TITLE PAGE

Protocol Title: A randomised, double-blind, placebo controlled, parallel group Phase III study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab in adults with chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS) MERIT: **M**epolizumab in **E**osinophilic chronic **R**hinosinus**IT**is study

Protocol Number: 209692 Amendment 03

Compound Number: SB240563

Brief Title: Efficacy and safety of mepolizumab in adults with CRSwNP / ECRS

Study Phase: Phase 3

Sponsor Name and Legal Registered Address:

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**Document Number**
Amendment 03	21 Jul 2022	TMF-14790303
Amendment 02	29-JUN-2021	TMF-13841979
Amendment 01	08-OCT-2020	TMF-2114641
Original Protocol	14-AUG-2020	2020N441602_00

Amendment 03: 21 Jul 2022

This amendment is considered substantial because it significantly impacts the scientific value of the study.

Overall Rationale for the Amendment: The primary reason for this amendment is to change the summary measure and analysis method for the co-primary and secondary endpoints. This is to align with draft FDA regulatory guidance for this indication [FDA, 2021].

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 3 Objectives and Endpoints – Summary Measure	Change in summary measure from difference in medians to difference in means.	Align with draft FDA regulatory guidance for this indication. The analysis of difference in means is the primary comparison for both co-primary endpoints.
9.2 Sample Size Determination	Sample size re-calculated in line with change to summary measure for co-primary endpoint analysis.	The sample size calculation is re-performed using difference of means to confirm that the study is sufficiently powered with the change in summary measure from difference of medians to difference of means.
1.1 Synopsis 3 Objectives and Endpoints – Summary Measure 9.4.1 Primary Endpoint	Participants experiencing an intercurrent event of surgery will be assigned the worst possible score for the endpoint from surgery onwards.	The score assigned to a participant following surgery is changed to the worst possible score for the endpoint following consideration of the most appropriate approach.
1.1 Synopsis	Addition of intercurrent event of course of systemic	It is anticipated that some participants may receive short courses of systemic CS for CRSwNP / ECRS as part of

Section # and Name	Description of Change	Brief Rationale
3 Objectives and Endpoints – Summary Measure 9.4.1 Primary Endpoint	corticosteroid (CS) for CRSwNP / ECRS.	standard of care during the study. Data collected following a course of systemic CS for CRSwNP / ECRS will be included in the analysis of the primary estimand (treatment policy). A supplementary estimand has been added whereby a course of systemic CS for CRSwNP / ECRS will be considered as a treatment failure, this will be incorporated into the endpoint (composite strategy) by assigning the worst possible score for the endpoint following the initiation of the course of systemic CS.
1.1 Synopsis 3 Objectives and Endpoints – Summary Measure 9.4.1 Primary Endpoint	Addition of intercurrent event of 2 or more consecutive missed doses of investigational product.	There is expected to be cases where some participants have missed 2 or more consecutive doses of investigational product. Data collected during and after the occurrence of these missed doses will be included in the analysis of the primary estimand (treatment policy).
9.4.1 Primary Endpoint	Missing data for participants who withdraw from the study without having experienced surgery will be handled as missing at random (MAR).	The handling of missing participant data following withdrawal from study has been clarified with the change in summary measure to a difference of means. Sensitivity analyses will be carried out to examine the potential impact of choices for the handling of participants with missing data. Further details of the multiple imputation strategies using an off-treatment imputation have been specified.
11 References	Removal/addition of references	To align with updates to the text.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A randomised, double-blind, placebo-controlled, parallel group Phase III study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab in adults with chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS) – MERIT: **M**epolizumab in **E**osinophilic chronic **R**hinosinus**IT**is study

Brief Title: Efficacy and safety of mepolizumab in adults with CRSwNP / ECRS

Rationale:

Nasal polyps (NP) is a chronic inflammatory disease of the nasal mucosa, characterised 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 health related Quality of Life (HRQoL). The European Position Paper on Rhinosinusitis and NP [Fokkens, 2020] defines the severity of disease using a total severity visual analogue 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 computerised tomography (CT). The aetiology of NP is currently unknown.

In Japan, chronic rhinosinusitis (CRS) is recognised as a common chronic disease [Tokunaga, 2015]. In recent years, cases of CRS with NP (CRSwNP) associated with eosinophilic infiltration have increased in Japan due to westernisation of eating habits and environments [Tokunaga, 2015]. Patients are diagnosed with eosinophilic chronic rhinosinusitis (ECRS) using the JESREC (Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis) scoring system based on the presence of bilateral NP, CT findings, and eosinophilia in peripheral blood. This scoring system provide a criterion to diagnose and classify ECRS without the use of biopsy or operational specimens. A patient is diagnosed as having ECRS if the JESREC score is 11 points or higher. Additionally, patients CRS is further classified into four groups according to blood eosinophilia, ethmoid-dominant shadow in CT, and comorbidity (bronchial asthma, aspirin intolerance [AI], non-steroidal anti-inflammatory drugs [NSAIDs] intolerance). These four groups were significantly correlated with the rate of recurrence and refractory disease [Tokunaga, 2015].

Similarly, CRS is among the most prevalent chronic disease in China. A recent study found that the proportion of eosinophilic CRSwNP patients significantly increased over the past 11 years [Wang, 2019]. Although there are no established diagnosis criteria for eosinophilic CRSwNP in China so far, these patients differ significantly from non-eosinophilic patients in clinical characteristics and treatment outcomes: they have higher risk of having comorbid allergic rhinitis and asthma, are frequently associated

with extensive sinus disease, and have higher polyp recurrence rate after surgery. Hence, precision medicine on inflammatory endotypes by verification and mapping of the eosinophilic disease are of great importance to optimise care pathways in Asia.

IL-5 is the predominant cytokine in NP associated with tissue eosinophilia, promoting the activation and prolonged survival of eosinophils. 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.

Mepolizumab (NUCALA) is a humanised 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 signalling. Neutralisation of IL-5 with mepolizumab has been shown to reduce blood, sputum and tissue eosinophils. This led GSK to develop mepolizumab as a treatment option in a number of eosinophilic diseases including chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS).

Mepolizumab is licensed for i) add-on maintenance treatment for severe eosinophilic asthma at a dose of 100 mg administered subcutaneously (SC) every 4 weeks in over 20 countries worldwide (40 mg SC in patients 6 to 11 years in the European Union [EU], United States of America [US], Japan and in other markets), ii) treatment of eosinophilic granulomatosis with polyangiitis (EGPA) at a dose of 300 mg SC every 4 weeks in the US, Japan, and other markets. Mepolizumab is currently approved as a lyophilised powder in a vial requiring reconstitution with sterile water for injection for administration by a healthcare professional (Mepolizumab for Injection), and as liquid formulation in both a prefilled safety syringe (SSD) and prefilled autoinjector for in-clinic or at-home patient self-administration or administration by a caregiver (Mepolizumab Injection). Mepolizumab injection is currently approved in several markets such as the EU, US and Japan.

As of September 2019, over 4600 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 900 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 1500 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 clinical studies (CRT110178 and MPP111782) and 206 participants been exposed to 100 mg SC every 4 weeks for up to 12 months in a Phase III study (SYNAPSE, 205687). All 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.

Study CRT110178 was an investigator-led, collaborative research study of randomised, double-blind, placebo-controlled design comparing mepolizumab versus placebo in participants with severe NPs that were recurrent after surgery. Participants were

randomised to receive two single IV injections (28 days apart) of mepolizumab 750 mg IV (n=20) or placebo (n=10). The primary endpoint was the change from baseline in total endoscopic NP score which was the sum of left and right nostril scores assessed by endoscopy at Week 8 versus baseline. An improvement was observed for mepolizumab patients compared to placebo at Week 8 (-1.22, 90% CI: -2.28, -0.17; one–sided p=0.0258).

Study MPP111782 was a GSK Phase II study that was a two-part (Part A and Part B) randomised, 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 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 randomised 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 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 following a protocol amendment.

The primary endpoint was reduction in the need for surgery at the end of Part A (4 weeks post last dose, Week 25). A significantly greater proportion of participants in the mepolizumab group compared to placebo no longer required surgery at the end of Part A (33% vs 10% respectively, p=0.003). 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). These improvements were supported by changes in individual VAS symptom scores and SNOT-22, a disease specific measure of HRQoL.

The above evidence supported the initiation of a single Phase III pivotal trial entitled, “A randomised, double-blind, parallel group Phase III 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).

In this study, mepolizumab was administered by the Investigator or delegate via a pre-filled safety syringe every 4 weeks for 52 weeks. The efficacy of mepolizumab was assessed using co-primary endpoints of change from baseline in endoscopic NP score at Week 52 and nasal obstruction VAS symptom score during the 4 weeks prior to Week 52. Key secondary endpoint was time to first confirmed surgery for NP by Week 52. The study population consisted of adult participants with recurrent severe bilateral NP. They had to present with a history of at least one prior surgery for NP despite treatment with current SoC, which included intranasal corticosteroid, and need for NP surgery.

The study met both co-primary endpoints, with mepolizumab demonstrating statistically significant improvements in both the size of polyps and in nasal obstruction, compared to placebo, when added to standard of care:

- Difference of -0.73 (95% CI: -1.11, -0.34; p<0.001) in the median change from baseline total endoscopic nasal polyps score at week 52
- Difference of -3.14 (95% CI: -4.09, -2.18; p<0.001) in the median change from baseline in mean nasal obstruction VAS score during weeks 49-52

The key secondary endpoint of time to first confirmed nasal surgery up to week 52 was also statistically significant, with mepolizumab showing a 57% reduction (p=0.003) versus placebo in rate of undertaking a NP surgery (hazard ratio [95% CI]: 0.43 [0.25, 0.76]). All other secondary endpoints were statistically significant consistent with the findings of the co-primary and key secondary endpoints thus supporting the overall efficacy of mepolizumab in patients with CRSwNP. There were no new safety concerns identified for mepolizumab compared with placebo.

The aim of this study is to assess the efficacy and safety of mepolizumab on top of standard of care (SoC) therapy in the treatment of CRSwNP / ECRS for the purpose of registration in Japan and China.

Objectives and Endpoints

Objectives	**Endpoints**
Primary	
• To evaluate the efficacy of mepolizumab 100mg SC compared to placebo at Week 52 in patients with a diagnosis of CRSwNP / ECRS	The primary estimands are defined as follows: **Treatment Comparison:** Mepolizumab 100 mg SC compared to placebo **Population:** entire trial population of patients with a diagnosis of CRSwNP / ECRS randomised and receiving treatment **Co-primary variables**: a) Change from baseline in total endoscopic NP score at Week 52 b) Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52 **Summary measure**: Difference in mean scores between mepolizumab and placebo **Main Intercurrent events (ICE) anticipated**: a) Premature discontinuation of study treatment unrelated to the COVID-19 pandemic – to be handled using a treatment policy strategy

Objectives	**Endpoints**
	b) Changes in background medication or start of a prohibited medication unrelated to the COVID-19 pandemic (e.g. start INCS therapy where absent at baseline) – to be handled using a treatment policy strategy c) Premature discontinuation of study treatment, change in background medication or start of prohibited medication related to the COVID-19 pandemic – to be handled using a hypothetical strategy d) Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g. polypectomy) – to be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who undergo surgery will be assigned the worst possible score for the endpoint from the day of surgery onwards for inclusion in the analysis. e) Course of systemic corticosteroids (CS) for CRSwNP / ECRS – to be handled using a treatment policy strategy f) Interruption to investigational product of 2 or more consecutive doses – to be handled using a treatment policy
Secondary	
• To evaluate the impact on quality of life of 100mg mepolizumab compared to placebo at Week 52 in patients with a diagnosis of CRSwNP / ECRS	• Change from baseline in SNOT-22 total score at Week 52
• To evaluate the efficacy of 100 mg mepolizumab compared to placebo at Week 52 in terms of mean overall VAS symptom score, mean composite VAS score, Lund Mackay CT score, mean individual VAS symptom score for loss of smell and impact on time to first nasal surgery or course of systemic	• Change from baseline in mean overall VAS symptom score 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 and loss of smell) during the 4 weeks prior to Week 52 • Change from baseline in Lund Mackay CT score at Week 52

Objectives	**Endpoints**
CS in patients with a diagnosis of CRSwNP / ECRS	• Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52 • Time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52
Other	
CCI [redacted]	

Objectives	Endpoints
CCI	[redacted]

Objectives	Endpoints
CCI [redacted]	
Safety	
• To evaluate the safety and immunogenicity of 100 mg mepolizumab compared placebo in patients with a diagnosis of CRSwNP / ECRS	• Frequency of Adverse events (AEs)/ Serious adverse events (SAEs) including systemic reactions and local injection site reactions reported • Vital signs (pulse rate, systolic and diastolic blood pressure) • Haematological and clinical chemistry parameters • 12 lead ECG derived endpoints • Presence of anti-mepolizumab antibodies and neutralising antibodies
Pharmacokinetics and pharmacodynamics	
• To evaluate the pharmacokinetics and pharmacodynamics of 100 mg mepolizumab in a subgroup of participants from Japan and China with a diagnosis of CRSwNP / ECRS	• Plasma concentration of mepolizumab • PK/PD (blood eosinophil count) analysis

The primary estimands are the difference between mepolizumab 100 mg SC and placebo in a) mean change from baseline in total endoscopic NP score to Week 52 and b) mean change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to

Week 52 in participants with a diagnosis of CRSwNP / ECRS, regardless of IP discontinuation or changes in background medication/starting a prohibited medication unrelated to the COVID-19 pandemic, use of systemic CS for CRSwNP / ECRS or interruption of 2 or more consecutive doses of IP, with participants experiencing surgery being assigned the worst possible score from the day of surgery onwards.

Secondary estimands for SNOT-22, VAS scores and Lund Mackay CT score will use the same population, summary measure and strategies for intercurrent events as for the primary estimands. Time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52 will be summarised by the hazard ratio between mepolizumab and placebo. The same population and strategies for intercurrent events of treatment discontinuation, changes in background medication/starting a prohibited medication, interruptions of 2 or more consecutive doses of IP and COVID-19 pandemic related intercurrent events will be used as for the primary estimands. For this endpoint, both surgery and a course of systemic CS for CRSwNP / ECRS will be considered events within the analysis and therefore will not be considered an intercurrent event.

Overall Design:

This is a randomised, double-blind, placebo controlled, parallel group Phase III study designed to assess the clinical efficacy and safety of 100 mg SC Mepolizumab treatment in adults with chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS).

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

The study population will consist of adult participants (≥18 years of age) with CRSwNP / ECRS as defined by the JESREC guideline. In addition, they must have 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 prior treatment with systemic corticosteroids (SCS) anytime within the past 2 years; and/or have a medical contraindication/intolerance to SCS; and/or had a documented history of prior surgery for NP at the screening visit.

The study will include a 4-week run-in period followed by randomisation to a 52-week treatment period as a double-blind, placebo-controlled phase. Throughout the 52-week treatment period, participants will be on the SoC for CRSwNP / ECRS. Depending on local practice SoC may include intranasal corticosteroids (INCS), saline nasal douching, occasional short courses of systemic corticosteroids and/or antibiotics. Depending on local SoC/treatment, patients treated with intranasal corticosteroids (INCS) and/or leukotriene receptor antagonists (LTRA) are expected, if possible, to continue with these treatments with no interruption nor alteration to the doses throughout the study duration. If a patient is not on INCS or LTRA prior to screening, the patient is prohibited to start any INCS or LTRA during the study.

There is a trend especially in Japan, to use orally inhaled corticosteroids exhalation through nose (ICS/ETN) method of administration for the management of NP for patients with both ECRS and concomitant asthma disease [Kobayashi, 2018]. Although longer term effects on ECRS disease are yet to be fully evaluated, the short-term effects of ICS/ETN on NP size can be significant. Therefore, participants in this study who use ICS/ETN method of administration for their asthma and NP disease are maintain this method throughout the study period.

The treatment period will consist of thirteen, 4-weekly doses of mepolizumab or placebo, delivered by a pre-filled safety syringe device (SSD) injection.

Number of Participants:

Assuming a screen failure rate of 40%, approximately 270 participants will need to be screened in order to allow for approximately 160 participants to be randomised in a 1:1 ratio to mepolizumab or placebo treatment (approximately 80 participants per arm).

Intervention Groups and Duration:

A liquid formulation of mepolizumab, which has currently been approved in the EU, US, Japan and some other markets, will be provided in a SSD. There will also be a matched SSD with matched placebo. For non-Japanese participants, study treatment must be administered by a health care professional (HCP) until week 52 (last dose at week 48). For Japanese participants who are willing to self-administer they can self-administer study treatment under observation of the HCP from Week 32 onwards. Participants who are successfully enrolled into the study will be randomised in a 1:1 ratio into one of two treatment groups, receiving a total of thirteen doses (one every four weeks) in a double-blind manner:

- Group 1: 100 mg SC of mepolizumab on top of SoC
- Group 2: Placebo SC on top of SoC

A participant is considered to have completed study treatment if he/she receives study treatment at Visit 14 (Week 48). A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (Visit 15/Week 52) or the last scheduled procedure shown in the SoA, whichever is earlier.

The end of the 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, whichever is earlier.

Initiation or changes in the dosing regimen of LTRA or allergen immunotherapy from screening to end of the study are not allowed. Changes in the dosing regimen of INCS and/or ICS/ETN from screening to end of the study are also not allowed.

The following medications may be used by all participants:

1. Short courses of systemic CS (for example of systemic CS for treatment of CRSwNP / ECRS). The use of rescue medications such as systemic CS is allowable during the 52-week treatment phase of the study (Visit 2 and onwards) but not during the run-in

period; the date and time of rescue medication administration as well as the name and dosage regimen (dose and duration) of the rescue medication must be recorded in the eCRF for NP as well as for other comorbidities.

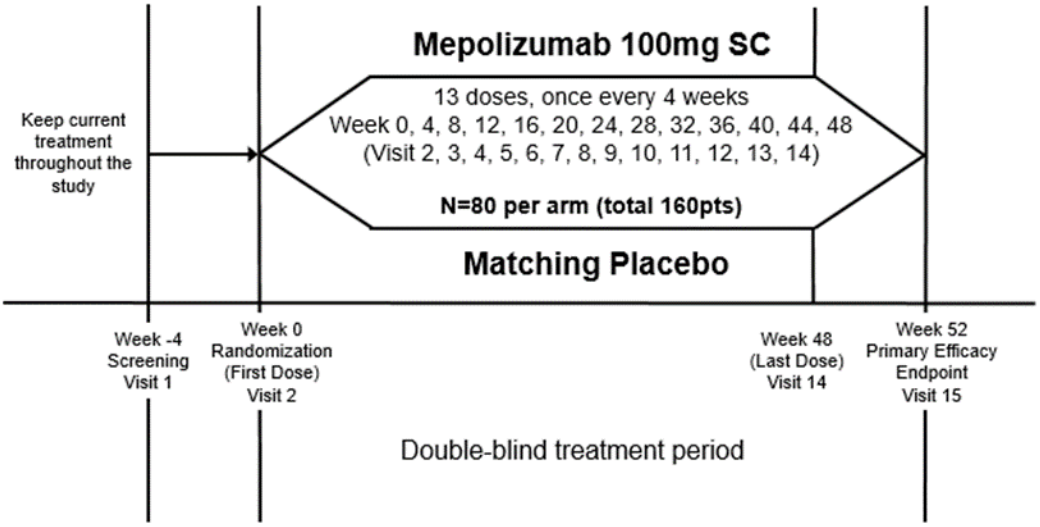
2. Throughout the study, asthmatic participants are to be maintained on their baseline SoC asthma treatment.
3. For antibiotic treatment for CRSwNP / ECRS, the type, dose and duration must also be recorded in the eCRF.

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 products (biologic or non-biologic)	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 CRSwNP / ECRS	6 months

Data Monitoring/Other Committee: Not applicable

1.2. Schema


Mepolizumab 100mg SC
13 doses, once every 4 weeks
Week 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48
(Visit 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14)
N=80 per arm (total 160pts)
Matching Placebo
Keep current treatment throughout the study
Week -4 Screening Visit 1
Week 0 Randomization (First Dose) Visit 2
Week 48 (Last Dose) Visit 14
Week 52 Primary Efficacy Endpoint Visit 15
Double-blind treatment period

1.3. Schedule of Activities (SoA)

	Procedure	Pre-screening[1]	Screening[1]	Treatment															
Visit		0	1	2	3	4	5	6	7	8	9	9a	10	11	12	13	14	15	IP DISC / EW Visit
Study Day (visit window **±7** days)			up to **28 ±7** days prior to Day 1	1	29	57	85	113	141	169	197	204 (±1day)	225	253	281	309	337	365	**28 ±7** days **post last dose**
Week				0	4	8	12	16	20	24	28	29	32	36	40	44	48	52	
Screening/ baseline	Informed consent	X																	
	Blood collection for eosinophils eligibility confirmation (if required) [2]	X																	
	Inclusion and exclusion criteria		X																
	Demography		X																
	Full physical exam including height and weight		X																
	Medical history (includes substance usage and family history of premature CV disease CRSwNP/ECRS and asthma therapy, asthma and exacerbation history and concomitant medications)		X																
	SAE Review		X																
	History of HIV and Hep B, Hep C screen		X																
	Past and current medical conditions including cardiovascular medical history		X																
	History of systemic CS use for NP		X																
	History of NP surgery		X																

	Procedure	Pre-screening[1]	Screening[1]	Treatment															
Visit		0	1	2	3	4	5	6	7	8	9	9a	10	11	12	13	14	15	IP DISC / EW Visit
Study Day (visit window **±7** days)			up to **28 ±7** days prior to Day 1	1	29	57	85	113	141	169	197	204 (±1day)	225	253	281	309	337	365	**28 ±7** days **post last dose**
Week				0	4	8	12	16	20	24	28	29	32	36	40	44	48	52	
	Parasitic screening [3]		X																
	Screening 12-lead ECG		X																
	Screening Vital signs		X																
	Assessment of endoscopic NP score[11]		X																
	Assessment of VAS for NP symptoms including Overall VAS [6]		X																
	Assessment of Screening CT[4]		X																
	Screening Laboratory assessments: Haematology (including blood eosinophils) and chemistry (including liver chemistries)		X																
	Screening Urinalysis		X																
	Urine pregnancy test (WOCBP only)[5]		X																
	Dispense and Train in the use of eDiary[6]		X																
	Register visit	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
	Randomisation			X															
	Genetics sample[7]												X						
Efficacy	Assessment of NP Surgery			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
	Assessment of systemic CS and antibiotics dose and duration for NP			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X

	Procedure	Pre-screening[1]	Screening[1]	Treatment															
Visit		0	1	2	3	4	5	6	7	8	9	9a	10	11	12	13	14	15	IP DISC / EW Visit
Study Day (visit window **±7** days)			up to **28 ±7** days prior to Day 1	1	29	57	85	113	141	169	197	204 (±1day)	225	253	281	309	337	365	**28 ±7** days **post last dose**
Week				0	4	8	12	16	20	24	28	29	32	36	40	44	48	52	
	VAS symptom score for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, facial pain[6]			←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
	Overall VAS symptom score[6]			←	—	—	—	—	—	—	—	—	—	—	—	—	—	→	
	SNOT-22[8, 9, 17]			X	X	X	X	X	X	X				X				X	X
	SF-36[8, 9, 10]			X	X					X								X	X
	WPAI-GH[8, 9, 10]			X	X					X								X	X
	ACQ – 5[8, 9, 17]			X	X	X	X	X	X	X				X				X	X
	Endoscopic NP score[11]			X	X	X		X		X			X		X		X	X	X
	Assessment of CT[4, 5]																	X	X
	Asthma exacerbation[12]			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
	Blood for PK[13]				X						X	X[13]						X	X
	Blood for Immunogenicity			X						X								X	X
Safety	AE/SAE review			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
	Concomitant medication review (including INCS)			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
	12-lead ECG			X						X								X	X
	Vital signs (HR and BP)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
	Laboratory assessments: Haematology (including blood eosinophils)[15]			X	X	X			X	X			X			X	X	X	X
	Laboratory assessments: chemistry (including liver chemistries)[16]			X	X	X			X				X			X		X	X

	Procedure	Pre-screening[1]	Screening[1]	Treatment															
Visit		0	1	2	3	4	5	6	7	8	9	9a	10	11	12	13	14	15	IP DISC / EW Visit
Study Day (visit window **±7** days)			up to **28 ±7** days prior to Day 1	1	29	57	85	113	141	169	197	204 (±1day)	225	253	281	309	337	365	**28 ±7** days **post last dose**
Week				0	4	8	12	16	20	24	28	29	32	36	40	44	48	52	
	Urinalysis			X	X										X			X	X
	Urine pregnancy test (WOCBP)[5]			X	X	X	X	X	X	X	X		X	X	X	X	X	X[5]	X[5]
	Dosing with study Drug/Placebo[14]			X	X	X	X	X	X	X	X		X	X	X	X	X		
	eDiary Compliance Check			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
	eDiary Collection																	X	X
	Early withdrawal, intervention discontinuation																		X

1. Pre-screening and screening can be performed on the same day
2. A documented blood eosinophil count of >2% in the 12 months prior to Visit 0 OR through a blood sample taken between Visit 0 and Visit 1. ALL participants must meet blood eosinophil count of >2% by Visit 1
3. 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
4. A CT scan should be performed anytime during the run-in period up to a week prior randomisation. A second CT scan should be performed at V15 or IP discontinuation/Early Withdrawal visit (up to 14 days prior to the nominal study visit)
5. Urine Pregnancy test results to be assessed at all visits and prior to CT scan at Screening, V15 or IP discontinuation/Early Withdrawal Visit. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
6. eDiary completion by participants will be daily every morning between Screening Visit and Visit 15 (or IP discontinuation/Early Withdrawal Visit)
7. Genetics informed consent to be obtained any time prior sampling, Genetics sampling to be performed anytime while on treatment (Genetics sampling not applicable for participants in China)
8. Performed using eDiary device
9. All questionnaires will be performed before any other assessments on each particular visit, VAS scores (if not already completed at home), SNOT-22, (ACQ-5), SF-36 and WPAI. ACQ-5 should only be performed in Asthmatic participants. Order of questionnaires will be detailed in the Study Reference Manual.
10. SF-36 and WPAI will be performed at visits Baseline, week 4, week 24 and week 52 (or IP discontinuation/Early Withdrawal Visit) only
11. For endoscopic NP scores performed at V1, 3, 4, 6, 8, 10, 12, 14, 15 (or IP discontinuation/Early Withdrawal Visit), the nasal 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. For V2, the endoscopic NP score cannot be performed earlier than V2 but must be performed at V2 upon completion of all screening procedures and prior to administration of IP.

12. For asthmatic participants only. 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 hospitalisation
13. Blood for PK will be collected at Visits 3 (pre-dose), 9 (pre-dose) and 15 (or IP discontinuation/early withdrawal). In addition, one post-dose PK collection will be at Week 29 (Visit 9a, one week after dose at Visit 9) with a collection visit allowance of ±1 day. As for Week 29, blood sample will be collected from up to approximately first 30 Japanese and all Chinese participants randomised, no PK samples will be collected outside Japan and China
14. For participants who are willing to perform self-administration within the Japanese participants cohort: self-administer from Week 32 onwards (after receiving at least two trainings by investigator or delegate beforehand)
15. Laboratory assessments: Haematology (including blood eosinophils) will be taken at visits 1, 2, 3, 4, 7, 8, 10, 13, 14, 15 (or IP discontinuation/Early Withdrawal Visit)
16. Laboratory assessments: chemistry (including liver chemistries) will be taken at visits 1, 2, 3, 4, 7, 10, 13, 15 (or IP discontinuation/Early Withdrawal Visit)
17. ACQ-5 and SNOT-22 will be performed at baseline (visit 2), 3, 4, 5, 6, 7, 8, 11, 15, IP discontinuation/Early Withdrawal Visit

2. INTRODUCTION

2.1. Study Rationale

Mepolizumab (NUCALA) is a humanised 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 signalling. Neutralisation of IL-5 with mepolizumab has been shown to reduce blood, sputum and tissue eosinophils. This led GSK to develop mepolizumab as a treatment option in a number of eosinophilic diseases including chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS).

Mepolizumab is licensed for i) add-on maintenance treatment for severe eosinophilic asthma at a dose of 100 mg administered subcutaneously (SC) every 4 weeks in over 20 countries worldwide (40 mg SC in patients 6 to 11 years in the European Union [EU], United States of America [US], Japan and in other markets), ii) treatment of eosinophilic granulomatosis with polyangiitis (EGPA) at a dose of 300 mg SC every 4 weeks in the US, Japan, and other markets. Mepolizumab is currently approved as a lyophilised powder in a vial requiring reconstitution with sterile water for injection for administration by a healthcare professional (Mepolizumab for Injection), and as liquid formulation in both a prefilled safety syringe (SSD) and prefilled autoinjector for in-clinic or at-home patient self-administration or administration by a caregiver (Mepolizumab Injection). Mepolizumab Injection is currently approved in several markets such as the EU, US and Japan.

As of September 2019, over 4600 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 900 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 1500 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 clinical studies (CRT110178 and MPP111782) and 206 participants been exposed to 100 mg SC every 4 weeks for up to 12 months in a Phase III study (SYNAPSE, 205687). All 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.

The aim of this study is to assess the efficacy and safety of mepolizumab on top of standard of care (SoC) therapy in the treatment of CRSwNP/ ECRS for the purpose of registration in Japan and China.

2.2. Background

Background on CRSwNP / ECRS

Nasal polyps (NP) is a chronic inflammatory disease of the nasal mucosa, characterised 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 health related Quality of Life (HRQoL). The European Position Paper on Rhinosinusitis and NP [Fokkens, 2020] defines the severity of disease using a total severity visual analogue 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 computerised tomography (CT). The aetiology of NP is currently unknown.

The current standard of care (SoC) for CRSwNP is treatment with INCS and, for severe symptoms, intermittent courses of systemic corticosteroids, when short term relief is required [Fokkens, 2020]. 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; Brescia, 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.

In Japan, chronic rhinosinusitis (CRS) is recognised as a common chronic disease [Tokunaga, 2015]. In recent years, cases of CRS with NP (CRSwNP) associated with eosinophilic infiltration have increased in Japan due to westernisation of eating habits and environments [Tokunaga, 2015]. Patients are diagnosed as eosinophilic chronic rhinosinusitis (ECRS) using the JESREC (Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis) scoring system based on the presence of bilateral NP, CT findings, and eosinophilia in peripheral blood. This scoring system provide a criterion to diagnose and classify ECRS without the use of biopsy or operational specimens. A patient is diagnosed as having ECRS if the JESREC score is 11 points or higher. Additionally, patients CRS is further classified into four groups according to blood eosinophilia, ethmoid-dominant shadow in CT, and comorbidity (bronchial asthma, aspirin intolerance (AI) non-steroidal anti-inflammatory drugs

[NSAIDs] intolerance). These four groups were significantly correlated with the rate of recurrence and refractory disease [Tokunaga, 2015].

Similarly, CRS is among the most prevalent chronic disease in China. A recent report found that the proportion of eosinophilic CRSwNP patients significantly increased over 11 years [Wang, 2019]. Although there are no established diagnosis criteria for eosinophilic CRSwNP in China so far, these patients differ significantly from non-eosinophilic patients in clinical characteristics and treatment outcomes: they have higher risk of having comorbid allergic rhinitis and asthma, are frequently associated with extensive sinus disease, and have higher polyp recurrence rate after surgery. Hence, precision medicine on inflammatory endotypes by verification and mapping of the eosinophilic disease are of great importance to optimise care pathways in Asia.

Standard of care for ECRS is systemic corticosteroids in Japan and there is a trend to use orally inhaled corticosteroids exhalation through nose (ICS/ETN) method of administration for the management of NP for patients with both ECRS and concomitant asthma disease [Kobayashi, 2018]. Although longer term effects on nasal polyp disease are yet to be fully evaluated, the short-term effects of ICS/ETN on NP size can be significant. Of note, in Japan INCS is not licensed for ECRS.

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; Fokkens, 2020]. 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 [Fokkens, 2020]. Antrochoanal polyps are also another form of NP more common in children that are usually unilateral and associated with low eosinophil tissue levels [Fokkens, 2020].

The role of mepolizumab in CRSwNP / ECRS

Mepolizumab (NUCALA™) is a humanised 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 signalling. Neutralisation of IL-5 with mepolizumab has been shown to reduce blood, sputum and tissue eosinophils. This led GSK to develop mepolizumab as a treatment option in a number of eosinophilic diseases including CRSwNP / ECRS.

Mepolizumab is licensed for i) add-on maintenance treatment for severe eosinophilic asthma at a dose of 100 mg administered subcutaneously (SC) every 4 weeks in over 20 countries worldwide (40 mg SC in patients 6 to 11 years in the European Union [EU], United States of America [US], Japan and in other markets), ii) treatment of eosinophilic granulomatosis with polyangiitis (EGPA) at a dose of 300 mg SC every 4 weeks in the US, Japan, and other markets. Mepolizumab is currently approved as a lyophilised

powder in a vial requiring reconstitution with sterile water for injection for administration by a healthcare professional (Mepolizumab for Injection), and as liquid formulation in both a prefilled safety syringe (SSD) and prefilled autoinjector for in-clinic or at-home patient self-administration or administration by a caregiver (Mepolizumab Injection). Mepolizumab Injection is currently approved in several markets such as the EU, US and Japan.

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 clinical studies (CRT110178 and MPP111782) and 206 participants been exposed to 100 mg SC every 4 weeks for up to 12 months in a Phase III study (SYNAPSE, 205687). All 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 comparing mepolizumab versus placebo in participants with severe NPs that were recurrent after surgery. Participants were randomised to receive two single intravenous (IV) injections (28 days apart) of mepolizumab 750 mg IV (n=20) or placebo (n=10). The primary endpoint was the change from baseline in total endoscopic NP score which was the sum of left and right nostril scores assessed by endoscopy at Week 8 versus baseline. An improvement was observed for mepolizumab patients compared to placebo at Week 8 (-1.22, 90% CI: -2.28, -0.17; one–sided p=0.0258).

Study MPP111782 was a GSK Phase II study that was a two-part (Part A and Part B) randomised, 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 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 randomised 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 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 following a protocol amendment.

The primary endpoint was reduction in the need for surgery at the end of Part A (4 weeks post last dose, Week 25). A significantly greater proportion of participants in the mepolizumab group compared to placebo no longer required surgery at the end of Part A (33% vs 10% respectively, p=0.003). 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). These improvements were supported by changes in individual VAS symptom scores and SNOT-22, a disease specific measure of HRQoL.

The above evidence supported the initiation of a single Phase III pivotal trial entitled, "A randomised, double-blind, parallel group Phase III 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).

In this study, mepolizumab was administered by the Investigator or delegate via a pre-filled safety syringe every 4 weeks for 52 weeks. The efficacy of mepolizumab was assessed using co-primary endpoints of change from baseline in endoscopic NP score at Week 52 and nasal obstruction VAS symptom score during the 4 weeks prior to Week 52. Key secondary endpoint was time to first confirmed surgery for NP by Week 52. The study population consisted of adult participants with recurrent severe bilateral NP. They must present with a history of at least one prior surgery for NP despite treatment with current SoC, which include intranasal corticosteroid, and in need for NP surgery.

The study met both co-primary endpoints, with mepolizumab demonstrating statistically significant improvements in both the size of polyps and in nasal obstruction, compared to placebo, when added to standard of care:

- Difference of -0.73 (95% CI: -1.11, -0.34; $p<0.001$) in the median change from baseline total endoscopic nasal polyps score at week 52
- Difference of -3.14 (95% CI: -4.09, -2.18; $p<0.001$) in the median change from baseline in mean nasal obstruction VAS score during weeks 49-52

The key secondary endpoint of time to first confirmed nasal surgery up to week 52 was also statistically significant, with mepolizumab showing a 57% reduction ($p=0.003$) versus placebo in rate of undertaking a NP surgery (hazard ratio [95% CI]: 0.43 [0.25, 0.76]). All other secondary endpoints were statistically significant consistent with the findings of the co-primary and key secondary endpoints thus supporting the overall efficacy of mepolizumab in patients with CRSwNP.

Mepolizumab was well tolerated in this population with CRSwNP with no new safety issues identified. 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 CRSwNP/ ECRS and recurrent disease despite current optimal medical management.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of mepolizumab may be found in the Investigator's Brochure (IB), summaries of findings from both clinical and non-clinical studies conducted with mepolizumab (SB-240563) lyophilised drug product and pre-filled liquid formulation can be found in the Investigator's Brochure [GSK Document Number CM2003/00010/10, 2015].

2.3.1. Risk Assessment

The following section outlines the key risks, risk assessment and mitigation strategy for this protocol:

Important Identified Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP)		
Risk of Systemic Allergic [type I hypersensitivity] and other systemic reactions, including Anaphylaxis	In the placebo controlled CRSwNP study 205687, 1 of 201 (<1%) on placebo and 2 of 206 (<1%) in the mepolizumab 100 mg SC group reported systemic reactions. One participant in the mepolizumab group reported rash, the other reported erythema. Both were considered to represent allergic type 1 hypersensitivity reactions by the investigator. Both events resolved and both participants continued treatment with mepolizumab. One participant on placebo reported an event of asthenia which was considered to represent systemic reaction - other by the investigator. The event resolved with continued study treatment. 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.	Regular 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 4: 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. In the event of an acute severe reaction (e.g., anaphylaxis) following administration of study treatment, there must be personnel/staff onsite at the treatment facility who are appropriately trained in basic life support to manage the patient 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.

Important Identified Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
	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 summarised in the IB "Adverse Events of Special Interest" section; see also '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, 2015].	
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 summarised 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, 2015].	Regular 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.

Important Identified Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
Potential risk of immunogenicity	Mepolizumab has low immunogenic potential. Overall, the immunogenicity results from clinical studies across the mepolizumab program demonstrate that the presence of anti-drug antibodies (ADAs) is not associated with any specific adverse events, anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics (PK) or pharmacodynamics (PD) of mepolizumab in the majority of participants and there was no evidence of a correlation between antibody titres and change in eosinophil level. Immunogenicity data reported to date across the mepolizumab development program are summarized in the IB; See Section 5.4 'Clinical Immunogenicity' and in Section 6 'Summary of Data and guidance for the Investigator' [GSK Document Number CM2003/00010/10, 2015].	Blood samples will be collected for detection of both ADA and neutralising antibodies (NAb).
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)
Exposure of subjects to ionising radiation from Cranial CT	Two cranial CT scans are included at visits 1 and 15, or in the event of IP discontinuation / Early Withdrawal. The total effective radiation dose from the two cranial CT procedures is estimated to be 4mSv. The average annual global background radiation dose is 2.4mSv and therefore the total estimated	The minimum number of CT procedures will be performed to achieve study objectives (with a 52 weeks spacing between procedures). Application of an increased minimum age for inclusion in the study was considered to further mitigate the risks. However, such a restriction is impracticable in this population and might also result in the study sample being skewed and unrepresentative. Therefore,

Important Identified Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
	dose from study procedures is less than 2-years of background radiation. The additional risk of developing a fatal malignancy as a result of this radiation exposure is around 1 in 5000.	given the moderate radiation dose, a minimum age for inclusion of 18 years is considered justifiable.
Exposure of foetus to ionising radiation from Cranial CT	As the study procedure is a cranial CT, the abdomen is out of the field of view and in the event of an undetected pregnancy the foetal radiation dose will be limited to scatter and hence very small. Nevertheless, steps are required to avoid accidental exposure of pregnant subjects.	WOCBP will be required to have a negative highly sensitive urine pregnancy test within the 24 hours before each CT scan. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant will be excluded from participation if the serum pregnancy result at screening is positive.
Blinding eosinophil counts	This study is a double-blind, placebo-controlled study which may be used to support approval for the use of mepolizumab in patients with CRSwNP / ECRS. Unblinded eosinophil counts after the first administration of IP may compromise the integrity of the study.	Patients will be seen every four weeks by site staff. After Randomisation, neither the site staff nor blinded GSK personnel will be sent results from the central laboratory for: absolute and differential values for eosinophils, lymphocytes, basophils, neutrophils and monocytes. However, sites will be sent total white blood counts throughout the study.
COVID-19 pandemic	The COVID-19 pandemic may impact the conduct of clinical studies. Challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for the IP or other considerations if site personnel or study participants become infected with COVID-19. These challenges may lead to difficulties in meeting protocol-specified procedures.	Missing protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation. Visits that were conducted via the telephone will not be classified as missed visits, however missed assessments (e.g. nasal endoscopy) should be recorded as COVID-19 protocol deviations. Intercurrent events of IP discontinuation or changes to background therapy/use of prohibited medications related to the COVID-19 pandemic (such as quarantines, site closures or other related issues) will be accounted for within the analysis of the study. Intercurrent events related to COVID-19

Important Identified Risk	Summary of Data/Rationale for Risk	Mitigation Strategy
		pandemic will be handled using a hypothetical strategy.

2.3.2. 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].

Recently the Phase III study of mepolizumab in CRSwNP (SYNAPSE) finished. This study demonstrated the efficacy of mepolizumab 100 mg SC by showing statistically significant and clinically meaningful improvement in the co-primary endpoints of total endoscopic nasal polyp score and symptoms of nasal obstruction associated with nasal polyps compared with placebo when administered every 4 weeks for up to 52 weeks in addition to SoC therapy.

These efficacy and safety data confirm a positive benefit: risk for mepolizumab in a population with CRSwNP despite SoC treatment.

Participants in this study will be required to attend monthly visits and continue optimized maintenance CRSwNP / ECRS therapy and therefore may benefit both from the additional assurance of medicine compliance and monitoring of their current maintenance therapy.

Participants may also benefit from regular monitoring of their CRSwNP / ECRS symptoms and potential identification of asthma exacerbations.

Data obtained from this study will provide additional evaluation of the efficacy and safety of mepolizumab delivered as a pre-filled liquid formulation in a safety syringe both administered by an HCP or self-injection.

2.3.3. Overall Benefit: Risk Conclusion

Current data from mepolizumab pre-clinical 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 and III studies in CRSwNP 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. No new safety signal was detected in the SYNAPSE on top of the safety data observed in asthma studies.

The higher morbidity and mortality in severe asthma compared with CRSwNP 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 CRSwNP / ECRS.

Treatment will be administered by a trained health care professional at the clinic and participants will be closely observed for at least 1 hour following administration of IP for

the first 3 doses then per institutional guidelines at all subsequent visits. A subgroup of participants in Japan will be given the opportunity to self-inject at least once under the supervision of the health care professional during visit 10 (week 32) to 14 (week 48) inclusive.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of mepolizumab 100 mg SC compared to placebo at Week 52 in patients with a diagnosis of CRSwNP / ECRS	The primary estimands are defined as follows: **Treatment Comparison:** Mepolizumab 100 mg SC compared to placebo **Population:** entire trial population of patients with a diagnosis of CRSwNP / ECRS randomised and receiving treatment **Co-primary variables**: a) Change from baseline in total endoscopic NP score at Week 52 b) Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52 **Summary measure**: Difference in mean scores between mepolizumab and placebo **Main Intercurrent events (ICE) anticipated**: a) Premature discontinuation of study treatment unrelated to the COVID-19 pandemic – to be handled using a treatment policy strategy b) Changes in background medication or start of a prohibited medication unrelated to the COVID-19 pandemic (e.g. start INCS therapy where absent at baseline) – to be handled using a treatment policy strategy c) Premature discontinuation of study treatment, change in background medication or start of prohibited medication related to the COVID-19 pandemic – to be handled using a hypothetical strategy d) Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g.

Objectives	Endpoints
	polypectomy) – to be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who undergo surgery will be assigned the worst possible score for the endpoint from the day of surgery onwards for inclusion in the analysis. e) Course of systemic CS for CRSwNP / ECRS – to be handled using a treatment policy strategy f) Interruption to investigational product of 2 or more consecutive doses – to be handled using a treatment policy
Secondary	
• To evaluate the impact on quality of life of 100 mg mepolizumab compared to placebo at Week 52 in patients with a diagnosis of CRSwNP / ECRS	• Change from baseline in SNOT-22 total score at Week 52
• To evaluate the efficacy of 100 mg mepolizumab compared to placebo at Week 52 in terms of mean overall VAS symptom score, mean composite VAS score, Lund Mackay CT score, mean individual VAS symptom score for loss of smell and impact on time to first nasal surgery or course of systemic CS in patients with a diagnosis of CRSwNP / ECRS	• Change from baseline in mean overall VAS symptom score 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 and loss of smell) during the 4 weeks prior to Week 52 • Change from baseline in Lund Mackay CT score at Week 52 • Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52 • Time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52
Other	
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	

Objectives	Endpoints
CCI [redacted]	
Safety	
• To evaluate the safety and immunogenicity of 100 mg mepolizumab compared placebo in patients with a diagnosis of CRSwNP / ECRS	• Frequency of Adverse events (AEs)/ Serious adverse events (SAEs) including systemic reactions and local injection site reactions reported • Vital signs (pulse rate, systolic and diastolic blood pressure) • Haematological and clinical chemistry parameters • 12 lead ECG derived endpoints • Presence of anti-mepolizumab antibodies and neutralising antibodies
Pharmacokinetics and pharmacodynamics	
• To evaluate the pharmacokinetics and pharmacodynamics of 100 mg mepolizumab in a subgroup of participants from Japan and China with a diagnosis of CRSwNP / ECRS	• Plasma concentration of mepolizumab • PK/PD (blood eosinophil count) analysis

The primary estimands are the difference between mepolizumab 100 mg SC and placebo in a) mean change from baseline in total endoscopic NP score to Week 52 and b) mean change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52 in participants with a diagnosis of CRSwNP / ECRS, regardless of IP discontinuation or changes in background medication/starting a prohibited medication unrelated to the COVID-19 pandemic, use of systemic CS for CRSwNP / ECRS or interruption of 2 or more consecutive doses of IP, with participants experiencing surgery being assigned the worst possible score from the day of surgery onwards.

Secondary estimands for SNOT-22, VAS scores and Lund Mackay CT score will use the same population, summary measure and strategies for intercurrent events as for the primary estimands. Time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52 will be summarised by the hazard ratio between mepolizumab and placebo. The same population and strategies for intercurrent events of treatment discontinuation, changes in background medication/starting a prohibited medication,

interruptions of 2 or more consecutive doses of IP and COVID-19 pandemic related intercurrent events will be used as for the primary estimands. For this endpoint, both surgery and a course of systemic CS for CRSwNP / ECRS will be considered events within the analysis and therefore will not be considered an intercurrent event.

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, double-blind, placebo controlled, parallel group Phase III study designed to assess the clinical efficacy and safety of 100 mg SC Mepolizumab treatment in adults with chronic rhinosinusitis with nasal polyps (CRSwNP) / eosinophilic chronic rhinosinusitis (ECRS).

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

The secondary endpoints are described in Section 3.

CCI [redacted].

The study population will consist of adult participants (≥18 years of age) with CRSwNP / ECRS as defined by the JESREC guideline. In addition, they must have 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 prior treatment with systemic corticosteroids (SCS) anytime within the past 2 years; and/or have a medical contraindication/intolerance to SCS; and/or had a documented history of prior surgery for NP at the screening visit. For the purpose of 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 driven by eosinophilia or not.

Any nasal surgical procedures can influence the co-primary endpoints, therefore the impact of occurrence of surgery will be taken into consideration when assessing efficacy endpoints. Diagnostic or investigative procedures such as nasal endoscopy or dilatation of the air passages (e.g. balloon sinuplasty) will not be considered as surgery.

The study will include a 4-week run-in period followed by randomisation to a 52-week treatment period as a double-blind, placebo-controlled phase. Throughout the 52-week treatment period, participants will be on the SoC for CRSwNP / ECRS. Depending on local practice SoC may include intranasal corticosteroids (INCS), saline nasal douching, occasional short courses of systemic CS and/or antibiotics. Depending on local SoC / treatment, patients treated with INCS and/ or LTRA are expected, if possible, to continue with these treatments with no interruption nor alteration to the doses throughout the study duration. If a patient is not on INCS or LTRA prior to screening, the patient is prohibited to start any INCS or LTRA during the study.

There is a trend especially in Japan, to use oral ICS/ETN method of administration for the management of NP for patients with both ECRS and concomitant asthma disease. Although longer term effects on ECRS disease are yet to be fully evaluated, the short-term effects of ICS/ETN on NP size can be significant. Therefore, participants in this study who use ICS/ETN method of administration for their asthma and NP disease are to maintain this method throughout the study period.

The treatment period will consist of thirteen, 4-weekly doses of mepolizumab or placebo, delivered by a pre-filled safety syringe device (SSD) injection.

The Schedule of Activities (SOA) is included in Section 1.3.

4.2. Scientific Rationale for Study Design

Recently the Phase III study of mepolizumab in CRSwNP (SYNAPSE) completed. This study demonstrated the efficacy of mepolizumab 100 mg SC by showing statistically significant and clinically meaningful improvement in the co-primary endpoints of total endoscopic nasal polyp score and symptoms of nasal obstruction associated with nasal polyps compared with placebo when administered every 4 weeks for up to 52 weeks in addition to SoC therapy.

Consistent with the SYNPASE study this study assesses the efficacy of mepolizumab by measuring its ability to reduce the NP size and improve nasal obstruction (VAS score) as co-primary endpoints. This study will use centrally read total endoscopic NP score by assessing the change from baseline at Week 52. Nasal obstruction VAS score will additionally assess patient symptoms during the 4 weeks prior to Week 52. Secondary endpoints for this study are change from baseline in overall VAS symptom scores, SNOT-22 total score, mean composite VAS score, Lund Mackay CT score, mean individual VAS symptom score for loss of smell and time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52.

This study will recruit patients who have CRSwNP / ECRS that are refractory to SoC medical treatment. In most cases these patients are at the stage of needing surgical intervention [Fokkens, 2020]. 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. CCI

CCI [redacted]

Short courses of systemic CS 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.

Given the importance of short courses of systemic CS and surgical events, a composite endpoint of time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52 will also be assessed as a secondary endpoint.

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.

The target population for mepolizumab is CRSwNP / ECRS patients who are refractory to SoC and highly symptomatic as a consequence. Depending on local practice SoC may include INCS, saline nasal douching, occasional short courses of systemic CS and/or antibiotics before surgery is considered.

In Japan, as INCS is not licensed for the indication of CRSwNP, participants not on INCS will be allowed into the study. In order to ensure balance between treatment groups, randomisation will be stratified by participants on INCS and not on INCS.

Participants are treated with mepolizumab or placebo for 13 doses at 4 weeks intervals. Therefore, assessment of the co-primary endpoints will be conducted 52 weeks after initiation of therapy.

All participants randomised to IP will have their efficacy and safety endpoints 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.

4.2.1. Participant Input into Design

Ten CRSwNP / ECRS patients, five from Japan and five from China, were recruited in line with the Inclusion Criteria.

Insights were gained via two, 15-minute, online qualitative surveys.

The focus of the insights request and questions put to the patients were around:

1. Study Rationale, Background, Benefit/Risk Assessment
2. Study Assessments and Procedures
3. eDiary and Informed Consent Form.

In line with the feedback received the number of time points endpoints are taken has been reduced and enhanced participant training will be implemented. This includes, number of PK samples, Haematology draws, Nasal Endoscopies, SF-36 and WPAI questionnaires.

4.3. Justification for Dose

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, indications and ethnic groups 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.

Mepolizumab demonstrates ethnically insensitive in completed clinical trials with participation of patient with various indications. The population PK and PK-PD meta-analysis across studies, and indications and ethnic groups [GSK Document Number 2015N238436_00, 2015] did not identify any intrinsic ethnicity or disease covariates of clinical interest. The results of MEA115588 revealed that there was no major difference in plasma exposure between East Asian (Japanese and Korean) and non-East Asian following 100 mg SC and blood eosinophil count was suppressed throughout the treatment period in both East Asian (Japanese and Korean) and overall populations, with comparable efficacy and safety results.

The efficacy and safety of mepolizumab 100 mg SC in patients with CRSwNP have been confirmed in SYNAPSE study. Population PK-PD analysis for the study demonstrated comparable PK profile and dose-response relationship of mepolizumab in patients with CRSwNP and other indications studied before. The effects of bodyweight and creatinine clearance, which were identified as covariates of mepolizumab clearance in historical studies, were also comparable with the previous population PK model.

Given no ethnic differences in efficacy and safety of mepolizumab observed from completed clinical studies across various indications including asthma and CRSwNP, it would therefore seem reasonable to assess this dose for potential efficacy in the target population of majority Japanese and Chinese patients with CRSwNP / ECRS. With confirmed efficacy and safety of mepolizumab in patients with NP in SYNAPSE study, and 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 Japanese and Chinese population is warranted.

4.4. End of Study Definition

A participant is considered to have completed study treatment if he/she receives study treatment at Visit 14 (Week 48). A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit (Visit 15/Week 52) or the last scheduled procedure shown in the SoA, (Section 1.3) whichever is earlier.

The end of the 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, whichever is earlier.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

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

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

GENDER
3. Male or female participants (with appropriate contraceptive methods) to be eligible for entry into the study; NOTES: Contraceptive use by Women of Childbearing Potential (WOCBP) should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. To be eligible for entry into the study Woman of Childbearing Potential must commit to consistent and correct use of an acceptable method of birth control from the time of consent. • A female participant is eligible to participate if she is not pregnant or breastfeeding, one of the following conditions applies: o Is a woman of non- childbearing potential (WONCBP) as defined in Section 10.5: Contraception and Barrier Guidance OR o Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.5 during the study intervention period and for at least 105 days after the last dose of study intervention. The investigator should evaluate the potential for contraceptive method failure (e.g., non-

compliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive urine pregnancy test within 24 hours before the first dose of study intervention.
    - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive (see Section 8.3.5: Pregnancy Testing).
- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5 Pregnancy Testing.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

CRSwNP / ECRS DIAGNOSIS

4. Blood eosinophils

   A documented blood eosinophil count of over 2% in the 12 months prior to Visit 0 OR through a blood sample taken between Visit 0 and Visit 1. ALL participants must meet blood eosinophil count of over 2% by Visit 1.

   Participants with peripheral blood eosinophil count over 2% to 5% must also have comorbid bronchial asthma, aspirin intolerance, or nonsteroidal anti-inflammatory drug intolerance at Visit 1 assessment in order to return for Visit 2.

5. 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) assessed by the investigator
6. Participants who have had at least one of the following at Visit 1:
    - previous nasal surgery for the removal of NP,
    - have used at least three consecutive days of systemic corticosteroids in the previous 2 years for the treatment of NP,
    - medically unsuitable or intolerant to systemic corticosteroid
7. Participants with **severe NP** symptoms defined as a nasal obstruction VAS symptom score of >5
8. Presence of symptoms of CRS as described by at least two different symptoms for at least 12 weeks prior to Visit 1, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip), plus
    - facial pain/pressure

and/or

• reduction or loss of smell

INFORMED CONSENT
9. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this study protocol.

5.2. 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. (e.g. symptomatic herpes zoster within 3 months prior to screening, evidence of tuberculosis (TB) active or latent)
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. Severe nasal septal deviation preventing full assessment of nasal polyps in both nostrils
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 to Visit 1; nasal biopsy prior to Visit 0 for diagnostic purposes only is excepted.
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 first mepolizumab dose, chemotherapy, 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. Participants that have taken part in previous mepolizumab clinical studies.
17. Patients currently using INCS and inhaled corticosteroids exhalation through nose (ICS/ETN) for the management of their ECRS who are not willing to maintain using this method of administration throughout the study.

CONCOMITANT MEDICATIONS

18. Use of systemic corticosteroids, including oral corticosteroids (intranasal corticosteroid is excepted), within 4 weeks prior to screening or planned use of such medications during the double-blind period
19. INCS and/or inhaled corticosteroids exhalation through nose (ICS/ETN) dose changes within 1 month prior to Visit 1 (if applicable).
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 LTRA 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.

OTHER DISEASES/ABNORMALITIES:

25. 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.

26. **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.

- Subjects with symptoms suggestive of active COVID-19 infection (i.e. fever, cough, etc) are excluded.

- Subjects with known COVID-19 positive contacts within the past 14 days should be excluded for at least 14 days since the exposure and the subject remains symptom free.

27. **Immunodeficiency:** A known immunodeficiency (e.g. human immunodeficiency virus – HIV), other than that explained by the use of corticosteroids taken as therapy.

28. 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:

29. **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 subject 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:
30. **12-lead ECG at Screening Visit 1**: Participants with a QT interval, from the ECG conducted at Screening Visit 1, corrected with Fridericia's formula (QTcF) >450msec (or QTcF >480msec in participants with bundle branch block). QTcF is the QT interval corrected for heart rate according to Fridericia's formula that is selected for this study. It is either machine-read or manually over-read when not automatically machine read. This specific formula must be used to determine eligibility and discontinuation for an individual participant. Participants are excluded if an abnormal ECG finding from the 12-lead ECG conducted at Screening Visit 1 is considered to be clinically significant and would impact the participant's participation during the study, based on the evaluation of the Investigator.

DRUG OR ALCOHOL ABUSE:
31. 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:
32. Is an investigator, sub-investigator, study coordinator, employee of a participating investigator or study site, or immediate family member of the aforementioned that is involved in this study.
INABILITY TO READ:
33. In the opinion of the investigator, any subject who is unable to read and/or would not be able to complete a questionnaire.

5.3. Randomisation Criteria

Those participants who meet the randomisation criteria below will be randomised into the study until the target of approximately 160 randomised participants is reached.

Participants will be randomised in a 1:1 ratio into one of two treatment groups, receiving a total of thirteen doses (one every four weeks):

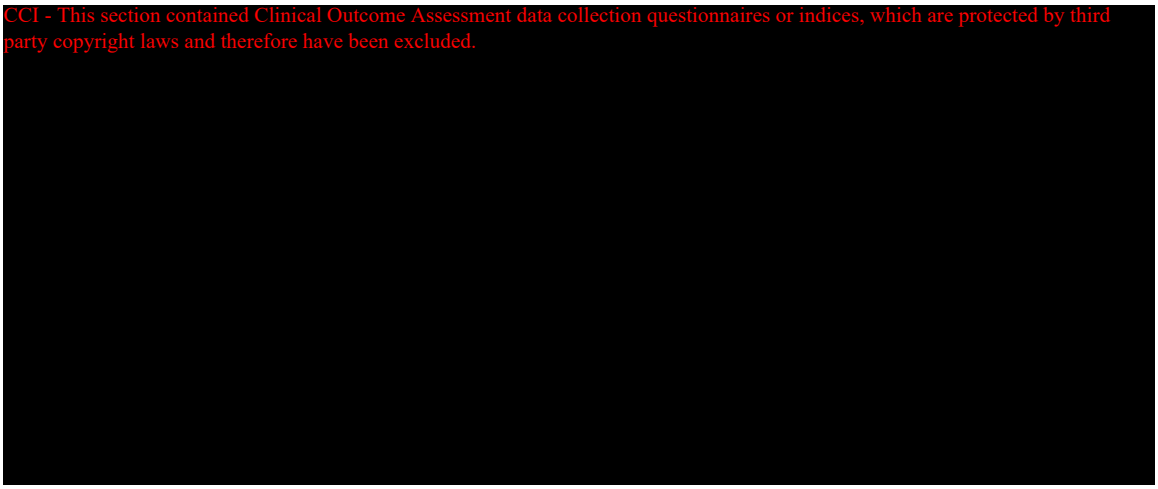
- Group 1: 100 mg SC of mepolizumab on top of SoC
- Group 2: Placebo SC on top of SoC

The study will be randomised separately for each country and the randomisation will be stratified by background INCS use. Equal numbers of participants will be allocated to each treatment.

In rare instances and if following consultation with the Medical Monitor a participant can be rescreened. Rescreened participants are required to sign a new ICF.

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

1. Confirmation of CRSwNP / ECRS with a JESREC Score ≥11* [Tokunaga, 2015] using values measured between Visit 1 and 2 (central laboratory blood eosinophilic count, CT scan, nasal endoscopy as assessed by central laboratory).



2. Confirmation of at least moderate CRSwNP / ECRS for participants with peripheral blood eosinophil count taken in the 12 months prior to Visit 0 OR through a blood sample taken between Visit 0 and Visit 1 of over 2% to 5% must have documented co-morbid disease of bronchial asthma, aspirin intolerance, or nonsteroidal anti-inflammatory drug intolerance. Participants with peripheral blood eosinophil count over 5% in the 12 months prior to Visit 0 OR through a blood sample taken between Visit 0 and Visit 1 do not require the presence of fore mentioned co-morbid diseases, and if the participant meets CT shadow: ethmoid ≥ maxillary.
3. 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) taken at Visit 1 as assessed at central laboratory
4. Mean nasal obstruction VAS >5 over the last 7 days preceding Visit 2 (excluding Visit 2) (from eDiary)
5. eDiary compliance for VAS (at least 4 out of the last 7 days preceding Visit 2, (excluding Visit 2)).
6. Not had any NP surgery or have been included into a waiting list for NP surgery between Visit 1 and Visit 2.
7. Laboratory abnormality: No evidence of clinically significant abnormality in the haematological, biochemical or urinalysis screen at Visit 1, as judged by the investigator.
8. Liver Function Tests: obtained at Visit 1:

- ALT<2x ULN (upper limit of normal)
- AST<2x ULN
- Alk Phos ≤ 2.0x ULN
- Bilirubin ≤ 1.5x ULN (isolated bilirubin>1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

9. Asthma Exacerbation: No asthma exacerbations during run-in period. An exacerbation is defined as worsening of asthma requiring the use of systemic corticosteroids for at least 3 days and/or emergency department visit, or hospitalization.
10. Maintenance Therapy: No changes or commencement during the run-in period in the dose or regimen of any regular baseline medication including
    a. INCS (if relevant)
    b. Inhaled corticosteroids exhalation through nose (ICS/ETN)
    c. LTRA
    d. allergen immunotherapy
    e. course of systemic corticosteroids
11. If the participant has an upper respiratory tract infection or cold during run-in then run-in should be extended so to have the Visit 2, 2 weeks post the resolution of the cold but no greater than a total of 6 weeks from Visit 1. Colds that are not resolved within the 4th week of the nominal run-in period (28 days after screening) will be ineligible for randomisation as they would have exceeded this 6 weeks period.

5.4. 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) related to study screening procedures.

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 randomised, will be designated as run-in failures.

Re screening of participants will be permitted, however, advanced approval to proceed with rescreening the participant must be obtained from the Medical Monitor (for contact

details, see SRM). Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying

N/A

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

6.1. Study Intervention(s) Administered

Study intervention or 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.

A liquid formulation of mepolizumab will be provided as pre-filled syringes in a safety syringe device (SSD) for this study. The liquid formulation has a distinct advantage over the lyophilised product as it does not require reconstitution, and the devices (upon commercial registration) will simplify and facilitate administration.

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 consists of up to 17 visits with a maximal total treatment duration of approximately 52 weeks and maximum study duration of approximately 56 weeks. Screened participants will enter a 4 weeks run-in period, followed by up to 52 weeks double-blind treatment period.

Participants who are successfully enrolled into the study will be randomised in a 1:1 ratio 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
- Group 2: Placebo SC on top of SoC

The end of study assessments for each individual participant will be performed at Visit 15 (Week 52), 4 weeks following the last dose of IP.

	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 for HCP:	SC dose in thigh, abdomen or upper arm every 4 weeks
Dosing instruction for self-injection:	SC dose in thigh or abdomen 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 for HCP:	SC dose in thigh, abdomen or upper arm every 4 weeks
Dosing instruction for self-injection:	SC dose in thigh or abdomen 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.

6.1.1. 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 SRM. 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 8.4.8.

6.2. Self-administration for Japanese cohort

Participants from Japanese cohorts may transition to self-administration from Week 32 onwards. Before allowing the self-administration, the principal investigator/delegate must assess their knowledge/technique and document that they are competent to undertake self-administration.

Following the training (see Section 6.2.1) for at least 2 visits between the Visit 5/Week 12 and Visit 10/Week 32, the participants will self-administer study treatment by SC injection under medical supervision of the investigator or designee at the study site. Observations about the injection will be recorded by the investigator/designee using eCRF. The date, time of the dose, and site of administration (thigh or abdomen) of each dose administered in the clinic will be recorded in the source documents.

All self-administered injections will be assessed by the investigator for success based on direct observation of the self-administration.

A self-administered injection is considered successful if the following criteria are met:

- Use of a correct injection site (abdomen or thigh)
- Full dose administered: subject fully inserts the needle, slowly depresses the plunger until the stopper reaches the bottom of the syringe and activates the needle guard by moving the thumb up

If the above criteria are met, the investigator will confirm the injection was successfully delivered.

6.2.1. Training for self-administration

Training of study treatment, handling and administration techniques by qualified study site personnel will be provided to the study participants prior to self-administration. The training is designed to be representative of the instruction and training materials that will be used in the post-marketing setting. Participants will be trained by site personnel to self-administer the study treatment independently and will be provided with detailed written instructions (refer to IFU).

6.3. 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 SRM.
- 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.

6.4. Measures to Minimize Bias: Randomisation and Blinding

Participants eligible to enter the study will be assigned to intervention randomly via RAMOS NG, an Interactive Web Response System (IWRS). The randomisation schedule will be generated using the GSK validated randomisation software RandAll NG. The study will be randomised separately for each country and the randomisation will be

stratified by background INCS use. Equal numbers of participants will be allocated to each treatment.

Participants will be assigned in a 1:1 ratio to study intervention (mepolizumab or placebo to match) in accordance with the randomisation schedule. Once a randomisation number has been assigned to a participant, it cannot be reassigned to any other participant in the study.

Before the study is initiated, the web location and the log in information and directions for the IWRS will be provided to each site.

Study intervention will be assigned by RAMOS NG and dispensed at the study visits summarized in the SoA.

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

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

RAMOS NG will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact GSK prior to unblinding a participant's intervention assignment unless this could delay emergency intervention of the participant. If a participant's intervention assignment is unblinded 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 case report form, as applicable.

In the case of a medical emergency or in the event of a serious medical condition, when knowledge of the IP 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.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention 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 intervention 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 intervention.

When participants self-administer study intervention(s) at the study site, compliance with the Mepolizumab Injection, 100 mg/mL or Placebo to match Mepolizumab will be assessed by observation of healthcare professionals.

Deviation(s) from the prescribed dosage regimen should be recorded. A record of the quantity of the Mepolizumab Injection, 100 mg/mL or Placebo to match Mepolizumab dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

- 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.

6.6. Dose Modification

Not applicable.

6.7. Continued Access to Study Intervention 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 to study participants following study completion.

6.8. 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.

6.9. 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.

It is permissible for subjects to be vaccinated against COVID-19 with vaccines authorized or approved by a regulatory authority; vaccination with an unapproved or unauthorized COVID-19 vaccine (i.e., a candidate vaccine) is not permissible.

Initiation or changes in the dosing regimen of LTRA or allergen immunotherapy from screening to end of the study are not allowed. Changes in the dosing regimen of INCS and/or ICS/ETN from screening to end of the study are also not allowed.

The following medications may be used for all participants:

1. Short courses of systemic CS (for example systemic CS for treatment of CRSwNP / ECRS). The use of rescue medications such as systemic CS is allowable during the 52-week treatment phase of the study (Visit 2 and onwards) but not during the run-in period; the date and time of rescue medication administration as well as the name and dosage regimen (dose and duration) of the rescue medication must be recorded in the eCRF for CRSwNP / ECRS as well as for other comorbidities.
2. Throughout the study, asthmatic participants are to be maintained on their baseline SoC asthma treatment.
3. For antibiotic treatment for CRSwNP / ECRS, 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 products (biologic or non-biologic)	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 CRSwNP / ECRS	6 months

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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 up to Week 52 even if they discontinue study treatment in order to capture NP scores, symptom score, any subsequent surgical procedures or entry into a waiting list for NP surgery.

7.1. Premature Discontinuation of Study Intervention

7.1.1. Discontinuation Criteria for Intervention

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 Week 52 Visit assessments. The participant's NP surgical status will be tracked for the duration of the study. The participants are also allowed to have nasal surgery during the study without discontinuation from IP. 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 confirmed NP surgery can distort the anatomical architecture of the nasal cavity nullifying the NP score and VAS, participants who have had NP surgery prior to Week 52 will be considered as treatment failures (taking the participant's worst score prior to surgery) in the analysis of the primary endpoints.

As a minimum the participants should agree to be contacted by telephone to enquire regarding any safety assessments and any NP surgery events.

Participants will be allowed short courses of systemic CS as medically required during the study.

7.1.2. Study Specific Intervention 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 >600msec 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 systemic CS or Surgery are not a reason for Study withdrawal or IP discontinuation.

7.1.3. Primary Reasons for Intervention 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
- Protocol deviation
- Lack of efficacy
- Study closed/terminated

- Participant reached protocol-defined stopping criteria
    - Liver event
    - Pregnancy
    - QTc
- Investigator discretion

7.1.4. IP Discontinuation Visit

Prematurely discontinuation of study treatment will be defined as any participant who is randomised to blinded medication and, for any reason, does not receive study treatment at Visit 14 (Week 48).

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 Week 52 Visit assessments.

Participants that discontinue from study treatment should return to the clinic 4 weeks after the last dose for an IP Discontinuation Visit. If possible, at the IP Discontinuation 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)
- Vital signs
- Collect/review electronic diary
- Urine pregnancy test - for all WOCBP
- Assessment of endoscopic nasal polyp score
- Assessment of surgery
- Assessment of systemic CS use
- Assessment of INCS use
- Assessments of symptoms
- Assessment of HRQoL
- WPAI
- PK (Japan and China only)
- Lab assessments including liver chemistry and immunogenicity

- CT scan
- Assessment of asthma exacerbations
- Collection of eDiary
- Access the RAMOS NG to report participant's IP discontinuation visit from the study

After completion of the IP Discontinuation Visit, in cases where the participant cannot attend subsequent study visits in person telephone visits may be performed.

7.1.5. Liver Chemistry Stopping Criteria

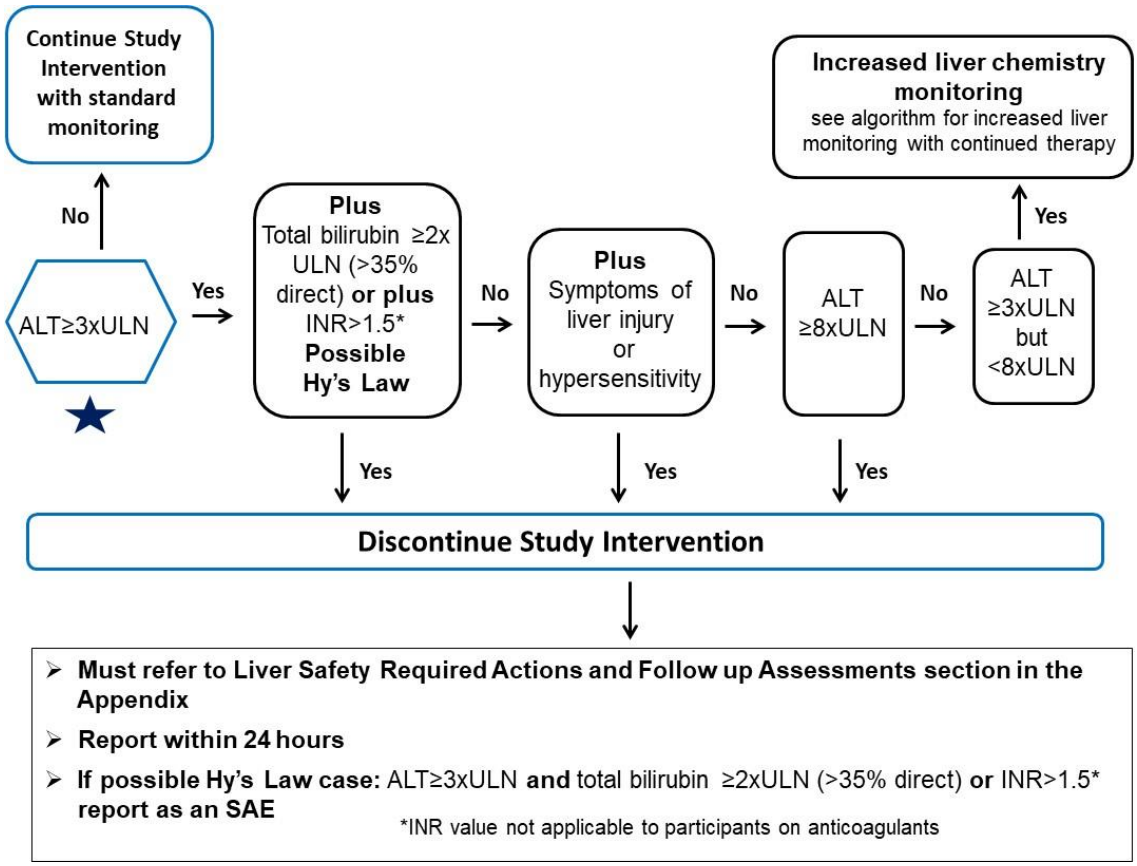
Liver chemistry stopping and increased monitoring criteria have been designed to assure participant safety and evaluate liver event aetiology.

Discontinuation of study treatment for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm below or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, the investigator believes that it is in the best interest of the participant.

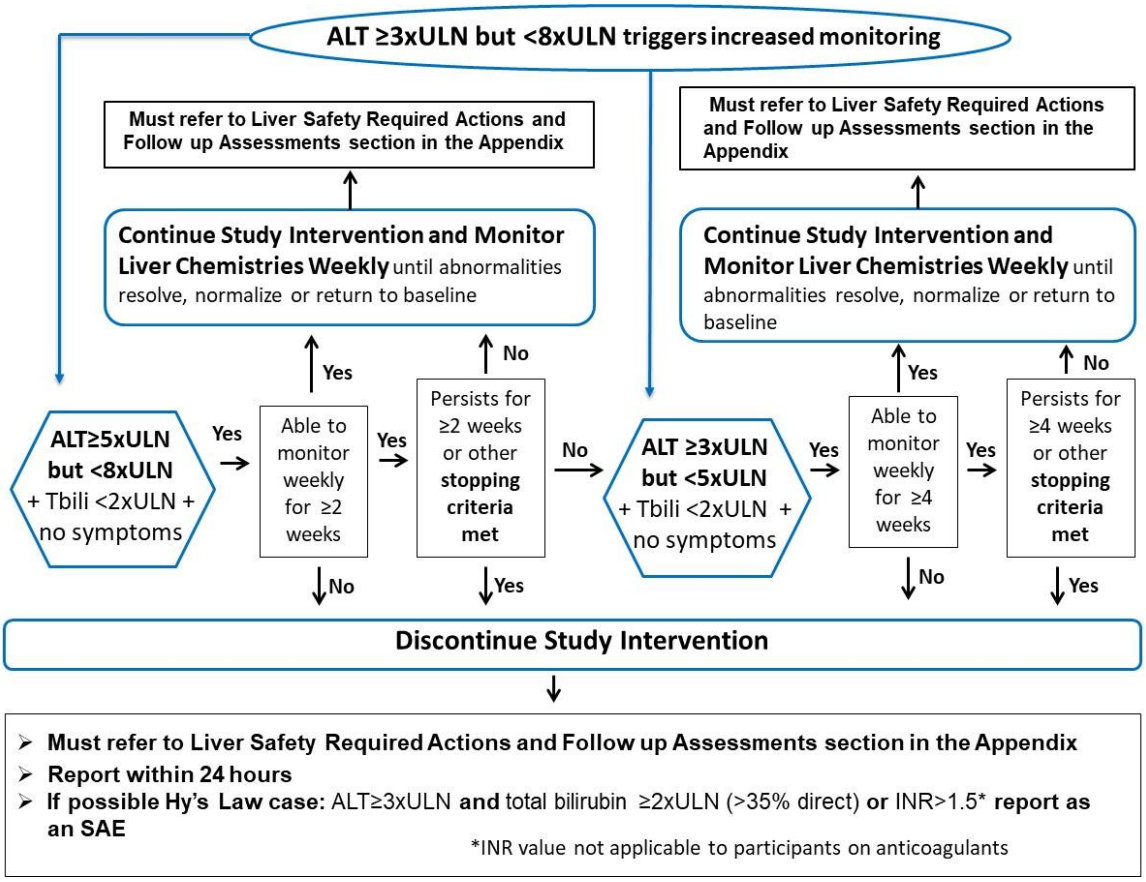
Refer to Appendix 7 for required Liver Safety Actions, Monitoring and Follow-up Assessments.

Algorithm A: Liver Chemistry Stopping Algorithm



Abbreviations: ALT = alanine transaminase; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin

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



Abbreviations: ALT = alanine transaminase; Tbili = total bilirubin; INR = international normalized ratio; SAE = serious adverse event; ULN = upper limit of normal, Tbili = Total bilirubin.

7.1.6. QTc Stopping Criteria

- QTc is the QT interval corrected for heart rate according to Fridericia's formula. It is either machine-read or manually over-read when not automatically machine read. This specific formula must be used to determine eligibility and discontinuation for an individual participant.
- The QTc should be based on two or more ECG tracings obtained over a brief (e.g., 5-10 minute) recording period, with each recording separated by at least 5 minutes.

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

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

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**
< 450msec	> 500msec
450 – 480msec	≥ 530msec

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

7.1.7. COVID-19 testing

Participants that test positive for COVID-19 do not have to discontinue study intervention. Participants are encouraged to remain in the study and be followed up per study schedule as participants well-being allows. Effort should be made by the Investigator/site staff to keep the participant in the study until their nominal 52 weeks post randomisation date.

- COVID-19 tests during the study may be performed, as determined by the investigator or local guidelines.
- All positive COVID-19 tests should be reported on the COVID-19 eCRFs and the AE/SAE eCRFs, as appropriate.
- Participants that test positive for COVID-19 do not have to discontinue study intervention.
- Positive tests should be reported to the appropriate local government authorities, per local regulations.

7.1.8. Temporary Discontinuation

Not applicable.

7.1.9. Rechallenge

Not applicable.

7.1.9.1. Study Intervention Restart or Rechallenge after liver stopping criteria

Study intervention restart or rechallenge after liver chemistry stopping criteria are met by any participant in this study is not allowed.

7.2. Participant 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 (Section 1.3) for data to be collected at the time of study withdrawal and for any further evaluations that need to be completed.

7.2.1. Primary reasons for withdrawal from the study

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

- Adverse event
- Lost to follow-up
- Withdrew consent
    - participant relocated
    - frequency of visits
    - burden of procedures
- Protocol deviation
- Lack of efficacy
- Study closed/terminated
- Participant reached protocol-defined stopping criteria
    - Liver event
    - Pregnancy
    - QTc
- Investigator discretion

7.2.2. Early Withdrawal Visit

The definition of an early participant withdrawal from the study will be any participant who is randomised to blinded medication and, for any reason, is withdrawn prior to completion of the Visit 15 (Week 52) procedures.

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

Participants that withdraw from the study should return to the clinic 4 weeks after the previous clinic visit 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)
- Vital signs
- Collect/review electronic diary
- Urine pregnancy test - for all WOCBP
- Assessment of endoscopic nasal polyp score
- Assessment of surgery
- Assessment of systemic CS use
- Assessment of INCS use
- Assessments of symptoms
- Assessment of HRQoL
- WPAI
- PK (Japan and China only)
- Lab assessments including liver chemistry and immunogenicity
- CT scan
- Assessment of asthma exacerbations
- Access the RAMOS NG to report participant's early withdrawal from the study

If an IP discontinuation visit has been previously performed (i.e. the participant is continuing within the study off-treatment and subsequently decides to withdraw), an early withdrawal visit is not required.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and 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.
- Before a 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, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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 (e.g., 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.
- Following randomisation laboratory results as well as central read nasal polyps scores that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples or during transfer to a central laboratory.

8.1. Critical Pre-screening, Screening and Baseline Assessments

8.1.1. 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.

8.1.2. 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.

8.1.3. 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 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

Blood for eosinophilia entry criteria

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 and oestradiol will be assessed to confirm menopausal state (if applicable)
- Parasitic screening (only in countries with a high-risk or in participants who have visited a high-risk country)
- Endoscopic NP score
- Baseline Cranial CT scan (to be performed at Screening or during run-in period, see SoA and SRM for details)
- 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.

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

- Review eDiary compliance and retrain participant if required
- Review randomisation criteria
- Review the Endoscopic NP score recorded during Visit 1 (Screening) as rated by the central laboratory
- Vital signs
- Laboratory tests. This should include
    - Clinical Chemistry including liver chemistry
    - Haematology with differential

- Blood for baseline immunogenicity
- Urine pregnancy test - for all WOCBP

8.1.5. Critical procedures performed throughout treatment period

8.1.5.1. Daily eDiary

All to be performed daily at home, including at study visit days.

- Overall VAS symptom score
- VAS for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, facial pain

8.1.5.2. (Visits 2 - 15)

- eDiary at site
  - SNOT-22 questionnaire (selected visits only)
  - ACQ-5 (for asthmatics) (selected visits only)
  - SF-36 (selected visits only)
  - WPAI-GH (selected visits only)
  - Review eDiary and retrain if required
- Assessment of nasal surgery (confirmed and waiting list)
- Assessment of systemic CS dose and duration
- Endoscopic NP score (be performed at selected visits only, refer to SoA)
- End of study cranial CT scan (V15 or IP discontinuation/Early Withdrawal Visit, – performed within the visit window and up to 14 days before study visit)
- Blood for PK (to be done only at visits and in countries indicated in the SoA)
- Genetic sample (to be done one time only in any of the visits for non-Chinese participants) as per SoA
- AE/SAE review
- Concomitant medication review
- 12-lead ECG as per SoA

- Vital signs as per SoA
- Laboratory assessments as per SoA
- Blood for immunogenicity as per SoA
- Urinalysis as per SoA
- Urine pregnancy test (for all WOCBP) as per SoA
- FSH and oestradiol will be assessed to confirm child-bearing status (following a positive urine test)

8.2. Efficacy Assessments

8.2.1. 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 9) recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status).

All 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. There is potential for the site score to differ from the central score. In such cases the output from the central labs is considered final and will be utilised for patient eligibility and for the analysis of the 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.

8.2.2. Computed Tomography (CT) Scan

The Lund Mackay (LMK) CT scoring system is based on localization with points given for degree of opacification: 0 = CCI [redacted], 1 = CCI [redacted], 2 = CCI [redacted]. These points are then applied to the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, frontal sinus on each side. The osteomeatal complex (OC) is graded as 0 = CCI [redacted] or 2 = CCI [redacted]. This scoring system has been validated in several studies.

For patients in whom the OC is missing (because of a previous surgery) the reader should consider the location of the former OC and provide a scoring (as if the OC was there).

CT scan should be performed anytime during the run-in, and at Visit 15 (Week 52) and IP discontinuation/Early Withdrawal Visit.

Details for CT will be available in a separate operational manual provided to the sites. CT scans central reading for LMK scoring will be used in the statistical analysis Appendix 10.

8.2.3. Individual Symptoms Visual Analogue Scale (VAS)

All VAS to be used in the study will be administered using 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 6 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.

The left-hand side of the scale (0) represents "CCI" and the right-hand side of the scale (100) represents "CCI". Participants will be instructed on how to use the scale prior to using the scale.

VAS measure a characteristic or attitude that is believed to range across a continuum of values and cannot easily be directly measured. The participant selects a point on the line that represents their current state on the continuum. In this study symptom VAS will be collected using an eDiary, suitably pixilated to allow the selection of all integers from 0 to 100. A number of publications which shows the applicability of VAS administered electronically and comparability to traditional paper [Hollen, 2013; Reips, 2008; Cook, 2004; Jamison, 2002]. VAS scores will be analysed using a 0 and 10 scale reported to 1 decimal point.

8.2.4. 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 confirmed 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 from the nasal cavity (polypectomy). Dilatation of the air passages in the nasal cavity (e.g. balloon sinuplasty) will not be included in this endpoint. Procedures occurring on the same date were considered as part of the same surgery event. A clinical review will be carried out prior to the unblinding of treatment codes to identify all events to be considered as part of this endpoint.

The study will also record whether a participant had received sinuplasty and/or was on a waiting list for NP surgery.

8.2.5. Medication

The number of courses of systemic steroids as well as the dose and duration of the courses will be recorded in the CRF. The dose for a course of systemic CS will be

according to the participants SoC for systemic CS use for its NP condition. The dose and duration of the systemic CS 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 systemic CS will be provided in the SRM.

8.2.6. Health Related Quality of Life (HRQoL) assessment

Participants are to be provided with a quiet location, free from distraction to complete study visit questionnaires. They should be instructed to select the single response option for each question that most closely reflects their health over the time period indicated for each questionnaire.

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

SNOT-22 is a 22-item measure of disease specific HRQoL It will be completed by the participant at study visits according to the SoA (Section 1.3) on the eDiary.

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].

Participants will be asked to rate the severity of their condition on each of the 22 items over the previous 2 weeks using a 6-point rating scale of 0-5 including: CCI [redacted] 1 = CCI [redacted]; 2 = CCI [redacted]; 3 = CCI [redacted]; 4 = CCI [redacted]; 5 = CCI [redacted] The total score range for the SNOT-22 is 0-110, where higher scores indicate greater disease impact. Psychometric analyses of data from the 205687 study indicate that a decrease of 28 points or greater is a clinically meaningful within participant change. The previously published MCID of a difference of >8.9 will also be reported [Hopkins, 2009].

8.2.7. Assessments for asthmatic participants only

8.2.7.1. Asthma Control Questionnaire (ACQ-5)

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 (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall period is the past week.

ACQ-5 will be assessed at clinic visits, during the study according to the SoA (Section 1.3). Please refer to the SRM for further details.

8.3. Safety Assessments

8.3.1. 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.

8.3.2. Vital Signs

As detailed in the SoA vital signs will be measured in semi-supine position after at least 5 minutes rest and will include systolic and diastolic blood pressure and pulse rate.

- Blood pressure and pulse measurements will preferably be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs assessments will be taken before measurement of any ECGs at the specified time point.

8.3.3. 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 the SRM).

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 SRM.

8.3.4. 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 maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 100 mL.

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 aetiology 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 (e.g., SAE or AE or dose modification), then the results must be recorded in the CRF.

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

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing should be conducted at monthly intervals during the study intervention period, preferably as part of the regular onsite study visits. If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required.
- Pregnancy testing must be conducted for each WOCBP prior to the cranial CT scan assessment which will be performed anytime during the run-in, and at Visit 15 (Week 52) and the IP discontinuation/Early Withdrawal Visit.
- Pregnancy testing should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female participant contraception in Section 5.1 Inclusion Criteria (contraception to be taken during the study intervention period and for at least 105 days after the last dose of study intervention).
- Additional pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3.

The definitions of device-related safety events, (adverse device effects [ADEs] and serious adverse device effects [SADEs]), can be found in Section 10.8.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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 study intervention or the study, or that caused the participant to discontinue the study (see Section 7).

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

- Systemic reactions
- Local injection site reactions

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

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

- All SAEs will be collected from the start of study intervention until the Exit visit/EW visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a participant consents to participate in the study.
- All AEs will be collected from the start of intervention until the end of study at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.
- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. 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 information on AEs or SAEs after the conclusion of the study participation. 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 intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. 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.

8.4.3. 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 (as defined in Section 8.4), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) 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.

8.4.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until 16 weeks after the last dose.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. 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 in the study will discontinue study intervention.

8.4.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3. 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.

8.4.7. Adverse Events of Special Interest

The definitions of an AE or SAE can be found in Appendix 3.

Systemic reactions, local injection site reactions, infections, malignancies and cardiovascular events are considered Adverse Events of Special Interest (AESI).

In addition, the information whether an event of systemic reaction met the diagnostic criteria for anaphylaxis as outlined by the Second Symposium on Anaphylaxis [Sampson, 2006] and in Appendix 4 will be collected on the AE and SAE CRF pages.

Systemic reactions and local injection site reactions will have targeted CRF pages. The remaining AESI will be identified and evaluated using MedDRA SMQs.

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.

8.4.8. Medical Device Incidents (Including Malfunctions)

GSK Medical devices are being provided for use in this study as a delivery method for mepolizumab or matching placebo injections. 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 6.1.1).

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 3 of the protocol.

8.4.8.1. 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.

8.4.8.2. 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 7.3. 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.

8.4.8.3. 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.

8.4.8.4. Safety syringe functionality assessment

If there is an error with the medical device then refer to the Safety syringe Error / Failure Reporting Form in Appendix 12 returning defective Medical Devices to GSK.

- Please refer to the SRM for process and contact details

8.4.8.5. 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 (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.5. Pharmacokinetics

Blood samples of approximately 5 mL for analysis of mepolizumab plasma concentration will be obtained as per the SoA. Samples obtained at Visits 3 and 9 should be drawn prior to dosing. One post-dose PK collection will be at Week 29 (one week after dose at Visit 9/Week 28) with a visit allowance of ±1 day. The Week 29 PK sample will be collected approximately from up to first 30 Japanese and all Chinese subjects randomised. The date and exact time of collection for each sample will be documented in the eCRF.

A parametric modelling framework using non-linear mixed effects will be applied for mepolizumab population PK and population PK-PD analyses in Japanese and Chinese patients. The analysis will determine population PK, PK-PD parameters, e.g. Systemic clearance (CL), volume of distribution (V), covariate effects on systemic levels, between- and within-subject variability in PK parameters, as well as relationship between exposure of mepolizumab and reduction of blood eosinophil level if data permit. Other systemic exposure-clinical outcomes may be explored if deemed appropriate.

Details for collection and processing of samples may be found in the central lab manual and SRM.

- Genetic analyses will not be performed on these blood/plasma samples. Participant confidentiality will be maintained.
- Intervention concentration information that would unblind the study will not be reported to investigative sites or blinded personnel.

8.6. Pharmacodynamics

Blood eosinophil counts will be recorded as part of the standard haematological assessments performed at the visits specified in the SoA.

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

8.7. 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.

Please see Appendix 6 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in SRM.

Genetics samples will not be collected from participants in China.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. 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 central lab user manual and the SRM.

8.10. Health Outcomes

Additional health outcomes are evaluated in this study by means of the Short Form-36 (SF-36) and the Work Productivity and Activity Impairment Questionnaire (WPAI) questionnaires.

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

SF-36 will be performed by the participant at visits Baseline, week 4, week 24 and week 52 (and IP discontinuation / Early Withdrawal Visits).

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 scores range from 0 to 100 and higher scores indicate better QoL. 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] demonstrated a high internal validity and reliability in patients with NP and reported that NP impaired QoL in all SF-36 domains. [Khan, 2019]. also found that patients with CRSwNP had significantly lower mean SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores than the general population, demonstrating that CRSwNP negatively affects HRQoL.

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.

8.10.2. Work Productivity and Activity Impairment Questionnaire (WPAI)

WPAI will be assessed by the participant at study visits described in the SoA (Section 1.3).

The WPAI questionnaire is an instrument to measure impairments in both paid work and unpaid work [Reilly, 2002]. 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, 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: 1 = CCI ; 2 = CCI ; 3 = CCI ; 4 = CCI ; 5 = CCI ; 6 = CCI [Reilly, 1993]. 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, 2002]. 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.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

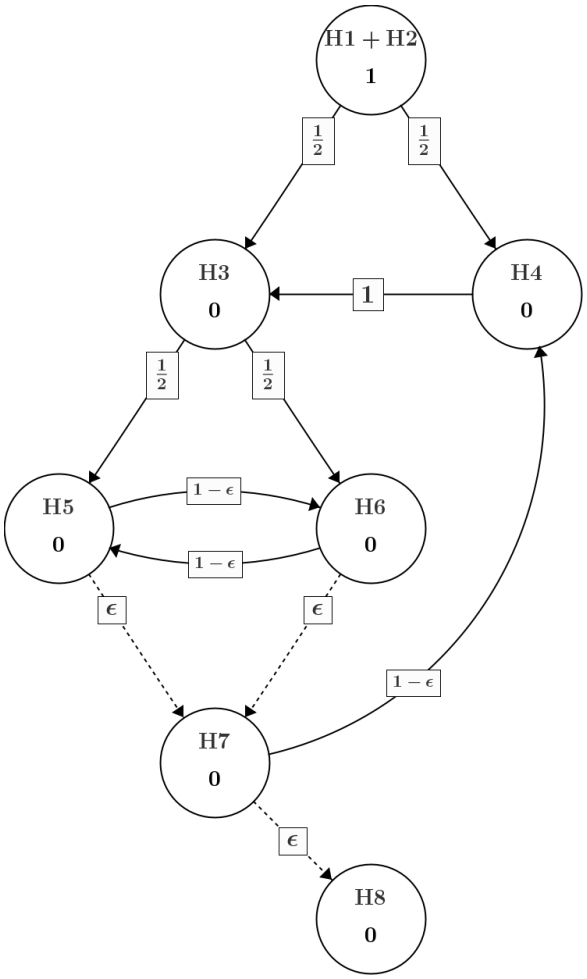
The study is designed to test the superiority of mepolizumab 100 mg SC vs. placebo in both co-primary efficacy endpoints of total endoscopic nasal polyp score at Week 52 and nasal obstruction VAS score during the 4 weeks prior to Week 52. Each co-primary endpoint will be tested at the two-sided 5% alpha level (one-sided 2.5%) and both tests are required to be significant to achieve the primary objective of the study.

9.1.1. Multiple Comparisons and Multiplicity

Multiplicity arising from the multiple secondary endpoints will be controlled using the closed testing procedure specified below for strong control of type I error. Hypotheses associated with the two primary (H_1 and H_2) and six secondary endpoints (H_3 to H_8) will be tested using a gatekeeping procedure based on the graphical approach to sequentially rejective multiple test procedures [Bretz, 2009]. The two primary hypotheses H_1 and H_2 will each be tested first and will be allocated the level α, where α = 0.05 (two-sided). If these are both rejected at level α, the procedure then is as follows: the hypotheses H_i , i = 3, ..., 8 are tested each at its local significance level α_i . If a hypothesis H_i can be rejected,

its level is reallocated to one of the other hypotheses according to the pre-specified rules represented by Figure 1. The reallocation weights are updated in the reduced graph and the testing step repeated for the remaining, non-rejected hypotheses with the updated local significance levels. This possibly leads to further rejected null hypotheses with associated reallocation of the local significance levels. The procedure is repeated until no further hypothesis can be rejected. The reallocation of the local alpha levels is fully determined by the initial graph (Figure 1) and the update algorithm described by Bretz, 2009.

Figure 1 Multiplicity Testing Strategy Across Primary and Secondary Endpoints



Primary:
H_1: Total Endoscopic Nasal Polyps score at Week 52
H_2: Nasal Obstruction VAS score during the 4 weeks prior to Week 52
Secondary:
H_3: Overall VAS score during the 4 weeks prior to Week 52
H_4: Lund Mackay CT score at Week 52
H_5: Composite VAS score during the 4 weeks prior to Week 52
H_6: SNOT-22 Total score at Week 52
H_7: Loss of smell VAS score during the 4 weeks prior to Week 52
H_8: Time to First Nasal Surgery or course of systemic CS for CRSwNP / ECRS up to Week 52
where ε reflects an infinitesimally small value, indicating the potential for alpha to be reallocated dependent on the rejection of all previous tests

For the initial graph above the resulting test procedure can be summarized as follows:

- If both co-primary endpoints (H_1 and H_2) are rejected, the first two secondary endpoints (Overall VAS Symptom Score [H_3] and Lund Mackay CT score [H_4]) will each be tested at a significance level of α/2 (0.025). If either endpoint is rejected at the α/2 (0.025) level, the α/2 (0.025) from that given endpoint will be reallocated and re-used within the subsequent test of the next secondary endpoint according to the pre-specified rules represented by Figure 1.
- If the Overall VAS score endpoint (H_3) endpoint is rejected at the α/2 (0.025) level, the Composite VAS score (H_5) and SNOT-22 total score (H_6) will then also be tested. Only following rejection of both endpoints (H_5 and H_6) will the Loss of Smell VAS symptom endpoint (H_7) be tested.
- If able to reject the loss of smell VAS endpoint (H_7), the α/2 level from this endpoint will be reallocated to the testing of the Lund Mackay CT score (H_4), to allow a test at a full level of α, if not already rejected at the α/2 significance level.
- Only following rejection of all other secondary endpoints (H_3 to H_7), will the final secondary endpoint of Time to First Nasal Surgery or course of systemic CS for CRSwNP / ECRS (H_8) be tested.

Lund Mackay CT score (H_4) is an important endpoint in the clinical practice of Japan and China, however, has not been studied previously within the mepolizumab clinical development program. The above testing strategy demonstrates the importance of this endpoint, whilst permitting testing of other secondary endpoints if not initially rejected at a significance level of α/2. The Composite VAS, SNOT-22 and Loss of Smell VAS secondary endpoints are all correlated patient reported endpoints measuring improvements in symptoms; these endpoints are grouped within the above strategy for testing in sequence following the rejection of the of Overall VAS Score (H_3) to increase power across these symptom endpoints. If all symptom endpoints (H_3, H_5, H_6, H_7) are rejected, the above strategy permits a test of the Lund Mackay CT score (H_4) a full level of α, if not already rejected at the initial α/2 significance level.

9.2. Sample Size Determination

The sample size is based on the co-primary efficacy endpoints of total endoscopic nasal polyp score at Week 52 and nasal obstruction VAS score during the 4 weeks prior to Week 52.

The sample size of 160 participants randomised in a 1:1 ratio to each treatment arm provides at least 90% power to demonstrate a statistically significant result for both co-primary endpoints using a mixed model repeated measures (MMRM) analysis model.

Estimates of residual standard deviation (SD) of 1.82 for total endoscopic nasal polyp score at Week 52 and 3.25 for nasal obstruction VAS score during the 4 weeks prior to Week 52 are taken from a post-hoc MMRM analysis of observed data from study 205687 (SYNAPSE) which assumed a "missing at random" (MAR) assumption for missing data.

With the above assumptions and a sample size of 160 randomized subjects (80 per arm), it is estimated that the null hypothesis will be rejected at the two-sided 5% level of

significance for total endoscopic nasal polyp score if the observed difference between treatments is at least 0.57 units and for nasal obstruction VAS score if the observed difference between treatments is at least 1.01.

For total endoscopic nasal polyp score, if the true difference between treatments is 1.00 units, then the study has a probability of 93.2% of observing a difference in total endoscopic nasal polyp score between treatments of at least 0.57 units and therefore 93.2% power for declaring significance on this endpoint. The estimated improvement observed in total endoscopic nasal polyp score for mepolizumab 100 mg SC compared to placebo within study 205687 (SYNAPSE) was 0.99 units (95% CI: 0.61 to 1.36).

For nasal obstruction VAS score, if the true difference between treatments is 2.00, then the study has a probability of 97.2% of observing a difference in nasal obstruction VAS score between treatments of at least 1.01 units and therefore a 97.2% power for declaring significance on this endpoint. The measured improvement observed in nasal obstruction VAS score for mepolizumab 100 mg SC compared to placebo within study 205687 (SYNAPSE) was 1.97 units (95% CI: 1.31 to 2.63).

If the true population distribution of each co-primary endpoint is as described above, a study with sample size of 80 randomised participants randomised in 1:1 ratio to each treatment arm (total 160 participants) is estimated to have at least 90% power regardless of the degree of (positive) correlation of the endpoints.

Assuming a screen failure rate of 40%, approximately 270 participants will need to be screened to achieve approximately 160 randomly assigned to study intervention for a total of approximately 80 participants per intervention group. All participants within the Intent-to-Treat analysis set (randomised participants who receive at least 1 dose of study treatment) will be considered evaluable within the study analysis. See Section 9.4 regarding the strategy of handling of intercurrent events for the primary estimands.

9.2.1. Sample Size Sensitivity

Table 1 illustrates the effect of varying standard deviation and treatment effects on power (based on 80 subjects per arm) for of the co-primary efficacy endpoints of total endoscopic nasal polyp score at Week 52 and nasal obstruction VAS score during the 4 weeks prior to Week 52.

Table 1 Effect on Power with Varying Standard Deviation and Treatment Effect Sizes

Total endoscopic nasal polyp score at Week 52					
Standard Deviation	**Treatment Difference**				
	0.8	0.9	1.0	1.1	1.2
1.74	82.4%	90.2%	95.1%	97.8%	99.1%
1.78	80.7%	88.8%	94.2%	97.3%	98.9%
1.82	78.9%	87.5%	**93.2%**	96.7%	98.6%
1.86	77.1%	86.0%	92.2%	96.1%	98.2%
1.90	75.4%	84.6%	91.1%	95.3%	97.8%
Nasal obstruction VAS score during the 4 weeks prior to Week 52					
Standard Deviation	**Treatment Difference**				
	1.8	1.9	2.0	2.1	2.2
2.95	97.0%	98.2%	98.9%	99.4%	99.7%
3.10	95.4%	97.1%	98.2%	98.9%	99.4%
3.25	93.6%	95.7%	**97.2%**	98.2%	98.9%
3.40	91.4%	94.0%	95.9%	97.3%	98.2%
3.55	89.0%	92.0%	94.3%	96.1%	97.4%

If required, additional participants may be randomised to mitigate against unforeseen events arising at a local country level or worldwide, such changes will be reported in the CSR.

9.3. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	**Description**
All Participants Enrolled	All participants enrolled and for whom a record exists on the study database
Randomised	All randomised participants
Intent-to-Treat	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they are allocated at randomisation.
Safety	All randomised participants who take at least 1 dose of study treatment. Participants will be analysed according to the treatment they actually received for more than 50% of treatment administrations.

Note: "Enrolled" means a participant's, or their legally acceptable representative's (LAR's), agreement to participate in a clinical study following completion of the informed consent process.

9.4. Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database release and unblinding and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.1. Primary Endpoint(s)

Endpoint	Statistical Analysis Methods
Co-Primaries	**Primary Estimands** The difference between mepolizumab 100 mg SC and placebo in a) mean change from baseline in total endoscopic NP score to Week 52 and b) mean change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52 in participants with a diagnosis of CRSwNP / ECRS, regardless of IP discontinuation or, changes in background medication/starting a prohibited medication unrelated to COVID-19, interruptions to IP of 2 or more consecutive doses, or use of systemic CS for CRSwNP / ECRS, with participants experiencing surgery being assigned the worst possible score for the endpoint from the day of surgery onwards. The primary treatment effect to be estimated will be the comparison of mepolizumab 100 mg SC to placebo. The population will be the entire trial population (patients meeting the study inclusion/exclusion criteria with a diagnosis of CRSwNP / ECRS) randomised and receiving treatment. Co-primary variables: • Change from baseline in total endoscopic nasal polyp score at Week 52 (based on centrally read data) • Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52 The summary measure of treatment effect for both co-primary endpoints will be the difference in mean scores between mepolizumab and placebo. The main intercurrent events (ICE) anticipated which may affect subsequent scores for the co-primary endpoints are: a) Premature discontinuation of study treatment unrelated to the COVID-19 pandemic – to be handled using a treatment policy strategy. The study will continue collecting data for participants who prematurely discontinue from randomised treatment. b) Changes in background medication or to start a prohibited medication (e.g. start INCS therapy where absent at baseline) unrelated to the COVID-19 pandemic – to be handled using a treatment policy strategy. These events will be captured as a protocol deviations and the study will continue treatment and to collect data for participants following this change in background medication / starting of a prohibited medication. Participants will not be expected to discontinue treatment or withdraw from the study. c) Premature discontinuation of study treatment, change in background medication or start of prohibited medication related to the COVID-19 pandemic measures (such as quarantines, site closures or other related issues) – to be handled using a hypothetical strategy. Data

Endpoint	Statistical Analysis Methods
	impacted by COVID-19 related events will not be included in the statistical analyses and will be treated as missing data.. d) Surgery, which includes any procedure involving instruments resulting in incision and removal of tissue from the nasal cavity (e.g. polypectomy) – to be handled using a composite strategy by incorporating occurrence of the event into the definition of the endpoint. Specifically, participants who undergo surgery will be assigned the worst possible score for the endpoint from the day of surgery onwards for inclusion in the analysis. e) Course of systemic CS for CRSwNP / ECRS – to be handled using a treatment policy strategy. Data collected following a course of systemic CS for CRSwNP / ECRS will be included in the analysis where systemic CS will be considered as SoC treatment. f) Interruption to IP of 2 or more consecutive doses – to be handled using a treatment policy. These events will be recorded as protocol deviations and participants are expected to continue IP per-protocol after interruption. Data collected will be included in the analysis regardless of IP interruption. Any changes to the estimand strategy arising as result of unforeseen local or worldwide events will be documented in the Statistical Analysis Plan prior to unblinding of the study. Independent reviewers, blinded to treatment, grade the total endoscopic nasal polyp score from image recording of endoscopies. The total score is reported as the sum of the right and left nostril scores and ranges from 0 to 8, with higher scores indicating greater disease severity. Participants rate individual symptoms including nasal obstruction daily on a visual analogue scale (VAS) using an eDiary on a line with 101 individually selectable points ranging from 0 (none) to 100 (as bad as you can imagine). The final VAS scores for inclusion in summary and analysis tables will be derived from the electronically captured score by dividing each score by 10, and therefore will range from 0 to 10. 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. The mean VAS score over the last 7 days before Visit 2 will be used to determine the baseline value. For the co-primary analyses the change from baseline value for participants with surgery will be based on the worst possible score for the endpoint from the day of surgery onwards. Missing data due to study withdrawal, intercurrent events due to the COVID-19 pandemic or missing data for another reason will be assumed to be missing at random (MAR). The comparison of mepolizumab with placebo will be expressed as a difference in mean change from baseline presented with corresponding 95% confidence intervals and associated p-value. The analysis will be performed for each co-primary endpoint using a mixed model repeated measures (MMRM) analysis, with covariates of treatment group, baseline score, log of baseline blood eosinophil count, background INCS use ,country and time point, plus interaction terms for time point by baseline value and time point by treatment group.

Endpoint	Statistical Analysis Methods
	Sensitivity Analyses The following sensitivity analysis will be carried out to examine the potential impact of choices for the handling of participants with missing data.. Missing data unrelated to the COVID-19 pandemic (due to premature withdrawal from the study or another reason) will be imputed based on off-treatment data. Missing data due intercurrent events related to the COVID-19 pandemic will be assumed to be missing at random and imputed based on on and off-treatment data. Observed and imputed data will be combined and analysed using the same methods as specified for the co-primary analysis **Supplementary Estimands** The following additional analysis will be carried out to examine the potential impact of choices for the handling of data for participants starting a course of systemic CS for CRSwNP / ECRS. The analysis will be performed for each co-primary endpoint where: • change from baseline for participants starting a course of systemic CS is based on the worst possible score for the endpoint following the initiation of the course of systemic CS. An additional analysis will be carried out to examine the potential impact of choices for the handling of data for participants undergoing surgery. The analysis will be performed for each co-primary endpoint where: • change from baseline for participants with surgery is based on the worst observed score for the participant prior to surgery. Further details of these analyses will be included within the SAP.

9.4.2. Secondary Endpoint(s)

Endpoint	Statistical Analysis Methods
Secondary	Estimands for the secondary variables of change from baseline in SNOT-22 total score at Week 52, 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 for 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 Lund Mackay CT score at Week 52 will use the same population, summary measure and strategies for intercurrent events as for the primary estimands. Analysis methods will be the same as for the co-primary endpoints. For the endpoint of time to first nasal surgery or course of systemic CS for CRSwNP / ECRS up to Week 52, the summary measure will be the hazard ratio. The anticipated intercurrent events of premature discontinuation of study treatment or changes in background medication/starting of a prohibited medication will be handled using a treatment policy strategy, such that available event times will be included in the analysis regardless of whether the event (surgery or course of systemic CS for CRSwNP / ECRS) occurred before or after discontinuation of randomised treatment or changes in background medication/starting of a prohibited medication. Data impacted by COVID-19 related intercurrent events will not be included in the statistical analyses and each subject will be censored at the time of the COVID-19 related intercurrent event. Statistical analysis will use the Cox proportional hazards model with covariates of treatment group, log of baseline blood eosinophil count, number of previous surgeries (1, 2, >2; ordinal), background INCS use and country. A graph of the Kaplan-Meier estimates of the proportion of participants with events over time will be produced by treatment group. If a participant withdraws from the study before experiencing nasal surgery or having a course of systemic CS for CRSwNP / ECRS, the event time will be censored at the time of study withdrawal.

9.4.3. Safety Analysis

All safety analyses will be performed on the Safety Analysis Set and will be described in the SAP.

9.4.4. Other Analysis

All analyses of other endpoints (including self-administration of IP, PK, pharmacodynamic, and exploratory analyses) will be described in the SAP.

9.5. Interim Analysis

No interim analysis of data is planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB and other relevant documents (e.g., 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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/IEC
    - 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, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their 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 centre.
- 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 their legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about Mepolizumab or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have Mepolizumab approved for medical use or approved for payment coverage.

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.

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.

10.1.5. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their patients received. The investigator(s) is/are encouraged to share the summary results with the study subjects, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.
- GSK will provide the investigator with the randomisation codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.

10.1.6. 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 (e.g., laboratory, endoscopy, CT scan or Patient Reported Outcomes data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in study-specific CRF Completion Guidelines for Investigators.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL Plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as

Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary 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.

10.1.7. 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.
- Definition of what constitutes source data and its origin can be found in the Source Data Acknowledgment
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.1.8. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

First IC obtained by a participant, irrespective if successfully randomised to study intervention or screen fail is considered the first act of recruitment and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the subject and should assure appropriate participant therapy and/or follow-up

10.1.9. 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 multicentre 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 2 will be performed by a central laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention 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 intervention decision or response evaluation, the results must be recorded.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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

Table 2 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Haematology	Platelet Count RBC Count Haemoglobin Haematocrit	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 [non-fasting]	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick			

Laboratory Assessments	Parameters
	• Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential) • Follicle-stimulating hormone and oestradiol to confirm menopausal state (if applicable) • All study-required laboratory assessments will be performed by a central laboratory. • Hepatitis B and C testing at screening visit

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 7.1.4 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.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

• **Definition of Unsolicited and Solicited AE**
• An unsolicited adverse event is an adverse event that was not solicited using a Participant Diary and that is communicated by a participant/ LAR(s) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. • Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalisation, or emergency room visit, or visit to/by a health care provider). The participants/LAR(s) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records. • Unsolicited AEs that are not medically attended nor perceived as a concern by participant/LAR(s) will be collected during interview with the participants/ LAR(s) and by review of available medical records at the next visit. • Solicited AEs are predefined local and systemic events for which the participant is specifically questioned, and which are noted by the participant in their diary.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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 fulfil the definition of an AE or SAE.

Events NOT 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 (e.g., 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.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (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 or significant 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, diarrhoea, influenza, and accidental trauma (e.g. 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:

- Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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 for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. 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

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- 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 sufficient 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 intervention 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 intervention 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.
- New or updated information will be recorded in the originally submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. 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) to report the event 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). • Contacts for SAE reporting can be found in the SRM and Investigator Site File.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the medical monitor or the SAE coordinator. • 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 data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM and Investigator Site File.

10.4. Appendix 4: 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., dyspnoea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)

b) Reduced blood pressure (BP) 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., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c) Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

d) Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3) Reduced BP 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 BP

b) Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s Baseline

10.5. Appendix 5: Contraceptive and Barrier Guidance

10.5.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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, confirmation with more than one FSH measurement is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-oestrogen 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 enrolment.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.
- **Note:** Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

10.5.2. Contraception Guidance

CONTRACEPTIVES [a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods [b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Implantable progestogen-only hormone contraception associated with inhibition of ovulation [c]
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS) [c]
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.)
Highly Effective Methods [b] That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*

• Combined (oestrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation [c]
  • oral
  • intravaginal
  • transdermal
  • injectable

• Progestogen-only hormone contraception associated with inhibition of ovulation [c]
  • oral
  • injectable

• 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 intervention. 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.*
Effective Methods [d] That Are Not Considered Highly Effective *Failure rate of ≥ 1% per year when used consistently and correctly.*
• Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action
• Male or female condom with or without spermicide [e]
• Cervical cap, diaphragm, or sponge with spermicide
• A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods) [c]

a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.
d. Considered effective, but not highly effective - failure rate of ≥1% per year. Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception.
e. Male condom and female condom should not be used together (due to risk of failure from friction).

10.6. Appendix 6: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility, severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease aetiology; 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 CRSwNP / ECRS and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to mepolizumab or study interventions of this drug class, and indication. 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).
- Additional analyses of DNA samples may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analysed as part of a multi-study assessment of genetic factors involved in the response to mepolizumab or study interventions 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 interventions of this class) or nasal polyposis continues but no longer than 15 years after the last subject last visit or other period as per local requirements.

10.7. Appendix 7: Liver Safety: Required Actions, Monitoring and Follow-up Assessments

Liver Chemistry Stopping Criteria and Increased Monitoring Criteria are designed to assure participant safety and evaluate liver event aetiology.

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** total bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5
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, Monitoring and Follow-up Assessments	
Actions	**Follow-Up Assessments**
• **Immediately** discontinue study intervention • Report the event to GSK **within 24 hours** • Complete the liver event form and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform follow up assessments as described in the Follow-up Assessment column • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) **MONITORING:** **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5:**	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the aminotransferases values show downward trend • Obtain blood sample for pharmacokinetic (PK) analysis within a week of meeting increased liver monitoring criteria[5] • Obtain a serum creatine phosphokinase (CPK), lactate dehydrogenase (LDH), gamma glutamyl transferase [GGT], glutamate dehydrogenase [GLDH], and serum albumin. • Fractionate bilirubin, if total bilirubin≥2xULN

• Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow up assessments within **24 hours** • Monitor participant twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **For all other stopping criteria (total bilirubin <2xULN and INR ≤1.5):** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, total bilirubin and INR) and perform liver event follow-up assessments within **24-72 hours** • Monitor participant weekly until liver chemistries resolve, stabilize or return to within baseline **RESTART/RECHALLENGE** • **Do not restart/rechallenge** participant with study intervention since **it is not allowed per protocol**; continue participant in the study for any protocol specified follow-up assessments.	• Obtain complete blood count with differential to assess eosinophilia. • Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on liver event form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, recreational drugs and other over the counter medications. • Record alcohol use on the liver event alcohol intake form **If ALT ≥3xULN AND total bilirubin ≥2xULN or INR >1.5** obtain the following in addition to the assessments listed above: • 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 assay should be conducted (where available) to assess potential acetaminophen contribution to liver injury unless acetaminophen use is very unlikely in the preceding week. **NOTE: not required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) to evaluate liver disease: complete Liver Imaging form. • Liver biopsy may be considered and discussed with local specialist if available, for instance: o In patients when serology raises the possibility of autoimmune hepatitis (AIH) o In patients when suspected DILI progresses or fails to resolve on withdrawal of study intervention o In patients with acute or chronic atypical presentation

	• If liver biopsy conducted complete liver biopsy form

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 which may indicate severe liver injury (possible 'Hy's Law'), **must be reported to GSK as an SAE**; the INR 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 Immunoglobulin M (IgM) antibody; Hepatitis B surface antigen (HbsAg) and Hepatitis B Core Antibody (HBcAb); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, heterophile antibody or monospot testing); and Hepatitis E IgM antibody. 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. If hepatitis delta antibody assay cannot be performed, it can be replaced with a polymerase chain reaction (PCR) of hepatitis D RNA virus (where needed) [Le Gal, 2005].
5. Record the date/time of the PK blood sample draw and the date/time of the last dose of study intervention 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.

Liver Chemistry Increased Monitoring Criteria with Continued Study Intervention

Liver Chemistry Increased Monitoring Criteria and Actions with Continued Study Intervention	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** total bilirubin <2xULN or INR≤1.5 **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** total bilirubin <2xULN or INR≤1.5 **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, total bilirubin and INR) 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 (total bilirubin <2xULN and INR≤1.5), continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN and INR≤1.5, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

10.8. Appendix 8: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study (see Section 8.4.8**.** for the list of GSK medical devices).

10.8.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.8.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function. • Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to foetal distress, foetal death or a congenital abnormality or birth defect
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

10.8.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.8.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.
- It is not acceptable for the investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the medical monitor. 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 the medical monitor.
- 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.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - 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 a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one 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 sufficient 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 used for rating the intensity of an event; both AEs and SAEs 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.

- Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- 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 intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or IDFU or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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/SAE/device deficiency

- 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/SAE/device deficiency 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 may be asked to provide GSK with a copy of any available 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 GSK within 24 hours of receipt of the information.

10.8.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an 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 Table) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline 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 GSK medical monitor by telephone or email. • Contacts for SAE reporting can be found in the SRM and Investigator Site File.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the GSK medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper 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 paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the SRM and the Investigator Site File.

10.8.6. Reporting of SADEs

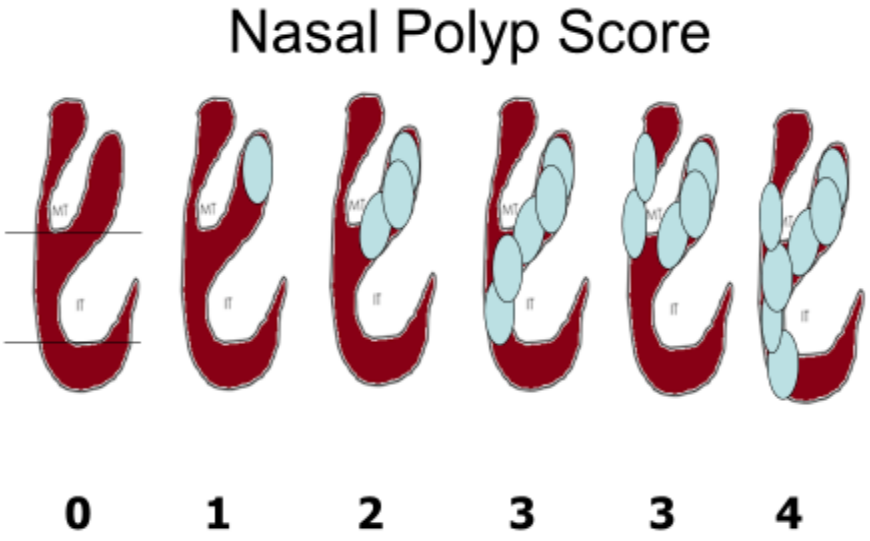
• **SADE Reporting to GSK**
• NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations. • Contacts for SAE reporting can be found in the SRM and the Investigator Site File.

10.9. Appendix 9: 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

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.



10.10. Appendix 10: Lund-Mackay CT score

Change in the Lund-Mackay CT score percentage of maxillary sinus volume occupied by disease will be assessed in all participants.

The Lund-Mackay CT score evaluates the patency of each sinus using a 0 to 2 scale (CCI [redacted]) and has a total score range from 0 to 24 (higher scores indicate more opacification) (Lund, 1993; Bhattacharyya, 1999).

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 [redacted]

Maximum total score: 24

10.11. Appendix 11: Abbreviations and Trademarks

ACQ-5	Asthma Control Questionnaire
ADA	Antidrug Antibodies
ADE	Adverse Device Effect
AE	Adverse Event
AI	Aspirin intolerance
ALT	Alanine aminotransferase (SGPT)
AST	Aspartate aminotransferase (SGOT)
BEC	Blood eosinophil counts
BMI	Body mass index
BP	Blood Pressure
BUN	Blood urea nitrogen
CPK	Serum creatine phosphokinase
CRF	Case Report Form
CRS	Chronic rhinosinusitis
CRSwNP	Chronic rhinosinusitis with nasal polyposis
CS	Corticosteroid
CT	Computed tomography
CV	Cardiovascular
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ECRS	Eosinophilic chronic rhinosinusitis
eDiary	Electronic Diary
ESS	Endoscopic sinus surgery
EW	Early Withdrawal
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GH	General health
GSK	GlaxoSmithKline
h/hr	Hour(s)
HBsAg	Presence of hepatitis B surface antigen
hCG	Human chorionic gonadotropin
HCP	Health care practitioner
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HRQoL	Health Related Quality of Life
HRT	Hormone Replacement Therapy
IB	Investigator’s Brochure
IBS	Irritable bowel syndrome
ICE	Intercurrent event
ICF	Informed consent form

ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS/ETN	Inhaled corticosteroids exhalation through nose
IEC	Independent Ethics Committee
IL-5	Interleukin-5
IL-5Ra	Interleukin-5 receptor alpha
IM	Intramuscular
IMCS	Intramuscular corticosteroid
INCS	Intranasal Corticosteroids
INR	International normalised ratio
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-to-Treat
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
kg	Kilogram
L	Litre
LAR	Legally Acceptable Representative
LDH	lactate dehydrogenase
MAR	Missing at random
MCH	Mean Corpuscular Haemoglobin
MCS	Mental Component Summary
MCV	Mean Corpuscula Volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligrams
MH	Mental health
mL	Millilitre
MMRM	Mixed Model Repeated Measures
msec	Milliseconds
NP	Nasal Polyps
OC	Osteomeatal complex
OCS	Oral Corticosteroids
PCS	Physical Component Summary
PCSA	Placebo controlled severe asthma
PD	Pharmacodynamic
PEF	Peak expiratory flow
PF	Physical functioning
PK	Pharmacokinetic
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

QTL	Quality Tolerance Limit
RAMOS NG	Registration and Medication Ordering System Next Generation
RBC	Red blood cells
RE	Role emotional
RP	Role physical
SADE	Serious Adverse Device Effect
SAE	Serious adverse event(s)
SAP	Statistical Analysis Plan
SC	Subcutaneously
SCS	Systemic corticosteroids
SCT	Study conduct team
SD	Standard deviation
SF	Social functioning
SF-36	Short Form Health Survey 36
SNOT	Sino-Nasal Outcome Test
SoA	Schedule of activities
SoC	Standard of Care
SOP	Standard Operating Procedure
SRM	Study Reference Manual
SUSAR	Suspected unexpected serious adverse reactions
UK	United Kingdom
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VAS	Visual Analogue Scale
VT	Vitality
WBC	White Blood Count
WOCBP	Woman of Childbearing Potential
WPAI	Work Productivity and Activity Impairment
µg	Microgram
µL	Microlitre

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
NUCALA

Trademarks not owned by the GlaxoSmithKline group of companies
ACQ-5
SF-36
SNOT-22
WPAI
Xolair

10.12. Appendix 12: Medical Device or Combination Product with Device Deficiency/Incident Report Form

INVESTIGATOR INSTRUCTIONS

Complete the Medical Device or Combination Product with Device Deficiency/Incident Report Form for each person who has a deficiency/incident with medical device or combination product with device component defined in the protocol. Please send a copy of the form to GSK within 24 hours as follows.

If the device incident is linked to an SAE please send email to both uk.gsk-rd-gcsp-ctsm-admin@gsk.com (or fax+44(0)20 8754 7822) and gsk-rd-complaints@gsk.com.

If the device deficiency/incident is a non-serious AE/ product complaint and not linked to an SAE, please send email to gsk-rd-complaints@gsk.com only.

If a subject experienced medical device or combination product with device component deficiency/incident, all of the header information must be completed before sending back to GSK. Ensure to file original pages with the site study file.

If an associated person (non-subject) e.g. caregiver, site staff, experienced medical device or combination product with device deficiency/incident, complete header information for the associated subject. If the person experienced the event is not related to a subject, enter header information where appropriate, e.g. Protocol Identifier, Centre Number.

In addition, for deficiencies/incidents fulfilling the definition of an Adverse Event (AE) or a Serious Adverse Event (SAE), the appropriate pages of the CRF (for associated person)/eCRF (for subject) must be completed as described in the protocol. If there is a SAE, the completed CRF/eCRF pages should be sent together with this report form. If the subject is withdrawn due to this deficiency/incident, ensure the Study Conclusion page is completed.

Note: If a copy of the SAE CRF/eCRF pages is sent with this form, this does not replace the procedure to report a SAE.

Refer to the protocol for definition of Device Deficiency/Incident.

DEFICIENCY/INCIDENT REPORT FORM

Who experienced the deficiency/incident?

Subject

☐ Associated person

Relationship to the subject *(select one)*

☐ Caregiver

☐ Clinician

☐ Nurse

☐ Other, specify _

Year of birth ☐☐☐☐ (Year) Sex ☐ Male ☐ Female

DEVICE OR COMBINATION PRODUCT WITH DEVICE DETAILS *(complete all applicable details)*

Manufacturer name _

Medical device or combination product with device (commercial name)_ _ _ _ _ _ _ _ _ _ _ _ _ _ _

Type of device _

Model number _

Catalogue number _

Serial number(s) _

Lot number(s) _

Accessories/Associated device _

Software version _

Did the deficiency/incident fulfil the definition of an AE or SAE? ☐ Yes ☐ No

If Yes, complete Non-Serious AE or SAE pages/forms as appropriate.

STUDY TREATMENT AND CONCOMITANT MEDICATIONS

*If a subject experienced the event, enter the study treatment details on the first line (if the study treatment is blinded, enter "Study Treatment" on this line). List the **relevant** concomitant medications the subject received during the study period. If there are extensive concomitant medications, attach a copy of the Concomitant Medications pages/forms (where applicable). If an associated person experienced the event, list the relevant medications.*

Drug Name *(Trade Name preferred)*	**Dose**	**Unit**	**Frequency**	**Route**	**Date Started** Day Month Year	**Taken Prior to Study?** Y=Yes N=No	**Date Stopped** Day Month Year	**Ongoing Medication?** Y=Yes N=No	**Reason for Medication**
e.g., Zantac	150	mg	BID	PO	05 AUG 08	N	07 AUG 08	N	Gastric ulcer
1.									
2.									
3.									

4.									
5.									

DETAILS OF DEFICIENCY/INCIDENT

Onset date of deficiency/incident ☐☐☐☐☐☐☐

Day Month Year

Deficiency/Incident description _

_ _

_ _

_ _

Treatment given _

_ _

_ _

Outcome, ☐ *one*:

- ☐ Recovered/Resolved
- ☐ Recovering/Resolving (*leave outcome date blank*)
- ☐ Not recovered/Not resolved (*leave outcome date blank*)
- ☐ Recovered/Resolved with sequelae
- ☐ Fatal (*complete SAE form*)
- ☐ Not Applicable

Outcome date ☐☐☐☐☐☐☐

Day Month Year

Corrective action (e.g., adjustment to device or combination product with device, return of device or combination product with device to manufacturer for investigation, including any device or combination product with device decontamination procedures necessary)

_ _

_ _

_ _

Was the subject withdrawn from the study as a result of this deficiency/incident?
☐ Yes ☐ No ☐ Not Applicable

Is there a reasonable possibility that the deficiency/incident was caused by the medical device or combination product with device component?
☐ Yes ☐ No

Is device or combination product with device component available for evaluation?
☐ Yes ☐ No

Investigator's signature _

(*confirming that the data on these pages are accurate and complete*)

Investigator's name (print) _

10.13. Appendix 13: Country-specific requirements

Country-specific local requirements will be added, as and when applicable.

10.14. 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).

Amendment 01: 08-OCT-2020

This amendment was considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for Amendment 01: The primary driver for the protocol amendment was to simply further clarify some points in the protocol that were raised as questions when translating into different languages. There was an attempt to clarify the study visit schedule, the exclusion criteria, the expected standard of care (SoC) and the concomitant medications permitted during the study.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	Addition of 'Study Day' along with visit number and week number	To completely clarify the visit windows and in what days study visits can occur
Section 1.3 Schedule of Activities and Section 8.5	Clarification to a footnote on collection of PK samples	To clarify that PK samples are to be collected pre-dose only at Visit 3 and Visit 9
Section 1.3 Schedule of Activities	Addition of ACQ-5 should only be performed in Asthmatic participants. Order of questionnaires will be detailed in the Study Reference Manual	To clarify that ACQ5 is only to be performed in Asthmatic participants and that the order of assessments of questionnaires will be detailed in the SRM
Section 5.2.1 Exclusion Criterion 5	Replacement of wording regarding 'occlusion of one nostril' by referring to any severe nasal septal deviation preventing full assessment of nasal polyps in both nostrils	To clarify the anatomy leading to participant being ineligible for randomisation and highlight the fact that the important thing is the inability to perform the assessment of nasal polyps
Section 5.3 Randomisation Criteria	Deletion of corticosteroids as SoC criteria from treatment group descriptions	To clarify that there is no requirement for corticosteroids to be part of SoC. Some of the participants will be on INCS but others will not

Section 5.3 Randomisation Criteria	Addition to randomisation criterion number 2: 'Participant must meet CT shadow: ethmoid ≥ maxillary' if not presenting co-morbidities	To highlight the importance of the required combination of factors to classify eosinophilic chronic rhinosinusitis (ECRS) as moderate
Section 6.2 Self-Administration for Japanese Cohort	Deletion of 'the first dose of' from wording explaining when the first self-administration can occur	To clarify that the first self-administration can only occur from Visit 11 onwards, after training has been completed at least twice between Visit 5 and Visit 10
Section 8.1.4 Critical Procedures Performed at the First Treatment Visit (Baseline Visit 2)	Deletion of laboratory test text: Blood for PK assessment (Japan and China only)	To clarify that this test will be conducted at Visit 3 as per Section 8.5 Pharmacokinetics
Section 8.2.2 Computed Tomography (CT) Scan	Deletion of wording: 'whenever possible a cone beam CT scan should be utilised'	To avoid confusion about what to do if not possible and to allow flexibility
Section 10.10 Appendix 10	Correction to the 'total' row of the Lund-Mackay CT score table	The total score row was incorrect and has now been corrected

Amendment 02: 29-JUN-2021

This amendment is considered non-substantial because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment: The primary reason for this amendment is to clarify a relevant exception to exclusion criterion #9, namely that nasal biopsies for diagnostic purposes conducted prior to pre-screening (Visit 0) are not to be considered nasal surgery.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 – Synopsis (Overall Design) and Section 4.1 – Overall Design	Specification that Standard of Care (SoC) applies to 52-week treatment period.	To clarify that SoC, which may include short courses of systemic corticosteroids, applies to 52-week treatment phase and not to run-in period.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 – Synopsis (Overall Design)	First occurrence of acronym LTRA expanded and acronym used where applicable.	To clarify meaning of LTRA acronym and to apply it consistently throughout protocol.
Section 1.1 – Synopsis (Intervention Groups and Duration) and Section 6.9 – Concomitant Therapy	Specification of when rescue medications can be used (e.g., short courses of systemic corticosteroids).	To clarify the allowance of rescue medications (e.g., short courses of systemic corticosteroids) during the 52-week treatment phase but not during the run-in period of the study.
Section 1.3 – Schedule of Activities (SoA)	Footer 11 has been reworded to clarify endoscopic NP scoring on V2.	To ensure that the baseline endoscopy performed at V2 is conducted after completion of all screening procedures.
Section 5.1 – Inclusion Criteria	For inclusion criterion #1 (age), the term 'inclusive' was removed.	Term 'inclusive' is not applicable since no defined age range stated.
Section 5.2 – Exclusion Criteria	For exclusion criterion #9, text was added to clarify that nasal biopsies for diagnostic purposes conducted prior to pre-screening (Visit 0) are not to be considered nasal surgery.	Relevant symptoms and signs resulting from a minor surgery (such as a nasal biopsy for diagnostic purposes) conducted prior to Visit 0 are expected to have resolved by randomization on Visit 2 (Study Day 1).
Section 5.2 – Exclusion Criteria	For exclusion criterion #18, 'corticosteroid nasal solution' was removed.	Corticosteroid nasal solution is not a systemic corticosteroid.
Section 6.9 – Concomitant Therapy	Inclusion of wording pertaining to COVID-19 vaccines.	To clarify the permissibility for subjects to be vaccinated with authorized or approved COVID-19 vaccines.
Section 7.1.5 – Liver Chemistry Stopping Criteria	Language regarding actions, monitoring, and follow-up assessments, and Algorithms A and B	To align with current liver safety practices.

Section # and Name	**Description of Change**	**Brief Rationale**
and Appendix 7 – Liver Safety	updated albeit discontinuation thresholds remain unchanged.	
Section 7.2.2- Early Withdrawal Visit	Second last bullet ('Collection of eDiary') removed from list of procedures.	Collection of electronic diary already listed (6th bullet from top).

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