

## 1. NAME OF THE MEDICINAL PRODUCT

Nucala solution for injection in pre-filled pen

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nucala solution for injection in pre-filled pen

Each 1 ml pre-filled pen contains 100 mg of mepolizumab.

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

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Severe eosinophilic asthma

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients.

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 corticosteroids and surgery in the last 10 years do not provide adequate disease control.

Chronic obstructive pulmonary disease (COPD)

Nucala is indicated as an add-on maintenance treatment of adult patients with inadequately controlled chronic obstructive pulmonary disease with an eosinophilic phenotype.

Eosinophilic granulomatosis with polyangiitis (EGPA)

Nucala is indicated for the treatment of adult patients with 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

Nucala should be prescribed by physicians experienced in the diagnosis and treatment of severe refractory eosinophilic asthma, CRSwNP, COPD, EGPA or HES.

## Posology

### Severe eosinophilic asthma

#### *Adults*

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 should 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.

#### *Limitations:*

For the indication of COPD, mepolizumab may be used in patients with an eosinophil level above 150 cells/ $\mu$ L.

### EGPA

#### *Adults*

The recommended dosage of Nucala is 300 mg administered once every 4 weeks by subcutaneous injection as 3 separate 100-mg injections into the upper arm, thigh, or abdomen [see Special precautions for disposal and other handling (6.6)]. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

### 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 should 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 should 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 (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*

Nucala is not indicated for children and adolescents under 18 years of age.

#### Method of administration

The pre-filled pen should 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 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 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 of the administered product should be clearly recorded. It is recommended to record the batch number as well.

#### Asthma or COPD exacerbations

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

Asthma-related or COPD-related adverse symptoms or exacerbations may occur during treatment. Patients should 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, should 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 should 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.

#### 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 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 subjects 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

##### Adverse Reactions in Adults with Chronic Obstructive Pulmonary Disease

The safety data below reflects the safety of NUCALA in adults with inadequately controlled COPD and an eosinophilic phenotype. NUCALA was evaluated in a pooled safety population that consisted of 2089 patients with COPD in 3 randomized, placebo-controlled, multicenter trials of 52 to 104 weeks duration, including MATINEE and METREX , and Trial 3. Trial 3 enrolled COPD adults with a peripheral blood eosinophil count  $\geq 150$  cells/ $\mu\text{L}$  at screening or  $\geq 300$  cells/ $\mu\text{L}$  in the year prior. The pooled safety population received NUCALA 100 mg (n = 1043) or placebo (n = 1046), administered subcutaneously once every 4 weeks, in addition to background triple inhaled therapies (e.g., ICS, long-acting beta agonist [LABA], and long-acting muscarinic antagonist [LAMA]).

The table below summarizes adverse reactions that occurred in  $\geq 3\%$  of patients treated with NUCALA and more frequently than in patients treated with placebo in COPD trials.

**Adverse Reactions with NUCALA with  $\geq 3\%$  Incidence and More Common than Placebo  
in Patients with Chronic Obstructive Pulmonary Disease in a Pooled Safety Population  
(MATINEE, METREX, and Trial 3)**

<b>Adverse Reaction</b>	<b>NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 1043) %</b>	<b>Placebo (n = 1046) %</b>
Back pain	7	6
Diarrhea	5	4
Cough	5	4
Oropharyngeal pain	4	2
Urinary tract infection	4	3
Pain in extremity	4	3

*Herpes Zoster:* In the pooled safety population, 14 (1%) patients in the NUCALA group compared to 7 (0.7%) patients in the placebo group experienced herpes zoster.

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 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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.

<b>System Organ Class</b>	<b>Adverse reactions</b>	<b>Frequency</b>
Infections and infestations	Lower respiratory tract infection	Common
	Urinary tract infection	
	Pharyngitis	
	Herpes zoster**	
Immune system disorders	Hypersensitivity reactions (systemic allergic)*	Common
	Anaphylaxis**	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	Common
	Arthralgia**	
General disorders and administration site conditions	Administration-related reactions (systemic non allergic)***	Common
	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 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.

\*\*\* The most common manifestations associated with reports of systemic non-allergic administration-related reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; 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 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.

#### 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.

### Special data from clinical studies:

#### HES

##### Haemorrhage

In phase 3 placebo-controlled study 200622, a higher number of subjects reporting hemorrhages was observed for mepolizumab 300 mg SC group (10/54 patients, 19%) compared to the placebo arm, (4/54 patients, 7%).

The majority of cases were mild or moderate in intensity and resolved. Five out of 10 of the patients treated with mepolizumab had concomitant medications that could increase the risk of bleeding (including anticoagulants). No causal relationship with mepolizumab has been determined yet.

#### Paediatric population

Nucala is not indicated for children and adolescents under 18 years of age.

#### 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.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

<https://sideeffects.health.gov.il>

Additionally, you should also report to GSK Israel ([il.safety@gsk.com](mailto:il.safety@gsk.com))

#### **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, the patient should 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). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, COPD, EGPA, and HES. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma, CRSwNP, COPD, EGPA, and HES has not been definitively established.

##### Pharmacodynamic effects

###### *Severe eosinophilic asthma*

In patients with severe refractory eosinophilic asthma, 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/ $\mu$ L 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.

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/ $\mu$ L (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

Following subcutaneous administration of NUCALA 100 mg every 4 weeks blood eosinophils were reduced to a similar magnitude to that observed in patients with severe asthma compared to placebo.

For adults with COPD, following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 52 to 104 weeks, blood eosinophils were reduced to a geometric mean count of 50-60 cells/ $\mu$ L. There was a geometric mean reduction of approximately 79% compared with placebo, and this magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period.

### *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/ $\mu$ L (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, 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 1460 (n=54) to 70 cells/ $\mu$ L (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 subjects with severe refractory eosinophilic asthma treated with 100 mg dose, 6/196 (3%) of adults with CRSwNP treated with 100 mg dose, 1/68 (<2%) of adults with EGPA treated with 300 mg dose and 1/53 (2%) of subjects 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.

In patients receiving NUCALA 100 mg over 52 to 104 weeks for COPD, 36/996 (4%) had detectable anti-mepolizumab antibodies.

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<sub>2</sub>-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 1192 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<sub>1</sub><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<sub>1</sub> 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 n=153	250mg n=152	750mg 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/ $\mu$ L at initiation of treatment or greater than or equal to 300 cells/ $\mu$ L 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
<b>Primary endpoint</b>		
<b>Frequency of clinically significant exacerbations</b>		
Exacerbation rate per year	0.83	1.74
Percent reduction	53%	-
Rate ratio (95% CI)	0.47 (0.35, 0.64)	
p-value	<0.001	
<b>Secondary endpoints</b>		
<b>Frequency of exacerbations requiring hospitalisations/emergency room visits</b>		
Exacerbation rate per year	0.08	0.20
Percent reduction	61%	-
Rate ratio (95% CI)	0.39 (0.18, 0.83)	
p-value	0.015	
<b>Frequency of exacerbations requiring hospitalisation</b>		
Exacerbations rate per year	0.03	0.10
Percent reduction	69%	-
Rate ratio (95% CI)	0.31 (0.11, 0.91)	
p-value	0.034	
<b>Pre-bronchodilator FEV<sub>1</sub> (mL) at week 32</b>		
Baseline (SD)	1730 (659)	1860 (631)
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11, 184)	
p-value	0.028	
<b>St. George's Respiratory Questionnaire (SGRQ) at week 32</b>		
Baseline (SD)	47.9 (19.5)	46.9 (19.8)

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
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
<b>MEA112997+MEA115588</b>		
<b>&lt;150 cells/<math>\mu</math>L</b>		
n	123	66
Exacerbation rate per year	1.16	1.73
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.67 (0.46,0.98)	---
<b>150 to &lt;300 cells/<math>\mu</math>L</b>		
n	139	86
Exacerbation rate per year	1.01	1.41
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.72 (0.47,1.10)	---
<b>300 to &lt;500 cells/<math>\mu</math>L</b>		
n	109	76
Exacerbation rate per year	1.02	1.64
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.62 (0.41,0.93)	---
<b><math>\geq</math>500 cells/<math>\mu</math>L</b>		
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  $\geq$ 150/ $\mu$ L at baseline or a blood eosinophil count of  $\geq$ 300/ $\mu$ L 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
<b>Primary endpoint</b>		
<b>Percent reduction in OCS from baseline (weeks 20-24)</b>		
90% - 100%	16 (23%)	7(11%)
75% - <90%	12 (17%)	5 (8%)
50% - <75%	9 (13%)	10 (15%)
>0% - <50%	7 (10%)	7(11%)
No decrease in OCS/lack of asthma control/ withdrawal from treatment	25 (36%)	37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	
p-value	0.008	
<b>Secondary endpoints (weeks 20-24)</b>		
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  $\geq 5$  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)**

	<b>Placebo (N=201)</b>	<b>Mepolizumab 100 mg SC (N=206)</b>
<b>Co-primary endpoints</b>		
<b>Total endoscopic score at week 52<sup>a</sup></b>		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value <sup>b</sup>		<0.001
Difference in medians (95% CI) <sup>c</sup>		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
<b>Nasal obstruction VAS score (weeks 49 to 52)<sup>a</sup></b>		
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 <sup>b</sup>		<0.001
Difference in medians (95% CI) <sup>c</sup>		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%) <sup>d</sup>	73 (36)	124 (60)
<b>Key secondary endpoint</b>		
<b>Time to first nasal polyps surgery</b>		
Participants with surgery	46 (23)	18 (9)
Hazard ratio (Mepolizumab/Placebo) (95% CI) <sup>e</sup>		0.43 (0.25, 0.76)
p-value <sup>e</sup>		0.003
<b>Other secondary endpoints</b>		
<b>Overall VAS score (Weeks 49-52)<sup>a</sup></b>		
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 <sup>b</sup>		<0.001
Difference in medians (95% CI) <sup>c</sup>		-3.18 (-4.10, -2.26)
≥2.5-point improvement (%) <sup>f</sup>	40	64
<b>SNOT-22 total score at week 52<sup>a, g</sup></b>		
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 <sup>b</sup>		<0.001
Difference in medians (95% CI) <sup>c</sup>		-16.49 (-23.57, -9.42)
≥28-point improvement (%) <sup>f</sup>	32	54

<b>Patients requiring systemic corticosteroids for nasal polyps up to Week 52</b>		
Number of patients with $\geq 1$ course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI) <sup>h</sup>		0.58 (0.36, 0.92)
p-value <sup>h</sup>		0.020
<b>Composite VAS score - nasal symptoms (Weeks 49-52)</b> <sup>a, i</sup>		
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 <sup>b</sup>		<0.001
Difference in medians (95% CI) <sup>c</sup>		-2.68 (-3.44, -1.91)
$\geq 2$ -point improvement (%) <sup>f</sup>	40	66
<b>Loss of smell VAS score (Weeks 49-52)</b> <sup>a</sup>		
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 <sup>b</sup>		<0.001
Difference in medians (95% CI) <sup>c</sup>		-0.37 (-0.65, -0.08)
$\geq 3$ -point improvement (%) <sup>f</sup>	19	36

<sup>a</sup> 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.

<sup>b</sup> Based on Wilcoxon rank-sum test.

<sup>c</sup> Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.

<sup>d</sup> A three-point improvement in nasal obstruction VAS has been identified as a meaningful within-patient change for this assessment.

<sup>e</sup> 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).

<sup>f</sup> Threshold for improvement has been identified as a meaningful within-patient change for this assessment

<sup>g</sup> Improvement seen in all 6 domains of symptoms and impact associated with CRSwNP.

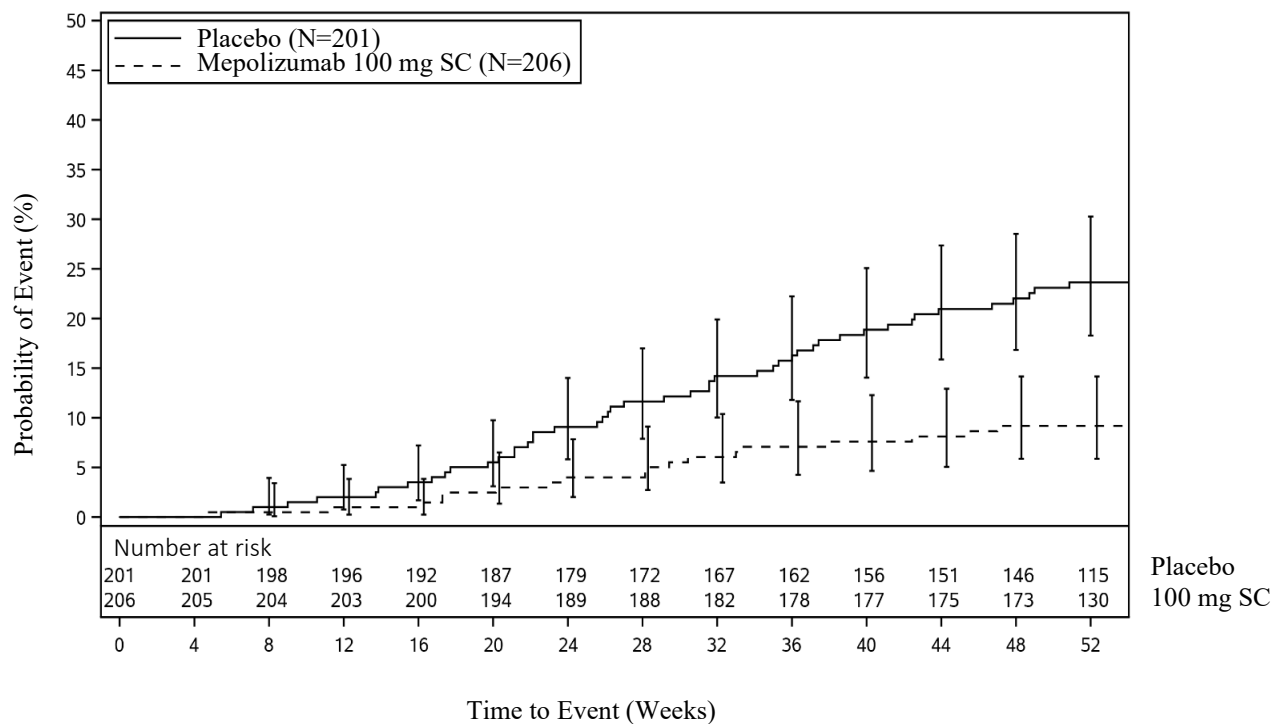
<sup>h</sup> Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total Endoscopic Nasal Polyps score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood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

<sup>i</sup> 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 NUCALA as add-on maintenance treatment for adult patients with inadequately controlled chronic obstructive pulmonary disease (COPD) and an eosinophilic phenotype was evaluated in two randomized, double-blind, placebo-controlled, multicenter trials (MATINEE [NCT04133909] and METREX [NCT02105948]). The two trials enrolled a total of 1640 adults who were randomized to receive NUCALA 100 mg or placebo administered subcutaneously every 4 weeks for a treatment duration of 52 to 104 weeks in MATINEE or 52 weeks in METREX. While 1640 adults were enrolled in the two clinical trials (MATINEE and METREX), the efficacy population consisted of 1266 adults.

Both trials enrolled patients with a diagnosis of COPD with moderate to very severe airflow limitation (post-bronchodilator FEV<sub>1</sub>/FVC ratio <0.7 and post-bronchodilator FEV<sub>1</sub> 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 cell/mcL at screening. In METREX, there was no minimum blood eosinophil count requirement, but

randomization was stratified by baseline blood eosinophil count:  $\geq 150$  cell/mcL at screening or  $\geq 300$  cell/mcL in the previous 12 months, or blood eosinophil count  $< 150$  cells/mcL at screening with no evidence of blood eosinophil count  $\geq 300$  cell/mcL in the previous 12 months. There was insufficient data from METREX to support the efficacy of NUCALA in patients with COPD with blood eosinophil count  $< 150$  cells/mcL at screening with no evidence of blood eosinophil count  $\geq 300$  cell/mcL in the previous 12 months. Thus, the efficacy population (N = 1266) included patients from MATINEE (n = 804) and patients from METREX who had a blood eosinophil count  $\geq 150$  cell/mcL at screening or  $\geq 300$  cell/mcL in the previous 12 months (n = 462). The data from this efficacy population is described below.

The demographic and baseline characteristics of MATINEE and METREX efficacy population are provided in the table below.

**Demographics and Baseline Characteristics of Patients with Chronic Obstructive Pulmonary Disease in MATINEE and METREX<sup>a</sup> Trials**

	<b>MATINEE</b>	<b>METREX<sup>a</sup></b>
	<b>N = 804</b>	<b>N = 462</b>
Mean age (y) (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) (SD)	43 (24.9)	44 (25.8)
Post-bronchodilator % predicted FEV <sub>1</sub> , mean (SD)	48 (15.8)	44 (14.8)
Post-bronchodilator FEV <sub>1</sub> /FVC, mean (SD)	0.5 (0.12)	0.5 (0.12)
Mean number of moderate <sup>b</sup> or severe <sup>c</sup> exacerbations in previous year (SD)	2.3 (0.94)	2.5 (1.29)
Background COPD medications at randomization: ICS/LAMA/LABA, n (%)	794 (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)

SD = standard deviation, FEV<sub>1</sub> = forced expiratory volume in 1 second, FVC = forced vital capacity, COPD = chronic obstructive pulmonary disease, ICS = inhaled corticosteroids, LAMA = long-acting muscarinic antagonist, LABA = long-acting beta agonist, SGRQ = St. George’s Respiratory Questionnaire, CI = confidence interval.

<sup>a</sup> Patients with blood eosinophil count  $\geq 150$  cell/mcL at screening or  $\geq 300$  cell/mcL in the previous 12 months only.

<sup>b</sup> Exacerbations treated with either systemic corticosteroids with or without antibiotics.

<sup>c</sup> Exacerbations requiring hospitalization.

**Annualized Rate of Moderate or Severe Exacerbations in Adult Patients with Chronic Obstructive Pulmonary Disease**

The primary endpoint for the MATINEE and METREX trials was the annualized rate of moderate or severe exacerbations during the 52 to 104-week and 52-week treatment periods, respectively. Moderate exacerbations are defined per protocol as clinically significant exacerbations that require treatment with oral/systemic corticosteroids and/or antibiotics. Severe exacerbations are defined per protocol as clinically significant exacerbations that require in-patient hospitalization (i.e.,  $\geq 24$  hours) or result in death.

In both trials, NUCALA demonstrated a statistically significant reduction in the annualized rate of moderate or severe exacerbations compared with placebo when added to triple inhaled therapy (see Table below).

**Annualized Rate of Moderate<sup>a</sup> or Severe<sup>b</sup> Exacerbations in MATINEE and METREX Trials**

	MATINEE		METREX <sup>c</sup>	
	NUCALA N = 403	Placebo N = 401	NUCALA N = 233	Placebo N = 229
Exacerbation rate per year	0.80	1.01	1.40	1.71
Rate ratio vs. placebo (95% CI)	0.79 (0.66, 0.94)		0.82 (0.68, 0.98)	

CI = confidence interval.

<sup>a</sup> Exacerbations treated with either systemic corticosteroids/antibiotics.

<sup>b</sup> Exacerbations requiring hospitalization or resulting in death.

<sup>c</sup> Patients with baseline eosinophils  $\geq 150$  cell/mcL at screening or  $\geq 300$  cell/mcL in the previous 12 months.

The time to first event analysis showed a statistically significant reduction in the risk of moderate or severe exacerbation for patients receiving NUCALA compared to placebo (HR: 0.77; 95% CI: 0.64, 0.93) through 104 weeks in MATINEE.

NUCALA reduced the annualized rate of COPD exacerbations requiring emergency department visits and/or hospitalization when compared with placebo (rate ratio [RR] of 0.65; 95% CI: 0.43, 0.96 [not statistically significant due to failure of an endpoint higher in the pre-defined testing hierarchy]) in MATINEE.

#### Health Related Quality of Life

In MATINEE and METREX, the St. George's Respiratory Questionnaire (SGRQ) total score responder rate (defined as the proportion of subjects with SGRQ improvement from baseline of at least 4 points) at Week 52 was evaluated. In MATINEE, the responder rate was 50% in the NUCALA group compared with 46% in the placebo group (N = 783, odds ratio [OR]: 1.17; 95% CI: 0.87, 1.57). In the METREX efficacy population, the responder rate was 42% in the NUCALA group compared to 40% in the placebo group (N = 451, odds ratio [OR]: 1.08; 95% CI: 0.74, 1.59).

#### 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;  $\geq 7.5$  to  $\leq 50$  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  $\leq 4$  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 6).

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  $\leq 7.5$  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 6: Analyses of Co-Primary Endpoints**

	Number (%) of patients	
	Placebo N=68	Mepolizumab 300mg N=68
<b>Accrued Duration of Remission Over 52 Weeks</b>		
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)
$\geq 36$ weeks	2 (3)	9 (13)
Odds ratio (mepolizumab/placebo)		5.91
95% CI	---	2.68, 13.03
p-value	---	<0.001
<b>Patients in remission at Weeks 36 and 48</b>	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  $\leq 4$ mg / 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  $\leq 7.5$  mg and  $\leq 4$  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  $\geq 12$  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  $\geq 1000$  cells/ $\mu$ L during screening. Patients who were FIP1L1-PDGFR $\alpha$  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  $\geq 2$  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 7). 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 2 and Table 8).

**Table 7: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)**

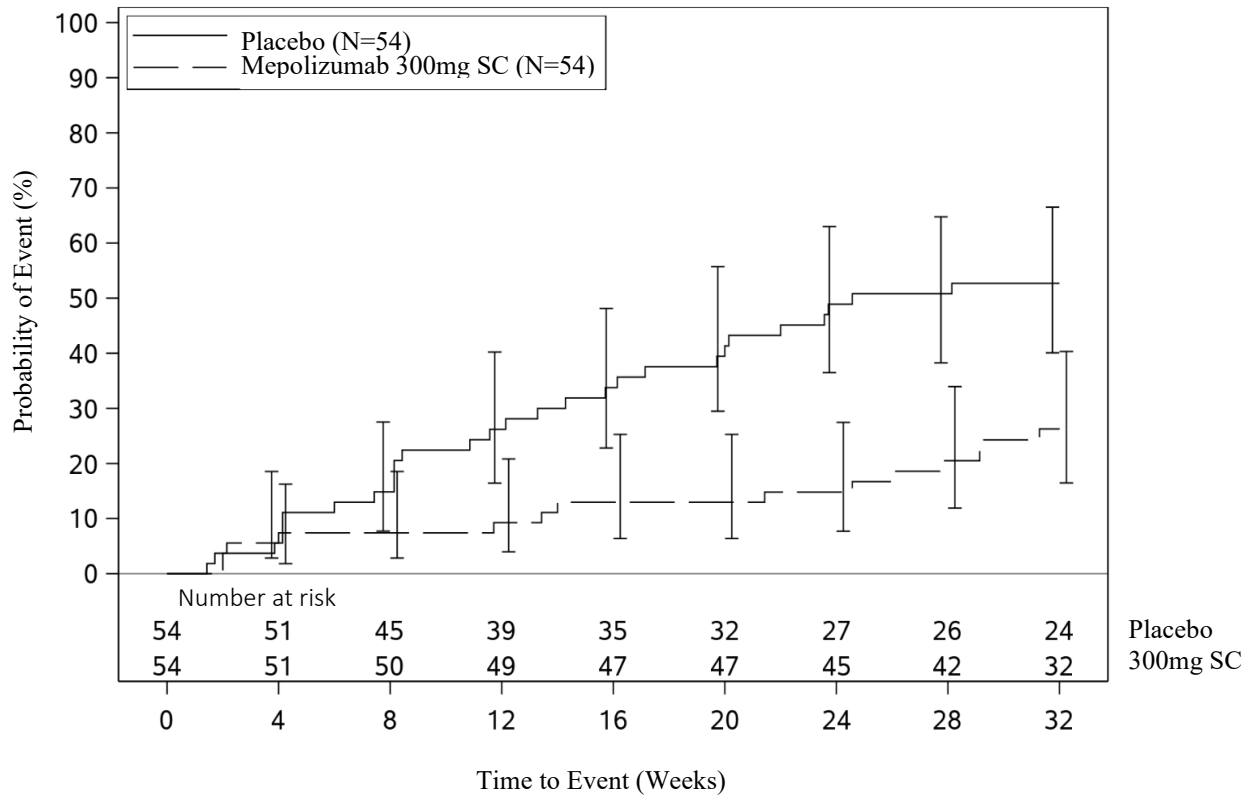
	<b>Mepolizumab 300 mg N= 54</b>	<b>Placebo N= 54</b>
<b>Proportion of patients who experienced a HES flare</b>		
Patients with $\geq 1$ HES flare or who withdrew from study (%)	15 (28)	30 (56)
Patients with $\geq 1$ HES flare (%)	14 (26)	28 (52)
Patients with no HES flare who withdrew (%)	1 (2)	2 (4)
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 2: Kaplan Meier Curve for Time to First HES Flare**



**Table 8: Results of other secondary endpoints in the Intent to Treat population (Study 200622)**

	<b>Mepolizumab 300 mg N= 54</b>	<b>Placebo N= 54</b>
<b>HES flares during week 20 and up to and including week 32</b>		
Patients with $\geq 1$ 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	
<b>Rate of HES flares</b>		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI) <sup>a</sup>	0.34 (0.19, 0.63)	
Wilcoxon Rank Sum Test p-value	0.002	
<b>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<sup>b</sup></b>		
Median change in BFI item 3	-0.66	0.32
Comparison (mepolizumab vs. placebo) Wilcoxon Rank Sum Test p-value	0.036	

<sup>a</sup> rate ratio <1 favours mepolizumab.

<sup>b</sup> 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  $\geq 50\%$  during Weeks 16 to 20.

### Paediatric population

Nucala is not indicated for children and adolescents under 18 years of age.

## **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. 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*

Nucala is not indicated for children and adolescents under 18 years of age.

## **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  
EDTA Disodium Dihydrate  
Water for injection

### **6.2 Incompatibilities**

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

### **6.3 Shelf life**

The expiry date of the product is indicated on the packaging materials.

### **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 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 should be discarded if left out of the refrigerator for more than 7 days.

The pre-filled pen must be administered within 8 hours once the pack is opened. The pack should be discarded if not administered within 8 hours.

### **6.5 Nature and contents of container**

#### Nucala solution for injection in pre-filled pen

1 mL solution in a Type 1 glass syringe with a fixed needle (stainless steel) in a pre-filled pen.

Pack sizes:  
1 pre-filled pen  
Multipack containing 3 (3 packs of 1) pre-filled pens

Not all pack-sizes may be marketed.

### **6.6 Special precautions for disposal and other handling**

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

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

Comprehensive instructions for subcutaneous administration of Nucala in a pre-filled pen 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. MANUFACTURER**

GlaxoSmithKline Trading Services Limited, Dublin, Ireland.

### **8. LICENSE HOLDER AND IMPORTER**

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

### **9. LICENSE NUMBERS**

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