16 September 2021
EMA/560926/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Nucala

International non-proprietary name: mepolizumab

Procedure No. EMEA/H/C/003860/II/0035

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

# Table of contents

# List of abbreviations

ACQ Asthma Control Test
AERD Aspirin exacerbated respiratory disease
BEC Blood eosinophil count
CI Confidence interval
CRS Chronic rhinosinusitis
CRSsNP Chronic rhinosinusitis without nasal polyps
CRSwNP Chronic rhinosinusitis with nasal polyps
CSR Clinical study report
ENP Endoscopic nasal polyp
GSK GlaxoSmithKline
HRQoL Health-related quality of life
IgG1 Immunoglobulin G1
IL-5 Interleukin-5
INCS Intranasal corticosteroid
ITT Intent-to-treat
IV Intravenous
mAb Monoclonal antibody
MCID Minimum clinically important difference
MF Mometasone furoate
MIC Minimal important change
NP Nasal polyps
OCS Oral corticosteroid
PD Pharmacodynamic
PK Pharmacokinetic
PnIF Peak nasal inspiratory flow
PP Per Protocol
PRO Patient reported outcomes
Q4W Every 4 weeks
RAP Reporting and Analysis Plan
SC Subcutaneous
SCE Summary of Clinical Efficacy
SCS Summary of Clinical Safety
SNOT-22 Sino-nasal Outcome Test - 22 items
SoC Standard of care
sRAP Supplemental Reporting and Analysis Plan
UK United Kingdom
US United States
VAS Visual analogue scale

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Trading Services Limited submitted to the European Medicines Agency on 9 October 2020 an application for a variation.

The following variation was requested:

| **Variation requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication to include Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) for Nucala (mepolizumab). As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 7 of the RMP has also been submitted. In addition, the Marketing authorisation holder took the opportunity to update the local (IT) representative in the PL.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0119/2017 on the granting of a product-specific waiver.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

## *Scientific advice*

The MAH did seek Scientific Advice at the CHMP on the 17th of May 2016. (Procedure No.: EMEA/H/SA/156/4/2016/III).

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Peter Kiely Co-Rapporteur: Ondřej Slanař

| Timetable | Actual dates |
|---|---|
| Start of procedure | 31 Oct 2020 |
| CHMP Co-Rapporteur Assessment Report | 21 Dec 2020 |
| CHMP Rapporteur Assessment Report | 22 Dec 2020 |
| PRAC Rapporteur Assessment Report | 04 Jan 2021 |
| PRAC members comments | N/A |
| Updated PRAC Rapporteur Assessment Report | N/A |
| PRAC endorsed relevant sections of the assessment report[3] | 14 Jan 2021 |
| CHMP members comments | 18 Jan 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 21 Jan 2021 |
| Request for supplementary information | 28 Jan 2021 |
| Submission | 15 Apr 2021 |
| Re-start of procedure | 26 Apr 2021 |
| CHMP Rapporteur Assessment Report | 03 Jun 2021 |
| CHMP members comments | 14 Jun 2021 |
| Updated CHMP Rapporteur(s) Assessment Report | 17 Jun 2021 |
| 2nd Request for Supplementary Information | 26 Jun 2021 |
| Submission of MAH responses | 12 July 2021 |
| Re-start of procedure | 19 Jul 2021 |
| CHMP Rapporteur Assessment Report | 17 Aug 2021 |
| CHMP members comments | 30 Aug 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 10 Sep 2021 |
| Opinion | 16 Sept 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

### 2.1.1. Problem statement

Mepolizumab is licensed in a number of countries for add-on maintenance treatment for severe eosinophilic asthma and for add-on maintenance treatment for eosinophilic granulomatosis with polyangiitis (EGPA). Mepolizumab is available as a powder for solution for subcutaneous (SC) injection, and as a solution for SC injection in a pre-filled pen [auto-injector (AI)] or pre-filled syringe [safety syringe device (SSD)]. Mepolizumab is also in development for other eosinophilic indications.

### *Disease or condition*

Nasal polyps (NP) develop in the setting of chronic paranasal sinus inflammation and are therefore associated with CRS.NP are chronic inflammatory outgrowths of the paranasal sinus mucosa (commonly the ethmoid sinuses) that present bilaterally along the middle and superior meatus and occur primarily in adults. NP greatly impacts a patient's health-related quality of life (HRQoL) through increases in nasal obstruction, loss of sense of smell, facial pain, facial pressure and nasal discharge; and the persistence of these symptoms leads to chronic rhinosinusitis (CRS).

### *State the claimed the therapeutic indication*

The MAH is seeking an extension of indication for use in chronic rhinosinusitis with nasal polyps (CRSwNP) as follows:

*Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyps.*

### *Epidemiology and risk factors, screening tools/prevention*

The prevalence of CRSwNP ranges from 1.1% in the United States of America (USA) and China to 4.3% in Finland.
In general, up to 55% of patients with CRSwNP have asthma and the presence of NP increases with the severity of asthma.

According to the European Position Paper on Rhinosinusitis and NP which is consistent with the 2007 American Academy of Otolaryngology guideline the diagnosis of CRS (with or without NP) in adults is defined as:

- inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):
    - ± facial pain/pressure
    - ± reduction or loss of smell

for ≥12 weeks and either

- endoscopic signs of:
    - NP and/or

    - mucopurulent discharge primarily from middle meatus and/or
    - oedema/mucosal obstruction primarily in middle meatus and/or
- Computerised tomography (CT) changes:
    - mucosal changes within the ostiomeatal complex and/or sinuses

In addition, the European EPOS 2020 guidance defines disease severity using a total severity VAS: 0-3 as mild disease, >3-7 as moderate and >7-10 as severe.

Collectively, symptoms of CRSwNP have a significant impact on HRQoL

### *Aetiology and pathogenesis*

The aetiology of CRSwNP is currently unknown although, in adults, eosinophils are the main inflammatory cell in the substantial proportion of NP tissue and are considered potentially responsible for the etiopathogenesis and prognosis of the disease.

In Western countries, the majority of patients with CRSwNP have a type 2 inflammation characterised by eosinophilia (~80%) and elevated levels of interleukin-4, interleukin-5, and interleukin-13 cytokines.
It should be noted that the aetiology of NP in children appears to be different to that in adults and has less correlation with tissue eosinophilia.

The standard of care (SoC) for CRSwNP in adults is treatment with intranasal corticosteroids (INCS) and nasal saline irrigation and, for severe symptoms, intermittent courses of oral corticosteroids (OCS) when short term relief is required.

Dupilumab was approved in the USA in June 2019 and the EU in October 2019 as an add-on therapy to SoC in adult patients with CRSwNP. This was the first biologic treatment to be approved in this indication. Omalizumab has recently been approved in the EU (July 2020), and is under review in the USA, as an add-on therapy to SoC in adult patients with inadequately controlled CRSwNP.

Surgery to remove the NP tissue may also be indicated for severe cases of CRSwNP.
Surgery involves the removal of the NP tissue and diseased nasal mucosa, restoring aeration of the nasal passage and sinuses.

A recent meta-analysis of surgery revision rates among patients with CRSwNP reported a mean revision rate of 16.2% over a weighted mean follow-up of 89.6 months: rates were higher among patients with asthma than without asthma (22.6% vs. 8.0%) and among patients with multiple previous surgeries than just one (26.4% vs. 14.3%).

## 2.1.2. About the product

Mepolizumab (NUCALA), a humanized monoclonal antibody (immunoglobulin-G1 [IgG1], kappa, mAb), binds with high specificity and affinity to human interleukin (IL)-5, the key cytokine responsible for the regulation of blood and tissue eosinophils.

The recommended dose is 100 mg of mepolizumab administered by SC injection once every 4 weeks.

Mepolizumab can be provided as either 100 mg of lyophilized powder in single-dose vials for reconstitution or 100 mg/mL solution in single-dose prefilled AI or SSD.

### 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The MAH did seek Scientific Advice at the CHMP on the 17th of May 2016. (Procedure No.: EMEA/H/SA/156/4/2016/III).

In particular, the MAH previously planned two replicate phase 3 studies with the primary endpoint at week 24. This was amended to a single pivotal trial and the timing of the co-primary endpoints amended form week 24 to week 52, following discussion with FDA.

## *2.2. Non-clinical aspects*

### 2.2.1. Introduction

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

No non-clinical studies have been performed. An overview has been provided discussing the mechanism of action of mepolizumab to inhibit IL-5 signalling, reducing the production and survival of eosinophils and thereby a scientific rationale for potential efficacy in the proposed indication.

### 2.2.2. Ecotoxicity/environmental risk assessment

Being natural proteins, therapeutic antibodies such as mepolizumab, are not excreted unchanged and do not give rise to metabolites with potential biological activity. In view of this, guidance on the environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00) specifically exempts amino acids, peptides and proteins from the need for a complete environmental assessment.

### 2.2.3. Discussion on non-clinical aspects

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of mepolizumab.

Considering the above data, mepolizumab is not expected to pose a risk to the environment.

The weight of evidence from a critical review of non-clinical toxicity data do not raise a concern for new indications in proposed dosing regimen and aimed patient population.

### 2.2.4. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of mepolizumab.

Considering the above data, mepolizumab is not expected to pose a risk to the environment.

No concerns are raised from non-clinical point of view.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The clinical development program for CRSwNP consists of the pivotal Phase III study, 205687, with supportive data from the Phase II study MPP111782.

Study 205687 was a multicentre, Phase III randomised, double-blind, parallel group study which investigated the clinical efficacy and safety of 100 mg SC mepolizumab in adult participants with CRSwNP receiving SoC therapy.

Study MPP111782 was a Phase II, two-part (Part A and Part B), randomised, double-blind, placebo-controlled, multi-centre study to investigate the use of mepolizumab 750mg IV versus placebo in reducing the need for surgery in participants with CRSwNP refractory to current Standard of Care. Based on the findings from this study, an exposure-response (PK/PD) model was developed and used to support the progress to Phase III at a single dose level of mepolizumab 100 mg SC.

An investigator led study (CRT110178) randomised placebo controlled was also submitted in adult patients.

### GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

| Protocol No. | No. Study Centres Location(s) | Study Start; Enrolments Status and Date; Total Randomised /Target Random. | Study Objectives | Study Design | Diagnosis; Key Inclusion Criteria | Treatment Details (Drug; Dose; Form; Route; Frequency; Duration) | No. of Participants by Group Entered (Treated)/ Completed (Study) | Gender M/F; Mean Age (Range) | Primary Endpoint(S) |
|---|---|---|---|---|---|---|---|---|---|
| **Pivotal Study** | | | | | | | | | |
| 205687 | 86 centres:<br>Argentina 11,<br>Australia 4,<br>Canada 7,<br>Germany 9,<br>Netherlands 1,<br>Republic of Korea 4,<br>Romania 4,<br>Russian Federation 9,<br>Sweden 5,<br>UK 8,<br>US 24. | May 2015;<br>Completed;<br>December 2019;<br>414/400 | Efficacy and Safety, PK and Population PKPD analysis | Randomised, double-blind, placebo-controlled, parallel group | Adult participants (aged ≥18 years) with bilateral NP.<br>≥1 surgery for the removal of NP within the previous 10 years.<br>Need for INCS treatment for ≥8 weeks prior to Screening.<br>Symptoms of CRS for ≥12 weeks prior to Screening.<br>Severe NP symptoms (obstruction VAS symptom score of >5).<br>Severity of NP consistent with a need for surgery (overall VAS symptom score >7 and bilateral ENP score of ≥5). | Treatment Period:<br>Mepolizumab 100 mg SC<br>Placebo SC<br>One injection from a pre-filled safety syringe Q4W for 52 weeks in addition to SoC for NP.<br>No treatment follow-up Period:<br>SoC for NP for 24 weeks. | Treatment Period:<br>Mepolizumab: 206/189<br>Placebo: 201/184<br>No treatment follow-up Period:<br>From mepolizumab arm: 69/68<br>From placebo arm: 65/65 | Gender: 264M/143F<br>Mean Age: 48.8 (18, 82) | Co-primary endpoints:<br>Change from baseline in total ENP score at Week 52.<br>Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52. |

| Supportive Study | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| MPP111782 | 6 centres: Belgium 1, Netherlands 1, UK 4. | May 2009; Completed; December 2014; 109/110 | Efficacy and Safety, PK, PD and Population PKPD analysis | Randomised, double-blind, placebo-controlled, parallel group | Adult participants (aged 18 to 70 years, inclusive) with severe bilateral NP.<br>≥1 surgery for the removal of NP.<br>Need for INCS treatment for ≥ 12 weeks prior to Screening or a history of oral steroid treatment.<br>Severity of NP consistent with a need for surgery. | Part A (Treatment Period):<br>Mepolizumab 750 mg IV<br>Placebo IV<br>One infusion of reconstituted lyophilised product Q4W for 24 weeks in addition to SoC for NP.<br>Part B:<br>SoC for NP for 20 weeks. | Part A (Treatment Period):<br>Mepolizumab 54/22<br>Placebo: 51/19<br>Part B:<br>From mepolizumab arm: 14/10<br>From placebo arm: 7/5 | Gender: 75M/30F<br>Mean Age: 50.2 (23, 70) | Number of participants with reduced need for surgery at the end of Part A of the study (based on the assessment of nasal polyposis at Visit 8 [Week 25] and Decision Table 2, Appendix 3 of the protocol). |

Abbreviations: CRS=chronic rhinosinusitis; ENP=endoscopic nasal polyp; INCS=intranasal corticosteroids; IV=intravenous; NP=nasal polyps; PD=pharmacodynamics; PK=pharmacokinetics; Q4W=every 4 weeks; Random=randomisation; SC=subcutaneous; SoC=standard of care; UK=United Kingdom; US=United States; VAS=visual analogue scale.

| Investigator Led Study | | | | | |
|---|---|---|---|---|---|
| CRT110178 | E/ E, S | R, PC, DB | Adult participants with severe CRSwNP (grade 3 or 4)[a] or NP that were recurrent after surgery (grade 1-4)[a] refractory to corticosteroid therapy. | 750 mg mepolizumab IV q4W for 8 weeks<br>Placebo=10<br>Mepolizumab=20 | Completed [Gevaert, 2011] |

Abbreviations: CRS= chronic rhinosinusitis, DB=double-blind; E=efficacy; IV=intravenous; HRQoL=health-related quality of life; NP=nasal polyps; PC=placebo-controlled; PK=pharmacokinetics; R=randomised; S=safety; SC=subcutaneous; SoC=standard of care.

## 2.3.2. Pharmacokinetics

### *Bioanalytical methods*

An overview of the clinical studies for severe chronic rhinosinusitis with nasal polyps (CRSwNP) with their respective sample analysis reports and bioanalytical method validation reports is presented below in **Table 1.**

**Table 1: List of Bioanalytical Reports, respective validation reports and submission status**

| Assay | PK | ADA | NAb |
|---|---|---|---|
| **205687** Sample Analysis Report(s) | 2020n431368_00 | 2020n431369_00 | 2020n431370_00 |
| Validation Report(s) | 2017n332000—00***<br>2017n342098--00*** | 2018n366495—00**<br>2018n366496—00**<br>2018n366497—00** | 2018n381947—00*** |
| **MPP111782** Sample Analysis Report(s) | 2015n263183--00 | 2020n430596--00 | 2020n430597--00 |
| Validation Report(s) | 2011N113224—02*<br>2012n133378—02*<br>2014n218461—00***<br>2015n263226—00**<br>2016n297144—00***<br>2017n321052—00** | 2012n137701—00* | cd2010-00319—00* |

ADA=anti-drug antibody; NAb=neutralizing antibody; PK=pharmacokinetics.
Note: Unless indicated otherwise, reports are included in this CRSwNP submission, *°previously submitted in the initial severe asthma submission; **°previously submitted in the liquid formulation submission; ***°previously submitted in the HES submission.

*Analytical methods for the evaluation of Mepolizumab Plasma Concentrations.*

The measurement of mepolizumab plasma concentrations for clinical study 205687 was carried out using method 111202M01. For clinical study MPP111782, two different validated ELISA methods were used.

These methods are the same as those used during the initial MAA procedures for the lyophilised and liquid formulations. For assay runs to be acceptable, no more than one-third of the QC samples could deviate from the nominal concentration by more than 20% with %CV ≤ 20%. In addition, at least 50% of the results from each QC concentration had to meet the aforementioned criteria for accuracy and precision. There are also additional assay acceptance criteria in place for the calibration curve accuracy and precision.

*Analytical methods for the evaluation of anti-drug antibodies (ADA)*

The measurement of ADA are the same as those used during the initial MAAs for the lyophilisate and the liquid formulations.

For clinical study 200622, 494 sample clinical sample results are reported. 59 samples screened positive (12%) and 9 samples confirmed positive (1.8%). Titers were determined for confirmed positive results. The sample analysis report for MPP111782 briefly details the determination of in-study cut points from 50 pre-dose subjects. A standard approach was taken for derivation of cut points. Details of removal of outliers and assessment of normality are provided. A fixed screening cut point was derived based on the upper 95% prediction interval (5% false positive rate) and a 0.1% titration cut point was established.

Given the drug concentrations in the immunogenicity sampling time points for clinical trial MPP111782, the ADA assay demonstrates sufficient drug tolerance to detect ADA. Only 7 out of 53 subjects had immunogenicity samples that contained greater than 100 μg/ml mepolizumab (drug tolerance of the assay) and the applicant describes only one potential false negative .The drug concentrations in the immunogenicity sample time points are presented for study 205687 and serum levels of mepolizumab were below the tolerance of the assay.

*Analytical methods for the evaluation of neutralising antibodies (NAb)*

The measurement of NAb for clinical study 205687 was carried out using the electrochemiluminescent (ECL) as bridging assay. In brief, quality controls and human serum samples were incubated with

mepolizumab and biotinylated recombinant human IL-5 (bio IL-5). The samples are then transferred to a previously blocked streptavidin-coated MSD plate and a sulfo-tab labelled anti-human $IgG_1$ is added. After washing the MSD plate, read buffer is added. In the absence of NAbs in the sample, the complex consisting of bio IL-5, mepolizumab and sulfo-tagged anti-$IgG_1$ will results in an ECL signal. However, if the sample contains NAbs, then the ECL signal is reduced. Any sample with a %response less than or equal to the cutpoint (i.e., ≤85.75%), as determined during method validation, is determined as positive for NAbs.

A summary of the method validation is presented below in **Table 2**.

**Table 2: Method validation summary for method M1707047**

| | |
|---|---|
| **Study Title:** | Validation of an Electrochemiluminescence-Based Method for the Detection of Anti-SB-240563 Neutralizing Antibodies in Human Serum |
| **Analyte:** | Anti-SB-240563 Neutralizing Antibodies |
| **Matrix:** | Human serum |
| **Type of assay:** | Electrochemiluminescence (ECL) immunoassay |
| **Minimum required dilution:** | 1:8 |
| **Intra-assay precision (%CV) for quality control samples:** | Negative control (NC, 0 µg/mL): 0.28% to 5.99%<br>Low quality control (LQC, 1.016 µg/mL): 2.29% to 5.75%<br>High quality control (HQC, 10.164 µg/mL): 2.67% to 8.33%<br>Background control (BC, 0 µg/mL, no drug): 4.55% to 13.04% |
| **Inter-assay precision (%CV) of quality controls (6 batches):** | NC (0 µg/mL): 10.14%<br>LQC (1.016 µg/mL): 14.64%<br>HQC (10.164 µg/mL): 12.94%<br>BC (0 µg/mL): 16.00% |
| **Neutralizing cutpoint:** | 85.75% |
| **Sensitivity:** | 0.494 µg/mL |
| **Acceptance criteria for negative control and quality controls:** | NC: ECL >10448.28<br>LQC: %Response <71.12%<br>HQC: %Response <1.06%<br>BC: %Response <0.33% |
| **Acceptable drug tolerance levels:** | Tolerated free drug concentration sensitivity limits:<br>≤1 µg/mL of drug at an assay sensitivity of 1.289 µg/mL of the positive control (PC)<br>≤2 µg/mL of drug at an assay sensitivity of 1.564 µg/mL of PC<br>≤4 µg/mL of drug at an assay sensitivity of 3.217 µg/mL of PC |
| **Acceptable IL-5 interference levels:** | No significant IL-5 interference was observed up to 2000 pg/mL of IL-5 |

| | |
|---|---|
| **Stability in matrix:** | Benchtop stability at room temperature: 26 hours<br>Freeze-thaw (−70°C/room temperature) stability: 6 cycles<br>Short-term storage stability at 4°C: 75 hours<br>Long-term storage stability at −70°C: 91 days<br>Long-term storage stability at −20°C: 48 days |
| **Experimental start date:** | 26 April 2018 |
| **Experimental end date:** | 25 July 2018 |
| **Validated test method:** | Alliance Pharma Bioanalytical Method 1707047M.02V [redacted] |

The measurement of NAb for clinical study MPP111782 was same NAb assay used for the initial lyophilisate and liquid formulations.

## *Absorption*

Mepolizumab subcutaneous absorption is slow, with a Tmax of 4 to 8 days. In healthy subjects, the absolute bioavailability of a single dose of SC mepolizumab ranged from 64%–75%, across administration sites (abdomen, thigh, upper arm). In a repeat dose study in moderate/severe asthmatic subjects, the SC absolute bioavailability was 74%, and in a Phase III severe asthma study was 80%.

## *Distribution*

Mepolizumab distributes into a volume of approximately plasma and interstitial space (55 to 85 mL/kg).

## *Elimination*

Mepolizumab is catabolized by ubiquitous proteolytic enzymes and does not undergo target-mediated clearance.

Mepolizumab is eliminated with a systemic clearance of 1.9-3.3 mL/day/kg and has a SC terminal-phase elimination half-life of 20 days, with two-fold accumulation following repeat dosing every four weeks, consistent with the long half-life.

## *Dose proportionality and time dependencies*

The pharmacokinetics of mepolizumab are linear, dose-proportional, and time-independent after both intravenous (IV) and subcutaneous (SC) administration.

## *Pharmacokinetics in target population*

**Study MPP111782 (Supportive Phase IIa Study)**

This was a multi-centre, randomised, double-blind, placebo-controlled, parallel-group study in adult subjects with severe bilateral NP. Subjects were randomised 1:1 to receive mepolizumab IV 750 mg or

placebo every 4 weeks over a period of 24 weeks. Sparse PK samples were collected throughout the study.

A total of 52 subjects contributed 461 mepolizumab PK samples. All concentration-time profiles were analysed using a previously established population PK model with 2 compartments and IV bolus input. Bodyweight was incorporated into the model as a fixed effect with conventional fixed allometric scaling powers of unity for volume and 0.75 for clearance.

Mepolizumab 750 mg IV showed expected PK, consistent with previous analyses, with bodyweight-adjusted clearance of 0.22 L/day, volume of distribution at steady-state of 7.1 L, distribution half-life of 1.5 days, and a t½ of 24 days.

No subjects in the mepolizumab treatment group tested positive for anti-mepolizumab antibodies.

**Study 205687**

In the pivotal Phase III 205687 study, adult patients with CRSwNP were randomised 1:1 to receive either mepolizumab SC 100 mg or placebo SC treatments every 4 weeks for 52 weeks. Sparse PK samples were collected pre-dose at Baseline, Week 4, Week 52 and Week 68, and, when applicable early withdrawal (EW).

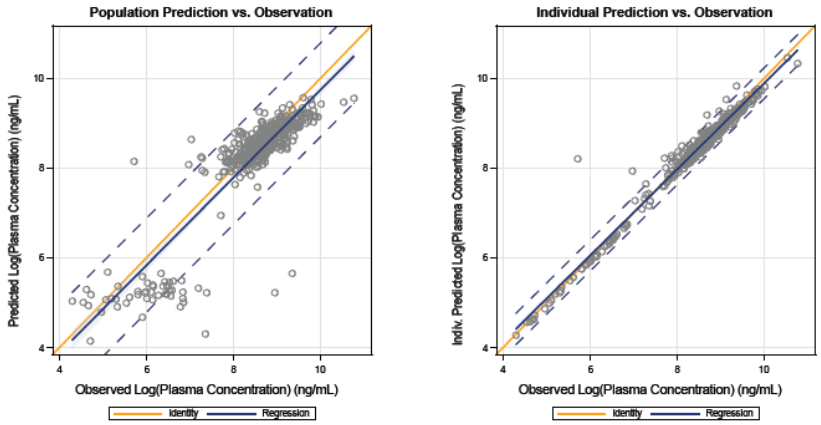
In order to investigate whether mepolizumab PK in adults with CRSwNP was similar to other eosinophilic conditions, the most recent meta-analysis population PK model was applied directly to the dataset of Study 205687 without modification and without parameter estimation. Observations from Study 205687 and model predictions were then subjected to statistical goodness of fit tests to assess the degree of comparability.

The effect of prospectively selected covariates on mepolizumab exposure was evaluated graphically (PK parameters vs. covariates), and formally using a forward/backward approach. Albumin was not collected in this study and was set to previous population mean of 44 g/L.

***Results***

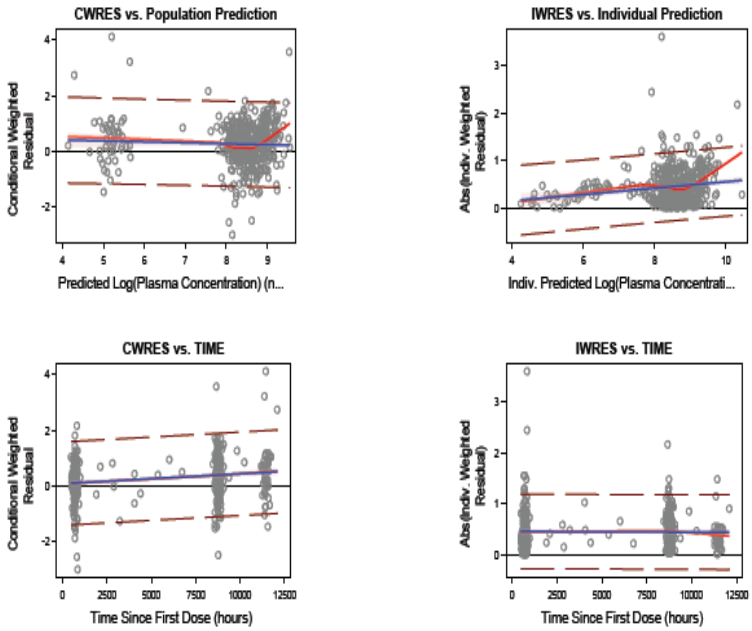
Of the 206 participants randomised to the mepolizumab group, 202 contributed 434 concentrations to the analysis. No additional covariates beyond the ones already included in the model (bodyweight and creatinine clearance) were identified. Goodness of fit plots are shown in **Figure 1**, **Figure 2**, **Figure 3**. A Visual Predictive Check (VPC) is presented in **Figure 4**.

## Figure 1: Goodness of Fit Plots (Regression)



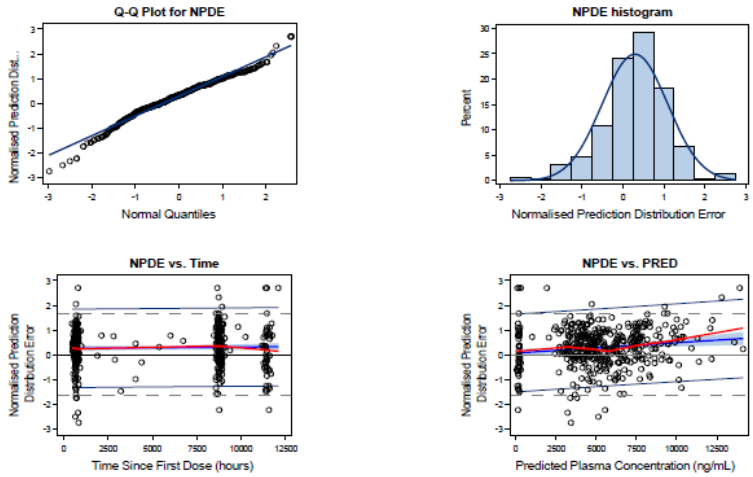

Plots show linear regression with 95% prediction interval (dashed lines)

## Figure 2: Goodness of Fit Regression (Summary Plots)



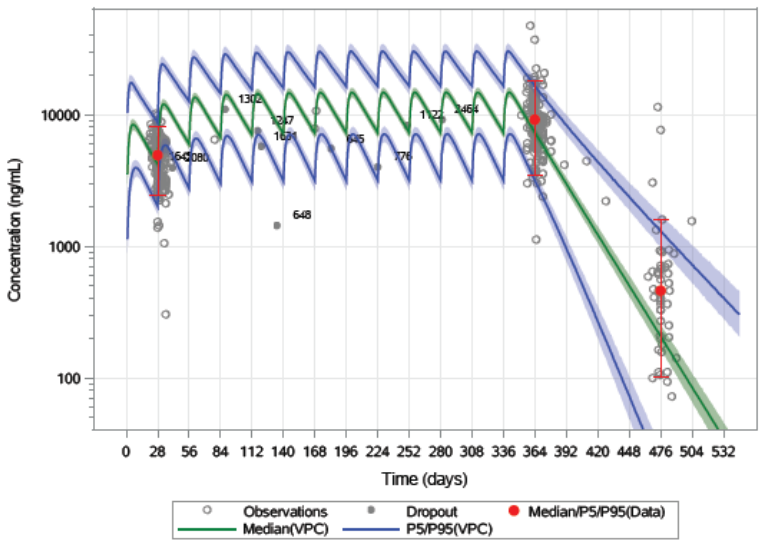

CWRES = Conditional weighted residuals, IWRES = Individual weighted residuals

**Figure 3: Normalised Prediction Distribution Error**




Plots show linear regression (blue) with 95% prediction interval (dashed lines) and loess regression (red)

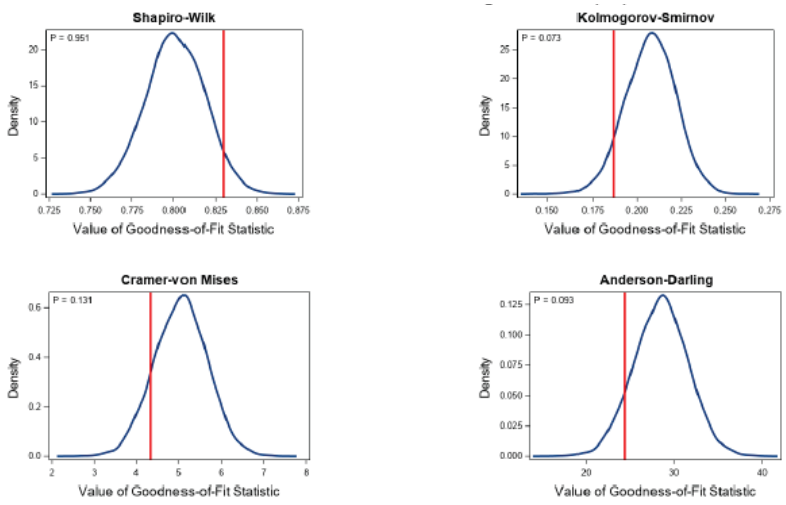
**Figure 4: model Visual Predictive Check (Semi-log plot)**




N=1000 bootstrap resampled trials are shown with data and final model predictions

Concordance between the predicted and observed plasma concentrations in the study was evaluated using the following goodness of fit tests: Shapiro-Wilks, Kolmogorov-Smirnov, Cramer-von-Mises and Anderson-Darling. There was no evidence to suggest, at the 5% significance level, that observations and model predictions were drawn from different distributions (**Figure 5**). It was therefore concluded that the existing population PK model was able to accurately predict 100 mg SC mepolizumab plasma concentrations in participants with nasal polyposis.

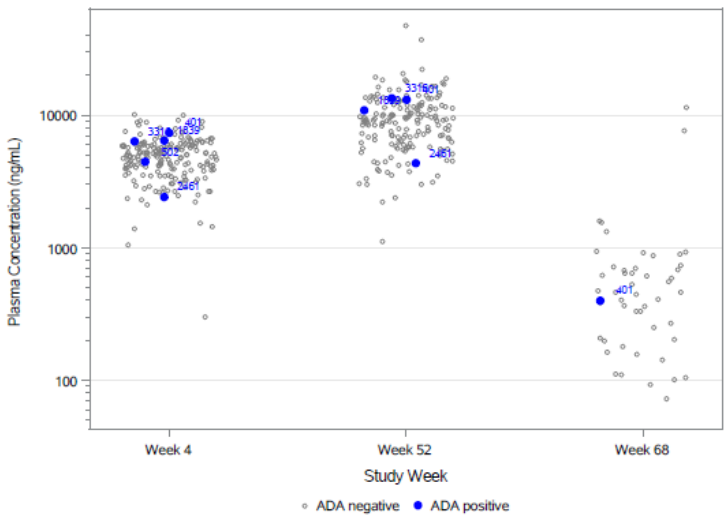
**Figure 5: PK Model Goodness of fit Statistics Showing Observation (red)**




Distributions derived from 10000 bootstrap simulations of the model predictions

Three participants (2%, 3/187) in the placebo group and 6 participants (3%, 6/196) in the mepolizumab group tested positive for ADAs at the Week 52 or EW visits. From these groups, one participant (1%, 1/183) in the placebo and 6 participants (3%, 6/196) in the mepolizumab group tested positive for emergent ADAs. None of the participants were positive for NAbs. There was no evidence that anti-drug antibodies influenced mepolizumab exposure (**Figure 6**).

**Figure 6: Plasma Mepolizumab Observed Concentration – Time Profiles (ADA Positive versus ADA Negative Subjects)**

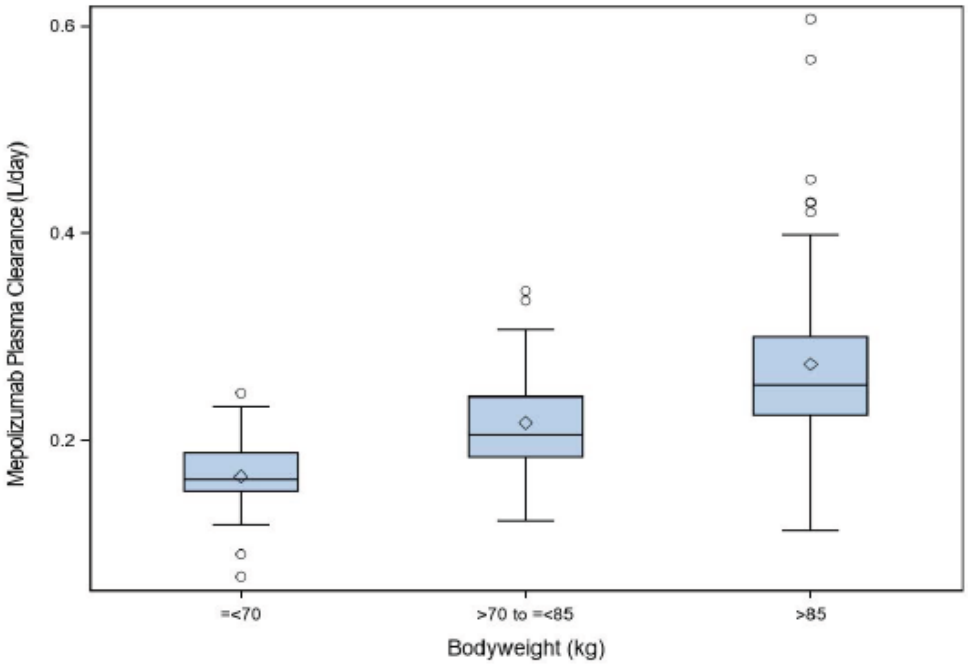



## *Special populations*

No conventional clinical pharmacology studies were conducted due to the nature of the molecule, its mechanism of action and elimination pathways. Dose adjustments in special populations other than children (i.e., elderly, renal- and hepatic-impaired subjects) are not required.

Age, race, gender and disease have not been identified as covariates of mepolizumab exposure across indications. In the population PK analysis (Study 205687), there was an increase in clearance was noted with increasing bodyweight in adults with CRSwNP. Systemic clearance (CL) by bodyweight category defined as ≤70 kg, >70 to ≤85 kg and >85 kg is presented **Figure 7**.

**Figure 7: Box Plot of Systematic Clearance versus Bodyweight**




The effect of bodyweight on mepolizumab exposure was comparable with the previous population PK model; the predicted exposure ratio for 40 vs. 70 kg was 1.47 (95% CI 1.17, 1.84), 70 vs. 120 kg was 0.69 (95% CI 0.55, 0.86) and 70 vs. 160 kg was 0.57 (95% CI 0.40, 0.79).

**Appendix**
**Table 3: Summary of Patient Covariate in Meta-analysis (from Various Eosinophilic Conditions)**

| Pharmacokinetic Parameter | Covariate | Effect when covariate is doubled/halved (IV) |
|---|---|---|
| Clearance | Weight (BWT) | $CL=0.212\times(BWT/70)^{0.75}$<br>68% increase/41% decrease |
| | Albumin (ALB) | $CL=0.212\times(ALB/44)^{-0.496}$<br>29% decrease /41% increase<br>Not measured for CRSwNP |
| | Creatinine clearance (CrCL) | $CL=0.212\times(CrCL/112)^{0.123}$<br>9% increase/8% decrease |
| Volume of central compartment (L) | Weight (BWT) | $V2=3.46\times(BWT/70)^{1}$<br>100% increase/50% decrease |
| Volume of peripheral compartment (L) | Weight (BWT) | $V3=2.18\times(BWT/70)^{1}$<br>100% increase/50% decrease |

## *Pharmacokinetic interaction studies*

No interaction studies have been performed. The potential for drug-drug interaction is deemed low because IL-5 does not signal via hepatocytes.

### 2.3.1. Pharmacodynamics

## *Mechanism of action*

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa) that blocks interleukin-5 (IL-5) from binding to the IL-5 receptor complex expressed on the eosinophil cell surface and thus inhibits signaling, resulting in the reduction in production and survival of eosinophils.

Nasal polyposis is an eosinophil-mediated disease; eosinophils are the most common infiltrating inflammatory cells in nasal polyps with eosinophils being prominent in over 80% of polyps in European nasal polyposis patients [Fokkens, 2007; Stoop, 1993]. Overproduction of IL-5 has been reported in patients with a variety of eosinophilic associated disorders; therefore, anti-IL-5 therapy is a potential therapeutic target for the treatment of eosinophil-mediated diseases such as nasal polyposis.

## *Primary pharmacology*

**Study MPP111782**

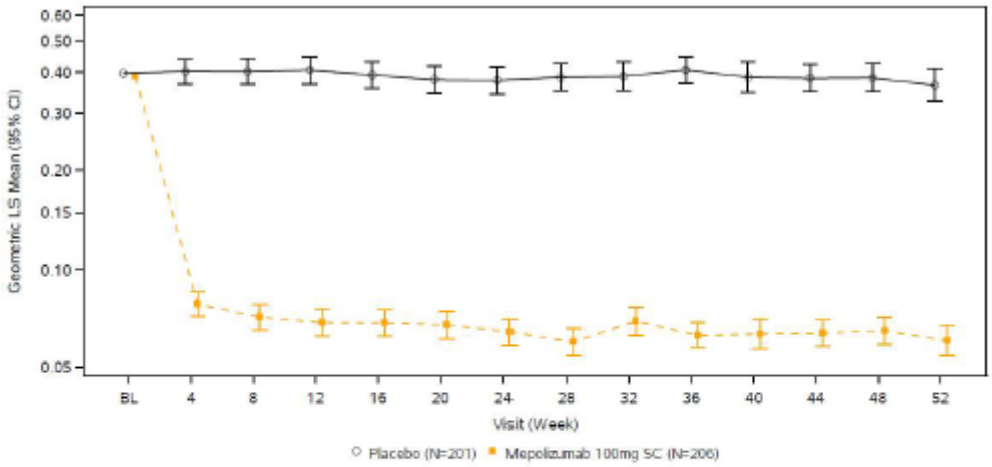
A marked decrease in eosinophils in the mepolizumab group was observed over the course of the study, which was apparent as early as Week 2. At Week 25, the median ratio to baseline was 0.10 for mepolizumab and 0.93 for placebo.

**Study 205687**

In adult subjects with CRSwNP from the pivotal Phase III study 205687, geometric mean blood eosinophil counts at baseline were similar in both treatment groups (0.39 GI/L and 0.40 GI/L in the mepolizumab and placebo groups, respectively). In the mepolizumab group, the geometric mean blood eosinophil count was reduced to 0.08 GI/L by Week 4 and remained at this level until Week 52 (0.06 GI/L).

The reduction in blood eosinophil counts was statistically significantly greater in the mepolizumab group compared with the placebo group at every 4-week timepoint, with an 81% reduction at Week 4 (ratio: 0.19, 95% CI: 0.17, 0.22; p<0.001) which was maintained through an 83% reduction at Week 52 (ratio: 0.17, 95% CI: 0.14, 0.19; p<0.001) (**Figure 8**).

**Figure 8: On-Treatment Blood Eosinophils (GI/L) Absolute Values (Study 205687, ITT Population)**




[redacted]

Note: Baseline (BL) represents geometric means based on actual data, all other visits represent geometric LS means.

Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, visit, baseline log(e) blood eosinophil count plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Note: For blood eosinophil counts of 0 the log transformation was based on a value of 0.005.

### *Secondary pharmacology*

Mepolizumab does not bind to the hERG channel and QT-mediated proarrhythmia due to blockade is not a concern with mAbs due to their very high molecular weight. In clinical studies there were no adverse effects on cardiac conduction or repolarisation at doses in excess of the proposed marketed dose in the various indications. Furthermore, a concentration-response analysis did not show any effects of mepolizumab on QT interval corrected for heart rate (QTc). A thorough QTc study has not therefore been conducted.

## 2.3.2. PK/PD modelling

**Study MPP111782**

A total of 104 subjects contributed 673 pharmacodynamic samples.

An Imax direct response model was fitted to serial blood eosinophil count data from both mepolizumab and placebo treatment using model-predicted mepolizumab concentrations, on account of the rapid eosinophil dynamics (compared with PK). Consistent with previous analyses, baseline blood eosinophil count was included as the only covariate and baseline and maximum inhibitory effect were modelled as random effects. The concentration associated with 50% of the maximal effect (IC50) was estimated at 4.4 µg/mL and maximum inhibition at 90.1%.

The IC50 of 4.4 µg/mL is higher than estimates in previous analyses, which might reflect the higher baseline blood eosinophil count in this study that was observed in absence of inhaled and oral corticosteroids compared with previous studies in other eosinophilic conditions.

**Study 205687**

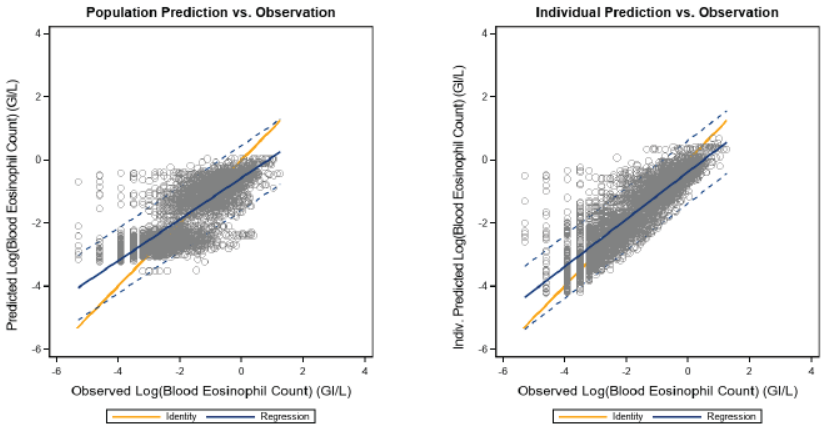
A PK/PD analysis was conducted to investigate whether the blood eosinophil response to mepolizumab treatment in patients with CRSwNP was consistent with the response observed in patients with other eosinophilic conditions. 407 adults with CRSwNP from the pivotal Phase III study 205687 were included in the PKPD dataset. Post-hoc individual predicted mepolizumab concentrations were merged with blood eosinophil count data before model fitting.

The most recent meta-analysis population PKPD model was applied directly to the dataset without parameter estimation. An additional class of nasal polyposis for the fixed effect of disease on baseline blood eosinophil count was, however, added to the model in order to capture more specifically the baseline blood eosinophil count in subjects with CRSwNP.

The impact of covariates on individual parameter estimates was examined graphically and formally using a forward/backward approach. No additional covariates beyond that already included in the model [baseline blood eosinophil count effect on baseline blood eosinophil count (KRO) and maximum effect (Imax)] were identified.

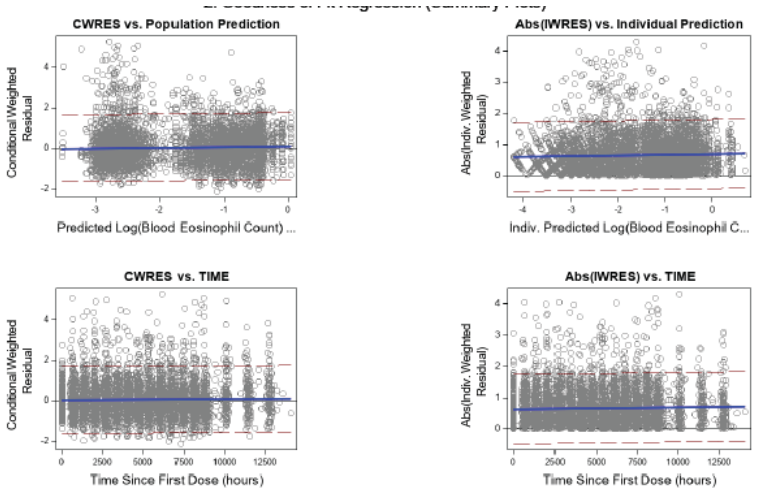
Goodness of fit plots are shown in **Figure 9**, **Figure 10 and Figure 11**

## Figure 9: Goodness of Fit Regression



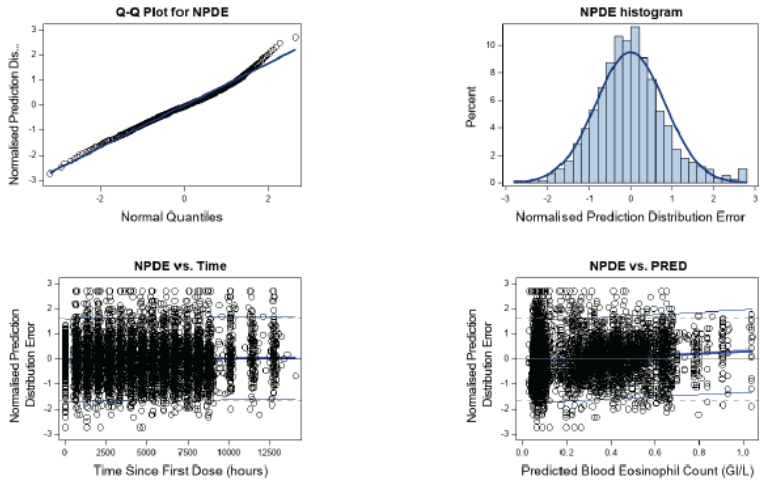

Plots show linear regression with 95% prediction interval (dashed lines)

## Figure 10: Goodness of Fit Regression (Summary Plots)




CWRES = Conditional weighted residuals, IWRES = Individual weighted residuals

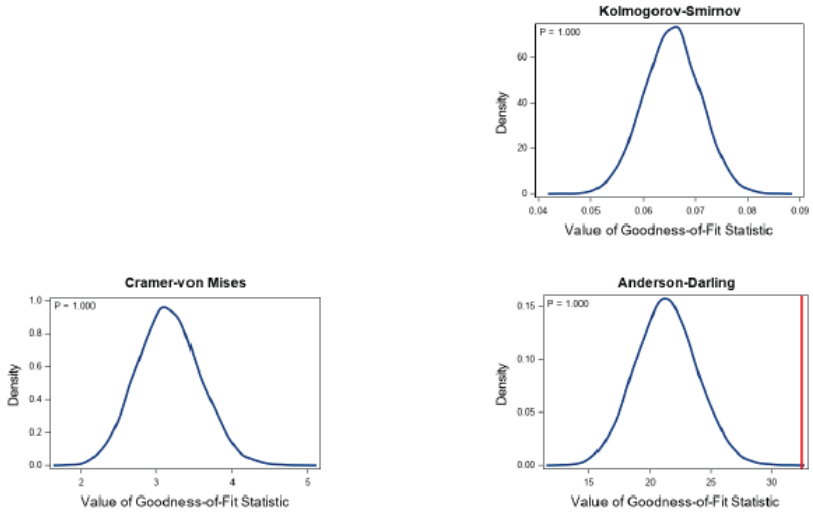
**Figure 11: Normalised Prediction Distribution Error**




Plots show linear regression (blue) with 95% prediction interval (dashed lines) and loess regression (red)

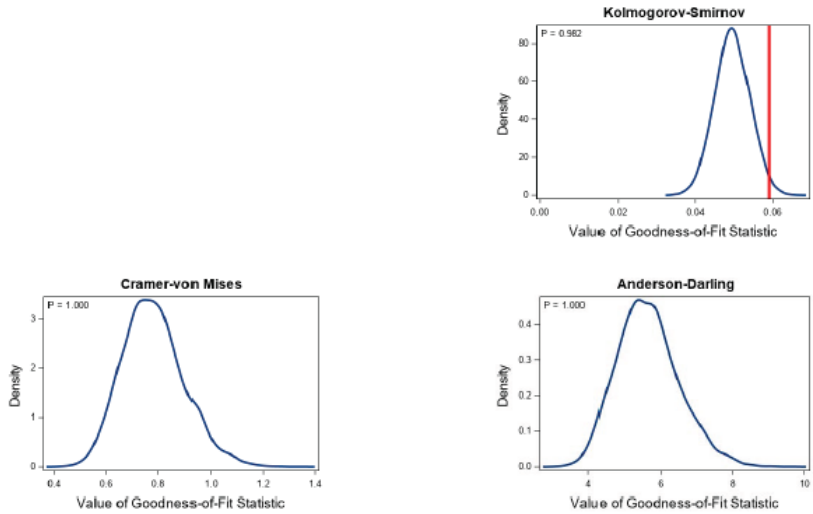
Concordance between the predicted and observed blood eosinophil counts in the study was evaluated using the following goodness of fit tests: Kolmogorov-Smirnov (location), Cramér–von Mises (tails of the distribution) and Anderson-Darling (tails of the distribution). In contrast to the PK analysis, there was evidence to suggest, at the 5% significance level, that observations and model predictions were drawn from different distributions (**Figure 12** and ***Figure 13***), possibly reflecting the different disease population and large sample size.

**Figure 12: Mepolizumab PKPD Model Goodness of fit Statistics Showing Observation (red)**




Distributions derived from 10000 bootstrap simulations of the model predictions

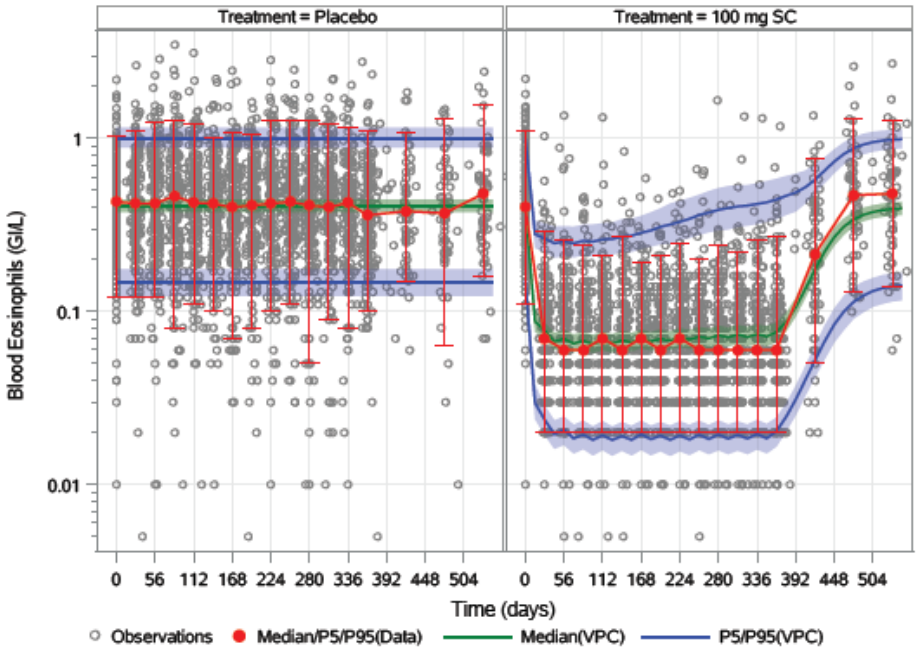
**Figure 13: Placebo PKPD Model Goodness of fit Statistics Showing Observation (red)**




Distributions derived from 10000 bootstrap simulations of the model predictions

However, based on the VPC analysis (**Figure 14**), it was concluded that the existing population PD model with adjustment for baseline, was able to adequately predict blood eosinophil counts in participants with nasal polyposis.

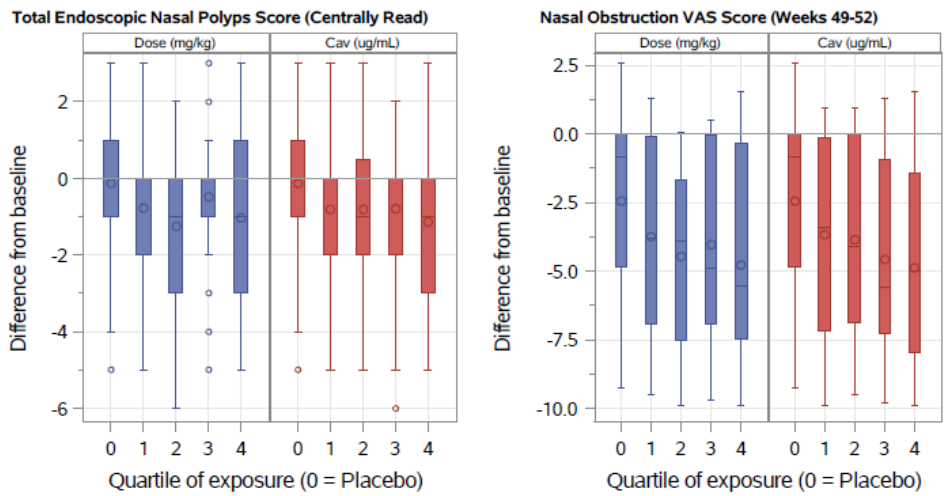
**Figure 14: Model Visual Predictive Check (Semi-log plot)**




**Exposure response analysis (Study 205687)**

Individual exposure, measured by both weight-based dose (i.e., mg/kg) and average concentration (defined as Cav = dose/(clearance(L/d) x 28day dosing interval)) was estimated from screening bodyweight and posterior-predicted individual clearance. Individuals were ranked by exposure quartile (0 = placebo, 1 – 4 for mepolizumab) and data merged with efficacy data for Total Endoscopic Score and VAS, and change from baseline plotted by exposure quartile (***Figure 15***). Analysis by quantile regression showed no significant effect of exposure on clinical response beyond treatment as a class effect, implying that mepolizumab exposure and blood eosinophil inhibition achieved by 100 mg SC Q28D is optimal for response.

**Figure 15: Exploratory Exposure-Efficacy Response Box Plots**



## 2.3.3. Discussion on clinical pharmacology

The clinical development program for CRSwNP consists of the pivotal Phase III study, 205687, with supportive data from the Phase II study MPP111782.

Bioanalytical methods

For clinical studies 205687 and MPP111782, plasma concentrations of mepolizumab were determined using the same methods as were used during the initial MAA procedures for the lyophilised and liquid formulations. All samples were analyzed within the demonstrated storage stability parameters established in GSK and Alliance Pharma. The sample analysis reports confirm acceptable assay performance. The results of incurred samples reanalysis confirm the acceptability and reproducibility of the assays (at least two thirds of re-assayed samples were within ± 30% of their initial result). No sample was repeated in the study 205687. The MAH had requested confirmation reanalysis for 23 study samples from the study MPP111782. However, due to the constraints of established stability parameters, 12 of these samples were not able to be repeated. Eleven samples out of 572 samples were repeated to confirm results. This approach is fully acceptable as this study MPP111782 is not bioequivalence study and thus is not threatened by suspicious adjustment of results.

For clinical studies 205687 and MPP111782, ADA were determined using the same method(s) used during the initial MAA procedures for the lyophilised and liquid formulations. The sample analysis reports are provided for the clinical studies and confirm acceptable assay performance. For analysis of samples from clinical study 205687, 39 out of 43 runs met the acceptance criteria. For analysis of samples from MPP111782, 25 out of 28 runs met the acceptance criteria.

For clinical study 205687, 917 sample results are reported. 126 samples screened positive (screening positive rate of 13.7%) and 16 samples confirmed positive (true positive rate of 1.7%). Titers were established for the confirmed positive results.

For clinical study 200622, 494 sample clinical sample results are reported. 59 samples screened positive (12%) and 9 samples confirmed positive (1.8%). Titers were determined for confirmed positive results. The sample analysis report for MPP111782 briefly details the determination of in-study cut points from 50 pre-dose subjects. A standard approach was taken for derivation of cut points. Details of removal of outliers and assessment of normality are provided. A fixed screening cut point was derived based on the upper 95% prediction interval (5% false positive rate) and a 0.1% titration cut point was established.

Given the drug concentrations in the immunogenicity sampling time points for clinical trial MPP111782, the ADA assay demonstrates sufficient drug tolerance to detect ADA. Only 7 out of 53 subjects had immunogenicity samples that contained greater than 100 μg/ml mepolizumab (drug tolerance of the assay) and the applicant describes only one potential false negative. The drug concentrations in the immunogenicity sample time points are presented for study 205687 and serum levels of mepolizumab were below the tolerance of the assay.

The measurement of NAb for clinical study 205687 was carried out using the electrochemiluminescent (ECL) method M1707047 (version 3). Appropriate assay validity criteria have been defined for the method. In general, the method has been validated in line with the Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 rev.1) and the Guideline on Immunogenicity assessment of biotechnology-derived therapeutic proteins (EMEA/CHMP/BMWP/14327/2006). Data has been presented to support the specificity and selectivity (lack of matrix interference) for the method. This assay has similar sensitivity and improved drug tolerance with reference to the previously used assay. The screening assay cut point was determined using 50 normal human serum samples. A standard approach was taken for derivation of cut point. Details of removal of outliers and assessment of

normality are provided. A fixed screening cut point (85.75%) was derived using the parametric method (1% false positive rate).

For clinical study 205687, 16 ADA positive samples were screened to assess for Nab. A total of 1 run was analysed and met the assay acceptance criteria confirming acceptable assay performance. All 16 samples were determined to be negative for NAbs.

The measurement of NAb for clinical study MPP111782 was carried out the same NAb assay as was used for the original lyophilisate and liquid formulations. Using 50 pre-dose individuals from study MPP111782 a fixed screening cut point was determined. A standard approach is described for derivation of the cut point. Based on a one-sided low 99% prediction interval, and the exclusion of high CV samples, the in-study assay cut point of (87.46%) was established. The method for exclusion of outliers is described and is acceptable.

The NAb assay is susceptible to drug interference. Earlier time points during ADA sampling demonstrated drug concentrations greater than 10 μg/ml mepolizumab. Confirmed ADA positive samples would likely be negative in the NAb assay of such samples. Across the entire mepolizumab clinical program, only one participant was positive for neutralising antibodies (study MEA115575) and this individual did not have detectable levels of drug in their serum samples (due to reduction in free drug as a result of the strong ADA response). Thus, it is argued that while the NAb assay has limited drug tolerance it is sufficient to detect neutralising antibodies in the event of a strong ADA response. Taking into account the low immunogenicity of mepolizumab (low % confirmed ADA positive samples), this point will not be further pursued.

Study MPP111782

Mepolizumab 750 mg IV demonstrated expected PK in adults with severe bilateral NP, supporting the view that disease is not a covariate of mepolizumab exposure. No subjects treated with mepolizumab developed anti-drug antibodies, which is consistent with the low immunogenic potential of mepolizumab observed in other indications.

There was a profound reduction in blood eosinophil count with similar maximum inhibition of 90.1% as previously observed in other eosinophilic conditions.

Study 205687

After mepolizumab SC dose of 100 mg was administered to adult subjects with CRSwNP, mepolizumab PK data was analysed using the most recent meta-analysis population PK model without modification and without parameterisation. No additional covariates beyond those already included in the model (body weight, creatinine clearance) were identified. The analysis showed that the PK of mepolizumab in adults with CRSwNP is consistent with that of patients with other eosinophilic conditions and that CRSwNP disease is not a determinant of mepolizumab exposure.

6 participants (3%, 6/196) in the mepolizumab group tested positive for emergent ADAs and had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab. None of the participants were positive for NAbs. There was no evidence that anti-drug antibodies influenced mepolizumab exposure. The findings support the low immunogenic potential of mepolizumab however, this information is provided to the prescribers in section 5.1. of the SmPC.

Mepolizumab 100 mg SC in adult patients with CRSwNP resulted in a marked reduction in blood eosinophils early in treatment, which was sustained throughout the study. The magnitude of blood eosinophil count reduction was consistent with subjects with other eosinophilic conditions.

The most recent meta-analysis population PK/PD model was applied directly to the PK/PD data collected from adults with CRSwNP in study 205687, without adjustment except for a fixed effect

disease parameter for baseline blood eosinophil count to better capture the baseline in subjects with nasal polyposis. The GOF plots indicated that, in contrast to PK, the PKPD model did not fit the CRSwNP data particularly well, which was confirmed by the GOF statistical tests. This suggests that the PD response to mepolizumab in subjects with CRSwNP may not be similar to other eosinophilic conditions. The VPC showed that the model predicted the reduction in eosinophil count with mepolizumab treatment reasonably well, but there appears to be a tendency for over prediction of eosinophil counts. Thus, the applicant's conclusion that the existing model adequately predicts blood eosinophil counts in participants with nasal polyposis is not necessarily agreed. However, a single dose level was tested in the pivotal phase III study and no extrapolation to any other dose level or patient population is foreseen. Therefore, this issue is not pursued as it is unlikely to impact on the benefit risk assessment.

Based on the exposure response analysis, at the single dose of 100 mg SC Q4W investigated in the study 205687, there was no evidence of increased efficacy with increased mepolizumab exposure (individual weight-based dose or average plasma concentration).

Special populations

It is agreed that dose adjustments in special populations (i.e., elderly, renal- and hepatic-impaired subjects) are not warranted for adult patients with nasal polyposis. It is also agreed that a dose adjustment based on body weight is not warranted for adult patients with nasal polyposis. Despite a decrease in mepolizumab exposure with increasing body weight, the magnitude of the effect in adults with CRSwNP was comparable to other indications and not considered to be clinically relevant. This is supported by the efficacy exposure response analysis, which showed that mepolizumab exposure is not a significant predictor of clinical response in CRSwNP after adjusting for treatment effect.

### 2.3.4. Conclusions on clinical pharmacology

The clinical pharmacology of mepolizumab has been sufficiently characterised for the extension of indication to include Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) in adults.

## *2.4. Clinical efficacy*

As mentioned earlier, the clinical development program for CRSwNP consists of the pivotal Phase III study, 205687, with supportive data from the Phase II study MPP111782 (**Table 4**).

**Table 4:** CRSwNP Studies with Mepolizumab

| Study | Primary/ Secondary Objectives | Study Design | Target Patient Population | Dosing Regimen | Study Status Location |
|---|---|---|---|---|---|
| **Pivotal Phase III Study** | | | | | |
| 205687 | E/ E, S, HRQoL, PK | R, PC, DB | Adult participants with severe, bilateral NP (CRSwNP) despite treatment with current SoC, a history of at least one prior surgery for NP, and in current need of NP surgery. | 100 mg mepolizumab SC q4W for 52 weeks Placebo=201 Mepolizumab=206 | Report completed m5.3.5.1 |
| **Supportive Phase II Study** | | | | | |
| MPP111782 | E/ E, S, PK, PD | R, PC, DB | Adult participants with severe, bilateral NP (CRSwNP) despite treatment with current SoC, a history of at least one prior surgery for NP, and in current need of NP surgery. | 750 mg mepolizumab IV q4W for 24 weeks Placebo=51 Mepolizumab=54 | Report completed m5.3.5.1 |
| **Investigator Led Study** | | | | | |
| CRT110178 | E/ E, S | R, PC, DB | Adult participants with severe CRSwNP (grade 3 or 4)[a] or NP that were recurrent after surgery (grade 1-4)[a] refractory to corticosteroid therapy. | 750 mg mepolizumab IV q4W for 8 weeks Placebo=10 Mepolizumab=20 | Completed [Chyba: zdroj odkazu nenalezen, 2011] |

Abbreviations: CRS= chronic rhinosinusitis, DB=double-blind; E=efficacy; IV=intravenous; HRQoL=health-related quality of life; NP=nasal polyps; PC=placebo-controlled; PK=pharmacokinetics; R=randomised; S=safety; SC=subcutaneous; SoC=standard of care.

a. CRSwNP was graded based on polyp size: 0, no polyps; 1, small polyps in the middle meatus not reaching below the inferior border of the middle concha; 2, polyps reaching below the lower border of the middle turbinate; 3, large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; and 4, large polyps causing complete obstruction of the inferior meatus [Chyba: zdroj odkazu nenalezen, 2011].

## 2.4.1. Dose response study

No dose response studies were conducted.

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

- Clinical efficacy of mepolizumab in participants with NP has only been investigated at a supra-pharmacological dose of 750 mg IV Q4W to date, although participants were followed for six months of washout.
- Two studies in participants with severe asthma MEA112997 and MEA114092 provided evidence of a dose response to suppression of blood eosinophil count.
- In study MEA112997, the lowest dose of 75 mg IV (equivalent to the proposed 100 mg SC dose) gave 78% inhibition.
- Higher doses of 250 mg IV and 750 mg IV provided only modest increases in suppression (86% and 88%, respectively) indicating that the lowest dose provides approximately 90% of maximal pharmacological response attributable to drug.

A subsequent clinical pharmacology study MEA114092 confirmed equivalence of the SC route of administration and identified the half-maximal pharmacological dose of 11 mg SC, consistent with study MEA112997.

The approved severe asthma dosing regimen of 100 mg SC dose Q4W provides 55% overlap with 750 mg IV data when given 4-weekly.

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

There was no dose-response study in the clinical development.

## 2.4.2. Main study

**Title of Study : Study 205687 (Synapse)**

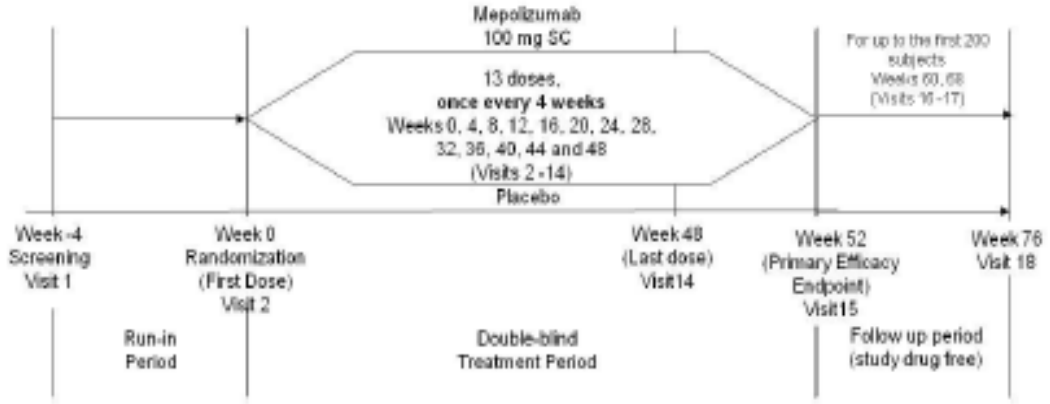
A randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab)

***Methods***

This was a randomised, double-blind, placebo-controlled, parallel group study to assess the clinical efficacy and safety of 100 mg SC mepolizumab as an add-on to maintenance treatment in adults with CRSwNP.

The objective was to evaluate the safety and efficacy of mepolizumab 100 mg, administered SC by the Investigator or delegate via a pre-filled safety syringe every 4 weeks for 52 weeks. The co-primary endpoints were change from baseline in endoscopic NP score at Week 52 and change from baseline in nasal obstruction VAS symptom score during the 4 weeks prior to Week 52.

**Figure 16: Study Schematic**




The study comprised of a 4-week run-in period, followed by a 52-week treatment period (**Figure 16**). Participants received a total of thirteen, 4-weekly doses of mepolizumab 100 mg or placebo, delivered by SC injection using a pre-filled safety syringe. The final dose of study treatment was administered at Week 48. Participants who withdrew from study treatment prematurely were encouraged to remain in the study per protocol until Week 52. Participants who completed the Week 52 assessment were considered to have completed the study.

In addition, it was planned for up to the first 200 randomised participants to enter a 6-month no-treatment follow-up period following their Week 52 visit in order to assess maintenance of response and to validate a physiological model derived from the previous Phase II study (MPP111782). Participants who completed the Week 76 visit were considered to have completed the no treatment follow-up period.

A total of 86 sites in 11 countries randomised participants: 24 sites in the United States (US), 11 sites in Argentina, 9 sites in Germany, 9 sites in the Russian Federation, 8 sites in the United Kingdom (UK), 7 sites in Canada, 5 sites in Sweden, 4 sites in Australia, 4 sites in the Republic of Korea, 4 sites in Romania and 1 site in the Netherlands. This study was initiated on 25 May 2017 (first participant first visit [FPFV]) and completed on 11 December 2019 (last participant last visit [LPLV]).

## Study participants

**Main Inclusion criteria**

- 18 Years and older, body weight greater or equal to 40 kgs.
- Participants who have had at least one previous surgery in the previous 10 years for the removal of NP. NP Surgery is defined as any procedure involving instruments with resulting incision (cutting open) and removal of polyp tissue from the nasal cavity (polypectomy).
- Participants with bilateral NP as diagnosed by endoscopy or CT scan
- Presence of at least two of the following symptoms one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip) and either nasal discharge (anterior/posterior nasal drip); facial pain/pressure; reduction or loss of smell for at least 12 weeks prior to screening
- Participants with severe NP symptoms defined as an obstruction VAS symptom score of >5

- Severity consistent with a need for surgery as described by:
  Participants with an overall VAS symptom score >7
  Participants with an endoscopic bilateral NP score of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity)
- Treatment with INCS for at least 8 weeks prior to screening

**Main exclusion criteria**

- Cystic fibrosis
- Eosinophilic granulomatosis with polyangiitis (also known as Churg Strauss syndrome), Young's, Kartagener's or dyskinetic ciliary syndromes

- Antrochoanal polyps
- Nasal septal deviation occluding one nostril
- Acute sinusitis or upper respiratory tract infection (URTI) at screening or in 2 weeks prior to screening
- Ongoing rhinitis medicamentosa (rebound or chemical induced rhinitis)
- Participants who have had an asthma exacerbation requiring admission to hospital within 4 weeks of Screening.
- Participants who have undergone any intranasal and/or sinus surgery (for example polypectomy, balloon dilatation or nasal stent insertion) within 6 months prior V1
- Participants where NP surgery is contraindicated in the opinion of the Investigator

- Participants on a waiting list for NP surgery while at screening
- Participants that have taken part in previous mepolizumab, reslizumab, dupilumab or benralizumab studies.

- Rapidly progressing disease or immediate life-threatening illness (e.g. cancer).

- Clinically significant medical conditions such as endocrine, autoimmune, cardiovascular, metabolic, neurological etc.

- Immuncompromised, unstable liver disease, QTc prolongation

**Treatments**

All participants were on SoC for CRSwNP throughout the study (run-in, treatment and no-treatment follow-up periods), which consisted of daily mometasone furoate nasal spray (MF), and if required, saline nasal douching, occasional short courses of high dose OCS and/or antibiotics. At the start of run-in and throughout the study, participants were placed on MF at the maximum prescribed dose (if not already) according to local label, if available, or in line with local SoC. The maximum dose was 2 actuations (50 mcg/actuation) in each nostril twice daily which equalled a total daily dose of 400 mcg. For participants intolerant to this dose, the lower dose of 200 mcg could have been used (2 actuations [50 mcg/actuation] in each nostril once daily).

**Concomitant medications excluded:**

Information on excluded concomitant treatments is provided in table below:

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

A description of the mepolizumab investigational product characteristics and matching placebo is provided in here:

| | Study Treatment | |
|---|---|---|
| **Product name:** | Mepolizumab Injection, 100 mg/mL | Placebo to match Mepolizumab Injection |
| **Device:** | Safety syringe | |
| **Formulation description:** | 100 mg/mL mepolizumab with sodium phosphate, citric acid, sucrose, Disodium EDTA, Water for Injection and polysorbate 80 | 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) | 1.0 mL (deliverable) |
| **Route of administration** | SC injection | |
| **Dosing instructions:** | SC dose in thigh, abdomen or upper arm every 4 weeks | |
| **Physical description:** | 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 IP 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 IP solution and assembled into a safety syringe device at GSK, Barnard Castle, UK. | |
| **Batch numbers:** | C783568, C785941, C812060, C816670, C824058 | C789815, 8V7E, AM6D |

Abbreviations: IP=investigational product; SC=subcutaneous.

**Permitted Medications**

Permitted SoC medication for CRSwNP, which was provided to participants by the site, was INCS (MF) and oral OCS (prednisolone, prednisone or methyl-prednisolone).

Concomitant use of leukotriene receptor antagonists and allergen immunotherapies were permitted, but their use could not be initiated or the dosing regimen changed between screening and end of the study. Changes in the dosing regimen of INCS from screening to end of the study was also not allowed.

The following medications were permitted for all participants:

1. Short courses of high doses of OCS (dose and duration as per SoC for CRSwNP).
2. Throughout the study, participants with asthma were maintained on their baseline SoC asthma treatment.
3. The use of rescue medications such as OCS was allowable at any time during the study.
4. Antibiotic treatment for CRSwNP.

## Objectives

Primary objective : To evaluate the efficacy of 100mg mepolizumab compared to placebo

## Outcomes/endpoints

Primary endpoint :

- Change from baseline in total endoscopic NP score at week 52
- Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to week 52.

Secondary endpoints

- Time to first nasal surgery up to week 52.
- Change from baseline in mean overall VAS symptom score during the 4 weeks prior to week 52.
- Change from baseline in SNOT-22 total score at week 52.
- Proportion of participants requiring systemic steroids for nasal polyps up to week 52.
- Change from baseline in the mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) during the 4 weeks prior to week 52.
- Change from baseline in the mean individual VAS symptom score for loss of smell during the 4 weeks prior to week 52.

**Endoscopic nasal score**

Endoscopic NP assessment was performed at the site by trained heath care staff (usually an ear, nose and throat [ENT] surgeon). The image recordings of these nasal endoscopies were sent to a central lab for blinded assessment by a centralised team of qualified and experienced ENT surgeons.

For endoscopies conducted at Screening, Randomisation (Baseline) and Week 52 (the primary endpoint), two independent members of the centralised team reviewed and recorded an endoscopic nasal polyp score. If the scores were in agreement, this value was considered the final score for the central read. If the scores were not in agreement, a third assessor was consulted and this adjudicator would decide between the two assessor's scores to provide a final score.

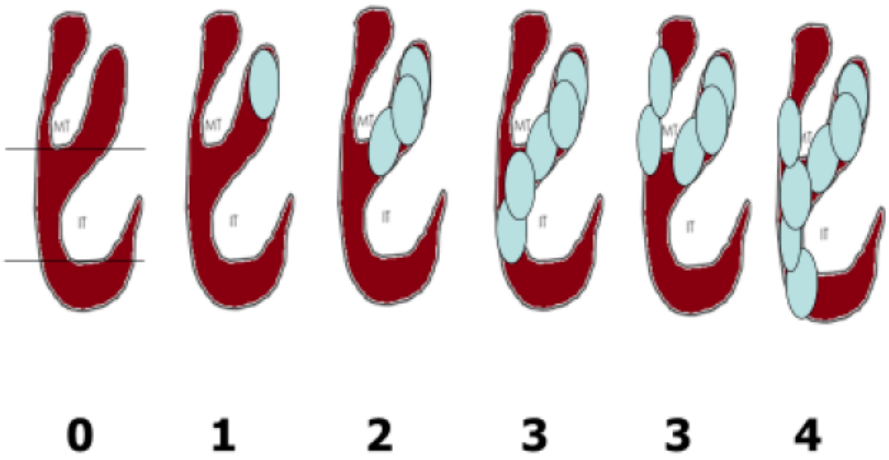
The total endoscopic NP score was the sum of the right and left nostril scores, with a range of 0-8; higher scores indicating worse status. A responder was defined as a participant who, in the absence of surgery/sinuplasty, achieved a ≥1-point improvement (decrease) from baseline in total endoscopic NP score (based on centrally read data) at a given timepoint.

For the purposes of randomisation, the site was notified if the central read of the Screening assessment was scored at ≥5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity) (i.e. if the participant met the inclusion criteria).

**Table 5: Description of Nasal Polyp Score**

| Polyp Score | Polyp Size |
|---|---|
| 0 | No polyps. |
| 1 | Small polyps in the middle meatus not reaching below the inferior border of the middle concha. |
| 2 | Polyps reaching below the lower border of the middle turbinate. |
| 3 | Large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha. |
| 4 | Large polyps causing almost complete congestion/obstruction of the inferior meatus. |

**Diagrammatic Representation of Nasal Polyp Score**




Abbreviations: IT= inferior turbinate; MT= middle turbinate.

**Symptoms Visual Analogue Scale (VAS)**

A VAS was used to collect participant perceived symptom data for the co-primary endpoint of nasal obstruction. VAS was also used to collect data on overall symptoms (a secondary endpoint), loss of smell (a secondary endpoint), nasal discharge, mucus in the throat and facial pain.

The nasal symptoms composite score, a secondary endpoint, combined the individual scores of nasal obstruction, nasal discharge, mucus in throat and loss of smell. The nasal symptoms and facial pain composite score, another endpoint, combined the individual scores of nasal obstruction, nasal discharge, mucus in throat, loss of smell and facial pain

All scales used in the study were presented on the eDiary and were collected daily in the morning from screening to the end of the study period. Participants were instructed on how to complete the VAS prior to first use.

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

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

*1. nasal obstruction; 2. nasal discharge; 3. feeling of mucus in the throat; 4. loss of smell; 5. facial pain; 6. nasal polyps symptoms.*

**Other endpoints**

**Nasal Polyp surgery**

As an endpoint, for the purpose of this study, NP surgery was defined as any procedure involving instruments resulting in incision and removal of tissue (polypectomy) in the nasal cavity. Dilatation of the air passages in the nasal cavity (e.g. balloon sinuplasty) was not included in this endpoint.

**Peak Nasal Inspiratory Flow (PnIF)**

Nasal peak inspiratory flow (NPIF) evaluation represents a physiologic measure of the air flow through both nasal cavities during forced inspiration expressed in liters per minute. A PnIF meter was used to derive forced inspiratory peak flow through the nose during the study according to the schedule of activities (SoA). PnIF was measured using an IN-CHECK flow meter.

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

UPSIT is a commercially available kit to measure an individual's ability to detect odours at a suprathreshold level. It is the gold standard of smell identification tests for its reliability and practicality.

**Health Related Quality of Life (HRQoL) Assessments**

- ***Sino-Nasal Outcome Test (SNOT-22) Questionnaire***

SNOT-22 is a 22-item self-reported questionnaire developed to measure symptoms and impacts related to chronic rhinosinusitis. The questions are self-completed by the participant based on their recall of their symptoms over the past 2 weeks. The possible response to each question ranges from 0 (no problem) to 5 (the problem is as bad as it can be). The score for each question is added to give the final SNOT-22 score, which has a theoretical range of 0 to 110, with a higher score indicating a greater impact of the disease state on the participant's health-related quality of life. The MCID for this instrument is a ≥ 8.9 change in SNOT-22 score.

- ***Asthma Control Questionnaire (ACQ-5)***

The ACQ-5 is a five-item questionnaire. The five questions enquire about the frequency and/or severity of symptoms over the previous week (nocturnal awakening due to symptoms, symptoms on waking in the morning, activity limitation, shortness of breath, and wheeze). The response options for all these questions range from 0 (no impairment/limitation) to 6 (total impairment/ limitation).

The score for each question is averaged to give the final ACQ-5 score, which has a theoretical range of 0 to 6. A score of ≤ 0.75 indicates well-controlled asthma and a score ≥1.5 indicates poorly controlled asthma. The MCID for this instrument is a ≥0.5 decrease in total score.

## Sample size

This study was designed to test the superiority of mepolizumab versus placebo.

The sample size calculations were based on the co-primary efficacy endpoints of total endoscopic nasal polyp score and nasal obstruction VAS score at Week 52 and the key secondary endpoint of time to actual surgery. A study of 200 participants per treatment group was estimated to have over 90%

power to observe statistical significance at the two-sided 5% level for both co-primary endpoints and for the key secondary endpoint of time to actual surgery.

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

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

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

**Randomisation**

The randomisation was stratified by country. Participants were assigned to study treatment through an interactive response technology (IRT), the Registration and Medication Ordering System Next Generation (RAMOS NG) in accordance with the randomisation schedule.

**Blinding (masking)**

Mepolizumab and placebo were identical in appearance (blinded, pre-filled safety syringes). Treatment was administered by a blinded member of the site staff. The blinding of those involved in the evaluation of the study, i.e., physician, nurse and participant was maintained at all times.

Post-randomisation, the site staff and central study team were blinded to each participant's eosinophil count (including white blood count differential).

Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the investigational product was essential for the clinical management or welfare of the participant. The MAH Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind treatment codes in the event of a serious adverse event (SAE).

**Protocol Amendments**

Four amendments were made to the protocol. Protocol Amendment 1 was made prior to FPFV (25 May 2017) and applied only to sites in South Korea. Protocol Amendments 2 and 3 were made after FPFV and applied to all sites. Protocol Amendment 4 was made after LPLV (11 December 2019) but before unbinding and related to the analysis of data.

- Protocol Amendment 1 was approved on 15 May 2017, before FPFV. The amendment was made to support country-specific requirements and amendments for South Korea. The changes included the IP label, provided additional clarification about the inclusion criteria age as per local regulations and provided details of OCS supplied for South Korea
- Protocol Amendment 2 was approved on 14 July 2017, 2 months after FPFV. The main purpose of this amendment was to reflect comments from investigators to clarify points in the protocol that might be confusing or inconsistent. In addition, it also reflected the removal of CT scans

and exit interviews as well as simplifying some of the endpoints such as reduction of endoscopic NP endpoints.

- Protocol Amendment 3 was approved on 20 February 2018, 9 months after FPFV. The purpose of this amendment was to clarify that screen failure could also be re-screened (not just run-in failures) and that the ECG machine did not need to be automated.
- Protocol Amendment 4 was approved on 13 February 2020, 2 months after LPLV and prior to unblinding. In order to reflect regulatory authority feedback, the protocol was amended to:

- update the analysis methodology for the co-primary endpoints, including imputation rules such that participants with surgery/sinuplasty prior to Week 52 were assigned their worst observed value (endoscopic NP score or nasal obstruction VAS score, as appropriate) prior to surgery/sinuplasty.

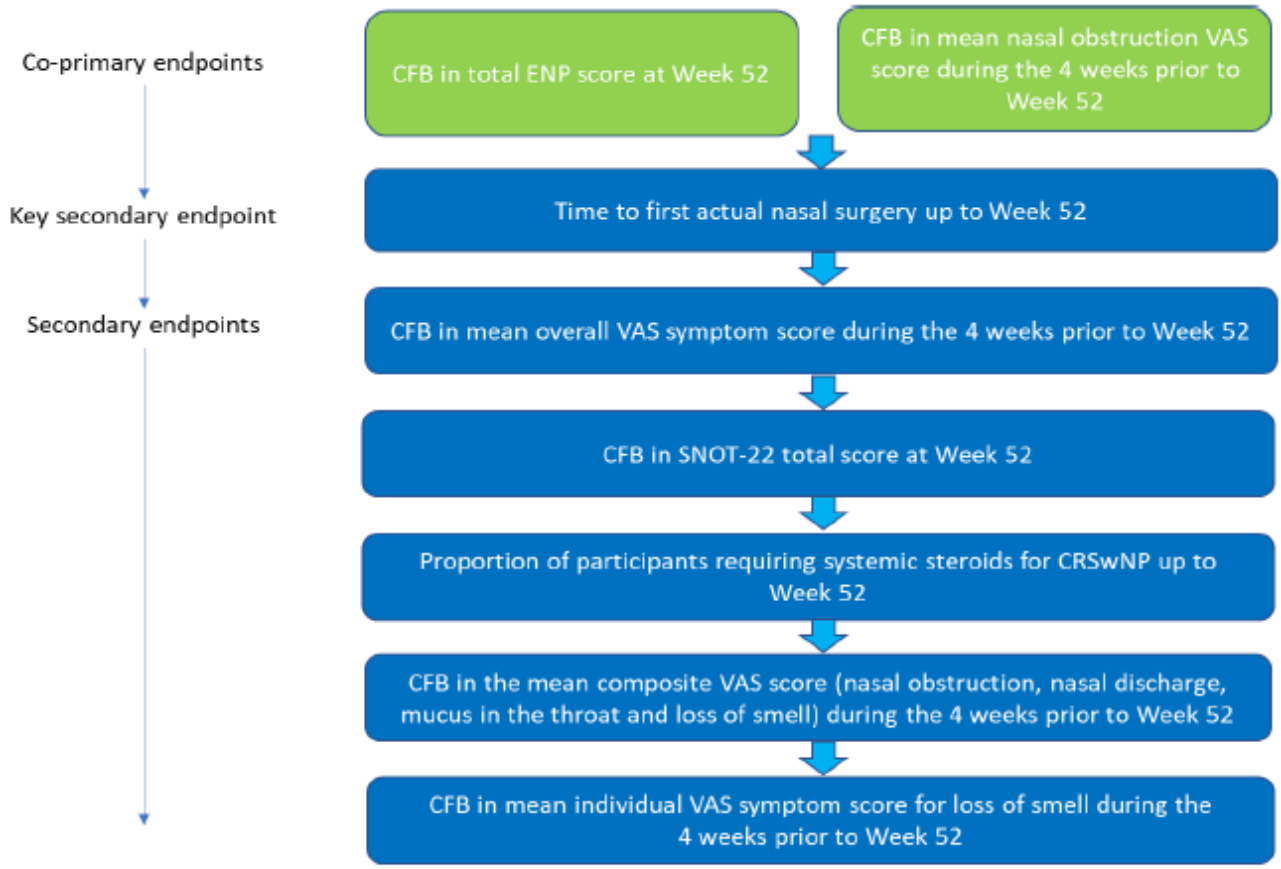
- limit the definition of surgery for the key secondary endpoint to include only events involving instruments resulting in incision and removal of tissue (polypectomy) in the nasal cavity. Dilatation of the air passages (e.g. balloon sinuplasty) if carried out alone were not considered as an event of surgery.

- update the OCS endpoint to the proportion of participants requiring systemic steroids for nasal polyps instead of the total burden of systemic steroids.

- include two additional secondary endpoints of composite nasal symptoms score and loss of smell symptom score that was previously included as 'other' endpoints.

## Statistical methods

Hierarchy of Endpoint Testing (Co-primary and Secondary Endpoints) Study 205687




CFB= change from Baseline; SNOT-22 = Sino-Nasal Outcome Test - 22 items; VAS=visual analogue scale

The primary estimand compared mepolizumab 100 mg SC to placebo for the co-primary endpoints of:

- Change from Baseline in total ENP 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

A composite strategy was used for the intercurrent event of surgery/sinuplasty, such that the occurrence of surgery/sinuplasty was incorporated into the definition of the endpoint.

Participants who had surgery/sinuplasty prior to Week 52 were assigned their worst observed score prior to the surgery/sinuplasty.

A treatment policy strategy was used for the intercurrent event of discontinuation of study medication.

The study was designed to continue collecting data for participants who prematurely discontinued from randomised treatment and all data reported were included in the primary analysis regardless of discontinuation from treatment. Missing data from participants who withdrew from study before Week 52 without having experienced surgery/sinuplasty; these participants were assigned their worst observed

Score prior to study withdrawal.

The Intent-to-Treat (ITT) Population was the primary population for efficacy analyses and consisted of all randomised participants who received at least one dose of study medication.

For each co-primary endpoint, the p-value for comparing the treatment groups was based on the non-parametric Wilcoxon rank-sum test. The difference in median change from Baseline with 95%

confidence intervals (CIs) was estimated by quantile regression using a bootstrap approach with covariates of treatment group, region, Baseline score and loge Baseline blood eosinophil count.

The key secondary efficacy endpoint, time to first nasal surgery up to Week 52, was analysed by a Cox proportional hazards model with covariates of treatment group, region, Baseline total ENP score (centrally read data), Baseline nasal obstruction VAS, $\log_e$

Baseline blood eosinophil count and number of previous surgeries for NP (1, 2, >2; ordinal). A treatment policy strategy was used for the intercurrent event of discontinuation of study medication.

Statistical Analyses of other secondary endpoints

- Change from Baseline in VAS symptom scores
- Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52
- Change from baseline in SNOT-22 total score at Week 52.
- Proportion of participants requiring systemic steroids for nasal polyps up to Week 52.
- Change from baseline in the mean composite VAS score (combining VAS scores for nasal obstruction, nasal discharge, mucus in the throat and loss of smell) during the 4 weeks prior to Week 52.
- Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52.

Change from Baseline in VAS symptom scores; Change from baseline in SNOT-22 total score at 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 and change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52 were analysed using non-parametric Wilcoxon rank-sum tests and Quantile regression methods.

For the analysis of the proportion of participants requiring systemic steroids for nasal polyps, a logistic regression model was used to compare the proportion of participants requiring a course of systemic steroids between the treatment groups. The odds ratio comparing treatment groups was estimated using the observed marginal distribution of the sample covariates. The analysis model included covariates of treatment group, region, number of OCS courses for NP in last 12 months (0, 1, >1; ordinal), baseline total endoscopic NP score (based on centrally read data), baseline nasal obstruction VAS score and $\log_e$ baseline blood eosinophil.

For the co-primary endpoints posthoc analyses were performed using a composite strategy for the intercurrent event of surgery where participants with surgery were assigned the worst possible score rather than their own worst observed score. Differences between treatments in mean scores were estimated using mixed model repeated measures (MMRM) and multiple imputation methods were used for missing data, firstly using missing at random (MAR) imputation and secondly imputing values using available 'off-treatment' data collected from participants who discontinued randomized treatment but continued in the trial.

## *Results*

All primary and secondary endpoints achieved statistical significance at the two-sided 5% level adjusted for multiplicity. In order to provide strong control of type I error when making inferences for the pre-defined secondary endpoints, multiplicity was controlled using a hierarchical closed testing approach.

**Table 6: Summary of Results for Primary and Secondary Efficacy Endpoints (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Co-Primary Endpoints** | | |
| **Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 (Section 6.1)** | | |
| n | 201 | 206 |
| Median change from baseline | 0.0 | -1.0 |
| p-value [a] | | <0.001 |
| Adjusted treatment difference in medians (95% CI) [b] | | -0.73 (-1.11, -0.34) |
| **VAS Nasal Obstruction Score (Weeks 49-52) (Section 6.2.1.1)** | | |
| n | 201 | 206 |
| Median change from baseline | -0.82 | -4.41 |
| p-value [a] | | <0.001 |
| Adjusted treatment difference in medians (95% CI) [b] | | -3.14 (-4.09, -2.18) |
| **Key Secondary Endpoint** | | |
| **Time to First Nasal Polyps Surgery (Section 6.3.1)** | | |
| Participants with surgery | 46 (23) | 18 (9) |
| Hazard ratio (Mepolizumab/Placebo) (95% CI) [c] | | 0.43 (0.25, 0.76) |
| Unadjusted p-value [c, d] | | 0.003 |
| Multiplicity adjusted p-value [c, d] | | 0.003 |
| **Other Secondary Endpoints** | | |
| **Overall VAS Score (Weeks 49-52) (Section 6.2.1)** | | |
| n | 201 | 206 |
| Median of the mean change from baseline | -0.90 | -4.48 |
| Unadjusted p-value [a, d] | | <0.001 |
| Multiplicity adjusted p-value [a, d] | | 0.003 |
| Adjusted treatment difference in medians (95% CI) [b] | | -3.18 (-4.10, -2.26) |
| **SNOT-22 Total Score at Week 52 (Section 6.4)** | | |
| n | 198 | 205 |
| Median of the mean change from baseline | -14.0 | -30.0 |
| Unadjusted p-value [a, d] | | <0.001 |
| Multiplicity adjusted p-value [a, d] | | 0.003 |
| Adjusted treatment difference in medians (95% CI) [b] | | -16.49 (-23.57, -9.42) |

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Participants Requiring Systemic Steroids for Nasal Polyps up to Week 52 (Section 6.5)** | | |
| Number of participants with ≥1 course | 74 (37) | 52 (25) |
| Odds Ratio to Placebo (95% CI) [e] | | 0.58 (0.36, 0.92) |
| Unadjusted p-value [d, e] | | 0.020 |
| Multiplicity adjusted p-value [d, e] | | 0.020 |
| **Composite VAS Score - Nasal Symptoms (Weeks 49-52) (Section 6.2.3.1)** | | |
| n | 201 | 206 |
| Median of the mean change from baseline | -0.89 | -3.96 |
| Unadjusted p-value [a, d] | | <0.001 |
| Multiplicity adjusted p-value [a, d] | | 0.020 |
| Adjusted treatment difference in medians (95% CI) [b] | | -2.68 (-3.44, -1.91) |
| **Loss of Smell VAS Score (Weeks 49-52) (Section 6.2.1.2)** | | |
| n | 201 | 206 |
| Median of the mean change from baseline | 0.00 | -0.53 |
| Unadjusted p-value [a, d] | | <0.001 |
| Multiplicity adjusted p-value [a, d] | | 0.020 |
| Adjusted treatment difference in medians (95% CI) [b] | | -0.37 (-0.65, -0.08) |

[redacted]

a. Based on Wilcoxon rank-sum test.
b. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
c. Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).
d. Multiplicity controlled through testing of endpoints following a pre-defined hierarchy.
e. Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.

**Populations Analysed**

A total of 414 participants were randomised (**Table 7**). Seven participants (2%) were randomised in error and did not receive a single dose of study treatment. The remaining 407 participants (98%) were included in the ITT and Safety Populations.

**Table 7: Summary of Study Populations (Study 205687)**

| Population | Not Randomised | Placebo | Mepolizumab 100 mg SC | Total |
|---|---|---|---|---|
| Enrolled | 440 | | | 854 |
| Randomised | | 207 | 207 | 414 |
| Intent-to-Treat (ITT) [a] | | 201 (97) | 206 (>99) | 407 (98) |
| Per-Protocol (PP) | | 187 (93) | 194 (94) | 381 (94) |
| Follow-Up after Week 52 (FU) | | 65 (32) | 69 (33) | 134 (33) |
| Pharmacokinetic (PK) | | 0 | 202 (98) | 202 (50) |
| Safety [a] | | 201 (100) | 206 (100) | 407 (100) |

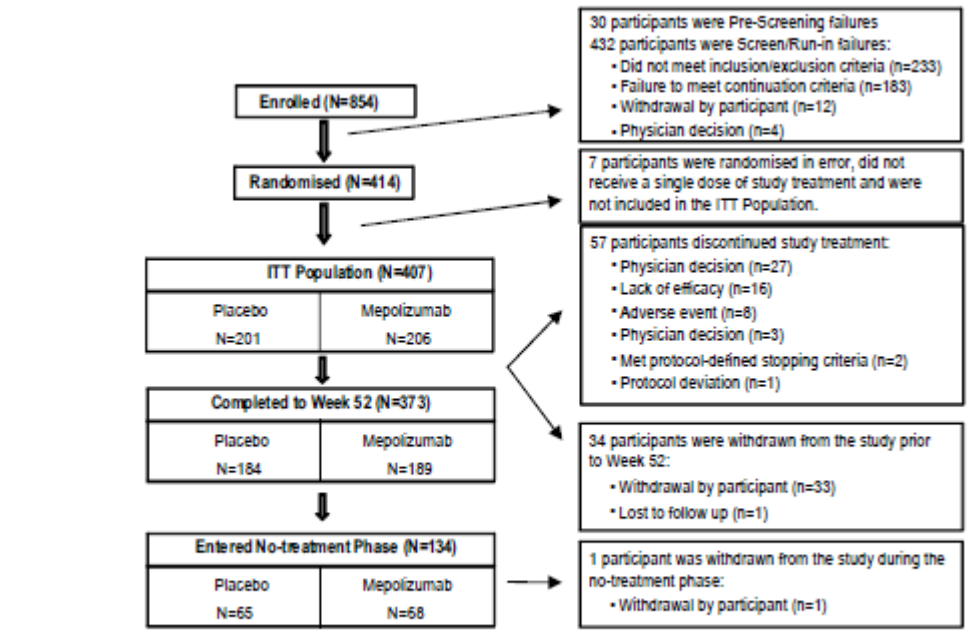
[redacted]

Note: Denominators for ITT are based on the number of participants randomised, all others are based on ITT.

a. Excludes randomised participants who did not receive any dose of IP.

## Participant flow

**Figure 17: Participant Disposition (Study 205687, Enrolled Population)**




[redacted]

Abbreviations: ITT=intent-to-treat.

**Table 8: Summary of Participant Disposition (Week 52) (Study 205687, ITT Population)**

| | Number (%) Participants | | |
|---|---|---|---|
| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) | Total (N=407) |
| **Participant Status** | | | |
| Completed to Week 52 | 184 (92) | 189 (92) | 373 (92) |
| Withdrawn Prior to Week 52 | 17 (8) | 17 (8) | 34 (8) |
| **Primary reason for study withdrawal [a]** | | | |
| **Subreason [b]** | | | |
| Lost to follow-up | 1 (<1) | 0 | 1 (<1) |
| Withdrawal by participant | 16 (8) | 17 (8) | 33 (8) |
| Participant relocated | 1 (<1) | 2 (<1) | 3 (<1) |
| Frequency of visits | 2 (<1) | 0 | 2 (<1) |
| Burden of procedures | 0 | 2 (<1) | 2 (<1) |
| Other [c] | 13 (6) | 12 (6) | 25 (6) |

[redacted]

a. Only one primary reason was permitted.
b. Participants were not required to indicate subreasons, therefore the percentages may not sum to 100%.
c. Includes 2 participants (1 Placebo, 1 Mepolizumab 100 mg SC) where specify field indicated withdrawal due to AE.

## Recruitment

A total of 86 sites in 11 countries randomised participants: 24 sites in the United States (US), 11 sites in Argentina, 9 sites in Germany, 9 sites in the Russian Federation, 8 sites in the United Kingdom (UK), 7 sites in Canada, 5 sites in Sweden, 4 sites in Australia, 4 sites in the Republic of Korea, 4 sites in Romania and 1 site in the Netherlands.

The trial was initiated on the 25th of May 2017 and completed on the 11th of December 2019.

## Conduct of the study

The MAH states that the study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP).

### Protocol deviations

Protocol deviations were identified for 60% participants. The incidence was greater in the placebo group (65%) compared to the mepolizumab group (55%). The most frequently reported deviations were related to assessment or time point completion (39% of participants), and this category predominately consisted of spoilt samples for which the analysis of clinical chemistry, haematology and/or urinalysis could not be completed by the central laboratory (Listing 7). Other frequently reported categories of protocol deviations were visit completion (17% of participants), study procedures (14% of participants) and wrong study treatment/administration/dose (9% of participants). No other category of deviation was report for 5% or more of participants.

Following unblinding, it was determined that 4 participants (<1%) had received a single dose of treatment which did not correspond to their randomised treatment. In the mepolizumab group, 2 participants received a single dose of placebo (one at Week 32 and the other at Week 40). In the

placebo group, 2 participants received a single dose of mepolizumab 100 mg SC one at Week 20 and the other at Week 20).

**Table 9: Summary of Important Protocol Deviations (Study 205687, ITT Population)**

| Category<br>Subcategory | Placebo<br>(N=201) | Mepolizumab 100 mg SC<br>(N=206) | Total<br>(N=407) |
|---|---|---|---|
| **Any important protocol deviations** | **130 (65)** | **114 (55)** | **244 (60)** |
| **Assessment or time point completion** | **91 (45)** | **69 (33)** | **160 (39)** |
| Incomplete assessment | 85 (42) | 64 (31) | 149 (37) |
| Missed assessment | 13 (6) | 9 (4) | 22 (5) |
| Assessment not properly performed | 2 (<1) | 0 | 2 (<1) |
| **Visit completion** | **38 (19)** | **31 (15)** | **69 (17)** |
| Out of window - visit/phone contact | 25 (12) | 23 (11) | 48 (12) |
| Missed visit/phone contact | 20 (10) | 10 (5) | 30 (7) |
| **Study procedures** | **25 (12)** | **30 (15)** | **55 (14)** |
| Study blinding/unblinding procedures | 11 (5) | 11 (5) | 22 (5) |
| Diary procedures | 11 (5) | 9 (4) | 20 (5) |
| Post study treatment observation not done | 3 (1) | 9 (4) | 12 (3) |
| Biological sample specimen procedures | 3 (1) | 4 (2) | 7 (2) |
| Equipment procedures | 1 (<1) | 5 (2) | 6 (1) |
| **Wrong study treatment/administration/dose** | **17 (8)** | **19 (9)** | **36 (9)** |
| Wrong study treatment or assignment administered | 9 (4) | 11 (5) | 20 (5) |
| Use of study treatment impacted by temperature excursion - not reported/approved/disapproved for further use | 5 (2) | 2 (<1) | 7 (2) |
| Other deviations related to wrong study treatment/administration/dose | 2 (<1) | 3 (1) | 5 (1) |
| Expired study treatment administered | 0 | 3 (1) | 3 (<1) |
| Study treatment not administered per protocol | 1 (<1) | 1 (<1) | 2 (<1) |
| **Eligibility criteria not met** | **5 (2)** | **7 (3)** | **12 (3)** |
| **Failure to report safety events per protocol** | **8 (4)** | **3 (1)** | **11 (3)** |
| Failure to confirm causality assessment within the expected time frame | 6 (3) | 2 (<1) | 8 (2) |
| SAE not reported within the expected time frame | 2 (<1) | 1 (<1) | 3 (<1) |
| **Excluded medication, vaccine or device** | **4 (2)** | **4 (2)** | **8 (2)** |
| Medication, excluded by the protocol, was administered | 4 (2) | 4 (2) | 8 (2) |
| **Informed consent** | **3 (1)** | **4 (2)** | **7 (2)** |
| Informed consent/assent not signed and/or dated by appropriate site staff | 2 (<1) | 0 | 2 (<1) |
| Informed consent/assent not signed and/or dated by participant (parent/legal representative, if applicable) | 0 | 2 (<1) | 2 (<1) |
| Wrong informed consent/assent version signed | 0 | 2 (<1) | 2 (<1) |
| Other informed consent/assent deviations | 1 (<1) | 0 | 1 (<1) |

[redacted]

Note: Participants could have more than one important protocol deviation.

## Baseline data

### Demographics

The mean age was 48.8 years, and 14% of participants were 65 years of age or older. Over half of the participants were male (65%). The mean BMI was 28.164 kg/m2, indicating that the study population tended to be overweight. The majority of participants were White (93%), and 13% of participants were of Hispanic or Latino ethnicity.

**Table 10: Summary of Demographic Characteristics (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) | Total (N=407) |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Male | 125 (62) | 139 (67) | 264 (65) |
| Female | 76 (38) | 67 (33) | 143 (35) |
| **Age (years) [a], n (%)** | | | |
| Mean (SD) | 48.9 (12.46) | 48.6 (13.55) | 48.8 (13.01) |
| Min, Max | 20, 82 | 18, 79 | 18, 82 |
| **Age group (years) [a], n (%)** | | | |
| 18-<40 | 52 (26) | 64 (31) | 116 (29) |
| 40-<65 | 122 (61) | 113 (55) | 235 (58) |
| ≥65 | 27 (13) | 29 (14) | 56 (14) |
| **Ethnicity, n (%)** | | | |
| Hispanic/Latino | 29 (14) | 24 (12) | 53 (13) |
| Not Hispanic/Latino | 172 (86) | 182 (88) | 354 (87) |
| **Race detail, n (%)** | | | |
| White - White/Caucasian/European Heritage | 183 (91) | 190 (92) | 373 (92) |
| Asian - East Asian Heritage | 7 (3) | 6 (3) | 13 (3) |
| Black or African American | 4 (2) | 5 (2) | 9 (2) |
| White - Arabic/North African Heritage | 4 (2) | 2 (<1) | 6 (1) |
| Asian - Central/South Asian Heritage | 1 (<1) | 2 (<1) | 3 (<1) |
| Asian - South East Asian Heritage | 1 (<1) | 1 (<1) | 2 (<1) |
| Multiple | 1 (<1) | 0 | 1 (<1) |
| **Body Mass Index (kg/m$^2$), n (%)** | | | |
| Mean (SD) | 28.174 (5.4583) | 28.153 (5.2684) | 28.164 (5.3564) |
| Min, Max | 17.34, 49.29 | 18.59, 44.71 | 17.34, 49.29 |

[redacted]

a. Age was derived at the date of the Screening visit from reported year of birth and imputed day and month of 30 June.

**Nasal Polyp Disease History and Characteristics**

The mean time since onset of NP at baseline was 11.41 years for the ITT population and similar between treatment groups. Approximately half of participants had a diagnosis of NP for 10 or more years and approximately 30% of participants for 15 years or more.

All participants had a history which included at least one surgery for NP in the past 10 years. The majority of participants had a history of 1 or 2 surgeries (70%). A greater proportion of participants had only 1 surgery in the mepolizumab group than the placebo group (52% and 40%, respectively). Approximately half of participants (48%) had received at least one course of OCS for NP in the 12 months prior to screening.

**Table 11: Summary of Nasal Polyp Disease History (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) | Total (N=407) |
|---|---|---|---|
| **Duration of nasal polyps, n (%)** | | | |
| n | 201 | 206 | 407 |
| <1 year | 4 (2) | 0 | 4 (<1) |
| ≥1 to <5 years | 35 (17) | 47 (23) | 82 (20) |
| ≥5 to <10 years | 61 (30) | 60 (29) | 121 (30) |
| ≥10 to <15 years | 40 (20) | 42 (20) | 82 (20) |
| ≥15 to <20 years | 35 (17) | 27 (13) | 62 (15) |
| ≥20 to <25 years | 13 (6) | 11 (5) | 24 (6) |
| ≥25 years | 13 (6) | 19 (9) | 32 (8) |
| **Duration of nasal polyps (years), n (%)** | | | |
| n | 201 | 206 | 407 |
| Mean (SD) | 11.46 (8.273) | 11.36 (8.522) | 11.41 (8.390) |
| Median | 10.00 | 9.00 | 9.50 |
| Min, Max | 0.6, 48.0 | 1.0, 42.0 | 0.6, 48.0 |
| **Number of previous surgeries for nasal polyps in the past 10 years, n (%)** | | | |
| n | 201 | 206 | 407 |
| 0 | 0 | 0 | 0 |
| 1 | 81 (40) | 108 (52) | 189 (46) |
| 2 | 47 (23) | 47 (23) | 94 (23) |
| 3 | 35 (17) | 27 (13) | 62 (15) |
| 4 | 12 (6) | 13 (6) | 25 (6) |
| 5 | 15 (7) | 4 (2) | 19 (5) |
| >5 | 11 (5) | 7 (3) | 18 (4) |
| **Number of courses of OCS for nasal polyps in the previous 12 months, n (%)** | | | |
| n | 201 | 206 | 407 |
| 0 | 110 (55) | 100 (49) | 210 (52) |
| 1 | 47 (23) | 64 (31) | 111 (27) |
| 2 | 18 (9) | 17 (8) | 35 (9) |
| >2 | 26 (13) | 25 (12) | 51 (13) |

[redacted]

Abbreviations: OCS=oral corticosteroid.

Both Screening and Baseline mean total endoscopic score was similar between the two treatment groups. The centrally read Screening assessment was used to assess eligibility for randomisation in the study, and 4 participants had protocol deviations (i.e., their screening endoscopic score did not meet the minimum threshold of 5); all of these participants had a Screening endoscopic nasal polyp score of 4 (3 participants [2%] in the placebo group and 1 participant [<1%] in the mepolizumab group).

The mean endoscopic nasal polyp score improved in both treatment groups between Screening and Baseline, and at Baseline, a total of 75 participants (27%) had an endoscopic score <5 (40 participants [20%] in the placebo group and 35 participants in the mepolizumab group [17%]).

Mean baseline nasal obstruction VAS score (8.97), mean baseline overall VAS score (9.07) and mean baseline SNOT-22 total score (64.1) were all similar between treatment groups.

**Table 12: Summary of Screening and Baseline Disease Characteristics (Study 205687, ITT Population**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) | Total (N=407) |
|---|---|---|---|
| **Screening total endoscopic score (centrally read) [a,b], n (%)** | | | |
| n | 200 | 206 | 406 |
| Mean (SD) | 5.9 (0.94) | 5.9 (0.86) | 5.9 (0.90) |
| Median | 6.0 | 6.0 | 6.0 |
| Min, Max | 4, 8 | 4, 8 | 4, 8 |
| **Baseline total endoscopic score (centrally read) [a], n (%)** | | | |
| n | 201 | 206 | 407 |
| Mean (SD) | 5.6 (1.41) | 5.4 (1.17) | 5.5 (1.29) |
| Median | 6.0 | 5.0 | 5.0 |
| Min, Max | 0, 8 | 2, 8 | 0, 8 |
| **Baseline total endoscopic score (investigator read) [a], n (%)** | | | |
| n | 201 | 206 | 407 |
| Mean (SD) | 6.2 (1.07) | 6.1 (0.95) | 6.2 (1.01) |
| Median | 6.0 | 6.0 | 6.0 |
| Min, Max | 2, 8 | 3, 8 | 2, 8 |
| **Baseline nasal obstruction VAS score [a], n (%)** | | | |
| n | 201 | 206 | 407 |
| Mean (SD) | 9.02 (0.828) | 8.92 (0.832) | 8.97 (0.830) |
| Median | 9.14 | 9.01 | 9.10 |
| Min, Max | 5.31, 10.00 | 6.54, 10.00 | 5.31, 10.00 |
| **Baseline overall VAS score [a], n (%)** | | | |
| n | 201 | 206 | 407 |
| Mean (SD) | 9.10 (0.721) | 9.04 (0.766) | 9.07 (0.744) |
| Median | 9.20 | 9.12 | 9.17 |
| Min, Max | 7.21, 10.00 | 7.17, 10.00 | 7.17, 10.00 |
| **Baseline SNOT-22 total score [c], n (%)** | | | |
| n | 198 | 205 | 403 |
| Mean (SD) | 64.4 (19.04) | 63.7 (17.64) | 64.1 (18.32) |
| Median | 64.0 | 64.0 | 64.0 |
| Min, Max | 19, 110 | 17, 105 | 17, 110 |

[redacted]

a. Higher scores indicate greater disease severity.
b. Participants (3 Placebo, 1 Mepolizumab 100 mg SC) had a screening total endoscopic score (centrally read) of 4.
c. Higher scores indicate worse quality of life.
Abbreviations: SNOT-22=Sino-Nasal Outcomes Test-22; VAS=visual analogue scale.

**Medical Conditions**

Overall, past medical conditions were reported for 17% of participants, the most common of which was pneumonia (9% of participants). Other frequently reported past medical conditions were cataract (3% of participants) and allergic rhinitis (2%). The incidence of past medical conditions was balanced between the treatment groups.

Current medical conditions were reported for >99% of participants.

Medical conditions classified as respiratory disorders were reported for >99% of participants, the most common of which were chronic sinusitis (99%), asthma (71%), allergic rhinitis (54%) and aspirin-exacerbated respiratory disease (27%). Other current medical conditions reported for more than 10%

of participants were hypertension (24%) and hypercholesterolemia (13%). The incidence of current medical conditions was balanced between the treatment groups.

**Asthma**

Overall, 71% of participants had a diagnosis of asthma at Screening. Few participants had experienced an asthma exacerbation in the 12 months prior to Screening (15% and 26% in the placebo and mepolizumab groups, respectively).

**Prior and Concomitant Medications**

98% of participants were receiving medication prior to the start of study treatment. The most common medications were in the respiratory system (98%) and dermatological (88%). In each ATC class, the proportion of participants receiving medication was similar between treatment groups. Eighty-seven percent (87%) of participants in the placebo group and 82% of participants in the mepolizumab group started a medication during the treatment period.

The most common medications were for respiratory system (66% and 56% of participants in the placebo and mepolizumab groups, respectively). A greater proportion of participants in the placebo group than the mepolizumab group started a systemic corticosteroid for any reason during the treatment period (46% compared with 34%, respectively).

**Exposure and Treatment Compliance**

Mean exposure to study treatment was similar between the placebo and mepolizumab treatment groups (11.2 and 11.3 months, respectively). Median exposure was 12.0 months in both treatment groups.

The mean number of treatments administered was similar between the placebo and mepolizumab treatment groups (12.0 and 12.2 injections, respectively).

The mean duration of time spent in the no-treatment follow-up period for the 134 participants in the Follow-Up after Week 52 Population was similar between the placebo and mepolizumab treatment groups (5.42 and 5.37 months, respectively).

## Numbers analysed

In the ITT population, 201 patients received placebo and 206 were treated with mepolizumab 100 mg SC.

## Outcomes and estimation

All primary and secondary endpoints achieved statistical significance at the two-sided 5% level adjusted for multiplicity.

**Endoscopic Nasal Polyp Score at Week 52 (Co-Primary Endpoint)**

At the end of the 52-week treatment period, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated a ≥1-point improvement in their total endoscopic NP score (50% compared with 28%, respectively.

Correspondingly, fewer participants in the mepolizumab group than the placebo group had a worsening of their total endoscopic NP score over the same period (22% compared with 30%, respectively).

For the co-primary endpoint of the change from baseline in total endoscopic NP score at Week 52, the median change in the mepolizumab group was -1.0 compared with 0 in the placebo group. There was a

statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001). Accounting for treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count, the adjusted treatment difference in medians was -0.73 (95% CI: -1.11, -0.34).

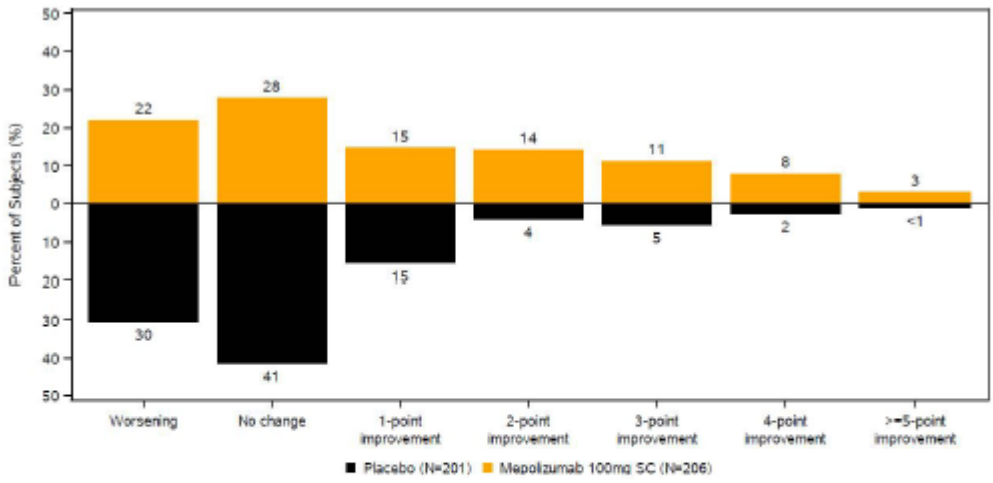
**Table 13: Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 (Study 205687, ITT Population)**

| Total Endoscopic Score | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n | 201 | 206 |
| Nasal surgery/sinuplasty prior to visit [a] | 46 | 18 |
| Missing due to study withdrawal [b] | 15 | 16 |
| Missing visit [c] | 6 | 6 |
| **Change from Baseline, n (%)** | | |
| ≥5-point improvement | 2 (<1) | 6 (3) |
| 4-point improvement | 5 (2) | 16 (8) |
| 3-point improvement | 11 (5) | 23 (11) |
| 2-point improvement | 8 (4) | 29 (14) |
| 1-point improvement | 31 (15) | 30 (15) |
| No change | 83 (41) | 57 (28) |
| Worsening | 61 (30) | 45 (22) |
| **Analysis of change from Baseline** | | |
| Median change from baseline | 0.0 | -1.0 |
| p-value [d] | | <0.001 |
| **Adjusted treatment difference** | | |
| Difference in medians (95% CI) [e] | | -0.73 (-1.11, -0.34) |

[redacted]

a. Participants with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty.
b. Participants with no nasal surgery/sinuplasty who withdrew from study prior to visit were assigned their worst observed score prior to study withdrawal.
c. Participants with missing visit data were assigned their worst observed score prior to the missing visit.
d. Based on Wilcoxon rank-sum test.
e. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

**Figure 18: Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 (Study 205687, ITT Population).**




[redacted]

Note: Participants with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty.
Note: Participants with no nasal surgery/sinuplasty who withdrew from study prior to visit were assigned their worst observed score prior to study withdrawal.
Note: Participants with missing visit data were assigned their worst observed score prior to the missing visit.

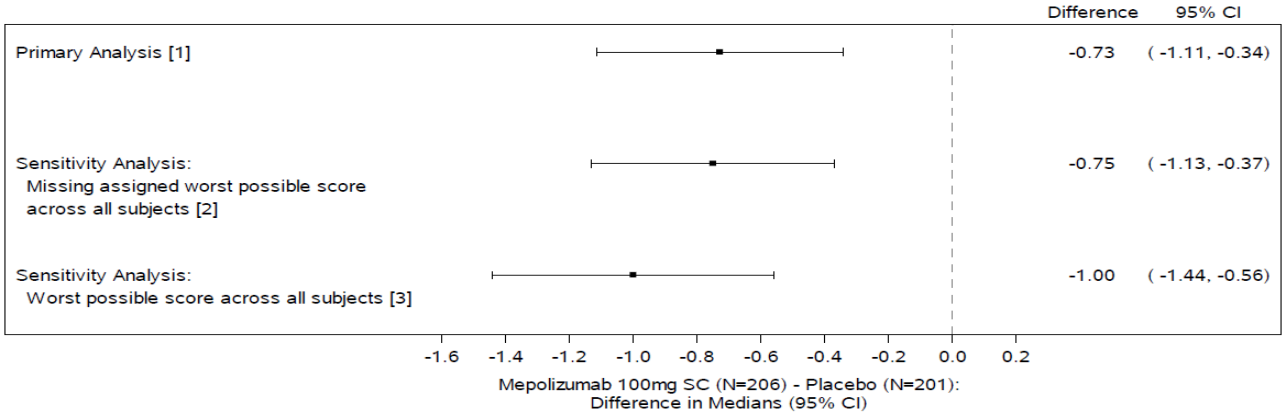
**Sensitivity and Supplementary Analyses of the Endoscopic Nasal Polyp Score Co-Primary Endpoint**

In the primary analysis, participants who had nasal surgery/sinuplasty were assigned their worst observed score prior to surgery/sinuplasty and participants with missing data (due to study withdrawal or otherwise) were assigned their worst observed score prior to study withdrawal or missing visit. Two sensitivity analyses were conducted using alternative imputation methods:

- participants who had nasal surgery/sinuplasty were assigned their worst observed score prior to surgery/sinuplasty and participants with missing data were assigned the worst possible score across all participants.
- participants who had nasal surgery/sinuplasty and/or missing data were assigned the worst possible score across all participants.

In both sensitivity analyses, there was a statistically significant improvement in favour of mepolizumab (p<0.001)

**Figure 19: Figure of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52: Primary and Sensitivity Analyses (Study 205687, ITT Population)**




In a supplementary analysis of the co-primary endpoint using the PP Population, the median change from baseline in total endoscopic NP score at Week 52 in the mepolizumab group was -1.0 compared with 0 in the placebo group. There was a statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001).

**Responder Analyses**

In the responder analysis of total endoscopic NP score, a responder was defined as a participant who had an improvement (decrease) of ≥ 1.0 point from baseline in the absence of surgery/sinuplasty at a given timepoint.

The odds of being a responder in the mepolizumab group were consistently statistically significantly greater than the odds of being a responder in the placebo group from Week 20. At Week 52, the odds of being a responder in the mepolizumab group was 2.74 (95% CI 1.80, 4.18; p<0.001) times greater than the odds of being a responder in the placebo group.

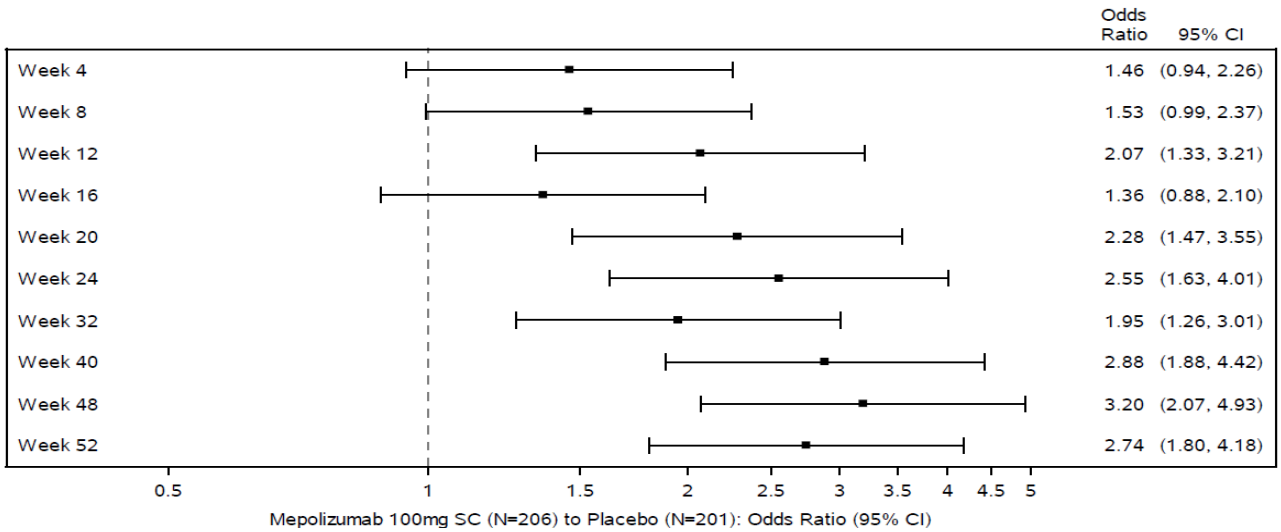
**Table 14: Summary and Analysis of Total Endoscopic Nasal Polyps Score (Centrally Read) Responders at Week 52 (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n | 201 | 206 |
| Responder, n (%) [a] | 57 (28) | 104 (50) |
| Non-responder, n (%) | 144 (72) | 102 (50) |
| No change/worsening, n (%) | 77 (38) | 62 (30) |
| Nasal surgery/sinuplasty prior to visit, n (%) | 46 (23) | 18 (9) |
| Withdrawal from study prior to visit, n (%) | 15 (7) | 16 (8) |
| Missing visit, n (%) | 6 (3) | 6 (3) |
| Odds Ratio to Placebo (95% CI) [b] | | 2.74 (1.80, 4.18) |
| p-value | | <0.001 |

[redacted]

a. Defined as a participant with a ≥1-point improvement from baseline in the absence of surgery/sinuplasty prior to that visit.
b. Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

**Figure 20 : Summary of Total Endoscopic Nasal Polyps Score (Centrally Read) Responders by Visit (Study 205687, ITT Population)**




Note: Includes data reported up to Week 52.
Note: Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

**Endoscopic Nasal Polyp Score (Investigator-Read)**

By Week 52, the total endoscopic NP scores were improved for participants in the mepolizumab group (median 5, mean 4.6, range 0-8), and to a lesser extent for participants in the placebo group (median 6, mean 5.7, range 0-8). The change from baseline in total endoscopic NP scores showed a greater improvement in the mepolizumab group (median change: -1.0, mean: -1.6, SD: 2.07) than the placebo group (median change: 0.0, mean: -0.5, SD: 1.77).

**VAS Symptoms Scores**

***Nasal Obstruction VAS Score at Week 49-52 (Co-Primary Endpoint)***

In the 4-week period Week 49-52, at the end of the 52-week treatment period, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated a >5-point improvement (decrease) in their nasal obstruction VAS score (44% compared with 23%, respectively).

For the co-primary endpoint of the change from baseline in nasal obstruction VAS score during the 4 weeks prior to Week 52, the median change in the mepolizumab group was -4.41 compared with -0.82 in the placebo group. There was a statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001). Accounting for treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count, the adjusted treatment difference in medians was -3.14 (95% CI: -4.09, -2.18).

**Table 15: Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) (Study 205687, ITT Population)**

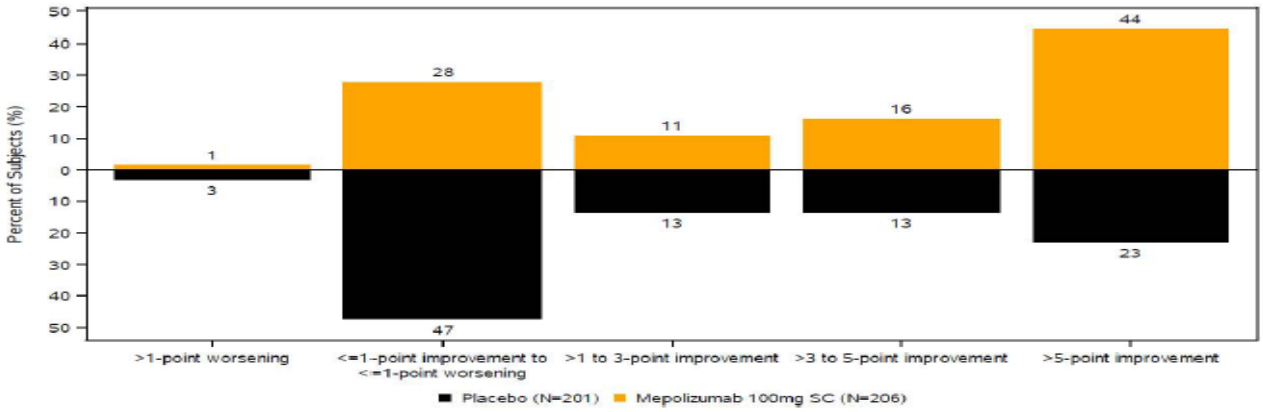
| Nasal Obstruction VAS Score | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n | 201 | 206 |
| Nasal surgery/sinuplasty prior to time period [a] | 44 | 18 |
| Missing due to study withdrawal [b] | 12 | 15 |
| Missing time period [c] | 6 | 4 |
| **Change from Baseline, n (%)** | | |
| >5-point improvement | 46 (23) | 91 (44) |
| >3 to 5-point improvement | 27 (13) | 33 (16) |
| >1 to 3-point improvement | 27 (13) | 22 (11) |
| ≤1-point improvement to ≤1-point worsening | 95 (47) | 57 (28) |
| >1-point worsening | 6 (3) | 3 (1) |
| **Analysis of change from Baseline** | | |
| Median change from baseline | -0.82 | -4.41 |
| p-value [d] | | <0.001 |
| **Adjusted treatment difference** | | |
| Difference in medians (95% CI) [e] | | -3.14 (-4.09, -2.18) |

[redacted]

a. Participants with nasal surgery/sinuplasty prior to time period were assigned their worst observed score prior to nasal surgery/sinuplasty.
b. Participants with no nasal surgery/sinuplasty who withdrew from study prior to time period were assigned their worst observed score prior to study withdrawal.
c. Participants with missing time period data were assigned their worst observed score prior to the missing time period.
d. Based on Wilcoxon rank-sum test.
e. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

**Figure 21: Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52)**

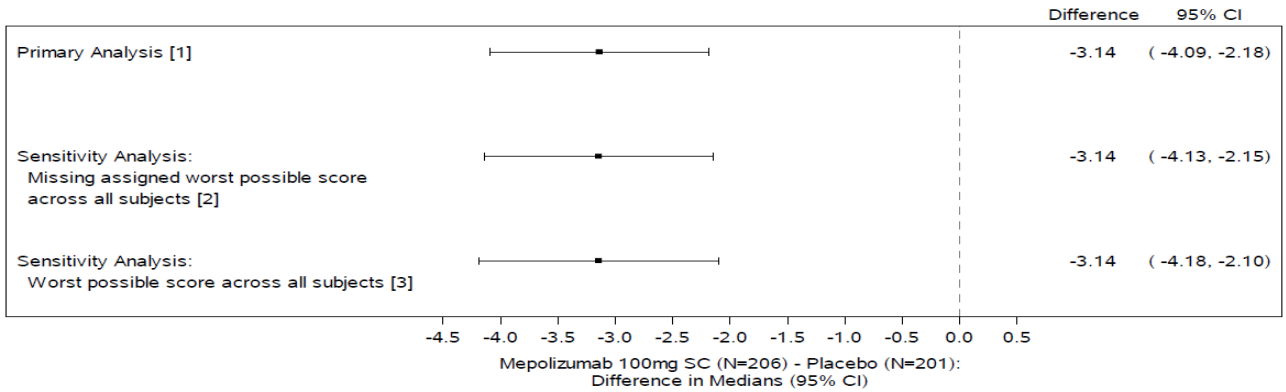
**(Study 205687, ITT Population)**




**Sensitivity and Supplementary Analyses of the Nasal Obstruction VAS Score Co-Primary Endpoint**

In both sensitivity analyses, there was a statistically significant improvement in favour of mepolizumab (p<0.001).

**Figure 22 : Figure of Change from Baseline Nasal Obstruction VAS Score (Week 49-52): Primary and Sensitivity Analyses (Study 205687, ITT Population).**



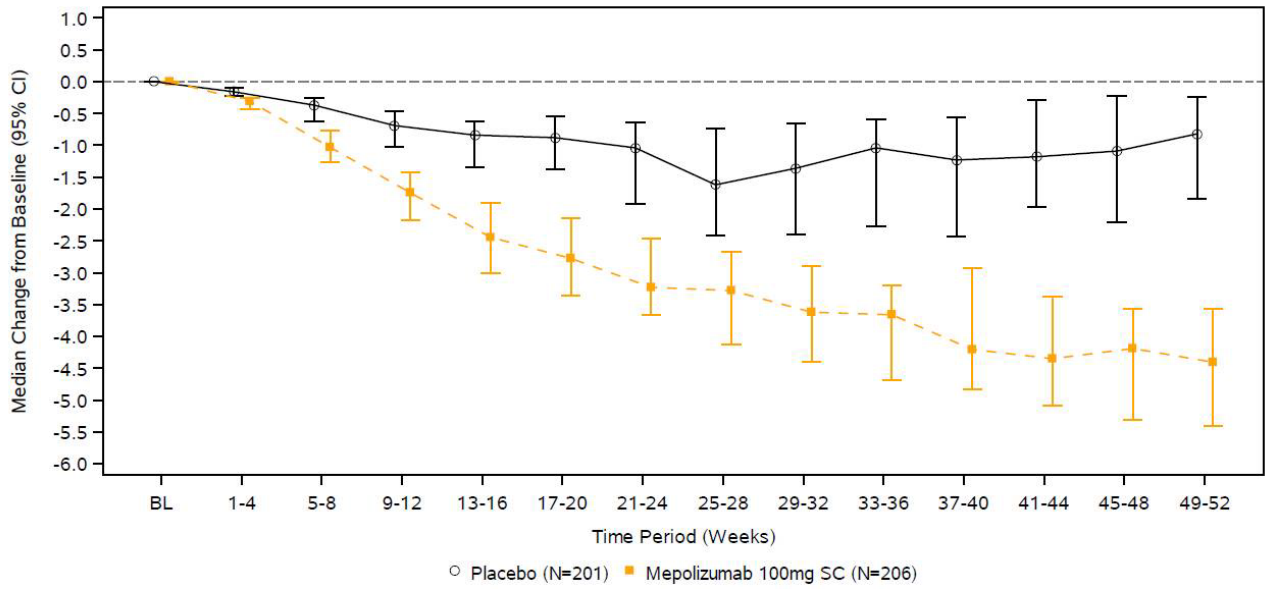

[1] Participants with nasal surgery/sinuplasty assigned worst observed score prior to surgery/sinuplasty, participants with missing data assigned worst observed score prior to visit.
[2] Participants with nasal surgery/sinuplasty assigned worst observed score prior to surgery/sinuplasty, participants with missing data assigned worst possible score across all participants.
[3] Participants with nasal surgery/sinuplasty, participants with missing data assigned worst possible score across all participants.

In a supplementary analysis of the co-primary endpoint using the PP Population, the median change from baseline in nasal obstruction VAS score at Weeks 49-52 in the mepolizumab group was -4.73 compared with -1.06 in the placebo group. There was a statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001).

***Nasal Obstruction VAS Score Across the 52-Week Treatment Period***

Across the treatment period, the median change from Baseline in nasal obstruction VAS score for each 4-week treatment period was consistently greater in the mepolizumab group than the placebo group

**Figure 23 : Median Change from Baseline Nasal Obstruction VAS Score in each4-Weekly Period (Study 205687, ITT Population)**




Note: Participants with nasal surgery/sinuplasty prior to time period were assigned their worst observed score prior to nasal surgery/sinuplasty.
Note: Participants with no nasal surgery/sinuplasty who withdrew from study prior to time period were assigned their worst observed score prior to study withdrawal
Note: Participants with missing time period data were assigned their worst observed score prior to the missing time period.

### Nasal Symptoms and Facial Pain Composite VAS Score

The nasal symptoms and facial pain composite VAS score was comprised of the individual VAS scores of nasal obstruction, nasal discharge, mucus in the throat, loss of smell and facial pain. The nasal symptoms and facial pain composite VAS scores were similar in both treatment groups at baseline.

Out of a maximum of 10, the median was 8.99 in the placebo group, with a mean of 8.77 (range: 5.48-10.00; SD: 1.077), and 8.87 in the mepolizumab group, with a mean of 8.72 (range: 4.11-10.00; SD: 1.002).

In the 4-week period Week 49-52, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated a >5-point improvement (decrease) in their nasal symptoms and facial pain composite VAS score (38% compared with 21%, respectively).

The median change in the mepolizumab group was -3.88 compared with -0.99 in the placebo group. There was a statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001).

## Secondary endpoints

### Time to First Nasal Polyps Surgery (Key Secondary Endpoint)

By Week 52, 18 participants (9%) in the mepolizumab group had undergone surgery compared with 46 participants (23%) in the placebo group. Most participants had only 1 surgery, with 2 participants (<1%) in the mepolizumab group and 3 participants (1%) in the placebo group having 2 surgeries.

The probability of undergoing surgery at any time prior to Week 52 was statistically significantly lower in the mepolizumab group than for participants in the placebo group (hazard ratio: 0.43, 95% CI: 0.25, 0.76; p=0.003). The estimated risk of having surgery prior to Week 52 was 9.2% (95% CI: 5.9%, 14.2%) for participants in the mepolizumab group compared to 23.6% (95% CI: 18.3%, 30.3%) for participants in the placebo group (Kaplan-Meier estimates).

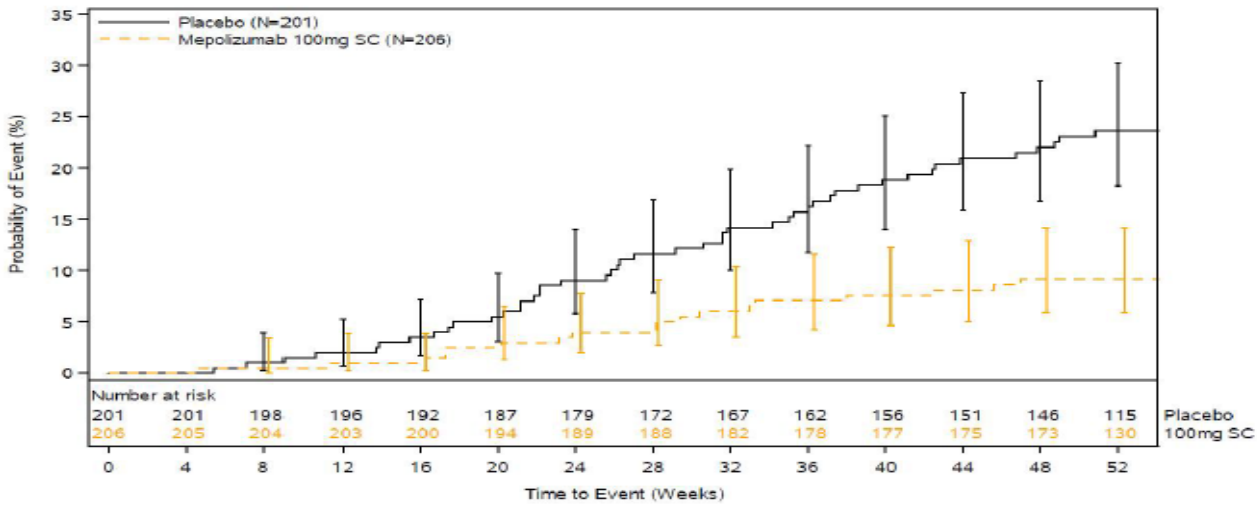
**Table 16: Analysis of Time to First Nasal Surgery (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **By Week 8, n (%)** | | |
| Participants with surgery | 2 (<1) | 1 (<1) |
| Probability of surgery (95% CI) [a] | 1.0 (0.3, 3.9) | 0.5 (0.1, 3.4) |
| **By Week 16, n (%)** | | |
| Participants with surgery | 7 (3) | 2 (<1) |
| Probability of surgery (95% CI) [a] | 3.5 (1.7, 7.2) | 1.0 (0.2, 3.8) |
| **By Week 24, n (%)** | | |
| Participants with surgery | 18 (9) | 8 (4) |
| Probability of surgery (95% CI) [a] | 9.1 (5.8, 14.0) | 4.0 (2.0, 7.8) |
| **By Week 32, n (%)** | | |
| Participants with surgery | 28 (14) | 12 (6) |
| Probability of surgery (95% CI) [a] | 14.2 (10.0, 19.9) | 6.0 (3.5, 10.4) |
| **By Week 40, n (%)** | | |
| Participants with surgery | 37 (18) | 15 (7) |
| Probability of surgery (95% CI) [a] | 18.9 (14.0, 25.1) | 7.6 (4.6, 12.3) |
| **By Week 48, n (%)** | | |
| Participants with surgery | 43 (21) | 18 (9) |
| Probability of surgery (95% CI) [a] | 22.0 (16.8, 28.5) | 9.2 (5.9, 14.2) |
| **By Week 52, n (%)** | | |
| Participants with surgery | 46 (23) | 18 (9) |
| Probability of surgery (95% CI) [a] | 23.6 (18.3, 30.3) | 9.2 (5.9, 14.2) |
| **Time to First Nasal Surgery** | | |
| Nasal surgery prior to Week 52 | 46 (23) | 18 (9) |
| No surgery prior to Week 52 [b] | 155 (77) | 188 (91) |
| Completed to Week 52 | 140 (70) | 172 (83) |
| Withdrew prior to Week 52 | 15 (7) | 16 (8) |
| Hazard ratio (Mepolizumab/Placebo) (95% CI) [c] | | 0.43 (0.25, 0.76) |
| p-value | | 0.003 |
| [redacted] | | |

a. Kaplan-Meier estimate.
a. Participants censored in the statistical analysis
b. Estimated from a Cox Proportional Hazards Model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).

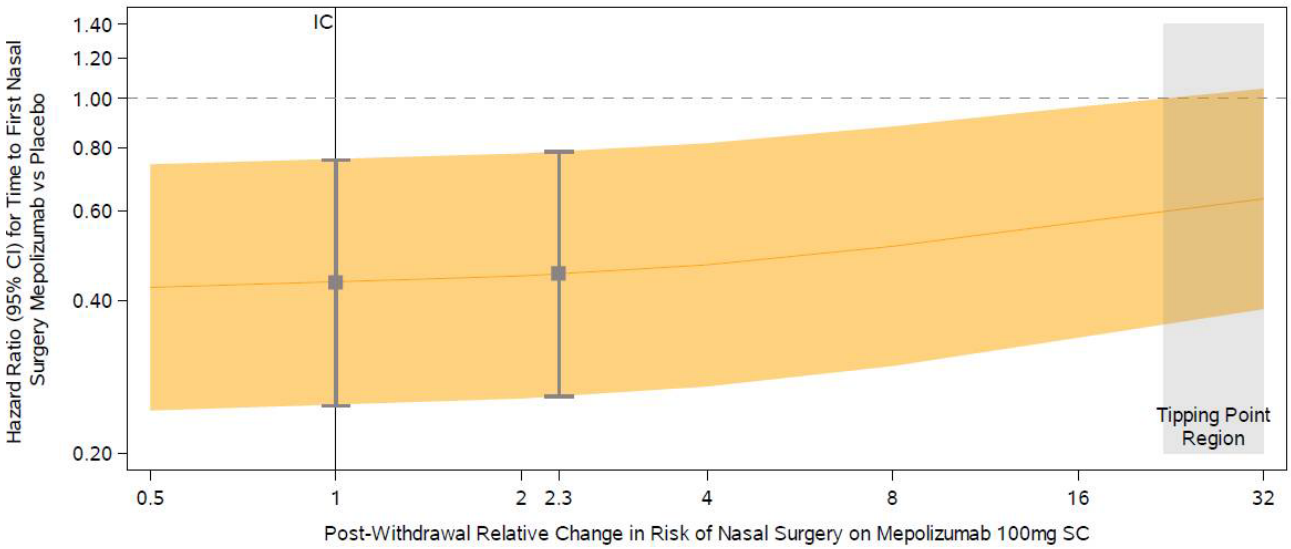
Note: Includes data reported up to Week 52.

**Figure 24: Kaplan-Meier Time to First Nasal Surgery (Study 205687, ITT Population).**




Note: Vertical bars represent 95% confidence intervals.
A tipping point sensitivity analysis shows that the results for time to first surgery are robust to the independent censoring assumption of the Cox proportional hazards model where participants who withdraw from the study before experiencing surgery have their event times censored at the time of study withdrawal.

**Figure 25: Sensitivity Time to First Nasal Surgery: Tipping Point – Independent Censoring Assumption for Placebo (Study 205687, ITT Population)**




Note: The vertical reference line denotes expected number of surgeries under the assumption of independent censoring (IC) for mepolizumab, i.e. the risk of surgery for the imputed period is the same as the risk seen in the observed data.
Note: The 2.3 post-withdrawal relative change in the risk of surgery for mepolizumab participants is equivalent to there being no treatment effect in the imputed period.
Note: The tipping point occurs at a post-withdrawal relative change of approximately 22 in the risk of surgery for mepolizumab.
Note: The risk of surgery for placebo is imputed under the assumption of independent censoring.

A tipping point sensitivity analysis shows that the results for time to first surgery are robust to the independent censoring assumption of the Cox proportional hazards model where participants who withdraw from the study before experiencing surgery have their event times censored at the time of study withdrawal.

A plausible assumption for mepolizumab withdrawals is the loss of any treatment benefit. This means a step-change in relative event rate equivalent to 1/(estimated treatment effect), i.e. 1/0.43 = 2.3-fold increase in event rate. Even under the best-case scenario for placebo withdrawals, such an increase in event rate among mepolizumab withdrawals would still produce a HR<0.50 and a statistically significant reduction. A plausible assumption for placebo withdrawals is independent censoring i.e. they continue to receive surgery at the same rate as participants who remain in the study (shown in the solid line on the y-axis). To tip the p-value ≥0.05, mepolizumab would need to experience an event rate over 20 times worse than that of participants in the same arm who stay longer and an event rate over 8 times worse than that of placebo participants. Such increases are biologically implausible.

### Time to First Nasal Surgery or Course of Systemic Steroids

By Week 52, the risk of having surgery or systemic steroids was 29% lower for participants in the mepolizumab group than participants in the placebo group (hazard ratio: 0.71, 95% CI: 0.50, 1.00; p=0.050).

### Need for surgery

The proportion of participants identified as having a need for surgery based on having an overall VAS symptom score of >7 (Weeks 49-52) and a total endoscopic score ≥5 (Week 52, centrally read), was lower in the mepolizumab group (57 participants, 28%) than the placebo group (98 participants, 49%). The odds of no longer having a need for surgery up to Week 52 was statistically significantly

higher for participants in the mepolizumab group than for participants in the placebo group (odds ratio: 2.46, 95% CI: 1.59, 3.79; p<0.001).

**SNOT-22 at Week 52 (Secondary Endpoint)**

At the end of the 52-week treatment period, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated an improvement (decrease) at least 1 point in their SNOT-22 score (77% compared with 60%, respectively).

A ≥ 45-point improvement (decrease) was observed for 27% of participants in the mepolizumab group compared with 13% in the placebo group.

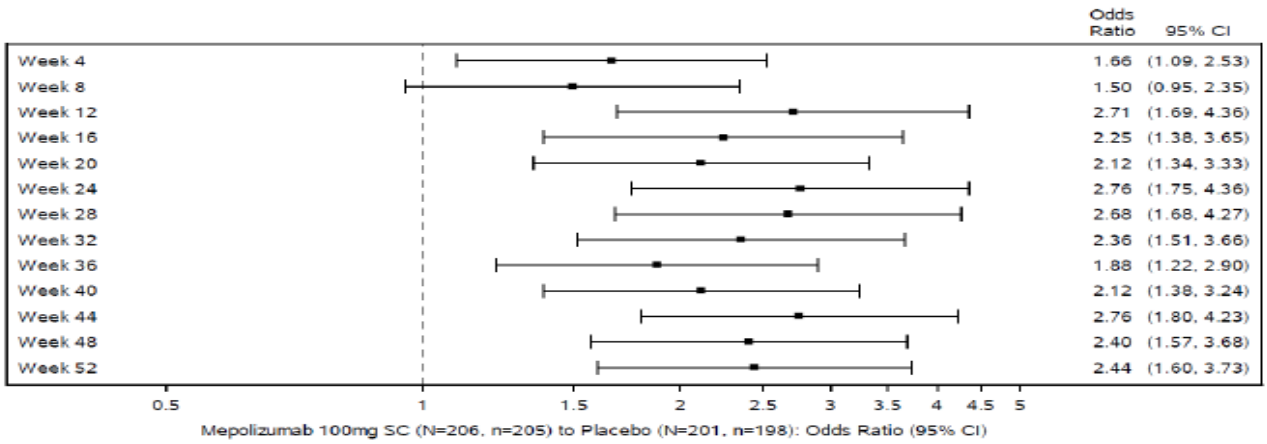
For the secondary endpoint of the change from baseline in SNOT-22 total score at Week 52, the median change from baseline in the mepolizumab group was -30.0 compared with -14.0 in the placebo group.

There was a statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001).

In the responder analysis of SNOT-22 total score, a responder was defined as a participant who had an improvement (decrease) of ≥8.9 points (the MCID) from baseline at a given timepoint.

At Week 52, the odds of being a responder in the mepolizumab group was 2.44 (95% CI 1.60, 3.73; p<0.001) times greater than the odds of being a responder in the placebo group.

**Figure 26: Summary of SNOT-22 Responders by Visit (Study 205687, ITT Population)**




Note: Analysis performed using a logistic regression model with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
Note: 1 participant in the mepolizumab group and 3 participants in the placebo group with a missing baseline score were excluded from the analysis.

**SNOT-22 Domain Scores at Week 52**

At Week 52, improvements (decreases) in the score for each domain were observed for participants in the mepolizumab group, which were in excess of improvements observed in the placebo group.

**Table 17: Summary of SNOT-22 Domain Scores at Week 52 (Study 205687, ITT Population)**

| Visit | | Placebo (N=201) SNOT-22 Total Score | Placebo (N=201) Change from Baseline | Mepolizumab 100 mg SC (N=206) SNOT-22 Total Score | Mepolizumab 100 mg SC (N=206) Change from Baseline |
|---|---|---|---|---|---|
| **Nasal Score; Range: 0 (no problem) to 30 (the problem is as bad as it can be)** | | | | | |
| Baseline | n | 198 | | 205 | |
| | Median | 23.0 | | 23.0 | |
| | Min, Max | 9, 30 | | 6, 30 | |
| | Mean (SD) | 22.8 (3.86) | | 22.2 (3.88) | |
| Week 52 | n | 201 | 198 | 206 | 205 |
| | Median | 19.0 | -3.5 | 12.0 | -10.0 |
| | Min, Max | 1, 30 | -24, 9 | 0, 29 | -29, 9 |
| | Mean (SD) | 17.7 (7.55) | -5.1 (7.00) | 12.8 (7.66) | -9.4 (7.38) |
| **Non-nasal Symptoms Score; Range: 0 (no problem) to 10 (the problem is as bad as it can be)** | | | | | |
| Baseline | n | 198 | | 205 | |
| | Median | 6.0 | | 6.0 | |
| | Min, Max | 0, 10 | | 0, 10 | |
| | Mean (SD) | 5.8 (2.08) | | 5.9 (2.05) | |
| Week 52 | n | 201 | 198 | 206 | 205 |
| | Median | 5.0 | 0.0 | 3.0 | -2.0 |
| | Min, Max | 0, 10 | -8, 6 | 0, 10 | -9, 4 |
| | Mean (SD) | 4.7 (2.63) | -1.2 (2.78) | 3.4 (2.63) | -2.5 (2.64) |
| **Ear/Facial Symptoms Score; Range: 0 (no problem) to 20 (the problem is as bad as it can be)** | | | | | |
| Baseline | n | 198 | | 205 | |
| | Median | 9.0 | | 9.0 | |
| | Min, Max | 0, 20 | | 0, 18 | |
| | Mean (SD) | 8.6 (4.61) | | 8.8 (4.43) | |
| Week 52 | n | 201 | 198 | 206 | 205 |
| | Median | 6.0 | -1.0 | 3.0 | -4.0 |
| | Min, Max | 0, 20 | -18, 14 | 0, 19 | -18, 9 |
| | Mean (SD) | 6.7 (5.26) | -1.9 (5.28) | 4.5 (4.73) | -4.3 (5.02) |
| **Sleep Score; Range: 0 (no problem) to 15 (the problem is as bad as it can be)** | | | | | |
| Baseline | n | 198 | | 205 | |
| | Median | 9.0 | | 9.0 | |
| | Min, Max | 0, 15 | | 0, 15 | |
| | Mean (SD) | 8.9 (3.89) | | 8.7 (3.82) | |
| Week 52 | n | 201 | 198 | 206 | 205 |
| | Median | 7.0 | -1.0 | 3.0 | -3.0 |
| | Min, Max | 0, 15 | -13, 9 | 0, 15 | -15, 11 |
| | Mean (SD) | 6.8 (4.72) | -2.1 (4.29) | 4.8 (4.37) | -3.9 (4.60) |
| **Fatigue Score; Range: 0 (no problem) to 20 (the problem is as bad as it can be)** | | | | | |
| Baseline | n | 198 | | 205 | |
| | Median | 12.0 | | 12.0 | |
| | Min, Max | 0, 20 | | 0, 20 | |
| | Mean (SD) | 11.3 (5.12) | | 11.2 (4.81) | |
| Week 52 | n | 201 | 198 | 206 | 205 |
| | Median | 9.0 | -1.0 | 4.0 | -5.0 |
| | Min, Max | 0, 20 | -17, 9 | 0, 20 | -18, 8 |
| | Mean (SD) | 8.7 (6.08) | -2.5 (5.38) | 5.9 (5.41) | -5.3 (5.74) |
| **Emotional Consequences Score; Range: 0 (no problem) to 15 (the problem is as bad as it can be)** | | | | | |
| Baseline | n | 198 | | 205 | |
| | Median | 7.0 | | 7.0 | |
| | Min, Max | 0, 15 | | 0, 15 | |
| | Mean (SD) | 7.0 (4.09) | | 6.8 (3.90) | |
| Week 52 | n | 201 | 198 | 206 | 205 |
| | Median | 4.0 | 0.0 | 2.0 | -3.0 |
| | Min, Max | 0, 15 | -14, 9 | 0, 15 | -13, 7 |
| | Mean (SD) | 5.1 (4.57) | -1.9 (4.22) | 3.4 (3.66) | -3.4 (4.06) |

Note: Higher scores indicate worse quality of life.
Note: Participants with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty.
Note: Participants with no surgery/sinuplasty who withdrew from study prior to visit were assigned their worst observed score prior to study withdrawal.
Note: Participants with missing visit data were assigned their worst observed score prior to the missing visit.

### Systemic Steroid Use Proportion of Participants Requiring Systemic Steroids for Nasal Polyps (Secondary Endpoint)

Over the 52-week treatment period, 25% of participants in the mepolizumab group required at least one course of systemic steroids for treatment of their NP, compared with 37% of participants in the

placebo group. The majority of participants who received systemic steroids only required 1 course (32 of 52 participants [62%] in the mepolizumab group and 43 of 74 participants [58%] in the placebo group).

For the secondary endpoint of the proportion of participants requiring systemic steroids for NP up to Week 52, the odds for participants in the mepolizumab group was statistically significantly lower than the odds for participants in the placebo group (odds ratio: 0.58, 95% CI: 0.36, 0.92; p=0.020).

**Table 18 : Summary and Analysis of Proportion of Participants Requiring Systemic Steroids for Nasal Polyps up to Week 52 (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| Number of participants with ≥1 course<br>Total number of courses | 74 (37)<br>124 | 52 (25)<br>82 |
| **Number of courses, n (%)** | | |
| n<br>0<br>1<br>2<br>3<br>4<br>5<br>6 | 201<br>127 (63)<br>43 (21)<br>18 (9)<br>9 (4)<br>3 (1)<br>0<br>1 (<1) | 206<br>154 (75)<br>32 (16)<br>17 (8)<br>0<br>0<br>2 (<1)<br>1 (<1) |
| **Analysis of Proportion of Participants Requiring Systemic Steroids for CRSwNP** | | |
| Odds Ratio to Placebo (95% CI) [a]<br>p-value | | 0.58 (0.36, 0.92)<br>0.020 |

[redacted]

a. Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total endoscopic score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.

Note: Courses of systemic steroids separated by <7 days were considered a continuation of the same course.

**Systemic Steroid Use for Nasal Polyps Across the 52-Week Treatment Period**

The number of days of use of systemic steroids for NP was similar between the two treatment groups. In the mepolizumab group, participants had a mean (SD) of 21.9 (45.81) days on systemic steroids, a mean (SD) of 6.22% (12.587) of days they were in the study up to Week 52.

In the placebo group, participants had a mean (SD) of 19.0 (18.54) days on systemic steroids, a mean (SD) of 5.25% (5.049) of days they were in the study up to Week 52.

The mean total prednisolone-equivalent use for NP was lower in the mepolizumab group (109.2 mg/year, SD: 257.43) than the placebo group (181.2 mg/year, SD: 364.14).

By Week 52, the probability of requiring an initial course of systemic steroid use for NP was lower in the mepolizumab group 25.4% (95% CI: 20.0, 32.1) than the placebo group 37.5% (95% CI: 31.1, 44.6%).

Over the 52-week treatment period, 25% of participants in the mepolizumab group required at least one course of systemic steroids for treatment of their NP, compared with 37% of participants in the placebo group. The majority of participants who received systemic steroids only required 1 course (32 of 52 participants [62%] in the mepolizumab group and 43 of 74 participants [58%] in the placebo group).

For the secondary endpoint of the proportion of participants requiring systemic steroids for NP up to Week 52, the odds for participants in the mepolizumab group was statistically significantly lower than the odds for participants in the placebo group (odds ratio: 0.58, 95% CI: 0.36, 0.92; p=0.020).

**University of Pennsylvania Smell Identification Test (UPSIT)**

At Week 52, the median change from baseline in UPSIT was 0.0 in both treatment groups. The difference between treatment groups was not statistically significant (p=0.302). Accounting for treatment group, country, baseline score and log(e) baseline blood eosinophil count, the difference in adjusted medians between treatment groups was 0.40 (95% CI: -1.49, 2.28).

***Loss of Smell VAS Score at Week 49-52 (Secondary Endpoint)***

In the 4-week period Week 49-52, at the end of the 52-week treatment period, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated a >5-point improvement (decrease) in their loss of smell VAS score (30% compared with 13%, respectively). For the secondary endpoint of the change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52, the median change in the mepolizumab group was -0.53 compared with 0.00 in the placebo group. There was a statistically significant improvement in this endpoint in favour of mepolizumab (p<0.001).

**Table 19 : Analysis of Change from Baseline Loss of Smell VAS Score (Weeks 49-52) (Study 205687, ITT Population)**

| Loss of Smell VAS Score | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n | 201 | 206 |
| Nasal surgery/sinuplasty prior to time period [a] | 44 | 18 |
| Missing due to study withdrawal [b] | 12 | 15 |
| Missing time period [c] | 6 | 4 |
| **Change from Baseline, n (%)** | | |
| >5-point improvement | 26 (13) | 61 (30) |
| >3 to 5-point improvement | 13 (6) | 13 (6) |
| >1 to 3-point improvement | 17 (8) | 21 (10) |
| ≤1-point improvement to ≤1-point worsening | 143 (71) | 109 (53) |
| >1-point worsening | 2 (<1) | 2 (<1) |
| **Analysis of change from Baseline** | | |
| Median change from baseline | 0.00 | -0.53 |
| p-value [d] | | <0.001 |
| **Adjusted treatment difference** | | |
| Difference in medians (95% CI) [e] | | -0.37 (-0.65, -0.08) |

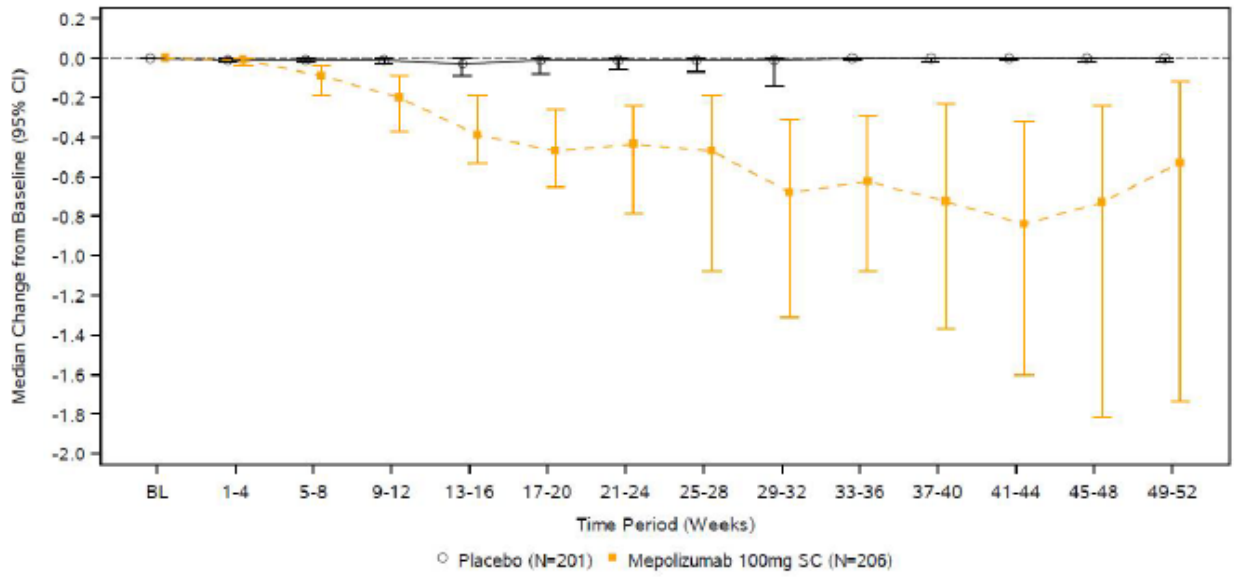
[redacted]

a. Participants with nasal surgery/sinuplasty prior to time period were assigned their worst observed score prior to nasal surgery/sinuplasty.
b. Participants with no nasal surgery/sinuplasty who withdrew from study prior to time period were assigned their worst observed score prior to study withdrawal.
c. Participants with missing time period data were assigned their worst observed score prior to the missing time period.
d. Based on Wilcoxon rank-sum test.
e. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

***Loss of Smell VAS Score Across the 52-Week Treatment Period***

Across the treatment period, the median change from Baseline in loss of smell VAS score for each 4-week treatment period was consistently greater in the mepolizumab group than the placebo group from Week 5-8 onward.

**Figure 27: Median Change from Baseline Loss of Smell VAS Score in each 4-Weekly Period (Study 205687, ITT Population)**




[redacted]

Note: Includes data reported up to Week 52.

Note: Participants with nasal surgery/sinuplasty prior to time period were assigned their worst observed score prior to nasal surgery/sinuplasty.

Note: Participants with no nasal surgery/sinuplasty who withdrew from study prior to time period were assigned their worst observed score prior to study withdrawal

Note: Participants with missing time period data were assigned their worst observed score prior to the missing time period.

**Peak Nasal Inspiratory Flow (PnIF)**

At Week 52, the change from Baseline in PnIF was greater for the mepolizumab group (median: 30.0 L/min, mean: 32.5 L/min, range -180 to 230, SD: 57.98), than for the placebo group (median: 0.0 L/min, mean: 11.2 L/min, range -350 to 180, SD: 65.78). The improvement in the mepolizumab group was also in excess of the 20 L/min MCID for this assessment.

**Nasal Discharge**

Nasal discharge VAS scores were similar in both treatment groups at Baseline. Out of a maximum of 10, the median was 9.04 in the placebo group, with a mean of 8.78 (range: 1.39-10.00; SD: 1.251), and 8.93 in the mepolizumab group, with a mean of 8.78 (range: 1.03-10.00; SD: 1.066).

In the 4-week period Week 49-52, a greater proportion of participants in the mepolizumab group than the placebo group demonstrated a >5-point improvement (decrease) in their nasal discharge VAS score (47% compared with 23%, respectively).

**Follow-up Period after Week 52**

A total of 134 participants (33%) entered the no-treatment follow-up period after Week 52, 69 participants (33%) in the mepolizumab group and 65 participants (32%) in the placebo group.

At Week 76, 24 weeks after the end of the treatment period, the change from Baseline for total endoscopic nasal polyp score remained greater for participants in the mepolizumab group (median change: -1.0, mean change: -1.2, range: -6 to 3, SD: 1.80) than the placebo group (median change: -0.0, mean change: -0.1, range: -4 to 4, SD: 1.59).

**Individual VAS Symptom Scores**

VAS scores for each individual symptom were similar in both treatment groups at baseline for participants in the Follow-Up after Week 52 Population. The treatment effect observed for the mepolizumab group at the end of the treatment period (Weeks 49-52) was observed to slowly decline to the end of the no treatment follow-up period (Weeks 73-76), although values were still clearly differentiated from baseline values and there was no evidence of rebound.

In the mepolizumab group the median change from baseline (min, max) at Weeks 49-52 was -5.76 (-10.00, 0.55) compared with -4.39 (-10.00, 0.65) at Weeks 73-76. In the placebo group the median change from baseline (min, max) at Weeks 49-52 was -1.56 (-8.97, 1.19) compared with -0.83 (-9.03, 1.39) at Weeks 73-76

**Nasal Polyp Surgery**

For the Follow-Up after Week 52 Population, the probability of having surgery prior to the end of treatment period (Week 52) was substantially lower for participants in the mepolizumab group than in the placebo group (4.3% and 24.6%, respectively). Participants in the mepolizumab group continued to have a substantially lower probability of surgery (8.7%) compared with the placebo group (30.8%) at the end of the no treatment follow-up period (Week 76).

**SF-36 Health Survey**

At Baseline, norm-based median scores for the SF-36 Health Survey ranged from lower values in General Health (40.35 for both the mepolizumab and placebo groups) to higher values for Social Functioning (75.00 for both the mepolizumab and placebo groups).

At the end of the treatment period (Week 52), the median change from baseline was 0.00 in all 8 SF-36 domains for the placebo group. The mepolizumab group had median improvements from baseline in the 6 domains of Physical Functioning (3.83), Role Physical (6.73), Body Pain (4.44), General Health (4.76), Vitality (5.94) and Mental Health (2.62). No improvement was observed in the 2 domains of Social Functioning (0.00) and Role Emotional (0.00).

The median change from baseline at Week 52 for the Mental and Physical Component Summary scores 0.00 for the placebo group. For the mepolizumab group, there was a larger median change from baseline in the Physical Component Summary score (6.75) than the Mental Component Summary Score (1.20).

**Work Productivity and Activity Impairment Questionnaire (WPAI-GH v2).**

Mean WPAI scores were similar at baseline (Randomisation) for each question in both the mepolizumab and placebo treatment groups: work time missed due to health (4.9% and 5.0%, respectively), impairment while working due to health (48.1% and 50.1%, respectively), overall work impairment due to health (49.5% and 50.8%) and activity impairment due to health (53.4% and 53.2%, respectively).

At Week 52, improvements were observed in both the mepolizumab and placebo groups, with lower impairment apparent in the mepolizumab group compared with the placebo group: impairment while working due to health (18.5% and 22.9%, respectively), overall work impairment due to health (20.6% and 27.0%) and activity impairment due to health (19.2% and 27.1%, respectively). Little improvement was observed in either the mepolizumab.

## Ancillary analyses

### Analysis of the Endoscopic Nasal Polyp Score Co-Primary Endpoint by Subgroup

Results of the subgroup analyses carried out on the co-primary endpoint of change from baseline in total endoscopic NP score at Week 52 were generally consistent with those seen in the ITT population.

**Table 20: Subgroup Analysis of Change from Baseline Total Endoscopic Nasal Polyps Score (Centrally Read) at Week 52 (Study 205687, ITT Population)**

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **ITT Population** | | |
| n | 201 | 206 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -0.73 (-1.11, -0.34) |
| Responder, n (%) [b] | 57 (28) | 104 (50) |
| **Asthma** | | |
| **Concurrent asthma** | | |
| n | 149 | 140 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-1.40, -0.60) |
| Responder, n (%) [b] | 44 (30) | 74 (53) |
| **No concurrent asthma** | | |
| n | 52 | 66 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | -0.42 (-0.98, 0.13) |
| Responder, n (%) [b] | 13 (25) | 30 (45) |
| **AERDS** | | |
| **Current AERDS** | | |
| n | 63 | 45 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -0.89 (-1.73, -0.05) |
| Responder, n (%) [b] | 13 (21) | 23 (51) |
| **No current AERDS** | | |
| n | 138 | 161 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -0.50 (-0.89, -0.11) |
| Responder, n (%) [b] | 44 (32) | 81 (50) |

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Number of previous surgeries** | | |
| **Number of previous surgeries: 1** | | |
| n | 81 | 108 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-1.51, -0.49) |
| Responder, n (%) [b] | 29 (36) | 60 (56) |
| **Number of previous surgeries: 2** | | |
| n | 47 | 47 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | 0.00 (-0.80, 0.80) |
| Responder, n (%) [b] | 15 (32) | 19 (40) |
| **Number of previous surgeries: >2** | | |
| n | 73 | 51 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | -0.20 (-0.86, 0.46) |
| Responder, n (%) [b] | 13 (18) | 25 (49) |
| **Baseline blood eosinophils** | | |
| **≤0.3 GI/L** | | |
| n | 66 | 69 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -0.80 (-1.43, -0.17) |
| Responder, n (%) [b] | 19 (29) | 35 (51) |
| **>0.3 to ≤0.5 GI/L** | | |
| n | 59 | 60 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | -0.33 (-1.05, 0.38) |
| Responder, n (%) [b] | 20 (34) | 29 (48) |
| **>0.5 to ≤0.7 GI/L** | | |
| n | 26 | 28 |
| Median change from baseline | 1.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -2.00 (-3.16, -0.84) |
| Responder, n (%) [b] | 4 (15) | 16 (57) |
| **>0.7 GI/L** | | |
| n | 50 | 49 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | 0.00 (-0.68, 0.68) |
| Responder, n (%) [b] | 14 (28) | 24 (49) |

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Region** | | |
| **Europe** | | |
| n | 85 | 86 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-1.59, -0.41) |
| Responder, n (%) [b] | 24 (28) | 45 (52) |
| **United States** | | |
| n | 28 | 28 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | -0.39 (-1.14, 0.36) |
| Responder, n (%) [b] | 6 (21) | 11 (39) |
| **Region: Rest of World** | | |
| n | 88 | 92 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-1.60, -0.40) |
| Responder, n (%) [b] | 27 (31) | 48 (52) |
| **Age** | | |
| **18 to <40 years** | | |
| n | 52 | 64 |
| Median change from baseline | 0.0 | -0.5 |
| Difference in medians (95% CI) [a] | | -0.43 (-1.04, 0.19) |
| Responder, n (%) [b] | 17 (33) | 32 (50) |
| **40 to <65 years** | | |
| n | 122 | 113 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | -0.65 (-1.10, -0.20) |
| Responder, n (%) [b] | 30 (25) | 56 (50) |
| **≥65 years** | | |
| n | 27 | 29 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-2.17, 0.17) |
| Responder, n (%) [b] | 10 (37) | 16 (55) |
| **Gender** | | |
| **Male** | | |
| n | 125 | 139 |
| Median change from baseline | 0.0 | 0.0 |
| Difference in medians (95% CI) [a] | | 0.00 (-0.38, 0.38) |
| Responder, n (%) [b] | 36 (29) | 65 (47) |
| **Female** | | |
| n | 76 | 67 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-1.59, -0.41) |
| Responder, n (%) [b] | 21 (28) | 39 (58) |

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Race** | | |
| **White** | | |
| n | 187 | 192 |
| Median change from baseline | 0.0 | -1.0 |
| Difference in medians (95% CI) [a] | | -1.00 (-1.36, -0.64) |
| Responder, n (%) [b] | 52 (28) | 99 (52) |
| **Asian** | | |
| n | 9 | 9 |
| Median change from baseline | 0.0 | 1.0 |
| Difference in medians (95% CI) [a] | | Non-estimable |
| Responder, n (%) [b] | 3 (33) | 3 (33) |
| **African American/African Heritage** | | |
| n | 5 | 5 |
| Median change from baseline | 0.0 | 1.0 |
| Difference in medians (95% CI) [a] | | Non-estimable |
| Responder, n (%) [b] | 2 (40) | 2 (40) |
| [redacted] | | |

***Analysis of the Nasal Obstruction VAS Score Co-Primary Endpoint by Subgroup***

Results of the subgroup analyses carried out on the co-primary endpoint of change from baseline in nasal obstruction VAS score at Week 49-52 were generally consistent with those seen in the ITT population.

**Table 21: Subgroup Analysis of Change from Baseline Nasal Obstruction VAS Score (Weeks 49-52) (Study 205687, ITT Population)**

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **ITT Population** | | |
| n | 201 | 206 |
| Median change from baseline | -0.82 | -4.42 |
| Difference in medians (95% CI) [a] | | -3.14 (--4.09, -2.18) |
| **Asthma** | | |
| **Concurrent asthma** | | |
| n | 149 | 140 |
| Median change from baseline | -0.75 | -4.27 |
| Difference in medians (95% CI) [a] | | -2.88 (-3.97, -1.79) |
| **No concurrent asthma** | | |
| n | 52 | 66 |
| Median change from baseline | -1.40 | -4.69 |
| Difference in medians (95% CI) [a] | | -3.12 (-5.23, -1.02) |
| **AERDS** | | |
| **Current AERDS** | | |
| n | 63 | 45 |
| Median change from baseline | -0.04 | -4.97 |
| Difference in medians (95% CI) [a] | | -4.43 (-5.82, -3.03) |
| **No current AERDS** | | |
| n | 138 | 161 |
| Median change from baseline | -1.67 | -4.31 |
| Difference in medians (95% CI) [a] | | -2.42 (-3.67, -1.18) |
| **Number of previous surgeries** | | |
| **Number of previous surgeries: 1** | | |
| n | 81 | 108 |
| Median change from baseline | -2.15 | -4.74 |
| Difference in medians (95% CI) [a] | | -2.46 (-3.94, -0.97) |
| **Number of previous surgeries: 2** | | |
| n | 47 | 47 |
| Median change from baseline | -0.75 | -4.31 |
| Difference in medians (95% CI) [a] | | -0.77 (-3.27, 1.72) |
| **Number of previous surgeries: >2** | | |
| n | 73 | 51 |
| Median change from baseline | -0.22 | -3.49 |
| Difference in medians (95% CI) [a] | | -3.50 (-4.90, -2.10) |

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Baseline blood eosinophils** | | |
| **≤0.3 GI/L** | | |
| n | 66 | 69 |
| Median change from baseline | -2.37 | -4.31 |
| Difference in medians (95% CI) [a] | | -1.88 (-3.89, 0.13) |
| **>0.3 to ≤0.5 GI/L** | | |
| n | 59 | 60 |
| Median change from baseline | -1.36 | -5.87 |
| Difference in medians (95% CI) [a] | | -4.30 (-6.37, -2.24) |
| **>0.5 to ≤0.7 GI/L** | | |
| n | 26 | 28 |
| Median change from baseline | -0.14 | -3.35 |
| Difference in medians (95% CI) [a] | | -3.58 (-5.84, -1.32) |
| **>0.7 GI/L** | | |
| n | 50 | 49 |
| Median change from baseline | 0.00 | -4.40 |
| Difference in medians (95% CI) [a] | | -3.55 (-5.40, -1.71) |
| **Region** | | |
| **Europe** | | |
| n | 85 | 86 |
| Median change from baseline | -1.01 | -4.27 |
| Difference in medians (95% CI) [a] | | -3.44 (-4.92, -1.97) |
| **United States** | | |
| n | 28 | 28 |
| Median change from baseline | 0.00 | -2.66 |
| Difference in medians (95% CI) [a] | | -1.39 (-3.02, 0.23) |
| **Rest of World** | | |
| n | 88 | 92 |
| Median change from baseline | -1.87 | -5.64 |
| Difference in medians (95% CI) [a] | | -4.42 (-6.66, -2.18) |
| **Age** | | |
| **18-<40 years** | | |
| n | 52 | 64 |
| Median change from baseline | -0.98 | -3.46 |
| Difference in medians (95% CI) [a] | | -1.54 (-3.34, 0.26) |
| **40-<65 years** | | |
| n | 122 | 113 |
| Median change from baseline | -0.63 | -4.97 |
| Difference in medians (95% CI) [a] | | -3.64 (-4.73, -2.56) |
| **≥65 years** | | |
| n | 27 | 29 |
| Median change from baseline | -2.67 | -5.07 |
| Difference in medians (95% CI) [a] | | -0.16 (-3.22, 2.91) |

| Subgroup | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| **Gender** | | |
| **Male** | | |
| n | 125 | 139 |
| Median change from baseline | -1.36 | -4.11 |
| Difference in medians (95% CI) [a] | | -2.59 (-3.85, -1.34) |
| **Female** | | |
| n | 76 | 67 |
| Median change from baseline | -0.23 | -4.98 |
| Difference in medians (95% CI) [a] | | -3.80 (-5.31, -2.29) |
| **Race** | | |
| **White** | | |
| n | 187 | 192 |
| Median change from baseline | -1.01 | -4.78 |
| Difference in medians (95% CI) [a] | | -3.36 (-4.37, -2.36) |
| **Asian** | | |
| n | 9 | 9 |
| Median change from baseline | -0.04 | -0.34 |
| Difference in medians (95% CI) [a] | | Non-estimable |
| **African American/African Heritage** | | |
| n | 5 | 5 |
| Median change from baseline | 0.00 | -0.10 |
| Difference in medians (95% CI) [a] | | Non-estimable |

## Summary of main studies

The following table(s) summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment.

**Table 22:Summary of Efficacy for Trial 205687**

| **Title: A randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab)** | | |
|---|---|---|
| Study Identifier | Study 205687<br>EudraCT number: 2016-004255-70<br>ClinicalTrials.gov Identifier: NCT03085797 | |
| Design | Multicentre, randomised, double-blind, placebo-controlled, parallel-group. | |
| | Duration of Main Phase:<br>Duration of Run-in Phase:<br>Duration of Extension Phase: | 52 weeks<br>4 weeks<br>24 weeks (for a subset of participants only) |
| Hypothesis | Superiority | |
| Treatments groups | Mepolizumab | Mepolizumab 100 mg Solution for Injection administered as a subcutaneous injection once every 4 weeks for 52 weeks.<br>206 participants treated. |
| | Placebo | Placebo to match Mepolizumab Solution for Injection administered as a subcutaneous injection once every 4 weeks for 52 weeks.<br>201 participants treated. |
| Endpoints and definitions | Co-Primary Endpoints | • Change from baseline in total endoscopic nasal polyp (NP) score at Week 52.<br>• Change from baseline in mean nasal obstruction visual analogue scale (VAS) score during the 4 weeks prior to Week 52. |

| | | |
|---|---|---|
| | Key Secondary Endpoint | • Time to first nasal surgery up to Week 52. |
| | Other Secondary Endpoints | • Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52.<br>• Change from baseline in Sino-nasal Outcome Test – 22 item (SNOT-22) total score at Week 52.<br>• Proportion of participants requiring systemic steroids for nasal polyps up to Week 52.<br>• 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.<br>• Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52. |
| Database lock | 03 March 2020 (data unblinding) | |

## Results and Analysis

| **Analysis description** | **Primary Analysis of Co-Primary Endpoint - Change from baseline in total endoscopic NP score at Week 52.** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: Week 52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Median change from Baseline | | 0.0 | -1.0 |
| | Min, max | | -5, 3 | -6, 3 |
| Effect estimate per comparison | Co-Primary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | p-value (Wilcoxon rank-sum test) | | <0.001 |
| | | Adjusted treatment difference in medians (Quantile Regression) | | -0.73 |
| | | 95% CI | | -1.11, -0.34 |

| **Analysis description** | **Primary Analysis of Co-Primary Endpoint - Change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52.** | | | |
|---|---|---|---|---|
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: Weeks 49-52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Median change from Baseline | | -0.82 | -4.41 |
| Effect estimate per comparison | Co-Primary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | p-value (Wilcoxon rank-sum test) | | <0.001 |
| | | Adjusted treatment difference in medians (Quantile Regression) | | -3.14 |
| | | 95% CI | | -4.09, -2.18 |

| **Analysis description** | **Key Secondary Analysis - Time to first nasal surgery up to Week 52.** | | |
|---|---|---|---|
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: up to Week 52 | | |
| Descriptive statistics and estimate variability | Treatment group | Placebo | Mepolizumab |
| | Number of participants | 201 | 206 |
| | Participants with nasal surgery prior to Week 52 | 46 (23%) | 18 (9%) |

| | | | | |
|---|---|---|---|---|
| Effect estimate per comparison | Key Secondary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | Hazard ratio | | 0.43 |
| | | 95% CI | | 0.25, 0.76 |
| | | p-value (Kaplan-Meier estimate) | | p=0.003 |
| **Analysis description** | **Secondary Analysis - Change from baseline in mean overall VAS symptom score during the 4 weeks prior to Week 52.** | | | |
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: Weeks 49-52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Median change from Baseline | | -0.90 | -4.48 |
| Effect estimate per comparison | Secondary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | p-value<br>(Wilcoxon rank-sum test) | | <0.001 |
| | | Adjusted treatment difference in medians<br>(Quantile Regression) | | -3.18 |
| | | 95% CI | | -4.10, -2.26 |
| **Analysis description** | **Secondary Analysis - Change from baseline in SNOT-22 total score at Week 52.** | | | |
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: Week 52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Median change from Baseline | | -14.0 | -30.0 |
| Effect estimate per comparison | Secondary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | p-value<br>(Wilcoxon rank-sum test) | | <0.001 |
| | | Adjusted treatment difference in medians<br>(Quantile Regression) | | -16.49 |
| | | 95% CI | | -23.57, -9.42 |
| **Analysis description** | **Secondary Analysis - Proportion of participants requiring systemic steroids for nasal polyps up to Week 52.** | | | |
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: up to Week 52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Participants with ≥1 course | | 74 (37%) | 52 (25%) |
| Effect estimate per comparison | Secondary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | Odds ratio to placebo<br>(Logistic Regression) | | 0.58 |
| | | 95% CI | | 0.36, 0.92 |
| | | p-value | | p=0.020 |
| **Analysis description** | **Secondary Analysis - 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.** | | | |

| | | | | |
|---|---|---|---|---|
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: Weeks 49- 52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Median change from Baseline | | -0.89 | -3.96 |
| Effect estimate per comparison | Secondary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | p-value<br>(Wilcoxon rank-sum test) | | <0.001 |
| | | Adjusted treatment difference in medians | | -2.68 |
| | | 95% CI | | -3.44, -1.91 |
| **Analysis description** | **Secondary Analysis - Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52.** | | | |
| Analysis population and time point description | Intent to treat (All randomised participants who had at least 1 dose of study treatment)<br>Timepoint: Weeks 49-52 | | | |
| Descriptive statistics and estimate variability | Treatment group | | Placebo | Mepolizumab |
| | Number of participants | | 201 | 206 |
| | Median change from Baseline | | 0 | -0.53 |
| Effect estimate per comparison | Secondary Endpoint | Comparison groups | | Mepolizumab vs Placebo |
| | | p-value<br>(Wilcoxon rank-sum test) | | <0.001 |
| | | Adjusted treatment difference in medians<br>(Quantile Regression) | | -0.37 |
| | | 95% CI | | -0.65, -0.08 |

**Additional post HOC analyses**

**Co-Primary Endpoints**

Post-hoc supplementary analyses were carried out using a regression-based parametric mixed model repeated measures (MMRM) approach for the co-primary endpoints of:

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

For these analyses, the summary measure of treatment effect was the difference between mepolizumab and placebo in variable means for the intent to treat (ITT) population.

Nasal surgery represents an intercurrent event as any nasal surgical procedure can affect subsequent scores for the co-primary endpoints.

Missing data from participants who prematurely withdrew from the study was imputed using multiple imputation. Two strategies were for the imputation of missing data:

a) missing at random (MAR) imputation implemented which assumes that future outcomes for those who withdraw can be predicted from a combination of participant characteristics, the participant's past observations and the patterns of response of participants who remain in the trial (i.e. conditional on the data observed for each participant, their unavailable data are randomly missing).

b) off-treatment imputation which assumes that future outcomes for those who withdraw can be predicted from a combination of participant characteristics, the participant's past observations and the patterns of response of participants who withdrew from the investigational product but continued in the trial.

Stepwise imputation methods were implemented where imputations for a visit are conditioned on data from previous visits. For both models missing values were imputed sequentially at post-baseline visits *1,…,T*. At a given visit *t* the imputation regression model included both observed and imputed outcome values from previous visits *1,…,t-1*, baseline score, region, log(e) baseline blood eosinophil count and treatment at visit *t*.

Both observed and imputed outcome values from previous visits were used in the regression models. For the MAR model the treatment covariate at visit *t* was equal to the participants randomised treatment regardless of the on or off-treatment status. For participants who had already discontinued from the study at visit *t*, missing values were imputed based on the regression model and assuming those observations are per randomised treatment.

For the off-treatment model, the treatment covariate at visit *t* was equal to the randomised treatment if the participant was still on-treatment or a generic 'off-treatment' if the participant had already discontinued treatment. For participants who had already discontinued from the study at visit *t*, missing values were imputed based on the regression model and assuming those observations are off-treatment.

For each co-primary endpoint, analysis of the completed datasets was carried out using a mixed model repeated measures analysis with covariates of treatment group, geographic region, baseline value, log(e) baseline blood eosinophil count and time point, plus interaction terms for time point by baseline value and time point by treatment group. The results were combined across 2000 imputations using Rubin's rules.

**Nasal Polyp Surgery**

A post-hoc analysis of the proportion of participants in the ITT population requiring nasal surgery was carried out. The summary measure of treatment effect was the odds ratio representing the relative odds of a participant undergoing nasal surgery up to Week 52 in the mepolizumab arm compared with placebo. A treatment policy strategy was used for the intercurrent event of premature discontinuation of interventional product. All nasal surgeries were included in the analysis regardless of whether the surgery occurred before or after discontinuation of interventional product. The analysis was conducted using a logistic regression model with covariates of treatment group, geographic region, baseline total endoscopic score (centrally read), baseline nasal obstruction VAS, log(e) baseline blood eosinophil count and number of previous surgeries (1, 2, >2 as ordinal).

**Health-Quality of Life: SNOT-22 Total and Domain Scores**

Post-hoc supplementary analyses of the Sino-nasal Outcome Test - 22 items (SNOT-22) total score and individual domain scores were conducted, the summary measure of treatment effect being the difference between mepolizumab and placebo in variable means for the ITT population (the summary measure for the primary analysis of SNOT-22 was the difference in medians). For this post-hoc analysis, handling of intercurrent events was the same as for the primary analysis.

Analysis was carried out using mixed model repeated measures with covariates of treatment group, geographic region, baseline, log(e) baseline blood eosinophil count and visit, plus interaction terms for visit by baseline and visit by treatment group.

**Summary of the results of the post hoc analysis**

- **Endoscopic Nasal Polyp Score and Symptoms of Nasal Obstruction (Co-Primary Endpoints)**

Total ENP Score (Centrally Read)

The total ENP score was the sum of the right and left nostril scores, with a range of 0 (no polyps in either nostril) to 8 (large polyps causing almost complete congestion/ obstruction of the inferior meatus in both nostrils). Total ENP scores were similar in both treatment groups at Baseline, with a mean (SD) score of 5.4 (1.17) in the mepolizumab group and 5.6 (1.41) in the placebo group.

**Table 23 : Analysis of Mean Change from Baseline at Week 52 in Total Endoscopic Nasal Polyps Score (Centrally Read) (MMRM Analysis) (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n[1] | 180 | 184 |
| n[2] | 21 | 22 |
| **Multiple Imputation - Missing at Random (MAR)[3]** | | |
| LS mean (SE) | 5.49 (0.136) | 4.50 (0.134) |
| LS mean change (SE) | 0.01 (0.136) | -0.98 (0.134) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -0.99 (-1.36, -0.61) |
| p-value | | <0.001 |
| **Multiple Imputation - Off-Treatment Imputation[4]** | | |
| LS mean (SE) | 5.54 (0.140) | 4.61 (0.139) |
| LS mean change (SE) | 0.06 (0.140) | -0.87 (0.139) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -0.93 (-1.31, -0.55) |
| p-value | | <0.001 |

[redacted]

1. Number with data at Week 52 or nasal surgery prior to Week 52.
2. Number with missing data imputed at Week 52 in the absence of nasal surgery.
3. Missing data imputed as though participants continued to receive their randomised treatment. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model. Estimates combined using Rubin's rule. Based on 2000 imputations.
4. Missing data imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model. Estimates combined using Rubin's rule. Based on 2000 imputations.

Analysis using MMRM, covariates treatment, geographic region, baseline, log(e) baseline blood eosinophil count, visit, interaction terms for visit by baseline and visit by treatment. Estimates based on weighting applied to each level of class variable from observed proportions.

Note: Participants with nasal surgery prior to visit were assigned worst possible score.

- **Symptoms of Nasal Obstruction**

**Table 24 : Analysis of Mean Change from Baseline at Weeks 49-52 in Nasal Obstruction VAS Score (MMRM Analysis) (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n[1] | 183 | 187 |
| n[2] | 18 | 19 |
| **Multiple Imputation - Missing at Random (MAR)[3]** | | |
| LS mean (SE) | 6.44 (0.240) | 4.47 (0.238) |
| LS mean change (SE) | -2.53 (0.240) | -4.50 (0.238) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -1.97 (-2.63, -1.31) |
| p-value | | <0.001 |
| **Multiple Imputation - Off-Treatment Imputation[4]** | | |
| LS mean (SE) | 6.43 (0.251) | 4.57 (0.250) |
| LS mean change (SE) | -2.54 (0.251) | -4.40 (0.250) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -1.86 (-2.53, -1.19) |
| p-value | | <0.001 |

[redacted]

1. Number with data at Weeks 49- 52 or nasal surgery prior to Weeks 49-52.
2. Number with missing data imputed for Weeks 49-52 in the absence of nasal surgery.
3. Missing data imputed as though participants continued to receive their randomised treatment. Imputations were made stepwise by time period and conditioned on data from previous time periods with the same covariates used in the analysis model. Estimates combined using Rubin's rule. Based on 2000 imputations.
4. Missing data imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by time period and conditioned on data from previous time periods with the same covariates used in the analysis model. Estimates combined using Rubin's rule. Based on 2000 imputations.

Analysis using MMRM, covariates treatment, geographic region, baseline, log(e) baseline blood eosinophil count, time period, interaction terms for time period by baseline and time period by treatment. Estimates based on weighting applied to each level of class variable from observed proportions.
Note: Participants with nasal surgery prior to time period were assigned worst possible score.

- **Nasal Polyp Surgery**

By Week 52, 18 participants (9%) in the mepolizumab group and 46 participants (23%) in the placebo group had undergone nasal surgery. In a post-hoc analysis of the proportion of participants requiring nasal surgery, the odds of surgery were statistically significantly lower for participants in the mepolizumab group compared with the placebo group (odds ratio: 0.39, 95% CI: 0.21, 0.72; p=0.003)

- **Health-Related Quality of Life**

**Table 25: Analysis of Mean Change from Baseline at Week 52 in SNOT-22 Total Score (MMRM Analysis) (Study 205687, ITT Population)**

| | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n[1] | 198 | 205 |
| n[2] | 198 | 205 |
| LS mean (SE) | 48.4 (1.65) | 34.5 (1.62) |
| LS mean change (SE) | -15.6 (1.65) | -29.5 (1.62) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -13.9 (-18.5, -9.4) |
| p-value | | <0.001 |

[redacted]

1. Number with analysable data for one/more time point.
2. Number with analysable data at given time point.

Note: Analysis performed using mixed model repeated measures with covariates of treatment group, geographic region, baseline, log(e) baseline blood eosinophil count, visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Note: 1 Mepolizumab and 3 Placebo participants with missing baseline were excluded from the analysis.

Note: Participants with nasal surgery/sinuplasty prior to visit, participants who withdrew from study with no surgery/sinuplasty and participants with missing visit data were assigned their worst observed score prior to nasal surgery/sinuplasty or study withdrawal or the missing visit respectively.

**Table 26: Analysis of Mean Change from Baseline in SNOT-22 Domain Scores at Week 52 (MMRM Analysis) (Study 205687, ITT Population)**

| Domain | Placebo (N=201) | Mepolizumab 100 mg SC (N=206) |
|---|---|---|
| n[1] | 198 | 205 |
| n[2] | 198 | 205 |
| Nasal Score; Range: 0 (no problem) to 30 (the problem is as bad as it can be) | | |
| LS mean (SE) | 17.4 (0.50) | 13.0 (0.49) |
| LS mean change (SE) | -5.1 (0.50) | -9.5 (0.49) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -4.4 (-5.8, -3.0) |
| Non-nasal Symptoms Score; Range: 0 (no problem) to 10 (the problem is as bad as it can be) | | |
| LS mean (SE) | 4.7 (0.18) | 3.4 (0.17) |
| LS mean change (SE) | -1.2 (0.18) | -2.5 (0.17) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -1.3 (-1.8, -0.8) |
| Ear/Facial Symptoms Score; Range: 0 (no problem) to 20 (the problem is as bad as it can be) | | |
| LS mean (SE) | 6.7 (0.32) | 4.5 (0.31) |
| LS mean change (SE) | -2.0 (0.32) | -4.2 (0.31) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -2.2 (-3.1, -1.4) |
| Sleep Score; Range: 0 (no problem) to 15 (the problem is as bad as it can be) | | |
| LS mean (SE) | 6.8 (0.29) | 4.9 (0.28) |
| LS mean change (SE) | -2.0 (0.29) | -3.9 (0.28) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -1.9 (-2.7, -1.1) |
| Fatigue Score; Range: 0 (no problem) to 20 (the problem is as bad as it can be) | | |
| LS mean (SE) | 8.7 (0.36) | 6.0 (0.36) |
| LS mean change (SE) | -2.5 (0.36) | -5.3 (0.36) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -2.8 (-3.8, -1.8) |
| Emotional Consequences Score; Range: 0 (no problem) to 15 (the problem is as bad as it can be) | | |
| LS mean (SE) | 5.1 (0.26) | 3.4 (0.25) |
| LS mean change (SE) | -1.8 (0.26) | -3.5 (0.25) |
| Mepolizumab vs Placebo | | |
| Difference (95% CI) | | -1.7 (-2.4, -0.9) |

[redacted]

1. Number with analysable data for one/more time point.
2. Number with analysable data at given time point.

Note: Analysis performed separately for each domain using mixed model repeated measures with covariates of treatment group, geographic region, baseline, log(e) baseline blood eosinophil count, visit plus interaction terms for visit by baseline and visit by treatment group. Estimates are based on weighting applied to each level of class variable determined from observed proportions.

Note: 1 Mepolizumab and 3 Placebo participants with missing baseline were excluded from the analysis.

Note: Participants with nasal surgery/sinuplasty prior to visit, participants who withdrew from study with no surgery/sinuplasty and participants with missing visit data were assigned their worst observed score prior to nasal surgery/sinuplasty or study withdrawal or the missing visit respectively.

The treatment effect estimates from the post-hoc analyses for the total nasal polyps score are aligned with the results from the primary analysis and from the pre-specified sensitivity analysis.

For the nasal obstruction VAS, the treatment effect estimates from the post-hoc MMRM analyses are smaller than the adjusted treatment difference in medians from the primary and pre-specified sensitivity analyses. The MMRM LS mean improvement in the placebo arm of -2.5 is larger than the median of -0.82 (205687 CSR Table, reflecting the skewed nature of the distribution of nasal obstruction VAS scores.

**Table 27: Analyses of Change from Baseline for Total ENP Score (Week 52) and Nasal Obstruction Score (Weeks 49-52) (Study 205687, ITT Population)**

| | Total ENP Score | Nasal Obstruction VAS Score |
|---|---|---|
| Median Change from Baseline | | |
| Primary Analysis[1,2] | | |
| Difference in medians (95% CI)<br>p-value | -0.73 (-1.11, -0.34)<br><0.001 | -3.14 (-4.09, -2.18)<br><0.001 |
| Pre-specified Sensitivity Analysis[1,3] | | |
| Difference in medians (95% CI)<br>p-value | -1.00 (-1.44, -0.56)<br><0.001 | -3.14 (-4.13, -2.15)<br><0.001 |
| Post-Hoc MMRM Analysis[3,4] | | |
| Multiple Imputation - Missing at Random (MAR) | | |
| Difference in LS means (95% CI)<br>p-value | -0.99 (-1.36, -0.61)<br><0.001 | -1.97 (-2.63, -1.31)<br><0.001 |
| Multiple Imputation - Off-Treatment Imputation | | |
| Difference in LS means (95% CI)<br>p-value | -0.93 (-1.31, -0.55)<br><0.001 | -1.86 (-2.53, -1.19)<br><0.001 |

[redacted]

1. Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count. P-value based on Wilcoxon rank-sum test.
2. Participants with nasal surgery prior to the time period were assigned their worst observed score prior to nasal surgery.
3. Participants with nasal surgery prior to the time period were assigned the worst possible score.
4. Mixed model repeated measures with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count, time period, interaction terms for time period by baseline and time period by treatment. Estimates based on weighting applied to each level of class variable from observed proportions.

**Supportive study -**

**Study MPP111782**

This phase 2 study was originally designed as a two-part (Part A and Part B) randomised, double-blind, placebo controlled, multi-center study to investigate the use of 750 mg mepolizumab in reducing the need for surgery in subjects with severe bilateral nasal polyposis. Part A of the study consisted of Screening, Run-in and Treatment Periods.

Part B of the study was the follow-up phase and was intended to give an indication of potential trends in post-treatment nasal polyposis dynamics with a focus on time to recurrence and/or surgery; no formal hypothesis was to be tested.

Subjects who were successfully enrolled in the study were randomized into one of two treatment groups, receiving a total of six doses (one every four weeks):

- Group 1: 750 mg of mepolizumab by intravenous (IV) infusion
- Group 2: Placebo by IV infusion

The total duration of the study for each subject enrolled was up to 11 months if completing Part A only or 13 months if eligible for Part B.

**Number of Subjects:**

It was planned to enrol up to 110 subjects in this study. A total of 109 were enrolled of whom 105 subjects were included in the Safety and Intent-to-Treat (ITT) populations.

An un-blinded sample size re-estimation was performed after 46 subjects completed the study.

| | Number (%) of Subjects | | |
|---|---|---|---|
| | Placebo (N=51) | Mepolizumab (N=54) | Total (N=105) |
| **Number of Subjects Overall** | | | |
| **Planned, N** | **55** | **55** | **110** |
| **Randomized** | **53** | **54** | **109[a]** |
| **Part A[b], N** | **51** | **54** | **105** |
| Completion status | | | |
| Completed | 19 (37) | 22 (41) | 41 (39) |
| Withdrawn | 32 (63) | 32 (59) | 64 (61) |
| Primary reason for Withdrawal | | | |
| Adverse event | 5 (10) | 3 (6) | 8 (8) |
| Did not meet continuation criteria | 11 (22) | 17 (31) | 28 (27) |
| Lack of efficacy | 11 (22) | 5 (9) | 16 (15) |
| Lost to follow-up | 2 (4) | 0 | 2 (2) |
| Protocol deviation | 1 (2) | 5 (9) | 6 (6) |
| Subject reached protocol-defined stopping criteria | 1 (2) | 0 | 1 (<1) |
| Withdrawal by subject | 1 (2) | 2 (4) | 3 (3) |
| **Part B[c], N** | 7 | 14 | 21 |
| Completion status | | | |
| Completed | 5 (71) | 10 (71) | 15 (71) |
| Withdrawn | 2 (29) | 4 (29) | 6 (29) |
| Primary reason for Withdrawal | | | |
| Did not meet continuation criteria | 2 (29) | 3 (21) | 5 (24) |
| Withdrawal by subject | 0 | 1 (7) | 1 (5) |

NOTE: Prior to Protocol Amendment 5, a subject was considered to have completed the study if they completed Part B and was considered a non-completer if they completed Part A but did not meet the continuation criteria for Part B (for this reason completion rates appear low). After Protocol Amendment 5, a subject was considered to have completed the study if they completed Part A.

a. Two enrolled subjects were unassigned at randomization and a further 2 subjects were randomized but did not receive study drug.
b. The total number of subjects who participated in Part A (including those who continued to Part B) are included under Part A.
c. Subjects who participated in Parts A and B are included under Part B.

**Study participants**

Main inclusion criteria:

Subjects who had a diagnosis of severe bilateral nasal polyposis at the Screening Visit and Visit 1 (i.e., at end of run-in period) which met the definition of the need for surgery as described in the study protocol.

Subjects who had at least one previous surgery for the removal of nasal polyps.

1. Subjects had a history of refractory response to steroid therapy as shown by being deemed potentially eligible for surgery despite having been on a regular/continuous course of nasal corticosteroids for the treatment of nasal polyposis for at least 3 months and/or have received a short course of oral steroids in the past for nasal polyp treatment.
2. Male or female between 18 and 70 years of age, inclusive at time of signing informed consent.
3. Subjects were to be free of any clinically significant disease that would interfere with the study schedule or procedures or compromise his/her safety.
4. Subjects with concurrent asthma were to be maintained on no more than 10 mg/day of prednisolone or the equivalent.

Main Exclusion criteria:

A subject was not eligible for inclusion in this study if any of the following criteria applied:

1. As a result of medical interview, physical examination, or screening investigation the physician responsible considered the subject unfit for the study.
2. Subjects requiring oral corticosteroids at a dose greater than 10 mg Prednisolone or equivalent during the study were terminated from the study.
3. Subjects who had an asthma exacerbation requiring admission to hospital within 4 weeks of Screening.
4. Subjects who had received immunotherapy within the previous 12 months.
5. Subjects who were currently receiving or had received within 3 months prior to first mepolizumab dose, chemotherapy, radiotherapy or investigational medications/therapies.

**Treatments**

**Treatment Administration:**

| | Investigational Product | |
|---|---|---|
| **Product name** | Mepolizumab (SB-240563) | Placebo (saline) |
| **Mepolizumab concentration** | 750 mg | NA |
| **Administration route** | IV infusion | IV infusion |
| **Batch/Lot Numbers** | 0001*10000000014175/101253703<br>6001/061115577<br>7001/091227068 | NA |

NOTE: Saline for use as placebo was obtained by each site so no batch number is available.

**Objectives**

Primary objective

- To define the effect of mepolizumab in reducing the need for surgery, defined as reduced endoscopic polyp score and symptom score after six months of treatment.

Secondary objectives

- To investigate the effects of 750 mg doses of mepolizumab on nasal polyp size in subjects with severe bilateral nasal polyposis.
- To investigate actual requirement for polyp surgery during the study between the treatment groups.
- To further assess the safety and tolerability of mepolizumab in subjects with severe bilateral nasal polyposis.
- To assess effects of mepolizumab on associated lower respiratory tract symptoms, inflammation and function.
- To assess effects of mepolizumab on clinical Pharmacodynamic (PD) assessments.
- To characterize the population pharmacokinetics (PK) and PK-PD of mepolizumab.
- Investigation of immunogenicity.

Exploratory objectives

- Evaluation of potential genetic relationship to subject handling or response to mepolizumab.
- Investigation of local (nasal secretions) and systemic (blood) PD markers of clinical response.

**Outcomes /Endpoints**

The primary endpoint for this study was the number of subjects with reduced need for surgery at the end of Part A of the study

Secondary endpoints for this study included endoscopic nasal polyp score dynamics for 750 mg dose levels and placebo subjects; the number of subjects requiring polyp surgery per treatment group; FEV1, FVC, and PEFR parameters. Clinical PD was also assessed as a secondary endpoint including symptoms, PnIF, olfaction testing and VAS questionnaires.

**Randomisation**

Subjects were assigned to the 750 mg mepolizumab or placebo treatment groups in accordance with the randomization schedule generated by Clinical Statistics prior to the start of the study using validated internal software. A centre-based randomization schedule was used for this study.

**Blinding**

This was a double-blind study. A site third-party un-blinded pharmacist was required for investigational product (IP) dispensing.

Treatment codes could be unblinded by an investigator or treating physician only in case of medical emergency or in the event of a serious medical condition, when knowledge of the investigational

product was essential for the clinical management or welfare of the subject. The investigator was to make every effort to contact the medical monitor or appropriate study personnel to discuss options before unblinding the subject's treatment assignment.

If the blind was broken for any reason and the investigator was unable to contact the Sponsor prior to un-blinding, the investigator was to notify the sponsor as soon as possible after the unblinding incident but without revealing the subject's study treatment assignment, unless the information was important to the safety of subjects remaining in the study. The date and reason for the unblinding of treatment assignment of that subject was fully documented by the investigator in the appropriate data collection tool.

Global Clinical Safety and Pharmacovigilance (GCSP) staff could unblind the treatment codes for individual subject in the event of serious adverse event (SAE). If an expedited regulatory report was to be sent to one or more regulatory agencies, a copy of the regulatory report identifying the subject's treatment assignment was sent to investigators in accordance with relevant regulations and/or the MAH policy.

Individuals in World-Wide Bioanalysis, Drug Metabolism and Pharmacokinetics (DMPK), directly involved in the bioanalysis of PK samples for mepolizumab were unblinded. Operating procedures were in place which were strictly followed to ensure that all other personnel involved in the study remained blinded.

The intention for this study was for the treatment blind to remain intact until Inform Database Lock (also known as Source Data Lock and formally Database Freeze), at which point the blind would be officially broken. It was intended that Data management and site staff would remain blinded during the conduct of the study and during the data cleaning, although treatment was dispensed at the site using an unblinded pharmacist. During the final cleaning effort prior to database release the Data Quality Lead (DQL) discovered two incidences of unblinding to actual treatment. Both subjects were withdrawn from the study at the time of unblinding due to misdosing. There was no compromise to subject safety as a result of this unblinding and these subjects' data were fully excluded from the Per Protocol (PP) statistical analysis.

Since the PK concentration data would have unblinded the study team, partial Database Lock was declared on all the study data except for PK. Only after partial database lock were data unblinded and the PK concentration dataset processed to allow the derivation of the PK parameters.

**Sample size**

The sample size was determined using a technique called 'predictive' power whereby interim data were planned to be collected after 40 subjects (in total) completed the study (approximately 20 subjects per treatment group). In total, 42 subjects had completed the study and a further 4 subjects were considered withdrawals and their data were included in the interim analyses. Based on these interim data, the predictive power was determined. A 1-sided alpha level of 0.05 was used when determining the predictive power. Following a review of operational characteristics assessing the impact of decision rules for the sample size determination it was deemed necessary for a prior distribution to be included in the derivation of predictive power when determining sample size re-estimation. A Beta (20, 80) prior was be used for placebo and a Beta (50, 50) was used for the mepolizumab dose.

***Sample Size Re-estimation***

Given that stopping rules (both for efficacy and for futility) were applied, the sample size re-estimation was only to be carried out if the efficacy and futility rules were not met. The sample size could be re-estimated using the interim data and Bayesian priors mentioned above so that the final sample size

gave a 'predicted' power of at least 90%. For logistical purposes, the maximum sample size was however set to approximately 55 per group, even if the predictive power suggested more subjects were required to achieve 90% power.

Analysis populations

All subjects' population included all subjects who were enrolled into the study and included run-in failures.

Safety population comprised of all subjects who received at least one dose of study treatment. This population was based on the treatment the subject actually received. In cases where there was a discrepancy between randomised and actual treatment, the analysis used the actual treatment received by the subject (for more than 50% of their treatment administrations) rather than the randomised treatment. If a subject received an equal number of both treatments then they were assigned to the treatment to which they were randomised.

Intent-To-Treat population (Treated or Exposed) comprised all randomised subjects who received at least one dose of study treatment. This population was based on the treatment to which the subject was randomised. Any subject who received a treatment randomization number was to be considered to have been randomized.

Per-Protocol population (Treated or Exposed) comprised all randomized subjects who received at least one dose of study treatment and who complied with the protocol.

Pharmacokinetic population included subjects in the 'Safety' population for whom at least one pharmacokinetic sample was obtained and analysed.

**Statistical Methods**

The main aim of this study was to test for superiority of mepolizumab against placebo. The null hypothesis for the treatment comparison was that there is no difference between mepolizumab and placebo in the proportion of subjects who do not require surgery following 6 months of treatment. The alternative hypothesis was that the proportion of subjects with a reduction in the need for surgery at Week 25 is greater in mepolizumab then placebo.

An adaptive design incorporating an interim analysis was used with two separate alpha levels. At the interim the mepolizumab dose was deemed to have shown to reject H0 if the p-value was less than or equal to 0.025 (1-sided); i.e., alpha was set to a 1-sided 0.025 level at the interim. The interim showed that the efficacy results met the criteria specified in the protocol to continue recruiting subjects. There was no qualitative difference in the conclusion contingent upon the missing data methods (last observation carried forward [LOCF] or set to non-responder). The predictive power calculation suggested a revised sample size of 50 per arm in total.

A one-sided test with $\alpha=0.05$ could be used to test the above hypothesis at the final look. Different alpha levels were chosen at interim and final lock so that the study would only be stopped early for efficacy if there was overwhelming evidence of effect. No formal alpha adjustments were made as a consequence of the interim look. The resultant study-wise overall estimated significance level for the adaptive design was estimated as 0.0527. This was based on an assumption that the placebo proportion of subjects requiring surgery was 20%. Slight changes were seen in the overall estimated significance as the assumed placebo rate changed.

Efficacy data were analysed using three methods:

- The "per protocol" missing method, which set any missing responses or steroid excluded responses to non-responder status.

- The LOCF method, where the last non-missing or non-steroid-excluded responder status was carried forward to the final Part A visit.
- The multiple imputation method, which imputed missing data (and any steroid excluded data) in a chronological order from the first missing visit up to and including the final Part A visit (separate imputation models were used for each treatment arm [via by-group processing]).

**Results**

**Participant flow**

A total of 105 subjects were randomized, received at least one dose of study drug, and were included in the ITT Population.

Prior to Protocol Amendment 5, subjects were considered to have completed the study if they completed Part A and Part B; they were considered a non-completer if they completed Part A but did not meet the continuation criteria for Part B. For this reason, completion rates appear artificially low. Most subjects did not go into part B and therefore were reported as "withdrawn" at the end of Part A, even though they did complete Part A.

After Protocol Amendment 5, a subject was considered to have completed the study if they completed Part A; the requirement for subjects to enter Part B of the study was removed.

**Table 28: Subject Disposition (Study MPP111782, ITT Population)**

| | Number (%) of Subjects | | |
|---|---|---|---|
| | Placebo (N=51) | Mepolizumab 750 mg IV (N=54) | Total (N=105) |
| **Number of Subjects Overall**<br>**Planned, N**<br>**Randomized** | **55**<br>**53** | **55**<br>**54** | **110**<br>**109[a]** |
| **Part A[b], N** | **51** | **54** | **105** |
| Completion status | | | |
| Completed | 19 (37) | 22 (41) | 41 (39) |
| Withdrawn | 32 (63) | 32 (59) | 64 (61) |
| Primary reason for Withdrawal | | | |
| Adverse event | 5 (10) | 3 (6) | 8 (8) |
| Did not meet continuation criteria | 11 (22) | 17 (31) | 28 (27) |
| Lack of efficacy | 11 (22) | 5 (9) | 16 (15) |
| Lost to follow-up | 2 (4) | 0 | 2 (2) |
| Protocol deviation | 1 (2) | 5 (9) | 6 (6) |
| Subject reached protocol-defined stopping criteria | 1 (2) | 0 | 1 (<1) |
| Withdrawal by subject | 1 (2) | 2 (4) | 3 (3) |
| **Part B[c], N** | **7** | **14** | **21** |
| Completion status | | | |
| Completed | 5 (71) | 10 (71) | 15 (71) |
| Withdrawn | 2 (29) | 4 (29) | 6 (29) |
| Primary reason for Withdrawal | | | |
| Did not meet continuation criteria | 2 (29) | 3 (21) | 5 (24) |
| Withdrawal by subject | 0 | 1 (7) | 1 (5) |

Fourteen subjects in the mepolizumab treatment group and 7 subjects in the placebo treatment group chose to continue to Part B. Of these, 4 subjects in the placebo group and 4 subjects in the mepolizumab continued into Part B despite not meeting the continuation requirements

**Baseline data**

Demographic characteristics were well balanced between the treatment groups. The study population was primarily White (97%) and over half were male (71%).

The majority of subjects had a history of asthma (44 [81%] subjects in the mepolizumab treatment group and 38 [75%] subjects in the placebo treatment group). All subjects with a history of asthma had mild or moderate disease and most had not had an exacerbation in the last year (93% in the mepolizumab treatment group and 92% in the placebo group).

The mean duration of asthma for the asthmatic subjects was 160.4 months in the placebo group and 180.3 months in the mepolizumab group.

**Table 29: Demographics (Study MPP111782, ITT Population)**

| Demographics | Placebo (N=51) | Mepolizumab 750 mg IV (N=54) | Total (N=105) |
|---|---|---|---|
| **Age in Years**, Mean (SD) | 49.7 (10.38) | 50.6 (10.73) | 50.2 (10.52) |
| **Sex**, n (%) | | | |
| Female | 17 (33) | 13 (24) | 30 (29) |
| Male | 34 (67) | 41 (76) | 75 (71) |
| **BMI** (kg/m$^2$), Mean (SD) | 25.090 (2.9592) | 26.074 (2.6510) | 25.596 (2.8347) |
| **Height** (cm), Mean (SD) | 175.0 (8.90) | 176.3 (9.05) | 175.6 (8.96) |
| **Weight** (kg), Mean (SD) | 77.2 (13.11) | 81.1 (10.73) | 79.2 (12.05) |
| **Ethnicity**, n (%) | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 51 (100) | 54 (100) | 105 (100) |
| **Race**, n (%) | | | |
| Asian – Central/South Asian Heritage | 0 | 2 (4) | 2 (2) |
| Asian – Japanese/East Asian Heritage/ South East Asian Heritage | 1 (2) | 0 | 1 (<1) |
| White | 50 (98) | 52 (96) | 102 (97) |

Concomitant medication

Prior medications were not collected for this study. Concomitant medications were used during the Run-in Period by all subjects. The most frequently used concomitant medications during Run-in (≥10% overall) were: fluticasone (104 subjects [>99%]), salmeterol (37 subjects [35%]), budesonide 28 subjects [(27%]), formoterol (27 subjects [26%]), salbutamol (22 subjects [21%]), montelukast (11 subjects [10%]) and paracetamol (10 subjects [10%]).

During the Treatment Period, concomitant medications were used by all subjects in the mepolizumab treatment group and 98% of subjects in the placebo group. The most frequently used concomitant medications during treatment (≥10% in either treatment group) were: fluticasone (54 subjects [100%] and 49 subjects [96%] in the mepolizumab and placebo treatment groups, respectively), paracetamol (17 subjects [31%] and 22 subjects [43%], respectively), ibuprofen (4 subjects [7%] and 9 subjects [18%], respectively) and diclofenac (7 subjects [13%] and 0%, respectively).

**Numbers analysed**

Of the subjects who received at least one dose of study treatment, 54 subjects were randomized to the mepolizumab treatment group and 51 subjects were randomized to the placebo treatment group. However, 1 subject who was randomized to mepolizumab received placebo in error. Hence, the Safety Population comprised 53 subjects in the mepolizumab group and 52 subjects in the placebo group.

**Table 30: Summary of Analysis Populations (Study MPP111782)**

| Population | Placebo | Mepolizumab | Not Assigned | Total |
|---|---|---|---|---|
| All Subjects | 53 | 54 | 2 | 109 |
| Safety | 52 | 53 | 0 | 105 |
| Intent-to-Treat | 51 (98) | 54 (102) | 0 | 105 (100) |
| Per Protocol | 51 (98) | 49 (92) | 0 | 100 (95) |
| Pharmacokinetic | 1 (2) | 53 (100) | 0 | 54 (51) |

**Outcomes and estimation**

At Week 25, a significantly greater proportion of subjects in the mepolizumab group compared with the placebo group no longer required surgery (33% versus 10%; p=0.003 for the Per Protocol (PP) Population where missing data were set to non-responder). A supportive analysis using the last observation carried forward (LOCF) method also confirmed these results (35% versus 16% for the mepolizumab and placebo groups, respectively; p=0.016). Analyses of the data using the ITT Population (when missing data were either set to non-responder or using LOCF) supported the main analyses. Nucala vs placebo showed responses 30% versus 10% resp; p=0.006. The additional analysis using the LOCF method also confirmed these results (35% versus 16% for the mepolizumab and placebo groups, respectively; p=0.012).

The increase (compared with placebo) in the number of subjects receiving mepolizumab who did not require polyp surgery by Week 25 could be observed from Week 9 onwards.

The difference between the treatment groups then increased steadily until the end of Part A when 33% of subjects in the mepolizumab group were considered responders compared with 10% in the placebo group.

**Table 31: Summary and Analysis of the Reduction of Subjects Who Require Polyp Surgery by Week 25 (Study MPP111782, PP Population)**

| | | Number (%) of Subjects | | |
|---|---|---|---|---|
| | | Placebo N=51 | Mepolizumab 750 mg IV N=49 | Mid-point P-value |
| Missing = NR | Responder | 5 (10) | 16 (33) | 0.003 |
| | Non-responder | 46 (90) | 33 (67) | |
| Missing = LOCF | Responder | 8 (16) | 17 (35) | 0.016 |
| | Non-responder | 43 (84) | 32 (65) | |

More limited data were available for Part B of the study as only 7 subjects in the placebo group and 14 subjects in the mepolizumab group entered this part of the study. By Week 45 of the study, 36% of subjects in the mepolizumab group were considered to be responders compared with 29% of the placebo group.

Endoscopic nasal polyp score of the worst affected nostril was included in the composite primary endpoint and was a secondary endpoint of this study. The probability of having a lower endoscopic nasal polyp score of the worst affected nostril at Week 25 was higher in the mepolizumab group than in the placebo group for the PP Population (odds ratio: 5.22; 95% CI: 0.99, 27.44; p=0.051). Note that the p-value represents the odds of a lower endoscopic nasal polyp score of the worst affected nostril in the mepolizumab group compared with the placebo group. Similar results were observed in the ITT Population at Week 25 (odds ratio: 6.62; 95% CI: 1.27, 34.49; p=0.025).

The assessment of nasal polyposis using VAS was also part of the composite primary endpoint of the study as well as a secondary endpoint. The nasal polyposis VAS represented as the treatment

difference (mepolizumab - placebo) at Week 25 was -1.81 (CI: -2.90, -0.71; p=0.001). These results were supported by the ITT Population at Week 25 (treatment difference: -1.84; 95% CI: -2.92, -0.76; p=0.001).

Based on the post-hoc definition of responders (subjects who improved from baseline by at least 1 point in total [sum of left and right nostril scores] endoscopic nasal polyp score by Week 25 of the study), in the PP Population at Week 25, a significantly greater proportion of subjects in the mepolizumab group compared with the placebo group had an improvement of at least 1 point over baseline in the total endoscopic nasal polyp score (57% versus 27%; p=0.001). The supportive analysis using the LOCF method also confirmed these results (61% versus 33% for the mepolizumab and placebo groups, respectively; p=0.003). Data from the ITT Population were supportive of the PP Population findings.

**Secondary endpoints:**

**Endoscopic Nasal Polyp Score**

Endoscopic nasal polyp score of the worst affected nostril was included in the composite primary endpoint of this study and was a secondary endpoint of this study.

The probability of having a lower endoscopic nasal polyp score of the worst affected nostril at Week 25 was higher in the mepolizumab group than in the placebo group (odds ratio: 5.22; 95% CI: 0.99, 27.44; p=0.051). Note that the p-value represents the odds of a lower endoscopic nasal polyp score of the worst

affected nostril in the mepolizumab group compared with the placebo group. Similar results were observed in the ITT Population at Week 25 (odds ratio: 6.62; 95% CI: 1.27, 34.49; p=0.025).

**Table 32: Endoscopic Nasal Polyp Score of the Worst Affected Nostril at Week 25 (Study MPP111782, PP Population**

| Worst affected nostril nasal polyp score | Number (%) of Subjects | |
|---|---|---|
| | Placebo N=51 | Mepolizumab 750 mg IV N=49 |
| n | 31 | 42 |
| 0 | 1 (3) | 3 (7) |
| 1 | 2 (6) | 7 (17) |
| 2 | 4 (13) | 7 (17) |
| ≥3 | 24 (77) | 25 (60) |

In both treatment groups, there was a tendency for the distribution of endoscopic nasal polyp scores of the worst affected nostril to shift over time towards lower scores, although this was more marked in the mepolizumab group than in the placebo group.

**Nasal Polyposis VAS**

Severity of condition was assessed by asking subjects to indicate on a VAS (0 – 10 cm) the severity of their nasal polyposis in the mepolizumab and placebo groups at Week 25. The treatment difference (mepolizumab – placebo) at Week 25 was -1.81 (CI: -2.90, -0.71; p=0.001). Similar results were observed in the ITT Population at Week 25 (treatment difference: -1.84; 95% CI: -2.92, -0.76; p=0.001).

In Part A, the difference between treatments in the assessment of severity of nasal polyps was apparent from Week 9 and persisted through Week 25. In general, the response seemed to persist through Part

B of the study but there were limited subjects included in Part B. Therefore, caution should be taken when interpreting this data due to the limited number of subjects. Similar results were observed for the ITT Population.

**Table 33: Assessment of Nasal Polyposis by Visit – VAS (cm) at Week 25 (Study MPP111782, PP Population**

| Nasal polyposis | Placebo N=51 | Mepolizumab 750 mg IV N=49 |
|---|---|---|
| N | 31 | 42 |
| Mean (SD) | 6.21 (3.357) | 4.16 (3.582) |
| Median | 7.40 | 3.05 |
| Min, Max | 0.6, 10.0 | 0.0, 10.0 |
| Confidence interval | 4.98, 7.44 | 3.05, 5.28 |

**Post-Hoc Analyses of Responders Based on Total Endoscopic Nasal Polyp Score Improvement**
The increase (compared with placebo) in the number of subjects receiving mepolizumab who improved from baseline by at least 1 point by Week 25 was observed from Week 9 onwards (27 subjects [55%] and 15 subjects [29%] responders in the mepolizumab and placebo groups, respectively [p=0.005). This improvement was maintained until the end of Part A with very little change in either treatment group during the intervening visits. Although the number of responders and the magnitude of response was greater with the new definition of responders it was observed for both the mepolizumab and placebo groups. There was therefore no overall change in the magnitude of difference between treatments. Overall, these results support the primary analysis.

Results from the PP Population where missing data were imputed using the LOCF method supported these findings.

This difference between the mepolizumab and placebo groups in the number of subjects who improved from baseline by at least 1 point in total endoscopic nasal polyp score was maintained in Part B of the study. In the mepolizumab and placebo groups, respectively, 10 subjects [71%] and 3 subjects [43%] were responders at Week 29, and 8 subjects [57%] and 3 subjects [43%] were responders at Week 45 (PP Population, missing data set to non-responders.

At Week 25, a significantly greater proportion of subjects in the mepolizumab group compared with the placebo group had an improvement of at least 1 point over baseline in the total endoscopic nasal polyp score (57% versus 27%; p=0.001).

A post-hoc summary of subject response based on the total endoscopic nasal polyp score improvement from baseline at Week 25 were performed on the PP Population.

**Subgroup Summary for Subjects with Asthma**
A post-hoc summary of subject response based on the total endoscopic nasal polyp score improvement from baseline at Week 25 for subjects with asthma was performed on the PP Population. As in the main analysis, a greater proportion of subjects in the mepolizumab group compared with the placebo group were considered responders at Week 25 (60% versus 22%). The additional analysis using the LOCF method also confirmed these results (65% versus 30% for the mepolizumab and placebo groups, respectively).

**Subgroup Summary for Subjects with Rhinitis**
A greater proportion of subjects in the mepolizumab group compared with the placebo group were considered responders at Week 25 (53% versus 26%). The additional analysis using the LOCF method also confirmed these results (55% versus 33% for the mepolizumab and placebo groups, respectively).

**Subgroup Summary for Subjects with Rhinosinusitis**
A greater proportion of subjects in the mepolizumab group compared with the placebo group were considered responders at Week 25 (54% versus 27%). The additional analysis using the LOCF method also confirmed these results (56% versus 34% for the mepolizumab and placebo groups, respectively).

**Subgroup Summary for Subjects with Aspirin Sensitivity**
A greater proportion of subjects in the mepolizumab group compared with the placebo group were considered responders at Week 25 (53% versus 16%). The additional analysis using the LOCF method also confirmed these results (58% versus 24% for the mepolizumab and placebo groups, respectively).

**Subgroup Summary for Subjects with Baseline Blood Eosinophil**
Concentrations of >0.3 cells x 109/L A greater proportion of subjects in the mepolizumab group compared with the placebo group were considered responders at Week 25 (58% versus 22%).

The additional analysis using the LOCF method also confirmed these results (63% versus 24% for the mepolizumab and placebo groups, respectively).

**Individual Symptoms Visual Analogue Scales**
Individual symptoms VAS scores were a secondary efficacy endpoint of this study.

Subjects were asked to indicate on a VAS (0 – 10 cm) the severity of 4 nasal polyposis symptoms (1 VAS for each symptom): rhinorrhea, mucus in the throat, nasal blockage and loss of smell.

Assessment of rhinorrhea at Week 25 for the PP Population: The treatment difference (mepolizumab – placebo) at Week 25 was -2.33 (CI: -3.44, -1.22; p<0.001).

Assessment of mucus in the throat at Week 25 for the PP Population: The treatment difference (mepolizumab – placebo) at Week 25 was -2.11 (CI:-3.22, -1.01; p<0.001).

Assessment of nasal blockage at Week 25 for the PP Population: The treatment difference (mepolizumab – placebo) at Week 25 was -1.76 (CI: -2.87, -0.65; p=0.002).

Assessment of loss of smell at Week 25 for the PP Population: The treatment difference (mepolizumab – placebo) at Week 25 was -1.81 (CI: -2.84, -0.78; p=0.001).

## 2.4.3. Discussion on clinical efficacy

The MAH initially submitted a variation application for the following indication:

*Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyps.*

Scientific advice was given by CHMP on May 17th 2016 (Procedure No.: EMEA/H/SA/156/4/2016/III).

The MAH previously planned two replicate phase 3 studies with the primary endpoint at week 24. This was amended to a single pivotal trial and the timing of the co-primary endpoints amended from week 24 to week 52, following discussion with FDA. For the additional aspects the advice was followed by the MAH.

**Design and conduct of clinical studies**

Three studies were submitted by the MAH.

The first study (CRT110178) was an investigator led randomised, double-blind, placebo-controlled, single centre study to investigate the use of mepolizumab 750 mg IV versus placebo study in adult patients with severe CRSwNP (grade 3-4) or NP that were recurrent after surgery or refractory to corticosteroid therapy. Based on the results of this study the MAH initiated the Phase II study MPP111782.

Mepolizumab 750 mg IV demonstrated expected PK in adults with severe bilateral NP, supporting the view that disease is not a covariate of mepolizumab exposure.

No subjects treated with mepolizumab developed anti-drug antibodies, which is consistent with the low immunogenic potential of mepolizumab observed in other indications.

The second (Phase II study MPP111782) was a supportive phase 2b randomised, double-blind, placebo-controlled parallel groups study. Consisting of part A which was 24 weeks duration. Patients received mepolizumab 750 mg iv or placebo Q4W. Part B was for 20 weeks patients received standard of care for NP. 110 patients enrolled and 109 were randomised.

No formal dose-response study was performed in patients with nasal polyps. The dose regimens were selected based on the totality of clinical evidence in the Nucala program including data from Phase 2 study MPP111782 in patients with nasal polyps and symptoms of chronic sinusitis.

The PK data demonstrated that Mepolizumab 100 mg SC in adult patients with CRSwNP resulted in a marked reduction in blood eosinophils early in treatment, which was sustained throughout the study. The magnitude of blood eosinophil count reduction was consistent with subjects with other eosinophilic conditions.

A recent meta-analysis population PK/PD model was applied directly to the PK/PD data collected from adults with CRSwNP in study 205687, without adjustment except for a fixed effect disease parameter for baseline blood eosinophil count to better capture the baseline in subjects with nasal polyposis.

The GOF plots indicated that, in contrast to PK, the PKPD model did not fit the CRSwNS data particularly well, which was confirmed by the GOF statistical tests. This suggests that the PD response to mepolizumab in subjects with CRSwNP may not be similar to other eosinophilic conditions. It appears to be a tendency for over-prediction of eosinophil counts. Based on the exposure-response analysis, at the single dose of 100 mg SC Q4W investigated in the study 205687, there was no evidence of increased efficacy with increased mepolizumab exposure (individual weight-based dose or average plasma concentration). Therefore, the 100mg regimen is acceptable.

There are no proposed dose adjustments in special populations (i.e., elderly, renal- and hepatic-impaired subjects) are not warranted for adult patients with nasal polyposis.

Phase 3 SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab) – study 205687

A single pivotal phase 3 study was conducted. This was a randomised, double-blind, parallel group PhIII study to assess the clinical efficacy and safety of 100 mg SC Mepolizumab as an add-on to maintenance treatment in adults with severe bilateral nasal polyps - SYNAPSE (StudY in NAsal Polyps patients to assess the Safety and Efficacy of mepolizumab).

The study comprised of a 4-week run-in period, followed by a 52-week treatment period. Participants received a total of thirteen, 4-weekly doses of mepolizumab 100 mg or placebo, delivered by SC injection using a pre-filled safety syringe. The final dose of study treatment was administered at Week 48. Patients were followed up to week 76.

All participants were on SoC for CRSwNP throughout the study (run-in, treatment and no-treatment follow-up periods), which consisted of daily mometasone furoate nasal spray (MF), and if required,

saline nasal douching, occasional short courses of high dose OCS and/or antibiotics. At the start of run-in and throughout the study, participants were placed on MF at the maximum prescribed dose (if not already) according to local label.

The patient population consisted of patients 18 years and older with body weight > 40 kgs. Participants who have had at least one previous surgery in the previous 10 years for the removal of NP, high CRSwNP disease burden (based on polyps score) and symptoms of NC. Patients were to have at least 2 symptoms of nasal blockage/congestion, nasal discharge, facial pain/pressure, reduction or loss of smell or rhinorrhea for at least 12 weeks prior to randomization (8 weeks prior to screening) despite therapy with intranasal corticosteroids, systemic corticosteroids in the past 2 years or sino-nasal surgery.

The demographic and baseline characteristics were generally similar between treatment groups in the randomized population. Chronic rhinosinusitis with nasal polyps (CRSwNP) history was comparable among the treatment groups as well as the disease baseline characteristics.

Some protocol amendments and changes in the planned analyses were made in both studies. These changes were unlikely to have a significant impact on the study results.

There were 2 co-primary endpoints:

- Change from Baseline in total ENP 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.

This approach is acceptable as change in nasal polyp size on its own is not considered sufficient as the primary endpoint as the interpretation of the clinical relevance of a reduction is difficult as no MCID has been established and therefore, adding an endpoint evaluating the impact of symptoms is of key importance in measuring outcomes in nasal polyposis.

**Efficacy data and additional analyses**

- Phase 2 study

The phase 2 study demonstrated a statistically significant reduction in the need for surgery at Week 25. 33% versus 10%; p=0.003 for the Per Protocol (PP) Population where missing data were set to non-responder). The secondary endpoints also demonstrated efficacy for mepolizumab treatment.

The probability of having a lower endoscopic nasal polyp score of the worst affected nostril at Week 25 was higher in the mepolizumab group than in the placebo group for the PP Population (odds ratio: 5.22; 95% CI: 0.99, 27.44; p=0.051.

The assessment of nasal polyposis using VAS was also part of the composite primary endpoint of the study as well as a secondary endpoint. The nasal polyposis VAS represented as the treatment difference (mepolizumab - placebo) at Week 25 was -1.81 (CI: -2.90, -0.71; p=0.001). These results were supported by the ITT Population at Week 25 (treatment difference: -1.84; 95% CI: -2.92, -0.76; p=0.001). However, there was a very high withdrawal rate in this study only 39% completed the study, however it is viewed as supportive evidence.

The immunogenicity results support the low immunogenic potential of mepolizumab.

Dose Justification

An SC mepolizumab dose regimen of 100 mg every 28 days was selected in place of 750 mg IV (used in the MPP111782 Phase II study) for this Phase III confirmatory study for several reasons. First, the exposure-response for mepolizumab is independent of administration route. Secondly, the lower (SC) dose provides substantial pharmacological overlap with the higher (IV) dose, with at least a 75% inhibition of blood eosinophils compared to placebo. Thirdly, in study MPP111782, participants

continued to experience benefit from mepolizumab treatment during drug wash-out when their higher dose of 750mg IV had declined to exposures commensurate with a lower dose of 100 mg SC. Finally, during the Phase III severe asthma confirmatory study, MEA115588, participants with concomitant NP experienced clinical benefit for symptoms of NP, in addition to reductions in clinical exacerbations of their severe asthma.

Treatments

- Phase 3 study

Of the 407 patients that were randomised to treatment, 373 completed to week 52. 134 entered the follow-on stage where no treatment was given.

All primary and secondary endpoints achieved statistical significance at the two-sided 5% level adjusted for multiplicity.

The Intent-to-Treat (ITT) Population was the primary population for efficacy analyses and consisted of all randomised participants who received at least one dose of study medication.

For each co-primary endpoint, the p-value for comparing the treatment groups was based on the non-parametric Wilcoxon rank-sum test. The difference in median change from Baseline with 95% confidence intervals (CIs) was estimated by quantile regression using a bootstrap approach with covariates of treatment group, region, baseline score and loge baseline blood eosinophil count.

The median change from baseline in total endoscopic NP score at week 52 was -1.0 ($p<0.001$) in favour of mepolizumab. The adjusted treatment difference in medians (Quantile Regression)- 0.73.

For the other co-primary endpoint the median change from baseline in mean nasal obstruction VAS score during the 4 weeks prior to Week 52 (i.e. weeks 49-52) showed a difference of -3.59 in favour of mepolizumab ($p<0.001$).

Thus, the primary objectives to show superiority of mepolizumab to placebo were formally met.

The results of the sensitivity analyses performed (including as-observed analysis taking into account all data in patients who receive SCS for any reason or missing data) were similar and support the results from the primary analysis.

The MAH was requested to conduct additional analyses for the co-primary endpoints. Post-hoc supplementary analyses were carried out using a regression-based parametric mixed model repeated measures (MMRM) approach for the co-primary endpoints.

For the co-primary endpoint Week 52 in Total Endoscopic Nasal Polyps Score using multiple imputation missing at random (MAR) showed an LS Mean difference of -0.99 (-1.36, -0.61) $p < 0.001$.

Using an off-treatment imputation an LS Mean difference of -0.93 (-1.31, -0.55) $p < 0.001$. These were similar to the initial analysis results.

For the other co-primary endpoint there were lower results observed in the Weeks 49-52 in Nasal Obstruction VAS Score.

For MAR, the LS mean difference was -1.97 (-2.63, -1.31) $p < 0.001$, and with off treatment imputation the LS Mean difference was -1.86 (-2.52, -1.19) $p < 0.001$. These are below the MCID (> 3) quoted by the MAH.

The Applicant was requested to further justify the clinical relevance for results seen in the Weeks 49-52 in Nasal Obstruction VAS Score and the responses were accepted as clinically meaningful.

Subgroup analyses show consistent results across demographic and baseline characteristics, however for gender, the NPS showed no effect in males even though 139 males were enrolled while it would be expected that both males and females would respond similarly. There is no apparent biological rationale to suspect that there would be a difference in outcomes between genders. As well no effect seemed also demonstrated in patients that had 2 or more surgeries. However, additional subgroup analyses provided by the MAH using MMRM upon CHMP request, demonstrated that effects are seen in these 2 subgroups, therefore the issue in these two populations was considered solved and not relevant for further investigation.

Secondary endpoints

- Participants with nasal surgery prior to Week 52 showed a lower percentage of patients treated with mepolizumab needing surgery (9% of patients) compared to 23% in the placebo group. HR 0.43.
- Change from baseline in median overall VAS symptom score during the 4 weeks prior to Week 52, was in favour of Mepolizumab treatment versus placebo -3.58 (adjusted -3.18, $p < 0.001$).
- Change from baseline in Sino-nasal Outcome Test – 22 item (SNOT-22) total score at Week 52 showed a median difference of -16.0, (adjusted -16.49, $p < 0.001$) this is above the MCID of 8.9.
- The proportion of participants requiring systemic steroids for nasal polyps up to Week 52 was lower 12% in patients receiving mepolizumab. Odds ratio 0.58.
- 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, showed a favourable effect in mepolizumab versus placebo with a median difference of -3.07 (adjusted -2.68, $p < 0.001$)

Change from baseline in mean individual VAS symptom score for loss of smell during the 4 weeks prior to Week 52, a median difference of -0.53 (adjusted -0.37, $p <0.001$). At Week 52, the median change from baseline in UPSIT was 0.0 in both treatment groups. The difference between treatment groups was not statistically significant ($p=0.302$). Accounting for treatment group, country, baseline score and log(e) baseline blood eosinophil count, the difference in adjusted medians between treatment groups was 0.40 (95% CI: -1.49, 2.28).

A total of 134 participants (33%) entered the no-treatment follow-up period after Week 52, 69 participants (33%) in the mepolizumab group and 65 participants (32%) in the placebo group.

At Week 76, 24 weeks after the end of the treatment period, the change from Baseline for total endoscopic nasal polyp score remained greater for participants in the mepolizumab group (median change: -1.0, mean change: -1.2, range: -6 to 3, SD: 1.80) than the placebo group (median change: -0.0, mean change: -0.1, range: -4 to 4, SD: 1.59). There was no evidence of rebound effects during the follow up period.

## Assessment of paediatric data on clinical efficacy

The Paediatric committee granted a product-specific waiver on the ground that mepolizumab (in the treatment of CRSwNP) did not represent a significant therapeutic benefit over existing treatment for paediatric patients. The applicant proposed to add the following information to the SmPC which is acceptable.

*Children less than 18 years old*

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established (see section 4.2 of the SmPC). No data are available.

### 2.4.4. Conclusions on the clinical efficacy

The effects of mepolizumab as an add-on therapy to intranasal corticosteroids for the treatment of adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyps have been sufficiently demonstrated.

The final indication granted by CHMP is as follows:
Nucala is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adult patients with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.´

## *2.5. Clinical safety*

**Introduction**

Safety data from the 512 participants with CRSwNP (259 exposed to mepolizumab) participating in the 2 completed placebo-controlled studies, a Phase III study 205687 and a Phase II study MPP111782, have been integrated. The 100 mg subcutaneous (SC) dose of mepolizumab (NUCALA), which is the dose intended for registration, was assessed in the pivotal Phase III placebo-controlled study 205687 and the 750 mg intravenous (IV) dose was assessed in the supportive Phase II placebo-controlled study MPP111782. Key safety data from the broader MAH-sponsored mepolizumab clinical development program have also been integrated.

CRSwNP Placebo-Controlled Studies: The 2 completed MAH-sponsored placebo-controlled studies in the CRSwNP indication, 205687 and MPP111782, were integrated and are referred to as "CRSwNP Placebo-Controlled Studies"; these data are the primary focus of this safety summary.

All Studies Combined: The study grouping referred to as "All Studies Combined" comprises of completed MAH-sponsored studies and ongoing studies with an interim report across all indications. The integrated summaries of demographics, exposure, incidence of SAEs, and deaths are presented.

**Patient exposure**

A total of 259 participants received at least 1 dose of mepolizumab in the CRSwNP placebo-controlled studies. Of these, 206 participants were treated with mepolizumab 100 mg SC and 53 participants were treated with mepolizumab 750 mg IV. Total treatment exposure in the CRSwNP placebo-controlled studies was 207.32 subject-years in the integrated placebo group and 216.44 subject-years in the mepolizumab all doses group (194.79 subject-years in the mepolizumab 100 mg SC group and 21.65 subject-years in the mepolizumab 750 mg IV group (***Table* 34**). By the study design, the study treatment duration was 52 weeks for Study 205687 and was 24 weeks for Study MPP111782.

The majority of participants (88% mepolizumab and 84% placebo) in Study 205687 were exposed to study treatment for 52 weeks; 87% of mepolizumab-treated participants and 80% of placebo-treated participants received 13 doses of study treatment. Two participants in the mepolizumab group and 8 participants in the placebo group received less than 13 doses over 52 weeks.

For Study MPP111782, 72% of mepolizumab-treated participants and 52% of placebo-treated participants were exposed to study treatment for 24 weeks; 79% of mepolizumab-treated participants and 63% of placebo-treated participants received 6 doses of study treatment; Four participants in the mepolizumab group and 6 participants in the placebo group received 6 doses in less than 24.

**Table 34: Summary of Exposure to Study Treatment by Dose (CRSwNP Placebo-Controlled Studies), Safety Population**

| Treatment Exposure | 205687 PBO N=201 | 205687 Mepo 100mg SC N=206 | MPP111782 PBO N=52 | MPP111782 Mepo 750mg IV N=53 | Both studies[1] PBO N=253 | Both studies[1] Mepo all doses N=259 |
|---|---|---|---|---|---|---|
| **Exposure (therapeutic coverage)[1], (months)** | | | | | | |
| n | 201 | 206 | 52 | 53 | 253 | 259 |
| Mean (SD) | 11.2 (2.33) | 11.3 (2.21) | 4.4 (1.66) | 4.9 (1.37) | 9.8 (3.53) | 10.0 (3.32) |
| Median | 12.0 | 12.0 | 5.6 | 5.6 | 12.0 | 12.0 |
| Min to Max | 1 to 14 | 1 to 15 | 1 to 6 | 1 to 6 | 1 to 14 | 1 to 15 |
| **Range of Exposure[2] (Month), n (%)** | | | | | | |
| n | 201 | 206 | 52 | 53 | 253 | 259 |
| 1 to <3 | 5 (2) | 2 (<1) | 8 (15) | 7 (13) | 13 (5) | 9 (3) |
| 3 to <6 | 5 (2) | 9 (4) | 17 (33) | 8 (15) | 22 (9) | 17 (7) |
| 6 to <9 | 12 (6) | 8 (4) | 27 (52) | 38 (72) | 39 (15) | 46 (18) |
| 9 to <12 | 11 (5) | 5 (2) | 0 | 0 | 11 (4) | 5 (2) |
| 12 to <24 | 168 (84) | 182 (88) | 0 | 0 | 168 (66) | 182 (70) |
| **Total Subject-years Exposure[3]** | | | | | | |
| Subject-year exposure | 188.17 | 194.79 | 19.15 | 21.65 | 207.32 | 216.44 |
| **Treatments Administered** | | | | | | |
| n | 201 | 206 | 52 | 53 | 253 | 259 |
| Mean (SD) | 12.0 (2.53) | 12.2 (2.40) | 4.8 (1.79) | 5.3 (1.49) | 10.5 (3.79) | 10.8 (3.59) |
| Median | 13.0 | 13.0 | 6.0 | 6.0 | 13.0 | 13.0 |
| Min to Max | 1 to 13 | 1 to 13 | 1 to 6 | 1 to 6 | 1 to 13 | 1 to 13 |

[redacted]

Abbreviations: Max, maximum; Min, minimum; Mepo, mepolizumab; PBO, placebo; SD, standard deviation.

1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.
2. Exposure Duration (Months) = (Treatment stop date - Treatment start date + 29) x 12/365.25.
3. Sum across participants of (treatment stop date - treatment start date + 29)/365.25.

**Extent of Exposure in All Indications (All Studies Combined)**

A total of 4363 participants received at least 1 dose of mepolizumab in a MAH-sponsored study or program, and 2087 participants received placebo (***Table 35***).

Across all indications, total treatment exposure for the 2722 participants who received mepolizumab 100 mg SC was 4035.87 subject-years, and for the 446 participants who received mepolizumab 750 mg IV, this was 517.69 subject-years. The 750 mg IV dose group in the summary tables does not include those participants who received 750 mg IV in the mepolizumab HES EAP (all participants receiving mepolizumab in the mepolizumab HES EAP are included in the 'other' dose group).

**Table 35: Summary of Participants in the Safety Population by Indication and Dose (All Studies Combined, Safety Population)**

| | Number (%) of Participants | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | PBO | Mepolizumab | | | | | | |
| Indications | | 100 mg SC | 300 mg SC | 75 mg IV | 250 mg IV | 750 mg IV | Other [1] | All doses |
| All, n | 2087 | 2722 | 458 | 361 | 294 | 446 | 607 | 4363 |
| HES | 96 (5) | 0 | 106 (23) | 0 | 0 | 81 (18) | 359 (59) | 462 (11) |
| Asthma | 972 (47) | 1613 (59) | 0 | 355 (98) | 275 (94) | 285 (64) | 130 (21) | 2217 (51) |
| Severe asthma | 803 (38) | 1613 (59) | 0 | 344 (95) | 152 (52) | 156 (35) | 26 (4) | 1850 (42) |
| EoE | 6 (<1) | 0 | 0 | 0 | 0 | 0 | 64 (11) | 64 (1) |
| Atopic dermatitis | 38 (2) | 19 (<1) | 0 | 0 | 0 | 20 (4) | 0 | 39 (<1) |
| Healthy volunteers | 9 (<1) | 244 (9) | 0 | 6 (2) | 19 (6) | 7 (2) | 54 (9) | 330 (8) |
| EGPA | 68 (3) | 0 | 127 (28) | 0 | 0 | 0 | 0 | 127 (3) |
| CRSwNP | 253 (12) | 206 (8) | 0 | 0 | 0 | 53 (12) | 0 | 259 (6) |
| COPD | 645 (31) | 640 (24) | 225 (49) | 0 | 0 | 0 | 0 | 865 (20) |

[redacted]

Abbreviations: EAP, Expanded Access Program; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; IM = intramuscularly; LAP = Long-term Access Program; PBO = placebo.

1. Includes IV doses: 10 mg, 750 mg/1500 mg, 0.05, 0.5, 0.55, 2.5 and 10 mg/kg, SC doses: 12.5, 40, 40/100, 125, and 250 mg, and IM dose: 250 mg, as well as all subjects enrolled in the mepolizumab HES EAP.

Note: In the mepolizumab HES EAP, patients received: mepolizumab 300 mg SC as a starting dose; with a stepwise increase permitted to 500 mg IV and 700 mg IV (current protocol) or mepolizumab 750/700 mg IV, with a stepwise reduction to 500 mg IV and 250 mg IV or 300 mg SC (previous protocol). Subsequent dose and dosing intervals were adjusted throughout the study based on physician assessment of the clinical status of the patient.

Note:

a. A subject who participated in more than 1 study and received different doses was counted once in each dose.

b.Studies included: Asthma - MEA114092, SB240563/001, SB240563/006, SB240563/017, SB240563/035, SB240563/036; Severe Asthma - 200363, 200862, 201312, 204471, 204959, 205667, MEA112997, 201810, MEA115575, MEA115588, MEA115661, MEA115666; HES - 200622, MHE100185, MHE100901, MHE104317, 205203; EoE - MEE103219, MEE103226; Atopic Dermatitis - 205050, SB240563/045; Healthy Volunteers - 204958, MEA115705, SB240563/018; EGPA - MEA115921, MEA116841, 201607; CRSwNP - MPP111782, 205687; COPD - MEA117106, MEA117113.

**Table 36: Summary of Exposure to Study Treatment by Dose (All Studies Combined, Safety Population)**

| | PBO | Mepolizumab | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment Exposure | N=2087 | 100 mg SC N=2722 | 300 mg SC N=458 | 75 mg IV N=361 | 250 mg IV N=294 | 750 mg IV N=446 | Other[1,4] N=607 | All doses[4] N=4363 |
| Exposure (Months)[2] n | 2087 | 2722 | 458 | 361 | 294 | 446 | 601 | 4357 |
| Mean (SD) | 8.3 (4.06) | 17.8 (17.97) | 16.8 (14.40) | 8.6 (3.10) | 7.0 (4.74) | 13.9 (19.04) | 31.6 (44.48) | 19.8 (27.34) |
| Median | 7.6 | 12.0 | 12.0 | 7.6 | 3.3 | 5.6 | 4.9 | 12.0 |
| Min to Max | 1 to 25 | 1 to 70 | 1 to 65 | 1 to 13 | 1 to 13 | 1 to 71 | 1 to 201 | 1 to 201 |
| Range of Exposure[2], n(%) | 2087 | 2722 | 458 | 361 | 294 | 446 | 601 | 4357 |
| 1 to <3 months | 156 (7) | 309 (11) | 9 (2) | 16 (4) | 29 (10) | 44 (10) | 129 (21) | 522 (12) |
| 3 to <6 months | 356 (17) | 275 (10) | 67 (15) | 29 (8) | 125 (43) | 146 (33) | 178 (30) | 779 (18) |
| 6 to <9 months | 604 (29) | 416 (15) | 20 (4) | 180 (50) | 3 (1) | 51 (11) | 30 (5) | 514 (12) |
| 9 to <12 months | 60 (3) | 56 (2) | 12 (3) | 9 (2) | 7 (2) | 6 (1) | 12 (2) | 88 (2) |
| 12 to <24 months | 902 (43) | 1032 (38) | 262 (57) | 127 (35) | 130 (44) | 139 (31) | 56 (9) | 1507 (35) |
| 24 to <36 months | 9 (<1) | 54 (2) | 30 (7) | 0 | 0 | 1 (<1) | 24 (4) | 98 (2) |
| 36 to <48 months | 0 | 208 (8) | 22 (5) | 0 | 0 | 1 (<1) | 12 (2) | 167 (4) |
| 48 to <60 months | 0 | 293 (11) | 21 (5) | 0 | 0 | 21 (5) | 17 (3) | 289 (7) |
| ≥60 months | 0 | 79 (3) | 15 (3) | 0 | 0 | 37 (8) | 143 (24) | 393 (9) |
| Subject-years Exposure[3] | 1435.74 | 4035.87 | 641.06 | 257.25 | 171.87 | 517.69 | 1582.71 | 7204.61 |

[redacted]

Abbreviations: EAP, Expanded Access Program; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; IM, intramuscularly; LAP, Long-term Access Program; Max, maximum; Min, minimum; PBO, placebo;

1. Includes IV doses: 10 mg, 750 mg/1500 mg, 0.05, 0.5, 0.55, 2.5, and 10 mg/kg, SC doses: 12.5, 40, 40/100, 125, and 250 mg, and IM dose: 250 mg, as well as all participants enrolled in the mepolizumab HES EAP.
2. Exposure Duration (Months) = (Treatment stop date - Treatment start date + 29)/365.25. For the categorical summary, exposure is rounded to the nearest whole month.
3. Sum across subjects of (treatment stop date - treatment start date + 29)/365.25.
4. For 6 subjects in the HES EAP, exposure duration was not recorded.

Note:

a. A subject who participated in more than 1 study and received different doses was counted once in each dose.

b. Participants included: Asthma - MEA114092, SB240563/001, SB240563/006, SB240563/017, SB240563/035, SB240563/036; Severe Asthma - 200363, 200862, 201312, 204471, 204959, 205667, MEA112997, 201810, MEA115575, MEA115588, MEA115661, MEA115666; HES - 200622, MHE100185, MHE100901, MHE104317, 205203; EoE - MEE103219, MEE103226; Atopic Dermatitis - 205050, SB240563/045; Healthy Volunteers - 204958, MEA115705, SB240563/018; EGPA - MEA115921, MEA116841, 201607; CRSwNP - MPP111782, 205687; COPD - MEA117106, MEA117113.

### Adverse events

**Table 37** shows the proportion of participants reporting the most common on-treatment AEs (defined as AEs with an incidence of ≥3% in any treatment group) in the CRSwNP placebo-controlled studies and the corresponding event rate adjusted for exposure (frequency of events per 1000 subject-years of exposure).

The incidence of on-treatment AEs was similar between the placebo (83%) and mepolizumab all doses groups (81%). The most frequently reported on-treatment AEs were nasopharyngitis and headache in both groups. Participants treated with placebo had a higher incidence of headache, asthma, and sinusitis than participants treated with mepolizumab (≥5% difference). There were no individual AE where incidence was ≥5% higher in the mepolizumab all doses group compared with the placebo group.

The SOC with the highest incidence of on-treatment AEs in both treatment groups was Infections and Infestations, the incidence was 63% in the placebo group and 54% in the mepolizumab all doses group. None of SOCs where there was ≥10% difference between treatment groups.

Relative risks using the CMH method were calculated for the most common on-treatment AEs for placebo and mepolizumab (all doses), together with the corresponding CMH-adjusted proportions (***Figure 28***).

The relative risk for mepolizumab vs. placebo was ≥2.0 for AEs of rash and arthralgia: 3.1% of participants (8/259) in the mepolizumab group and 0.8% of participants (2/253) in the placebo group reported rash with the RR of 3.91 (95% CI: 0.84, 18.21); 6.2% of participants (16/259) in the mepolizumab group and 3.2% of participants (8/253) in the placebo group reported arthralgia with the RR of 1.95 (95% CI: 0.85, 4.49). The relative risk for mepolizumab vs. placebo was ≤0.5 for the AEs of asthma, ear pain, fatigue, sinusitis, otitis media, and nasal polyps.

**Table 37: On Treatment AEs Occurring in ≥3% of Participants in any Treatment Group (CRSwNP Placebo-Controlled Studies), Safety Population**

| | 205687 | | | | MPP111782 | | | | Both studies[1] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo N=201 Subject yrs: 188.17 | | Mepo 100mg SC N=206 Subject yrs: 194.79 | | Placebo N=52 Subject yrs: 19.15 | | Mepo 750mg IV N=53 Subject yrs: 21.65 | | Placebo N=253 Subject yrs: 207.32 | | Mepo all doses N=259 Subject yrs: 216.44 | |
| Preferred Term | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] |
| **Any Event** | **168 (84)** | **4735.0 [891]** | **169 (82)** | **4481.8 [873]** | **42 (81)** | **10599.8 [203]** | **40 (75)** | **7805.7 [169]** | **210 (83)** | **5276.8 [1094]** | **209 (81)** | **4814.3 [1042]** |
| Nasopharyngitis | 46 (23) | 340.1 [64] | 52 (25) | 426.1 [83] | 12 (23) | 783.2 [15] | 10 (19) | 554.2 [12] | 58 (23) | 381.0 [79] | 62 (24) | 438.9 [95] |
| Headache | 44 (22) | 749.3 [141] | 37 (18) | 585.3 [114] | 20 (38) | 1618.7 [31] | 13 (25) | 2078.4 [45] | 64 (25) | 829.6 [172] | 50 (19) | 734.6 [159] |
| Oropharyngeal pain | 10 (5) | 58.5 [11] | 16 (8) | 97.5 [19] | 4 (8) | 208.9 [4] | 6 (11) | 277.1 [6] | 14 (6) | 72.4 [15] | 22 (8) | 115.5 [25] |
| Back pain | 14 (7) | 85.0 [16] | 15 (7) | 123.2 [24] | 0 | 0 | 5 (9) | 230.9 [5] | 14 (6) | 77.2 [16] | 20 (8) | 134.0 [29] |
| Epistaxis | 18 (9) | 106.3 [20] | 17 (8) | 123.2 [24] | 3 (6) | 208.9 [4] | 1 (2) | 277.1 [6] | 21 (8) | 115.8 [24] | 18 (7) | 138.6 [30] |
| Arthralgia | 5 (2) | 31.9 [6] | 13 (6) | 71.9 [14] | 3 (6) | 208.9 [4] | 3 (6) | 138.6 [3] | 8 (3) | 48.2 [10] | 16 (6) | 78.5 [17] |
| Upper respiratory tract infection | 14 (7) | 95.7 [18] | 12 (6) | 102.7 [20] | 2 (4) | 104.4 [2] | 2 (4) | 92.4 [2] | 16 (6) | 96.5 [20] | 14 (5) | 101.6 [22] |
| Acute sinusitis | 13 (6) | 101.0 [19] | 13 (6) | 87.3 [17] | 1 (2) | 52.2 [1] | 0 | 0 | 14 (6) | 96.5 [20] | 13 (5) | 78.5 [17] |
| Influenza | 9 (4) | 58.5 [11] | 7 (3) | 35.9 [7] | 2 (4) | 104.4 [2] | 4 (8) | 184.7 [4] | 11 (4) | 62.7 [13] | 11 (4) | 50.8 [11] |
| Sinusitis | 22 (11) | 154.1 [29] | 10 (5) | 61.6 [12] | 2 (4) | 104.4 [2] | 1 (2) | 46.2 [1] | 24 (9) | 149.5 [31] | 11 (4) | 60.1 [13] |
| Bronchitis | 13 (6) | 85.0 [16] | 10 (5) | 51.3 [10] | 0 | 0 | 0 | 0 | 13 (5) | 77.2 [16] | 10 (4) | 46.2 [10] |
| Cough | 13 (6) | 79.7 [15] | 7 (3) | 46.2 [9] | 3 (6) | 156.6 [3] | 2 (4) | 92.4 [2] | 16 (6) | 86.8 [18] | 9 (3) | 50.8 [11] |
| Pyrexia | 5 (2) | 42.5 [8] | 6 (3) | 35.9 [7] | 1 (2) | 52.2 [1] | 3 (6) | 138.6 [3] | 6 (2) | 43.4 [9] | 9 (3) | 46.2 [10] |
| Abdominal pain upper | 5 (2) | 26.6 [5] | 7 (3) | 56.5 [11] | 0 | 0 | 1 (2) | 46.2 [1] | 5 (2) | 24.1 [5] | 8 (3) | 55.4 [12] |
| Hypertension | 9 (4) | 58.5 [11] | 8 (4) | 56.5 [11] | 1 (2) | 52.2 [1] | 0 | 0 | 10 (4) | 57.9 [12] | 8 (3) | 50.8 [11] |
| Nasal polyps | 16 (8) | 148.8 [28] | 8 (4) | 56.5 [11] | 0 | 0 | 0 | 0 | 16 (6) | 135.1 [28] | 8 (3) | 50.8 [11] |
| Rash | 2 (<1) | 10.6 [2] | 6 (3) | 35.9 [7] | 0 | 0 | 2 (4) | 277.1 [6] | 2 (<1) | 9.6 [2] | 8 (3) | 60.1 [13] |
| Nasal congestion | 6 (3) | 47.8 [9] | 7 (3) | 61.6 [12] | 0 | 0 | 0 | 0 | 6 (2) | 43.4 [9] | 7 (3) | 55.4 [12] |
| Asthma | 18 (9) | 111.6 [21] | 4 (2) | 159.1 [31] | 3 (6) | 156.6 [3] | 2 (4) | 138.6 [3] | 21 (8) | 115.8 [24] | 6 (2) | 157.1 [34] |
| Ear discomfort | 1 (<1) | 5.3 [1] | 4 (2) | 20.5 [4] | 0 | 0 | 2 (4) | 138.6 [3] | 1 (<1) | 4.8 [1] | 6 (2) | 32.3 [7] |

| | 205687 | | | | MPP111782 | | | | Both studies[1] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Placebo N=201 Subject yrs: 188.17 | | Mepo 100mg SC N=206 Subject yrs: 194.79 | | Placebo N=52 Subject yrs: 19.15 | | Mepo 750mg IV N=53 Subject yrs: 21.65 | | Placebo N=253 Subject yrs: 207.32 | | Mepo all doses N=259 Subject yrs: 216.44 | |
| Preferred Term | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] | n (%) | Rate[2] [# events] |
| Nausea | 5 (2) | 31.9 [6] | 4 (2) | 46.2 [9] | 4 (8) | 313.3 [6] | 2 (4) | 369.5 [8] | 9 (4) | 57.9 [12] | 6 (2) | 78.5 [17] |
| Toothache | 4 (2) | 31.9 [6] | 4 (2) | 35.9 [7] | 0 | 0 | 2 (4) | 92.4 [2] | 4 (2) | 28.9 [6] | 6 (2) | 41.6 [9] |
| Dizziness | 5 (2) | 37.2 [7] | 5 (2) | 25.7 [5] | 2 (4) | 104.4 [2] | 0 | 0 | 7 (3) | 43.4 [9] | 5 (2) | 23.1 [5] |
| Dyspnoea | 0 | 0 | 3 (1) | 35.9 [7] | 4 (8) | 261.1 [5] | 2 (4) | 92.4 [2] | 4 (2) | 24.1 [5] | 5 (2) | 41.6 [9] |
| Ear pain | 8 (4) | 74.4 [14] | 4 (2) | 25.7 [5] | 5 (10) | 313.3 [6] | 1 (2) | 92.4 [2] | 13 (5) | 96.5 [20] | 5 (2) | 32.3 [7] |
| Pain in extremity | 2 (<1) | 10.6 [2] | 4 (2) | 20.5 [4] | 2 (4) | 104.4 [2] | 1 (2) | 46.2 [1] | 4 (2) | 19.3 [4] | 5 (2) | 23.1 [5] |
| Pruritus | 2 (<1) | 10.6 [2] | 4 (2) | 20.5 [4] | 2 (4) | 156.6 [3] | 1 (2) | 46.2 [1] | 4 (2) | 24.1 [5] | 5 (2) | 23.1 [5] |
| Otitis media | 10 (5) | 63.8 [12] | 5 (2) | 25.7 [5] | 0 | 0 | 0 | 0 | 10 (4) | 57.9 [12] | 5 (2) | 23.1 [5] |
| Rhinitis | 8 (4) | 53.1 [10] | 5 (2) | 25.7 [5] | 0 | 0 | 0 | 0 | 8 (3) | 48.2 [10] | 5 (2) | 23.1 [5] |
| Fatigue | 5 (2) | 37.2 [7] | 3 (1) | 15.4 [3] | 4 (8) | 417.7 [8] | 1 (2) | 46.2 [1] | 9 (4) | 72.4 [15] | 4 (2) | 18.5 [4] |
| Insomnia | 1 (<1) | 5.3 [1] | 4 (2) | 30.8 [6] | 3 (6) | 261.1 [5] | 0 | 0 | 4 (2) | 28.9 [6] | 4 (2) | 27.7 [6] |
| Tinnitus | 2 (<1) | 10.6 [2] | 2 (<1) | 10.3 [2] | 1 (2) | 52.2 [1] | 2 (4) | 138.6 [3] | 3 (1) | 14.5 [3] | 4 (2) | 23.1 [5] |
| Conjunctivitis | 0 | 0 | 2 (<1) | 10.3 [2] | 2 (4) | 104.4 [2] | 1 (2) | 46.2 [1] | 2 (<1) | 9.6 [2] | 3 (1) | 13.9 [3] |
| Cystitis | 1 (<1) | 5.3 [1] | 1 (<1) | 5.1 [1] | 1 (2) | 52.2 [1] | 2 (4) | 92.4 [2] | 2 (<1) | 9.6 [2] | 3 (1) | 13.9 [3] |
| Influenza like illness | 2 (<1) | 15.9 [3] | 1 (<1) | 5.1 [1] | 1 (2) | 52.2 [1] | 2 (4) | 92.4 [2] | 3 (1) | 19.3 [4] | 3 (1) | 13.9 [3] |
| Muscle spasms | 1 (<1) | 5.3 [1] | 1 (<1) | 5.1 [1] | 1 (2) | 52.2 [1] | 2 (4) | 92.4 [2] | 2 (<1) | 9.6 [2] | 3 (1) | 13.9 [3] |
| Otorrhoea | 0 | 0 | 1 (<1) | 51.3 [10] | 0 | 0 | 2 (4) | 92.4 [2] | 0 | 0 | 3 (1) | 55.4 [12] |
| Contusion | 3 (1) | 21.3 [4] | 2 (<1) | 25.7 [5] | 2 (4) | 104.4 [2] | 0 | 0 | 5 (2) | 28.9 [6] | 2 (<1) | 23.1 [5] |
| Haematuria | 0 | 0 | 0 | 0 | 0 | 0 | 2 (4) | 92.4 [2] | 0 | 0 | 2 (<1) | 9.2 [2] |
| Abdominal pain | 4 (2) | 26.6 [5] | 1 (<1) | 10.3 [2] | 2 (4) | 104.4 [2] | 0 | 0 | 6 (2) | 33.8 [7] | 1 (<1) | 9.2 [2] |
| Presyncope | 1 (<1) | 5.3 [1] | 1 (<1) | 5.1 [1] | 2 (4) | 156.6 [3] | 0 | 0 | 3 (1) | 19.3 [4] | 1 (<1) | 4.6 [1] |
| Sinus headache | 4 (2) | 31.9 [6] | 1 (<1) | 15.4 [3] | 2 (4) | 104.4 [2] | 0 | 0 | 6 (2) | 38.6 [8] | 1 (<1) | 13.9 [3] |
| Wheezing | 2 (<1) | 10.6 [2] | 1 (<1) | 10.3 [2] | 2 (4) | 104.4 [2] | 0 | 0 | 4 (2) | 19.3 [4] | 1 (<1) | 9.2 [2] |
| Feeling abnormal | 0 | 0 | 0 | 0 | 2 (4) | 104.4 [2] | 0 | 0 | 2 (<1) | 9.6 [2] | 0 | 0 |
| Increased viscosity of bronchial secretion | 0 | 0 | 0 | 0 | 2 (4) | 104.4 [2] | 0 | 0 | 2 (<1) | 9.6 [2] | 0 | 0 |
| Paranasal sinus discomfort | 1 (<1) | 5.3 [1] | 0 | 0 | 2 (4) | 156.6 [3] | 0 | 0 | 3 (1) | 19.3 [4] | 0 | 0 |
| Rhinorrhoea | 3 (1) | 15.9 [3] | 0 | 0 | 3 (6) | 156.6 [3] | 0 | 0 | 6 (2) | 28.9 [6] | 0 | 0 |

[redacted]

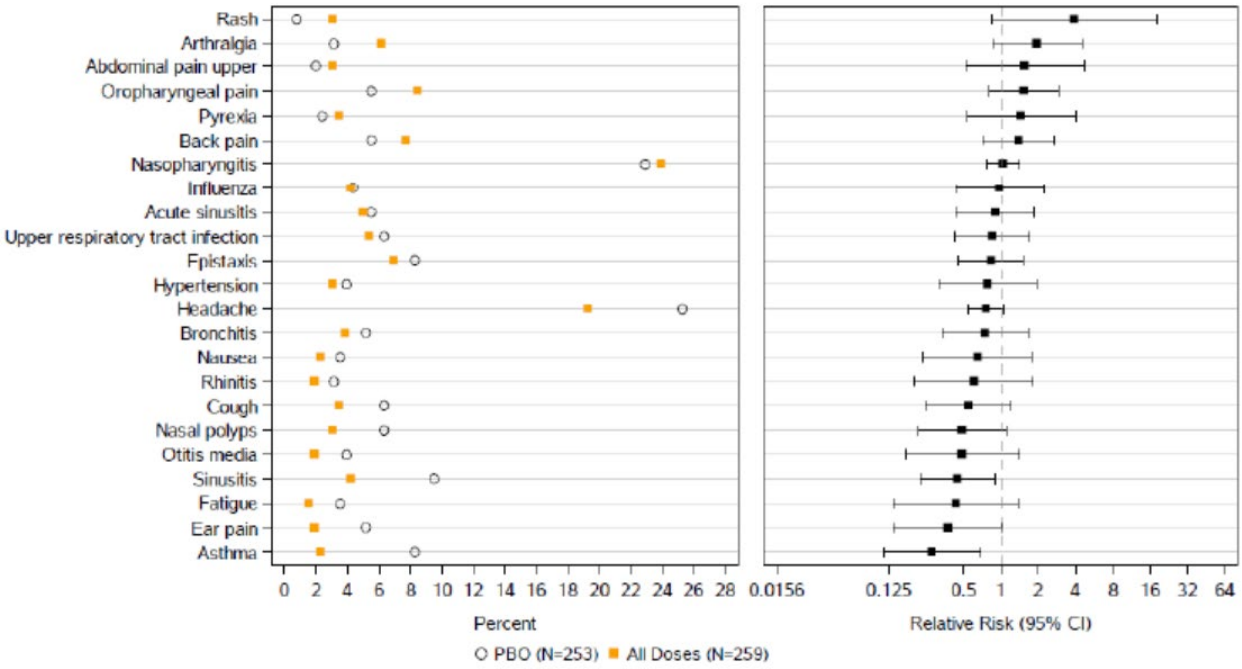
Abbreviations: Mepo, mepolizumab; PBO, placebo.

1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.
2. Represents the frequency of events per 1000 subject-years of exposure.

Note:

a. Common AEs are defined as AEs with frequency ≥3% prior to rounding in any treatment group.
b. Exposure-adjusted frequency is calculated as: (Total number of AEs/ Total Duration of Exposure in days)/ 365.25*1000.

**Figure 28: On-Treatment AEs (≥3% of Participants in any Treatment Group) Cumulative Proportion and CMH Adjusted Relative Risk (Mepolizumab All Doses vs Placebo) (CRSwNP Placebo-Controlled Studies), Safety Population**




- Adverse Events by Maximum Intensity

In the CRSwNP placebo-controlled studies, the majority of participants reported on treatment AEs with a maximum intensity of mild or moderate (66% in the placebo group and 68% in the mepolizumab all doses group). The incidence of events of severe intensity was 15% in the placebo group and 11% in the mepolizumab all doses group. Headache was the most frequently reported severe AE for both treatment groups (3% each group). The other severe AEs, which occurred with an incidence of 2%, were Nasopharyngitis and fatigue in the placebo group.

- Drug-Related Adverse Events

The overall incidence of on-treatment AEs considered by the investigator to be related to study treatment was 14% in the mepolizumab all doses group and 9% in the placebo group (**Table 38**). Headache was the most frequently reported drug-related AE for both treatment groups.

**Table 38: On-Treatment Drug-Related AEs Occurring in >1 Participant in either Integrated Treatment Group (CRSwNP Placebo-Controlled Studies), Safety Population**

| Preferred Term, n, (%) | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| **Any Event** | 19 (9) | 30 (15) | 3 (6) | 5 (9) | 22 (9) | 35 (14) |
| Headache | 2 (<1) | 8 (4) | 1 (2) | 1 (2) | 3 (1) | 9 (3) |
| Erythema | 0 | 3 (1) | 0 | 0 | 0 | 3 (1) |
| Injection site pain | 2 (<1) | 3 (1) | 0 | 0 | 2 (<1) | 3 (1) |
| Nasopharyngitis | 1 (<1) | 3 (1) | 0 | 0 | 1 (<1) | 3 (1) |
| Abdominal pain upper | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| Asthma | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) | 2 (<1) |
| Nasal congestion | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| Rash | 0 | 1 (<1) | 0 | 1 (2) | 0 | 2 (<1) |
| Urticaria | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.
1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.

- Adverse Events Reported on the Day of Dosing

The overall incidence of AEs reported on the day of dosing (pre- or post-dose) was comparable between treatment groups, 26% in the placebo group and 24% in the mepolizumab all doses group (**Table 39**). The most frequently reported AE on the day of dosing was headache for both treatment groups.

**Table 39: AEs Reported on Day of Dosing (≥2 Participants in either Integrated Treatment Group) (CRSwNP Placebo-Controlled Studies), Safety Population**

| | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| Preferred Term, n, (%) | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| **Any Event** | 49 (24) | 56 (27) | 18 (35) | 7 (13) | 67 (26) | 63 (24) |
| Headache | 5 (2) | 6 (3) | 2 (4) | 3 (6) | 7 (3) | 9 (3) |
| Hypertension | 0 | 4 (2) | 0 | 0 | 0 | 4 (2) |
| Injection site pain | 2 (<1) | 4 (2) | 0 | 0 | 2 (<1) | 4 (2) |
| Nasal polyps | 5 (2) | 4 (2) | 0 | 0 | 5 (2) | 4 (2) |
| Sinusitis | 6 (3) | 3 (1) | 1 (2) | 1 (2) | 7 (3) | 4 (2) |
| Back pain | 1 (<1) | 2 (<1) | 0 | 1 (2) | 1 (<1) | 3 (1) |
| Asthma | 3 (1) | 2 (<1) | 0 | 0 | 3 (1) | 2 (<1) |
| Arthralgia | 1 (<1) | 2 (<1) | 1 (2) | 0 | 2 (<1) | 2 (<1) |
| Epistaxis | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) | 2 (<1) |
| Erythema | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| Nausea | 2 (<1) | 1 (<1) | 0 | 1 (2) | 2 (<1) | 2 (<1) |
| Otitis media | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) | 2 (<1) |
| Oropharyngeal pain | 2 (<1) | 1 (<1) | 0 | 1 (2) | 2 (<1) | 2 (<1) |
| Rhinitis | 3 (1) | 2 (<1) | 0 | 0 | 3 (1) | 2 (<1) |
| Acute sinusitis | 5 (2) | 1 (<1) | 0) | 0 | 5 (2) | 1 (<1) |
| Ear pain | 0 | 1 (<1) | 2 (4) | 0 | 2 (<1) | 1 (<1) |
| Nasopharyngitis | 3 (1) | 1 (<1) | 1 (2) | 0 | 4 (2) | 1 (<1) |
| Contusion | 1 (<1) | 0 | 1 (2) | 0 | 2 (<1) | 0 |
| Cough | 1 (<1) | 0 | 1 (2) | 0 | 2 (<1) | 0 |
| Fatigue | 3 (1) | 0 | 2 (4) | 0 | 5 (2) | 0 |
| Feeling abnormal | 0 | 0 | 2 (4) | 0 | 2 (<1) | 0 |
| Upper respiratory tract infection | 1 (<1) | 0 | 1 (2) | 0 | 2 (<1) | 0 |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.
1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.

- Post-Treatment Adverse Events

For the CRSwNP placebo-controlled studies, post-treatment AEs were defined as any event which started more than 28 days after the last dose of study treatment; this included all events reported during the no-treatment post-week 52 follow-up period of Study. Post-treatment AEs were reported in 18% (46/253) of participants in the placebo group and 17% (44/259) in the mepolizumab all doses group. Post-treatment AEs which occurred with an incidence of ≥2% included headache (3%), nasopharyngitis, cough, and

ear pain (2% each) in the placebo group and nasopharyngitis (3%), back pain, headache, and sinusitis (2% each) in the mepolizumab group. In Study 205687, 134 participants (65, 32% in the placebo group and 69, 33% in the mepolizumab group) were enrolled in a No Treatment Post-Week 52 Follow-up Period and were followed-up for additional 24 weeks. The incidence of non-serious AEs in the no treatment post-week 52 follow-up period was 20% in each treatment group (13/65 placebo and 14/69 mepolizumab); the incidence of SAEs was 6% in the placebo group and 3% in the mepolizumab group. The most frequently reported AE was headache (5, 8%) in the placebo group and nasopharyngitis (6, 9%) in the mepolizumab group.

Adverse Events of Special Interest

Within the mepolizumab clinical development program, the following are considered AESIs: systemic (allergic [Type I hypersensitivity] and other systemic) reactions, local injection site reactions, infections (including potentially opportunistic), malignancies, and cardiac disorders including serious cardiac, vascular, and thromboembolic (CVT) events and serious ischemic events.

The relative risk and risk difference for SAEs and AESIs in the CRSwNP placebo-controlled studies are presented in ***Table 40*** and ***Figure 29***. Infections were the most frequently reported AESI category for both treatment groups (63% for placebo, 54% for mepolizumab all doses. With the exception of all infections, participant numbers in each category of AESIs were low (≤5%).

**Table 40: On-Treatment Serious Adverse Events and Adverse Events of Special Interest: Incidence, Relative Risk, and Risk Difference (CRSwNP Placebo-Controlled Studies), Safety Population**

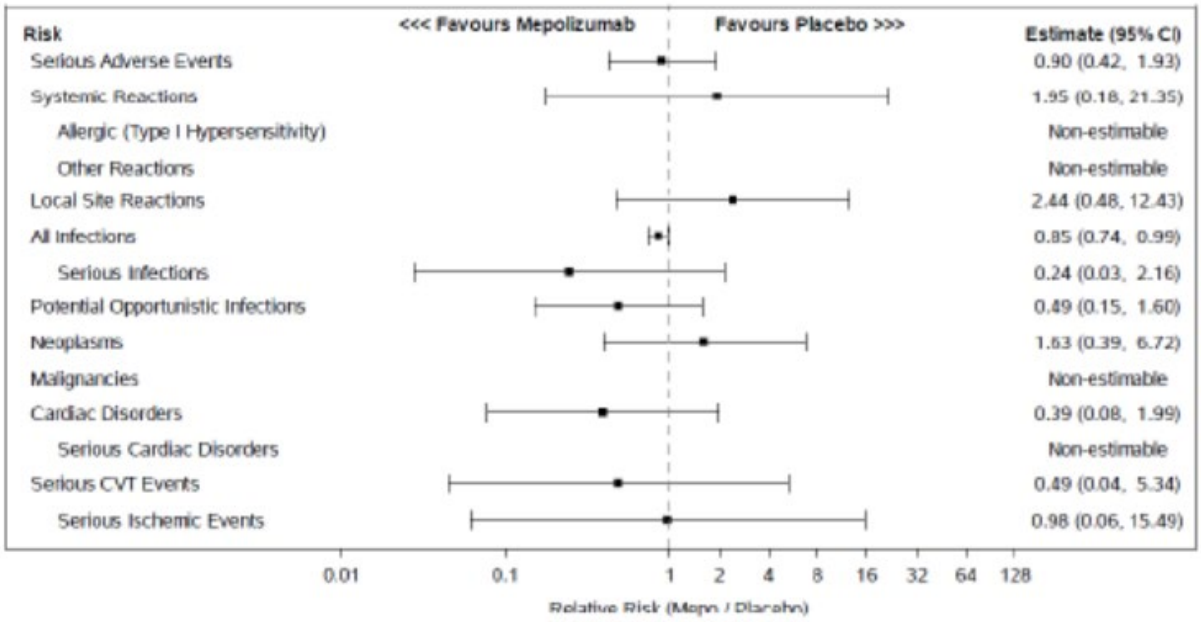
| | Both CRSwNP studies[1] | | Mepolizumab (All Doses) vs Placebo | |
|---|---|---|---|---|
| SAE/AESI, n, (%) | PBO N=253 | Mepo All Doses N=259 | CMH-Adjusted Relative Risk (95% CI)[2] | % Risk Difference (Exact 95% CI) |
| **Any on-treatment SAE** | 13 (5.1) | 12 (4.6) | 0.90 (0.42, 1.93) | -0.5% ( -9.2, 8.1) |
| **Systemic Reactions[3]** | 1 (0.5) | 2 (1.0) | 1.95 (0.18, 21.35) | 0.5% ( -9.3, 10.2) |
| Allergic (Type I) Hypersensitivity | 0 | 2 (1.0) | -- | 1.0% ( -8.8, 10.7) |
| Other Systemic | 1 (0.5) | 0 | -- | -0.5% (-10.2, 9.3) |
| Anaphylaxis[4] | 0 | 0 | -- | -- |
| **Local Injection Site Reactions[3]** | 2 (1.0) | 5 (2.4) | 2.44 (0.48, 12.43) | 1.4% ( -8.3, 11.2) |
| **All Infections[5]** | 160 (63.2) | 140 (54.1) | 0.85 (0.74, 0.99) | -9.2% (-17.8, -0.5) |
| Serious Infections | 4 (1.6) | 1 (0.4) | 0.24 (0.03, 2.16) | -1.2% ( -9.9, 7.5) |
| **Potential Opportunistic Infections[6]** | 8 (3.2) | 4 (1.5) | 0.49 (0.15, 1.60) | -1.6% (-10.3, 7.1 |
| **Neoplasms[5]** | 3 (1.2) | 5 (1.9) | 1.63 (0.39, 6.72) | 0.7% ( -8.0, 9.4) |
| **Malignancies[7]** | 2 (0.8) | 0 | -- | -0.8% ( -9.5, 7.9) |
| **Cardiac Disorders[5]** | 5 (2.0) | 2 (0.8) | 0.39 (0.08, 1.99) | -1.2% ( -9.9, 7.5) |
| Serious Cardiac Disorders | 0 | 1 (0.4) | -- | 0.4% ( -8.3, 9.1) |
| **Serious CVT Events[7]** | 2 (0.8) | 1 (0.4) | 0.49 (0.04, 5.34) | -0.4% ( -9.1, 8.3) |
| Serious Ischemic Events[8] | 1 (0.4) | 1 (0.4) | 0.98 (0.06, 15.49) | 0.0% ( -8.7, 8.7) |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo; SMQ, standardized MedDRA query; SOC, system organ class.

1. Integrated data (with the exceptions of systemic reactions and local injection site reactions) from CRSwNP placebo-controlled studies 205687 and MPP111782.
2. Calculated using the CMH method.
3. Events collected via targeted eCRF in Study 205687 only (PBO N=201, mepo N=206).
4. Considered by the investigator to represent systemic reactions meeting the Sampson's criteria for anaphylaxis.
5. Infections from Infections and infestations SOC; Neoplasms from Neoplasms benign, malignant and unspecified (including cysts and polyps) SOC; Cardiac disorders from Cardiac disorders SOC.
6. Identified based on published list of pathogens and/or presentations of specific pathogens to be considered as opportunistic infections in the setting of biologic therapy [Winthrop, 2015].
7. Identified from pre-specified SMQs.
8. Subset of Serious CVT events identified through SMQs.

**Figure 29: On-Treatment Serious Adverse Events and Adverse Events of Special Interest CMH-Adjusted Relative Risk – Mepolizumab All Doses vs Placebo (CRSwNP Placebo-Controlled Studies), Safety Population**




[redacted]

1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782

- Systemic Reactions

Systemic reactions were collected via a targeted eCRF in Study 205687 only. Therefore, systemic reactions in Study 205687 and AEs identified by MAH as hypersensitivity in Study MPP111782 are presented separately below.

In Study 205687, systemic reactions were reported in 3 participants: systemic allergic (type I hypersensitivity) reactions in 2 participants in the mepolizumab group and other systemic reactions in 1 participant in the placebo group (***Table 40***). All events were nonserious, mild or moderate in intensity, considered related to study treatment by the investigator, resolved, and did not lead to discontinuation of study treatment.

One event was considered to represent a potential hypersensitivity reaction following the MAH review of AEs in Study MPP111782.

*Anaphylaxis*

In Study 205687, systemic reactions were collected via a targeted eCRF, and investigators were asked to assess systemic reactions against Sampson's criteria of anaphylaxis. There were no events of systemic reactions meeting Sampson's criteria for anaphylaxis in Study 205687, and no other events of anaphylaxis reported in Study 205687 or MPP117872.

- Local Injection Site Reactions

Local injection site reactions were collected via targeted eCRF in Study 205687 only. In Study 205687, AEs of local injection site reactions were reported in 7 participants (2 with 5 events in the placebo group and 5 with 6 events in the mepolizumab group). All events in both treatment groups were non-serious, of mild intensity, resolved, and did not lead to discontinuation of study treatment. All AEs of local injection site reactions but 1 were considered to be drug-related by the investigator.

With the exceptions of 2 participants*, all received 13 doses of study treatment and completed the study. (*Note: 1 participant in the placebo group discontinued study treatment due to a protocol deviation and 1 participant in the mepolizumab group was consent withdrawn from the study due to moving out of the area where the clinical study was being conducted.)

- Infections

The incidence of on-treatment AEs in the Infections and Infestations SOC in the CRSwNP placebo-controlled studies was 63% (160/253) in the placebo group and 54% (140/259) in the mepolizumab all doses group. The most frequently reported event within the SOC was nasopharyngitis for both treatment groups. The incidence of individual AEs where there was ≥5% difference between treatment groups was sinusitis (9% placebo, 4% mepolizumab).

*Serious Infections*

SAEs in the Infections and Infestations SOC were reported in 4 participants in the placebo group and 1 participant in the mepolizumab group, all in Study 205687. Pneumonia was reported in 2 participants (1 in each treatment group). The remaining SAEs in the placebo group were acute sinusitis*, cellulitis, influenza, and periorbital cellulitis*. All events resolved with continued study treatment and no events were considered drug-related by the investigator. (*Note: SAEs of acute sinusitis and periorbital cellulitis were reported in 1 participant in the placebo group on the same day.)

*Potential Opportunistic Infections*

AEs of potential opportunistic infections in the CRSwNP placebo-controlled studies were reported in 8 participants (3%) in the placebo group and 4 participants (2%) in the mepolizumab all doses group. According to Expert opinion on the criteria for opportunistic infections in the setting of biological therapy, herpes simplex infections are considered opportunistic only when invasive. In the CRSwNP placebo-controlled studies, the reported events of oral herpes, herpes simplex, and genital herpes are unlikely to represent an invasive disease based on being reported as non-serious, of mild intensity and verbatim terms suggestive of localized infection (e.g., cold sore). Similarly, the events of candida infection (verbatim term "thrush") are unlikely to represent an invasive disease based on event characteristics. The events of herpes zoster and oropharyngeal candidiasis meet the criteria for opportunistic infections by Winthrop in 2015.

All events in both studies were non-serious, mild/moderate in intensity, resolved, not considered drug-related by the investigator, and did not lead to permanent discontinuation of study treatment. An AE of herpes zoster in 1 participant in the placebo group in Study 205687 led to study treatment interruption. With the exception of 2 participants* in the placebo group in Study 205687, all completed study treatment and completed the study. (*Note: 2 participants in the placebo group in Study 205687 were consent withdrawn from the study.

- Malignancies

On-treatment AESI in the category of malignancies were reported in 2 participants, both in the placebo group in Study 205687. Both events (renal neoplasm and basal cell carcinoma) were non-serious, not considered related to study treatment by the investigator, and did not lead to discontinuation of study treatment. No malignancies were reported in MPP111782.

- Serious Cardiac, Vascular, and Thromboembolic Events and Serious Ischemic Events

On-treatment serious CVT events were reported in 3 participants (2 in the placebo group and 1 in the mepolizumab group), all in Study 205687. All events were resolved. The event of transient ischemic attack in the placebo-treated participant was considered by the investigator to be related to study

treatment. The event of myocardial infarction in the mepolizumab-treated participant led to the interruption of study treatment.

**Serious adverse event/deaths/other significant events**

The overall incidence of SAEs in the CRSwNP placebo-controlled studies was generally similar between mepolizumab all doses and placebo groups. In Study 205687, the incidence of on-treatment SAEs was comparable between treatment groups. In Study MPP111782, no SAEs were reported.

The incidence of on-treatment non-fatal SAEs in the CRSwNP placebo-controlled studies was similar between placebo and mepolizumab all doses groups (5% each treatment group) (**Table 41**). On-treatment non-fatal SAEs that occurred in more than 1 participant within a treatment group were anemia and contusion (2 each in the mepolizumab group). With the exception of type 2 diabetes mellitus in the mepolizumab group, all events were resolved. An SAE of transient ischemic attack in the placebo group was considered by the investigator to be related to study treatment.

**Table 41: On-Treatment Non-Fatal Serious Adverse Events (CRSwNP Placebo-Controlled Studies), Safety Population**

| | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| System Organ Class Preferred Term, n, (%) | PBO N=201 | Mepo 100µ SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| **Any Event** | 13 (6) | 12 (6) | 0 | 0 | 13 (5) | 12 (5) |
| **Infections and infestations** | 4 (2) | 1 (<1) | 0 | 0 | 4 (2) | 1 (<1) |
| Pneumonia | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) |
| Acute sinusitis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Cellulitis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Influenza | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Periorbital cellulitis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| **Gastrointestinal disorders** | 2 (<1) | 2 (<1) | 0 | 0 | 2 (<1) | 2 (<1) |
| Anal polyp | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Gastritis erosive | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Hiatus hernia | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Pancreatitis acute | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| **Nervous system disorders** | 1 (<1) | 3 (1) | 0 | 0 | 1 (<1) | 3 (1) |
| Facial paralysis | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Migraine with aura | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Syncope | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Transient ischaemic attack[2] | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| **Injury, poisoning and procedural complications** | 0 | 3 (1) | 0 | 0 | 0 | 3 (1) |
| Contusion | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| Procedural complication | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Rib fracture | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Road traffic accident | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Musculoskeletal and connective tissue disorders** | 3 (1) | 0 | 0 | 0 | 3 (1) | 0 |
| Foot deformity | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Intervertebral disc disorder | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Osteoarthritis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| **Respiratory, thoracic and mediastinal disorders** | 2 (<1) | 1 (<1) | 0 | 0 | 2 (<1) | 1 (<1) |
| Asthma | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Pleural effusion | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Pulmonary oedema | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| **Blood and lymphatic system disorders** | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| Anaemia | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| **Hepatobiliary disorders** | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) |
| Cholecystitis acute | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Cholelithiasis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |

| System Organ Class Preferred Term, n, (%) | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) |
| Benign vulval neoplasm | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Rectal adenoma | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| **Renal and urinary disorders** | 1 (<1) | 1 (<1) | 0 | 0 | 1 (<1) | 1 (<1) |
| Focal segmental glomerulosclerosis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Nephrolithiasis | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Nephrotic syndrome | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| **Reproductive system and breast disorders** | 0 | 2 (<1) | 0 | 0 | 0 | 2 (<1) |
| Prostatitis | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Uterine polyp | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| **Cardiac disorders** | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Angina pectoris | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Cardiac failure congestive | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Coronary artery stenosis | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Mitral valve incompetence | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Myocardial infarction | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Myocardial ischaemia | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| **Metabolism and nutrition disorders** | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| Type 2 diabetes mellitus | 0 | 1 (<1) | 0 | 0 | 0 | 1 (<1) |
| **Vascular disorders** | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Hypertensive crisis | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.

1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.
2. Drug-related SAE.

Post-treatment SAEs were reported in 5 participants (2%) in the placebo group and 3 participants (1%) in the mepolizumab group, all reported in Study 205687. SAEs reported in the placebo group

included abortion missed, anemia*, asthma, deep vein thrombosis*, duodenal ulcer, myocardial infarction, pulmonary embolism*, and urticaria. SAEs reported in the mepolizumab group included back pain, pneumonia, and type 2 diabetes mellitus. (*Note: Three SAEs were reported in 1 placebo-treated participant.)

A summary of frequently reported on-treatment nonfatal SAEs in the placebo and mepolizumab all doses group is presented in **Table 42**.

**Table 42: On-Treatment Non-Fatal Serious Adverse Events Occurring In >5 Subjects Overall (All Studies Combined), Safety Population**

| System Organ Class<br>Preferred term | Number (%) Participants<br>PBO<br>N=2087 | <br>Mepolizumab all doses<br>N=4363 |
|---|---|---|
| Any on-treatment non-fatal SAE | 310 (15) | 833 (19) |
| Respiratory, Thoracic and Mediastinal Disorders | 169 (8) | 358 (8) |
| Asthma | 58 (3) | 187 (4) |
| COPD | 97 (5) | 110 (3) |
| Dyspnea | 0 | 15 (<1) |
| Acute respiratory failure | 7 (<1) | 9 (<1) |
| Respiratory failure | 6 (<1) | 8 (<1) |
| Pulmonary embolism | 0 | 8 (<1) |
| Nasal polyps | 0 | 8 (<1) |
| Pneumothorax | 1 (<1) | 7 (<1) |
| Infections and Infestations | 93 (4) | 290 (7) |
| Pneumonia | 46 (2) | 102 (2) |
| Cellulitis | 4 (<1) | 15 (<1) |
| Sepsis | 2 (<1) | 15 (<1) |
| Bronchitis | 7 (<1) | 13 (<1) |
| Influenza | 5 (<1) | 13 (<1) |
| Diverticulitis | 0 | 13 (<1) |
| Urinary tract infection | 3 (<1) | 12 (<1) |
| Gastroenteritis | 1 (<1) | 11 (<1) |
| Lower respiratory tract infection | 3 (<1) | 10 (<1) |
| Appendicitis | 1 (<1) | 9 (<1) |
| Respiratory tract infection | 1 (<1) | 8 (<1) |
| Infective exacerbation of COPD | 4 (<1) | 6 (<1) |
| URTI | 1 (<1) | 6 (<1) |
| Cardiac Disorders | 25 (1) | 95 (2) |
| Atrial fibrillation | 6 (<1) | 17 (<1) |
| Myocardial infarction | 1 (<1) | 10 (<1) |
| Acute myocardial infarction | 4 (<1) | 9 (<1) |
| Cardiac failure congestive | 2 (<1) | 8 (<1) |
| Cardiac failure | 1 (<1) | 7 (<1) |
| Coronary artery disease | 2 (<1) | 5 (<1) |
| Gastrointestinal Disorders | 9 (<1) | 96 (2) |
| Abdominal pain | 1 (<1) | 12 (<1) |
| Diarrhea | 0 | 12 (<1) |
| Abdominal pain upper | 1 (<1) | 6 (<1) |
| Injury, Poisoning and Procedural Complications | 23 (1) | 75 (2) |
| Foot fracture | 1 (<1) | 6 (<1) |
| Rib fracture | 0 | 7 (<1) |
| Spinal compression fracture | 1 (<1) | 6 (<1) |
| Tendon rupture | 1 (<1) | 5 (<1) |
| Nervous System Disorders | 13 (<1) | 73 (2) |
| Syncope | 2 (<1) | 11 (<1) |
| Transient ischemic attack | 2 (<1) | 8 (<1) |
| Dizziness | 1 (<1) | 8 (<1) |
| Cerebrovascular accident | 2 (<1) | 5 (<1) |

| System Organ Class<br>Preferred term | Number (%) Participants<br>PBO<br>N=2087 | <br>Mepolizumab all doses<br>N=4363 |
|---|---|---|
| Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps) | 16 (<1) | 57 (1) |
| Prostate cancer | 2 (<1) | 8 (<1) |
| General Disorders and Administration Site Conditions | 7 (<1) | 52 (1) |
| Pyrexia | 3 (<1) | 11 (<1) |
| Chest pain | 0 | 12 (<1) |
| Non-cardiac chest pain | 3 (<1) | 4 (<1) |
| Musculoskeletal and Connective Tissue Disorders | 11 (<1) | 52 (1) |
| Back pain | 1 (<1) | 10 (<1) |
| Intervertebral disc protrusion | 1 (<1) | 8 (<1) |
| Osteoarthritis | 1 (<1) | 5 (<1) |
| Vascular Disorders | 9 (<1) | 41 (<1) |
| Hypotension | 2 (<1) | 9 (<1) |
| Hypertension | 2 (<1) | 7 (<1) |
| Renal and Urinary Disorders | 12 (<1) | 39 (<1) |
| Acute kidney injury | 2 (<1) | 10 (<1) |
| Renal colic | 2 (<1) | 5 (<1) |
| Renal failure | 1 (<1) | 5 (<1) |
| Nephrolithiasis | 4 (<1) | 3 (<1) |
| Metabolism and Nutrition Disorders | 7 (<1) | 29 (<1) |
| Dehydration | 2 (<1) | 8 (<1) |
| Hyponatremia | 2 (<1) | 4 (<1) |
| Blood and Lymphatic System Disorders | 5 (<1) | 21 (<1) |
| Anemia | 2 (<1) | 8 (<1) |
| HES | 2 (<1) | 5 (<1) |
| Hepatobiliary Disorders | 5 (<1) | 23 (<1) |
| Cholelithiasis | 3 (<1) | 6 (<1) |
| Cholecystitis acute | 1 (<1) | 5 (<1) |
| Immune System Disorders | 4 (<1) | 22 (<1) |
| Anaphylactic reaction | 1 (<1) | 6 (<1) |
| EGPA | 1 (<1) | 5 (<1) |
| Skin and Subcutaneous Tissue Disorders | 2 (<1) | 21 (<1) |
| Investigations | 3 (<1) | 14 (<1) |
| Reproductive System and Breast Disorders | 3 (<1) | 13 (<1) |
| Psychiatric Disorders | 4 (<1) | 12 (<1) |
| Endocrine Disorders | 1 (<1) | 6 (<1) |

| System Organ Class<br>Preferred term | Number (%) Participants<br>PBO<br>N=2087 | <br>Mepolizumab all doses<br>N=4363 |
|---|---|---|
| Eye Disorders | 1 (<1) | 6 (<1) |

[redacted]

Abbreviations: EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; PBO, placebo; URTI, upper respiratory tract infection.

Note: A subject who participated in more than 1 study and received different doses was counted once in each dose.

Note: Studies included: Asthma - MEA114092, SB240563/001, SB240563/006, SB240563/017, SB240563/035, SB240563/036; Severe Asthma - 200363, 200862, 201312, 204471, 204959, 205667, MEA112997, 201810, MEA115575, MEA115588, MEA115661, MEA115666; HES - 200622, MHE100185, MHE100901, MHE104317, 205203; EoE - MEE103219, MEE103226; Atopic Dermatitis - 205050, SB240563/045; Healthy Volunteers - 204958, MEA115705, SB240563/018; EGPA - MEA115921, MEA116841, 201607; CRSwNP - MPP111782, 205687; COPD - MEA117106, MEA117113.

Deaths

No deaths were reported in Study MPP111782. No deaths were reported during the 52-week treatment period in Study 205687. One death due to an SAE of myocardial infarction in the placebo group in Study 205687 was reported during follow-up after Week 52.

**Laboratory findings**

- Clinical Chemistry

On-Treatment Chemistry Data Change from Baseline

In Study 205687, clinical chemistry assessments were performed at baseline, Week 52, early withdrawal, and as clinically indicated. The definition of an on-treatment sample was one taken after the first dose and within 28 days after the last dose. Samples taken more than 28 days after last dose are defined as post-treatment. For completeness, in addition to the planned presentation of on-treatment clinical laboratory evaluations, post-hoc presentations of on- and post-treatment data were prepared. There were no meaningful differences between the on-treatment and on- and post-treatment data, and therefore this section presents on- and post-treatment results. In Study MPP111782, clinical chemistry assessments were performed at baseline, at Week 2, and every 4 weeks thereafter up to Week 24.

There was no evidence of treatment effect on clinical chemistry parameters for both studies. For all post-baseline clinical chemistry parameters in the CRSwNP placebo-controlled studies, the majority of participants in each treatment group had values shift to the normal range or no change. Shifts from baseline in clinical chemistry parameters with an incidence ≥10% in integrated treatment group was glucose (to high; 12% placebo and 9% mepolizumab). The incidence of clinical chemistry parameter values outside the normal range at any time post-baseline occurred with comparable incidence across the treatment groups, with the exception of urea in Study MPP111782 (10% placebo and 19% mepolizumab).

One participant (in the placebo group) in Study MPP111782 had a clinical chemistry change from baseline that met pre-defined potential clinical importance (PCI) value. This participant had a high calcium value of PCI at Week 9 during the study; the calcium values were within normal reference range at baseline and at all the rest of the post baseline assessments.

No participants in Study 205687 had clinical chemistry change from baseline values of PCI. No clinical chemistry abnormalities were reported as AEs in both studies.

- Liver Function Tests

In the CRSwNP placebo-controlled studies, there were no possible 'Hy's Law' events (i.e., drug-induced liver injury with hyperbilirubinemia, defined as alanine aminotransferase [ALT] ≥3x upper limit of normal [ULN] and bilirubin ≥2x ULN [>35% direct] [or ALT ≥3x ULN and international normalized ratio [INR] >1.5, if INR measured]).

No participant had liver function test values that met protocol-defined liver chemistry monitoring/stopping criteria.

- Hematology

Laboratory parameters for hematology that were assessed in both Study 205687 and MPP111782 were integrated. Eosinophil data were pharmacodynamics assessments in both studies and are presented in the Summary of Clinical Pharmacology. With the exception of blood eosinophil counts, there were no

evidence of treatment effect on hematology parameters. For most post-baseline hematology parameters in the CRSwNP placebo-controlled studies, the majority of participants in each treatment group had values shift to the normal range or no change. The incidence of hematology parameter values outside the normal range at any time post-baseline occurred with comparable incidence across the treatment groups, with the exceptions of eosinophils and leukocytes. Shifts from baseline in hematology parameters with an incidence ≥10% in either integrated treatment group are presented in **Table 43**.

**Table 43: On- and Post-Treatment hematology Data Changes from Baseline Relative to the Normal Range Any Time Post-baseline (Incidence ≥10% in either Integrated Treatment Group) (CRSwNP Placebo-Controlled Studies), Safety Population**

| Hematology Parameter, n (%) | Change from Baseline | 205687[1] | | MPP111782[2] | | Both studies | |
|---|---|---|---|---|---|---|---|
| | | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| Hemoglobin (g/L) | To low | 33 (17) | 26 (13) | 1 (2) | 2 (4) | 34 (13) | 28 (11) |
| Leukocytes ($10^9$/L) | To low | 8 (4) | 20 (10) | 0 | 7 (13) | 8 (3) | 27 (10) |
| | To high | 42 (21) | 22 (11) | 3 (6) | 2 (4) | 45 (18) | 24 (9) |
| Monocytes ($10^9$/L) | To Low | 38 (19) | 33 (16) | 1 (2) | 0 | 39 (15) | 33 (13) |
| Neutrophils ($10^9$/L) | To high | 35 (18) | 30 (15) | 2 (4) | 3 (6) | 37 (15) | 33 (13) |

Abbreviations: Mepo, mepolizumab; PBO, placebo.

1. Including data reported up to Week 52 in Study 205687.
2. Including data reported up to Week 24 (4 weeks post last dose) in MPP111782.

Note:

a. Participants were counted in the category that their value changes to (low, normal, or high), unless there is no change in their category.
b. Participants whose lab value category was unchanged (e.g., High to High), or whose value became normal, were recorded in the "To Normal or No Change" category. Participants were counted twice if the participant has values that changed 'To Low' and 'To High', so the percentages may not add to 100%.
c. participants with missing baseline value were assumed to have normal baseline value.

One participant in the mepolizumab group in Study 205687 had hematology laboratory values that met the pre-defined criteria for low values of PCI. Of 4 participants who reported anemia, 2 cases were reported as SAEs.

**Vital Signs**

Mean values for systolic blood pressure, diastolic blood pressure, and pulse rate were similar to baseline throughout the course of CRSwNP studies for both placebo and mepolizumab all doses groups.

- ECG

In Study 205687, electrocardiograms (ECGs) were assessed at baseline, at Week 52 (4 weeks after the last dose) and at early withdrawal visit. In Study MPP111782, ECGs were assessed at baseline, at Week 2, and at each 4-week visit thereafter, as well as at early withdrawal visit. The majority of participants had normal ECGs at baseline and at post-baseline visits in both studies and summarized in the respective CSRs. No participants had a clinically significant ECG during the studies.

QTc Intervals

On- and post-treatment maximum value of QTc interval and maximum change from baseline are presented in ***Table 44***. No participants in Study MPP111782 met the protocol-defined QTc stopping criteria (defined as QTc >500 msec or change from baseline >60 msec).

QTc values that met protocols-defined stopping criteria were reported in 7 participants (4 in the placebo group and 3 in the mepolizumab group) in Study 205687. All of values were from Week 52 (4 weeks after the last dose of study treatment). No follow-up ECGs were available for these participants.

AEs reported by these participants were unremarkable compared to the AEs reported by other participants in the study. No QT prolongation-related AE was reported during the study.

**Table 44: On- and Post-Treatment Maximum Value of QTc Interval and Maximum Change from Baseline (CRSwNP Placebo-Controlled Studies), Safety Population**

| Category[1] n, (%) | PBO N=201 | Mepo 100mg SC N=206 |
|---|---|---|
| **Study 205687** | | |
| **QTcF Interval, aggregate (msec), n** | 140 | 136 |
| No Change or Decrease to ≤450 | 133 (95) | 134 (99) |
| Increase To >450 to ≤480 | 6 (4) | 2 (1) |
| Increase To >480 to ≤500 | 1 (<1) | 0 |
| Increase of ≤30 msec | 135 (96) | 131 (96) |
| Increase of >30-60 msec | 3 (2) | 3 (2%) |
| Increase of >60 msec | 2 (1) | 2 (1) |
| **QTcB Interval, aggregate (msec), n** | 140 | 136 |
| No Change or Decrease to ≤450 | 132 (94) | 130 (96) |
| Increase To >450 to ≤480 | 6 (4) | 5 (4) |
| Increase To >500 | 2 (1) | 1 (<1) |
| Increase of ≤30 msec | 133 (95) | 130 (96) |
| Increase of >30-60 msec | 5 (4) | 4 (3) |
| Increase of >60 msec | 2 (1) | 2 (1) |
| **QTc Correction Method Unspecified (msec), n** | 49 | 59 |
| No Change or Decrease to ≤450 | 47 (96) | 58 (98) |
| Increase To >450 to ≤480 | 2 (4) | 1 (2) |
| Increase of ≤30 msec | 46 (94) | 55 (93) |
| Increase of >30-60 msec | 2 (4) | 4 (7) |
| Increase of >60 msec | 1 (2) | 0 |
| **Study MPP111782** | | |
| **QTc Interval, aggregate (msec), n** | 52 | 53 |
| No Change or Decrease to ≤450 | 49 (94) | 44 (83) |
| Increase To >450 to ≤480 | 3 (6) | 9 (17) |
| Increase of ≤30 msec | 46 (88) | 44 (83) |
| Increase of >30-60 msec | 6 (12) | 9 (17) |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.

1. Number of participants with values at the specified planned time.

Note:

a. An increase is defined as an increase in category relative to baseline category. Participants with missing baseline values are assumed to have baseline value <450. The summary contains a combination of machine read and calculated values.

- Immunogenicity Results

Serum samples were assessed for immunogenicity using a tiered analysis approach with validated assays: 1) for binding anti-drug antibodies (ADA): screening, confirmation, and titration analysis; and 2) for neutralizing antibodies (NAb). Both Study 205687 and MMP111782 used the same methods to detect binding ADA (6th generation assay) and NAb (3rd generation assay). Both binding ADA and Nab assay life cycles have been captured in the Integrated Summary of Immunogenicity for Mepolizumab. Both programs used the same generation binding ADA and NAb assays as the mepolizumab severe asthma clinical program.

In Study 205687, serum samples for binding ADA analyses were collected at baseline, Week 52 (end of treatment), and at early withdrawal visits (if applicable). Participants who entered the post-Week 52 follow-up period had an additional sample taken at Week 68.

In Study MPP111782, serum samples were collected for binding ADA analyses at baseline, Week 5, Week 13, Week 25 (exit or early withdrawal), and follow-up (4-6 months after the last dose).

In CRSwNP placebo-controlled studies, 3% (6/237) of participants in the placebo group and 2% (6/249) of participants in the mepolizumab group were positive for binding ADA any time post-baseline. Treatment emergent ADA participants had titer values of 32 or less, similar to other indications using mepolizumab. None of the participants were positive for neutralizing.

For participants who were ADA positive post-baseline in Study 205687, 8 participants (3 placebo and 5 mepolizumab) reported at least 1 on-treatment AE. AEs reported in more than 1 participant were acute sinusitis, headache, and rhinitis (1 participant in each treatment group for all these 3 individual AEs).

**Table 45: Summary of Binding Antibody Assay Results: Highest Confirmatory Result Any Time Post Baseline (NP Studies)**

Summary of Binding Antibody Assay Results: Highest Confirmatory Result Any Time Post Baseline (NP Studies)

| | | | 205687 | | MPP111782 | | 205687 + MPP111782 | |
|---|---|---|---|---|---|---|---|---|
| Visit | Assay Result | | PBO (N=201) | 100 SC (N=206) | PBO (N=52) | 750 IV (N=53) | PBO (N=253) | All Doses (N=259) |
| Baseline | n | | 25 | 24 | 7 | 2 | 32 | 26 |
| | NEGATIVE | | 21 (84%) | 23 (96%) | 5 (71%) | 2 (100%) | 26 (81%) | 25 (96%) |
| | POSITIVE | | 4 (16%) | 1 (4%) | 2 (29%) | 0 | 6 (19%) | 1 (4%) |
| Highest post baseline | n | | 187 | 196 | 50 | 53 | 237 | 249 |
| | NEGATIVE | | 183 (98%) | 190 (97%) | 48 (96%) | 53 (100%) | 231 (97%) | 243 (98%) |
| | POSITIVE | | 4 (2%) | 6 (3%) | 2 (4%) | 0 | 6 (3%) | 6 (2%) |
| | Titre value | Min. | 4 | 4 | 32 | | 4 | 4 |
| | | Median | 8.0 | 16.0 | 80.0 | | 12.0 | 16.0 |
| | | Max. | 16 | 32 | 128 | | 128 | 32 |

**Safety in special populations**

- Adverse Events by Age

In the CRSwNP placebo-controlled studies, the majority of participants in both treatment groups were aged 18 to 64 years. The incidence of on-treatment AEs in this age group was similar to that observed in the Safety Population (83% in the placebo group and 81% in the mepolizumab all doses group) (***Table 46***). The most frequently reported AEs were nasopharyngitis and headache in both treatment groups.

Sixty-seven participants (32 placebo and 35 mepolizumab) were aged ≥65 years. The incidence of on-treatment AEs in this age group was 81% (26/32) in the placebo group and 77% (27/35) in the mepolizumab group. Nasopharyngitis was the most frequently reported AE in both treatment groups.

**Table 46: On- Treatment AEs Occurring in ≥10% of Participants in either Integrated Treatment Group by Age (CRSwNP Placebo-Controlled Studies), Safety Population**

| Preferred Term, n, (%) | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| **18-64 Years of Age** | | | | | | |
| n | 174 | 177 | 47 | 47 | 221 | 224 |
| **Any Event** | 146 (84) | 147 (83) | 38 (81) | 35 (74) | 184 (83) | 182 (81) |
| Nasopharyngitis | 43 (25) | 47 (27) | 10 (21) | 8 (17) | 53 (24) | 55 (25) |
| Headache | 43 (25) | 33 (19) | 19 (40) | 11 (23) | 62 (28) | 44 (20) |
| **≥65 Years of Age** | | | | | | |
| n | 27 | 29 | 5 | 6 | 32 | 35 |
| **Any Event** | 22 (81) | 22 (76) | 4 (80) | 5 (83) | 26 (81) | 27 (77) |
| Nasopharyngitis | 3 (11) | 5 (17) | 2 (40) | 2 (33) | 5 (16) | 7 (20) |
| Headache | 1 (4) | 4 (14) | 1 (20) | 2 (33) | 2 (6) | 6 (17) |
| Back pain | 2 (7) | 4 (14) | 0 | 0 | 2 (6) | 4 (11) |
| Upper respiratory tract infection | 1 (4) | 3 (10) | 1 (20) | 1 (17) | 2 (6) | 4 (11) |
| Hypertension | 3 (11) | 1 (3) | 1 (20) | 0 | 4 (13) | 1 (3) |
| Sinusitis | 4 (15) | 1 (3) | 0 | 0 | 4 (13) | 1 (3) |
| Nasal polyps | 4 (15) | 0 | 0 | 0 | 4 (13) | 0 |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.
1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.

- Adverse Events by Gender

The incidence of AEs within each gender was similar for placebo and mepolizumab in all doses groups. Headache and nasopharyngitis were the most frequently reported AEs for both gender subgroups for both placebo and mepolizumab all doses groups (**Table 47**).

**Table 47: On-Treatment AEs Occurring in ≥10% of Participants in either Integrated Treatment Group by Gender (CRSwNP Placebo-Controlled Studies), Safety Population**

| Preferred Term, n, (%) | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| **Female** | | | | | | |
| n | 76 | 67 | 17 | 13 | 93 | 80 |
| **Any Event** | 67 (88) | 60 (90) | 15 (88) | 13 (100) | 82 (88) | 73 (91) |
| Headache | 22 (29) | 17 (25) | 9 (53) | 4 (31) | 31 (33) | 21 (26) |
| Nasopharyngitis | 17 (22) | 11 (16) | 3 (18) | 1 (8) | 20 (22) | 12 (15) |
| Epistaxis | 9 (12) | 7 (10) | 1 (6) | 0 | 10 (11) | 7 (9) |
| Oropharyngeal pain | 7 (9) | 6 (9) | 2 (12) | 0 | 9 (10) | 6 (8) |
| Sinusitis | 10 (13) | 5 (7) | 1 (6) | 0 | 11 (12) | 5 (6) |
| Asthma | 11 (14) | 2 (3) | 1 (6) | 0 | 12 (13) | 2 (3) |
| **Male** | | | | | | |
| n | 125 | 139 | 35 | 40 | 160 | 179 |
| **Any Event** | 101 (81) | 109 (78) | 27 (77) | 27 (68) | 128 (80) | 136 (76) |
| Nasopharyngitis | 29 (23) | 41 (29) | 9 (26) | 9 (23) | 38 (24) | 50 (28) |
| Headache | 22 (18) | 20 (14) | 11 (31) | 9 (23) | 33 (21) | 29 (16) |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.
1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.

- Adverse Events by Race

Most participants in the Safety Population were White (94%). Amongst White participants, the incidence of on-treatment AEs and the incidence of the most frequently reported SOC and preferred terms was similar to that observed in the Safety Population.

Given the low proportion of participants in the Safety Population who were of Asian (4%), African American/African Heritage (2%), or Multiple Race (<1%), there is a limited ability to compare the incidence and pattern of on-treatment AEs in these subgroups to the Safety Population.

- Use in Pregnancy and Lactation

During the conduct of the mepolizumab clinical development program, female subjects were required to commit to consistent and correct use of an acceptable method of birth control (defined as the failure rate of <1%) from the time of consent, for the duration of the study, and for 4 months after the last dose of study drug administration.

As of 23 September 2019 (cut-off date for current Investigator's Brochure), 33 pregnancies were reported for 31 female subjects receiving investigational product in the completed and ongoing mepolizumab studies (all indications) (***Table 48***). Of the 33 pregnancies, 2 were reported in subjects who received placebo. There was 1 report of congenital anomalies for the live births (see description below). Two additional pregnancies were reported for the female partners of study subjects: 1 on placebo which resulted in spontaneous abortion (Study SB-240563/035), 1 on mepolizumab 100 mg SC which resulted in live birth with congenital anomaly (study 201312). These exposures via partner cases are not included in **Table 48**.

**Table 48: Reported Pregnancies in the Mepolizumab Clinical Development Program (Completed and Ongoing GSK-Sponsored Studies and Expanded Access Program; Status as of 23 September 2019)**

| Pregnancy outcome | Blinded | PBO | Mepolizumab | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | 100mg SC | 300mg SC | 75mg IV | 500mg IV | 750mg IV | All doses |
| Total | 3 | 2 | 12 | 1 | 4 | 2 | 9[1] | 33[2] |
| Ongoing | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 |
| Live birth | 2 | 1 | 7 | 1 | 3 | 1 | 5[3] | 20[2] |
| Elective termination | 0 | 0 | 0 | 0 | 0 | 1 | 2 | 3 |
| Spontaneous abortion | 1 | 1 | 3 | 0 | 1 | 0 | 2 | 8 |

[redacted]

Abbreviations: PBO, placebo.

1. One participant with HES who received mepolizumab 750 mg IV had 2 pregnancies; 1 electively terminated and 1 resulting in a live birth.
2. Two live births were reported from blinded studies 201810 and 205687; treatment is currently unknown.
3. One participant with HES (MHE104317; mepolizumab HES EAP) received mepolizumab dose of 700 mg IV.

The live birth of a healthy neonate in Study 201810 (***Table 48***) was reported for a female participant who was randomized to continued mepolizumab 100 mg SC in Part C of the study. The live birth with congenital anomalies of low hemoglobin, mild pulmonary valve stenosis, and heart murmur in Study 205687 (***Table 48***) was reported for a female participant who received mepolizumab 100 mg SC. The pregnancy was confirmed after the 4th dose of mepolizumab, and study treatment was discontinued. Another female participant in Study 205687 (***Table 48***), who was randomized to receive placebo, reported a missed abortion 41 days after her first dose of placebo and was withdrawn from the study.

- Overdose

The dose of mepolizumab considered to be an overdose has not been defined. Single doses of up to 1500 mg have been administered intravenously without evidence of dose-related toxicities. There are no known antidotes and the MAH does not recommend a specific treatment in the event of a suspected overdose. Clinical judgment should be used in treating the symptoms of a suspected overdose.

- Drug Abuse

There is no evidence for and no anticipation of patient abuse of mepolizumab

- Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There have been no studies to investigate the effect of mepolizumab on driving performance or the ability to operate machinery. A detrimental effect on such activities would not be anticipated from the pharmacology or adverse reaction profile of mepolizumab.

**Safety related to drug-drug interactions and other interactions**

No formal drug interaction studies have been conducted with mepolizumab in participants with severe bilateral nasal polyposis.

**Discontinuation due to adverse events**

By study design, participants who permanently discontinued study treatment in Study MPP111782 were withdrawn from the study and AEs which led to withdrawal from the study are presented elsewhere. In Study 205687, participants who permanently discontinued study treatment could continue in the study off study treatment. Therefore, AEs leading to discontinuation of study treatment

are presented for Study 205687 only. In Study 205687, 4 participants (2%) in each treatment group discontinued treatment due to an AE (***Table 49***). Of these 8 participants, all but 1 placebo-treated participant* remained in the study.

Two events leading to permanent discontinuation of study treatment (focal segmental glomerulosclerosis in 1 participant and pancreatitis acute in 1 participant) were reported as SAEs, both occurred in the placebo group. Four events leading to permanent discontinuation of study treatment in 2 participants were considered by the investigator to be related to study treatment: eczema in 1 participant in the placebo group; abdominal pain upper, diarrhea, and headache in 1 participant in the mepolizumab group.

**Table 49: Adverse Events Leading to Permanent Discontinuation of Study Treatment (Study 205687), Safety Population**

| | 205687[1] | |
|---|---|---|
| **Preferred Term, n, (%)** | **PBO N=201** | **Mepo 100mg SC N=206** |
| Any Event | 4 (2) | 4 (2) |
| Abdominal pain upper[2,3] | 0 | 1 (<1) |
| Angioedema | 0 | 1 (<1) |
| Arthralgia | 0 | 1 (<1) |
| Diarrhoea[2,3] | 0 | 1 (<1) |
| Headache[3,4] | 0 | 1 (<1) |
| Pulmonary embolism | 0 | 1 (<1) |
| Venous thrombosis limb | 0 | 1 (<1) |
| Eczema[2] | 1 (<1) | 0 |
| Pancreatitis acute[4] | 1 (<1) | 0 |
| Burnout syndrome[5] | 1 (<1) | 0 |
| Focal segmental glomerulosclerosis[4] | 1 (<1) | 0 |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.
1. In Study 205687, participants discontinuing investigational product were able to continue in the study off treatment.
2. Drug-related events.
3. Concurrent 3 severe AEs were reported in 1 participant.
4. SAE.
5. The event was also led to withdrawal from the study.

Study Treatment Interruption

On-treatment AEs/SAEs led to study treatment interruption in 4 participants in the placebo group (herpes zoster, cellulitis*†, rash†, nasal polyps, and viral upper respiratory tract infection) and in 2 participants in the mepolizumab group (depressive symptom, hiatus hernia*†, and myocardial infarction*†). None of these events were considered by the investigator to be related to study treatment. (*Note: the events were SAEs. †Note: the events reported by the same participant.)

Adverse Events Leading to Withdrawal from the Study

As described previously, participants who permanently discontinued study treatment in Study MPP111782 were withdrawn from the study. In the CRSwNP placebo-controlled studies, 9 participants (6, 2% in the placebo group and 3, 1% in the mepolizumab group) were withdrawn from the study due to their AEs (***Table 50***). All participants but 1 were in Study MPP111782. No individual AE leading to

withdrawal was reported in more than 1 participant. Events of rash and toxic skin eruption in the mepolizumab group in Study MPP111782 were considered by the investigator to be drug-related.

**Table 50: Adverse Events Leading to Withdrawal from the Study (CRSwNP Placebo-Controlled Studies), Safety Population**

| | 205687 | | MPP111782 | | Both studies[1] | |
|---|---|---|---|---|---|---|
| Preferred Term, n, (%) | PBO N=201 | Mepo 100mg SC N=206 | PBO N=52 | Mepo 750mg IV N=53 | PBO N=253 | Mepo all doses N=259 |
| Any Event | 1 (<1) | 0 | 5 (10) | 3 (6) | 6 (2) | 3 (1) |
| Haematuria | 0 | 0 | 0 | 1 (2) | 0 | 1 (<1) |
| Rash[2] | 0 | 0 | 0 | 1 (2) | 0 | 1 (<1) |
| Toxic skin eruption[2] | 0 | 0 | 0 | 1 (2) | 0 | 1 (<1) |
| Cellulitis orbital | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 |
| Burnout syndrome[3] | 1 (<1) | 0 | 0 | 0 | 1 (<1) | 0 |
| Eosinophilic pneumonia | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 |
| Anosmia | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 |
| Lower respiratory tract infection | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 |
| Syncope | 0 | 0 | 1 (2) | 0 | 1 (<1) | 0 |

[redacted]

Abbreviations: Mepo, mepolizumab; PBO, placebo.
1. Integrated data from CRSwNP placebo-controlled studies 205687 and MPP111782.
2. Drug-related events.
3. The event also led to discontinuation study treatment.
Note:
a. Included events reported up to and including 28 days after last dose.

**Post marketing experience**

At the time of submission, the most recent PBRER/EU-PSUR has a cut-off date of 23 September 2019. The cumulative exposure to NUCALA in the post-marketing setting is estimated to be 76,383 patient-years.

The safety profile of mepolizumab from post-marketing sources remains generally similar to that known at initial market authorization. During the post-marketing period, following a review of spontaneous post-marketing reports of anaphylaxis, the mepolizumab label was updated to include "anaphylaxis" in the existing Warning regarding hypersensitivity reactions and in the Adverse Reactions section.

## 2.5.1. Discussion on clinical safety

Safety data from the 512 participants with CRSwNP (259 exposed to mepolizumab) participating in the 2 completed placebo-controlled studies (Phase III study 205687 and Phase II study MPP111782) have been integrated. The 100 mg subcutaneous (SC) dose of mepolizumab (NUCALA) was assessed in the pivotal Phase III placebo-controlled study 205687 and the 750 mg intravenous (IV) dose was assessed in the supportive Phase II placebo-controlled study MPP111782. Key safety data from the broader MAH-sponsored mepolizumab clinical development program have also been integrated.

The overall incidence and percentage of CRSwNP patients that experienced any AE was similar across all main studies, 81% and 83% in mepolizumab and placebo treatment arms respectively. The most common AEs were nasopharyngitis, headache, oropharyngeal pain, back pain and epistaxis.

Across both studies, the CMH adjusted relative risk was highest for the PT rash at 3.91 (95% CI: 0.84, 18.21) in the mepolizumab all doses group compared with the placebo group. Rash is considered expected for mepolizumab and is included in the SPC under systemic non-allergic administration-related reactions. Most of these AEs were mild to moderate in severity.

Headache was the most common adverse reaction and the most common AE to occur on the day of treatment, headache is expected as per the Nucala SmPC with a frequency of very common. Other adverse reactions occurred in ≤1% of subjects.

The SOC with the highest incidence of on-treatment AEs in both treatment groups was Infections and Infestations, the incidence was 63% in the placebo group and 54% in the mepolizumab all doses group.

AESI include systemic reactions, local injection site reactions, infections, malignancies, and cardiovascular safety events.

Systemic reactions including hypersensitivity reactions occurred with a higher frequency in mepolizumab-treated participants, with a RR of 1.95. This is in line with hypersensitivity reactions being listed in the SmPC section 4.8 with a frequency of common, while systemic reactions are considered an important identified risk in the RMP and subject to routine risk minimisation procedures. In addition, a targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis. The following text is proposed to be added to the SmPC section 4.8. and is accepted *"In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving Nucala 100 mg and in no patients in the placebo group. Other systemic reactions were reported by no patients in the group receiving* mepolizumab *100 mg and in 1 patient (<1%) in the placebo group."*

Injection site reactions occurred with a higher frequency in mepolizumab-treated participants, with a RR of 2.44. This is in line with Injection site reactions being listed in the SmPC section 4.8 with a frequency of common. All events were non-serious, of mild intensity and resolved and plausibly related to the method of administration. The following text is proposed to be added to the SmPC which is accepted "*In the placebo-controlled study, injection site reactions (e.g., erythema, pruritus) occurred at a rate of 2% in patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.*"

Infections and serious infections occurred with a lower frequency in mepolizumab-treated participants, with a RR of 0.85 and 0.29 respectively and does not raise any concerns. The most frequently reported event within the SOC was nasopharyngitis for both treatment groups.

No malignancies were reported in mepolizumab-treated participants. Serious Cardiac, Vascular, Thromboembolic and Ischemic Events occurred at a lower frequency in mepolizumab-treated participants than placebo patients. Alterations in immune response (malignancies) and alterations in cardiovascular safety are important potential risks in the RMP, subject to routine risk minimisation procedures. In addition, targeted follow-up questionnaires are employed to collect data on MI/Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism.

Overall, for the AESIs where an imbalance in frequency was observed for mepolizumab-treated patients compared to placebo patients, data from the CRSwNP indication is in line with previous safety profile of Nucala and appropriately risk minimised.

On-treatment non-fatal SAEs that occurred in more than 1 participant within a treatment group were anaemia and contusion (2 each in the mepolizumab group). One SAE of anaemia was mild in severity and the patient was hospitalised along with numerous cardiac issues, the other case was likely caused by bleeding associated with erosive gastritis and unlikely to be related to mepolizumab. Based on case narratives the SAEs of contusion were likely related to injury. Other SAEs occurred in no more than one subject.

The SOC with the highest number of SAEs in the mepolizumab group was the cardiac disorder SOC (6 v 0 SAEs in the mepolizumab group compared to the placebo group). Cardiovascular, thrombotic and ischemic disorders are discussed elsewhere as AESIs. No SAE in the mepolizumab group was considered related to the IMP.

The only fatality in the nasal polyp trials occurred in the placebo group and therefore raises no safety concerns.

For the majority of chemistry laboratory results, haematological laboratory results, and liver function tests there was no evidence of treatment effect. Exceptions included eosinophils and leukocytes which is expected and linked to the mechanism of action of the IMP; and urea where an imbalance between arms for values outside the normal range was noted. This was only observed in Study MPP111782 (10% placebo and 19% mepolizumab) and not in the pivotal study.

Mean values for vital signs were similar to baseline throughout the course of CRSwNP studies for both placebo and mepolizumab all doses groups, with the majority of patients having results in the normal ranges.

Immunogenicity with mepolizumab in CRSwNP patients was low at 3% in the pivotal study and 2% across both studies. This is in line with the level of immunogenicity seen in severe asthma patients. No neutralising antibodies were detected in any patient that tested positive for ADAs. The SmPC section 5.1. has been updated accordingly.

Mepolizumab is not indicated for paediatric or adolescent CRSwNP patients and the clinical trial programme did not recruit this age group. In patients greater than 65 years of age, headache occurred with a greater frequency in mepolizumab patients compared to placebo and younger patients, however this AE is already listed as expected in the SmPC. Otherwise, in patients less than or greater than 65 years, the safety profile is broadly similar across both treatment arms, although numbers are low in the over 65 years group. This is in line with no dose adjustment being required for elderly patients as per SmPC. There was a low number of Asian (4%), African American/African Heritage (2%), or Multiple Race (<1%) CRSwNP patients treated with mepolizumab limiting safety analysis in these sub-groups.

The incidence of AEs across both treatment arms was generally similar regardless of sex, the number of females recruited to both studies were lower than for males.

No formal studies have been performed on renal and hepatic impairment, however, based on population pharmacokinetic analyses no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min, while changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab due to mepolizumab being degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue. Renal and hepatic impairment have not been discussed by the MAH in relation to CRSwNP patients, however no differences are anticipated in these patients.

The numbers of pregnancies in mepolizumab-treated clinical trial subjects is low (n=33) and as per the SmPC use in pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the foetus.

The levels of discontinuations, treatment interruptions and withdrawals due to AEs was low across both treatment groups, and the same or lower for mepolizumab treated patients compared to placebo-treated patients and raises no concerns.

### 2.5.2. Conclusions on clinical safety

Overall, the safety profile of mepolizumab in CRSwNP patients is consistent with the known safety profile of mepolizumab. The SmPC adequately reflects the data submitted in CRSwNP patients.

### 2.5.3. PSUR cycle

Nucala is being approved for Eosinophilic Granulomatosis with Polyangiitis (EGPA), Hypereosinophilic Syndrome (HES) and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) indications in parallel at the same time. Therefore, an increase in PSUR frequency is warranted to monitor adequately the safety profile of mepolizumab in the new patient populations, mainly for the indication EPGA. The PSUR frequency is therefore increased to 6 monthly basis. The MAH should plan at least a further 6-month DLP period after the next December 2021 submission.

Based on the above considerations, the CHMP is of the opinion that the already existing entry in the EURD list for mepolizumab needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 23.9.2021.

## *2.6. Risk management plan*

The MAH was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.2 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.2 with the following content:

## *Safety concerns*

| | |
|---|---|
| **Important identified risks** | • Systemic Reactions including anaphylaxis |
| **Important potential risks** | • Alterations in immune response (malignancies)<br>• Alterations in cardiovascular safety |
| **Missing information** | • Limited data in pregnant and lactating patients<br>• Safety of mepolizumab in children with EGPA<br>• Safety of mepolizumab in patients with organ- or life-threatening EGPA |

## *Pharmacovigilance plan*

| **Study**<br><br>**Status** | **Summary of objectives** | **Safety concerns addressed** | **Milestones** | **Due dates** |
|---|---|---|---|---|
| **Category 1** - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation | | | | |
| None | | | | |
| **Category 2** – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization under exceptional circumstances | | | | |
| None | | | | |
| **Category 3**- Required additional pharmacovigilance activities | | | | |
| 200870<br>The Mepolizumab Pregnancy Exposure Study: a VAMPSS post-marketing surveillance study of Mepolizumab safety in pregnancy | To evaluate outcomes for pregnant women with asthma and their infants exposed to mepolizumab | Use in patients who become pregnant while taking mepolizumab. | Final Report | 2Q-2024 |
| A post-marketing study to evaluate the safety and efficacy of mepolizumab in children aged 6 – 17 years with EGPA (the protocol will be developed and submitted to PRAC within 3 months of European Commission for procedure EMEA/H/C/3860/II/36/G) | To evaluate the safety and efficacy of mepolizumab in children aged 6 – 17 years with EGPA | Use in children aged 6 – 17 years | Protocol submission<br><br>Final Report | 28 February 2022<br><br>Q1 2031 |

The post-marketing study to evaluate the safety and efficacy of mepolizumab in children aged 6-17 years with EGPA is added in the context of an extension of indication for EGPA (EMEA/H/C/003860/II/0036/G) running in parallel whose positive opinion is granted at September CHMP.

## *Risk minimisation measures*

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| Safety concern 1<br><br>Systemic reactions including anaphylaxis | **Routine risk minimisation measures:**<br><br>The SmPC includes appropriate information in Section 4.4 (Special Warnings and Precautions) and Section 4.8 (Undesirable effects).<br><br>Equivalent wording is included in the patient leaflet Section 2 and Section 4.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**:<br><br>As standard across all GSK products, a targeted follow-up questionnaire is used to collect data on severe hypersensitivity/anaphylaxis.<br><br>**Additional pharmacovigilance activities**:<br><br>None |
| Safety concern 2<br><br>Potential Risk of Alterations in immune response (malignancies) | **Routine risk minimisation measures:**<br><br>None proposed<br><br>**Additional risk minimisation measures**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>None |
| Safety concern 3<br><br>Potential Risk of Alterations in cardiovascular safety | **Routine risk minimisation measures:**<br><br>None proposed<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>To further evaluate this potential risk targeted follow-up questionnaires to collect data on MI/Unstable Angina, Cerebral Vascular Accident/Transient Ischemic Attack, Deep Vein Thrombosis/Pulmonary Embolism and Peripheral Arterial Thromboembolism.<br><br>**Additional pharmacovigilance activities:**<br><br>None |
| Safety concern 4<br>Limited data in | **Routine risk minimisation measures:**<br><br>The SmPC Section 4.6, Fertility, Pregnancy and Lactation, of the SmPC advises | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** |

| Safety concern | Risk minimisation measures | Pharmacovigilance activities |
|---|---|---|
| pregnant and lactating patients | prescribers on the non-clinical reproductive toxicity data available on NUCALA.<br><br>**Additional risk minimisation measures:**<br><br>None | None<br><br>**Additional pharmacovigilance activities:**<br><br>The Mepolizumab Pregnancy Exposure Study (200870): a VAMPSS post-marketing surveillance study of Mepolizumab safety in pregnancy |
| Safety concern 5<br><br>Safety of mepolizumab in children with EGPA | **Routine risk minimisation measures:**<br><br>SmPC Section 4.2, Posology and method of administration, advises prescribers on the dose of mepolizumab for children.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>A post-marketing study is proposed to evaluate the safety and efficacy of mepolizumab in children aged 6 – 17 years with EGPA. |
| Safety concern 6<br><br>Safety of mepolizumab in patients with organ- or life-threatening EGPA | **Routine risk minimisation measures:**<br><br>SmPC Section 4.4 Warnings and Precautions, and Section 5.1 Pharmacodynamic properties, advises prescribers on the exclusion of patients with organ-threatening or life-threatening EGPA from the study.<br><br>**Additional risk minimisation measures:**<br><br>None | **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**<br><br>None<br><br>**Additional pharmacovigilance activities:**<br><br>None |

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Lithuania, Bulgaria, Hungary, Estonia, Croatia, Slovenia, Slovakia, Italia and Latvia.

An editorial change in Annex II has also been introduced.

### 2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package

leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The bridging report submitted by the MAH has been found acceptable.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Nasal polyps (NP) are chronic inflammatory outgrowths of the paranasal sinus mucosa (commonly the ethmoid sinuses) that present bilaterally along the middle and superior meatus and occur primarily in adults. NP greatly impacts a patient's health-related quality of life (HRQoL) through increases in nasal obstruction, loss of sense of smell, facial pain, facial pressure and nasal discharge; and the persistence of these symptoms leads to chronic rhinosinusitis (CRS). NP develop in the setting of chronic paranasal sinus inflammation and are therefore associated with CRS.

CRSwNP is a disease of middle age with the average age of onset being approximately 42 years and the typical age of diagnosis ranging from 40–60 years. Males are more likely to have CRSwNP than females, however, disease may be more severe in females than males. Using cross-sectional patient surveys of random samples of the general population, the prevalence of CRSwNP ranges from 1.1% in the United States of America (USA) and China to 4.3% in Finland.

In general, up to 55% of patients with CRSwNP have asthma and the presence of NP increases with the severity of asthma.

The aetiology of CRSwNP is currently unknown although, in adults, eosinophils are the main inflammatory cell in the substantial proportion of NP tissue and are considered potentially responsible for the etiopathogenesis and prognosis of the disease. In Western countries, the majority of patients with CRSwNP have a type 2 inflammation characterised by eosinophilia (~80%) and elevated levels of interleukin-4, interleukin-5, and interleukin-13 cytokines.

In general, patients with CRSwNP have higher blood eosinophil levels than patients with CRS without NP (CRSsNP) and CRSwNP patients that additionally have asthma had higher eosinophil levels compared to CRSwNP patients without asthma.

### 3.1.2. Available therapies and unmet medical need

The standard of care (SoC) for CRSwNP in adults is a treatment with intranasal corticosteroids (INCS) and nasal saline irrigation and, for severe symptoms, intermittent courses of oral corticosteroids (OCS) when short term relief is required. Surgery to remove the NP tissue may also be indicated for severe cases of CRSwNP. Surgery involves the removal of the NP tissue and diseased nasal mucosa, restoring aeration of the nasal passage and sinuses. However, without control of the underlying inflammation NP have a strong tendency to recur.

A recent meta-analysis of surgery revision rates among patients with CRSwNP reported a mean revision rate of 16.2% over a weighted mean follow-up of 89.6 months: rates were higher among patients with asthma than without asthma (22.6% vs. 8.0%) and among patients with multiple previous surgeries than just one (26.4% vs. 14.3%).

Dupilumab was approved in the EU in October 2019 as an add-on therapy to Standard of Care (SoC) in adult patients with CRSwNP. This was the first biologic treatment to be approved in this indication. Omalizumab has recently been approved in the EU (July 2020).

### 3.1.3. Main clinical studies

A single pivotal study is submitted to support the use in adult patients with CRSwNP. Study 205687 was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, Phase III study of mepolizumab in adult participants with CRSwNP receiving SoC therapy. The study was designed to provide confirmatory evidence that mepolizumab 100 mg SC every 4 weeks is effective in improving symptoms, reducing NP size (as primary endpoint) and reducing the occurrence of nasal surgery in patients with the recurrent disease despite current optimal medical management (as secondary endpoint). The study enrolled 407 participants with severe, bilateral NP (CRSwNP) despite treatment with current SoC, a history of at least one prior surgery for NP. SoC consisted of daily mometasone furoate nasal spray (MF), and if required, saline nasal douching, occasional short courses of high dose OCS and/or antibiotics. At the start of run-in and throughout the study, participants were placed on MF at the maximum prescribed dose in line with local SoC. The maximum dose was 2 actuations (50 mcg/actuation) in each nostril twice daily which equaled a total daily dose of 400 mcg. For participants intolerant to this dose, the lower dose of 200 mcg could have been used (2 actuations [50 mcg/actuation] in each nostril once daily).

The study comprised of a 4-week run-in period, followed by a 52-week treatment period. Participants had a history of at least one prior surgery for nasal polyps (NP) in the last 10 years, had recurrent NP despite treatment with current SoC and were in current need for NP surgery (at study enrolment).

The co-primary endpoints were the change from Baseline in total ENP score at Week 52 and change from Baseline in nasal obstruction VAS score in the 4-week period Week 49-52.

## *3.2. Favourable effects*

For the co-primary endpoint, change from Baseline in total ENP score at Week 52, the median change in the mepolizumab group was -1.0 compared with 0 in the placebo group ($p<0.001$). A greater proportion of participants who received mepolizumab demonstrated an improvement (decrease) of ≥1.0 point compared with placebo in their total ENP score (50% vs 28%) at Week 52 [odds ratio: 2.74 (95% CI: 1.80, 4.18); $p<0.001$].

Similarly, a greater proportion of participants who received mepolizumab demonstrated an improvement (decrease) of ≥2.0 points compared with placebo in their total ENP score (36% vs 13%) at Week 52 [odds ratio: 4.05 (95% CI: 2.43, 6.76); $p<0.001$].

For the second co-primary endpoint, change from Baseline in nasal obstruction VAS score in the 4-week period Week 49-52, the median change from Baseline in the mepolizumab group was -4.41 (compared with -0.82 in the placebo group ($p<0.001$). The minimal important change (MIC) is considered to be ≥3.0). A greater proportion of participants who received mepolizumab demonstrated a clinically meaningful improvement (decrease) of ≥3.0 points compared with placebo in their nasal obstruction VAS score (60% vs 36%) in the 4-week period Week 49-52 [odds ratio: 2.66 (95% CI: 1.77, 4.00); $p<0.001$]**.**

For the key secondary endpoint of time to first nasal surgery up to Week 52, there was a clinically and statistically significant 57% reduction for the mepolizumab treated group compared to placebo in the risk of having surgery (hazard ratio: 0.43, 95% CI: 0.25, 0.76, $p=0.003$).

Treatment with mepolizumab resulted in clinically significant improvements in overall VAS score ($p<0.001$), composite VAS score ($p<0.001$), and loss of sense of smell VAS score ($p<0.001$) compared to placebo.

HRQoL showed improvements in HRQoL (in excess of the MIC of ≥28), as determined by SNOT-22, compared to placebo ($p<0.001$).

There was a statistically significant 42% reduction compared to placebo in the odds of requiring systemic corticosteroid treatment ($p=0.020$).

## *3.3. Uncertainties and limitations about favourable effects*

There is only a single pivotal trial supporting this extension of indication.

Post-hoc supplementary analyses were carried out using a regression-based parametric mixed model repeated measures (MMRM) approach for the co-primary endpoints. This analyse provides an estimate of a treatment effect that assumes all patients completed treatment as planned and is consequently biased. However, the analysis showed similar results for the NPS score, a lower response rate was demonstrated for Nasal Obstruction VAS Score. For missing at random the LS mean difference was -1.97 (-2.63, -1.31) $p < 0.001$, and with off treatment imputation the LS Mean difference was -1.86 (-2.52, -1.19) $p < 0.001$. This would appear to be below the minimal important change limit of 3.0.

It is not known whether the effects of treatment over a more prolonged duration of years would be maintained as demonstrated at week 52, however this will be followed up in the post marketing setting.

Nucala is intended for long-term treatment. Consideration can be given to alternative treatments in patients who have shown no response after 24 weeks of treatment for CRSwNP. Some patients with initial partial response may subsequently improve with continued treatment beyond 24 weeks. This is reflected in section 4.2. of the SmPC.

## *3.4. Unfavourable effects*

The safety assessment of mepolizumab in patients with CRSwNP (chronic rhinosinusitis with nasal polyposis) was mainly focused on 2 completed placebo-controlled studies, concretely Study 205687 (phase III) and Study MPP111782 (phase II). Within Study 205687 (phase III), a total of 206 adult patients were treated with mepolizumab 100 mg SC and within Study MPP111782 (phase II), a total of 53 adult patients were treated with mepolizumab 750 mg IV.

Overall, for both studies, there were 35 drug-related AEs (14%) in the mepolizumab group and 22 drug-related AEs (9%) in the placebo group. The most frequently reported on-treatment AEs were nasopharyngitis and headache in both groups.

From clinical trial data in patients with nasal polyps, mepolizumab has an acceptable safety profile. Most AEs were mild to moderate in severity. The overall rates for AEs and SAEs were similar across treatment arms. Headache was the most common adverse reaction with a frequency of very common. No new ADRs were added in the existing tabulated list of ADRs of the section 4.8 of SmPC.

## *3.5. Uncertainties and limitations about unfavourable effects*

While the safety analysis of the current clinical development programme appears to demonstrate that the safety profile is consistent with what is already known about mepolizumab, the long-term safety

profile in adult patients with nasal polyps will be fully characterised in the post-marketing setting though routine pharmacovigilance.

## *3.6. Effects Table*

**Table 51: Effects Table for mepolizumab and nasal polyps (data cut off 23rd of June 2020)**

| Effect | Short description | Unit | Treatment mep | Control plac | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| NPS at week 52 | Median Change from baseline in total endoscopic NPS score at week 52 | | -1.0 | 0 | P< 0.001<br><br>Adjusted difference – minus 0.73 95% CI (-1.11, -0.34) | Trial 205687 |
| Nasal obstruction VAS at week 52 | Median change from baseline Nasal obstruction VAS during 4 weeks prior to week 52 | | -4.41 | -0.82 | P< 0.001 Adjusted difference -3.14 95% CI (-4.09, -2.18) | Trial 205687 |
| Time to first nasal surgery up to Week 52. | Participants with nasal surgery prior to Week 52. | % | 18 (9%) | 46 (23%) | Hazard ratio 0.43 95% CI 0.25, 0.76 | Trial 205687 |
| SNOT-22 total score at Week 52. | Median Change from baseline in SNOT-22 total score at Week 52. | | -30.0 | -14.0 | P< 0.001<br><br>Adjusted difference – minus 16.49 95% CI (-23.57, -9.42) | Trial 205687 |
| **Unfavourable Effects** | | | | | | |
| AEs | Treatment: 52 weeks 100mg s.c. 4 q4w<br><br>Treatment:24 weeks 750mg i.v. q4w | No. of events n(%) | Mep 169/206(82)<br><br>Mep 41/53(77) | Plac 170/201(85)<br><br>Plac 45/52(87) | | 205687<br><br>MPP111782 |

| Effect | Short description | Unit | Treatment mep | Control plac | Uncertainties / Strength of evidence | References |
|---|---|---|---|---|---|---|
| SAEs | Treatment: 52 weeks 100mg s.c. 4 q4w | No. of events n(%) | Mep 12/206(6) | Plac 14/201(7) | | 205687 |
| | Treatment:24 weeks 750mg i.v. q4w | | Mep 0(0) | Plac 0(0) | | MPP111782 |

Abbreviations: Mep = mepolizumab, plac= placebo.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

The MAH has demonstrated the beneficial treatment effects of Nucala add-on therapy to intranasal corticosteroids in patients with CRSwNP.

In the pivotal studies, statistical significance was reached for the 2 co-primary efficacy endpoints (change from baseline in total endoscopic NPS and change from baseline in VAS NC score at Week 52) and all multiplicity adjusted key secondary endpoints demonstrated beneficial effect with Nucala treatment on top of intranasal corticosteroid compared to intranasal corticosteroid alone.

The safety profile is similar to the current known safety profile and therefore acceptable. The immunogenicity effects were low and also in line with the known profile of this product. Nucala is not significantly associated with a higher risk of experiencing systemic hypersensitivity reactions in the CRSwNP population.

### 3.7.2. Balance of benefits and risks

The overall benefit-risk is considered positive as an add-on treatment for patients with severe CRSwNP.

### 3.7.3. Additional considerations on the benefit-risk balance

None.

## *3.8. Conclusions*

The overall B/R of Nucala is positive.

# 4. Recommendations

## *Outcome*

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, II and IIIB |

Extension of indication to include Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) for Nucala (mepolizumab). As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Editorial changes have also been introduced in section 5.2, 6.1 and in Annex II. Version 7.2 of the RMP has also been adopted. In addition, the Marketing authorisation holder took the opportunity to update local representative information in the package leaflet.

The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and the Risk Management Plan (RMP).

## *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and the Risk Management Plan are recommended.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

## Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

# 5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion Nucala-H-C-3860-II-35.

## Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted), as a relevant example with changes highlighted as adopted by the CHMP on 16 September 2021.