NEW ZEALAND DATA SHEET

1. PRODUCT NAME

NUCALA (mepolizumab) solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa) directed against human interleukin-5 (IL-5). Mepolizumab is expressed as a soluble glycoprotein secreted from a recombinant Chinese hamster (rch) ovary cell line.

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

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Clear to opalescent, colourless to pale yellow to pale brown solution in a single-use, pre-filled pen or syringe. It contains no preservative.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe eosinophilic asthma

NUCALA is indicated as an add-on treatment for severe eosinophilic asthma in patients aged 12 years and over (see Section 5.1 Pharmacodynamic properties).

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

NUCALA is indicated as an add-on treatment in adult patients (18 years and above) with severe chronic rhinosinusitis with nasal polyps (CRSwNP) with an inadequate response to intranasal corticosteroids (see Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical efficacy and safety).

Relapsed or refractory EGPA

NUCALA is indicated as an add-on treatment for relapsing or refractory Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients aged 18 years and over (see section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Efficacy and Safety).

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 PHARMACODYNAMIC PROPERTIES, Clinical efficacy and safety).

4.2 Dose and method of administration

NUCALA should be prescribed by a specialist physician, or a healthcare professional in consultation with a specialist physician, experienced in the diagnosis and treatment of severe asthma or EGPA.

NUCALA should only be administered as a subcutaneous (SC) injection (see Section 6.6 Special precautions for disposal and other handling).

Dose

Severe eosinophilic asthma

Adults and adolescents (12 years or older)

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

The safety and efficacy of NUCALA have not been established in adolescents weighing less than 45 kg.

Children (below 12 years)

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

CRSwNP

Adults (18 years or older)

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

Children (below 18 years)

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

Relapsed or refractory EGPA

It is recommended that the sites for each injection are separated by at least 5 cm (see Method of administration below and Section 6.6 Special precautions for disposal and other handling).

Adults (18 years or older)

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

HES

Injection sites should be at least 5 cm apart (see Method of administration below and Section 6.6 Special precautions for disposal and other handling).

Adults (18 years and older)

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

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.

Children

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

Special populations

Elderly (65 years or older)

No dosage adjustment is recommended in patients 65 years or older (see Section 5.2 Pharmacokinetics, Special patient populations).

Renal impairment

Dose adjustments in patients with renal impairment are unlikely to be required (see Section 5.2 Pharmacokinetics, Special patient populations).

Hepatic impairment

Dose adjustments in patients with hepatic impairment are unlikely to be required (see Section 5.2 Pharmacokinetics, Special patient populations).

Method of administration

NUCALA solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe) 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 (see Section 6.6 Special precautions for disposal and other handling).

4.3 Contraindications

Hypersensitivity to mepolizumab or to any of the excipients listed in Section 6.1 List of excipients.

4.4 Special warnings and precautions for use

NUCALA should not be used to treat acute asthma exacerbations.

Asthma-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.

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). These reactions may occur for the first time after a long duration of treatment (see Section 4.8 Undesirable effects). In the event of a hypersensitivity reaction, NUCALA should be discontinued.

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 program. 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.

Opportunistic infections: Herpes Zoster

In controlled clinical trials, 2 serious adverse reactions of herpes zoster occurred in patients treated with NUCALA versus none in the placebo group.

EGPA: Cessation of NUCALA

NUCALA treated patients may experience a return of EGPA symptoms upon cessation of NUCALA. As patients may decrease their other EGPA treatments during treatment with NUCALA, if NUCALA treatment is discontinued then other EGPA treatments may need to be increased accordingly.

Paediatric population

Severe eosinophilic asthma

The safety and efficacy of NUCALA in children under the age of 12 years has not yet been established.

Relapsed or refractory EGPA

The safety and efficacy of NUCALA in children under the age of 18 years has not been established.

Elderly population

No formal studies have been conducted in elderly patients (see Section 5.2 Pharmacokinetics, Special patient populations).

4.5 Interaction with other medicines and other forms of interaction

No formal interaction studies have been performed with NUCALA.

4.6 Fertility, pregnancy and lactation

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 Section 5.3 Preclinical safety data).

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

Breastfeeding

There are no data regarding the excretion of NUCALA in human milk. However, mepolizumab was excreted into the milk of cynomolgus monkeys postpartum following dosing during pregnancy 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.

Fertility

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

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

Summary of the safety profile

The following adverse reactions are described in greater detail in other sections:

- Hypersensitivity reactions (see Section 4.4 Special warnings and precautions for use)
- Opportunistic infections: herpes zoster (see Section 4.4 Special warnings and precautions for use).

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Severe eosinophilic asthma

A total of 1,327 subjects with asthma were evaluated in 3 randomised, placebo-controlled, multicentre trials of 24 to 52 weeks' duration (MEA112997, MEA115588 and MEA115575). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrolment despite regular use of high-dose inhaled corticosteroids (ICS) plus an additional controller(s) (MEA112997 and MEA115588), and 135 subjects required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus an additional controller(s) to maintain asthma control (MEA115575). All subjects had markers of eosinophilic airway inflammation (see Section 5.1 Pharmacodynamic properties, Clinical efficacy and safety). Of the subjects enrolled, 59% were female, 85% were white, and subjects ranged in age from 12 to 82 years. Mepolizumab was administered SC or intravenously (IV) once every 4 weeks; 263 subjects received NUCALA (mepolizumab 100 mg SC) for at least 24 weeks. Serious adverse events that occurred in more than 1 subject and in a greater percentage of subjects treated with NUCALA (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 subjects vs. 0 subjects, respectively). Approximately 2% of subjects receiving NUCALA withdrew from clinical trials due to adverse events compared with 3% of subjects receiving placebo.

Tabulated summary of adverse reactions

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (MEA115588 and MEA115575) with NUCALA is shown in Table 1.

Table 1: Adverse Reactions with NUCALA with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with Asthma (MEA115588 and MEA115575)

Adverse Reaction	NUCALA (Mepolizumab 100 mg SC) (n=263) %	Placebo (n=257) %
Headache	19	18
Injection site reaction	8	3
Back pain	5	4
Fatigue	5	4
Influenza	3	2
Urinary tract infection	3	2
Abdominal pain upper	3	2
Pruritus	3	2
Eczema	3	<1
Muscle spasms	3	<1

52-Week Trial

Adverse reactions from MEA112997 with 52 weeks of treatment with mepolizumab 75 mg IV (n = 153) or placebo (n = 155) and with greater than or equal to 3% incidence and more common than placebo and not shown in Table 1 were: abdominal pain, allergic rhinitis, asthenia, bronchitis, cystitis, dizziness, dyspnoea, ear infection, gastroenteritis, lower respiratory tract infection, musculoskeletal pain, nasal congestion, nasopharyngitis, nausea, pharyngitis, pyrexia, rash, toothache, viral infection, viral respiratory tract infection, and vomiting. In addition, 3 cases of herpes zoster occurred in subjects treated with mepolizumab 75 mg IV, compared with 2 subjects in the placebo group.

Description of selected adverse reactions

Systemic reactions, including Hypersensitivity reactions

In MEA112997, MEA115588 and MEA115575 described above, the percentage of subjects who experienced systemic (allergic and non-allergic) reactions was 7% in the placebo group and 10% in the group receiving NUCALA. Systemic allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving NUCALA. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of subjects in the group receiving NUCALA and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA included rash, flushing, and myalgia. A majority of the systemic reactions in subjects receiving NUCALA (5/7) were experienced on the day of dosing.

Injection site reactions

Injection site reactions (e.g. pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in subjects treated with NUCALA compared with 3% in subjects treated with placebo.

Long-term safety

The safety profile of NUCALA in nine hundred and ninety-eight (998) subjects treated for a median of 2.8 years (range 4 weeks to 4.5 years) in ongoing open-label extension studies was similar to the placebo-controlled asthma trials described above. Additional cases of herpes zoster have been reported during these studies.

CRSwNP

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

Relapsed or refractory EGPA

A total of 136 subjects with EGPA were evaluated in a double-blind, placebo-controlled study in which 300 mg mepolizumab (n=68) or placebo (n=68) was administered SC every 4 weeks for 13 treatments (see Section 5.1 PHARMACODYNAMIC PROPERTIES - Clinical Efficacy and Safety). Approximately 3% of subjects receiving NUCALA withdrew due to adverse events compared with 2% of subjects receiving placebo. The following AEs were most commonly reported.

Table 2: Adverse Events with NUCALA with Greater than or Equal to 15% Incidence and More Common than Placebo in Subjects with EGPA (MEA115921)

Adverse Event	NUCALA (Mepolizumab 300 mg Subcutaneous) (n = 68) %	Placebo (n = 68) %
Any	90	96
Headache	32	18
Arthralgia	22	18
Nausea	19	16
Sinusitis	21	16
Upper respiratory tract infection	21	16
Diarrhoea	18	12
Vomiting	16	6
Injection site reaction	15	13

HES

In a randomised, double-blind placebo-controlled 32-weeks study in subjects with HES (300 mg mepolizumab 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.

Immunogenicity

Subjects with severe asthma and EGPA received at least one dose of 100 mg and 300 mg

mepolizumab respectively, administered subcutaneously every four weeks. Of these subjects, 15/260 (6%) with severe asthma and 1/68 (1%) with EGPA had detectable anti-mepolizumab antibodies. The reported frequency may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration.

Neutralising antibodies were detected in 1 subject with severe asthma receiving mepolizumab. Anti-mepolizumab antibodies slightly increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titres and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to mepolizumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Post-marketing data
Adverse reactions are listed below by system organ class and frequency. The following convention has been used for the classification of adverse reactions:

Rare: ≥1/10,000 to <1/1,000.

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

There is no clinical experience with overdose of NUCALA.

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

There is no specific treatment for an overdose with NUCALA. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

For advice on the management of overdose, please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

ATC Code: R03DX09

Molecular weight

The total estimated molecular weight for mepolizumab is 149 kDa.

Mechanism of action

Mepolizumab is a humanised monoclonal antibody (IgG1, kappa), which targets human 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.

Mepolizumab 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 signaling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

Severe eosinophilic asthma

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with mepolizumab. The magnitude and duration of this reduction was dose-dependent. Following a dose of 100 mg SC administered every 4 weeks for 32 weeks, blood eosinophils were reduced to a geometric mean count of 40 cells/µL. This corresponds to a geometric mean reduction of 84% compared to placebo. This magnitude of blood eosinophils reduction was maintained in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

CRSwNP

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.

Relapsed or refractory EGPA

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

HES

In patients with HES, following a dose of 300 mg administered subcutaneously every 4weeks 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 mepolizumab 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.

Subjects received at least one dose of mepolizumab administered subcutaneously every four weeks. Of these subjects, 15/260 (6%) (100 mg, severe 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 asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) or in HES (n=102) treated for 20 weeks in open-label extension studies was similar to that observed in the placebo-controlled studies.

Neutralising antibodies were detected in one subject receiving mepolizumab. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetic or pharmacodynamic effects 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 efficacy and safety

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 studies were designed to evaluate the efficacy of mepolizumab administered once every 4 weeks by SC or IV injection in severe eosinophilic asthma patients not controlled on their standard of care [e.g. ICS, OCS, combination ICS and long-acting beta$_2$-adrenergic agonists (LABA), leukotriene modifiers, short-acting beta$_2$-adrenergic agonists (SABA)].

Placebo-controlled studies

Dose-ranging efficacy (MEA112997)

In study MEA112997, a randomised, double-blind, placebo-controlled, parallel-group, multi-centre study of 52 weeks duration in 616 patients, results demonstrated that mepolizumab IV (75 mg, 250 mg or 750 mg) significantly reduced asthma exacerbations compared to placebo. There was no statistically significant difference in effect seen between the 3 studied doses. Blood eosinophil counts greater than or equal to 150 cells/µL at screening; or blood eosinophils ≥300 cells/µL in the past 12 months predicted subjects who would benefit most from mepolizumab therapy. Results from this study were used to determine dose selection for the studies using S C mepolizumab administration. Mepolizumab is not indicated for IV use, and should only be administered by the SC route.

Exacerbation reduction (MEA115588)

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 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 therapies (i.e. high-dose ICS in combination with at least another controller such as LABA or leukotriene modifiers). Patients were allowed to be on OCS 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 mepolizumab 100 mg SC, mepolizumab 75 mg 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 3 provides the results of the primary endpoint and secondary endpoints of MEA115588.

Table 3. Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

	Mepolizumab (100 mg SC)	**Placebo**
	N=194	**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	-
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	-

Oral corticosteroid reduction (MEA115575)

Study MEA115575 evaluated the effect of mepolizumab 100 mg SC on reducing the use of maintenance 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 cells/μL in the 12 months prior screening or a peripheral blood eosinophil count of ≥150 cells/μL at baseline. Patients were administered mepolizumab 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 ICS in combination with at least another controller such as 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)

	Number (%) of Subjects	
	Mepolizumab (100 mg SC)	**Placebo**
	N=69	**N=66**
Primary Endpoint		
Percent Reduction in OCS from Baseline at Weeks 20-24 (%)		
n		
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	-
Secondary Endpoints:		
Reduction in the daily OCS dose		
At least 50% reduction in daily OCS dose from baseline, n (%)	37 (54%)	22 (33%)
Odds ratio (95% CI)	2.26 (1.10, 4.65)	-
p-value	0.027	-
Reduction to ≤5 mg/day in daily OCS dose, n (%)	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	-
p-value	0.025	-
Reduction to 0 mg/day in daily OCS dose, n (%)	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	

OCS: prednisone/prednisolone

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 mepolizumab 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 mepolizumab (58%, 40/69) compared with

placebo (41%, 27/66).

The long-term efficacy profile of mepolizumab in severe 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.

Open-label extension study (MEA115661)

Following completion of the double-blind MEA115575 and MEA115588 studies, all patients were offered the opportunity to participate in MEA115661, a 52-week open-label extension (OLE) study, during which time all patients received open label mepolizumab (100 mg SC). In total, 651 patients (126 subjects who had previously participated in study MEA115575 and 525 subjects who had previously participated in Study MEA115588), received 100 mg of mepolizumab SC every 4 weeks. During open-label treatment of all subjects with mepolizumab in MEA115661, the rates of exacerbations per year remained low in the subjects who were previously treated with mepolizumab and were consistent with results demonstrated during the 32-week double-blind period of study MEA115588. In addition, the impact of mepolizumab on steroid reduction was maintained following MEA115575 with average daily steroid dose remaining consistent with the level achieved with mepolizumab treatment at Weeks 20-24 during MEA115575.

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 mepolizumab, 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 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 (see Table 6).

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

	Placebo (N=201)	Mepolizumab 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 mepolizumab 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 mepolizumab group had undergone NP surgery compared with 46 patients (23%) in the placebo group.

Patients who received mepolizumab 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 mepolizumab 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

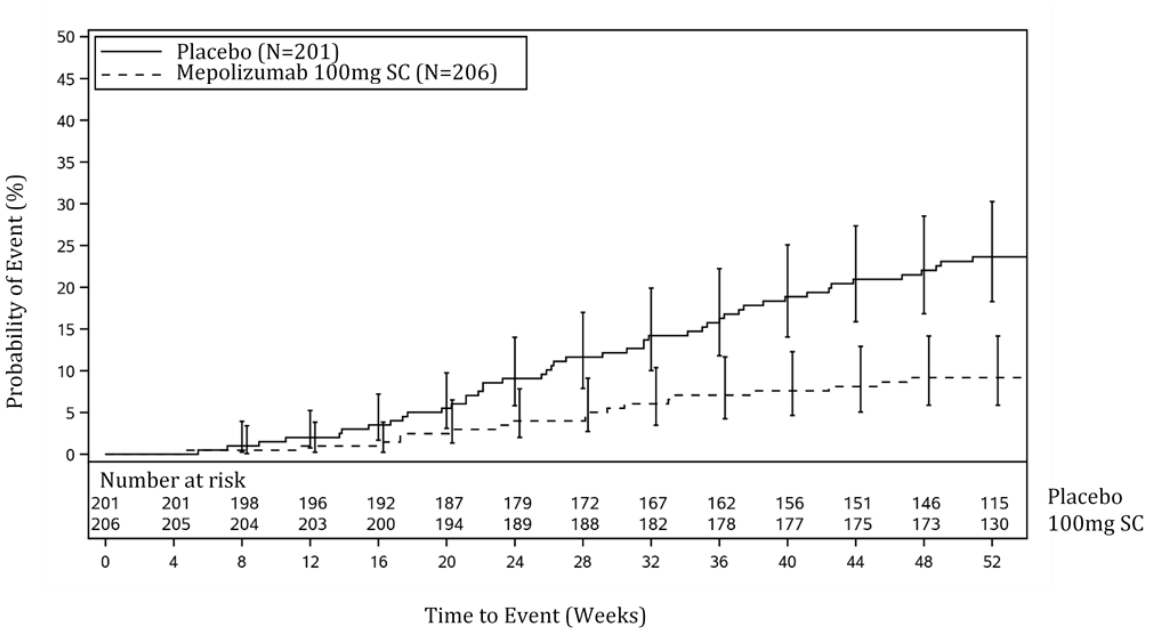

Table 7: Results of other secondary endpoints in the Intent to Treat population

	Placebo (N=201)	Mepolizumab (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

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 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).

Relapsed or refractory EGPA

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 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).

Patients 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.

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.

A total of 136 subjects were enrolled. Demographic and disease characteristics were balanced between the treatment groups. The mean age was 48.5 years (17 subjects were aged 65 years or more); 59% were female; and 92% white. The mean duration of EGPA was 5.5 years (SD 4.63) and 74% had had one or more confirmed relapse in the past 2 years. The median baseline daily oral corticosteroid dose was 12 mg (prednisone or prednisolone equivalent) (range 7.5 to 50 mg) and 53% (n=72) were receiving other immunosuppressant therapy (e.g., azathioprine, methotrexate, mycophenolic acid.)

Remission

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

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

	Number (%) of Subjects	
	Placebo	**Mepolizumab 300 mg**
	N=68	**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
Subjects in Remission at Weeks 36 and 48	**2 (3)**	**22 (32)**
Odds ratio (mepolizumab/placebo)		16.74
95% CI	-	3.61, 77.56
p-value	-	<0.001

An odds ratio >1 favours mepolizumab

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤7.5 mg/day. There was a greater accrued time in remission in the mepolizumab group compared with placebo, in subjects with a baseline blood eosinophil count (BEC) ≥150 cells/μL.

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

mepolizumab 300 mg (p<0.001). Additionally, subjects receiving mepolizumab 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 mepolizumab 300 mg had a lower average daily oral corticosteroid dose during Weeks 48 to 52 (p<0.001). In the mepolizumab 300 mg group, 30 subjects (44%) were able to taper OCS therapy to ≤ 4 mg daily, compared with 5 subjects (7%) in the placebo group and 12 subjects compared to 2 were able to taper completely off OCS therapy.

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 mepolizumab, 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 mepolizumab, 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 mepolizumab 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 mepolizumab 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)

	Mepolizumab N= 54	**Placebo** N= 54
Proportion of subjects who experienced a HES flare		
	Mepolizumab N= 54	Placebo N= 54
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 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 subjects 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

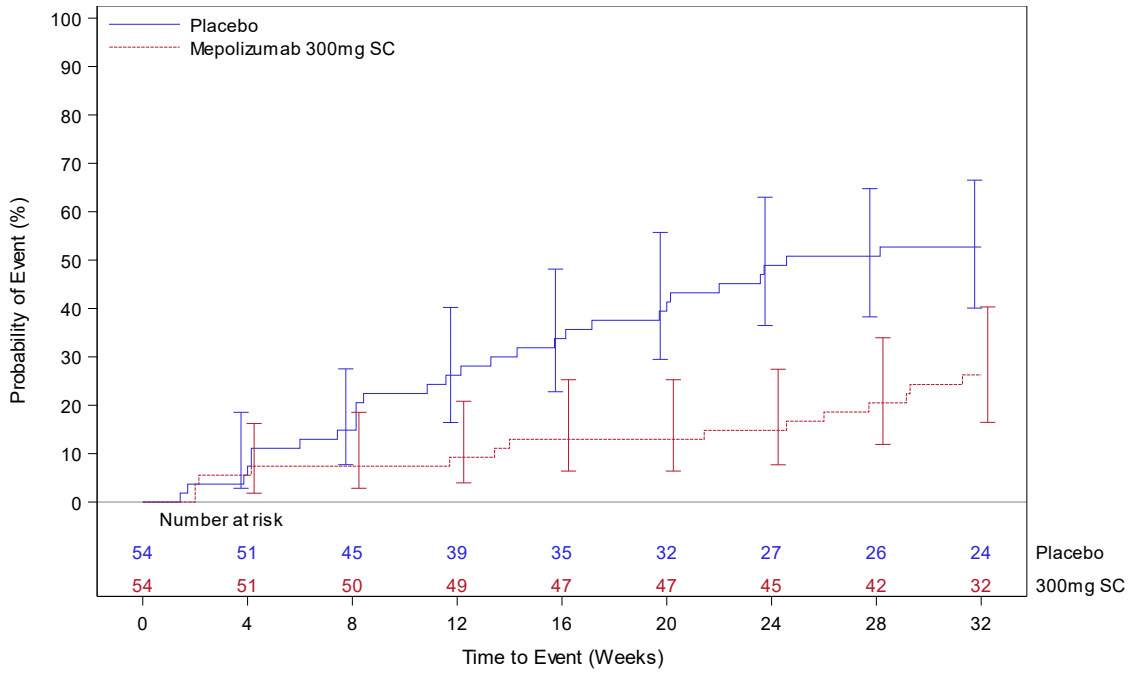

Table 10: Results of other secondary end-points in the Intent to Treat population (Study 200622)

	Mepolizumab 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 (mepolizumab 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 mepolizumab in HES patients beyond 32 weeks.

The effect of treatment with mepolizumab on the reduction of HES flares seen during Study 200622 was sustained for subjects who continued mepolizumab 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 mepolizumab is sustained to 52 weeks and allows for reduction in OCS treatment in subjects with HES.

Real-World Use Studies

Two open-label, single-arm, multi-dose, multicenter, 12-week studies were conducted to investigate the real-world use of a safety syringe (Study 205667) and an autoinjector (Study 204959) in subjects greater than 12 year of age with severe eosinophilic asthma. In Study 205667, 100% of subjects successfully self-administered mepolizumab in a safety syringe at week 8 (primary endpoint). In Study 204959, 98% of subjects successfully self-administered mepolizumab in an autoinjector at week 8 (primary endpoint).

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 mepolizumab 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg.

Absorption

Following SC 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 SC 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 SC in the arm ranged from 74-80%. Following repeat SC administration every 4 weeks, there is approximately a two-fold accumulation at steady state.

Distribution

Following a single IV administration of mepolizumab to patients with asthma, the mean volume of distribution is 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 IV 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 ($t_{1/2}$) of approximately 20 days. Following subcutaneous administration of mepolizumab the mean ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis, estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special 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.

Elderly (65 years or older)

No formal studies have been conducted in elderly patients. However, in the population pharmacokinetic analysis, there was no indication of an effect of age (12-82 years of age) on the pharmacokinetics of mepolizumab.

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

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.

Genotoxicity
As mepolizumab is a monoclonal antibody, no genotoxicity studies have been conducted. Being a large protein molecule, mepolizumab is not expected to interact directly with DNA or other chromosomal material.

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

Reproductive/developmental toxicology
In cynomolgus monkeys, mepolizumab had no effect on pregnancy or on embryonic/fetal and postnatal development (including immune function) of the offspring when given doses up to 100 mg/kg IV per month throughout gestation (yielding 31 times the AUC in humans at the clinical dose). 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.

In addition, in a fertility, early embryonic, and embryo-fetal development study, pregnant CD-1 mice received a homologous antibody, which inhibits the activity of murine IL-5, at an IV dose of 50 mg/kg once per week throughout gestation. The homologous antibody did not produce obvious teratogenicity or otherwise affect embryo-fetal development in mice. Embryo-fetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

No impairment of fertility was observed in a fertility and general reproduction toxicity study in male and female mice performed with a homologous antibody that inhibits IL-5 in mice. This study did not include a littering or functional F1 assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Dibasic sodium phosphate heptahydrate
Citric acid monohydrate

Polysorbate 80
Disodium edetate
Water for injections

6.2 Incompatibilities

Do not mix the reconstituted solution for injection with other medicinal products.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at 2°C - 8°C (Refrigerate. 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)

NUCALA is presented as a 1 mL siliconised Type 1 glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled as an auto-injector.

NUCALA is supplied in a pack containing one single use pre-filled pen (auto-injector).

Solution for injection in pre-filled syringe (safety syringe)

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

NUCALA is supplied in a pack containing one single use pre-filled syringe (safety syringe).

Not all dose forms or container types may be distributed in New Zealand.

6.6 Special precautions for disposal and other handling

See the Instructions for Use leaflet for complete administration instructions with illustrations, which is appended to the CMI.

Disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine: 22 June 2017

10. DATE OF REVISION OF THE TEXT

3 December 2024

Summary table of changes:

Section changed	Summary of new information
All	Removal of powder presentation from Data Sheet prior to licence cancellation
4.8	Update to the adverse reactions reporting link
All	Editorial corrections

Version 8.0