward
µg	Microgram
µL	Microlitre
MCS	Mental Component Summary
MedDRA	Medical Dictionary for Regulatory Activities
MH	mental health
MF	Mometasone furoate
mg	Milligrams
mL	Millilitre
msec	Milliseconds
NP	Nasal Polyps
OCS	Oral Corticosteroids
PCS	Physical Component Summary
PCSA	placebo controlled severe asthma
PD	Pharmacodynamic
PF	physical functioning
PGx	Pharmacogenetics
PK	Pharmacokinetic
PnIF	Peak Nasal Inspiratory Flow
PP	Per Protocol
Q4W	every 4 weeks
QTc	Corrected QT interval
QTcB	QTc corrected by Bazett's formula
QTcF	QTc corrected by Fridericia's formula
RAMOS	Registration and Medication Ordering

	System
RAP	Reporting and Analysis Plan
RBC	Red blood cells
RE	role emotional
RP	role physical
SAE	Serious adverse event(s)
SC	Subcutaneously
SCT	Study conduct team
SD	Standard deviation
SF	social functioning
SF-36	Short Form Health Survey 36
SGRQ	St George questionnaire
SNOT	Sino-Nasal Outcome Test
SoA	Schedule of activities
SoC	Standard of Care
SOP	Standard Operating Procedure
SPM	Study Procedures Manual
SUSAR	suspected unexpected serious adverse reactions
ULN	Upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
UK	United Kingdom
US	United States
URTI	Upper respiratory tract infection
VAS	Visual Analogue Scale

VT	Vitality
WOCBP	Woman of Childbearing Potential
WPAI	Work Productivity and Activity Impairment

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
Acq-5
In-check
Mometasone Furorate (Mf)
Sf-36
Snot-22
Upsit
Wpai

12.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 1 will be performed by the central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[1]	BUN	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose [nonfasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	**Parameters**
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only and if urine positive) • Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[2] • All study-required laboratory assessments will be performed by a central laboratory. • Hepatitis B and C testing

NOTES :
1. Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 8.1 and Appendix 7 All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).
2. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
  - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, the Directive 2001/20/EC or European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH

guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorised representative.
- Participants who are rescreened are required to sign a new ICF.

The ICF may contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research in accordance with SOP-GSKF-410. The investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate will not provide this separate signature.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page. • There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe. An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment

administration will be considered and investigated.

- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable , then the site will use the paper SAE data collection tool (see next section) and fax the form to GSK within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- The investigator or medically-qualified sub-investigator must show evidence within the eCRF (e.g., check review box, signature, etc.) of review and verification of the

relationship of each SAE to IP/study participation (causality) within 72 hours of SAE entry into the eCRF.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the medical monitor by telephone.
- Contacts for SAE reporting can be found in SPM.

SAE Reporting to GSK via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor**.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in SPM.

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Male participants

Based on the absence of an identified reproductive hazard from preclinical studies, absence of a genotoxic potential, and very low levels of mepolizumab that might be present in semen, there is no recognized risk for mepolizumab to affect human sperm or the foetus if transferred to a female partner via semen. Therefore, the use of condoms or other methods of contraception in the male study participant is not required.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly from the time of consent, for the duration of the trial, and for 4 months after the last mepolizumab administration as described in Table 2.

Table 2 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device • Intrauterine hormone-releasing system • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.
b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least 4 months corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test
- Additional pregnancy testing should be performed as per SoA

- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 10 mIU/mL will be performed and assayed in the central laboratory

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating

- will discontinue study treatment or be withdrawn from the study

12.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis
- DNA samples will be used for research related to mepolizumab or Nasal polyposis and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to mepulizumab (or study treatments of this drug class), and nasal polyposis. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate)
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- DNA samples will be analyzed for investigate the relationship between genetic variants, Response to medicine, including mepolizumab or any concomitant medicines; NP susceptibility, severity, and progression and related conditions . Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to mepolizumab or study treatments of this class. The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on mepolizumab (or study treatments of this class) or nasal polyosis continues but no longer than 15 years or other period as per local requirements.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance). http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN and cannot be monitored weekly for ≥4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B DNA and Hepatitis delta antibody[5]. • Obtain blood sample for pharmacokinetic (PK) analysis, within 28 days after last dose[6]

Liver Chemistry Stopping Criteria	
granted • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment and continue participant in the study for any protocol specified follow up assessments **MONITORING:** **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	• Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total bilirubin≥2xULN • Obtain complete blood count with differential to assess eosinophilia • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG) or gamma globulins. • Serum acetaminophen adduct high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding**

studies of hepatic impairment or cirrhosis); INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants

3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If Hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of Hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to PK blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR ALT ≥3xULN and <5xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks.	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. Drug Metab Dispos 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. J Clin Microbiol. 2005;43(5):2363–2369.

12.8. Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition and Documentation of Medical Device Incidents

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study.

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
• Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened and
- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of incidents
• A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A participant's study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. • A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix 4. • The form will be completed as thoroughly as possible and signed by the investigator before transmittal to the GSK. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by GSK) at the time of the initial report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

12.9. Appendix 9: SYRINGE ERROR / FAILURE REPORTING FORM

Please write clearly using **BLOCK CAPITAL LETTERS.**

Please complete form within 24 hours of safety syringe failure/user error at site and submit to GSK

via email to PPD

Primary Investigator:	**Protocol #:** **205687**
Site Contact for IP Accountability:	**Site #:**
Contact Phone (print clearly):	**participant #:**
E-mail (print clearly):	
Site Address:	**Date Dispensed:**
	Date Returned:
Has the safety syringe been used by the HCP? ___ No ___ Yes (Considered a biohazard.)	
Was there an AE or SAE associated with this failure/error? ___ No ___Yes **If yes, please enter the eDC AE sequence number:_____**	
Please provide description of user error:	
Which of the following user errors apply? Tick all that apply: __ Did not check expiration date __ Incorrect preparation or incorrect choice of injection site __ Did not check product solution	

__ Needle shield not removed from safety syringe

__ Syringe pulled away before end of injection (i.e., before the plunger is pushed all the way down)

__ Did not check inspection window for white plunger

__ *Other* (*please specify below*).

Description of other user error:

Reason for Safety Syringe failure. Tick all that apply:

___ Safety Syringe leaking

__ Components broken / cracked

__ Cannot remove needle cap

__ Inspection window not clear

__ Bent needle

__ Liquid is cloudy, discoloured or contains large particles

__ Cannot push the plunger rod down (i.e., required force is too high)

__ *Other* (*please specify below*)

Description of other syringe failure:

Packaging failure. Tick all that apply:

___ Device damaged

___ Packaging damaged or can't read label __ Security seal was broken __ Syringe missing from kit __ *Other* (*please specify below*)	
Description of other packaging failure:	
Error/failure outcome (check one): ☐ Participant received no dose ☐ Participant received a partial dose (*ensure date used is captured above)*	**Resolution (check one) :** ☐ Replacement syringe provided ☐ Dose omitted ☐ Participant withdrawn
Replacement Syringe Dispensed Date:	

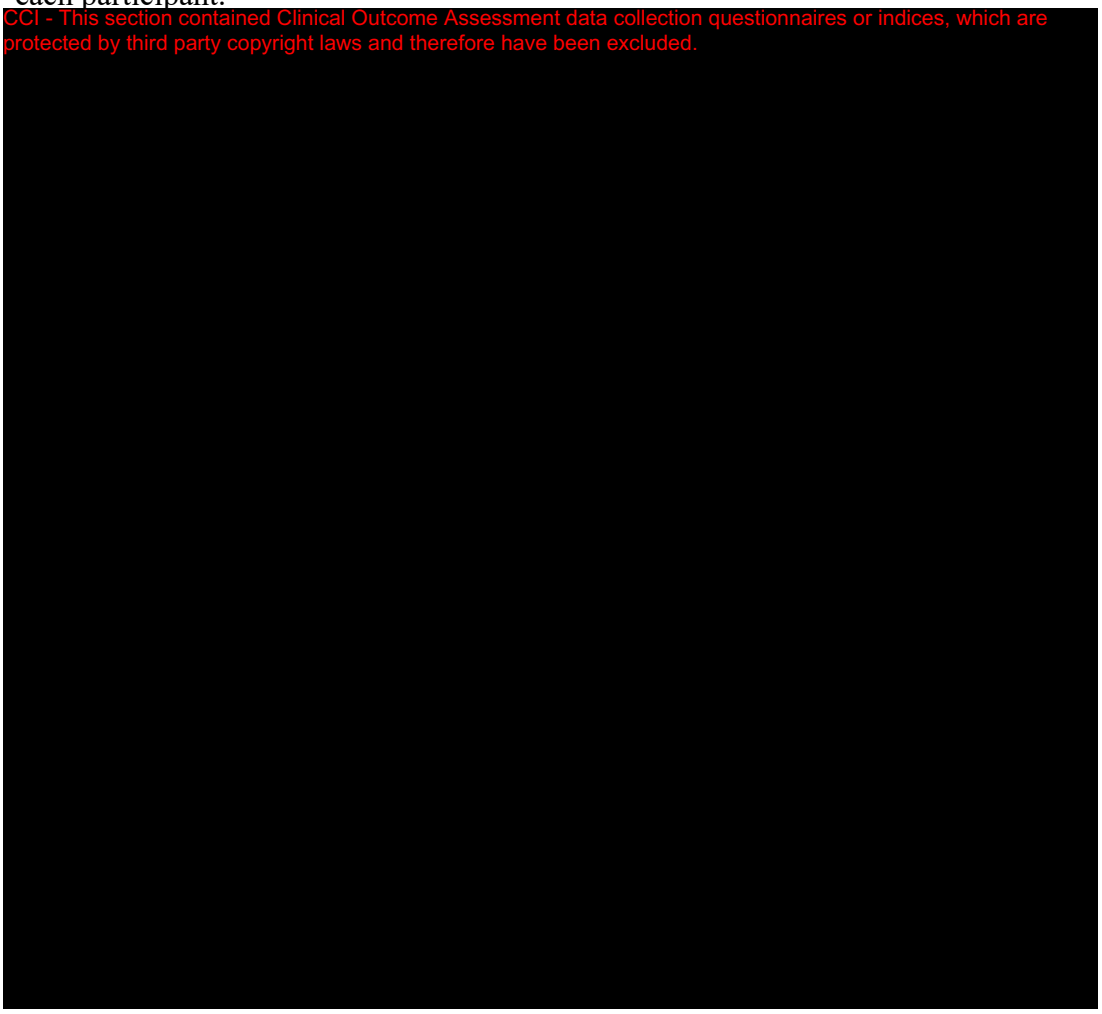
Instructions for further processing: Please fax or email completed Form to The GSK Pen Failure Processing Team at PPD or email address. Please contact your study monitor with any questions or for troubleshooting. Maintain the Form and in the participants' records. You may be contacted further concerning the malfunctioned safety syringe.

12.10. Appendix 10: Country-specific requirements

South Korea Investigational Product Labels

In this study participant identification number and visit number will not be included in the IP label. However, it will be tracked at site pharmacy when the IP is dispensed to each participant.

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.



Korea Participants: In regards to Inclusion criteria 1, only adult participants as per local laws at the time of signing the informed consent will be eligible for inclusion in this study.
The OCS supplied for Korea participants will be prednisolone, prednisone or methyl-prednisolone.

12.11. Appendix 11: Anaphylaxis Criteria

Joint NIAID/FAAN Second Symposium on Anaphylaxis [Sampson, 2006]. The criteria do not make a distinction based on underlying mechanism. These criteria are summarized as follows:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula), and at least one of the following:
    a) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    b) Reduce d blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a) Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b) Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c) Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):
    a) Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic blood pressure
    b) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

12.12. Appendix 12: Assessment of nasal polyposis

Endoscopic NP scoring:

For consistency across sites, it is important to score NP using the following standard. Each nostril will be scored and the results recorded individually

Polyp Score	Polyp Size

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.

Nasal Polyp Score

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.

12.13. Appendix 13 - Inspection of the Safety Syringe Form

Injection Assessment – Safety Syringe	
Was the full dose successfully administered?	☐ Yes, injection successful ☐ No, injection not successful (please complete the questions below[1]) ☐ No, injection not attempted
	Were there any observations with respect to the user tasks that indicate that the full dose has not been administered? Check all that apply. - Incorrect injection site selected, *record location below* - Needle not fully inserted into site - Plunger not slowly pushed down - Plunger not pushed all the way down until the stopper reaches the bottom of the syringe - Thumb not moved up, plunger not risen and needle guard not activated - Evidence of liquid leaking from injection site (i.e. potentially indicating a premature lift or a wet injection) - *Other (please specify below)* Were there any observations with respect to the device that indicate that the full dose has not been dispensed? Check all that apply. - Syringe leaking - Components broken / cracked - Cannot push the plunger rod down (i.e., required force is too high) - *Other (please specify below)*

Footnote 1 refers to the Safety Syringe Error / Failure Reporting Form Section 12.9. Failure in either of these two events requires the appropriate form to be completed. **HCP should review the user tasks in completing the injection, the device and the packaging and complete form in Section 12.9 to capture any issues.**

12.14. Appendix 14: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).