SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL pre-filled syringe contains 100 mg of mepolizumab.

Mepolizumab is a humanised monoclonal antibody produced in Chinese hamster ovary cells by recombinant DNA technology.

Excipient(s) with known effect

Nucala 100 mg solution for injection in pre-filled syringe

Each 1 mL pre-filled syringe contains 0.2 mg polysorbate 80

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection)
A clear to opalescent, colourless to pale yellow to pale brown solution, with a pH of 6.0-6.6 and an osmolality of 415-615 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe eosinophilic asthma

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adults, adolescents and children aged 6 years and older (see section 5.1).

Chronic rhinosinusitis with nasal polyps (CRSwNP)

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.

Chronic obstructive pulmonary disease (COPD)

Nucala is indicated as add-on maintenance treatment of adult patients with uncontrolled COPD of an eosinophilic phenotype on a combination of an inhaled corticosteroid (ICS), a long acting beta2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA). (see section 5.1).

Eosinophilic granulomatosis with polyangiitis (EGPA)

Nucala is indicated as an add-on treatment for patients aged 6 years and older with relapsing-remitting or refractory eosinophilic granulomatosis with polyangiitis (EGPA).

Hypereosinophilic syndrome (HES)

Nucala is indicated as an add-on treatment for adult patients with inadequately controlled hypereosinophilic syndrome without an identifiable non-haematologic secondary cause (see section 5.1).

4.2 Posology and method of administration

It is recommended that Nucala is prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma, CRSwNP, COPD, EGPA or HES.

Posology

Severe eosinophilic asthma

Adults and adolescents aged 12 years and over

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old

The recommended dose of mepolizumab is 40 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy is to be considered at least on an annual basis as determined by physician assessment of the patient's disease severity and level of control of exacerbations.

CRSwNP

Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

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.

COPD

Adults

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

EGPA

Adults and adolescents aged 12 years and older

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

The posology of mepolizumab in children and adolescents aged 6 to 17 years old with EGPA was supported by modelling and simulation data (see section 5.2).

Children aged 6 to 11 years old weighing ≥ 40 kg

The recommended dose of mepolizumab is 200 mg administered subcutaneously once every 4 weeks.

Children aged 6 to 11 years old weighing < 40 kg

The recommended dose of mepolizumab is 100 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy is to be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and improvement of symptom control.
Patients who develop life-threatening manifestations of EGPA must also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

HES

Adults

The recommended dose of mepolizumab is 300 mg administered subcutaneously once every 4 weeks.

Nucala is intended for long-term treatment. The need for continued therapy is to be reviewed at least on an annual basis as determined by physician assessment of the patient's disease severity and level of symptom control.

Patients who develop life-threatening manifestations of HES must also be evaluated for the need for continued therapy, as Nucala has not been studied in this population.

Special populations

Elderly patients

No dose adjustment is required for elderly patients aged ≥65 years old (see section 5.2).

Renal and hepatic impairment

No dose adjustment is required in patients with renal or hepatic impairment (see section 5.2).

Paediatric population

Severe eosinophilic asthma

Children aged 6 to 11 years old

Nucala 100 mg powder for solution for injection and 40 mg solution for injection in pre-filled syringe are appropriate for administration to this population.

Nucala 100 mg solution for injection in pre-filled pen and 100 mg solution for injection in pre-filled syringe are not indicated for administration to this population.

Children less than 6 years old

The safety and efficacy of mepolizumab in children less than 6 years old have not yet been established.

No data are available.

CRSwNP in children less than 18 years old

The safety and efficacy in children with CRSwNP below the age of 18 years have not been established.

No data are available.

COPD in children less than 18 years old

There is no relevant use of mepolizumab in the paediatric population (under 18 years of age) for the indication of COPD.

EGPA in children less than 6 years old

The safety and efficacy of mepolizumab has not been established in children below the age of 6 years old.

No data are available.

HES in children aged less than 18 years old

The safety and efficacy of mepolizumab in children and adolescents aged less than 18 years old have not yet been established.

Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration

Nucala 100 mg solution for injection in pre-filled pen or pre-filled syringe

The pre-filled pen or pre-filled syringe must be used for subcutaneous injection only.

Nucala may be self-administered by the patient or administered by a caregiver if their healthcare professional determines that it is appropriate, and the patient or caregiver are trained in injection techniques.

For children aged 6 to 11 years old, administration must be carried out by a healthcare professional or a trained caregiver.

For self-administration the recommended injection sites are the abdomen or thigh. A caregiver can also inject Nucala into the upper arm.

For doses which require more than one injection, it is recommended that each injection is administered at least 5 cm apart.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled pen or pre-filled syringe are provided in the instructions for use in the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Asthma or COPD exacerbations

Mepolizumab must not be used to treat acute asthma or COPD exacerbations.

Asthma-related or COPD-related adverse symptoms or exacerbations may occur during treatment. Patients must be instructed to seek medical advice if their asthma or COPD remains uncontrolled or worsens after initiation of treatment.

Corticosteroids

Abrupt discontinuation of corticosteroids after initiation of mepolizumab therapy is not recommended. Reduction in corticosteroid doses, if required, must be gradual and performed under the supervision of a physician.

Hypersensitivity and administration-related reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of mepolizumab. These reactions generally occur within hours of administration, but in some instances have a delayed onset (i.e., typically within several days). These reactions may occur for the first time after a long duration of treatment (see section 4.8). In the event of a hypersensitivity reaction, appropriate treatment as clinically indicated must be initiated.

Parasitic infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections should be treated before starting therapy. If patients become infected whilst receiving treatment with mepolizumab and do not respond to anti-helminth treatment, temporary discontinuation of therapy should be considered.

Organ threatening or life-threatening EGPA

Nucala has not been studied in patients with organ threatening or life-threatening manifestations of EGPA (see section 4.2).

Life-threatening HES

Nucala has not been studied in patients with life-threatening manifestations of HES (see section 4.2).

Excipients

This medicinal product contains polysorbate 80 (see section 2), which may cause allergic reactions.

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose,that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Cytochrome P450 enzymes, efflux pumps and protein-binding mechanisms are not involved in the clearance of mepolizumab. Increased levels of pro-inflammatory cytokines (e.g. IL-6), via interaction with their cognate receptors on hepatocytes, have been shown to suppress the formation of CYP450 enzymes and drug transporters, however, elevation of systemic pro-inflammatory markers in severe refractory eosinophilic asthma is minimal and there is no evidence of IL-5 receptor alpha expression on hepatocytes. The potential for interactions with mepolizumab is therefore considered low.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.
Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown.

As a precautionary measure, it is preferable to avoid the use of Nucala during pregnancy. Administration of Nucala to pregnant women should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus.

Breast-feeding

There are no data regarding the excretion of mepolizumab in human milk. However, mepolizumab was excreted into the milk of cynomolgus monkeys at concentrations of less than 0.5% of those detected in plasma.

A decision must be made whether to discontinue breast-feeding or to discontinue Nucala therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Nucala has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Severe eosinophilic asthma
In placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).

CRSwNP

In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were headache (18%) and back pain (7%).

COPD

In three placebo-controlled studies in patients with COPD, the most commonly reported adverse reactions during treatment were headache (10%), back pain (7%) and arthralgia (5%).

EGPA

In a placebo-controlled study in patients with EGPA, the most commonly reported adverse reactions during treatment were headache (32%), injection site reactions (15%) and back pain (13%). Systemic allergic/hypersensitivity reactions were reported by 4% of EGPA patients.

HES

In a placebo-controlled study in patients with HES, the most commonly reported adverse reactions during treatment were headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each).

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled severe eosinophilic asthma studies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n= 263), from a randomised, double-blind placebo-controlled 52-week study in patients with CRSwNP receiving mepolizumab 100 mg SC (n=206), in three double-blind placebo-controlled 52- to 104-week studies in patients with COPD receiving mepolizumab 100 mg SC (n=1043), in patients with EGPA receiving mepolizumab 300 mg SC (n=68), in a double-blind placebo-controlled 32-week study in patients with HES receiving mepolizumab 300 mg SC (n= 54), and from spontaneous post-marketing reports. Safety data is also available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years).

The safety profile of mepolizumab in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	**Adverse reactions**	**Frequency**
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis Herpes zoster**	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back pain Arthralgia**	Common
General disorders and administration site	Administration-related reactions (systemic non allergic)***	Common

System Organ Class	Adverse reactions	Frequency
conditions	Local injection site reactions Pyrexia	

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma and COPD studies. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4.

**From spontaneous post marketing reporting. Herpes zoster was reported uncommonly in severe asthma studies.
*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma and COPD studies were rash, flushing, myalgia and fatigue; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reactions

Systemic reactions, including hypersensitivity reactions, in CRSwNP

In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving mepolizumab 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.

Systemic reactions, including hypersensitivity reactions, in COPD

In the placebo-controlled study of 52 to 104 weeks duration, systemic allergic (type I hypersensitivity) reactions were reported in 1 patient (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by 4 patients (<1%) in the group receiving mepolizumab 100 mg and in 4 patients (<1%) in the placebo group.
In the two 52-week placebo-controlled studies, systemic allergic/hypersensitivity reactions were reported in 4 patients (<1%) in the groups receiving mepolizumab 100 mg and in 3 patients (<1%) in the placebo groups. Systemic non-allergic reactions were reported by 7 patients (1%) in the groups receiving mepolizumab 100 mg and in 10 patients (2%) in the placebo groups.

Systemic reactions, including hypersensitivity reactions, in EGPA

In the 52-week placebo-controlled study the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of mepolizumab and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of mepolizumab and 1% of patients in the placebo group. Systemic non-allergic reactions (angioedema) were reported by 1 (1%) patient in the group receiving 300 mg of mepolizumab and no patients in the placebo group.

Systemic reactions, including hypersensitivity reactions, in HES

In the 32-week placebo-controlled study, 1 patient (2%) reported a systemic (other) reaction in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group.

Local injection site reactions

Severe eosinophilic asthma

In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

CRSwNP

In the placebo-controlled study, local injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.

COPD

In the placebo-controlled studies, local injection site reactions (e.g., erythema, haematoma, swelling, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with 2% in patients receiving placebo.

EGPA

In the placebo-controlled study, local injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving mepolizumab 300 mg compared with 13% in patients receiving placebo.

HES

In the placebo-controlled study, local injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving mepolizumab 300 mg compared with 4% in patients receiving placebo.

Paediatric population

Severe eosinophilic asthma

Thirty-seven adolescents (aged 12-17) were enrolled in four placebo-controlled studies (25 mepolizumab treated intravenously or subcutaneously) of 24 to 52 weeks duration. Thirty -six paediatric patients (aged 6-11) received mepolizumab subcutaneously in an open-label study for 12 weeks. After a treatment interruption of 8 weeks, 30 of these patients, received mepolizumab for a further 52 weeks. The

safety profile was similar to that seen in adults. No additional adverse reactions were identified.
In addition, the long-term safety of mepolizumab was assessed in 9 adolescent patients (aged 12-17) and 15 paediatric patients (aged 6-11) who were enrolled in an open-label extension study (201956). In this study, patients received mepolizumab subcutaneously and were followed for up to 6.4 years. The safety profile was similar to that seen in pivotal asthma studies. No additional adverse reactions were identified.

HES

Four adolescents aged 12 to 17 years were enrolled in the placebo-controlled study 200622, one adolescent received 300 mg of mepolizumab, and 3 adolescents received placebo for 32 weeks. All 4 adolescents continued into a 20-week open-label extension study 205203 (see Section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

United Kingdom
Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the
Google Play or Apple App Store

4.9 Overdose

Single doses of up to 1,500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

There is no specific treatment for an overdose with mepolizumab. If overdose occurs, it is recommended that the patient be treated supportively with appropriate monitoring as necessary.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for obstructive airway diseases, other systemic drugs for obstructive airway diseases, ATC code: R03DX09.

Mechanism of action

Mepolizumab is an IL-5 antagonist (IgG1 kappa) that binds to IL-5 with a dissociation constant of 100 pM, inhibiting its bioactivity by blocking its binding to the IL-5R alpha complex on the cell surface. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. Type 2 inflammation driven by IL-5 is an important component in the pathogenesis of asthma, CRSwNP, COPD, EGPA and HES. Additional structural and inflammatory cell types also express the IL-5R alpha. In addition to the effects on eosinophils, binding IL-5 with mepolizumab inhibits the bioactivity of direct and indirect effects of IL-5 cytokine induced responses in multiple other cell types e.g., epithelial cells, mast cells, plasma cells, basophils, ILC-2 cells, T cells, smooth muscle cells, neutrophils and fibroblasts; however, the mechanism of action in these cells and across the different diseases has not been definitively established.

Pharmacodynamic effects

Severe eosinophilic asthma

In patients with severe refractory eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/μL at week 32 (n=182), a reduction of 84% compared to placebo. This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

In children aged 6 to 11 years old with severe refractory eosinophilic asthma administered mepolizumab subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 306 (n=16) to 48 (n=15) following 40 mg (for a weight < 40kg) and 331 to 44 cells/μL (n=10) following 100 mg (for a weight ≥ 40 kg), a reduction from baseline of 85% and 87%, respectively.

In adults, adolescents and children, this magnitude of reduction was observed within 4 weeks of treatment.

CRSwNP

In patients with CRSwNP, following a 100 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline to week 52 of 390 (n=206) to 60 cells/μL (n=126), which corresponds to a geometric mean reduction of 83% compared to placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period of 52 weeks.

COPD

In patients with COPD, following a 100 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 (and up to 104) weeks, blood eosinophils were

reduced from a geometric mean count at baseline of 480 cells/µL (n=403) to 60 cells/µL at week 52 (n=257) and week 104 (n=61), which corresponds to a geometric mean reduction of 79% at week 52 and 80% at week 104 compared to placebo. A similar magnitude of reduction was observed within 4 weeks of treatment.

EGPA

In patients with EGPA, following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 52 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 177 (n=68) to 38 cells/µL (n=64) at week 52. There was a geometric mean reduction of 83% compared to placebo and this magnitude of reduction was observed within 4 weeks of treatment.

HES

In patients with HES (adults/adolescents), following a 300 mg dose of mepolizumab administered subcutaneously every 4 weeks for 32 weeks, blood eosinophil reduction was observed within 2 weeks of treatment. At week 32, blood eosinophils were reduced from a geometric mean count at baseline of 1,460 (n=54) to 70 cells/µL (n=48) and a geometric mean reduction of 92% compared to placebo was observed. This magnitude of reduction was maintained for a further 20 weeks in patients that continued mepolizumab treatment in the open-label extension study.

Immunogenicity

Severe eosinophilic asthma, CRSwNP, COPD, EGPA and HES

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of adults and adolescents with severe refractory eosinophilic asthma treated with 100 mg dose , 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 9/381 (2%) of adults with COPD treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of adults and adolescents with HES treated with 300 mg dose of mepolizumab subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.

The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) or in HES patients (n=102) treated for 20 weeks in open-label extension studies was similar to that observed in the placebo-controlled studies. The immunogenicity data were collected in patients with CRSwNP for 68 weeks (n=68), in patients with COPD for 104 weeks (n=127) and in patients with EGPA for 60 weeks (n=65).

In children aged 6 to 11 years old with severe refractory eosinophilic asthma following either 40 mg subcutaneously (for a weight < 40kg) or 100 mg subcutaneously (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study. Neutralising antibodies were detected in one

adult patient with severe refractory eosinophilic asthma and in no patients with CRSwNP, COPD, EGPA or HES. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

Clinical efficacy

Severe eosinophilic asthma

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting $beta_2$ -adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1,192 patients, 60% females, with a mean age of 49 years (range 12– 82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV_1<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean predicted pre-bronchodilator FEV_1 was 60%. Patients continued to receive their existing asthma medicinal product during the studies**.**

For the oral corticosteroid-sparing study MEA115575, a total of 135 patients were enrolled (55% were female; mean age of 50 years) who were being treated daily with OCS (5-35 mg per day), and high-dose ICS plus an additional maintenance medicinal product.

Dose-ranging efficacy MEA112997 (DREAM) study

In MEA112997, a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of 52 weeks duration in 616 patients with severe refractory eosinophilic asthma, mepolizumab significantly reduced clinically significant asthma exacerbations (defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits) when administered in doses of 75 mg, 250 mg or 750 mg intravenously compared to placebo (see Table 1).

Table 1: Frequency of clinically significant exacerbations at week 52 in the intent to treat population

	Intravenous mepolizumab			Placebo
	75mg	250mg	750mg	

	n=153	n=152	n=156	n= 155
Exacerbation rate/year	1.24	1.46	1.15	2.40
Percent reduction	48%	39%	52%	
Rate ratio (95% CI)	0.52 (0.39, 0.69)	0.61(0.46, 0.81)	0.48 (0.36, 0.64)	
p-value	<0.001	<0.001	<0.001	-

Exacerbation reduction MEA115588 (MENSA) study

MEA115588 was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study which evaluated the efficacy and safety of mepolizumab as add-on therapy in 576 patients with severe refractory eosinophilic asthma defined as peripheral blood eosinophils greater than or equal to 150 cells/μL at initiation of treatment or greater than or equal to 300 cells/μL within the past 12 months.

Patients received mepolizumab 100 mg administered subcutaneously, mepolizumab 75 mg administered intravenously or placebo treatment once every 4 weeks over 32 weeks. The primary endpoint was the frequency of clinically significant exacerbations of asthma and the reductions for both mepolizumab treatment arms compared to placebo were statistically significant (p<0.001). Table 2 provides the results of the primary and secondary endpoints for patients treated with subcutaneous mepolizumab or placebo.

Table 2: Results of primary and secondary endpoints at week 32 in the intent to treat population (MEA115588)

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Primary endpoint		
Frequency of clinically significant exacerbations		
Exacerbation rate per year	0.83	1.74
Percent reduction Rate ratio (95% CI)	53% 0.47 (0.35, 0.64)	-
p-value	<0.001	
Secondary endpoints		
Frequency of exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction Rate ratio (95% CI)	61% 0.39 (0.18, 0.83)	–
p-value	0.015	
Frequency of exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Percent reduction Rate ratio (95% CI)	69% 0.31 (0.11, 0.91)	–
p-value	0.034	
Pre-bronchodilator FEV_1 (mL) at week 32		
Baseline (SD)	1,730 (659)	1,860 (631)
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11, 184)	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Baseline (SD)	47.9 (19. 5)	46.9 (19.8)
Mean change from baseline (SE)	-16.0 (1.1)	-9.0 (1.2)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	(-10.2, -3.8)	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

Table 3 shows the results of a combined analysis of the two exacerbation studies (MEA112997 and MEA115588) by baseline blood eosinophil count. The rate of exacerbations in the placebo arm increased with increasing baseline blood eosinophil count. The reduction rate with mepolizumab was greater in patients with higher blood eosinophil counts.

Table 3: Combined analysis of the rate of clinically significant exacerbations by baseline blood eosinophil count in patients with severe refractory eosinophilic asthma

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cells/μL		
n	123	66
Exacerbation rate per year	1.16	1.73
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.67 (0.46,0.98)	---
150 to <300 cells/μL		
n	139	86
Exacerbation rate per year	1.01	1.41
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.72 (0.47,1.10)	---

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
300 to <500 cells/µL		
n	109	76
Exacerbation rate per year	1.02	1.64
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.62 (0.41,0.93)	---
≥500 cells/µL		
n	162	116
Exacerbation rate per year	0.67	2.49
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.27 (0.19,0.37)	---

Oral corticosteroid reduction study MEA115575 (SIRIUS)

MEA115575 evaluated the effect of mepolizumab 100 mg administered subcutaneously on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe refractory eosinophilic asthma. Patients had a blood eosinophil count of ≥150/µL at baseline or a blood eosinophil count of ≥300/µL in the 12 months prior to screening. Patients were administered mepolizumab or placebo treatment once every 4 weeks over the treatment period. Patients continued to receive their existing asthma medicinal product during the study with the exception of their OCS dose which was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained.

A total of 135 patients were enrolled: mean age was 50 years, 55% were female, and 48% had been receiving oral steroid therapy for at least 5 years. The baseline mean prednisone equivalent dose was approximately 13 mg per day.

The primary endpoint was the percent reduction in daily OCS dose (weeks 20-24), whilst maintaining asthma control by defined dose reduction categories (see Table 4). Predefined categories included percent reductions ranging from 90-100% reduction, to no decrease in the prednisone dose from the end of the optimisation phase. The comparison between mepolizumab and placebo was statistically significant (p=0.008).

Table 4: Results of the primary and secondary endpoints in MEA115575

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
Primary endpoint		
Percent reduction in OCS from baseline (weeks 20-24)		
90% - 100% 75% - <90%	16 (23%) 12 (17%)	7(11%) 5 (8%)

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
50% - <75% >0% - <50% No decrease in OCS/lack of asthma control/ withdrawal from treatment	9 (13%) 7 (10%) 25 (36%)	10 (15%) 7 (11%) 37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	
p-value	0.008	
Secondary endpoints (weeks 20-24)		
Reduction in the daily OCS dose to 0 mg/d	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0. 414	
Reduction in the daily OCS dose to ≤5mg/day	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	
p-value	0.025	
Median % reduction in daily OCS dose from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

Open-label extension studies in severe refractory eosinophilic asthma MEA115666 (COLUMBA), MEA115661 (COSMOS) and 201312 (COSMEX)

The long-term efficacy profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies MEA115666, MEA115661 and 201312 was generally consistent with the 3 placebo-controlled studies.

Chronic rhinosinusitis with nasal polyps (CRSwNP)

Study 205687 (SYNAPSE) was a 52-week, randomised, double-blind, placebo-controlled study which evaluated 407 patients aged 18 years and older with CRSwNP.

Patients enrolled in the study were required to have a nasal obstruction VAS (Visual Analogue Scale) symptom score of >5 out of a maximum score of 10, an overall VAS symptom score >7 out of a maximum score of 10 and an endoscopic bilateral NP score of ≥5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity). Patients must also have had a history of at least one prior surgery for nasal polyps in the previous 10 years.

Key baseline characteristics included total endoscopic NP score mean (SD) 5.5 (1.29), nasal obstruction VAS score mean (SD) 9.0 (0.83), overall VAS symptom score mean (SD) 9.1 (0.74), loss of smell VAS score mean (SD) 9.7 (0.72) and Sino-Nasal

Outcome Test (SNOT-22) mean (SD) 64.1 (18.32). The geometric mean eosinophil count was 390 cells/mcL (95% CI: 360, 420). In addition, 27% of patients had aspirin-exacerbated respiratory disease (AERD) and 48% of patients had at least 1 course of OCS for CRSwNP in the past 12 months.

Patients received a 100 mg dose of mepolizumab or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. The key secondary endpoint was the time to first NP surgery up to Week 52 (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [e.g. polypectomy] in the nasal cavity). Patients who received mepolizumab had significantly greater improvements (decreases) in total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo, and all secondary endpoints were statistically significant in favour of mepolizumab (see Table 5 and Figure 1).

Table 5: Summary of results for primary and secondary endpoints (intent to treat population)

	Placebo (N=201)	**Mepolizumab 100 mg SC (N=206)**
Co-primary endpoints		
Total endoscopic score at week 52 [a]		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52) [a]		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%)[d]	73 (36)	124(60)
Key secondary endpoint		
Time to first nasal polyps surgery		
Participants with surgery	46 (23)	18 (9)
Hazard ratio (Mepolizumab/Placebo) (95% CI) [e]		0.43 (0.25, 0.76)
p-value [e]		0.003
Other secondary endpoints		
Overall VAS score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-3.18 (-4.10, -2.26)

≥2.5-point improvement (%)[f]	40	64
SNOT-22 total score at week 52 [a, g]		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-16.49 (-23.57, -9.42)
≥28-point improvement (%)[f]	32	54
Patients requiring systemic corticosteroids for nasal polyps up to Week 52		
Number of patients with ≥1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI)[h]		0.58 (0.36, 0.92)
p-value[h]		0.020
Composite VAS score - nasal symptoms (Weeks 49-52) [a, i]		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
p-value [b]		<0.001
Difference in medians (95% CI)[c]		-2.68 (-3.44, -1.91)
≥2-point improvement (%)[f]	40	66
Loss of smell VAS score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
p-value [b]		<0.001
Difference in medians (95% CI) [c]		-0.37 (-0.65, -0.08)
≥3-point improvement (%) [f]	19	36

[a] Patients with nasal surgery/sinuplasty prior to visit were assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty were assigned their worst observed score prior to study withdrawal.

[b] Based on Wilcoxon rank-sum test.

[c] Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

[d] A three-point improvement in nasal obstruction VAS has been identified as a meaningful within-patient change for this assessment.

[e] 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).

[f] Threshold for improvement has been identified as a meaningful within-patient change for this assessment

[g] Improvement seen in all 6 domains of symptoms and impact associated with CRSwNP.

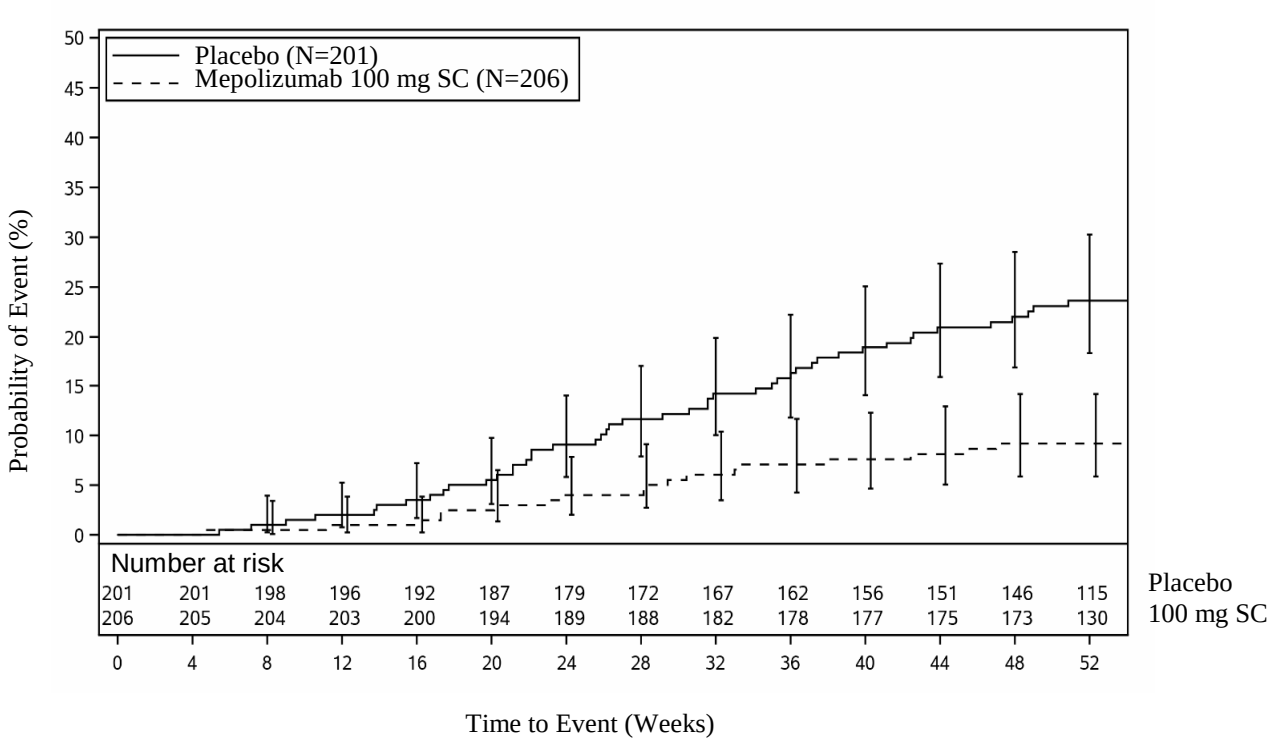
[h] Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total Endoscopic Nasal Polyps score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil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

[i] Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.

Time to first NP surgery

Across the 52-week treatment period, patients in the mepolizumab group had a lower probability of undergoing NP surgery than patients in the placebo group. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; p=0.003).

Figure 1: Kaplan Meier Curve for Time to First Nasal Polyps Surgery



A post-hoc analysis of the proportion of patients with surgery showed a 61% reduction in the odds of surgery versus placebo (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003).

CRSwNP patients with co-morbid asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received mepolizumab 100 mg compared with placebo. Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for mepolizumab 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Chronic obstructive pulmonary disease (COPD)

The efficacy of mepolizumab as add-on maintenance treatment for adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) of an eosinophilic phenotype was demonstrated in two pivotal randomised, double-blind, placebo-controlled, multicentre studies (MATINEE, 208657 and METREX, MEA117106).

In addition, another double-blind, randomised, placebo-controlled study (METREO, MEA117113) evaluated two dose levels of mepolizumab 100 mg and 300 mg every 4 weeks in adult patients with inadequately controlled COPD of an eosinophilic phenotype and this study showed that there was no additional benefit of using the higher dose

The two pivotal studies enrolled a total of 1 640 adults (aged 40 years and older) who were randomised to receive mepolizumab 100 mg or placebo (in addition to standard of care) administered subcutaneously every 4 weeks for a treatment duration of 52 to 104 weeks in MATINEE or 52 weeks in METREX. While 1 640 adults were enrolled in the two clinical studies (MATINEE and METREX), the efficacy population consisted of 1 266 adults.

Both studies enrolled patients with a diagnosis of COPD with moderate to very severe airflow limitation (post-bronchodilator FEV_1/FVC ratio <0.7 and post-bronchodilator FEV_1 of 20% to 80% predicted) and at least 2 moderate or 1 severe COPD exacerbation in the previous year despite receiving triple inhaled therapy.

In MATINEE, patients were required to have a minimum blood eosinophil count of 300 cells/mcL at screening. In METREX, there was no minimum blood eosinophil count requirement, but randomisation was stratified by baseline blood eosinophil count: ≥150 cells/mcL at screening or ≥300 cells/mcL in the previous 12 months, or blood eosinophil count <150 cells/mcL at screening with no evidence of blood eosinophil count ≥300 cell/mcL in the previous 12 months. There was insufficient data from METREX to support the efficacy of mepolizumab in patients with COPD with blood eosinophil count <150 cells/mcL at screening with no evidence of blood eosinophil count ≥300 cells/mcL in the previous 12 months. Thus, the efficacy population (N = 1 266) included patients from MATINEE (n = 804) and patients from METREX who had a blood eosinophil count ≥150 cells/mcL at screening or ≥300 cells/mcL in the previous 12 months (n = 462).

The demographic and baseline characteristics of the MATINEE and METREX efficacy population are provided in Table 6.

Table 6: Demographics and baseline characteristics in the MATINEE (mITT) and METREX studies

	MATINEE	**METREX[a]**
	(N=804)	**(N=462)**
Age (y) of patients, mean (SD)	66 (8.0)	65 (8.4)
Female, n (%)	253 (31)	163 (35)
White, n (%)	673 (84)	391 (85)
Asian, n (%)	112 (14)	5 (1)
Black or African American, n (%)	10 (1)	6 (1)
Other/Multiple, n (%)	9 (1)	60 (13)
Hispanic/Latino, n (%)	189 (24)	75 (16)
Current smokers, n (%)	222 (28)	134 (29)
Average smoking history (pack-years), mean (SD)	43.0 (24.9)	44 (25.8)
Duration of COPD (y), mean (SD)	10.0 (6.28)	9.5 (6.52)
mMRC score ≥2 (range 0-4), n (%)	611 (76)	371 (80)
Symptoms of chronic bronchitis (SGRQ assessed), n (%) [b]	544 (68)	274 (59)
Moderate airflow limitation: ≥50% to <80% predicted FEV_1, n (%)	349 (43)	144 (31)
Severe airflow limitation: ≥30% to <50% predicted FEV_1, n (%)	340 (42)	234 (51)
Very severe airflow limitation: <30% predicted FEV_1, n (%)	110 (14)	79 (17)
Post-bronchodilator % predicted FEV_1, mean (SD)	48 (15.8)	44 (14.8)
Post-bronchodilator FEV_1/FVC ratio, mean (SD)	0.5 (0.12)	0.5 (0.12)
Number of moderate [c] or severe [d] exacerbations in previous year, mean (SD)	2.3 (0.94)	2.5 (1.29)
Number of severe [d] exacerbations in previous year, mean (SD)	0.3 (0.67)	0.5 (0.89)
Background COPD treatment at randomisation: ICS/LAMA/LABA, n (%)	793 (99)	454 (98)
SGRQ score, mean (SD)	55 (17.8)	55 (16.7)
Geometric mean eosinophil count at screening, cells/mcL (95% CI)	480 (470, 490)	260 (250, 280)

mITT = modified Intent-to-Treat, SD = standard deviation, mMRC = modified Medical Research Council, SGRQ = St. George's Respiratory Questionnaire, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, ICS = inhaled corticosteroids, LAMA = long-acting muscarinic antagonist, LABA = long-acting beta agonist, CI = confidence interval.

[a] Patients with blood eosinophil count ≥150 cells/mcL at screening or ≥300 cells/mcL in the previous 12 months only.
[b] In MATINEE patients had the following COPD types by investigator assessment, n (%); chronic bronchitis only 338 (42%), emphysema only 252 (31%), emphysema and chronic bronchitis 143 (18%). These were not assessed in METREX.
[c] Exacerbations treated with either systemic corticosteroids with or without antibiotics.
[d] Exacerbations requiring hospitalisation.

The primary objective of the MATINEE and METREX studies was to evaluate the efficacy of mepolizumab on the annualised rate of moderate (defined as worsening of COPD symptoms requiring treatment with oral/systemic corticosteroids and/or antibiotics) or severe exacerbations (defined as requiring hospitalisation or resulting in death).

In both studies, mepolizumab demonstrated a statistically significant reduction in the annualised rate of moderate or severe exacerbations compared with placebo (see Table 7).

Table 7. Results of the primary endpoint in the MATINEE (mITT) and METREX studies

	MATINEE		**METREX [a]**	
	Mepolizumab N = 403	**Placebo N = 401**	**Mepolizumab N = 233**	**Placebo N = 229**
Rate of moderate [b] or severe [c] exacerbations				
Exacerbation rate per year	0.80	1.01	1.40	1.71
Percent rate reduction Rate ratio vs. placebo (95% CI)	21% 0.79 (0.66, 0.94)		18% 0.82 (0.68, 0.98)	
p-value	0.011		0.036	

CI = confidence interval.
[a] Patients with baseline eosinophils ≥150 cells/mcL at screening or ≥300 cells/mcL in the previous 12 months.
[b] Exacerbations treated with either systemic corticosteroids or antibiotics.
[c] Exacerbations requiring hospitalisation or resulting in death.

In MATINEE, mepolizumab also reduced the annualised rate of exacerbations requiring emergency department visit and/or hospitalisation by 35% compared with placebo (rate ratio [RR] of 0.65; 95% CI: 0.43, 0.96) but this reduction was not statistically significant after a break in the hierarchy. In METREX, mepolizumab did not have an effect on exacerbations requiring emergency department visit and/or hospitalisation, which was the next secondary endpoint in the pre-specified hierarchy.

The cumulative incidence of moderate or severe exacerbations was lower for patients receiving mepolizumab 100 mg compared to placebo in the MATINEE and METREX efficacy population (Figures 2 and 3).

Figure 2: Cumulative incidence of moderate or severe exacerbations in the MATINEE (mITT) study

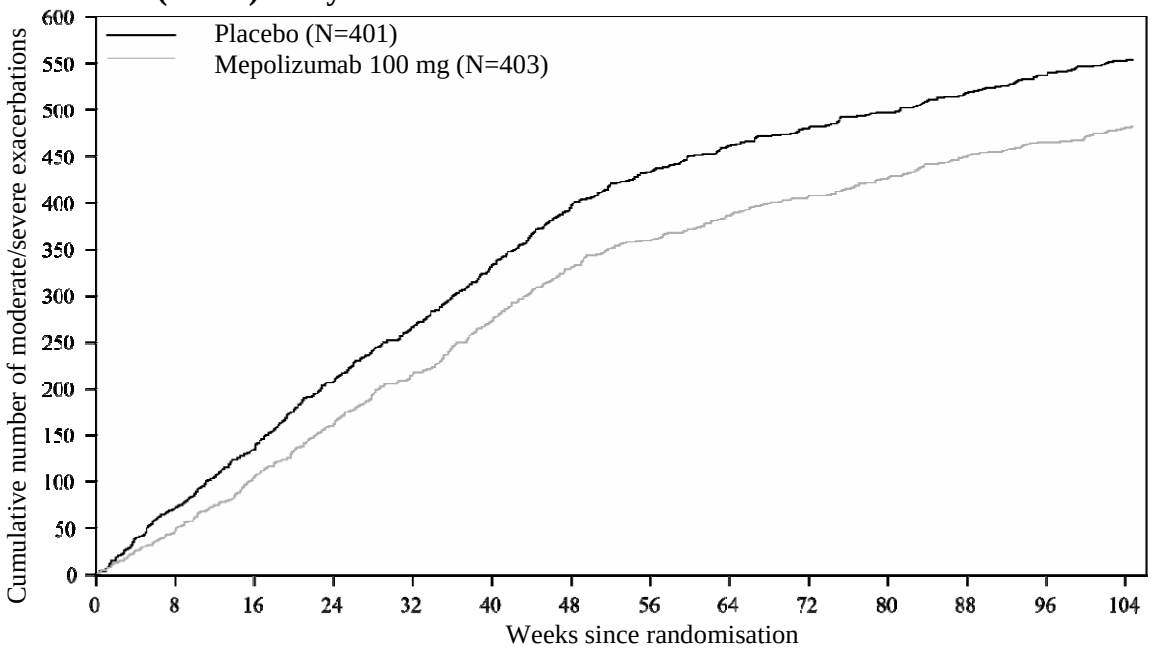
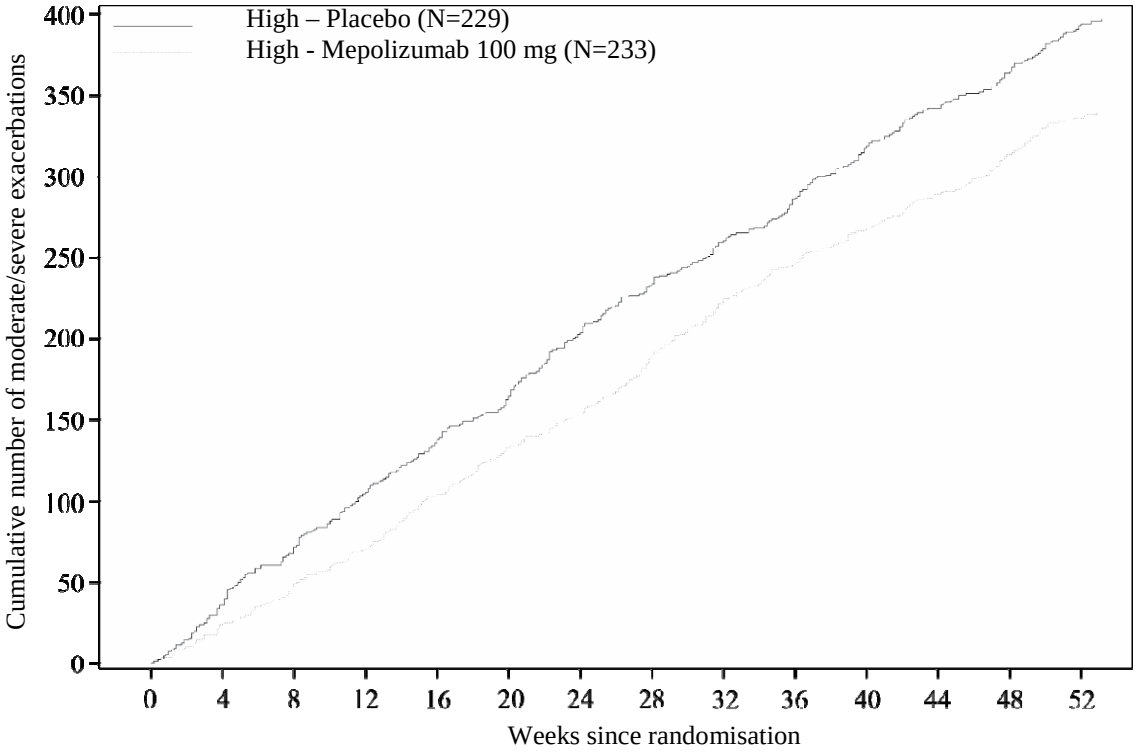


Figure 3: Cumulative incidence of moderate or severe exacerbations in the METREX study



Secondary Endpoints

In both studies, mepolizumab demonstrated a statistically significant lower risk of moderate/severe exacerbation compared with placebo (see Table 8).

Table 8. Time to first moderate or severe exacerbation in the MATINEE (mITT) and METREX studies

	MATINEE		METREX [a]	
	Mepolizumab N = 403	Placebo N = 401	Mepolizumab N = 233	Placebo N = 229
Time to first moderate or severe exacerbation				
Median time to first exacerbation[b] (days)	419	321	192	141
Percent risk reduction Hazard ratio vs. placebo (95% CI)	23% 0.77 (0.64, 0.93)		25% 0.75 (0.60, 0.94)	
p-value	0.009		0.036	

CI = confidence interval.

[a] Patients with baseline eosinophils >150 cells/mcL at screening or ≥300 cells/mcL in the previous 12 months.

[b] Kaplan Meier estimate

In MATINEE, the results of the health-related quality of life COPD Assessment Test (CAT) responder score (next endpoint in the hierarchy) were not statistically significant.

Health-related quality of life assessment

In MATINEE, the SGRQ responder rate (defined as a reduction in score of 4 or more from baseline) at Week 52 was 50% for mepolizumab 100 mg compared with 46% for placebo (Odds Ratio: 1.17; 95% CI: 0.87, 1.57). In the METREX efficacy population, the responder rate at Week 52 was 42% for mepolizumab 100 mg compared with 40% for placebo (N = 451, Odds Ratio: 1.08; 95% CI: 0.74, 1.59).

Other Endpoints

In MATINEE, changes from baseline in pre-bronchodilator FEV_1 over time were similar between the mepolizumab and placebo groups. Similarily, in METREX there was no improvement in lung function for mepolizumab compared with placebo, based on pre-bronchodilator FEV_1.

Eosinophilic granulomatosis with polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 adult patients with EGPA, who had a history of relapsing or refractory disease, and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to 50 mg/day prednisolone/prednisone), with or without stable immunosuppressant therapy (excluding cyclophosphamide). Other background standard of care therapy was allowed during the study. Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy. Patients with organ threatening or life-threatening EGPA were excluded from study MEA115921.

Patients either received a 300 mg dose of mepolizumab or placebo administered subcutaneously once every 4 weeks in addition to their background prednisolone/prednisone with or without immunosuppressive therapy. The OCS dose was tapered at the discretion of the investigator.

Remission

The co- primary endpoints were the total accrued duration of remission, defined as a Birmingham Vasculitis Activity Score (BVAS) =0 plus prednisolone/prednisone dose ≤4 mg/day, and the proportion of patients in remission at both 36 and 48 weeks of treatment. BVAS=0 represents no active vasculitis.

Compared with placebo, patients receiving mepolizumab 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of patients receiving mepolizumab 300 mg achieved remission at both Week 36 and Week 48 (Table 9).

For both co-primary endpoints, compared with placebo, the beneficial effect observed following mepolizumab 300 mg treatment was present irrespective of if patients were receiving immunosuppressant therapy in addition to background corticosteroids.

Using the secondary endpoint remission definition of BVAS=0 plus prednisolone/prednisone ≤7.5 mg/day, patients receiving mepolizumab 300 mg also achieved significantly greater accrued time in remission (p<0.001), and a higher proportion of patients were in remission at both Week 36 and Week 48 (p<0.001), compared to placebo.

Table 9: Analyses of Co-Primary Endpoints

	Number (%) of patients	
	Placebo N=68	**Mepolizumab 300mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
12 to <24 weeks	3 (4)	9 (13)
24 to <36 weeks	0	10 (15)
36 weeks	2 (3)	9 (13)
Odds ratio (mepolizumab/placebo)		5.91
95% CI	---	2.68, 13.03
p-value	---	<0.001
Patients in remission at Weeks 36 and 48	2 (3)	22 (32)
Odds ratio (mepolizumab/placebo)		16.74
95% CI	---	3.61, 77.56
p-value	---	<0.001

An odds ratio >1 favours mepolizumab. Remission: BVAS=0 and OCS dose ≤ 4mg / day.

Relapse

Compared with placebo, the time to first relapse was significantly longer for patients receiving mepolizumab 300 mg (p<0.001). Additionally, patients receiving mepolizumab had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral corticosteroid reduction

Patients treated with mepolizumab had a significantly lower average daily OCS during Weeks 48-52 compared with patients who received placebo. During Weeks 48 to 52, 59% and 44% of patients treated with mepolizumab achieved an average daily OCS dose of 7.5 mg and 4 mg respectively compared with 33% and 7% in the placebo group. 18% of patients in the mepolizumab group were able to taper off OCS completely compared with 3% in the placebo group.

Asthma Control Questionnaire – 6 (ACQ-6)

Patients treated with mepolizumab had significant improvements in mean ACQ 6 score during Weeks 49-52 compared with patients who received placebo.

Hypereosinophilic syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32-week study which evaluated 108 patients ≥12 years old with HES. Patients received 300 mg of

mepolizumab, or placebo administered subcutaneously once every 4 weeks while continuing their HES therapy. In study 200622, HES therapy included but was not limited to OCS, immunosuppressive, cytotoxic therapy or other symptomatic therapies associated with HES such as omeprazole.

Patients entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥1,000 cells/ L during screening. Patients who were FIP1L1-PDGFRα kinase-positive were excluded from the study.

The primary endpoint of study 200622 was the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy or receiving blinded active OCS due to increased blood eosinophils (on ≥2 occasions).

The primary analysis compared patients who experienced a HES flare or withdrew from the study in the mepolizumab and placebo treatment groups. Over the 32-week treatment period, 50% fewer patients experienced a HES flare or withdrew from the study when treated with 300 mg mepolizumab compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 10).

Secondary endpoints were time to first HES flare, proportion of patients who experienced a HES flare during Week 20 through Week 32, rate of HES flares and change from baseline in fatigue severity. All secondary endpoints were statistically significant and provided support for the primary endpoint (see Figure 3 and Table 11).

Table 10: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo** N= 54
Proportion of patients who experienced a HES flare		
Patients with ≥1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with ≥1 HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
Odds ratio (95% CI)	0.28 (0.12, 0.64)	
CMH p-value	0.002	

CMH =Cochran-Mantel-Haenszel

Time to first flare

Patients who received 300 mg mepolizumab had a significant increase in the time to first HES flare compared with placebo. The risk of first HES flare over the treatment period was 66 % lower for patients treated with mepolizumab compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67; p=0.002).

Figure 3: Kaplan Meier Curve for Time to First HES Flare

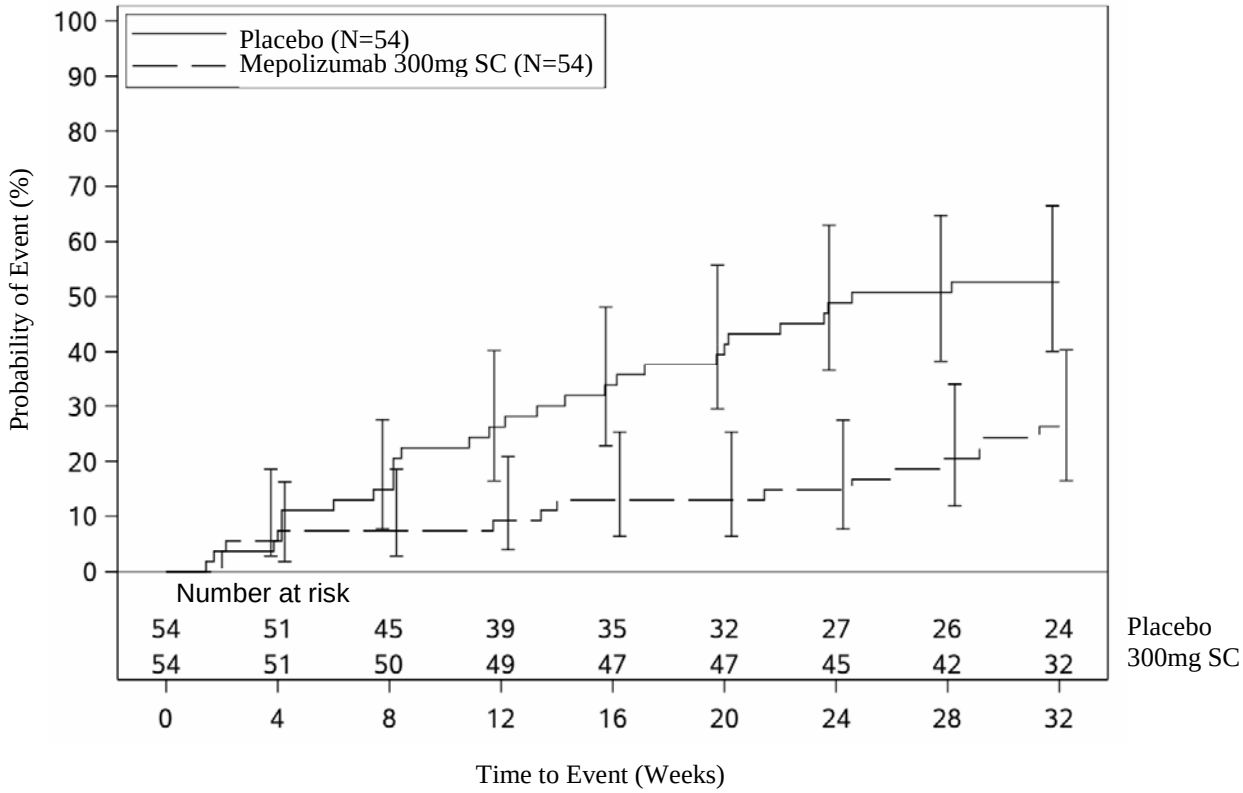


Table 11: Results of other secondary endpoints in the Intent to Treat population (Study 200622)

	Mepolizumab 300 mg N= 54	**Placebo** N= 54
HES flares during week 20 and up to and including week 32		
Patients with ≥1 HES flare or who withdrew from study (%)	9 (17)	19 (35)
Odds ratio (95% CI)	0.33 (0.13, 0.85)	
CMH p-value	0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI)[a]	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	
Change from baseline in fatigue severity based on Brief Fatigue Inventory (BFI) Item 3 (worst level of fatigue during past 24 hours) at week 32[b]		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

[a] rate ratio <1 favours mepolizumab.

[b] patients with missing data included with worst observed value. BFI item 3 scale: 0 = no fatigue to 10 = as bad as you can imagine
CMH =Cochran-Mantel-Haenszel

Open-label extension (OLE)

Study 205203 was a 20-week open-label extension of Study 200622. HES therapy was allowed to be adjusted per local standard of care while maintaining mepolizumab 300 mg treatment starting at Week 4. In this study the effect of treatment with mepolizumab on the reduction of HES flares reported during Study 200622 was sustained for patients who continued mepolizumab treatment in study 205203, in which 94% (47/50) of patients did not experience a flare.

In the 72 patients requiring OCS during Weeks 0 to 4 of the OLE, 28% of patients achieved a mean daily dose OCS dose reduction of ≥50% during Weeks 16 to 20.

Paediatric population

Severe refractory eosinophilic asthma

In MEA115588 and in the double-blind placebo-controlled study 200862, there were 34 adolescents (12 to 17 years old). Of these 34 subjects: 12 received placebo, 9 received mepolizumab 75 mg intravenously, and 13 received 100 mg subcutaneously. In a combined analysis of these studies, a 40% reduction in clinically significant exacerbations was observed in adolescents following mepolizumab treatment compared to placebo (rate ratio 0.60; 95% CI: 0.17, 2.10).

Eosinophilic granulomatosis with polyangiitis (EGPA)

The are no clinical data available in children and adolescents aged 6 to 17 years old.

HES

Four adolescents (12 to 17 years old) were enrolled in study 200622; one adolescent received mepolizumab 300 mg, and 3 adolescents received placebo for 32 weeks. The one adolescent treated with mepolizumab in the 32-week Study 200622 did not have a HES flare. All 4 adolescents that completed study 200622 continued into a 20-week open-label extension study 205203 in which one of the 4 adolescents experienced one HES flare.

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma and CRSwNP, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. Subcutaneous administration of mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. Mepolizumab pharmacokinetics were consistent in patients with asthma, CRSwNP, COPD, EGPA or HES. Following administration of a single 100 mg subcutaneous

dose in healthy subjects, mepolizumab systemic exposure was comparable between formulations.

Absorption

Following subcutaneous administration to healthy subjects or patients with asthma, mepolizumab was absorbed slowly with a median time to reach maximum plasma concentration (T_{max}) ranging from 4 to 8 days.

Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In patients with asthma the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeat subcutaneous administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single intravenous administration to patients with asthma, mepolizumab distributes into a mean volume of distribution of 55 to 85 mL/kg.

Biotransformation

Mepolizumab is a humanised IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special populations

Elderly patients (≥65 years old)

There are limited pharmacokinetic data available in elderly patients (≥65 years old) across all clinical studies (N=90). However, in the population pharmacokinetic analysis, there were no indications of an effect of age on the pharmacokinetics of mepolizumab over the age range of 12 to 82 years.

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values

between 50-80 mL/min. There are limited data available in patients with creatinine clearance values <50 mL/min.

Hepatic impairment

No formal studies have been conducted to investigate the effect of hepatic impairment on the pharmacokinetics of mepolizumab. Since mepolizumab is degraded by widely distributed proteolytic enzymes, not restricted to hepatic tissue, changes in hepatic function are unlikely to have any effect on the elimination of mepolizumab.

Paediatric population

Severe eosinophilic asthma and HES

There are limited pharmacokinetic data available in the paediatric population (59 patients with eosinophilic esophagitis, 55 patients with severe refractory eosinophilic asthma and 1 patient with HES)**.** Intravenous mepolizumab pharmacokinetics was evaluated by population pharmacokinetic analysis in a paediatric study conducted in patients aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was largely predictable from adults, after taking into account bodyweight. Mepolizumab pharmacokinetics in adolescent patients with severe refractory eosinophilic asthma or HES included in the phase 3 studies were consistent with adults (see section 4.2).

Paediatric pharmacokinetics following subcutaneous administration in patients 6 to 11 years old with severe refractory eosinophilic asthma was investigated in an open label, uncontrolled study of 12-weeks duration. Paediatric pharmacokinetics were broadly consistent with adults and adolescents after accounting for bodyweight and bioavailability. The absolute subcutaneous bioavailability appears complete compared to that observed in adults and adolescents of 76%. Exposure following subcutaneous administration of either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) was 1.32 and 1.97 times of that observed in adults at 100 mg.

Investigation of a 40 mg subcutaneous dosing regimen administered every 4 weeks in children 6 to 11 years old over a 15-70 kg broad weight range by PK modelling and simulation predicts that the exposure of this dosing regimen would remain on average within 38% of adults at 100 mg. This dosing regimen is considered acceptable due to the wide therapeutic index of mepolizumab.

EGPA

Mepolizumab pharmacokinetics in children (6 to 17 years old) with EGPA were predicted using modelling and simulation, based on pharmacokinetics in other eosinophilic diseases, and are expected to be consistent with those observed in children with severe eosinophilic asthma. The recommended posology in children 6 to 11 years old over a 15-70 kg broad weight range predicts that the exposure would remain on average within 26% of adults at 300 mg.

5.3 Preclinical safety data

As mepolizumab is a monoclonal antibody, no genotoxicity or carcinogenicity studies have been conducted.

Animal toxicology and/or pharmacology

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeated dose toxicity studies in monkeys. Intravenous and subcutaneous administration to monkeys was associated with reductions in peripheral and lung eosinophil counts, with no toxicological findings.

Eosinophils are thought to be associated with immune system responses to some parasitic infections. Studies conducted in mice treated with anti-IL-5 antibodies or genetically deficient in IL-5 or eosinophils have not shown impaired ability to clear parasitic infections. The relevance of these findings for humans is unknown.

Fertility

No impairment of fertility was observed in a fertility and general reproduction toxicity study in mice performed with an analogous antibody that inhibits IL-5 in mice. This study did not include a littering or functional offspring assessment.

Pregnancy

In monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal and postnatal development (including immune function) of the offspring. Examinations for internal or skeletal malformations were not performed. Data in cynomolgus monkeys demonstrate that mepolizumab crossed the placenta. Concentrations of mepolizumab were about 1.2-2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium phosphate dibasic heptahydrate
Citric acid monohydrate
Polysorbate 80 (E 433)
Disodium edetate
Water for injections

6.2 Incompatibilities

In the absence of compatability studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original carton in order to protect from light.

If necessary, the pre-filled pen and pre-filled syringe(s) can be removed from the refrigerator and kept in the unopened pack for up to 7 days at room temperature (up to 30°C), when protected from light. The pack must be discarded if left out of the refrigerator for more than 7 days.

The pre-filled pen or pre-filled syringe(s) must be administered within 8 hours once the pack is opened. The pack must be discarded if not administered within 8 hours.

6.5 Nature and contents of container

Nucala 100 mg solution for injection in pre-filled syringe

1 ml solution in a Type 1 glass syringe with a fixed needle (stainless steel) and passive safety needle guard.

Pack sizes:
1 pre-filled syringe
Multipack containing 3 (3 packs of 1) pre-filled syringes
Multipack containing 9 (9 packs of 1) pre-filled syringes

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal

Before administration, the solution must be inspected visually. The liquid must be clear to opalescent, colourless to pale yellow to pale brown. If the solution is cloudy, discoloured or contains particles, the solution must not be used.

After removing the pre-filled pen or pre-filled syringe(s) from the refrigerator, allow the pen or syringe(s) to reach room temperature for at least 30 minutes before injecting Nucala.

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled pen or pre-filled syringe(s) are provided at the end of the package leaflet.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 19494/0291

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

29/12/2025