NUCALA

Mepolizumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See Section 4 for how to report side effects.

1. NAME OF THE MEDICINAL PRODUCT

NUCALA, solution for injection

2. 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 syringe (safety-syringe) delivers 100 mg mepolizumab in 1 mL (100 mg/mL).

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

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

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

a. Maintenance Treatment of Severe Asthma

NUCALA is indicated for the add-on maintenance treatment of adult and adolescents aged 12 years and older with severe asthma and with an eosinophilic phenotype [see *Posology and method of administration* and *Clinical Studies*].

Limitations of Use

NUCALA is not indicated for the relief of acute bronchospasm or status asthmaticus.

b. Maintenance Treatment of Chronic Rhinosinusitis with Nasal Polyps

NUCALA is indicated for the add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids.

c. Eosinophilic Granulomatosis with Polyangiitis

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

d. Hypereosinophilic Syndrome

NUCALA is indicated for the treatment of adult and adolescents patients aged 12 years and older with hypereosinophilic syndrome (HES) for ≥6 months without an identifiable non-hematologic secondary cause.

4.2. Posology and method of administration

NUCALA is for subcutaneous use only.

a. Severe Asthma

Adults and Adolescents Aged 12 Years and Older

The recommended dosage of NUCALA in adults and adolescents aged 12 years and older is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen *[see Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe]*.

Pediatric population:

The safety and effectiveness in pediatric patients aged younger than 6 years with severe asthma have not been established.

b. Chronic Rhinosinusitis with Nasal Polyps

The recommended dosage of NUCALA is 100 mg administered once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen [*see Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe*].

Paediatric Population

The safety and effectiveness in patients aged younger than 18 years with CRSwNP have not been established.

c. 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 Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe]*. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

Paediatric Population

The safety and effectiveness in patients aged younger than 18 years with EGPA have not been established.

d. Hypereosinophilic Syndrome

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 Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe]. Administer individual 100-mg injections at least 5 cm (approximately 2 inches) apart.

Paediatric Population

The safety and effectiveness of NUCALA for HES have been established in adolescent patients aged 12 years and older. The safety and effectiveness in pediatric patients aged younger than 12 years with HES have not been established.

Use of NUCALA for this indication is supported by evidence from an adequate and well-controlled study (NCT02836496) in adults and adolescents and an open-label extension study (NCT03306043). One adolescent received NUCALA during the controlled study and this patient and an additional 3 adolescents received NUCALA during the open-label extension study *[see Clinical Studies]*. The 1 adolescent treated with NUCALA in the 32-week trial did not have a HES flare or an adverse event reported. All adolescents received 300 mg of NUCALA for 20 weeks in the open-label extension.

- **Preparation and Administration of NUCALA Injection Prefilled Autoinjector and Prefilled Syringe:**

NUCALA injection is intended for use under the guidance of a healthcare provider. The NUCALA injection prefilled autoinjector and prefilled syringe are only for use in adults and adolescents aged 12 years and older. A patient may self-inject, or the patient caregiver may administer NUCALA injection subcutaneously after the healthcare provider determines it is appropriate. Provide proper training in subcutaneous injection technique and on the preparation and administration of NUCALA injection prior to use according to the "Instructions for Use".

1. Remove the prefilled autoinjector or prefilled syringe from the refrigerator and allow it to sit at room temperature for 30 minutes prior to injection. Do not warm NUCALA injection in any other way.
2. Prior to administration, visually inspect the window of the prefilled autoinjector or the prefilled syringe for particulate matter or discoloration. NUCALA injection should be clear to opalescent, colorless to pale yellow to pale brown in color. Do not use NUCALA injection if the product exhibits discoloration, cloudiness, or particulate matter. Do not use the NUCALA prefilled autoinjector or prefilled syringe if dropped on a hard surface.
3. Administer the subcutaneous injection into the thigh or abdomen, avoiding the 5 cm (approximately 2 inches) around the navel. The upper arm can also be used if a caregiver administers the subcutaneous injection.
4. For use in EGPA and HES, ensure injection sites for each subcutaneous injection are separated by at least 5 cm (approximately 2 inches).
5. Never give injections into areas where the skin is tender, bruised, red, or hard.

If a dose is missed, administer a dose as soon as possible. Thereafter, the patient can resume dosing on the usual day of administration. If the next dose is already due, then administer as planned.

4.3. Contraindications

NUCALA is contraindicated in patients with a history of hypersensitivity to mepolizumab or excipients in the formulation *[see Special warnings and precautions for use, Pharmaceutical Particulars]*.

4.4. Special warnings and precautions for use

Hypersensitivity Reactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred following administration of NUCALA. These reactions generally occur within hours of administration, but in some instances can have a delayed onset (i.e., days). In the event of a hypersensitivity reaction, NUCALA should be discontinued *[see Contraindications]*.

Acute Asthma Symptoms or Deteriorating Disease

NUCALA should not be used to treat acute asthma symptoms or acute exacerbations. Do not use NUCALA to treat acute bronchospasm or status asthmaticus. Patients should seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with NUCALA.

Opportunistic Infections: Herpes Zoster

Herpes zoster has occurred in subjects receiving NUCALA 100 mg in controlled clinical trials *[see Adverse Reactions]*. Consider vaccination if medically appropriate.

Reduction of Corticosteroid Dosage

Do not discontinue systemic or inhaled corticosteroids (ICS) abruptly upon initiation of therapy with NUCALA. Reductions in corticosteroid dosage, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dosage may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection

Eosinophils may be involved in the immunological response to some helminth infections. Patients with known parasitic infections were excluded from participation in clinical trials. It is unknown if NUCALA will influence a patient's response against parasitic infections. Treat patients with pre-existing helminth infections before initiating therapy with NUCALA. If patients become infected while receiving treatment with NUCALA and do not respond to anti-helminth treatment, discontinue treatment with NUCALA until infection resolves.

4.5. Interaction with other medicinal products and other forms of interaction

Formal drug interaction trials have not been performed with NUCALA.

4.6. Fertility, Pregnancy and Lactation

Pregnancy

Risk Summary

The data on pregnancy exposure are insufficient to inform on drug-associated risk. Monoclonal antibodies, such as mepolizumab, are transported across the placenta in a linear fashion as pregnancy progresses; therefore, potential effects on a fetus are likely to be greater during the second and third trimester of pregnancy. In a prenatal and postnatal development study conducted in cynomolgus monkeys, there was no evidence of fetal harm with IV administration of mepolizumab throughout pregnancy at doses that produced exposures up to approximately 9 times the exposure at the maximum recommended human dose (MRHD) of 300 mg subcutaneous *(see Data)*.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryofetal Risk: In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

Data

Animal Data: In a prenatal and postnatal development study, pregnant cynomolgus monkeys received mepolizumab from gestation Days 20 to 140 at doses that produced exposures up to approximately 9 times that achieved with the MRHD (on an AUC basis with maternal IV doses up to 100 mg/kg once every 4 weeks). Mepolizumab did not elicit adverse effects on fetal or neonatal growth (including immune function) up to 9 months after birth. Examinations for internal or skeletal malformations were not performed. Mepolizumab crossed the placenta in cynomolgus monkeys. Concentrations of mepolizumab were approximately 2.4 times higher in infants than in mothers up to Day 178 postpartum. Levels of mepolizumab in milk were ≤0.5% of maternal serum concentration.

In a fertility, early embryonic, and embryofetal development study, pregnant CD-1 mice received an analogous antibody, which inhibits the activity of murine interleukin-5 (IL-5), at an IV dose of 50 mg/kg once per week throughout gestation. The analogous antibody was not teratogenic in mice. Embryofetal development of IL-5–deficient mice has been reported to be generally unaffected relative to wild-type mice.

Lactation

Risk Summary

There is no information regarding the presence of mepolizumab in human milk, the effects on the breastfed infant, or the effects on milk production. However, mepolizumab is a humanized monoclonal antibody (IgG1 kappa), and immunoglobulin G (IgG) is present in human milk in small amounts. Mepolizumab was present in the milk of cynomolgus monkeys postpartum following dosing during pregnancy [see *Pregnancy*]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NUCALA and any potential adverse effects on the breastfed infant from mepolizumab or from the underlying maternal condition.

4.7. Effects on Ability to Drive and Use Machines

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

4.8. Undesirable Effects

4.8.1 Adverse Reactions

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

- Hypersensitivity reactions *[see Special warnings and precautions for use]*
- Opportunistic infections: herpes zoster *[see Special warnings and precautions for use]*

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

4.8.2 Clinical Studies Experience

a. Clinical Trials Experience in Severe Asthma

Adult and Adolescent Patients Aged 12 Years and Older

A total of 1,327 patients with severe asthma were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks' duration (Trial 1, NCT01000506; Trial 2, NCT01691521; and Trial 3, NCT01691508). Of these, 1,192 had a history of 2 or more exacerbations in the year prior to enrollment despite regular use of high-dose ICS plus additional controller(s) (Trials 1 and 2), and 135 patients required daily oral corticosteroids (OCS) in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control (Trial 3). All patients had markers of eosinophilic airway inflammation *[see Clinical Studies]*. Of the patients enrolled, 59% were female, 85% were White, and ages ranged from 12 to 82 years. Mepolizumab was administered subcutaneously or intravenously once every 4 weeks; 263 patients received NUCALA (mepolizumab 100 mg subcutaneous) for at least 24 weeks. Serious adverse events that occurred in more than 1 patient and in a greater percentage of patients receiving NUCALA 100 mg (n = 263) than placebo (n = 257) included 1 event, herpes zoster (2 patients vs. 0 patients, respectively). Approximately 2% of patients receiving NUCALA 100 mg withdrew from clinical trials due to adverse events compared with 3% of patients receiving placebo.

The incidence of adverse reactions in the first 24 weeks of treatment in the 2 confirmatory efficacy and safety trials (Trials 2 and 3) with NUCALA 100 mg is shown in Table 1.

Table 1. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with Severe Asthma (Trials 2 and 3)

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

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

Systemic Reactions, including Hypersensitivity Reactions: In Trials 1, 2, and 3 described above, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 3% in the group receiving NUCALA 100 mg and 5% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 1% of patients in the group receiving NUCALA 100 mg and 2% of patients in the placebo group. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving NUCALA 100 mg included rash, pruritus, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving NUCALA 100 mg and 3% of patients in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions reported in the group receiving NUCALA 100 mg included rash, flushing, and myalgia. A majority of the systemic reactions in patients receiving NUCALA 100 mg (5/7) were experienced on the day of dosing.

Injection Site Reactions: Injection site reactions (e.g., pain, erythema, swelling, itching, burning sensation) occurred at a rate of 8% in patients receiving NUCALA 100 mg compared with 3% in patients receiving placebo.

Long-term Safety: Nine hundred ninety-eight patients received NUCALA 100 mg in ongoing open-label extension studies, during which additional cases of herpes zoster were reported. The overall adverse event profile has been similar to the severe asthma trials described above.

b. Clinical Trials Experience in Chronic Rhinosinusitis with Nasal Polyps

A total of 407 patients with CRSwNP were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received NUCALA 100 mg or placebo subcutaneously once every 4 weeks. Patients had recurrent CRSwNP with a history of prior surgery and were on nasal corticosteroids for at least 8 weeks prior to screening *[see Clinical Studies]*. Of the patients enrolled, 35% were female, 93% were White, and ages ranged from 18 to 82 years. Approximately 2% of patients receiving NUCALA 100 mg withdrew from study treatment due to adverse events compared with 2% of patients receiving placebo.

Table 2 summarizes adverse reactions that occurred in ≥ 3% of NUCALA-treated patients and more frequently than in patients treated with placebo in the CRSwNP trial.

Table 2. Adverse Reactions with NUCALA with ≥3% Incidence and More Common than Placebo in Patients with CRSwNP

Adverse Reaction	NUCALA (Mepolizumab 100 mg Subcutaneous) (n = 206) %	Placebo (n = 201) %
Oropharyngeal pain	8	5
Arthralgia	6	2
Abdominal Pain Upper	3	2
Diarrhea	3	2
Pyrexia	3	2
Nasal dryness	3	<1
Rash	3	<1

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic [type I hypersensitivity] and other) reactions was <1% in the group receiving NUCALA 100 mg and <1% in the placebo group. Systemic allergic (type I hypersensitivity) reactions were reported by <1% of patients in the group receiving NUCALA 100 mg and no patients in the placebo group. The manifestations of systemic allergic (type I hypersensitivity) reactions included urticaria, erythema, and rash and 1 of the 3 reactions occurred on the day of dosing. Other systemic reactions were reported by no patients in the group receiving NUCALA 100 mg and <1% of patients in the placebo group.

Injection Site Reactions

Injection site reactions (e.g., erythema, pruritus) occurred at a rate of 2% in patients receiving NUCALA 100 mg compared with <1% in patients receiving placebo.

c. Clinical Trials Experience in Eosinophilic Granulomatosis with Polyangiitis

A total of 136 patients with EGPA were evaluated in 1 randomized, placebo-controlled, multicenter, 52-week treatment trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a

stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment *[see Clinical Studies]*. Of the patients enrolled, 59% were female, 92% were White, and ages ranged from 20 to 71 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the 52-week trial, the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of NUCALA and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of NUCALA and 1% of patients in the placebo group. The manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving 300 mg of NUCALA included rash, pruritus, flushing, fatigue, hypertension, warm sensation in trunk and neck, cold extremities, dyspnea, and stridor. Systemic non-allergic reactions were reported by 1 (1%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of systemic non-allergic reactions reported in the group receiving 300 mg of NUCALA was angioedema. Half of the systemic reactions in patients receiving 300 mg of NUCALA (2/4) were experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving 300 mg of NUCALA compared with 13% in patients receiving placebo.

d. Clinical Trials Experience in Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES were evaluated in a randomized, placebo-controlled, multicenter, 32-week treatment trial. Patients with non-hematologic secondary HES or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks. Patients must have been on a stable dose of background HES therapy for the 4 weeks prior to randomization *[see Clinical Studies]*. Of the patients enrolled, 53% were female, 93% were White, and ages ranged from 12 to 82 years. No additional adverse reactions were identified to those reported in the severe asthma trials.

Systemic Reactions, including Hypersensitivity Reactions

In the trial, no systemic allergic (type I hypersensitivity) reactions were reported. Other systemic reactions were reported by 1 (2%) patient in the group receiving 300 mg of NUCALA and no patients in the placebo group. The reported manifestation of other systemic reaction was multifocal skin reaction experienced on the day of dosing.

Injection Site Reactions

Injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving 300 mg of NUCALA compared with 4% in patients receiving placebo.

e. Immunogenicity

In adult and adolescent patients with severe asthma receiving NUCALA 100 mg, 15/260 (6%) had detectable anti-mepolizumab antibodies. Neutralizing antibodies were detected in 1 patient with asthma receiving NUCALA 100 mg. Anti-mepolizumab antibodies slightly

increased (approximately 20%) the clearance of mepolizumab. There was no evidence of a correlation between anti-mepolizumab antibody titers and change in eosinophil level. The clinical relevance of the presence of anti-mepolizumab antibodies is not known.

In patients with CRSwNP receiving NUCALA 100 mg, 6/196 (3%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with CRSwNP.

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

In adult and adolescent patients with HES receiving 300 mg of NUCALA, 1/53 (2%) had detectable anti-mepolizumab antibodies. No neutralizing antibodies were detected in any patients with HES.

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.

4.8.3 Post-marketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post-approval use of NUCALA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to NUCALA or a combination of these factors.

Immune System Disorders

Hypersensitivity reactions, including anaphylaxis.

For any information about this medicinal product, please contact:

GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: gcc.medinfo@gsk.com
- Website: https://gskpro.com/en-sa/
- P.O. Box 55850, Jeddah 21544, Saudi Arabia

To report any side effect(s):

Kingdom of Saudi Arabia

-National Pharmacovigilance centre (NPC)

- SFDA Call Centre: 19999
- E-mail: npc.drug@sfda.gov.sa

- Website: https://ade.sfda.gov.sa

-GlaxoSmithKline - Head Office, Jeddah

- Tel: +966-12-6536666
- Mobile: +966-56-904-9882
- Email: saudi.safety@gsk.com
- Website: https://gskpro.com/en-sa/
- P.O. Box 55850, Jeddah 21544, Saudi Arabia

4.9. Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC code

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

R03DX09

Mechanism of Action

Mepolizumab is an IL-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab binds to IL-5 with a dissociation constant of 100 pM, inhibiting the bioactivity of IL-5 by blocking its binding to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. Inflammation is an important component in the pathogenesis of asthma, CRSwNP, EGPA, and HES. Multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) are involved in inflammation. Mepolizumab, by inhibiting IL-5 signaling, reduces the production and survival of eosinophils; however, the mechanism of mepolizumab action in asthma, CRSwNP, EGPA, and HES has not been definitively established.

Pharmacodynamic effects

The pharmacodynamic response (blood eosinophil reduction) following repeat doses of mepolizumab administered subcutaneously or intravenously was evaluated in adult subjects with asthma and blood eosinophil levels >200 cells/mcL. Subjects received 1 of 4 mepolizumab treatments (administered every 28 days for a total of 3 doses): 12.5 mg subcutaneous, 125 mg subcutaneous, 250 mg subcutaneous, or 75 mg IV. Sixty-six of the 70 randomized subjects completed the trial. Compared with baseline levels, blood eosinophils decreased in a dose-dependent manner. A reduction in blood eosinophil levels was observed in all treatment groups by Day 3 (48 hours post-dose). On Day 84 (4 weeks post-last dose), the observed geometric mean reduction from baseline in blood eosinophils was 64%, 78%, 84%, and 90% in the 12.5-mg subcutaneous, 75-mg IV, 125-mg subcutaneous, and 250-mg subcutaneous treatment groups, respectively. The model-predicted subcutaneous doses

providing 50% and 90% of maximal reduction of blood eosinophils at Day 84 were estimated to be 11 and 99 mg, respectively. These results, along with the clinical efficacy data from the dose-ranging exacerbation trial in adult and adolescent subjects with severe asthma (Trial 1) supported the evaluation of mepolizumab 75 mg IV and 100 mg subcutaneous in the confirmatory severe asthma trials *[see Clinical Studies]*. Following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 32 weeks in adult and adolescent subjects with severe asthma (Trial 2), blood eosinophils were reduced to a geometric mean count of 40 cells/mcL, which corresponds to a geometric mean reduction of 84% compared with placebo.

The magnitude of reduction in adults and adolescents was observed within 4 weeks of treatment and was maintained throughout the treatment periods.

For adults with CRSwNP, following subcutaneous administration of mepolizumab 100 mg every 4 weeks for 52 weeks, blood eosinophils were reduced to a geometric mean count of 60 cells/mcL. There was a geometric mean reduction of 83% compared with placebo. This magnitude of reduction was observed within 4 weeks of treatment and was maintained throughout the treatment period *[see Clinical Studies]*.

For adults with EGPA, following subcutaneous administration of mepolizumab 300 mg every 4 weeks for 52 weeks, blood eosinophils were reduced to a geometric mean count of 38 cells/mcL. 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 Studies]*.

For adults and adolescents with HES, following subcutaneous administration of mepolizumab 300 mg every 4 weeks for 32 weeks, blood eosinophils were reduced to a geometric mean count of 70 cells/mcL. There was a geometric mean reduction of 92% compared with placebo *[see Clinical Studies]*.

5.2. Pharmacokinetic properties

Following subcutaneous dosing in adult subjects with asthma, mepolizumab exhibited approximately dose-proportional pharmacokinetics over a dose range of 12.5 to 250 mg. The pharmacokinetic properties of mepolizumab observed in subjects with CRSwNP (adults), EGPA (adults) or HES (adults and adolescents) were similar to the pharmacokinetic properties observed in subjects with severe asthma (adults and adolescents).

Subcutaneous administration of mepolizumab 300 mg had approximately 3 times the systemic exposure of mepolizumab 100 mg.

Absorption

Following 100-mg subcutaneous administration in the upper arm of adult and adolescent subjects with asthma, the bioavailability of mepolizumab was estimated to be approximately 80%.

Following repeat subcutaneous administration once every 4 weeks, there was approximately a 2-fold accumulation at steady state.

Distribution

The population central volume of distribution of mepolizumab in adult subjects with asthma is estimated to be 3.6 L for a 70-kg individual.

Elimination

Following subcutaneous administration of mepolizumab in adult subjects with asthma, the mean terminal half-life ($t_{1/2}$) ranged from 16 to 22 days. The population apparent systemic clearance of mepolizumab in adult and adolescent subjects with asthma is estimated to be 0.28 L/day for a 70-kg individual.

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

Specific Populations

Racial Groups and Male and Female Patients: Population pharmacokinetics analyses indicated there was no significant effect of race and gender on mepolizumab clearance.

Age: Population pharmacokinetics analyses indicated there was no significant effect of age on mepolizumab clearance.

Geriatric Patients: Clinical trials of NUCALA did not include sufficient numbers of patients aged 65 years and older that received NUCALA (n = 79) to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Based on available data, no adjustment of the dosage of NUCALA in geriatric patients is necessary, but greater sensitivity in some older individuals cannot be ruled out.

Patients with Renal Impairment: No clinical trials have been conducted to investigate the effect of renal impairment on the pharmacokinetics of mepolizumab. Based on population pharmacokinetic analyses, mepolizumab clearance was comparable between subjects with creatinine clearance values between 50 and 80 mL/min and patients with normal renal function. There are limited data available in subjects with creatinine clearance values <50 mL/min; however, mepolizumab is not cleared renally.

Patients with Hepatic Impairment: No clinical trials 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.

Drug Interaction Studies

No formal drug interaction studies have been conducted with mepolizumab. In population pharmacokinetics analyses of Phase 3 studies, there was no evidence of an effect of commonly co-administered small molecule drugs on mepolizumab exposure.

CLINICAL STUDIES

a. Severe Asthma

The asthma development program for NUCALA in patients aged 12 years and older included 3 double-blind, randomized, placebo-controlled trials: 1 dose-ranging and exacerbation trial (Trial 1, NCT01000506) and 2 confirmatory trials (Trial 2, NCT01691521 and Trial 3, NCT01691508). Mepolizumab was administered every 4 weeks in all 3 trials as add-on to background treatment. All patients continued their background asthma therapy throughout the duration of the trials.

Dose-Ranging and Exacerbation Trial

Trial 1 was a 52-week dose-ranging and exacerbation-reduction trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients enrolled in this trial were required to have at least 1 of the following 4 pre-specified criteria in the previous 12 months: blood eosinophil count ≥300 cells/mcL, sputum eosinophil count ≥3%, exhaled nitric oxide concentration ≥50 ppb, or deterioration of asthma control after ≤25% reduction in regular maintenance ICS/OCS. Three IV dosages of mepolizumab (75, 250, and 750 mg) administered once every 4 weeks were evaluated compared with placebo. Results from this trial and the pharmacodynamic study supported the evaluation of mepolizumab 75 mg IV and 100 mg subcutaneous in the subsequent trials *[see Pharmacological Properties]*. NUCALA is not indicated for IV use and should only be administered by the subcutaneous route.

Confirmatory Trials

A total of 711 patients with severe asthma were studied in the 2 confirmatory trials (Trials 2 and 3). In these 2 trials patients were required to have blood eosinophils of ≥150 cells/mcL at screening (within 6 weeks of dosing) or blood eosinophils of ≥300 cells/mcL within 12 months of enrollment. The screening blood eosinophils of ≥150 cells/mcL criterion was derived from exploratory analyses of data from Trial 1. Trial 2 was a 32-week placebo- and active-controlled trial in patients with severe asthma with a history of 2 or more exacerbations in the previous year despite regular use of high-dose ICS plus additional controller(s) with or without OCS. Patients received mepolizumab 75 mg IV (n = 191), NUCALA 100 mg (n = 194), or placebo (n = 191) once every 4 weeks for 32 weeks.

Trial 3 was a 24-week OCS-reduction trial in patients with severe asthma who required daily OCS in addition to regular use of high-dose ICS plus additional controller(s) to maintain asthma control. Patients in Trial 3 were not required to have a history of exacerbations in the previous year. Patients received NUCALA 100 mg (n = 69) or placebo (n = 66) once every 4 weeks for 24 weeks. The baseline mean OCS use was similar in the 2 treatment groups: 13.2 mg in the placebo group and 12.4 mg in the group receiving NUCALA 100 mg.

The demographics and baseline characteristics of these 3 trials are provided in Table 3.

Table 3. Demographics and Baseline Characteristics of Severe Asthma Trials

	Trial 1 (N = 616)	**Trial 2 (N = 576)**	**Trial 3 (N = 135)**
Mean age, years	49	50	50
Female, n (%)	387 (63)	328 (57)	74 (55)
White, n (%)	554 (90)	450 (78)	128 (95)
Duration of asthma, years, mean	19	20	19
Never smoked, n (%)	483 (78)	417 (72)	82 (61)
Baseline FEV_1, L	1.88	1.82	1.95
Baseline % predicted FEV_1	60	61	59
Baseline % reversibility	25	27	26
Baseline post-SABA FEV_1/FVC	0.67	0.66	0.66
Geometric mean eosinophil count at baseline, cells/mcL	250	290	240
Mean number of exacerbations in previous year	3.6	3.6	3.1

FEV_1 = forced expiratory volume in 1 second, SABA = short-acting $beta_2$-agonist, FVC = forced vital capacity.

Exacerbations

Efficacy was assessed in Trials 1 and 2 using an endpoint of the frequency of exacerbations defined as worsening of asthma requiring use of oral/systemic corticosteroids and/or hospitalization and/or emergency department visits. For patients on maintenance OCS, an exacerbation requiring OCS was defined as the use of oral/systemic corticosteroids at least double the existing dose for at least 3 days. Compared with placebo, patients receiving NUCALA 100 mg or mepolizumab 75 mg IV experienced significantly fewer exacerbations. Additionally, compared with placebo, there were fewer exacerbations requiring hospitalization and/or emergency department visits and exacerbations requiring only in-patient hospitalization with NUCALA 100 mg (Table 4).

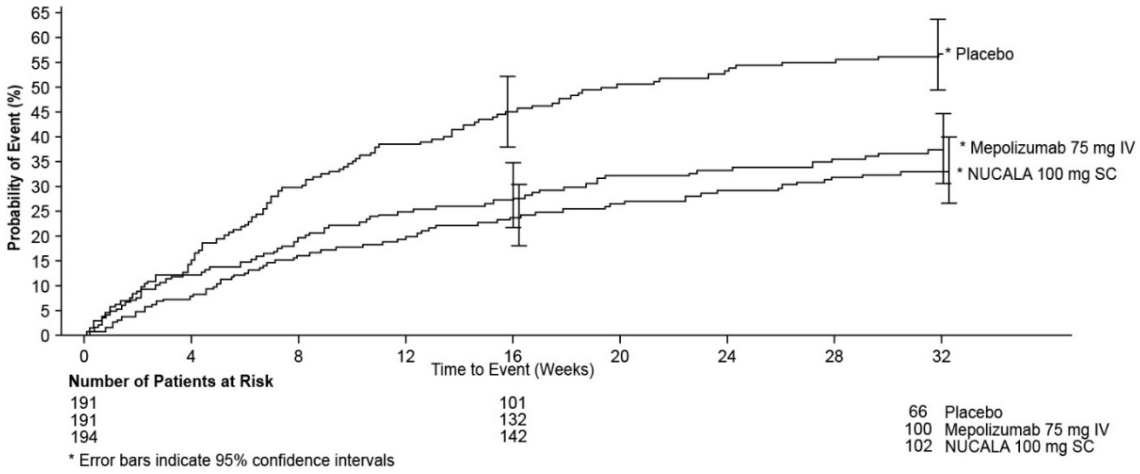
Table 4. Rate of Exacerbations in Severe Asthma Trials 1 and 2 (Intent-to-Treat Population)

Trial	Treatment	Exacerbations per Year		
		Rate	Difference	Rate Ratio (95% CI)
All exacerbations				
Trial 1	Placebo (n = 155)	2.40		
	Mepolizumab 75 mg IV (n = 153)	1.24	1.16	0.52 (0.39, 0.69)
Trial 2	Placebo (n = 191)	1.74		
	Mepolizumab 75 mg IV (n = 191)	0.93	0.81	0.53 (0.40, 0.72)
	NUCALA 100 mg SC (n = 194)	0.83	0.91	0.47 (0.35, 0.64)
Exacerbations requiring hospitalization/emergency room visit				
Trial 1	Placebo (n = 155)	0.43		
	Mepolizumab 75 mg IV (n = 153)	0.17	0.26	0.40 (0.19, 0.81)
Trial 2	Placebo (n = 191)	0.20		
	Mepolizumab 75 mg IV (n = 191)	0.14	0.06	0.68 (0.33, 1.41)
	NUCALA 100 mg SC (n = 194)	0.08	0.12	0.39 (0.18, 0.83)
Exacerbations requiring hospitalization				
Trial 1	Placebo (n = 155)	0.18		
	Mepolizumab 75 mg IV (n = 153)	0.11	0.07	0.61 (0.28, 1.33)
Trial 2	Placebo (n = 191)	0.10		
	Mepolizumab 75 mg IV (n = 191)	0.06	0.04	0.61 (0.23, 1.66)
	NUCALA 100 mg SC (n = 194)	0.03	0.07	0.31 (0.11, 0.91)

IV = intravenous, SC = subcutaneous, CI°=°Confidence Interval.

The time to first exacerbation was longer for the groups receiving NUCALA 100 mg and mepolizumab 75 mg IV compared with placebo in Trial 2 (Figure 1).

Figure 1. Kaplan-Meier Cumulative Incidence Curve for Time to First Exacerbation (Severe Asthma Trial 2)



IV = intravenous, SC = subcutaneous.

Trial 1 data were explored to determine criteria that could identify patients likely to benefit from treatment with NUCALA. The exploratory analysis suggested that baseline blood eosinophil count of ≥150 cells/mcL was a potential predictor of treatment benefit. Exploratory analysis of Trial 2 data also suggested that baseline blood eosinophil count (obtained within 6 weeks of initiation of dosing) of ≥150 cells/mcL was a potential predictor of efficacy and showed a trend of greater exacerbation benefit with increasing blood eosinophil count. In Trial 2, patients enrolled solely on the basis of the historical blood eosinophil count of ≥300 cells/mcL in the previous 12 months, but who had a baseline blood eosinophil count <150 cells/mcL, had virtually no exacerbation benefit following treatment with NUCALA 100 mg compared with placebo.

The Asthma Control Questionnaire-5 (ACQ-5) was assessed in Trials 1 and 2, and the St. George's Respiratory Questionnaire (SGRQ) was assessed in Trial 2. In Trial 1, the ACQ-5 responder rate (defined as a decrease in score of 0.5 or more as threshold) for the 75-mg IV mepolizumab arm was 47% compared with 50% for placebo with an odds ratio (OR) of 1.1 (95% CI: 0.7, 1.7). In Trial 2, the ACQ-5 responder rate for the treatment arm for NUCALA 100 mg was 57% compared with 45% for placebo with an OR of 1.8 (95% CI: 1.2, 2.8). In Trial 2, the SGRQ responder rate (defined as a decrease in score of 4 or more as threshold) for the treatment arm for NUCALA 100 mg was 71% compared with 55% for placebo with an OR of 2.1 (95% CI: 1.3, 3.2).

Oral Corticosteroid Reduction

Trial 3 evaluated the effect of NUCALA 100 mg on reducing the use of maintenance OCS. Efficacy was assessed using an endpoint of the percent reduction of OCS dose during Weeks 20 to 24 compared with baseline dose, while maintaining asthma control. Patients were classified according to their change in OCS use during the trial with the following categories: 90% to 100% decrease, 75% to <90% decrease, 50% to <75% decrease, >0% to <50% decrease, and no improvement (i.e., no change or any increase or lack of asthma control or withdrawal of treatment). Compared with placebo, patients receiving NUCALA 100 mg achieved greater reductions in daily maintenance OCS dose, while maintaining asthma

control. Sixteen (23%) patients in the group receiving NUCALA 100 mg versus 7 (11%) in the placebo group had a 90% to 100% reduction in their OCS dose. Twenty-five (36%) patients in the group receiving NUCALA 100 mg versus 37 (56%) in the placebo group were classified as having no improvement for OCS dose. Additionally, 54% of patients receiving NUCALA 100 mg achieved at least a 50% reduction in the daily prednisone dose compared with 33% of patients receiving placebo (95% CI for difference: 4%, 37%). An exploratory analysis was also performed on the subgroup of 29 patients in Trial 3 who had an average baseline and screening blood eosinophil count <150 cells/mcL. Five (29%) patients in the group receiving NUCALA 100 mg versus 0 (0%) in the placebo group had a 90% to 100% reduction in their dose. Four (24%) patients in the group receiving NUCALA 100 mg versus 8 (67%) in the placebo group were classified as having no improvement for OCS dose. The ACQ and SGRQ were also assessed in Trial 3 and showed results similar to those in Trial 2.

Lung Function

Change from baseline in mean forced expiratory volume in 1 second (FEV_1) was measured in all 3 trials and is presented in Table 5. Compared with placebo, NUCALA 100 mg did not provide consistent improvements in mean change from baseline in FEV_1.

Table 5. Change from Baseline in FEV_1 (mL) in Severe Asthma Trials

Trial	Difference from Placebo in Mean Change from Baseline FEV_1 (mL) (95% CI)		
	Week 12	Week 24	Weeks 32/52
1[a]	10 (-87, 108)	5 (-98, 108)	61 (-39, 161)[b]
2[c]	52 (-30, 134)	76 (-6, 159)	98 (11, 184)[d]
3[c]	56 (-91, 203)	114 (-42, 271)	NA

FEV_1 = Forced Expiratory Volume in 1 Second, CI = Confidence Interval.

[a] Dose = 75 mg intravenous.

[b] Forced expiratory volume in 1 second (FEV_1) at Week 52.

[c] Dose = 100 mg subcutaneous.

[d] FEV_1 at Week 32.

The effect of mepolizumab on lung function was also studied in a 12-week placebo-controlled trial enrolling patients with asthma on a moderate dose of ICS with evidence of symptoms and lung function impairment. Enrollment was not dependent on a history of exacerbations or a pre-specified eosinophil count. Change from baseline in FEV_1 at Week 12 was numerically lower in the mepolizumab treatment groups than the placebo group.

b. Chronic Rhinosinusitis with Nasal Polyps

A total of 407 adult patients with CRSwNP were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 52-week trial (NCT03085797). Patients received NUCALA 100 mg or placebo administered subcutaneously once every 4 weeks while continuing nasal corticosteroid therapy. Patients must have received background nasal corticosteroid for ≥8 weeks pre-screening. Patients had recurrent and symptomatic CRSwNP, and had at least 1 surgery for the removal of nasal polyps within the previous 10 years. Patients were required

to have nasal obstruction symptoms with a visual analog scale (VAS) score of >5 out of a maximum score of 10. Patients were also required to have an endoscopic bilateral nasal polyp score (NPS) of ≥5 out of 8 with NPS ≥2 in each nasal cavity. Patients reported nasal obstruction VAS scores daily by placing a single mark on a continuous line labeled from 0 (none) to 100 (as bad as you can imagine). The distance along the line was converted to a 0 to 10 point scale for scoring. For NPS, polyps on each side of the nose were graded on a categorical scale (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) for a total score of 0 to 8. Sinus CT scans were not performed at baseline nor during treatment to evaluate for sinus opacification.

The co-primary endpoints were change from baseline to Week 52 in total endoscopic NPS (0 to 8 scale) as graded by independent blinded assessors and change from baseline in nasal obstruction VAS score (0 to 10 scale) during Weeks 49 to 52. The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52 in this trial. Other secondary endpoints were change from baseline in loss of smell VAS score during Weeks 49 to 52, and proportion of patients requiring systemic steroids for nasal polyps up to Week 52. All VAS scores were collected daily by the patients and reported on a 0 to 10 scale (0 = none, 10 = as bad as you can imagine).

The demographics and baseline characteristics of patients in this trial are provided in Table 6.

Table 6. Demographics and Baseline Characteristics in CRSwNP

	N = 407
Mean age, years	49
Female, n (%)	143 (35)
White, n (%)	379 (93)
Mean CRSwNP duration in years (SD)	11.4 (8.4)
Patients with ≥1 surgery in past 10 years (%)	407 (100)
Patients with ≥3 surgeries in past 10 years (%)	124 (30)
OCS use (≥1 course) in past 12 months, n (%)	197 (48)
Mean bilateral endoscopic NPS[a], (SD), range 0-8	5.5 (1.29)
Mean nasal obstruction VAS score, (SD), range 0-10	9.0 (0.83)
Geometric mean blood eosinophil cells/mcL (95% CI)	390 (360, 420)
Asthma, n (%)	289 (71)
AERD, n (%)	108 (27)

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SD = standard deviation, OCS = Oral corticosteroid, NPS = nasal polyp score, VAS = visual analog scale, AERD = Aspirin-exacerbated respiratory disease.

[a]As graded by independent blinded assessors.

Endoscopic Nasal Polyp Score and Nasal Obstruction Visual Analog Scale Scores

Patients who received NUCALA 100 mg had a statistically significant improvement (decrease) in bilateral NPS at Week 52 and nasal obstruction VAS score from Weeks 49 to 52 at the end of the 52 week treatment period (Table 7).

Table 7. Analyses of Endpoints in CRSwNP

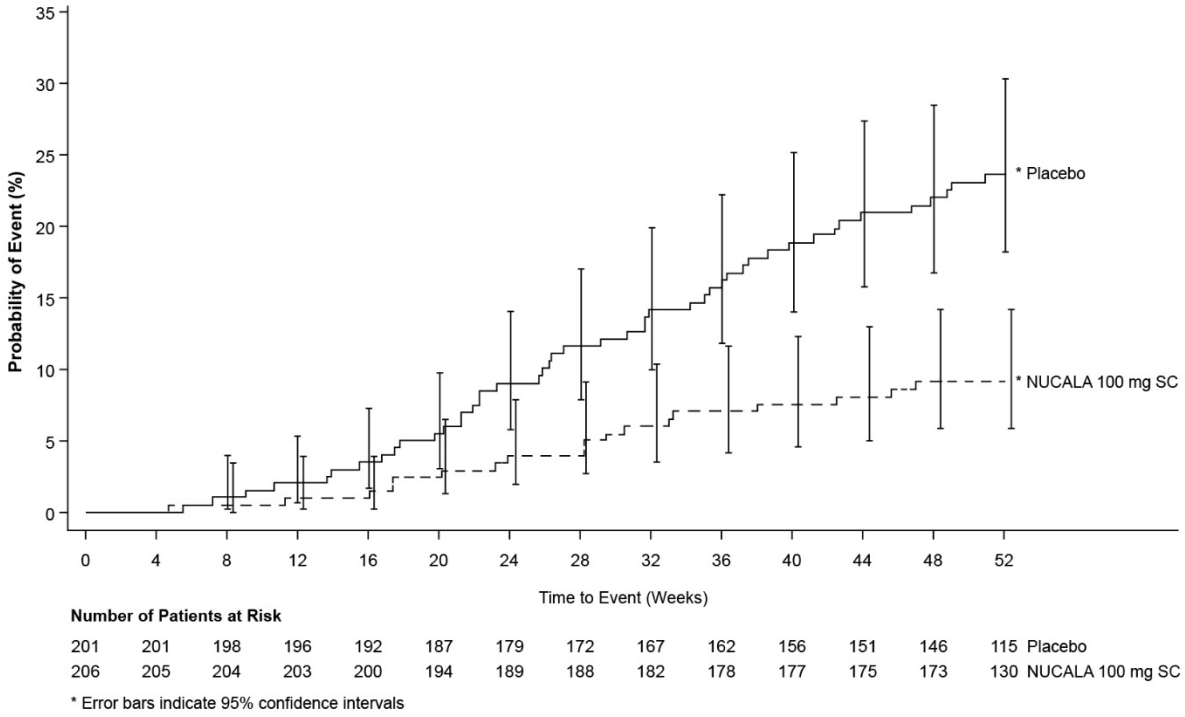
	Placebo n = 201		**NUCALA 100 mg n = 206**		
Scores[a] (range)	**Baseline Mean (SD)**	**Mean Change[b] (SE)**	**Baseline Mean (SD)**	**Mean Change[b] (SE)**	**Mean Difference vs. Placebo (95% CI)**
NPS (0-8)	5.6 (1.41)	0.06 (0.14)	5.4 (1.17)	-0.87 (0.14)	-0.93 (-1.31, -0.55)
Nasal obstruction (0-10)	9.02 (0.83)	-2.54 (0.25)	8.92 (0.83)	-4.40 (0.25)	-1.86 (-2.53, -1.19)

CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SD = standard deviation, SE = standard error, CI = Confidence Interval, NPS = Nasal polyp score at Week 52.
[a]Patients with nasal surgery were assigned worst possible score for the period after nasal surgery. Missing data were imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model.
[b]Least square means from analysis using mixed model repeated measures with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count, visit, interaction terms for visit by baseline and visit by treatment.

Nasal Polypectomy

The key secondary endpoint was the time to first nasal surgery (nasal polypectomy) up to Week 52. The proportion of patients who had surgery was significantly reduced by 57% (hazard ratio: 0.43, 95% CI: 0.25, 0.76) in the group treated with NUCALA 100 mg compared with the placebo group (Figure 2). By Week 52, 18 (9%) patients who received NUCALA 100 mg had surgery compared with 46 (23%) patients in the placebo group.

Figure 2. Kaplan-Meier Plot of Time to First Nasal Surgery in CRSwNP



CRSwNP = Chronic Rhinosinusitis with Nasal Polyps, SC = subcutaneous.

Additional CRSwNP Symptoms Scores

For patients who received NUCALA 100 mg, statistically significant improvement was observed in loss of smell compared to placebo and improvements were also observed in the individual VAS symptom scores compared with patients in the placebo group in the 4-weeks prior to the end of the 52-week treatment period (Table 8).

Table 8: Additional Visual Analog Scale Symptom Scores Assessed at Weeks 49-52

VAS Scores[a] (range)	Placebo n = 201		NUCALA 100 mg n = 206		Mean Difference vs. Placebo (95% CI)
	Baseline Mean (SD)	Mean Change[b] (SE)	Baseline Mean (SD)	Mean Change[b] (SE)	
Loss of smell (0-10)	9.68 (0.60)	-1.46 (0.24)	9.63 (0.83)	-2.92 (0.24)	-1.46 (-2.11, -0.81)
Nasal discharge[c] (0-10)	8.78 (1.25)	-2.49 (0.26)	8.78 (1.07)	-4.38 (0.25)	-1.89 (-2.58, -1.20)
Mucus in the throat[c] (0-10)	8.58 (1.63)	-2.37 (0.26)	8.51 (1.61)	-4.07 (0.26)	-1.70 (-2.41, -0.99)
Facial pain[c] (0-10)	7.77 (2.72)	-2.04 (0.28)	7.76 (2.51)	-3.73 (0.27)	-1.69 (-2.43, -0.95)

VAS = Visual Analog Scale; SD = Standard Deviation; SE = Standard Error; CI = Confidence Interval.

[a]Patients with nasal surgery were assigned the worst possible score for the period after nasal surgery. Missing data was imputed based on available off-treatment data across treatment arms. Imputations were made stepwise by visit and conditioned on data from previous visits with the same covariates used in the analysis model.

[b]Least square means from an analysis using mixed model repeated measures with covariates of treatment group, geographic region, baseline score, and log(e) baseline blood eosinophil count visit, interaction terms for visit by baseline and visit by treatment.

[c]This endpoint was not prespecified in the analysis plan to adjust for multiplicity.

Corticosteroid Reduction

Treatment with NUCALA 100 mg significantly reduced the need for systemic steroids for nasal polyps vs. placebo up to Week 52 (odds ratio: 0.58, 95% CI: 0.36, 0.92). In patients who received NUCALA 100 mg, 52 (25%) required ≥1 course of systemic steroids compared with 74 (37%) in the placebo group throughout the 52-week treatment period.

Results in Patients with Co-morbid Asthma

In 289 (71%) patients with co-morbid asthma, pre-specified analyses showed improvements in the co-primary endpoints consistent with those seen in the overall population in the patients who received NUCALA 100 mg compared with placebo. Additionally, based on a post-hoc analysis in these patients, there was a greater response from baseline at Week 52 in asthma control as measured by the Asthma Control Questionnaire (ACQ-5) for NUCALA 100 mg compared with placebo (57% of the NUCALA patients met the responder threshold reduction of ≥0.5, compared to 35% in the placebo group, with an odds ratio of 2.42 (95% CI 1.43, 4.11)).

c. Eosinophilic Granulomatosis with Polyangiitis

A total of 136 adult patients with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial (NCT02020889). Patients 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. Efficacy was assessed in this trial using co-endpoints of 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 patients 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 patients in this trial are provided in Table 9.

Table 9. Demographics and Baseline Characteristics in EGPA

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

EGPA = Eosinophilic Granulomatosis with Polyangiitis, SD = standard deviation.
[a] Prednisone or prednisolone equivalent.
[b] e.g., Azathioprine, methotrexate, mycophenolic acid.

Remission

Patients receiving 300 mg of NUCALA achieved a significantly greater accrued time in remission compared with placebo. A significantly higher proportion of patients receiving 300 mg of NUCALA achieved remission at both Week 36 and Week 48 compared with placebo (Table 10). Results of the components of remission are also shown in Table 10. In addition, significantly more patients receiving 300 mg of NUCALA achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week trial 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 10. Remission and Components of Remission in EGPA

	Remission (OCS ≤4 mg/day + BVAS = 0)		OCS ≤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)
≥36 weeks	2 (3)	9 (13)	2 (3)	14 (21)	19 (28)	45 (66)
Odds ratio (NUCALA/placebo)[a] (95% CI)		5.9 (2.7, 13.0)		5.1 (2.5, 10.4)		3.7 (1.8, 7.6)
Proportion of patients at both Weeks 36 and 48						
Patients, n (%)	2 (3)	22 (32)	7 (10)	28 (41)	23 (34)	34 (50)
Odds ratio (NUCALA/placebo)[a] (95% CI)		16.7 (3.6, 77.6)		6.6 (2.6, 17.1)		1.9 (0.9, 4.2)

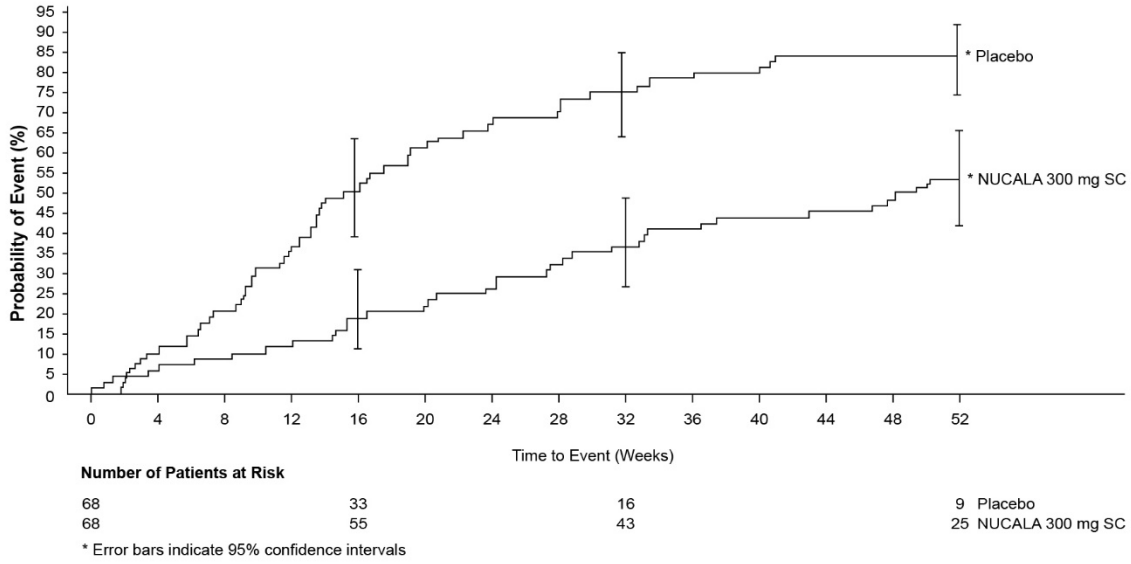
EGPA = Eosinophilic Granulomatosis with Polyangiitis, OCS = Oral Corticosteroid, BVAS = Birmingham Vasculitis Activity Score, CI = confidence interval.
[a] An odds ratio >1 favors NUCALA.

Additionally, a statistically significant benefit for these endpoints was demonstrated using remission defined as BVAS = 0 plus prednisolone/prednisone ≤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 patients receiving 300 mg of NUCALA compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5) (Figure 2). Additionally, patients receiving 300 mg of NUCALA had a reduction in rate of relapse compared with patients 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 NUCALA compared with placebo.

Figure 3. Kaplan-Meier Plot of Time to First Relapse in EGPA



EGPA = Eosinophilic Granulomatosis with Polyangiitis, SC = subcutaneous.

Corticosteroid Reduction

Patients receiving 300 mg of NUCALA had a significantly greater reduction in average daily OCS dose compared with patients receiving placebo during Weeks 48 to 52 (Table 11).

Table 11. Average Daily Oral Corticosteroid Dose during Weeks 48 to 52 in EGPA

	Number (%) of Patients	
	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: NUCALA/placebo[a]		
Odds ratio[b]		0.20
95% CI		0.09, 0.41

EGPA = Eosinophilic Granulomatosis with Polyangiitis, CI = confidence interval.

[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 NUCALA.

Asthma Control Questionnaire-6 (ACQ-6)

The ACQ-6, a 6-item questionnaire completed by the patient, 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).

d. Hypereosinophilic Syndrome

A total of 108 adult and adolescent patients aged 12 years and older with HES for at least 6 months were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 32-week trial (NCT02836496). Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of NUCALA or placebo subcutaneously once every 4 weeks while continuing their stable HES therapy. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and a blood eosinophil count of 1,000 cells/mcL or higher during screening. Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. Patients must have been on stable HES therapy for the 4 weeks prior to randomization. HES therapy could include chronic or episodic oral corticosteroids (OCS), immunosuppressive, or cytotoxic therapy.

The efficacy of NUCALA in HES was established based upon the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy.

The demographics and baseline characteristics of patients in this trial are provided in Table 12.

Table 12. Demographics and Baseline Characteristics in HES

	N = 108
Mean age, years (SD)	46.0 (15.78)
Female, n (%)	57 (53)
White, n (%)	100 (93)
Mean duration of HES, years	5.55

HES = Hypereosinophilic Syndrome, SD = standard deviation.

Flares

The trial compared the proportion of patients who experienced a HES flare or withdrew from the trial in the NUCALA and placebo treatment groups (Table 13). Over the 32-week treatment period, the incidence of HES flare over the treatment period was 56% for the placebo group and 28% for the group treated with NUCALA (50% reduction).

Table 13. Overview of HES Flares

	Number (%) of Patients	
	Placebo n = 54	**NUCALA 300 mg n = 54**
Patients with ⩾1 HES flare or who withdrew from trial	30 (56)	15 (28)
Patients with ⩾1 HES flare	28 (52)	14 (26)
Patients with no HES flare who withdrew from trial	2 (4)	1 (2)
Comparison: NUCALA/placebo[a]		
CMH *P* value		0.002
Odds ratio[b]		0.28
95% CI		(0.12, 0.64)

HES = Hypereosinophilic Syndrome, CMH = Cochran-Mantel-Haenszel, CI = confidence interval.

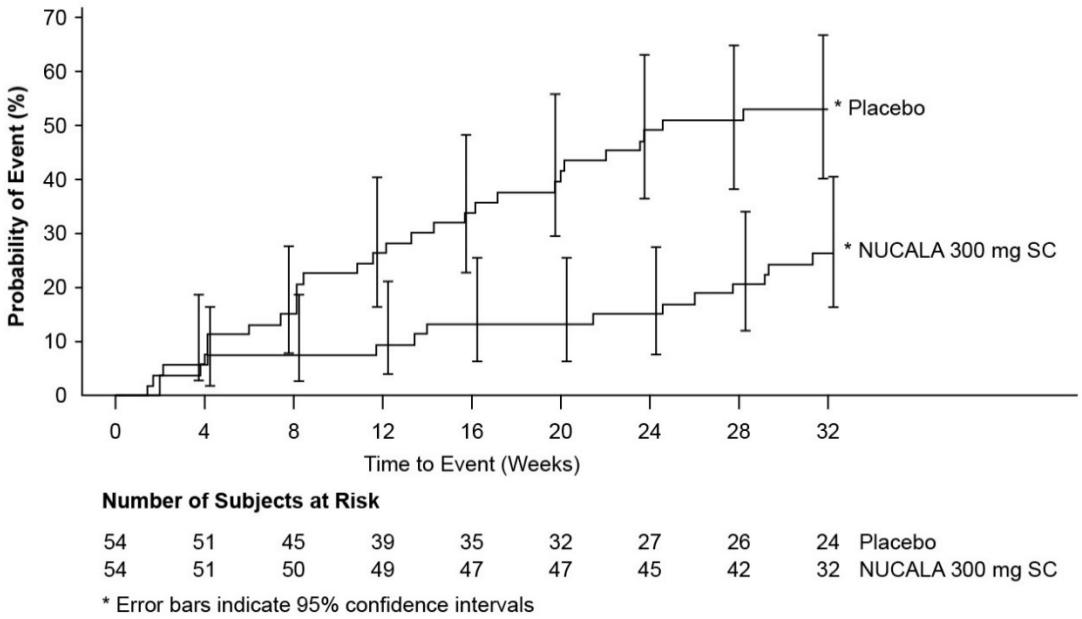
[a] Analysis compared the number of patients who experienced ≥1 HES flare and/or withdrew from the trial prematurely.

[b] An odds ratio <1 favors NUCALA.

Time to First Flare

Difference was observed between NUCALA and placebo arms in the time to first HES flare (Figure 4). The risk of first HES flare over the treatment period was 66 % lower for patients treated with NUCALA compared with placebo (Hazard Ratio: 0.34; 95 % CI 0.18, 0.67, *P* = 0.002).

Figure 4. Kaplan-Meier Curve for Time to First HES Flare



HES = Hypereosinophilic Syndrome, SC = subcutaneous.

Proportion of Patients Who Experienced Flares during Week 20 through Week 32

From Week 20 through Week 32, significantly fewer patients experienced a HES flare or withdrew from the trial when treated with 300 mg of NUCALA compared with placebo (17% vs. 35%, respectively, *P* = 0.020; OR: 0.33; 95 % CI: 0.13, 0.85).

Rate of Flares

Patients who received NUCALA experienced significantly fewer HES flares during the 32-week treatment period compared with the placebo group (Table 14). Treatment with NUCALA resulted in a statistically significant 66% reduction in the annualized rate of HES flares compared with placebo.

Table 14. Frequency of Flares

	Number (%) of Patients	
	Placebo n = 54	**NUCALA 300 mg n = 54**
0	26 (48)	40 (74)
1	15 (28)	11 (20)
2	7 (13)	3 (6)
3	5 (9)	0
4	1 (2)	0
⩾5	0	0
Comparison: NUCALA/placebo		
Wilcoxon *P* value (unadjusted/adjusted)[a]		0.002/0.02
Rate/year	1.46	0.50
Rate ratio[b]		0.34
95% CI		(0.19, 0.63)

CI = confidence interval.
[a] Adjusted *P* values based on pre-specified hierarchy of endpoints.
[b] A rate ratio <1 favors NUCALA.

Brief Fatigue Inventory

Brief Fatigue Inventory (BFI) Item 3 asks patients to record their worst level of weariness/tiredness severity during the past 24 hours (scale: 0 = no fatigue to 10 = as bad as you can imagine). At baseline, median BFI Item 3 scores were similar between treatment groups (4.46 for NUCALA 300 mg and 4.69 for placebo). At Week 32, BFI Item 3 scores improved with NUCALA compared with placebo (*P* = 0.036). The median change from baseline score for BFI Item 3 at Week 32 was -0.66 in the group treated with NUCALA and 0.32 in the placebo group.

5.3. Pre-clinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of mepolizumab. Published literature using animal models suggests that IL-5 and eosinophils are part of an early inflammatory reaction at the site of tumorigenesis and can promote tumor rejection. However, other reports indicate that eosinophil infiltration into tumors can promote tumor growth. Therefore, the malignancy risk in humans from an antibody to IL-5 such as mepolizumab is unknown.

Male and female fertility were unaffected based upon no adverse histopathological findings in the reproductive organs from cynomolgus monkeys receiving mepolizumab for 6 months at IV dosages up to 100 mg/kg once every 4 weeks (approximately 20 times the MRHD of 300 mg on an AUC basis). Mating and reproductive performance were unaffected in male and female CD-1 mice receiving an analogous antibody, which inhibits the activity of murine IL-5, at an IV dosage of 50 mg/kg once per week.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Excipient Name	Quantity	Unit
Sucrose	120	mg
Sodium phosphate dibasic heptahydrate	4.16	mg
Citric acid monohydrate	0.95	mg
Polysorbate 80	0.20	mg
EDTA disodium dehydrate	0.019	mg
Water for injection	QS 1	mL

6.2. Incompatibilities

No incompatibilities have been identified.

6.3. Shelf Life

The expiry date is indicated on the packaging.

6.4. Special Precautions for 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.

6.5. Nature and Contents of Container

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

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

6.6. Instructions for Use/Handling

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

Not all presentations are available in every country.

7. MARKETING AUTHORISATION HOLDER:

Glaxo Saudi Arabia Ltd.*, Jeddah, Kingdom of Saudi Arabia.

8. MANUFACTURED BY:

Glaxo Operations UK Ltd*, Barnard Castle, UK

*member of the GSK group of companies

9. DATE OF REVISION OF TEXT:

US CPI Version_29 July 2021