

Nucala

1. NAME OF THE MEDICINAL PRODUCT

Nucala

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg mepolizumab. After reconstitution, each ml of solution contains 100 mg mepolizumab.

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection.

Lyophilised white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Severe Asthma

Nucala is indicated as an add-on treatment for severe refractory eosinophilic asthma in adult patients (see section 5.1).

Eosinophilic Granulomatosis with Polyangiitis

NUCALA is indicated for the treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).

4.2 Posology and method of administration

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

Posology

Adults

Severe Asthma

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

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

Eosinophilic Granulomatosis with Polyangiitis

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

Special populations

Paediatric population

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

Elderly patients

No dose adjustment is required for elderly patients (see section 5.2).

Renal and hepatic impairment

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

Method of administration

Nucala is for subcutaneous injection only and should be administered by a healthcare professional. It may be injected into the upper arm, thigh, or abdomen.

The powder should be reconstituted prior to administration and the reconstituted solution should be used immediately. For instructions on the reconstitution of the medicinal product before administration, see section 6.6.

Each vial of mepolizumab should be used for a single patient, and any remainder of the vial should be discarded.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Nucala

Asthma exacerbations

Mepolizumab should not be used to treat acute asthma exacerbations.

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

Corticosteroids

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

Hypersensitivity and administration-related reactions

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

Parasitic infections

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

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data (less than 300 pregnancy outcomes) from the use of mepolizumab in pregnant women.

Mepolizumab crosses the placental barrier in monkeys. Animal studies do not indicate reproductive toxicity (see section 5.3). The potential for harm to a human fetus is unknown.

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

Breast-feeding

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

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The table below presents the adverse reactions from placebo-controlled studies with frequencies from subjects receiving mepolizumab 100 mg SC (n=263), and from spontaneous post-marketing reports. Safety data is available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years).

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

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

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

**From spontaneous post marketing reporting.

*** The most common manifestations associated with reports of systemic non-allergic administration-related reactions were rash, flushing and myalgia; these manifestations were reported infrequently and in $< 1\%$ of subjects receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reaction

Local injection site reactions

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.

Paediatric population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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

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

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

4.9 Overdose

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Mepolizumab is 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. 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 signalling and reducing the production and survival of eosinophils.

Pharmacodynamic effects

In patients with severe refractory eosinophilic asthma, following a dose of 100 mg administered subcutaneously every 4 weeks for 32 weeks, blood eosinophils were reduced from a geometric mean count at baseline of 290 to 40 cells/ μ L at week 32 (n=182), a reduction of 84% compared to placebo.

This magnitude of blood eosinophils reduction was maintained in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

Following SC administration of mepolizumab 300 mg every 4 weeks for 52 weeks in subjects with EGPA, blood eosinophils were reduced to a geometric mean count of 38 cells/mL. There was a geometric mean

reduction of 83% compared with placebo and this magnitude of reduction was observed within 4 weeks of treatment [see *Clinical efficacy*].

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to mepolizumab following treatment. In the placebo-controlled trials, 15/260 (6%) of subjects treated with 100 mg dose subcutaneously had detectable anti-mepolizumab antibodies after having received at least one dose of mepolizumab.

The immunogenicity profile of mepolizumab in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

Neutralising antibodies were detected in one adult subject. Anti-mepolizumab antibodies did not discernibly impact the pharmacokinetics and pharmacodynamics of mepolizumab in the majority of patients and there was no evidence of a correlation between antibody titres and change in blood eosinophil level.

In subjects with EGPA receiving 300 mg of NUCALA, 1/68 (<2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any subjects with EGPA.

The reported frequency of anti-mepolizumab antibodies may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentration. 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.

Clinical efficacy

Severe Asthma

The efficacy of mepolizumab in the treatment of a targeted group of patients with severe refractory eosinophilic asthma was evaluated in 3 randomised, double-blind, parallel-group clinical studies of between 24-52 weeks duration, in patients aged 12 years and older. These patients either remained uncontrolled (at least two severe exacerbations in the previous 12 months) on their current standard of care, including at least high doses of inhaled corticosteroids (ICS) plus an additional maintenance treatment(s), or were dependent on systemic corticosteroids. Additional maintenance treatments included long-acting beta₂-adrenergic agonists (LABA), leukotriene modifiers, long-acting muscarinic antagonists (LAMA), theophylline, and oral corticosteroids (OCS).

The two exacerbations studies MEA112997 and MEA115588 enrolled a total of 1192 patients, 60% females, with a mean age of 49 years (range 12– 82). The proportion of patients on maintenance OCS was 31% and 24%, respectively. Patients were required to have a history of two or more severe asthma exacerbations requiring oral or systemic corticosteroid treatment in the past 12 months and reduced lung function at baseline (pre-bronchodilator FEV₁<80% in adults and <90% in adolescents). The mean number of exacerbations in the previous year was 3.6 and the mean predicted pre-bronchodilator FEV₁ was 60%. Patients continued to receive their existing asthma medicine during the studies.

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

Dose-ranging efficacy MEA112997 (DREAM) study

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

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

	Intravenous mepolizumab			Placebo
	75mg n=153	250mg n=152	750mg n=156	n= 155
Exacerbation rate/year	1.24	1.46	1.15	2.40
Percent reduction	48%	39%	52%	
Rate ratio (95% CI)	0.52 (0.39, 0.69)	0.61(0.46, 0.81)	0.48 (0.36, 0.64)	
p-value	<0.001	<0.001	<0.001	-

Exacerbation reduction MEA115588 (MENSA) study

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

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

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

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Primary endpoint		
Frequency of clinically significant exacerbations		
Exacerbation rate per year	0.83	1.74
Percent reduction	53%	-
Rate ratio (95% CI)	0.47 (0.35, 0.64)	
p-value	<0.001	
Secondary endpoints		
Frequency of exacerbations requiring hospitalisations/emergency room visits		
Exacerbation rate per year	0.08	0.20
Percent reduction	61%	-
Rate ratio (95% CI)	0.39 (0.18, 0.83)	
p-value	0.015	
Frequency of exacerbations requiring hospitalisation		
Exacerbations rate per year	0.03	0.10
Percent reduction	69%	-
Rate ratio (95% CI)	0.31 (0.11, 0.91)	
p-value	0.034	
Pre-bronchodilator FEV₁ (mL) at week 32		
Baseline (SD)	1730 (659)	1860 (631)

	Mepolizumab 100 mg (subcutaneous) N= 194	Placebo N= 191
Mean change from baseline (SE)	183 (31)	86 (31)
Difference (mepolizumab vs. placebo)	98	
95% CI	(11, 184)	
p-value	0.028	
St. George's Respiratory Questionnaire (SGRQ) at week 32		
Baseline (SD)	47.9 (19. 5)	46.9 (19.8)
Mean change from baseline (SE)	-16.0 (1.1)	-9.0 (1.2)
Difference (mepolizumab vs. placebo)	-7.0	
95% CI	(-10.2, -3.8)	
p-value	<0.001	

Reduction of exacerbation rate by baseline blood eosinophil count

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

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

	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
MEA112997+MEA115588		
<150 cells/μL		
n	123	66
Exacerbation rate per year	1.16	1.73
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.67 (0.46,0.98)	---
150 to <300 cells/μL		
n	139	86
Exacerbation rate per year	1.01	1.41
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.72 (0.47,1.10)	---
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)	---
$\geq$500 cells/μL		
n	162	116
Exacerbation rate per year	0.67	2.49
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.27 (0.19,0.37)	---

Oral corticosteroid reduction study MEA115575 (SIRIUS)

MEA115575 evaluated the effect of mepolizumab 100 mg administered subcutaneously on reducing the requirement for maintenance oral corticosteroids (OCS) while maintaining asthma control in subjects with severe refractory eosinophilic asthma. Patients had a blood eosinophil count of $\geq$ 150/ μ L at baseline or a

blood eosinophil count of $\geq 300/\mu\text{L}$ in the 12 months prior to screening. Patients were administered mepolizumab or placebo treatment once every 4 weeks over the treatment period. Patients continued to receive their existing asthma medicine during the study with the exception of their OCS dose which was reduced every 4 weeks during the OCS reduction phase (Weeks 4-20), as long as asthma control was maintained.

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

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

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

	ITT Population	
	Mepolizumab 100 mg (subcutaneous) N= 69	Placebo N= 66
Primary endpoint		
Percent reduction in OCS from baseline (weeks 20-24)		
90% - 100%	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 (weeks 20-24)		
Reduction in the daily OCS dose to 0 mg/d	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0.414	
Reduction in the daily OCS dose to $\leq 5\text{mg/day}$	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	
p-value	0.025	
Median % reduction in daily OCS dose from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

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

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

Paediatric population

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

Eosinophilic Granulomatosis with Polyangiitis

A total of 136 subjects with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial (NCT #02020889). Subjects received 300 mg of NUCALA or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. Starting at Week 4, OCS was tapered during the treatment period at the discretion of the investigator. The co-primary endpoints were the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of subjects in remission at both Week 36 and Week 48 of treatment. The BVAS is a clinician-completed tool to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes.

The demographics and baseline characteristics of subjects in this trial are provided in Table 5.

Table 5. Demographics and Baseline Characteristics in EGPA

	N = 136
Mean age (y)	48.5
Female, n (%)	80 (59)
White, n (%)	125 (92)
Duration (y) of EGPA, mean (SD)	5.5 (4.63)
History of ≥ 1 confirmed relapse in past 2 years, n (%)	100 (74)
Refractory disease, n (%)	74 (54)
Recurrence of EGPA symptoms, n (%)	68 (50)
Failed induction treatment, n (%)	6 (4)
Baseline oral corticosteroid ^a daily dose (mg), median (range)	12 (7.5-50)
Receiving immunosuppressive therapy ^b , n (%)	72 (53)

^a Prednisone or prednisolone equivalent.

^b e.g., Azathioprine, methotrexate, mycophenolic acid.

EGPA = eosinophilic granulomatosis with polyangiitis, SD = standard deviation.

Remission

Subjects receiving 300 mg of NUCALA achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of subjects receiving 300 mg of NUCALA achieved remission at both Week 36 and Week 48 compared with placebo (Table 6). Results of the components of remission are also shown in Table 6. In addition, significantly more subjects receiving 300 mg of NUCALA achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for 300 mg of NUCALA versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).

Table 6. Remission and Components of Remission in EGPA

	Remission (OCS $\leq$4 mg/day + BVAS = 0)		OCS $\leq$4 mg/day		BVAS = 0	
	Placebo n = 68	NUCALA 300 mg n = 68	Placebo n = 68	NUCALA 300 mg n = 68	Placebo n = 68	NUCALA 300 mg n = 68
Accrued duration over 52 weeks, n (%)						
0	55 (81)	32 (47)	46 (68)	27 (40)	6 (9)	3 (4)
>0 to <12 weeks	8 (12)	8 (12)	12 (18)	5 (7)	15 (22)	13 (19)
12 to <24 weeks	3 (4)	9 (13)	6 (9)	12 (18)	11 (16)	5 (7)
24 to <36 weeks	0	10 (15)	2 (3)	10 (15)	17 (25)	2 (3)
$\geq$ 36 weeks	2 (3)	9 (13)	2 (3)	14 (21)	19 (28)	45 (66)
Odds ratio (mepolizumab/placebo) ^a (95% CI)		5.9 (2.7, 13.0)		5.1 (2.5, 10.4)		3.7 (1.8, 7.6)
Proportion of subjects at both Weeks 36 and 48						
Subjects, n (%)	2 (3)	22 (32)	7 (10)	28 (41)	23 (34)	34 (50)
Odds ratio (mepolizumab/placebo) ^a (95% CI)		16.7 (3.6, 77.6)		6.6 (2.6, 17.1)		1.9 (0.9, 4.2)

^a An odds ratio >1 favors mepolizumab.

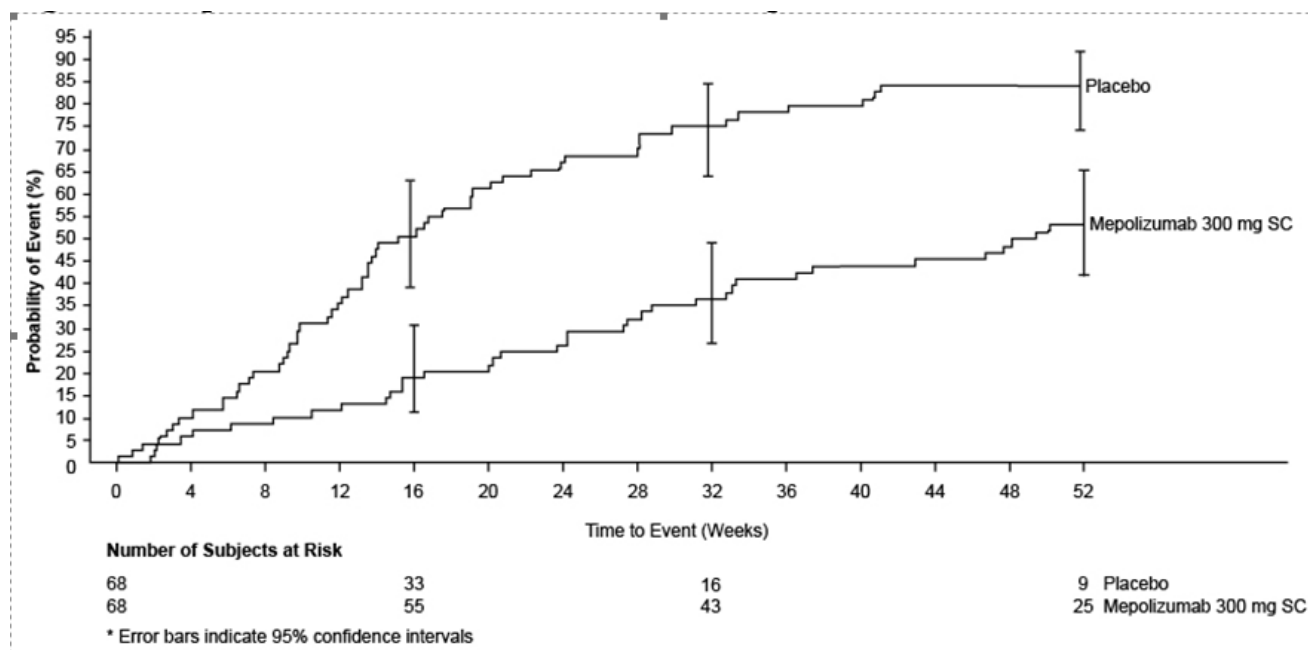
EGPA = eosinophilic granulomatosis with polyangiitis, OCS = oral corticosteroid, BVAS = Birmingham Vasculitis Activity Score.

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone $\leq$ 7.5 mg/day.

Relapse

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 hospitalization) was significantly longer for subjects receiving 300 mg of NUCALA compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5) (Figure 2). Additionally, subjects receiving 300 mg of NUCALA had a reduction in rate of relapse compared with subjects receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for 300 mg of NUCALA compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with mepolizumab compared with placebo.

Figure 2. Kaplan-Meier Plot of Time to First Relapse in EGPA



Corticosteroid Reduction

Subjects receiving 300 mg of NUCALA had a significantly greater reduction in average daily OCS dose compared with subjects receiving placebo during Weeks 48 to 52 (Table 7).

Table 7. Average Daily Oral Corticosteroid Dose during Weeks 48 to 52 in EGPA

	Number (%) of Subjects	
	Placebo n = 68	NUCALA 300 mg n = 68
0	2 (3)	12 (18)
>0 to ≤4.0 mg	3 (4)	18 (26)
>4.0 to ≤7.5 mg	18 (26)	10 (15)
>7.5 mg	45 (66)	28 (41)
Comparison: mepolizumab/placebo ^a		
Odds ratio ^b		0.20
95% CI		0.09, 0.41

^a Analyzed using a proportional odds model with covariates of treatment group, baseline oral corticosteroid daily dose, baseline Birmingham Vasculitis Activity Score, and region.

^b An odds ratio <1 favors mepolizumab.

Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6, a 6-item questionnaire completed by the subject, was developed to measure the adequacy of asthma control and change in asthma control. The on-treatment ACQ-6 responder rate during Weeks 48 to 52 (defined as a decrease in score of 0.5 or more compared with baseline) was 22% for 300 mg of NUCALA and 16% for placebo (OR 1.56; 95% CI: 0.63, 3.88 for 300 mg of NUCALA compared with placebo).

5.2 Pharmacokinetic properties

Following subcutaneous dosing in patients with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 mg to 250 mg.

The pharmacokinetic properties of mepolizumab observed in subjects with EGPA were similar to the pharmacokinetic properties observed in subjects with severe asthma.

Systemic exposure following administration of mepolizumab 300 mg subcutaneously in subjects with EGPA was approximately 3 times that of mepolizumab 100 mg administered subcutaneously in subjects with severe asthma (Trial 2).

Absorption

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

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

Distribution

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

Biotransformation

Mepolizumab is a 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 ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis estimated mepolizumab systemic clearance was 3.1 mL/day/kg.

Special populations

Elderly patients (≥ 65 years old)

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

Renal impairment

No formal studies have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, no dose adjustment is required in patients with creatinine clearance values between 50-80 mL/min. There are limited data available in patients with creatinine clearance values < 50 mL/min.

Hepatic impairment

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

Paediatric population

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

5.3 Preclinical safety data

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

Animal toxicology and/or pharmacology

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

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

Fertility

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

Pregnancy

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Sodium phosphate dibasic heptahydrate
Polysorbate 80
Hydrochloric Acid
Water for Injection

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the label and packaging

After reconstitution

Chemical and physical stability of the reconstituted medicinal product have been demonstrated for 8 hours when stored below 30°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of user.

6.4 Special precautions for storage

Store below 25°C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear, colourless 10 mL type I glass vial, with bromobutyl rubber stopper and a grey aluminium overseal with a plastic flip-cap containing 100 mg powder for solution for injection.

Pack sizes:

1 vial

Multipack comprising 3 (3 packs of 1) vials

Not all pack-sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution should be carried out under aseptic conditions.

Instructions for reconstitution for each vial

Reconstitute the contents of the vial with 1.2 mL of sterile water for injections preferably using a 2 to 3 mL syringe and a 21gauge needle. The stream of sterile water should be directed vertically, onto the centre of the lyophilised cake. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 10 seconds with circular motion at 15-second intervals until the powder is dissolved.

*Note: The reconstituted solution **must not be shaken** during the procedure as this may lead to product foaming or precipitation. Reconstitution is typically complete within 5 minutes after the sterile water has been added, but it may take additional time.*

1. If a mechanical reconstitution device (swirler) is used to reconstitute Nucala, reconstitution can be accomplished by swirling at 450 rpm for no longer than 10 minutes. Alternatively, swirling at 1000 rpm for no longer than 5 minutes is acceptable.
2. Following reconstitution, Nucala should be visually inspected for particulate matter and clarity prior to use. The solution should be clear to opalescent, and colourless to pale yellow or pale brown, free of visible particles. Small air bubbles, however, are expected and acceptable. If particulate matter remains in the solution or if the solution appears cloudy or milky, the solution must not be used.
3. The reconstituted solution, if not used immediately must be :
 - Protected from sunlight
 - Stored below 30°C, not frozen
 - Discarded if not used within 8 hours of reconstitution

Instructions for administration

1. For subcutaneous administration a 1 mL polypropylene syringe fitted with a disposable needle 21 gauge to 27 gauge x 0.5 inch (13 mm) should preferably be used.
2. Just prior to administration, remove 1 mL of reconstituted Nucala. Do not shake the reconstituted solution during the procedure as this could lead to product foaming or precipitation.
3. Administer the 1 mL injection (equivalent to 100 mg mepolizumab) subcutaneously into the upper arm, thigh, or abdomen.

Disposal

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

7. MANUFACTURER

GlaxoSmithKline Manufacturing S.p.A.,
Strada Provinciale Asolana, San Polo di Torrile, Parma, Italy

8. LICENSE HOLDER AND IMPORTER

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

9. LICENSE NUMBERS

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