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.

		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					

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.

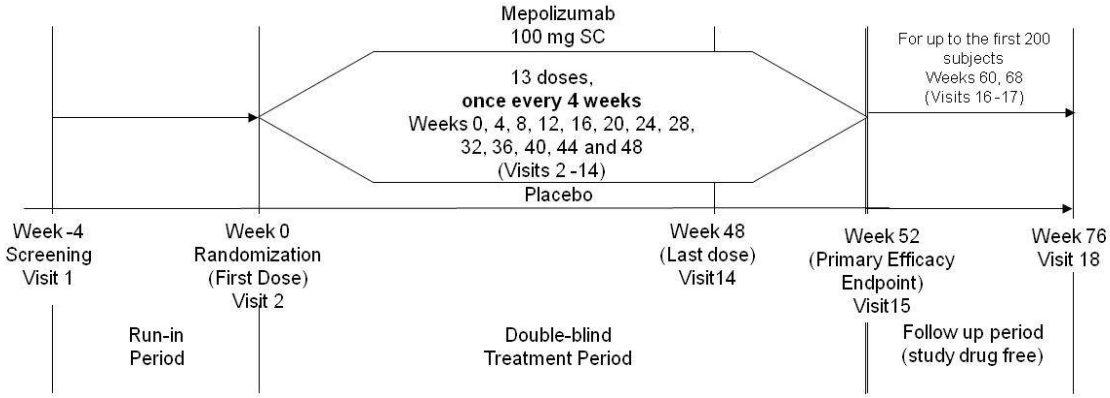
and recurrent NP despite treatment with current standard of care. Participants must be in current need for NP surgery as defined by an overall VAS symptom score greater than 7 in addition to a NP score ≥3 in at least one nostril.

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

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

- 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

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

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

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.

9.4.3. 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

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

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.

- 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.

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**

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.

		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			

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.

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.

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.

- 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)

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.

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.

9.3.8.4. 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.

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

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

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

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

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