NUCALA

1. NAME OF THE MEDICINAL PRODUCT

Nucala 100 mg solution for injection in pre-filled pen

Nucala 100 mg solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen (auto-injector) or pre-filled syringe (safety-syringe) delivers 100 mg mepolizumab in 1 mL (100 mg/mL).

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), directed against human interleukin-5 (IL-5) produced in Chinese hamster ovary cells by recombinant DNA technology.

3. PHARMACEUTICAL FORM

Solution for injection

A clear to opalescent, colourless to pale yellow to pale brown solution in a single-use, pre-filled pen or syringe.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Severe Eosinophilic Asthma

NUCALA is indicated as add-on maintenance treatment of severe eosinophilic asthma in patients 12 years and older.

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.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

NUCALA is indicated as add-on treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in patients 6 years and older.

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.

4.2 Posology and method of administration

NUCALA should only be administered as a subcutaneous injection (see *Use and Handling and Instructions for Use*).

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

Populations

Severe Eosinophilic Asthma

Adults and Adolescents (12 years and older)

The recommended dose is 100 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

CRSwNP

Adults

The recommended dose is 100 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

Children

Use in patients less than 18 years of age is not relevant for CRSwNP.

EGPA

Injection sites should be least 5 cm apart (see *Use and Handling*).

Adults and Adolescents (12 years and older)

The recommended dose is 300 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

Children aged 6 to 11 years old:

Children weighing ≥ 40 kg

The recommended dose is 200 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

Children weighing < 40 kg

The recommended dose is 100 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

The safety and efficacy of *NUCALA* have not been established in children less than 6 years of age.

HES

Injection sites should be at least 5 cm apart (see *Use and Handling*).

Adults and Adolescents (12 years and older)

The recommended dose is 300 mg of *NUCALA* administered by subcutaneous (SC) injection once every 4 weeks.

Children

The safety and efficacy of *NUCALA* have not been established in children less than 12 years of age.

Elderly (65 years or older)

No dosage adjustment is recommended in patients 65 years or older (see *Pharmacokinetics – Special Patient Populations*).

Renal Impairment

Dose adjustments in patients with renal impairment are unlikely to be required (see *Pharmacokinetics – Special Patient Populations*).

Hepatic Impairment

Dose adjustments in patients with hepatic impairment are unlikely to be required (see *Pharmacokinetics – Special Patient Populations*).

4.3 Contraindications

Hypersensitivity to mepolizumab or to any of the excipients.

4.4 Special warnings and precautions for use

Asthma exacerbations

NUCALA should not be used to treat acute asthma exacerbations.

Asthma-related related adverse events or exacerbations may occur during treatment with *NUCALA*. Patients should be instructed to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with *NUCALA*.

Corticosteroids

Abrupt discontinuation of corticosteroids after initiation of *NUCALA* therapy is not recommended. Reductions in corticosteroid doses, if required, should be gradual and performed under the supervision of a physician.

Hypersensitivity and Administration Reactions

Acute and delayed systemic reactions, including hypersensitivity reactions (e.g. anaphylaxis, urticaria, angioedema, rash, bronchospasm, hypotension), have occurred following administration of *NUCALA*. These reactions generally occur within hours of administration, but in some instances had a delayed onset (i.e., days).

Parasitic Infections

Eosinophils may be involved in the immunological response to some helminth infections. Patients with pre-existing helminth infections were excluded from participation in the clinical programme. Patients with pre-existing helminth infections should be treated for their infection prior to *NUCALA* therapy. If patients become infected whilst receiving treatment with *NUCALA* and do not respond to anti-helminth treatment, temporary discontinuation of *NUCALA* should be considered.

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 formal interaction studies have been performed with *NUCALA*.

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 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

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL5 treatment on fertility (see *Non-Clinical Information*).

Pregnancy

The effect of *NUCALA* on human pregnancy is unknown. No treatment related effects on embryo-foetal or postnatal development have been shown in animal studies (see *Non-Clinical Information*).

NUCALA should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

Lactation

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

A decision should be made whether to discontinue breast-feeding or discontinue *NUCALA*, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trial data

Severe eosinophilic asthma

The safety of *NUCALA* was studied in a clinical development program in adolescents and adults with severe eosinophilic asthma which included 3 randomised, placebo-controlled, multicentre studies (n=1327). Subjects received either subcutaneous (SC) or intravenous (IV) mepolizumab or placebo during clinical studies of 24-52 weeks duration. Adverse reactions associated with *NUCALA* 100 mg administered subcutaneously (n=263) are presented in the table below. The safety profile of *NUCALA* in severe 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 was similar to that observed in the placebo-controlled studies.

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) and rare (≥1/10,000 to <1/1,000).

System Organ Class	**Adverse Reactions**	**Frequency**
Infections & Infestations	Pharyngitis Lower respiratory tract infection Urinary tract infection	Common Common Common
Nervous System Disorders	Headache	Very common
Respiratory, Thoracic & 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
General disorders and administration site conditions	Pyrexia Injection site reactions*	Common Common

* The most common symptoms associated with subcutaneous injections included: pain, erythema, swelling, itching, and burning sensation.

CRSwNP

In a randomised, double-blind placebo-controlled 52-week study in subjects with CRSwNP (*NUCALA* 100 mg n= 206, placebo n= 201), no additional adverse reactions were identified to those reported for the severe asthma studies.

EGPA

In a double-blind placebo-controlled study in subjects with EGPA (300 mg *NUCALA* n=68, placebo n=68) no additional adverse reactions were identified to those reported for the severe eosinophilic asthma studies.

HES

In a randomised, double-blind placebo-controlled 32-week study in subjects with HES (300 mg *NUCALA* n= 54, placebo n= 54), no additional adverse reactions were identified to those reported for the severe asthma studies. The safety profile of *NUCALA* 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.

Post-marketing data

System Organ Class	Adverse reaction(s)	Frequency
Immune system disorders	Hypersensitivity reactions including anaphylaxis	Rare

Description of selected adverse reactions

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.

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.

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.

4.9 Overdose

There is no clinical experience with overdose of *NUCALA*.

Single doses of up to 1500 mg were administered intravenously in a clinical trial to patients with eosinophilic disease without evidence of dose-related toxicities.

Treatment of overdose

There is no specific treatment for an overdose with *NUCALA*. 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

ATC code

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

Mechanism of action

NUCALA is a humanised monoclonal antibody (IgG1, kappa), which targets human interleukin-5 (IL-5) with high affinity and specificity. IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation and survival of eosinophils. *NUCALA* inhibits the bioactivity of IL-5 with nanomolar potency by blocking the binding of IL-5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface, thereby inhibiting IL-5 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with *NUCALA*. The magnitude of reduction in the indicated populations described below were observed within 4 weeks of treatment and were maintained throughout the treatment period.
In patients with severe eosinophilic asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 and 52 weeks respectively, the blood eosinophils were reduced to a geometric mean count of 40 cells/µL. This corresponds to a geometric mean reduction of 84% and 79% compared to placebo, respectively. This magnitude of blood eosinophils reduction was maintained in severe 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 6 to 11 years old with severe eosinophilic asthma, following either 40 mg (for a weight < 40kg) or 100 mg (for a weight ≥ 40 kg) administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 48 and 44 cells/µL, respectively with a reduction from baseline of 85% and 87%, respectively.
In patients with CRSwNP, following a dose of 100 mg administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 60 cells/µL, 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.
In patients with EGPA, following a dose of 300 mg administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 38 cells/µL. There was a geometric mean reduction of 83% compared to placebo.
In patients with HES, following a dose of 300 mg administered subcutaneously every 4 weeks for 32 weeks, the blood eosinophils were reduced to a geometric mean count of 70 cells/µL. There was a geometric mean reduction of 92% compared to placebo. This magnitude of reduction was

maintained for a further 20 weeks in patients that continued *NUCALA* treatment in the open-label extension.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment.

In subjects who received at least one dose of mepolizumab administered subcutaneously every four weeks, 15/260 (6%) (100 mg, severe eosinophilic asthma), 6/196 (3%) (100 mg, CRSwNP), 1/68 (1%) (300 mg, EGPA) and 1/53 (2%) (300 mg, HES) had detectable anti-mepolizumab antibodies. The immunogenicity profile of mepolizumab in severe 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 children 6 to 11 years with severe eosinophilic asthma following either 40 mg SC (for a weight < 40kg) or 100 mg SC (for a weight ≥ 40 kg), 2/35 (6%) had detectable anti-mepolizumab antibodies during the initial short phase of the study. No children had detectable anti-mepolizumab antibodies during the long-term phase of the study. Across indications neutralising antibodies were detected in one adult subject (with severe eosinophilic asthma). Anti-mepolizumab antibodies did not discernibly impact the PK or PD of mepolizumab treatment in the majority of patients and there was no evidence of a correlation between antibody titres and change in eosinophil level.

Clinical Studies

Severe eosinophilic asthma

The efficacy of *NUCALA* in the treatment of a targeted group of subjects with severe 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 beta2 -adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

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 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)

MEA115588 was a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study which evaluated the efficacy and safety of *NUCALA* as add-on therapy in 576 patients with severe eosinophilic asthma. This study evaluated the frequency of clinically significant exacerbations of asthma, defined as: worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits.

Patients were aged 12 years of age or older, with a history of two or more asthma exacerbations in the past 12 months and not controlled on their current asthma drug therapies [i.e., high-dose inhaled corticosteroids (ICS) in combination with at least another controller such as long-acting beta$_2$-adrenergic agonists (LABA) or leukotriene modifiers]. Patients were allowed to be on oral corticosteroid therapy and continued to receive their existing asthma medication during the study. Severe eosinophilic asthma was defined as peripheral blood eosinophils greater than or equal to 150 cells/µl within 6 weeks of randomisation (first dose) or blood eosinophils greater than or equal to 300 cells/µl within the past 12 months of randomisation.

Patients received either *NUCALA* 100 mg administered subcutaneously (SC), *NUCALA* 75 mg administered intravenously (IV), or placebo treatment once every 4 weeks over 32-weeks.

The primary endpoint, reduction in the frequency of clinically significant exacerbations of asthma was statistically significant (p<0.001). Table 2, provides the results of the primary endpoint and secondary endpoints of MEA115588.

Table 2: Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

	NUCALA (100 mg SC) 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
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		
Mean Change from Baseline (SE)	183 (31.1)	86 (31.4)
Difference (mepolizumab vs. placebo)	98	
95% CI	11, 184	

	NUCALA (100 mg SC) N=194	Placebo N=191
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Mean Change from Baseline (SE)	-16.0 (1.13)	-9.0 (1.16)
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 (MEA115575)

MEA115575 evaluated the effect of *NUCALA* 100 mg SC on reducing the use of maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe eosinophilic asthma who were dependent on systemic corticosteroids. Patients had a peripheral blood eosinophil count of ≥300/μL in the 12 months prior screening or a peripheral blood eosinophil count of ≥150/μL at baseline. Patients were administered *NUCALA* or placebo treatment once every 4 weeks over the treatment period. The OCS dose was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained. During the study patients continued their baseline asthma therapy [i.e., high-dose inhaled corticosteroids (ICS) in combination with at least another controller such as long-acting beta$_2$-adrenergic agonists (LABA) or leukotriene modifiers].

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

The primary endpoint was the reduction in daily OCS dose (weeks 20-24) whilst maintaining asthma control compared with patients treated with placebo (see Table 4).

Table 4: Results of the primary and secondary endpoints in the Intent to Treat population (MEA115575).

	NUCALA (100 mg SC) N=69	Placebo N=66
Primary Endpoint		
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
90% - 100% 75% - <90% 50% - <75% >0% - <50% No decrease in OCS/lack of asthma control/ withdrawal from treatment	16 (23%) 12 (17%) 9 (13%) 7 (10%) 25 (36%)	7(11%) 5 (8%) 10 (15%) 7(11%) 37 (56%)
Odds ratio (95% CI)	2.39 (1.25, 4.56)	
p-value	0.008	
Secondary Endpoints		
Reduction in the daily OCS dose (%)		
At least 50% reduction	37 (54%)	22 (33%)
Odds ratio (95% CI)	2.26 (1.10, 4.65)	
p-value	0.027	
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	
Reduction in the daily OCS dose		
To 0 mg/Day	10 (14%)	*5* (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0.414	
Median Percentage Reduction in Daily OCS Dose		
Median % reduction 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	

Additionally, health-related quality of life was measured using SGRQ. At Week 24, there was a statistically significant improvement in the mean SGRQ score for *NUCALA* compared with placebo: -5.8 (95% CI: -10.6,-1.0; P=0.019). At Week 24, the proportion of subjects with a clinically meaningful decrease in SGRQ score (defined as a decrease of at least 4 units from baseline) was greater for *NUCALA* (58%, 40/69) compared with placebo (41%, 27/66).
The long-term efficacy profile of *NUCALA* in severe 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 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.
Patients received a 100 mg dose of *NUCALA*, or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy.
The demographics and baseline characteristics of patients in study 205687 are provided in Table 5 below:

Table 5 Demographics and baseline characteristics in CRSwNP

	N = 407
Age (y) of patients, mean (SD)	49 (13)
Female, n (%)	143 (35)
White, n (%)	379 (93)
Duration (y) of CRSwNP, mean (SD)	11.4 (8.39)
Patients with >= 1 previous surgery, n (%)	407 (100)
Patients with >= 3 previous surgeries, n (%)	124 (30)
OCS use for NP (≥1 course) in past 12 months, n (%)	197 (48)
Total endoscopic NP score[a b c], mean (SD), maximum score = 8	5.5 (1.29)
Nasal obstruction VAS score[a d], mean (SD), maximum score = 10	9.0 (0.83)

Overall VAS symptom score[a d], mean (SD), maximum score = 10	9.1 (0.74)
SNOT-22 total score[e], mean (SD), range 0-110	64.1 (18.32)
Composite VAS symptoms score[a], mean (SD), maximum score = 10	9.0 (0.82)
Loss of smell VAS score[a,d], mean (SD), maximum score = 10	9.7 (0.72)
Asthma, n (%)	289 (71)
AERD, n (%)	108 (27)
Geometric mean eosinophil count at baseline, cells/mcL (95% CI)	390 (360, 420)

CRSwNP = chronic rhinosinusitis with nasal polyps, SD = standard deviation, OCS = oral corticosteroid, NP = nasal polyps, VAS = visual analogue scale, SNOT-22 = Sino-Nasal Outcome Test, AERD = aspirin-exacerbated respiratory disease

[a] Higher scores indicate greater disease severity.

[b] As graded by independent blinded assessors

[c] NP score is the sum of scores from both nostrils (0-8 scale) where each nostril was graded (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle concha; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha; 4=large polyps causing almost complete congestion/obstruction of the inferior meatus).

[d] Collected daily by patients on a 0 to 10 scale (0=none; 10=as bad as you can imagine).

[e] SNOT-22 is a health-related quality of life assessment tool and included 22 items in 6 domains of symptoms and impact associated with CRSwNP (nasal, non-nasal, ear/facial, sleep, fatigue, emotional consequences). Higher scores indicate worse health related quality of life.

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. Patients who received NUCALA 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 (see Table 6).

Table 6: Analyses of co-primary endpoints (Intent To Treat population)

	Placebo **(N=201)**	***NUCALA*** **100 mg SC** **(N=206)**
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
Adjusted treatment 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
Adjusted treatment 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)

a) Subjects with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty 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.

All secondary endpoints were statistically significant and provided support for the co-primary endpoints. The key secondary endpoint was the time to first NP surgery up to Week 52 (see Figure 1). Data from the other secondary endpoints are presented in Table 7.

Time to First NP surgery

Across the 52-week treatment period, patients in the *NUCALA* group had a lower probability of undergoing NP surgery than patients in the placebo group (surgery was defined as any procedure involving instruments resulting in incision and removal of tissue [polypectomy] in the nasal cavity).

By Week 52, 18 patients (9%) in the *NUCALA* group had undergone NP surgery compared with 46 patients (23%) in the placebo group.

Patients who received *NUCALA* had an increase in the time to first NP surgery compared with placebo. The risk of surgery over the treatment period was significantly lower by 57% for patients treated with *NUCALA* compared with placebo (Hazard Ratio: 0.43; 95% CI 0.25, 0.76; unadjusted/adjusted p=0.003), a post-hoc analysis showed a 61% reduction in the odds of surgery (OR: 0.39, 95% CI: 0.21, 0.72; p= 0.003.

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

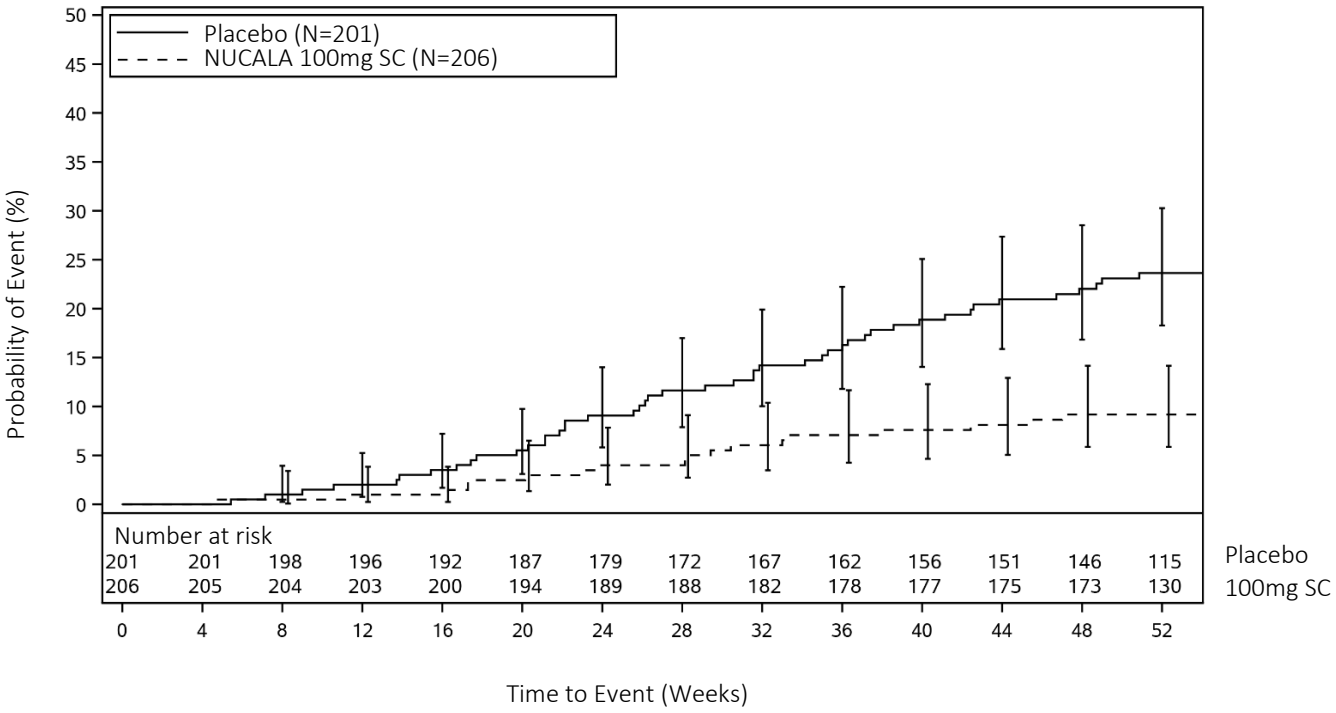

Table 7: Results of other secondary endpoints in the Intent to Treat population

	Placebo (N=201)	NUCALA (N=206)
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
Unadjusted/adjusted p-value [b,c]		<0.001/0.003
Adjusted treatment difference in medians (95% CI) [d]		-3.18 (-4.10, -2.26)
⩾2.5-point improvement (%)	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
Unadjusted/adjusted p-value [b,c]		<0.001/0.003
Adjusted treatment difference in medians (95% CI) [d]		-16.49 (-23.57, -9.42)
>=28-point improvement (%)[g]	32	54

	Placebo (N=201)	NUCALA (N=206)
Patients Requiring Systemic Steroids for Nasal Polyps up to Week 52		
Number of patients with ⩾1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI) [e]		0.58 (0.36, 0.92)
Unadjusted/adjusted p-value [c, e]		0.020/0.020
Composite VAS Score - Nasal Symptoms (Weeks 49-52) [a,f]		
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
Unadjusted/adjusted p-value [b,c]		<0.001/0.020
Adjusted treatment difference in medians (95% CI) [d]		-2.68 (-3.44, -1.91)
>=2-point improvement (%)[h]	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
Unadjusted/adjusted p-value [b,c]		<0.001/0.020
Adjusted treatment difference in medians (95% CI) [d]		-0.37 (-0.65, -0.08)
>=3-point improvement (%)[h]	19	36

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

[b] Based on Wilcoxon rank-sum test.

[c] Multiplicity controlled through testing of secondary endpoints following a pre-defined hierarchy.

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

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

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

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

[h] Threshold for improvement for each endpoint, has been identified as a meaningful within-patient change for this assessment.

Endpoints in patients with 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 *NUCALA* 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 *NUCALA* 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52 week study which evaluated 136 patients ≥18 years old with relapsing or refractory EGPA and who were on stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone). Fifty-three percent (n=72) were also on concomitant stable immunosuppressant therapy.

Patients received a 300 mg dose of *NUCALA* 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.

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

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 *NUCALA* 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of subjects receiving *NUCALA* 300 mg achieved remission at both Week 36 and Week 48 (Table 8).

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 8: Analyses of Co-Primary Endpoints (ITT Population)

	Number (%) of patients	
	Placebo N=68	***NUCALA* 300 mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0 weeks	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 *NUCALA*. Remission: BVAS=0 and OCS dose ≤ 4mg / day.

Relapse

Compared with placebo, the time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalisation), was significantly longer for subjects receiving *NUCALA* 300 mg ($p<0.001$) Additionally, subjects receiving *NUCALA* had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral Corticosteroid Reduction

Compared with placebo, subjects receiving *NUCALA* 300 mg had a lower average daily oral corticosteroid dose during Weeks 48 to 52 ($p <0.001$). In the *NUCALA* 300 mg group, 12 subjects (18%) were able to taper completely off OCS therapy compared with 2 subjects (3%) in the placebo group.

Hypereosinophilic Syndrome (HES)

Study 200622 was a randomised, double-blind, placebo-controlled, 32 week study which evaluated 108 subjects ≥ 12 years old with HES. Subjects received 300 mg of *NUCALA*, or placebo administered subcutaneously once every 4 weeks while continuing their stable HES therapy. Of the 4 adolescents enrolled, one adolescent received 300 mg of *NUCALA*, and 3 adolescents received placebo for 32 weeks. Standard HES therapy could include OCS and immunosuppressive or cytotoxic therapy. Subjects entering the study had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥ 1000 cells/μL during screening.

The primary endpoint of study 200622 was the proportion of subjects 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 or increasing eosinophils (on ≥ 2 occasions), resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy.

The primary analysis compared subjects who experienced a HES flare or withdrew from the study in the *NUCALA* and placebo treatment groups. Over the 32-week treatment period, 50% fewer subjects experienced a HES flare or withdrew from the study when treated with 300 mg *NUCALA* compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 9).

Secondary endpoints were time to first HES flare, proportion of subjects 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 10).

Table 9: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

	NUCALA N= 54	**Placebo** N= 54
Proportion of subjects who experienced a HES flare		
Subjects with ≥1 HES flare or who withdrew from study (%)	15 (28)	30 (56)
Subjects with ≥1 HES flare (%)	14 (26)	28 (52)
Subjects 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

Subjects who received 300 mg *NUCALA* 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 subjects treated with *NUCALA* 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

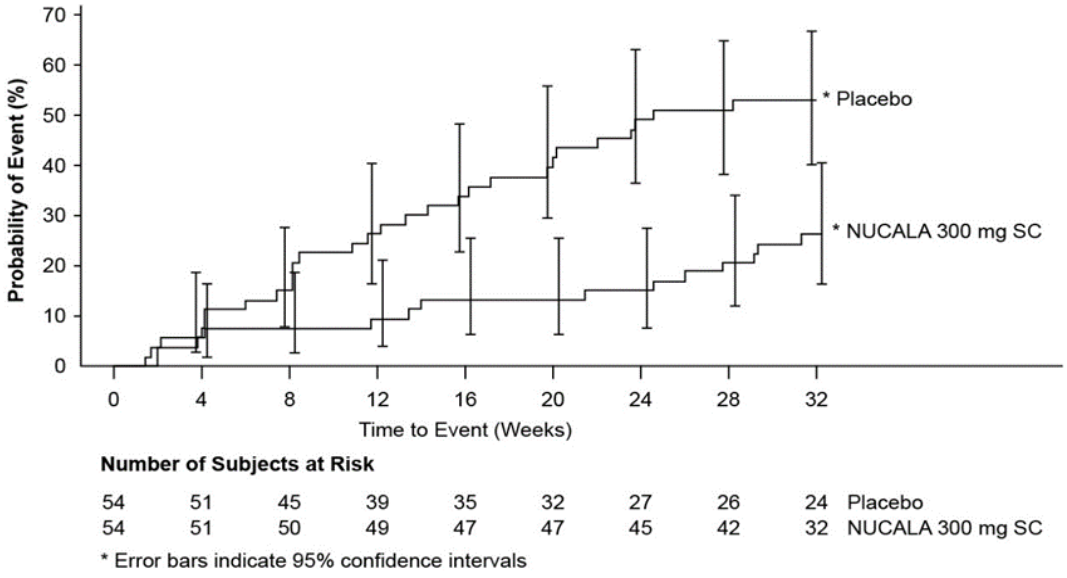

Table 10: Results of other secondary end-points in the Intent to Treat population (Study 200622)

	NUCALA N= 54	**Placebo** N= 54
HES flares during week 20 and up to and including week 32		
Subjects 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 (unadjusted/adjusted)[a]	0.02/0.02	
Rate of HES flares		
Estimated mean rate/year	0.50	1.46
Rate ratio (95% CI)	0.34 (0.19, 0.63)	
Wilcoxon p-value (unadjusted/adjusted)[a]	0.002/0.02	
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 (*NUCALA* vs. placebo) p-value (unadjusted/adjusted)[a]	0.036/0.036	

[a] adjusted p- values based on pre-specified hierarchy of endpoints.

[b] Patients with missing data included with worst observed value.

CMH =Cochran-Mantel-Haenszel

HES Open-Label extension

Eligible patients including 4 adolescents that completed study 200622 continued into a 20-week open-label extension study 205203 to investigate the long-term safety profile and provide additional data on the clinical benefit of *NUCALA* in HES patients beyond 32 weeks.

The effect of treatment with *NUCALA* on the reduction of HES flares seen during Study 200622 was sustained for subjects who continued *NUCALA* treatment in study 205203, in which 94% (47/50) of patients did not experience a flare.

During Week 16 to 20, 28% of all subjects with a mean Week 0 to 4 OCS dose >0 mg/day (prednisone or equivalent) had achieved a mean daily OCS dose reduction of ≥50%. Efficacy data from this study suggests that the clinical benefit of *NUCALA* is sustained to 52 weeks and allows for reduction in OCS treatment in subjects with HES.

5.2 Pharmacokinetic properties

Following subcutaneous dosing in subjects with moderate/severe asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg. Mepolizumab pharmacokinetics were consistent in subjects with asthma, CRSwNP, EGPA or HES. Subcutaneous administration of *NUCALA* 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. In a PK comparability study conducted in healthy subjects, following administration of a single 100 mg subcutaneous dose, mepolizumab pharmacokinetics were 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 of mepolizumab to patients with asthma, the mean volume of distribution is 55 to 85 mL/kg.

Metabolism

Mepolizumab is a humanized 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 (t1/2) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special Patient Populations

The population pharmacokinetics of mepolizumab were analysed to evaluate the effects of demographic characteristics. Analyses of these limited data suggest that no dose adjustments are necessary for race or gender.

Children

Severe Eosinophilic Asthma

Mepolizumab pharmacokinetics following subcutaneous administration in subjects 6 to 11 years old with severe eosinophilic asthma 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.

EPGA

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.

Elderly patients (≥65 years old)

No formal studies have been conducted in elderly patients. However, in the population pharmacokinetic analysis, there was no indication 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.

5.3 Preclinical safety data

Carcinogenesis/mutagenesis

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

Reproductive Toxicology

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/foetal 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 crosses the placenta. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers for several months post partum and did not affect the immune system of the infants.

Animal toxicology and 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 have been 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.

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

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

The expiry date is indicated on the packaging.

6.4 Special Precautions for Storage

The storage conditions are detailed on the packaging.
Store in refrigerator (2-8ºC). Do not freeze.
Protect from light. Store in the original carton until use.
The pre-filled pen and pre-filled syringe can be removed from the refrigerator and kept in the unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light. Discard if left out of the refrigerator for more than 7 days.
The pre-filled pen or pre-filled syringe must be administered within 8 hours once the pack is opened. Discard if not administered within 8 hours.

6.5 Nature and Contents of Container

Solution for injection in pre-filled pen (auto-injector)
1 mL siliconised, Type I glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled as an auto-injector.
Solution for injection in pre-filled syringe (safety syringe)

1 mL siliconised, Type I glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled with a needle guard.

6.6 Instructions for Use/Handling

See the Instructions for Use leaflet for complete administration instructions with illustrations in Patient Information Leaflet.
Not all presentations are available in every country.

7. MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Thailand) Ltd.

8. MARKETING AUTHORISATION NUMBER

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9. DATE OF FIRST AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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