NUCALA

Mepolizumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

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

CLINICAL INFORMATION

Indications

Severe Eosinophilic Asthma

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

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)
NUCALA is indicated as add-on maintenance treatment of severe chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

NUCALA is indicated as add-on treatment of Eosinophilic Granulomatosis with Polyangiitis (EGPA) in adult patients.

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.

Dosage and Administration

Pharmaceutical form:

Solution for injection in a pre-filled pen (auto-injector)

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

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

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

Populations

Severe Eosinophilic asthma

Adults and Adolescents (12 years and older)

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

CRSwNP

Adults

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

Children

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

EGPA

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

Adults

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

EGPA: *NUCALA* is not indicated in patients under 18 years of age.

Children (up to 12 years of age)

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

HES

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

Adults

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

Children

The safety and efficacy of *NUCALA* have not been established in children.

Elderly (65 years or older)

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

Renal Impairment

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

Hepatic Impairment

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

Contraindications

Hypersensitivity to mepolizumab or to any of the excipients.

Warnings and Precautions

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.

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.

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.

Parasitic Infections

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

Life-threatening HES

Nucala has not been studied in patients with life-threatening manifestations of HES.

Interactions

No formal interaction studies have been performed with *NUCALA*.

Pregnancy and Lactation

Fertility

There are no fertility data in humans. Animal studies showed no adverse effects of anti-IL-5 treatment on fertility (see *Non-Clinical Information*).

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 *Non-Clinical Information*). 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.

Lactation

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

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

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*.

Adverse Reactions

Clinical trial data

Severe asthma

The safety of *NUCALA* was studied in a clinical development program in adolescents and adults with severe eosinophilic asthma which included 3 randomised, placebo-controlled, multicentre studies (n=1327). Subjects received either subcutaneous (SC) or intravenous (IV) mepolizumab or placebo during clinical studies of 24-52 weeks duration. Adverse reactions associated with *NUCALA* 100 mg administered subcutaneously (n=263) are presented in the table below. The safety profile of *NUCALA* in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies was similar to that observed in the placebo-controlled studies.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000).

System Organ Class	**Adverse Reactions**	**Frequency**
Infections & Infestations	Pharyngitis	Common
	Lower respiratory tract infection	Common
	Urinary tract infection	Common
Nervous System Disorders	Headache	Very common
Respiratory, Thoracic & Mediastinal Disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common

System Organ Class	Adverse Reactions	Frequency
Skin and subcutaneous tissue disorders	Eczema	Common
Musculoskeletal and connective tissue disorders	Back Pain	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
General disorders and administration site conditions	Pyrexia Injection site reactions Administration-related reactions (systemic non-allergic)***	Common Common 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 *Warnings and Precaution*s.

**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 2 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

The clinical trial data currently available in paediatric patients is too limited to characterise the safety profile of mepolizumab in this population (see *Pharmacodynamics*). However, the frequency, type and severity of adverse reactions in the paediatric population are expected to be similar to those seen in adults.

CRSwNP

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

Table 1: On-Treatment Adverse Events with *NUCALA* with Greater than or Equal to 3% Incidence and More Common than Placebo in Subjects with CRSwNP (Study 205687)

Adverse Event	*NUCALA* (Mepolizumab 100 mg Subcutaneous) (n = 206) %	Placebo (n = 201) %
Any	82	84
Nasopharyngitis	25	23
Oropharyngeal pain	8	5
Athralgia	6	2
Abdominal pain upper	3	2
Pyrexia	3	2
Diarrhoea	3	2
Rash	3	<1
Nasal dryness	3	<1

EGPA

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

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 *Clinical Trials*). 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-week study in subjects with HES (300 mg *NUCALA* n= 54, placebo n= 54), no additional adverse reactions were identified to those reported for the severe asthma studies. The safety profile of *NUCALA* in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

Table 3: On-Treatment Adverse Events with *NUCALA* with Greater than or Equal to 10% Incidence and More Common than Placebo in Subjects with HES (Study 200622)

Adverse Event	*NUCALA* (Mepolizumab 300 mg Subcutaneous) (n = 54) %	Placebo (n = 54) %
Any	89	87
Upper respiratory tract infection	15	4
Pain in extremity	11	4

Post-marketing data

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

Overdose

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

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

Treatment

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

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC code

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

R03DX09

Mechanism of action

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

Pharmacodynamic effects

In clinical trials, reduction in blood eosinophils was observed consistently following treatment with *NUCALA*. The magnitude of reduction in the indicated populations described below were observed within 4 weeks of treatment and were maintained throughout the treatment period. The magnitude and duration of this reduction was dose-dependent.

In patients with severe asthma (adults/adolescents), following a dose of 100 mg administered subcutaneously every 4 weeks for 32 and 52 weeks respectively, the blood eosinophils were reduced to a geometric mean count of 40 cells/µL. This corresponds to a geometric mean reduction of 84% and 79% compared to placebo, respectively. This magnitude of blood eosinophils reduction was maintained in severe asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years) in open-label extension studies.

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

In patients with EGPA, following a dose of 300 mg administered subcutaneously every 4 weeks for 52 weeks, the blood eosinophils were reduced to a geometric mean count of 38 cells/µL. There was a geometric mean reduction of 83% compared to placebo.

In patients with HES, following a dose of 300 mg administered subcutaneously every 4 weeks for 32 weeks, the blood eosinophils were reduced to a geometric mean count of 70 cells/µL. There was a geometric mean reduction of 92% compared to placebo. This magnitude of reduction was maintained for a further 20 weeks in patients that continued *NUCALA* treatment in the open-label extension.

Immunogenicity

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

In subjects who received at least one dose of mepolizumab administered subcutaneously every four weeks, 15/260 (6%) (100 mg, severe 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 patients (n=102) treated for 20 weeks in open-label extension studies was similar to that observed in the placebo-controlled studies.

Across indications, neutralising antibodies were detected in one adult subject (with severe asthma). Anti-mepolizumab antibodies did not discernibly impact the PK or PD of mepolizumab treatment in the majority of patients and there was no evidence of a correlation between antibody titres and change in eosinophil level.

Pharmacokinetics

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

Mepolizumab pharmacokinetics were consistent in subjects with asthma, CRSwNP, EGPA or HES. Subcutaneous administration of *NUCALA* 300 mg had approximately three times the systemic exposure of mepolizumab 100 mg. In a PK comparability study conducted in healthy subjects, following administration of a single 100 mg subcutaneous dose, mepolizumab pharmacokinetics were comparable between formulations.

Absorption

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

Following a single subcutaneous administration in the abdomen, thigh or arm of healthy subjects, mepolizumab absolute bioavailability was 64%, 71% and 75%, respectively. In

patients with asthma, the absolute bioavailability of mepolizumab administered subcutaneously in the arm ranged from 74-80%. Following repeated subcutaneous administration every 4 weeks, there was approximately a two-fold accumulation at steady state.

Distribution

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

Metabolism

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

Elimination

Following a single intravenous administration to patients with asthma, the mean systemic clearance (CL) ranged from 1.9 to 3.3 mL/day/kg, with a mean terminal half-life of approximately 20 days. Following subcutaneous administration of mepolizumab, the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. In the population pharmacokinetic analysis, the 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 patients (>65 years old)

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

Paediatric population

There are limited pharmacokinetic data available in the paediatric population (59 subjects with eosinophilic esophagitis, 19 subjects with severe asthma). Of the 19 adolescents who received mepolizumab, 9 received *NUCALA* and the mean apparent clearance in these subjects was 35% less than that of adults.

Intravenous mepolizumab pharmacokinetics was evaluated by population pharmacokinetic analysis in a paediatric study conducted in subjects aged 2–17 years old with eosinophilic esophagitis. Paediatric pharmacokinetics was largely predictable from adults, after taking into account bodyweight. Mepolizumab pharmacokinetics in

adolescent subjects with severe eosinophilic asthma included in the phase 3 studies were consistent with adults.

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.

Clinical Studies

Severe 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 *NUCALA* administered once every 4 weeks by subcutaneous or intravenous injection in severe eosinophilic asthma patients not controlled on their standard of care [e.g. inhaled corticosteroids (ICS), oral corticosteroids (OCS), combination ICS and long-acting $beta_2$-adrenergic agonists (LABA), leukotriene modifiers, short-acting $beta_2$-adrenergic agonists (SABA)].

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 patients included in the Study MEA112997 and Study MEA115588 weigh ≥45kg. 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 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, results demonstrated that *NUCALA* significantly reduced 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 4).

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 *NUCALA* therapy. Results from this study were used to determine dose selection for the studies using subcutaneous *NUCALA* administration. *NUCALA* is not indicated for intravenous use and should only be administered by the subcutaneous route.

Table 4: 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 *NUCALA* as add-on therapy in 576 patients with severe eosinophilic asthma, defined as peripheral blood eosinophils greater than or equal to 150 cells/µL at initiation of treatment or greater than or equal to 300 cells/µL within the past 12 months.

This study evaluated the frequency of clinically significant exacerbations of asthma, defined as: worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalisation and/or emergency department visits.

Patients were aged 12 years of age or older, with a history of two or more asthma exacerbations in the past 12 months and not controlled on their current asthma drug therapies [i.e. high-dose inhaled corticosteroids (ICS) in combination with at least

another controller such as long-acting beta$_2$-adrenergic agonists (LABA) or leukotriene modifiers]. Patients were allowed to be on oral corticosteroid therapy and continued to receive their existing asthma medication during the study. Severe eosinophilic asthma was defined as peripheral blood eosinophils greater than or equal to 150 cells/µL within 6 weeks of randomisation (first dose) or blood eosinophils greater than or equal to 300 cells/µL within the past 12 months of randomisation.

Patients received either *NUCALA* 100 mg administered subcutaneously (SC), *NUCALA* 75 mg administered intravenously (IV), or placebo treatment once every 4 weeks over 32 weeks. The primary endpoint 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 5 provides the results of the primary endpoint and secondary endpoints of MEA115588.

Table 5: Results of primary and secondary endpoints at Week 32 in the Intent to Treat population (MEA115588)

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

Reduction of exacerbation rate by baseline blood eosinophil count

Table 6 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 6: 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		
	Mepolizumab 75 mg IV/100 mg SC N=538	Placebo N=346
Rate ratio (95% CI)	0.62 (0.41,0.93)	---
≥500 cells/µL		
n	162	116
Exacerbation rate per year	0.67	2.49
Mepolizumab vs. placebo		
Rate ratio (95% CI)	0.27 (0.19,0.37)	---

Oral Corticosteroid Reduction (MEA115575)

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

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

The primary endpoint was the reduction in daily OCS dose (weeks 20-24) whilst maintaining asthma control compared with patients treated with placebo (see Table 7).

Table 7: Results of the primary and secondary endpoints in the Intent to Treat population (MEA115575).

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

To ≤5mg/day	37 (54%)	21 (32%)
Odds ratio (95% CI)	2.45 (1.12, 5.37)	
p-value	0.025	
Reduction in the daily OCS dose		
To 0 mg/Day	10 (14%)	5 (8%)
Odds ratio (95% CI)	1.67 (0.49, 5.75)	
p-value	0.414	
Median Percentage Reduction in Daily OCS Dose		
Median % reduction from baseline (95% CI)	50.0 (20.0, 75.0)	0.0 (-20.0, 33.3)
Median difference (95% CI)	-30.0 (-66.7, 0.0)	
p-value	0.007	

Additionally, health-related quality of life was measured using SGRQ. At Week 24, there was a statistically significant improvement in the mean SGRQ score for *NUCALA* compared with placebo: -5.8 (95% CI: -10.6, -1.0; P=0.019). At Week 24, the proportion of subjects with a clinically meaningful decrease in SGRQ score (defined as a decrease of at least 4 units from baseline) was greater for *NUCALA* (58%, 40/69) compared with placebo (41%, 27/66).

The long-term efficacy profile of *NUCALA* in severe 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

The safety and efficacy in paediatric patients younger than 12 years have not been established. There were 25 adolescents - 13 girls and 12 boys, 9 aged 12 -14 years and 16 aged 15-17 - years enrolled in study MEA115588. Of the total 25 subjects: 9 received placebo, 9 received mepolizumab 75 mg intravenously, and 7 received 100 mg subcutaneously. The same proportion of subjects (3/9) receiving placebo and mepolizumab intravenously reported clinically significant exacerbations; no exacerbations were reported in those receiving mepolizumab subcutaneously.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

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

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

Patients received a 100 mg dose of *NUCALA*, or placebo, administered subcutaneously once every 4 weeks in addition to background intranasal corticosteroid therapy and if required, saline nasal douching, occasional short courses of high dose OCS and/or antibiotics.

The demographics and baseline characteristics of patients in study 205687 are provided in Table 8 below:

Table 8 Demographics and baseline characteristics in CRSwNP

	N = 407
Age (y) of patients, mean (SD)	49 (13)
Female, n (%)	143 (35)
White, n (%)	379 (93)
Asian	13 (3)
Duration (y) of CRSwNP, mean (SD)	11.4 (8.39)
Patients with >= 1 previous surgery, n (%)	407 (100)
Patients with >= 3 previous surgeries, n (%)	124 (30)
OCS use for NP (≥1 course) in past 12 months, n (%)	197 (48)
Total endoscopic NP score[a b c], mean (SD), maximum score = 8	5.5 (1.29)
Nasal obstruction VAS score[a d], mean (SD), maximum score = 10	9.0 (0.83)
Overall VAS symptom score[a d], mean (SD), maximum score = 10	9.1 (0.74)
SNOT-22 total score[e], mean (SD), range 0-110	64.1 (18.32)
Composite VAS symptoms score[a], mean (SD), maximum score = 10	9.0 (0.82)
Loss of smell VAS score[a,d], mean (SD), maximum score = 10	9.7 (0.72)
Asthma, n (%)	289 (71)
AERD, n (%)	108 (27)
Geometric mean eosinophil count at baseline, cells/mcL (95% CI)	390 (360, 420)

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

[a] Higher scores indicate greater disease severity.

[b] As graded by independent blinded assessors

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

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

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

The co-primary endpoints were change from baseline in total endoscopic NP score at week 52 and change from baseline in mean nasal obstruction VAS score during weeks 49-52. Patients who received *NUCALA* had significantly greater improvements (decreases) in total endoscopic NP score at Week 52 and in nasal obstruction VAS score during weeks 49-52 compared to placebo (see Table 9).

Table 9: Analyses of co-primary endpoints (Intent To Treat population)

	Placebo (N=201)	***NUCALA* 100 mg SC (N=206)**
Total Endoscopic Score at week 52 [a]		
Median score at baseline (min, max)	6.0 (0, 8)	5.0 (2, 8)
Median change from baseline	0.0	-1.0
p-value [b]		<0.001
Adjusted treatment difference in medians (95% CI) [c]		-0.73 (-1.11, -0.34)
≥1-point improvement, n (%)	57 (28)	104 (50)
≥2-point improvement, n (%)	26 (13)	74 (36)
Nasal obstruction VAS score (weeks 49 to 52) [a]		
Median score at baseline (min, max)	9.14 (5.31, 10.00)	9.01 (6.54, 10.00)
Median change from baseline	-0.82	-4.41
p-value [b]		<0.001
Adjusted treatment difference in medians (95% CI) [c]		-3.14 (-4.09, -2.18)
>1-point improvement, n (%)	100 (50)	146 (71)
≥3-point improvement, n (%) [d]	73 (36)	124 (60)

a) Subjects with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty assigned their worst observed score prior to study withdrawal.
b) Based on Wilcoxon rank-sum test.
c) Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
d) A three-point improvement in Nasal Obstruction VAS has been identified as a meaningful within-patient change for this assessment.

All secondary endpoints were statistically significant and provided support for the co-primary endpoints. The key secondary endpoint was the time to first NP surgery up to Week 52 (see Figure 1). Data from the other secondary endpoints are presented in Table 10.

Time to First NP surgery

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

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

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

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

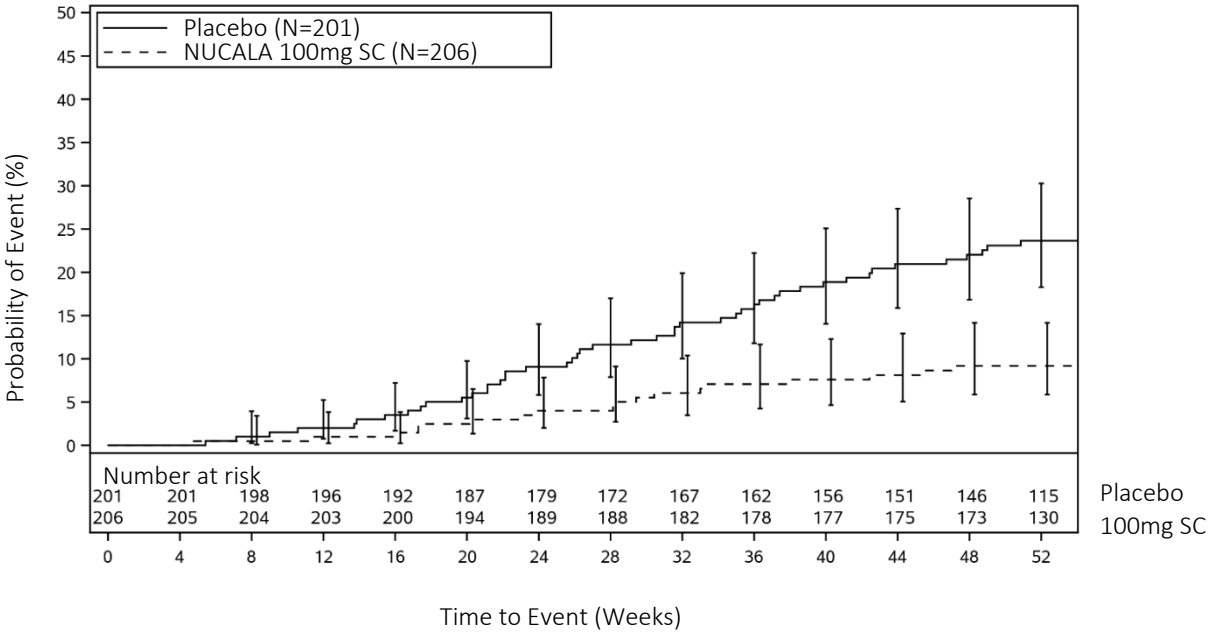


Table 10: Results of other secondary endpoints in the Intent to Treat population

	Placebo (N=201)	***NUCALA* (N=206)**
Overall VAS Score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.20 (7.21, 10.00)	9.12 (7.17, 10.00)
Median change from baseline	-0.90	-4.48
Unadjusted/adjusted p-value [b,c]		<0.001/0.003
Adjusted treatment difference in medians (95% CI) [d]		-3.18 (-4.10, -2.26)
⩾2.5-point improvement (%)	40	64
SNOT-22 Total Score at Week 52 [a, g]		
n	198	205
Median score at baseline (min, max)	64.0 (19, 110)	64.0 (17, 105)
Median change from baseline	-14.0	-30.0
Unadjusted/adjusted p-value [b,c]		<0.001/0.003
Adjusted treatment difference in medians (95% CI) [d]		-16.49 (-23.57, -9.42)
>=28-point improvement (%)[g]	32	54

Patients Requiring Systemic Steroids for Nasal Polyps up to Week 52		
Number of patients with ⩾1 course	74 (37)	52 (25)
Odds Ratio to Placebo (95% CI) [e]		0.58 (0.36, 0.92)
Unadjusted/adjusted p-value [c, e]		0.020/0.020
Composite VAS Score - Nasal Symptoms (Weeks 49-52) [a,f]		
Median score at baseline (min, max)	9.18 (6.03, 10.00)	9.11 (4.91, 10.00)
Median change from baseline	-0.89	-3.96
Unadjusted/adjusted p-value [b,c]		<0.001/0.020
Adjusted treatment difference in medians (95% CI) [d]		-2.68 (-3.44, -1.91)
>=2-point improvement (%)[h]	40	66
Loss of Smell VAS Score (Weeks 49-52) [a]		
Median score at baseline (min, max)	9.97 (6.69, 10.00)	9.97 (0.94, 10.00)
Median change from baseline	0.00	-0.53
Unadjusted/adjusted p-value [b,c]		<0.001/0.020
Adjusted treatment difference in medians (95% CI) [d]		-0.37 (-0.65, -0.08)
>=3-point improvement (%)[h]	19	36

[a] Patients with nasal surgery/sinuplasty prior to visit assigned their worst observed score prior to nasal surgery/sinuplasty. Those who withdrew from study with no nasal surgery/sinuplasty assigned their worst observed score prior to study withdrawal.
[b] Based on Wilcoxon rank-sum test.
[c] Multiplicity controlled through testing of secondary endpoints following a pre-defined hierarchy.
[d] Quantile regression with covariates of treatment group, geographic region, baseline score and log(e) baseline blood eosinophil count.
[e] Analysis using logistic regression model with covariates of treatment group, geographic region, number of OCS courses for NP in last 12 months (0, 1, >1 as ordinal), baseline total ENP score (centrally read), baseline nasal obstruction VAS score and log(e) baseline blood eosinophil count.
[f] Composite VAS score of nasal obstruction, nasal discharge, mucus in the throat and loss of smell.
[g] Improvement was seen in all 6 domains of symptoms and impact associated with CRSwNP.
[h] Threshold for improvement for each endpoint, has been identified as a meaningful within-patient change for this assessment.

Endpoints in patients with Asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received *NUCALA* 100 mg compared with placebo.

Additionally in these patients, there was a greater improvement from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for *NUCALA* 100 mg compared with placebo (median change [Q1, Q3] of -0.80 [-2.20, 0.00] and 0.00 [-1.10, 0.20], respectively).

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

MEA115921 was a randomised, double-blind, placebo-controlled, 52-week study which evaluated 136 patients ≥18 years old with relapsing or refractory EGPA and who were on

stable oral corticosteroid therapy (OCS; ≥7.5 to ≤50 mg/day prednisolone/prednisone). 53% (n=72) were also on concomitant stable immunosuppressant therapy.

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

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

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 and 74% 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 *NUCALA* 300 mg achieved a significantly greater accrued time in remission. Additionally, compared to placebo, a significantly higher proportion of subjects receiving *NUCALA* 300 mg achieved remission at both Week 36 and Week 48 (Table 11).

Table 11: Analyses of Co-Primary Endpoints (ITT Population)

	Number (%) of Subjects	
	Placebo N=68	***NUCALA* 300 mg N=68**
Accrued Duration of Remission Over 52 Weeks		
0 weeks	55 (81)	32 (47)
>0 to <12 weeks	8 (12)	8 (12)
12 to <24 weeks	3 (4)	9 (13)
24 to <36 weeks	0	10 (15)
≥36 weeks	2 (3)	9 (13)
Odds ratio (mepolizumab/placebo)		5.91
95% CI	---	2.68, 13.03
p-value	---	<0.001
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 *NUCALA*

Subjects receiving *NUCALA* 300 mg achieved significantly greater accrued time in remission ($p<0.001$), and a higher proportion of subjects receiving *NUCALA* 300 mg were in remission at both Week 36 and Week 48 ($p<0.001$), compared to placebo using the secondary endpoint remission definition of 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 ≥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 *NUCALA* 300 mg ($p<0.001$). Additionally, subjects receiving *NUCALA* had a 50% reduction in annualised relapse rate compared with placebo: 1.14 vs 2.27, respectively.

Oral Corticosteroid Reduction

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

Hypereosinophilic Syndrome (HES)

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

or placebo administered subcutaneously once every 4 weeks while continuing their stable HES therapy. Standard HES therapy could include OCS and immunosuppressive or cytotoxic therapy. The same regimen of HES therapy must have been maintained throughout the 32-week Treatment Period unless there was worsening of symptom(s) that required an increase in therapy which subject was considered to have a flare**.** Subjects entering the study were diagnosed with HES for at least 6 months at randomisation, had experienced at least two HES flares within the past 12 months and had a blood eosinophil count ≥ 1000 cells/μL during screening. Patients who were FIP1L1-PDGFRα kinase-positive were excluded from the study. Patients with clinically significant cardiac damage, current active liver or biliary disease (with ALT >2.5xULN or ALT>5xULN if HES with liver manifestations or Bilirubin >1.5xULN) or life-threatening HES were excluded from the study. 4 adolescents were enrolled, one adolescent received 300 mg of *NUCALA*, and 3 adolescents received placebo for 32 weeks.

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 receiving blinded active OCS due to increased blood eosinophils (on ≥2 occasions).

The primary analysis compared subjects who experienced a HES flare or withdrew from the study in the *NUCALA* and placebo treatment groups. Over the 32-week treatment period, 50% fewer subjects experienced a HES flare or withdrew from the study when treated with 300 mg *NUCALA* compared with placebo; 28% versus 56% respectively (OR 0.28, 95% CI: 0.12, 0.64) (see Table 12).

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 13).

Table 12: Results of primary endpoint/analysis in the Intent to Treat population (Study 200622)

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

CMH =Cochran-Mantel-Haenszel

Time to First Flare

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

Figure 2: Kaplan Meier Curve for Time to First HES Flare

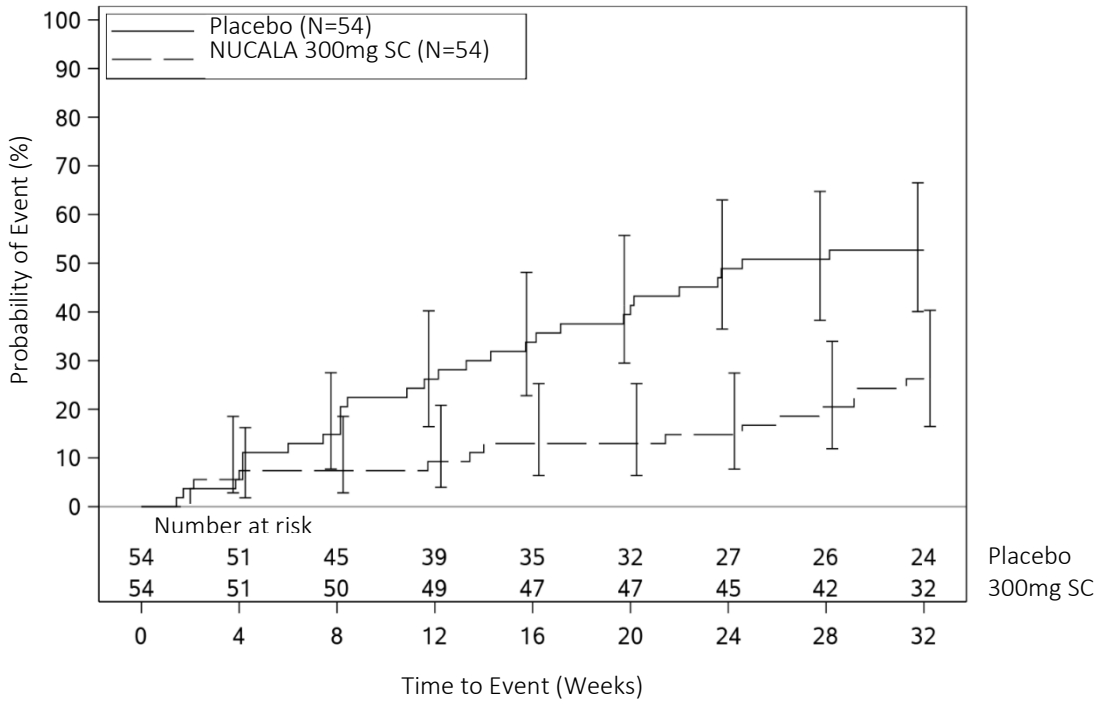


Table 13: Results of other secondary end-points in the Intent to Treat population (Study 200622)

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

[a] adjusted p-values based on pre-specified hierarchy of endpoints.
[b] Patients with missing data included with worst observed value.
CMH =Cochran-Mantel-Haenszel

HES Open-Label extension

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

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

Non-Clinical Information

Carcinogenesis/mutagenesis

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

Reproductive Toxicology

Fertility

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

Pregnancy

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

Animal toxicology and pharmacology

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

Eosinophils have been associated with immune system responses to some parasitic infections. Studies conducted in mice treated with anti-IL-5 antibodies or genetically deficient in IL-5 or eosinophils have not shown impaired ability to clear parasitic infections.

PHARMACEUTICAL INFORMATION

List of Excipients

Sucrose

Sodium phosphate dibasic heptahydrate

Citric acid monohydrate

Polysorbate 80

EDTA disodium dihydrate

Water for injection

Shelf Life

The expiry date is indicated on the packaging.

Storage

Store in refrigerator (2-8ºC). Do not freeze.

Protect from light. Store in the original carton until use.

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

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

Nature and Contents of Container

Solution for injection in pre-filled pen (auto-injector)

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

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

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

Incompatibilities

No incompatibilities have been identified.

Use and Handling

See the Instructions for Use leaflet for complete administration instructions with illustrations.

Not all presentations are available in every country.

Product Registrant: GlaxoSmithKline Pte Ltd, 23 Rochester Park, Singapore 139234

Version number: GDS14/IPI05a(SI)

Date of issue: 06 August 2020

[GSK logo]

PATIENT INFORMATION LEAFLET

NUCALA 100 mg in 1 mL pre-filled pen (auto-injector)
NUCALA 100 mg in 1 mL pre-filled syringe (safety syringe)

Mepolizumab

Read all of this leaflet carefully before you start using this medicine.

Keep this leaflet. You may need to read it again.

If you have any questions, ask your doctor or nurse.

If you notice any side effects that bother you or do not go away, please tell your doctor or nurse.

In this leaflet

1. What NUCALA is and what it is used for

NUCALA contains the active substance **mepolizumab**, a *monoclonal antibody*, a type of protein designed to recognise a specific target substance in the body. It is used to treat severe asthma in adults and adolescents and in EGPA (Eosinophilic Granulomatosis with Polyangiitis) in adults. NUCALA is also used to treat HES (Hypereosinophilic Syndrome) and CRSwNP (Chronic Rhinosinusitis with Nasal Polyps) in adults.

Mepolizumab, the active substance in NUCALA lowers the number of *eosinophils* **(a type of white blood cell)** in the bloodstream, lungs and tissues.

Severe Eosinophilic Asthma

Some people with severe asthma have too many *eosinophils* in the blood and lungs. This condition is called *eosinophilic asthma* – the type of asthma NUCALA can treat.

If your asthma is not well controlled by your existing treatment, NUCALA can reduce your number of asthma attacks.

If you are taking medicines called *oral corticosteroids*, NUCALA can also help reduce the daily dose you need to control your asthma.

Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)

CRSwNP is a condition in which people have too many eosinophils in the blood, nose and sinuses. This can cause symptoms such as a blocked nose and loss of smell, and soft jelly-like growths (called nasal polyps) to form inside the nose.

NUCALA reduces the number of eosinophils in the blood and can reduce the size of your polyps, relieves your nasal congestion and helps prevents surgery for nasal polyps.

NUCALA can also help reduce the need for oral corticosteroids to control your symptoms.

EGPA (Eosinophilic Granulomatosis with Polyangiitis)

EGPA is a condition where people have too many eosinophils in the blood and tissues and also have inflammation of the blood vessels (vasculitis). EGPA most commonly affects the lungs and sinuses but often affects other organs including the skin, heart, kidneys, nerves or bowels.

NUCALA can reduce the number of eosinophils in the blood and can reduce symptoms and delay a flare-up of these symptoms in people who are already taking corticosteroids.

NUCALA can also help reduce the daily dose of corticosteroids you need to control your symptoms.

Hypereosinophilic Syndrome (HES)

Hypereosinophilic Syndrome (HES), is a condition in which there are a high number of eosinophils in the blood. These cells can damage organs in the body, particularly the heart, lungs, nerves, and skin**.**

NUCALA reduces the number of eosinophils in the blood and helps reduce symptoms and prevents flares.

2. Before you are given NUCALA

You must not receive NUCALA

If you are allergic to mepolizumab or any of the other ingredients of this medicine (listed in section 6).

Check with your doctor if you think this applies to you.

Take special care with NUCALA

NUCALA should not be used to treat sudden breathing problems that may occur with asthma.

Some people get asthma-related side effects, or their asthma may become worse, during treatment with NUCALA.

Tell your doctor or nurse if your asthma remains uncontrolled, or gets worse, after you start NUCALA treatment.

Allergic and injection site reactions

Medicines of this type (*monoclonal antibodies*) can cause severe allergic reactions when injected into the body.

Tell your doctor before you are given NUCALA if you may have had a similar reaction to any injection or medicine.

Parasitic infections

NUCALA may weaken your resistance to infections caused by parasites. If you have a parasitic infection, it should be treated before you start treatment with NUCALA.
If you live in a region where these infections are common or if you are travelling to such a region: **Check with your doctor if you think any of these may apply to you.**

Children

This medicine is not intended for use in children below the age of 12 years for the treatment of severe asthma or in children below 18 years of age for the treatment of EGPA, CRSwNP or HES.

Other medicines and NUCALA

Tell your doctor if you are taking, have recently taken or might take any other medicines.

Other medicines for asthma, CRSwNP, EGPA or HES

- ✘ Don't suddenly stop taking your medicines for your asthma, CRSwNP, EGPA or HES once you have started NUCALA. These medicines (especially ones called corticosteroids) must be stopped gradually, under the direct supervision of your doctor and dependant on your response to NUCALA.

Pregnancy and breast-feeding

If you are pregnant, if you think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

It is not known whether the ingredients of NUCALA can pass into breast milk. If you are breast-feeding, you must check with your doctor before you use NUCALA.

Driving and using machines

The possible side effects of NUCALA are unlikely to affect your ability to drive or use machines.

3. How NUCALA is used

Solution for injection in pre-filled pen (auto-injector) or pre-filled syringe (safety syringe) (which can be given either by you, your caregiver or a doctor/nurse).

NUCALA is given by injection under your skin (subcutanous injection)
Your doctor or nurse will decide if you or your caregiver can inject NUCALA. If appropriate, they will then provide training to show you or your caregiver the correct way to use NUCALA.

You can inject NUCALA under your skin in your stomach area (abdomen) or upper leg (thigh). Your caregiver can also inject NUCALA into your upper arm. You should not give injections into areas where the skin is tender, bruised, red, or hard.

Severe asthma

Adults and adolescents aged 12 years and over

The recommended dose is one 100 mg injection every four weeks.

CRSwNP

The recommended dose for adults is one 100 mg injection every four weeks.

EGPA

Adults

The recommended dose for adults is 300 mg (three 100 mg injections) every four weeks. If you need more than one injection to complete your dose, the injection sites should be at least 5 cm apart.

HES

Adults

The recommended dose for adults is 300 mg (three 100 mg injections) every four weeks.

If you need more than one injection to complete your dose, the injection sites should be at least 5 cm apart.

If a dose of NUCALA is missed

If you or your caregiver forget to give the injection of NUCALA using a pre-filled pen or pre-filled syringe:

> You should inject the next dose of NUCALA as soon as you remember. If you do not notice that you have missed a dose until it is already time for your next dose, then just inject the next dose as planned. If you are not sure what to do, ask your doctor, pharmacist or nurse.

Don’t stop NUCALA without advice

Do not stop injections of NUCALA unless your doctor advises you to. Interrupting or stopping the treatment with NUCALA may cause your symptoms to come back.

> **➔If your symptoms get worse while receiving injections of NUCALA, call your doctor.**

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The side effects caused by NUCALA are usually mild to moderate but can occasionally be serious.

Allergic reactions

Allergic reactions, which may be severe (e.g. anaphylaxis) to NUCALA are rare (they may affect up to 1 in 1000 people).
If you have any of the following symptoms after taking NUCALA:

- skin rash (hives) or redness
- swelling, sometimes of the face or mouth (angioedema)
- becoming very wheezy, coughing or having difficulty in breathing
- suddenly feeling weak or light-headed (may lead to collapse or loss of consciousness)

➔Stop using NUCALA and seek medical help immediately

Very common side effects

These may affect **more than 1 in 10** people:

- headache

Common side effects

These may affect **up to 1 in 10** people:

- chest infection- symptoms of which may include cough and fever (high temperature)
- urinary tract infection (blood in urine, painful and frequent urination, fever, pain in lower back)
- upper abdominal pain (stomach pain or discomfort in the upper area of the stomach)
- fever (high temperature)
- eczema (itchy red patches on the skin)
- injection-site reaction (pain, redness, swelling, itching, and burning sensation of the skin near where the injection was given)
- back pain
- pharyngitis (sore throat)
- nasal congestion (stuffy nose)

Rare side effects

These may affect **up to 1 in 1,000** people:

- allergic reactions which may be severe (e.g. anaphylaxis) (See earlier in **Section 4**).

➔ **Tell your doctor or pharmacist if any of the side effects listed becomes severe or troublesome, or if you notice any side effects not listed in this leaflet.**

5. How to Store NUCALA

Keep this medicine out of the sight and reach of children.

Do not use NUCALA after the expiry date which is stated on the label and carton after EXP. The expiry date refers to the last day of that month.

Store in refrigerator (2-8ºC). Do not freeze.

Store in the original carton to protect from light.

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

The pre-filled pen and pre-filled syringe can be removed from the refrigerator and kept in its unopened carton for up to 7 days at room temperature (up to 30°C), when protected from light.

6. Further information

What NUCALA contains

The active substance is mepolizumab.

Solution for injection in pre-filled pen (auto-injector) and pre-filled syringe (safety syringe)

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

Other ingredients are:
Sucrose, sodium phosphate dibasic heptahydrate, citric acid monohydrate, polysorbate 80, EDTA disodium dihydrate and Water for injection.

What NUCALA looks like and contents of the pack

Solution for injection in pre-filled pen (auto-injector)

NUCALA is supplied as a clear, colourless to pale yellow to pale brown solution in a 1 mL siliconised, Type I glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled as an auto-injector.

NUCALA is available in a pack containing 1 single-use pre-filled pen.

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

NUCALA is supplied as a clear, colourless to pale yellow to pale brown solution in a 1 mL siliconised, Type I glass syringe with 0.5 inch (12.7 mm), 29 gauge, stainless steel needle assembled with a needle guard.

NUCALA is available in a pack containing 1 single-use pre-filled syringe.

[GSK logo]

INSTRUCTIONS FOR USE

Solution for injection in pre-filled pen (auto-injector)

NUCALA pre-filled pen (auto-injector)

(*mepolizumab*)

Administer once every 4 weeks.

Follow these instructions on how to use the pre-filled pen. Failure to follow these instructions may affect proper function of the pre-filled pen. You should also receive training on how to use the pre-filled pen. NUCALA pre-filled pen is for use **under the skin only** (subcutaneous).

How to store NUCALA

- Keep refrigerated before use.
- Do not freeze
- Keep in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled pen may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton.
- Do not store it above 30°C.
- Safely throw it away if it has been removed from the refrigerator and not been used within 7 days.

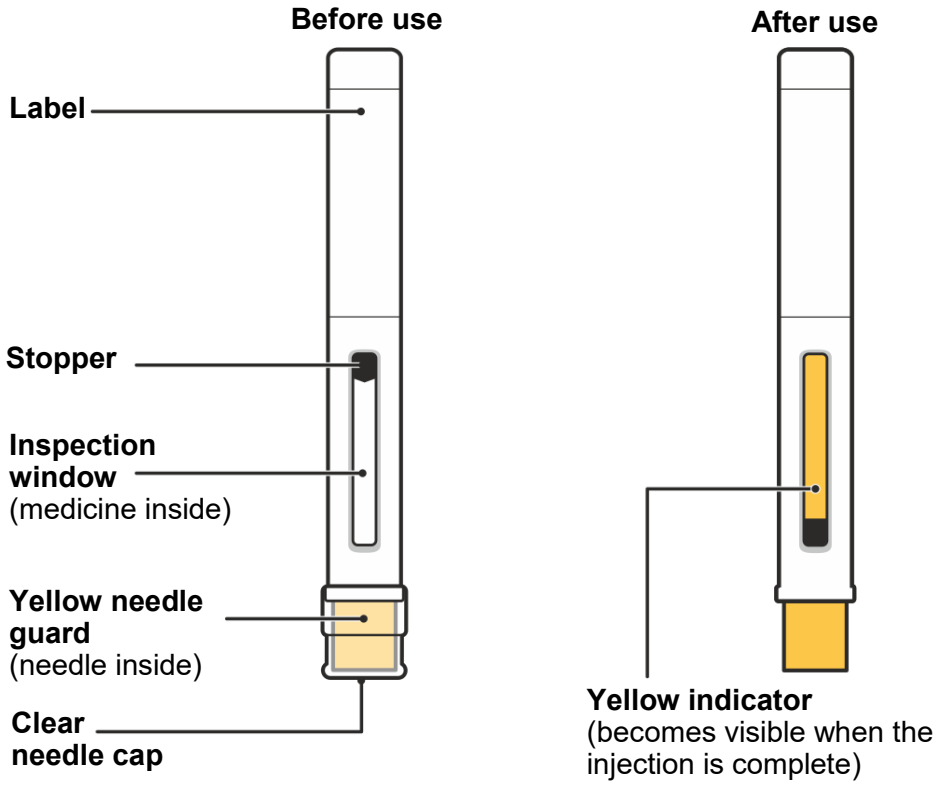
Before you use NUCALA

The pre-filled pen should be used only once and then discarded.

- **Do not** share your NUCALA pre-filled pen with another person.
- **Do not** shake the pen.
- **Do not** use the pen if dropped onto a hard surface.
- **Do not** use the pen if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled pen

Know your pre-filled pen



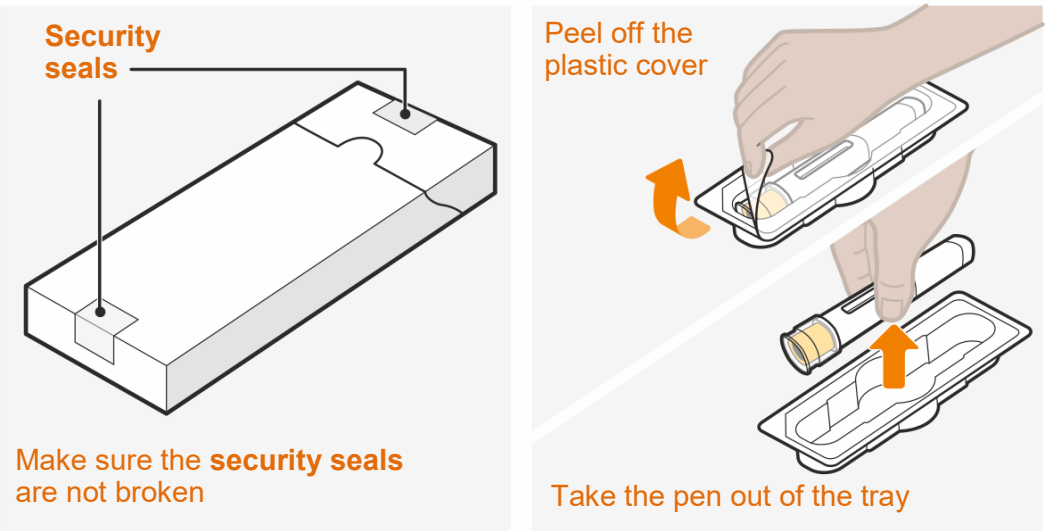
Prepare

1.Get ready what you need

- Find a comfortable, well-lit and clean surface. Make sure you have within reach:
  - NUCALA pre-filled pen
  - Alcohol wipe (not included)
  - Gauze pad or cotton wool ball (not included)

Do not perform the injection if you do not have all these.

2. Take out your pre-filled pen

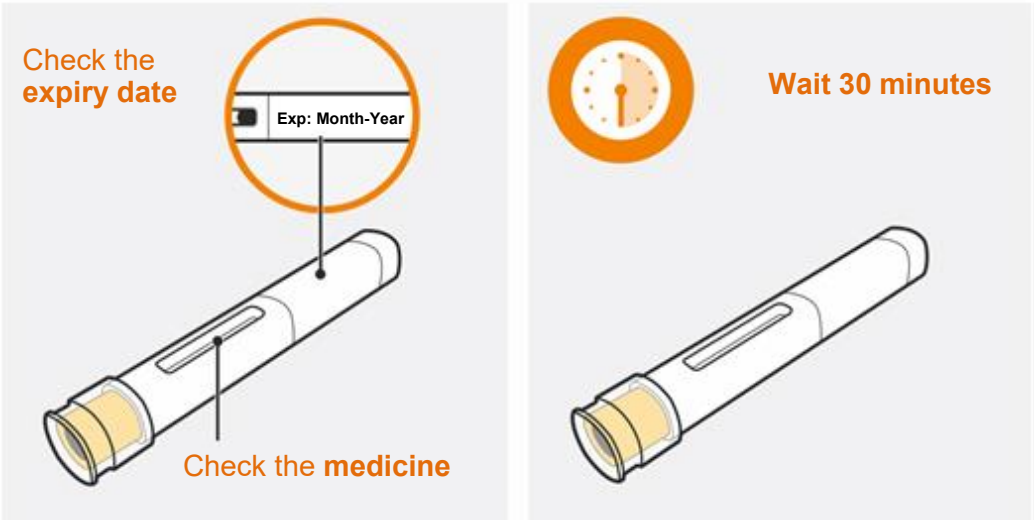


- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the pen, carefully take it out of the tray.
- Place the pen on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the pen if the security seal on the carton is broken.

Do not remove the needle cap at this stage.

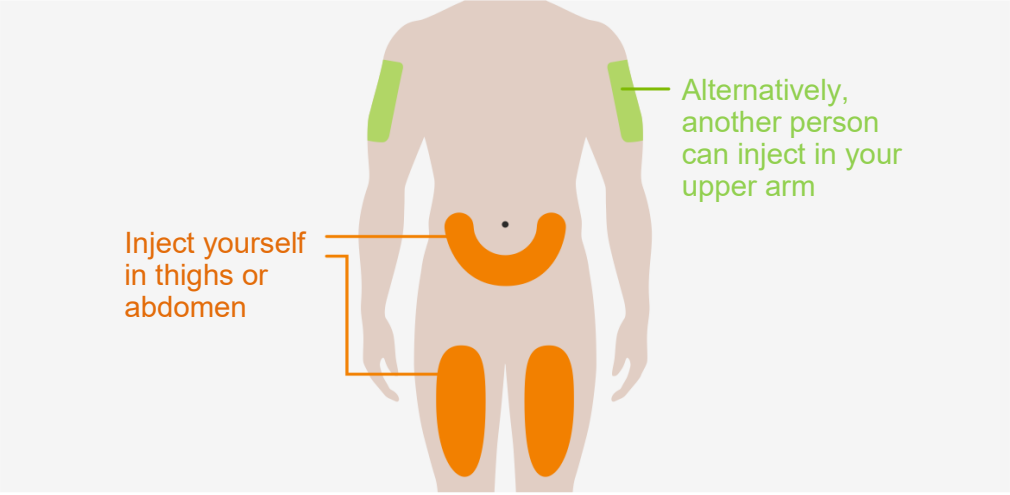
3. Inspect and wait 30 minutes before use



- Check the expiry date on the label of the pen.
- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the pen in a microwave, hot water, or direct sunlight.
Do not inject if the solution looks cloudy or discoloured, or has particles.
Do not use the pen if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step.

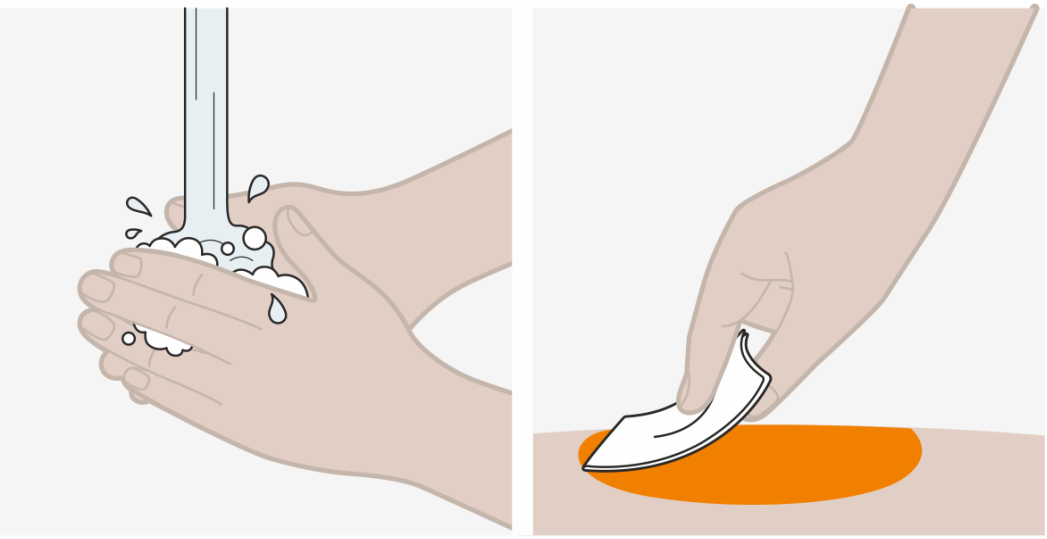
4. Choose your injection site



- You can inject NUCALA into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.
Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site

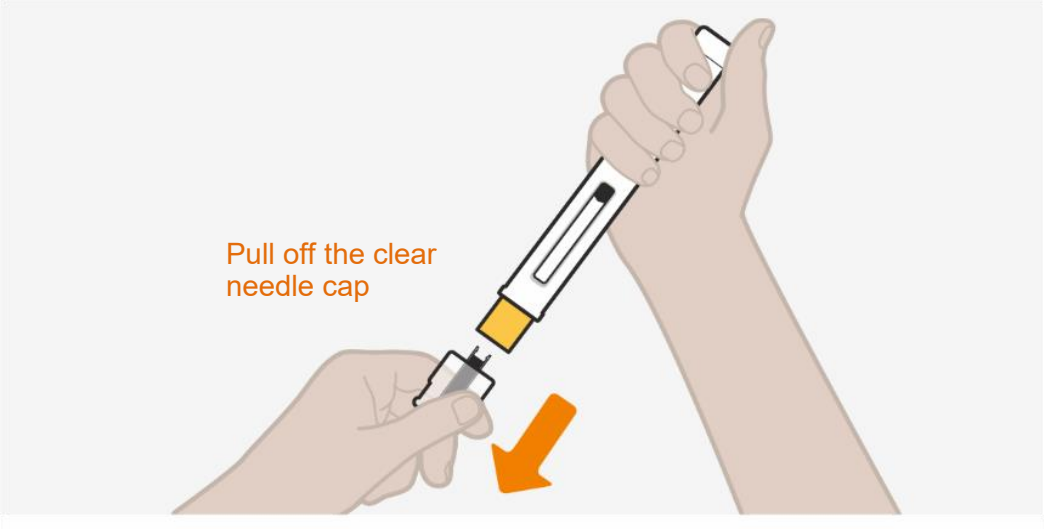


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the clear needle cap

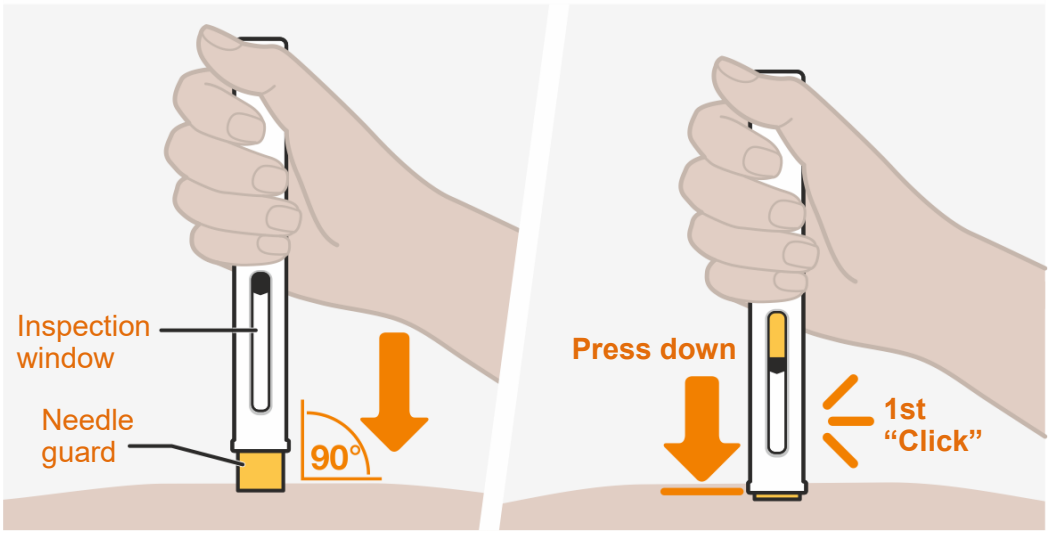


- Remove the clear needle cap from the pen by firmly pulling it straight off.
- Do not worry if you see a drop of liquid at the end of the needle. This is normal.
- Inject straight after removing the needle cap, and always within 5 minutes.

Do not touch the yellow needle guard with your fingers. This could activate the pen too soon and may cause a needle injury.

After removal, do not put the needle cap back onto the pen, as it may accidentally start the injection.

7. Start your injection

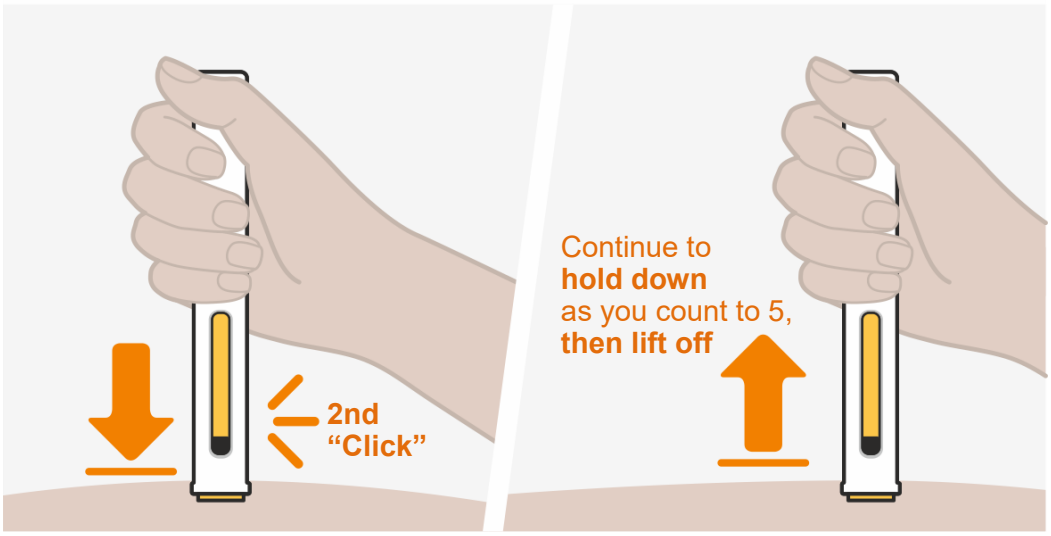


- Hold the pen with its inspection window facing towards you, so you can see it, and with the yellow needle guard facing down.
- Place the pen straight onto your injection site with the yellow needle guard flat against the surface of your skin, as shown.
- To start your injection, push the pen down all the way and keep it held down against your skin. The yellow needle guard will slide up into the pen.
- You should hear the 1st "click" to tell you your injection has started.
- The yellow indicator will move down through the inspection window as you receive your dose.

Do not lift the pen from your skin at this stage, as that may mean you don't get your full dose of medicine. Your injection may take up to 15 seconds to complete.

Do not use the pen if the yellow needle guard doesn't slide up as described. Dispose of it (see Step 9) and start again with a new pen.

8. Hold the pen in place to complete your injection



- Continue to hold the pen down until you hear the 2nd “click”, and the stopper and yellow indicator have stopped moving and filled the inspection window.
- Continue to hold the pen in place while you count to 5. Then lift the pen away from your skin.
- If you do not hear the 2nd “click”:
  - Check that the inspection window is filled with the yellow indicator.
  - If you are not sure, hold the pen down for another 15 seconds to make sure the injection is complete.

Do not lift the pen until you are sure you have completed your injection.

- You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.

Do not rub your injection site.

Dispose

9. Dispose of the used pen

- Dispose of the used pen and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- Keep your used pens and needle caps out of the reach of children.

INSTRUCTIONS FOR USE

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

NUCALA pre-filled syringe (Safety syringe)

(mepolizumab)

Administer once every 4 weeks.

Follow these instructions on how to use the pre-filled syringe. Failure to follow these instructions may affect proper function of the pre-filled syringe. You should also receive training on how to use the pre-filled syringe. NUCALA pre-filled syringe is for **use under the skin only** (subcutaneous).

How to store NUCALA

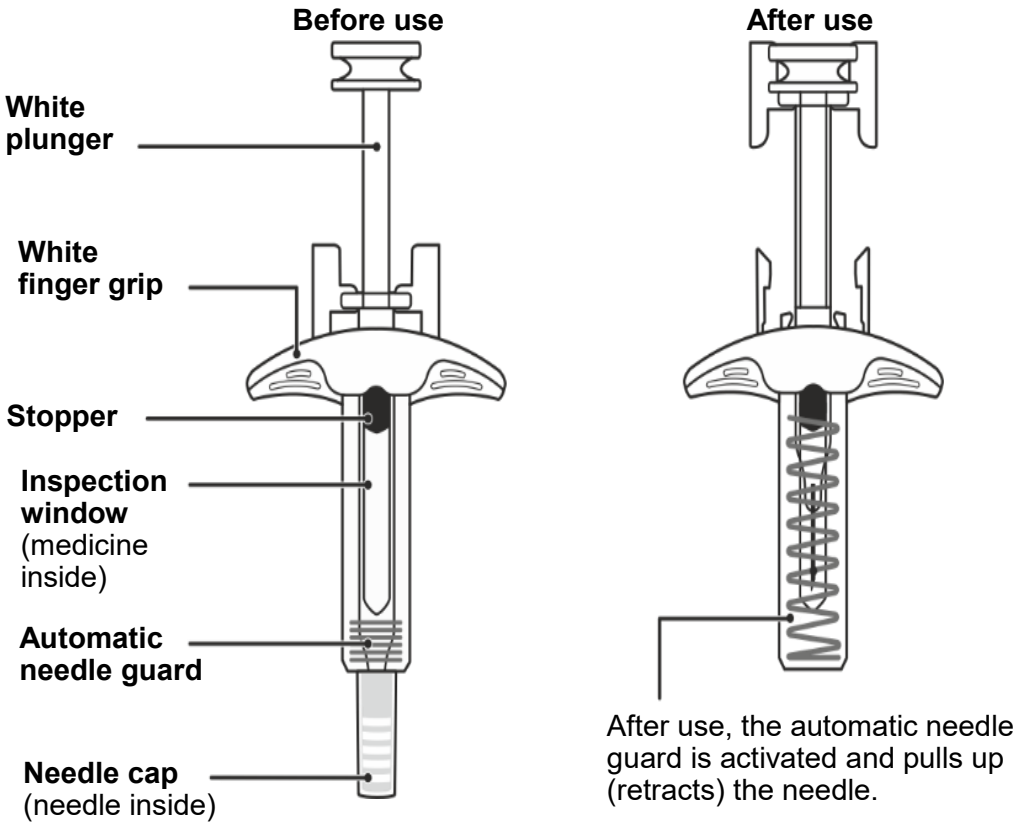
- Keep refrigerated before use.
- Do not freeze.
- Keep in the carton to protect from light.
- Keep out of the sight and reach of children.
- If necessary, the pre-filled syringe may be kept at room temperature, up to 30°C, for no more than 7 days, when stored in the original carton.
- Do not store it above 30°C.
- Safely throw it away if it has been removed from the refrigerator and not been used within 7 days.

Before you use NUCALA

The pre-filled syringe should be used only once and then discarded.

- **Do not** share your NUCALA pre-filled syringe with another person.
- **Do not** shake the syringe.
- **Do not** use the syringe if dropped onto a hard surface.
- **Do not** use the syringe if it appears damaged.
- **Do not** remove the needle cap until just before your injection.

Know your pre-filled syringe



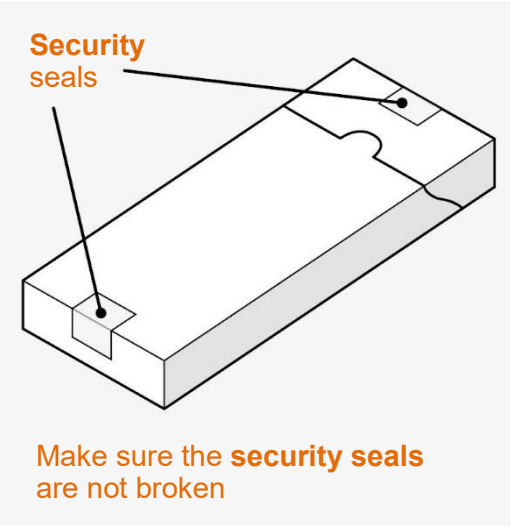
Prepare

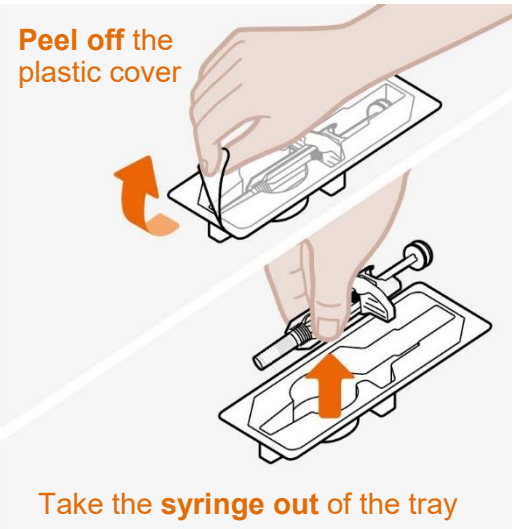
1. Get ready what you need

- Find a comfortable, well-lit and clean surface. Make sure you have within reach:
  - NUCALA pre-filled syringe
  - Alcohol wipe (not included)
  - Gauze pad or cotton wool ball (not included)

Do not perform the injection if you do not have all these.

2. Take out your pre-filled syringe

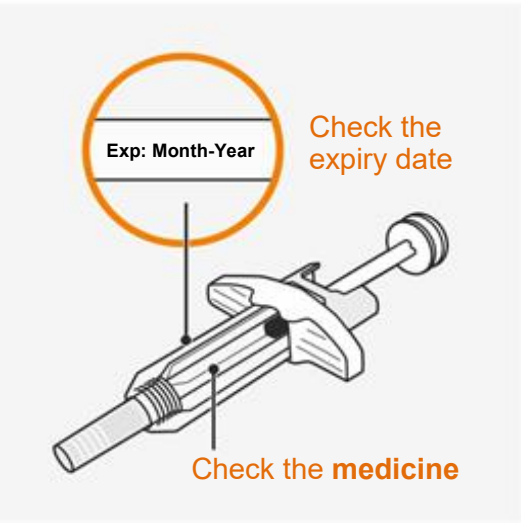




- Take the carton out of the refrigerator. Check the security seals are not broken.
- Remove the tray from the carton.
- Peel back the film cover from the tray.
- Holding the middle of the syringe, carefully take it out of the tray.
- Place the syringe on a clean, flat surface, at room temperature, away from direct sunlight and out of the reach of children.

Do not use the syringe if the security seal on the carton is broken.
Do not remove the needle cap at this stage.

3. Inspect and wait 30 minutes before use

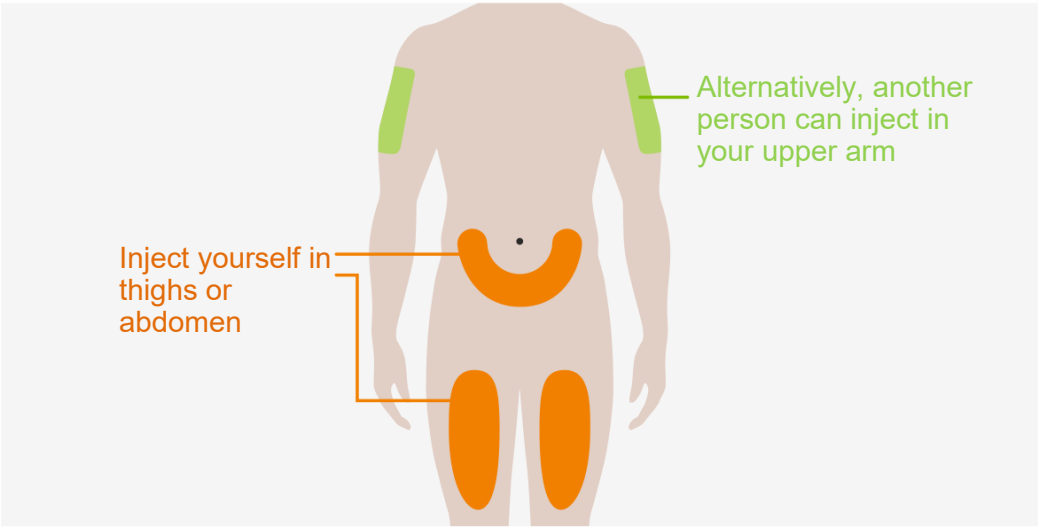


- Check the expiry date on the label of the syringe.

- Look in the inspection window to check that the liquid is clear (free from cloudiness or particles) and colourless to pale yellow to pale brown.
- It is normal to see one or more air bubbles.
- Wait 30 minutes (and no more than 8 hours) before use.

Do not use if the expiry date has passed.
Do not warm the syringe in a microwave, hot water, or direct sunlight.
Do not inject if the solution looks cloudy or discoloured, or has particles.
Do not use the syringe if left out of the carton for more than 8 hours.
Do not remove the needle cap during this step

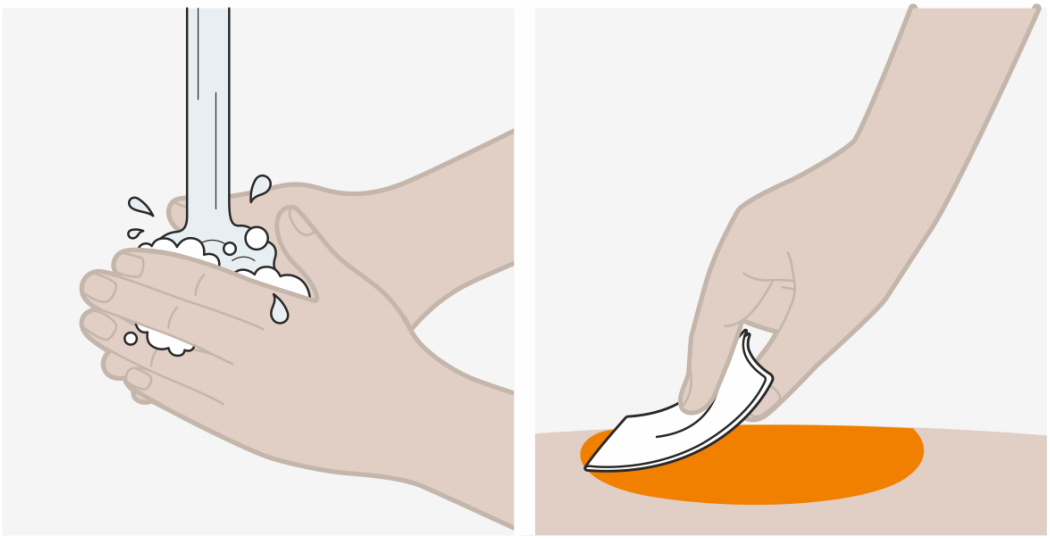
4. Choose your injection site



- You can inject NUCALA into your thighs or abdomen.
- If someone else gives you the injection, they can also use your upper arm.
- If you need more than one injection to complete your dose then leave at least 5 cm between each injection site.

Do not inject where your skin is bruised, tender, red or hard.
Do not inject within 5 cm of your navel (belly button).

5. Clean your injection site

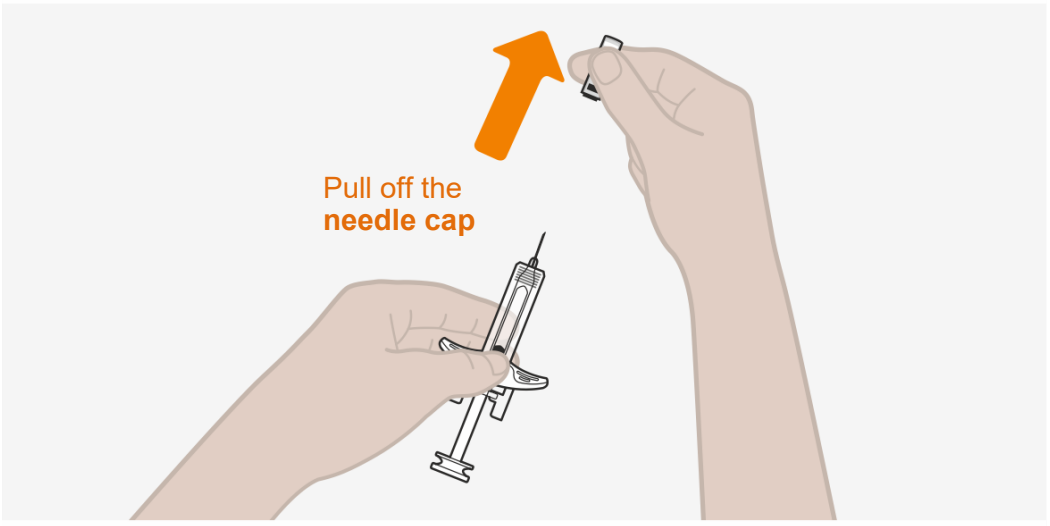


- Wash your hands with soap and water.
- Clean your injection site by wiping the skin with an alcohol wipe and allowing the skin to air dry.

Do not touch your injection site again until you have finished your injection.

Inject

6. Remove the needle cap



- Remove the needle cap from the syringe by firmly pulling it straight off, extending your hand away from the needle end (as shown). You may need to pull the needle cap quite firmly to remove it.
- **Do not** worry if you see a drop of liquid at the end of the needle. This is normal.

- Inject straight after removing the needle cap, and always within 5 minutes.

Do not let the needle touch any surface.

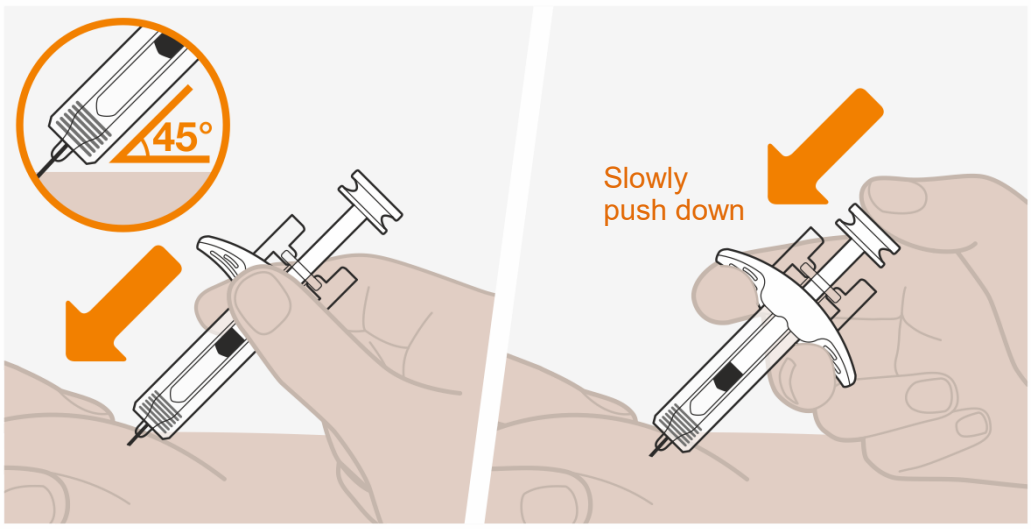
Do not touch the needle.

Do not touch the plunger at this stage, as you can accidentally push liquid out and will not receive your full dose.

Do not expel any air bubbles from the syringe.

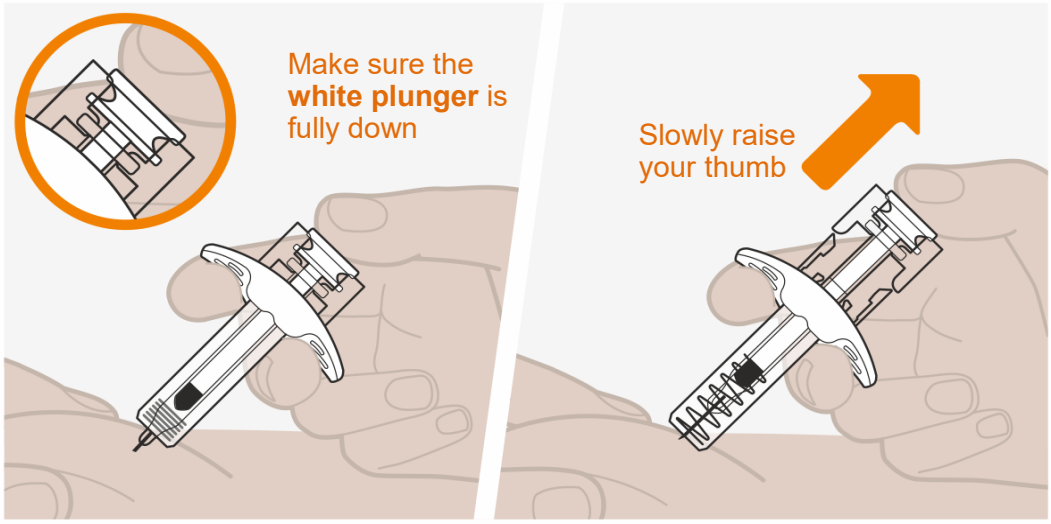
Do not put the needle cap back onto the syringe. This could cause a needle injury.

7. Start your injection



- Use your free hand to pinch the skin around your injection site. Keep the skin pinched throughout your injection.
- Insert the entire needle into the pinched skin at a 45° angle, as shown.
- Move your thumb to the plunger and place your fingers on the white finger grip, as shown.
- Slowly push down on the plunger to inject your full dose.

8. Complete your injection



- Make sure the plunger is pushed all the way down, until the stopper reaches the bottom of the syringe and all of the solution is injected.
- Slowly lift your thumb up. This will allow the plunger to come up and the needle to retract (rise up) into the body of the syringe.
- Once complete, release the pinched skin.
    - You may notice a small drop of blood at the injection site. This is normal. Press a cotton wool ball or gauze on the area for a few moments if necessary.
- **Do not** put the needle cap back onto the syringe.
- **Do not** rub your injection site.

Dispose

9. Dispose of the used syringe

- Dispose of the used syringe and needle cap according to local requirements. Ask your doctor or pharmacist for advice if necessary.
- Keep your used syringes and needle caps out of the sight and reach of children.