DUPIXENT (dupilumab) 100 mg solution for injection in a pre-filled syringe

DUPIXENT (dupilumab) 200 mg solution for injection in a pre-filled syringe

DUPIXENT (dupilumab) 300 mg solution for injection in a pre-filled syringe

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DUPIXENT is indicated for the following diseases:

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis who require chronic treatment and whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

DUPIXENT is indicated in patients 6 years and older as an add-on maintenance treatment for severe asthma with type 2 inflammation characterized by elevated blood eosinophils and/or elevated FeNO.

DUPIXENT is indicated as maintenance therapy for oral corticosteroid-dependent asthma

2 DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection.

2.1 Atopic Dermatitis

Dosing in Adults

The recommended dose of DUPIXENT for adult patients is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Dosing in Pediatric Patients (6 to 17 Years of Age)

The recommended dose of Dupixent for patients 6 to 17 years of age is specified in Table 1.

Table 1: Dose of DUPIXENT for Subcutaneous Administration in Pediatric Patients (6 to 17 Years of Age)

Body Weight	Initial Dose	Subsequent Doses
15 to less than 30kg	600mg (two 300mg injections)	300mg every 4 weeks (Q4W)
30 to less than 60kg	400mg (two 200mg injections)	200mg every other week (Q2W)
60kg or more	600mg (two 300mg injections)	300mg every other week (Q2W)

Concomitant Topical Therapies

DUPIXENT can be used with or without topical corticosteroids. Topical calcineurin inhibitors may be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

2.2 Asthma

Adults and adolescents

The recommended dose of DUPIXENT for adults and adolescents (12 years of age and older) is:

• An initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week.

• An initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week for patients with oral corticosteroids-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated.

Pediatric Patients (6 to 11 years of age)

The recommended dose of DUPIXENT for pediatric patients 6 to 11 years of age is specified in Table 2.

Table 2: Dose of DUPIXENT for Subcutaneous Administration Pediatric Patients 6 to 11 Years of Age with Asthma

Body Weight	Initial and Subsequent Doses
15 to less than 30 kg	100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
30 to less than 60 kg	200 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
60 kg or more	200 mg every other week (Q2W)

For pediatric patients (6-11 years old) with asthma and co-morbid moderate-to-severe atopic dermatitis, the recommended dose should be followed in Table 1.

2.3 Important Administration Instructions

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe.

Dupixent pre-filled syringe should be given by a caregiver in children 6-11 years of age.

Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the “Instructions for Use”.

For atopic dermatitis and asthma patients taking an initial 600 mg dose, administer each of the two DUPIXENT 300 mg injections at different injection sites.

For atopic dermatitis and asthma patients taking an initial 400 mg dose, administer each of the two DUPIXENT 200 mg injections at different injection sites.

Administer subcutaneous injection into the thigh or abdomen, except for the 2 inches (5 cm) around the navel. The upper arm can also be used if a caregiver administers the injection.

Rotate the injection site with each injection. DO NOT inject DUPIXENT into skin that is tender, damaged, bruised, or scarred.

If an every other week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

If an every 4 week dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to administer the dose, starting a new schedule based on this date.

The DUPIXENT "Instructions for Use" contains more detailed instructions on the preparation and administration of DUPIXENT *[see Instructions for Use]*.

2.4 Preparation for Use of DUPIXENT Pre-filled Syringe With Needle Shield

Before injection, remove DUPIXENT pre-filled syringe from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300mg/2mL pre-filled syringe, 30 minutes for the 200mg/1.14mL pre-filled syringe and 30 minutes for the 100 mg/0.67mL pre-filled syringe) without removing the needle cap.

Inspect DUPIXENT visually for particulate matter and discoloration prior to administration. DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution. Do not use if the liquid contains visible particulate matter, is discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow). DUPIXENT does not contain preservatives; therefore, discard any unused product remaining in the pre-filled syringe.

3 DOSAGE FORMS AND STRENGTHS

DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution available as:

- Injection: 300 mg/2 mL in a single-dose pre-filled syringe with needle shield
- Injection: 200 mg/1.14 mL in a single-dose pre-filled syringe with needle shield
- Injection: 100mg/0.67 mL in a single-dose pre-filled syringe with needle shield

4 CONTRAINDICATIONS

DUPIXENT is contraindicated in patients who have known hypersensitivity to dupilumab or any of its excipients *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including generalized urticaria, rash, erythema nodosum, anaphylaxis, serum sickness or serum sickness-like reactions and angioedema, have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT *[see Adverse Reactions (6.1, 6.2)]*.

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Some patients reported visual disturbances (e.g. blurred vision) associated with conjunctivitis or keratitis. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Among asthma subjects, the frequencies of conjunctivitis and keratitis were similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*.

Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Patients treated with DUPIXENT who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis should undergo ophthalmological examination, as appropriate.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be

associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.6 Patients with Co-morbid Asthma

Advise patients with atopic dermatitis who have co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

Patients with known helminth infections were excluded from participation in clinical studies. It is unknown if DUPIXENT will influence the immune response against helminth infections.

Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves. Cases of enterobiasis were reported in children 6 to 11 years old who participated in the pediatric asthma development program [see *Clinical Trials Experience (6.1*)]

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail elsewhere in the labeling:

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4):

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

	DUPIXENT Monotherapy[a]		**DUPIXENT + TCS[b]**	
Adverse Reaction	**DUPIXENT 300 mg Q2W[c]** **N=529** **n (%)**	**Placebo** **N=517** **n (%)**	**DUPIXENT 300 mg Q2W[c] + TCS** **N=110** **n (%)**	**Placebo + TCS** **N=315** **n (%)**
Injection site reactions	51 (10)	28 (5)	11 (10)	18 (6)
Conjunctivitis[d]	51 (10)	12 (2)	10 (9)	15 (5)
Blepharitis	2 (<1)	1 (<1)	5 (5)	2 (1)
Oral herpes	20 (4)	8 (2)	3 (3)	5 (2)
Keratitis[e]	1 (<1)	0	4 (4)	0
Eye pruritus	3 (1)	1 (<1)	2 (2)	2 (1)
Other herpes simplex virus infection[f]	10 (2)	6 (1)	1 (1)	1 (<1)
Dry eye	1 (<1)	0	2 (2)	1 (<1)

[a] pooled analysis of Trials 1, 2, and 4
[b] analysis of Trial 3 where subjects were on background TCS therapy
[c] DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks
[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
[e] Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.
[f] Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

Safety through Week 52 (Trial 3):

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

The safety profile of DUPIXENT + TCS through Week 52 was generally consistent with the safety profile observed at Week 16.

Adolescents with Atopic Dermatitis (12 to 17 Years of Age)

The safety of DUPIXENT was assessed in a trial of 250 subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 6). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Children with Atopic Dermatitis (6 to 11 Years of Age)

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 367 subjects 6 to 11 years of age with severe atopic dermatitis (Trial 8). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adults and adolescents with atopic dermatitis.

The long-term safety of DUPIXENT + TCS was assessed in an open-label extension study of 368 subjects 6 to 11 years of age with atopic dermatitis (Trial 7). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe atopic dermatitis at the time of enrollment in Trial 7. The safety profile of DUPIXENT + TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in Trial 8. The long-term safety profile of DUPIXENT + TCS observed in pediatric subjects was consistent with that seen in adults and adolescents with atopic dermatitis [see *Use in Specific Populations (8.4)*].

Asthma

A total of 2888 adult and adolescent subjects with asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were

white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

Table 4: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater than Placebo (6 Month Safety Pool)

Adverse Reaction	**AS Trials 1 and 2**		
	DUPIXENT 200 mg Q2W **N=779** **n (%)**	**DUPIXENT 300 mg Q2W** **N=788** **n (%)**	**Placebo** **N=792** **n (%)**
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.
[b] Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Warnings and Precautions (5.3)]*.

Injection site reactions were most common with the loading (initial) dose.

The safety profile of DUPIXENT through Week 52 was generally consistent with the safety profile observed at Week 24.

Pediatric patients (6 to 11 years of age)

The safety of DUPIXENT was assessed in 270 patients 6 to 11 years of age with asthma (VOYAGE). The safety profile of DUPIXENT in these patients through Week 52 was similar to the safety profile from studies in adults and adolescents with asthma, with the additional adverse reactions of enterobiasis and eosinophilia. Enterobiasis was reported in 1.8% (5 patients) in the DUPIXENT groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with anti-helminth treatment without DUPIXENT treatment discontinuation. Eosinophilia (blood eosinophils ≥3,000 cells/mcL or deemed by the investigator to be an adverse event) was reported in 6.6% of the DUPIXENT groups and 0.7% in the placebo group.

Specific Adverse Reactions

Conjunctivitis and Keratitis

During the 52-week treatment period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100

subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). In DUPIXENT atopic dermatitis monotherapy trials (Trials 1, 2, and 4) through Week 16, keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years). In the 52-week atopic dermatitis DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial (Trial 3), keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period. Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo. *[see Warnings and Precautions (5.2)]*.

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials.

Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included serum sickness reaction, serum sickness-like reaction, generalized urticaria, rash, erythema, nodosum and anaphylaxis*[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular

In the 1-year placebo controlled trial in subjects with asthma (AS Trial 2), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.2%) of the DUPIXENT 200 mg Q2W group, 4 (0.6%) of the DUPIXENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal

strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Approximately 5% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab, approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies**.** Similar results were observed in pediatric subjects (6 to 11 years of age) with atopic dermatitis who received DUPIXENT 200mg Q2W or 300mg Q4W for 16 weeks and pediatric subjects (6 to 11 years of age) with asthma who received DUPIXENT 100 mg Q2W or 200 mg Q2W for 52 weeks.

Approximately 16% of adolescent subjects with atopic dermatitis who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Approximately 9% of subjects with asthma who received DUPIXENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4% exhibited persistent ADA responses, and approximately 4% had neutralizing antibodies.

Regardless of age or population, approximately 2% to 4% of subjects in placebo groups were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

The antibody titers detected in both DUPIXENT and placebo subjects were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to dupilumab was associated with lower serum dupilumab concentrations *[see Clinical Pharmacology (12.3)]*.

Two subjects who experienced high titer antibody responses developed serum sickness or serum sickness-like reactions during DUPIXENT therapy *[see Warnings and Precautions (5.1)]*.

6.3 Post Marketing Experience

The following additional adverse reactions have been reported during post-approval use of DUPIXENT. The adverse reactions are derived from spontaneous reports and therefore, the frequency is “not known” (cannot be estimated from the available data).

Immune system disorders
Angioedema

Skin and subcutaneous tissue disorders
Facial rash

Musculoskeletal and connective tissue disorders
Arthralgia

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which adult subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (*see Clinical* Considerations). In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) *[see Data]*. The estimated background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. 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 Embryo-fetal 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 an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure to dupilumab on the breastfed infant are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for DUPIXENT and any potential adverse effects on the breastfed child from DUPIXENT or from the underlying maternal condition.

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 6 years of age and older with moderate-to-severe atopic dermatitis.

Use of DUPIXENT in this age group is supported by Trial 6 which included 251 adolescents age 12 to 17 years old with moderate-to-severe atopic dermatitis and Trial 8 which included 367 children age 6 to 11 years old with severe atopic dermatitis. The safety and efficacy were generally consistent between pediatric and adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

Use is also supported by Trial 7, an open-label extension study that enrolled subjects who completed Trials 6 and 8. Trial 7 included 136 adolescents from Trial 6 and 110 children from Trial 8 with moderate atopic dermatitis at enrollment into the extension study. Trial 7 included 64 adolescents from Trial 6 and 72 children from Trial 8 with severe atopic dermatitis at enrollment. No new safety signals were identified in Trial 7 [see *Adverse Reactions (6.1)*].

Safety and efficacy in pediatric patients (<6 years of age) with atopic dermatitis have not been established.

Asthma

Adolescents (12 to 17 years of age)

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200

mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults.Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3)]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

Children 6 to 11 years of age

A total of 408 children aged 6 to 11 years with asthma was enrolled in the VOYAGE study, which evaluated doses of 100 mg Q2W and 200 mg Q2W. The efficacy of DUPIXENT 300 mg Q4W in children aged 6 to 11 years is extrapolated from the efficacy of 100 mg and 200 mg Q2W in VOYAGE and 200 mg and 300 mg Q2W in adults and adolescents (AS Trial 2). Patients who completed the treatment period of the VOYAGE study could participate in the open label extension study (EXCURSION). Fourteen patients (≥15 to <30 kg) out of 365 patients were exposed to 300 mg Q4W in this study, and the safety profile was similar to that seen in VOYAGE.

Safety, efficacy, and pharmacokinetics in pediatric patients (<6 years of age) with asthma have not been studied.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

Of the 1977 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

10 OVERDOSE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

11 DESCRIPTION

Dupilumab, an interleukin-4 receptor alpha antagonist, is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4Rα subunit and inhibits IL-4 and IL-13 signaling. Dupilumab has an approximate molecular weight of 147 kDa.

Dupilumab is produced by recombinant DNA technology in Chinese Hamster Ovary cell suspension culture.

DUPIXENT (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection.

DUPIXENT 300mg Pre-Filled Syringe is provided as a single-dose pre-filled syringe with needle shield in a 2.25 mL siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300mg pre-filled syringe delivers 300 mg dupilumab in 2 mL which also contains L-arginine hydrochloride (10.5 mg), L-histidine (6.2 mg), polysorbate 80 (4 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.

DUPIXENT 200mg Pre-Filled Syringe is provided as a single dose pre-filled syringe with needle shield in a 1.14 mL siliconized Type-1 glass syringe. The needle cap is not made with natural rubber latex.

Each 200mg pre-filled syringe delivers 200 mg dupilumab in 1.14 mL which also contains L-arginine hydrochloride (12 mg), L-histidine (3.10 mg), L-histidine monohydrochloride monohydrate (0.60mg), polysorbate 80 (2.3 mg), sodium acetate trihydrate (1.50 mg), sucrose (57 mg), glacial acetic acid (0.19mg) and water for injection, pH 5.9.

DUPIXENT 100mg Pre-Filled Syringe is provided as a single dose pre-filled syringe with needle shield in a 0.67 mL siliconized Type-1 glass syringe. The needle cap is not made with natural rubber latex.

Each 100mg pre-filled syringe delivers 100 mg dupilumab in 0.67 mL which also contains L-arginine hydrochloride (3.53mg), L-histidine (1.82mg), L-histidine monohydrochloride monohydrate (0.35mg), polysorbate 80 (1.34mg), sodium acetate trihydrate (0.88mg), sucrose (33.5mg), glacial acetic acid (0.11mg) and water for injection, pH 5.9.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation is an important component in the pathogenesis of asthma and atopic dermatitis. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines, chemokines) are involved in inflammation.

Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide and IgE; however, the mechanism of dupilumab action in asthma has not been definitively established.

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. These reductions in biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (AS Trial 1) and 70% at Week 52 (AS Trial 2). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in AS Trials 1 and 2 respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

12.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with atopic dermatitis and asthma.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400mg or 300mg, dupilumab reached peak mean ±SD concentrations (C_{max}) of 70.1±24.1 mcg/mL,41.8±12.4 mcg/mL, or 30.5±9.39 mcg/mL respectively, by approximately 1 week post dose.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or Q2W, or 400 mg starting dose and 200 mg dose Q2W, or 300 mg Q2W without a loading dose . Across clinical trials, the mean ±SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.

The bioavailability of dupilumab following a SC dose is estimated similar between AD and, asthma patients, ranging between 61% and 64%.

Distribution

The estimated total volume of distribution was approximately 4.8±1.3 L.

Elimination

The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W, 300 mg QW or 200mg Q2W dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10-12, 13 and 9 weeks, respectively.

Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose

increased 8-fold following a single dose of dupilumab from 75 mg to 600 mg (i.e., 0.25-times to 2-times the recommended dose).

Weight

Dupilumab trough concentrations were lower in subjects with higher body weight.

Age

Based on population pharmacokinetic analysis, age did not affect dupilumab clearance.

Immunogenicity

Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations. A few subjects who had high antibody titers also had no detectable serum dupilumab concentrations.

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean ±SD steady-state trough concentrations of dupilumab were 69.4±31.4 mcg/mL and 166±62.3 mcg/mL, respectively, for 300 mg administered Q2W and weekly, and 39.7±21.7 mcg/mL for 200 mg administered Q2W.

Pediatric Patients

Atopic Dermatitis

For adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean ± SD steady-state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

For children 6 to 11 years of age with atopic dermatitis receiving every other week dosing (Q2W) with 200 mg (≥30 kg) or every four week dosing (Q4W) with 300 mg (<30 kg), mean ± SD steady-state trough concentration was 86.0±34.6 mcg/mL and 98.7±33.2 mcg/mL, respectively.

Asthma

A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in AS Trial 2. The mean ± SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL, respectively, for 300 mg or 200 mg administered Q2W.

In the VOYAGE study, dupilumab pharmacokinetics was investigated in270 patients with asthma following subcutaneous administration of either 100 mg Q2W (for 91 children weighing <30 kg) or 200 mg Q2W (for 179 children weighing ≥30 kg). The mean ± SD steady-state trough concentration was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥15 to <30 kg and ≥30 to <60 kg resulted in predicted steady-state trough concentrations similar to the observed trough concentrations of 200 mg Q2W (≥30 kg) and 100 mg Q2W (<30 kg), respectively. In addition, simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to 11 years with body weight of ≥15 to <60 kg resulted in predicted steady-state trough concentrations similar to those demonstrated to be efficacious in adults and adolescents.

Renal or Hepatic Impairment

No formal trial of the effect of hepatic or renal impairment on the pharmacokinetics of dupilumab was conducted.

Drug Interaction Studies

An effect of dupilumab on the PK of co-administered medications is not expected. Based on the population analysis, commonly co-administered medications had no effect on DUPIXENT pharmacokinetics in patients with moderate-to-severe asthma.

Cytochrome P450 Substrates

The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), metoprolol (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in a study with 12-13 evaluable subjects with atopic dermatitis (a SC loading dose of 600 mg followed by 300 mg SC weekly for six weeks). No clinically significant changes in AUC were observed. The largest effect was observed for metoprolol (CYP2D6) with an increase in AUC of 29%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab.

No effects on fertility parameters such as reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature mice that were subcutaneously administered a homologous antibody against IL-4Rα at doses up to 200 mg/kg/week.

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled trials (Trials 1, 2, and 3; NCT02277743, 02277769, and 02260986 respectively) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were white, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (Trials 1 and 2), subjects received DUPIXENT or placebo for 16 weeks.

In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

All three trials assessed the primary endpoint, the change from baseline to Week 16 in the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement. Other endpoints included the proportion of subjects with EASI-75 (improvement of at least 75% in EASI score from baseline), and reduction in itch as defined by at least a 4-point improvement in the peak pruritus NRS from baseline to Week 16.

Clinical Response at Week 16 (Trials 1, 2, and 3)

The results of the DUPIXENT monotherapy trials (Trials 1 and 2) and the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 5.

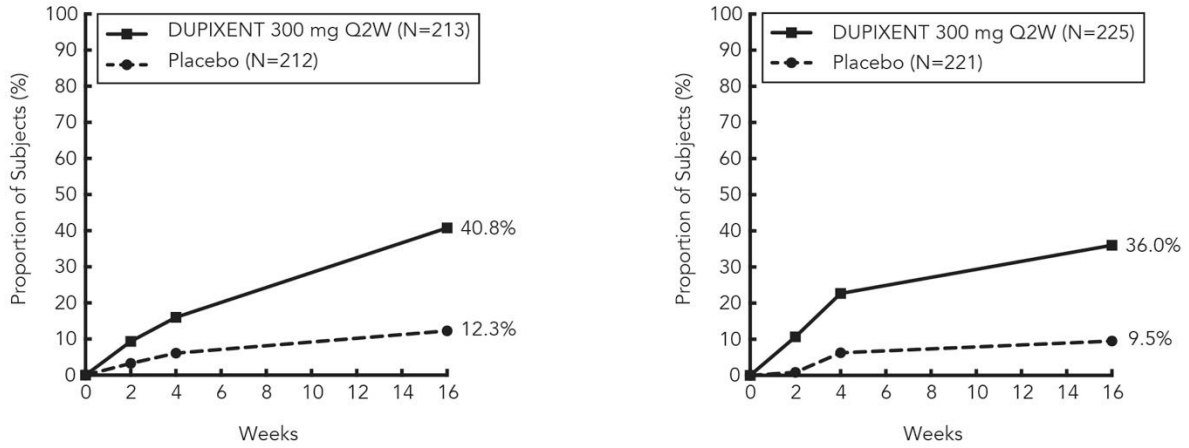
Table 5: Efficacy Results of DUPIXENT With or Without Concomitant TCS at Week 16 (FAS)

	Trial 1		**Trial 2**		**Trial 3**	
	DUPIXENT 300 mg Q2W	**Placebo**	**DUPIXENT 300 mg Q2W**	**Placebo**	**DUPIXENT 300 mg Q2W + TCS**	**Placebo + TCS**
Number of subjects randomized (FAS)[a]	224	224	233	236	106	315
IGA 0 or 1[b,c]	38%	10%	36%	9%	39%	12%
EASI-75[c]	51%	15%	44%	12%	69%	23%
EASI-90[c]	36%	8%	30%	7%	40%	11%
Number of subjects with baseline Peak Pruritus NRS score ≥4	213	212	225	221	102	299
Peak Pruritus NRS (≥4-point improvement)[c]	41%	12%	36%	10%	59%	20%

[a] Full Analysis Set (FAS) includes all subjects randomized.
[b] Responder was defined as a subject with IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

Figure 1: Proportion of Subjects with ≥4-point Improvement on the Peak Pruritus NRS in Trial 1[a] and Trial 2[a] Studies (FAS)[b]

Trial 1 **Trial 2**



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomized.

In Trial 3, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUPIXENT IGA 0 or 1 responders at Week 16 remained responders at Week 52) and subjects who were non-responders at Week 16 who later responded to treatment (e.g., 24% of DUPIXENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 6.

Table 6: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52

	DUPIXENT 300 mg Q2W + TCS	**Placebo + TCS**
Number of Subjects[a]	89	264
Responder[b,c] at Week 16 and 52	22%	7%
Responder at Week 16 but Non-responder at Week 52	20%	7%
Non-responder at Week 16 and Responder at Week 52	13%	6%
Non-responder at Week 16 and 52	44%	80%
Overall Responder[b,c] Rate at Week 52	36%	13%

[a] In Trial 3, of the 421 randomized and treated subjects, 68 subjects (16%) had not been on study for 52 weeks at the time of data analysis.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

Treatment effects in subgroups (weight, age, gender, race, and prior treatment, including immunosuppressants) in Trials 1, 2, and 3 were generally consistent with the results in the overall study population.

In Trials 1, 2, and 3, a third randomized treatment arm of DUPIXENT 300 mg QW did not demonstrate additional treatment benefit over DUPIXENT 300 mg Q2W.

Subjects in Trials 1 and 2 who had an IGA 0 or 1 with a reduction of ≥2 points were re- randomized into Trial 5. Trial 5 evaluated multiple DUPIXENT monotherapy dose regimens for maintaining treatment response. The study included subjects randomized to continue with DUPIXENT 300 mg Q2W (62 subjects) or switch to placebo (31 subjects) for 36 weeks. IGA 0 or 1 responses at Week 36 were as follows: 33 (53%) in the Q2W group and 3 (10%) in the placebo group.

Adolescents with Atopic Dermatitis (12 to 17 Years of Age)

The efficacy and safety of DUPIXENT monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 6; NCT03054428) in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.

Subjects in the DUPIXENT group with baseline weight of <60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight of ≥60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg Q2W for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In Trial 6, the mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 63% were White, 15% were Asian, and 12% were Black. At baseline 46% of subjects had an IGA score of 3 (moderate AD), 54% had an IGA score of 4 (severe AD), the mean BSA involvement was 57%, and 42% had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 36, and the weekly averaged Peak Pruritus NRS was 8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 54% had asthma, and 61% had food allergies.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 for Trial 6 are presented in Table 7.

Table 7: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)[a]

	DUPIXENT[d] 200 mg (<60 kg) or 300 mg (≥60 kg) Q2W N=82[a]	**Placebo N=85[a]**
IGA 0 or 1[b,c]	24%	2%
EASI-75[c]	42%	8%
EASI-90[c]	23%	2%
Peak Pruritus NRS (≥4-point improvement)[c]	37%	5%

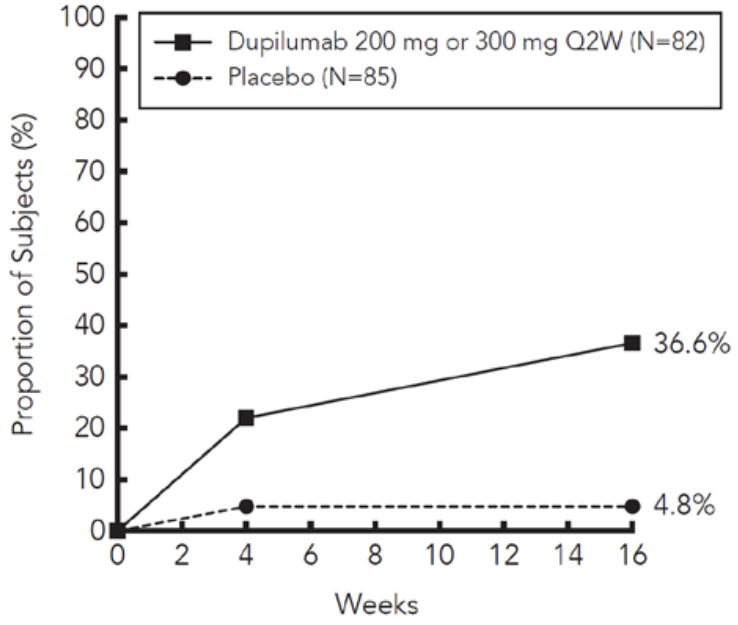
[a] Full Analysis Set (FAS) includes all subjects randomized.

[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.

[c] Subjects who received rescue treatment or with missing data were considered as non-responders (59% and 21% in the placebo and DUPIXENT arms, respectively). d At Week 0, subjects received 400 mg (baseline weight <60 kg) or 600 mg (baseline weight ≥60 kg) of DUPIXENT.

A greater proportion of subjects randomized to DUPIXENT achieved an improvement in the Peak Pruritus NRS compared to placebo (defined as ≥4-point improvement at Week 4). See Figure 2.

Figure 2: Proportion of Adolescent Subjects with ≥4-point Improvement on the Peak Pruritus NRS in Trial 6[a] (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.

[b] Full Analysis Set (FAS) includes all subjects randomized.

Children with Atopic Dermatitis (6 to 11 Years of Age)

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 8; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; ≥30 kg).

Subjects in the DUPIXENT Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12, regardless of weight. Subjects in the DUPIXENT Q2W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and subjects with baseline weight of ≥30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from Week 2 to Week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In Trial 8, the mean age was 8.5 years, the median weight was 29.8 kg, 50% of subjects were female, 69% were White, 17% were Black, and 8% were Asian. At baseline, the mean BSA involvement was 58%, and 17% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 64% had food allergies, 63% had other allergies, 60% had allergic rhinitis, and 47% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

Table 7 presents the results by baseline weight strata for the approved dose regimens.

Table 7: Efficacy Results of DUPIXENT with Concomitant TCS in Trial 8 at Week 16 (FAS)[a]

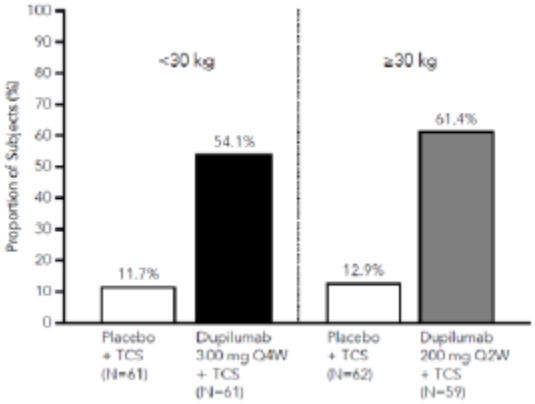
	DUPIXENT 300 mg Q4W[d] + TCS (N=61)	**Placebo + TCS (N=61)**	**DUPIXENT 200 mg Q2W[e] + TCS (N=59)**	**Placebo + TCS (N=62)**
	<30 kg	**<30 kg**	**≥30 kg**	**≥30 kg**
IGA 0 or 1[b,c]	30%	13%	39%	10%
EASI-75[c]	75%	28%	75%	26%
EASI-90[c]	46%	7%	36%	8%

Peak Pruritus NRS (≥4-point improvement)[c]	54%	12%	61%	13%

[a] Full Analysis Set (FAS) includes all subjects randomized.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear").
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.
[d] At Day 1, subjects received 600 mg of DUPIXENT.
[e] At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUPIXENT

A greater proportion of subjects randomized to DUPIXENT + TCS achieved an improvement in the Peak Pruritus NRS compared to placebo + TCS (defined as ≥4-point improvement at Week 16). See Figure 3.

Figure 3: Proportion of Pediatric Subjects with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in Trial 8[a] (FAS)[b]



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.

[b] Full Analysis Set (FAS) includes all subjects randomized

14.2 Asthma

The asthma development program included three randomized, double-blind, placebo-controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of >1500 cells/mcL (<1.3%) were excluded. DUPIXENT was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) DUPIXENT every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) DUPIXENT every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV1 (L) in subjects with baseline blood eosinophils ≥300 cells/mcL. Other endpoints included percent change from baseline in FEV1 and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (≥300 cells/mcL and <300 cells/mcL). Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2

AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 adolescent and 1795 adult subjects with asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) DUPIXENT Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in prebronchodilator FEV1 at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV1 in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3

AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg DUPIXENT (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their existing asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

The demographics and baseline characteristics of these 3 trials are provided in Table 8 below.

Table 8 : Demographics and Baseline Characteristics of Asthma Trials

Parameter	**Trial 1 (N=776)**	**Trial 2 (N=1902)**	**Trial 3 (N=210)**
Mean age (years) (SD)	49 (13)	48 (15)	51 (13)
% Female	63	63	61
% White	78	83	94
Duration of Asthma (years), mean (± SD)	22 (15)	21 (15)	20 (14)
Never smoked (%)	77	81	81
Mean exacerbations in previous year (± SD)	2.2 (2.1)	2.1 (2.2)	2.1 (2.2)
High dose ICS use (%)	50	52	89
Pre-dose FEV1 (L) at baseline (± SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV1 at baseline (%) (± SD)	61 (11)	58 (14)	52 (15)
% Reversibility (± SD)	27 (15)	26 (22)	19 (23)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	73 (8, 11, 62)	78 (10, 13, 69)	72 (8, 21, 56)
Mean FeNO ppb (± SD)	39 (35)	35 (33)	38 (31)
% patients with FeNO ppb			
≥25	49.9	49.6	54.3
≥50	21.6	20.5	25.2
Mean total IgE IU/mL (± SD)	435 (754)	432 (747)	431 (776)
Mean baseline blood Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)
% patients with EOS			
≥ 150 cells/mcL	77.8	71.4	71.4
≥ 300 cells/mcL	41.9	43.7	42.4

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

Exacerbations

AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis

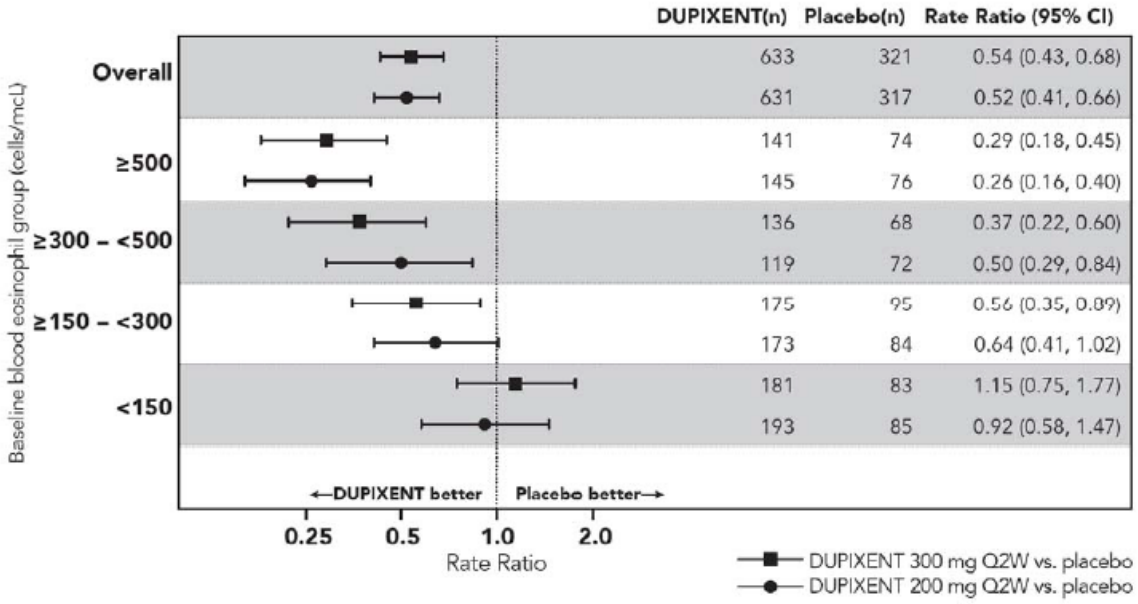
population (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either DUPIXENT 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mcL in AS Trials 1 and 2 are shown in Table 9.
Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 4. Pre-specified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥150 cells/mcL. In subjects with baseline blood eosinophil count <150 cells/mcL, similar severe exacerbation rates were observed between DUPIXENT and placebo.

In AS Trial 2, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits versus placebo was 0.53 (95% CI: 0.28, 1.03) and 0.74 (95% CI: 0.32, 1.70) with DUPIXENT 200 mg or 300 mg Q2W, respectively.

Table 9: Rate of Severe Exacerbations in AS Trials 1 and 2

Trial	Treatment	Baseline Blood EOS							
		≥150 cells/mcL				≥300 cells/mcL			
		Exacerbations per Year			Percent Reduction	Exacerbations per Year			Percent Reduction
		N	Rate (95% CI)	Rate Ratio (95%CI)		N	Rate (95% CI)	Rate Ratio (95%CI)	
All Severe Exacerbations									
AS Trial 1	DUPIXENT 200 mg Q2W	120	0.29 (0.16, 0.53)	0.28 (0.14, 0.55)	72 %	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)	71 %
	DUPIXENT 300 mg Q2W	129	0.28 (0.158, 0.496)	0.27 (0.14, 0.52)	73 %	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)	81 %
	Placebo	127	1.05 (0.69, 1.60)			68	1.04 (0.57, 1.90)		
AS Trial 2	DUPIXENT 200 mg Q2W	437	0.45 (0.37, 0.54)	0.44 (0.34,0.58)	56 %	264	0.37 (0.29, 0.48)	0.34 (0.24,0.48)	66 %
	Placebo	232	1.01 (0.81, 1.25)			148	1.08 (0.846, 1.382)		
	DUPIXENT 300 mg Q2W	452	0.43 (0.36, 0.53)	0.40 (0.31,0.53)	60 %	277	0.40 (0.32, 0.51)	0.33 (0.23,0.45)	67 %
	Placebo	237	1.08 (0.88, 1.33)			142	1.24 (0.97, 1.57)		

Figure 4: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline Blood Eosinophil Count (cells/mcL) in AS Trial 2



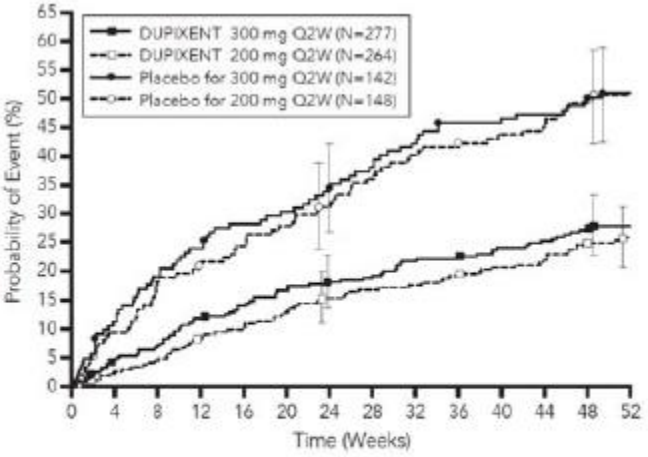
In AS Trial 2, when compared to placebo, greater reductions in severe exacerbations were also seen in patients with baseline FeNO ≥25 and FeNO ≥50 ppb as shown in Table 10.

Table 10: Rate of Severe Exacerbations in AS Trial 2 Defined by Baseline FeNO Subgroups

Treatment	Exacerbations per Year			Percent Reduction
	N	Rate (95% CI)	Rate Ratio (95%CI)	
FeNO ≥ 25 ppb				
DUPIXENT 200 mg Q2W	299	0.35 (0.27, 0.45)	0.35 (0.25, 0.50)	65%
Placebo	162	1.00 (0.78, 1.30)		
DUPIXENT 300 mg Q2W	310	0.43 (0.35, 0.54)	0.39 (0.28, 0.54)	61%
Placebo	172	1.12 (0.88, 1.43)		
FeNO ≥ 50 ppb				
DUPIXENT 200 mg Q2W	119	0.33 (0.22, 0.48)	0.31 (0.18, 0.52)	69%
Placebo	71	1.06 (0.72, 1.55)		
DUPIXENT 300 mg Q2W	124	0.39 (0.27, 0.56)	0.31 (0.19, 0.49)	69%
Placebo	75	1.27 (0.90, 1.80)		

The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in AS Trial 2 (Figure 5).

Figure 5: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Baseline Blood Eosinophils ≥300 cells/mcL (AS Trial 2)[a]



Number at Risk

DUPIXENT 300 mg Q2W	277	244	221	208	189	145
DUPIXENT 200 mg Q2W	264	240	220	210	195	154
Placebo for 300 mg Q2W	142	108	94	75	69	54
Placebo for 200 mg Q2W	148	116	100	84	72	52

[a] At the time of the database lock, not all patients had completed Week 52

Lung Function

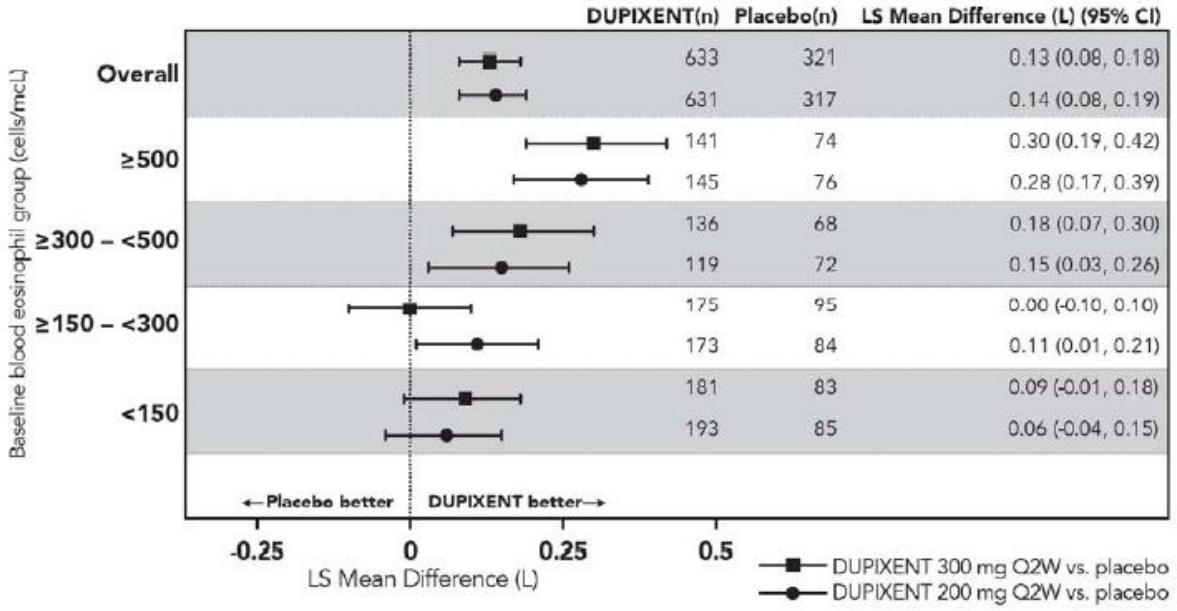
Significant increases in pre-bronchodilator FEV1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV1 LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mcL in AS Trials 1 and 2 are shown in Table 11.

Improvements in FEV1 by baseline blood eosinophils for AS Trial 2 are shown in Figure 6. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Table 11 : Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV1 at Week 12 in AS Trials 1 and 2

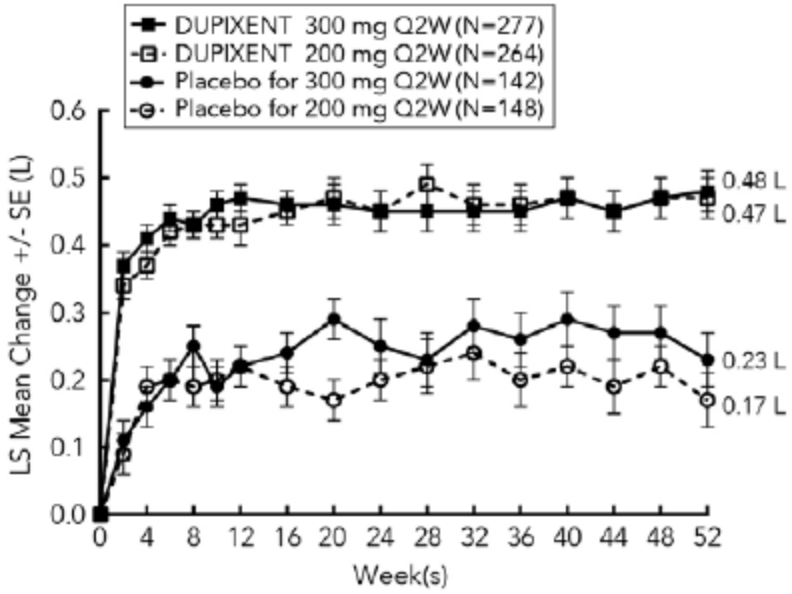
Trial	Treatment	Overall Population[a]			Baseline Blood EOS					
					≥150 cells/mcL			≥300 cells/mcL		
		N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	150	0.31 (18.0)	0.20 (0.11, 0.28)	120	0.32 (18.25)	0.23 (0.13, 0.33)	65	0.43 (25.9)	0.26 (0.11, 0.40)
	DUPIXENT 300 mg Q2W	157	0.28 (17.8)	0.16[c] (0.08, 0.25)	129	0.26[c] (17.1)	0.18 (0.08, 0.27)	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	158	0.12 (6.1)		127	0.09 (4.36)		68	0.18 (10.2)	
AS Trial 2	DUPIXENT 200 mg Q2W	631	0.32 (21.3)	0.14 (0.08, 0.19)	437	0.36 (23.6)	0.17 (0.11, 0.23)	264	0.43 (29.0)	0.21 (0.13, 0.29)
	Placebo	317	0.18 (12.1)		232	0.18 (12.4)		148	0.21 (15.6)	
	DUPIXENT 300 mg Q2W	633	0.34 (23.1)	0.13 (0.08, 0.18)	452	0.37 (25.3)	0.15 (0.09, 0.21)	277	0.47 (32.5)	0.24 (0.16, 0.32)
	Placebo	321	0.21 (13.7)		237	0.22 (14.2)		142	0.22 (14.4)	

Figure 6: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV1 across Baseline Blood Eosinophil Counts (cells/mcL) in AS Trial 2



Mean changes in FEV1 over time in AS Trial 2 are shown in Figure 7.

Figure 7: Mean Change from Baseline in Pre-Bronchodilator FEV1 (L) Over Time in Subjects with Baseline Blood Eosinophils ≥300 cells/mcL (AS Trial 2)



In the AS Trial 2, compared to placebo, greater improvements in FEV1 were also seen in patients with FeNO ≥25 and ≥ 50 ppb as shown in Table 12.

Table 12: Mean Change from Baseline in Pre-Bronchodilator FEV_1 at Week 12 and Week 52 in AS Trial 2 by Baseline FeNO Subgroups

Treatment		At Week 12		At Week 52	
	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
FeNO ≥ 25 ppb					
DUPIXENT 200 mg Q2W	288	0.44 (29.0%)	0.23 (0.15, 0.31)	0.49 (31.6%)	0.30 (0.22, 0.39)
Placebo	157	0.21 (14.1%)		0.18 (13.2%)	
DUPIXENT 300 mg Q2W	295	0.45 (29.8%)	0.24 (0.16, 0.31)	0.45 (30.5%)	0.23 (0.15, 0.31)
Placebo	167	0.21 (13.7%)		0.22 (13.6%)	
FeNO ≥ 50 ppb					
DUPIXENT 200 mg Q2W	114	0.53 (33.5%)	0.30 (0.17, 0.44)	0.59 (36.4%)	0.38 (0.24, 0.53)
Placebo	69	0.23 (14.9%)		0.21 (14.6%)	
DUPIXENT 300 mg Q2W	113	0.59 (37.6%)	0.39 (0.26, 0.52)	0.55 (35.8%)	0.30 (0.16, 0.44)
Placebo	73	0.19 (13.0%)		0.25 (13.6%)	

Additional Secondary Endpoints

ACQ-5 and AQLQ(S) were assessed in AS Trial 2 at 52 weeks. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ(S)).

- The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in the overall population was 69% vs 62% placebo (odds ratio 1.37; 95% CI: 1.01, 1.86) and 69% vs 63% placebo (odds ratio 1.28; 95% CI: 0.94, 1.73), respectively; and the AQLQ(S) responder rates were 62% vs 54% placebo (odds ratio 1.61; 95% CI: 1.17, 2.21) and 62% vs 57% placebo (odds ratio 1.33; 95% CI: 0.98, 1.81), respectively.
- The ACQ-5 responder rate for DUPIXENT 200 mg and 300 mg Q2W in subjects with baseline blood eosinophils ≥300 cells/mcL was 75% vs 67% placebo (odds ratio: 1.46; 95% CI: 0.90, 2.35) and 71% vs 64% placebo (odds ratio: 1.39; 95% CI: 0.88, 2.19), respectively; and the AQLQ(S) responder rates were 71% vs 55% placebo (odds ratio: 2.02; 95% CI: 1.24, 3.32) and 65% vs 55% placebo (odds ratio: 1.79; 95% CI: 1.13, 2.85), respectively.

<u>Oral Corticosteroid Reduction (AS Trial 3)</u>

AS Trial 3 evaluated the effect of DUPIXENT on reducing the use of maintenance oral corticosteroids. The baseline mean oral corticosteroid dose was 12 mg in the placebo group and 11 mg in the group receiving DUPIXENT. The primary endpoint was the percent reduction from baseline of the final oral corticosteroid dose at Week 24 while maintaining asthma control.

Compared with placebo, subjects receiving DUPIXENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The mean percent reduction in daily OCS dose from baseline was 70% (median 100%) in subjects receiving DUPIXENT (95% CI: 60%, 80%) compared to 42% (median 50%) in subjects receiving placebo (95% CI: 33%, 51%). Reductions of 50% or higher in the OCS dose were observed in 82 (80%) subjects receiving DUPIXENT compared to 57 (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Weeks 24 was 72% for DUPIXENT and 37% for placebo (odds ratio 4.48 95% CI: 2.39, 8.39). A total of 54 (52%) subjects receiving DUPIXENT versus 31 (29%) subjects in the placebo group had a 100% reduction in their OCS dose.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were lower in subjects receiving DUPIXENT compared with those receiving placebo (annualized rate 0.65 and 1.60 for the DUPIXENT and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV1 from baseline to Week 24 was greater in subjects receiving DUPIXENT compared with those receiving placebo (LS mean difference for DUPIXENT versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels. The ACQ-5 and AQLQ(S) were also assessed in AS Trial 3 and showed improvements similar to those in AS Trial 2.

Pediatric (6 to 11 years of age)
The efficacy and safety of DUPIXENT in pediatric patients was evaluated in a 52-week multicenter, randomized, double-blind, placebo-controlled study (VOYAGE) in 408 patients 6 to 11 years of age, with asthma on a medium- or high- dose ICS and one controller medication or high dose ICS alone. Patients were randomized to DUPIXENT (N=273) or matching placebo (N=135) every other week based on body weight ≤30 kg or >30 kg, respectively. The efficacy was evaluated in the populations with type 2 inflammation defined as blood eosinophils levels of ≥150 cells/mcL or FeNO ≥20 ppb.

The primary endpoint was the annualized rate of severe exacerbation events during the 52-week placebo-controlled period and the key secondary endpoint was the change from baseline in pre-bronchodilator FEV_1 percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA and PAQLQ(S)-IA scores.
The demographics and baseline characteristics for VOYAGE are provided in Table 13 below.

Table 13 Demographics and Baseline Characteristics for VOYAGE

Parameter	**EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb (N = 350)**	**EOS ≥ 300 cells/mcL (N = 259)**	**ITT (N=408)**
Mean age (years) (SD)	8.9 (1.6)	9.0 (1.6)	8.9 (1.6)
% Female	34.3	32.8	35.8
% White	88.6	87.3	88.2
Mean body weight (kg)	36.09	35.94	35.91
Mean exacerbations in previous year (± SD)	2.47 (2.30)	2.64 (2.58)	2.44 (2.18)
ICS dose (%) Medium High	 55.7 43.4	 54.4 44.4	 55.1 44.1
Pre-dose FEV_1 (L) at baseline (± SD)	1.49 (0.41)	1.47 (0.42)	1.48 (0.41)
Mean percent predicted FEV_1 (%) (±SD)	77.89 (14.40)	76.85 (14.78)	78.07 (14.72)
Mean % Reversibility (± SD)	27.79 (19.34)	22.59 (20.78)	19.58 (20.76)
Mean ACQ-7-IA score (± SD)	2.14 (0.72)	2.16 (0.75)	2.13 (0.73)
Mean PAQLQ(S)-IA score (± SD)	4.94 (1.10)	4.93 (1.12)	4.91 (1.13)
Atopic Medical History % Overall (AD %, AR %)	94 (38.9, 82.6)	96.5 (44.4, 85.7)	92.4 (36.3, 81.9)
Median total IgE IU/mL (± SD)	905.52 (1140.41)	1077.00 (1230.83)	792.28 (1093.46)
Mean FeNO ppb (± SD)	30.71 (24.42)	33.50 (25.11)	27.71 (23.84)

% patients with FeNO ppb≥20	58	64.1	49.7
Mean baseline Eosinophil count (± SD) cells/mcL	570 (380)	710 (360)	500 (400)
% patients with EOS ≥ 150 cells/mcL ≥ 300 cells/mcL	 94.6 74	 0 100	 81.1 63.5

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; ACQ-7-IA = Asthma Control Questionnaire-7 Interviewer Administered; PAQLQ(S)-IA = Paediatric Asthma Quality of Life Questionnaire with Standardised Activities–Interviewer Administered; AD = atopic dermatitis; AR = allergic rhinitis; EOS = blood eosinophil; FeNO = fraction of exhaled nitric oxide

Exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. DUPIXENT significantly reduced the annualized rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in the population with the type 2 inflammation and in population defined by baseline blood eosinophils ≥300 cells/mcL or by baseline FeNO ≥20 ppb. Clinically significant improvements in percent predicted pre-bronchodilator FEV_1 were observed at Week 12. Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The efficacy results for VOYAGE are presented in Table 14.

In the population with the type 2 inflammation, the LS mean change from baseline in pre-bronchodilator FEV_1 at Week 12 was 0.22 L in the DUPIXENT group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L (95% CI: 0.04, 0.16). The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at Week 52 of 0.17 L (95% CI: 0.09, 0.24).

In the population defined by baseline blood eosinophils ≥300 cells/mcL, the LS mean change from baseline in pre-bronchodilator FEV_1 at Week 12 was 0.22 L in the dupilumab group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L (95% CI: 0.03, 0.17), The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at Week 52 of 0.17 L (95% CI: 0.09, 0.26).

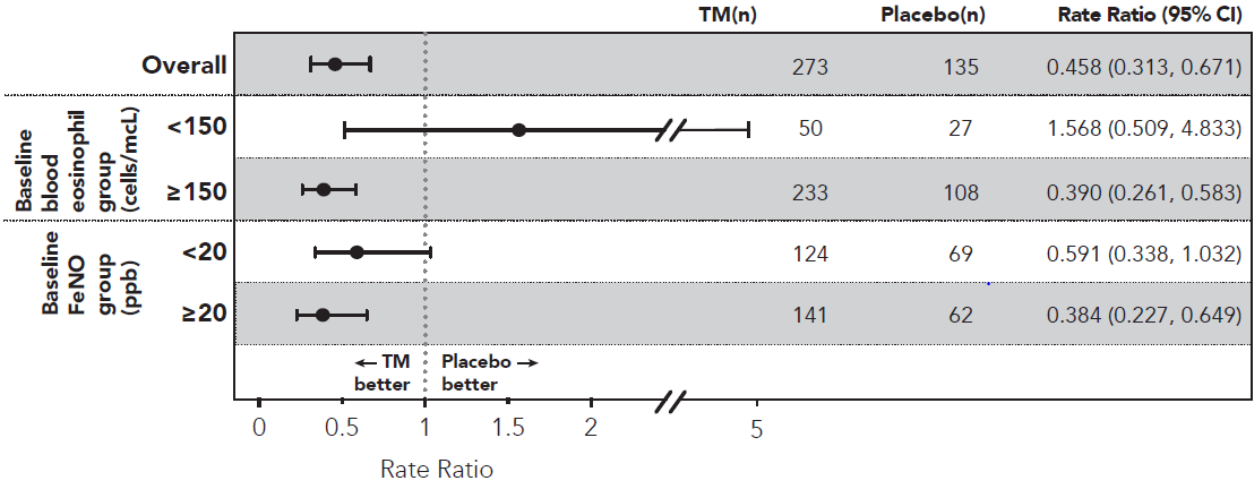
Table 14: Rate of Severe Exacerbations, Mean Change from Baseline in FEV_1, ACQ-7-IA and PAQLQ(S)-IA Responder Rates in VOYAGE

Treatment	EOS ≥ 150 cells/mcL or FeNO ≥ 20 ppb			EOS ≥ 300 cells/mcL			FeNO ≥20 ppb		
Annualized severe exacerbations rate over 52 weeks									
	N	**Rate (95% CI)**	**Rate Ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate Ratio (95% CI)**	**N**	**Rate (95% CI)**	**Rate Ratio (95% CI)**
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	0.305 (0.223, 0.416)	0.407 (0.274, 0.605)	175	0.235 (0.160, 0.345)	0.353 (0.222, 0.562)	141	0.271 (0.170, 0.432)	0.384 (0.227, 0.649)
Placebo	114	0.748 (0.542, 1.034)		84	0.665 (0.467, 0.949)		62	0.705 (0.421, 1.180)	
Mean Change from Baseline in percent predicted FEV_1 at Week 12									
	N	**LS mean Δ from baseline in percent predicted FEV_1**		**N**	**LS mean Δ from baseline in percent predicted FEV_1**		**N**	**LS mean Δ from baseline in percent predicted FEV_1**	
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	229	10.53		168	10.15		141	11.36	
Placebo	110	5.32		80	4.83		62	4.62	
ACQ-7-IA at Week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	236	79.2	1.82 (1.02, 3.24)	175	80.6	2.79 (1.43, 5.44)	141	80.9	2.60 (1.21, 5.59)
Placebo	114	69.3		84	64.3		62	66.1	
PAQLQ(S)-IA at Week 24[a]									
	N	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**	**N**	**Responder rate %**	**OR vs. placebo (95% CI)**
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	211	73.0	1.57 (0.87, 2.84)	158	72.8	1.84 (0.92, 3.65)	131	75.6	2.09 (0.95, 4.61)
Placebo	107	65.4		81	63.0		61	67.2	

[a]The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S))

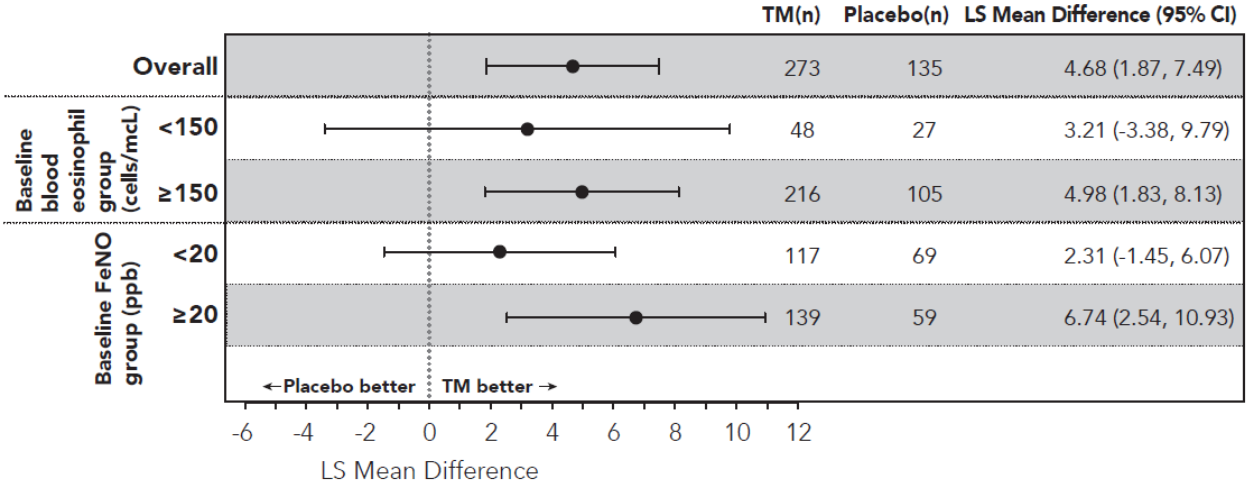
Response rates by baseline blood eosinophils and FeNO for VOYAGE are shown in Figure 8.

Figure 8: Relative Risk in Annualized Event Rate of Severe Exacerbations Across Baseline Blood Eosinophil Count (cells/mcL) and Baseline FeNO Group (ppb) in VOYAGE



Improvements in percent predicted FEV_1 by baseline blood eosinophils and FeNO for VOYAGE are shown in Figure 9.

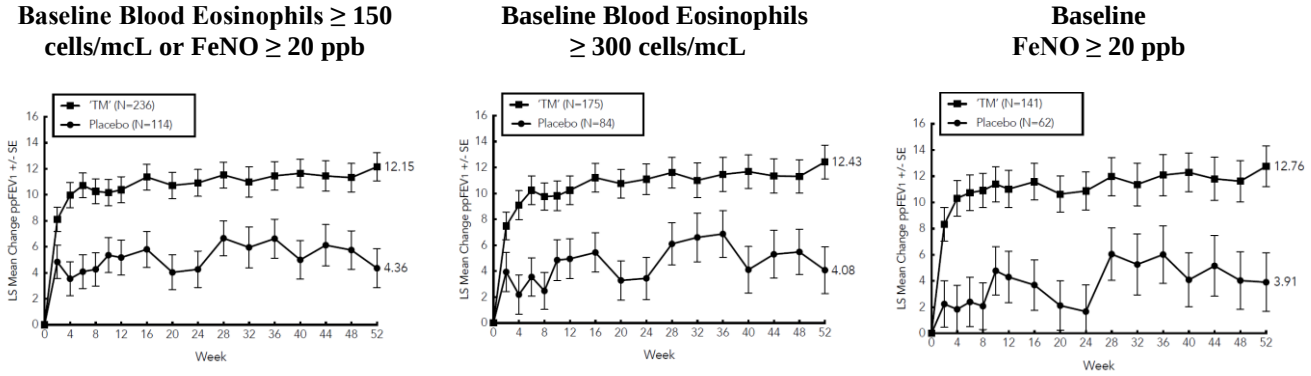
Figure 9: LS Mean Change from Baseline vs Placebo to Week 12 in percent predicted Pre-Bronchodilator FEV_1 across Baseline Blood Eosinophil Counts (cells/mcL) Baseline FeNO group (ppb) in VOYAGE.



Significant improvements in percent predicted FEV1 were observed as early as Week 2 and were maintained through Week 52 in VOYAGE study.

Improvements in percent predicted FEV_1 over time in VOYAGE are shown in Figure 10.

Figure 10: Mean Change from Baseline in Percent Predicted Pre-Bronchodilator FEV_1 (L) Over Time in VOYAGE (Baseline Blood Eosinophils ≥ 150 cells/mcL or FeNO ≥ 20 ppb, Baseline Eosinophils ≥ 300 cells/mcL, and Baseline FeNO ≥ 20 ppb)



In VOYAGE, in the population with the type 2 inflammation, the mean annualized total number of systemic corticosteroid courses due to asthma was reduced by 59.3% versus placebo (0.350 [95% CI: 0.256, 0.477] versus 0.860 [95% CI: 0.616, 1.200]). In the population defined by baseline blood eosinophils ≥300 cells/mcL, the mean annualized total number of systemic corticosteroid courses due to asthma was reduced by 66.0% versus placebo (0.274 [95% CI: 0.188, 0.399] versus 0.806 [95% CI: 0.563, 1.154].

DUPIXENT reduced the impact of pediatric patient's asthma on the caregiver quality of life as measured by the Pediatric Asthma Caregiver Quality of Life Questionnaire (PACQLQ) in both the type 2 inflammation and the baseline blood eosinophil count of ≥300 cells/mcL population at Week 52; the LS mean difference versus placebo was 0.47 (95% CI: 0.22, 0.72), and 0.50 (95% CI: 0.21, 0.79), respectively.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPIXENT (dupilumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield.

Each pre-filled syringe with needle shield is designed to deliver 300 mg of DUPIXENT in 2 mL solution, 200mg of DUPIXENT in 1.14mL solution or 100mg DUPIXENT in 0.67mL solution.

DUPIXENT is available in cartons containing 2 pre-filled syringes (PFS) or 2 pre-filled syringes with safety system (PFS-S).

Not all presentations may be available locally.

16.2 Storage and Handling

DUPIXENT is sterile and preservative-free. Discard any unused portion.

Store refrigerated at 2°C to 8°C in the original carton to protect from light.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.
Do not expose the syringe to heat or direct sunlight.
Do NOT freeze. Do NOT expose to heat. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the Instructions for Use.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations *[see Instructions for Use]*.

Hypersensitivity

Advise patients to discontinue DUPIXENT and to seek immediate medical attention if they experience any symptoms of systemic hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.

Conjunctivitis and Keratitis

Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop *[see Warnings and Precautions (5.2)]*.

Eosinophilic Conditions

Advise patients to notify their healthcare provider if they present with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis *[see Warnings and Precautions (5.3)]*.

Not for Acute Asthma Symptoms or Deteriorating Disease

Inform patients that DUPIXENT does not treat acute asthma symptoms or acute exacerbations. Inform patients to seek medical advice if their asthma remains uncontrolled or worsens after initiation of treatment with DUPIXENT *[see Warnings and Precautions (5.4)]*.

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic or inhaled corticosteroids except under the direct supervision of a physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions (5.5)]*.

Patients with Co-morbid Asthma

Advise patients with atopic dermatitis who have co-morbid asthma not to adjust or stop their asthma treatment without talking to their physicians *[see Warnings and Precautions (5.6)]*.

Parasitic (Helminth) Infections

Advise patients to notify their healthcare provider if they present with clinical features consistent with helminthic infection *[see Warnings and Precautions (5.6)]*.

Product Registrant:

Sanofi-aventis Singapore Pte Ltd

38 Beach Road #18-11

South Beach Tower

Last Revised: March 2022

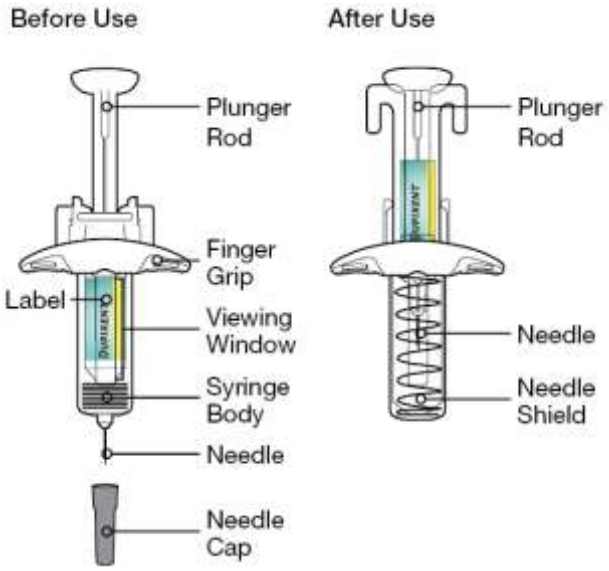
Instructions for Use

DUPIXENT
(dupilumab)
Injection, for subcutaneous use
Single-Dose Pre-filled Syringe with Safety System

Read this Instructions for Use before using the DUPIXENT Pre-filled Syringe. **Do not inject yourself or someone else until you have been shown how to inject DUPIXENT**. In adolescents 12 years of age and older, it is recommended that DUPIXENT be administered by or under supervision of an adult. Your healthcare provider can show you or your caregiver how to prepare and inject a dose of DUPIXENT before you try to do it yourself the first time. Keep these instructions for future use. Call your healthcare provider if you have any questions.

This device is a **Single-Dose** Pre-filled Syringe (called "DUPIXENT Syringe" in these instructions). It contains 300 mg of DUPIXENT for injection under the skin (subcutaneous injection).

The parts of the DUPIXENT Syringe are shown below:



Important Information	
▪ Read all of the instructions carefully before using the DUPIXENT Syringe. ▪ Ask your healthcare provider how often you will need to inject the medicine. ▪ Rotate the injection site each time you inject. ▪ **Do not** use the DUPIXENT Syringe if it has been damaged. ▪ **Do not** use the DUPIXENT Syringe if the Needle Cap is missing or not securely attached. ▪ **Do not** touch the Plunger Rod until you are ready to inject. ▪ **Do not** inject through clothes.	▪ To reduce the risk of accidental needle sticks, each pre-filled syringe has a Needle Shield that is automatically activated to cover the needle after you have given your injection. ▪ **Do not** pull back on the Plunger Rod at any time. ▪ **Do not** remove the Needle Cap until just before you give the injection. ▪ Throw away (dispose of) the used DUPIXENT Single-Dose Pre-filled Syringe right away after use. See "Step 13: Dispose" below. ▪ **Do not re-use a DUPIXENT Single-Dose Pre –filled Syringe**

▪ **Do not** get rid of any air bubbles in the DUPIXENT Syringe.	

How should I store DUPIXENT?

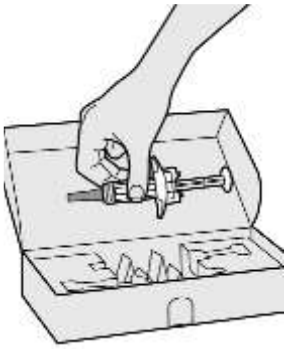
- Store DUPIXENT Syringes in the refrigerator between 2ºC and 8ºC.
- Store DUPIXENT Syringes in the original carton to protect it from light.
- DUPIXENT Syringes can be stored at room temperature up to 25°C up to 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.
- **Do not** shake the DUPIXENT Syringe.
- **Do not** heat the DUPIXENT Syringe.
- **Do not** freeze the DUPIXENT Syringe.
- **Do not** put the DUPIXENT Syringe into direct sunlight.
- **Keep DUPIXENT Syringes and all medicines out of the reach of children.**

Step 1: Remove

Remove the DUPIXENT Syringe from the carton by holding the middle of the Syringe Body.

⚠ **Do not pull off the Needle Cap until you are ready to inject.**

⚠ **Do not use the DUPIXENT Syringe if it has been dropped on a hard surface or damaged.**



Step 2: Prepare

Ensure you have the following:

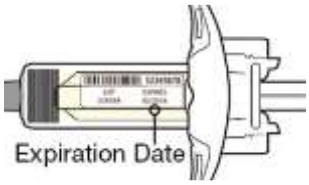
- the DUPIXENT Pre-filled Syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a sharps disposal container* (See Step 13)

**Items not included in the carton*

Step 3: Check
When you receive your DUPIXENT Syringes, always check to see that:

- you have the correct medicine and dose.
- the expiration date on the Single-Dose Pre-filled Syringe has not passed.

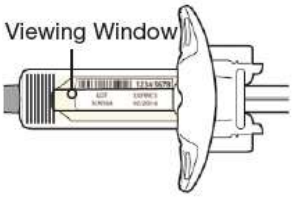
Do not use the DUPIXENT Syringe if the expiration date has passed.



Step 4: Inspect

Look at the medicine through the viewing window on the DUPIXENT Syringe:
Check to see if the liquid is clear and colorless to pale yellow.
Note: You may see an air bubble, this is normal.

Do not use the DUPIXENT Syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.

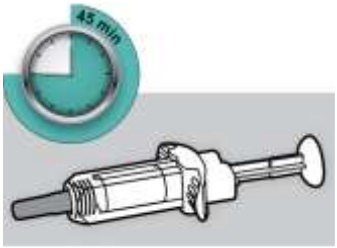


Step 5: Wait 45 minutes
Lay the DUPIXENT Syringe on a flat surface and let it naturally warm to room temperature for at least 45 minutes.

Do not heat the DUPIXENT Syringe.

Do not put the DUPIXENT Syringe into direct sunlight.

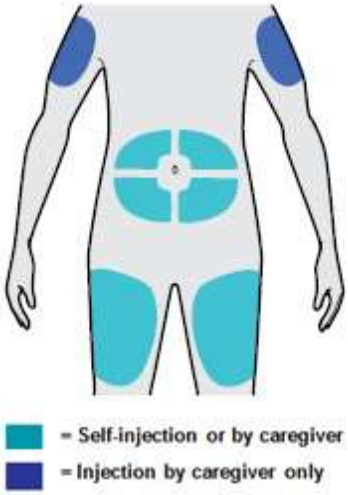
Do not keep DUPIXENT Syringes at room temperature for more than 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.



Step 6: Choose your injection site.

- You can inject into your thigh or stomach, except for the 2 inches (5 cm) around your belly button (navel).
- If a caregiver injects your dose, they can also use the outer area of the upper arm.
- Choose a different site each time you inject DUPIXENT.

Do not inject into skin that is tender, damaged, bruised or scarred.



Step 7: Clean

Wash your hands.
Clean the injection site with an alcohol wipe.
Let your skin dry before injecting.

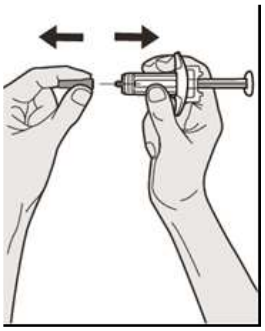
Do not touch the injection site again or blow on it before the injection.

Step 8: Remove Needle Cap
Hold the DUPIXENT Syringe in the middle of the Syringe Body with the Needle pointing away from you and pull off the Needle Cap.

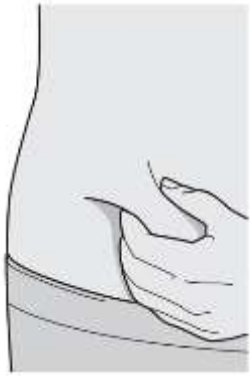
Do not put the Needle Cap back on.

Do not touch the Needle.

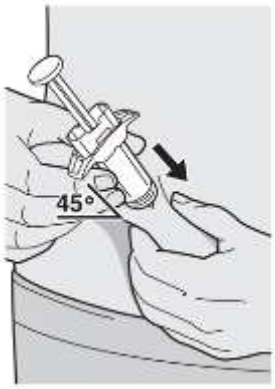
Inject your medicine right away after removing the Needle Cap.



Step 9: Pinch
Pinch a fold of skin at the injection site (thigh or stomach, except 2 inches around your belly button, or outer area of the upper arm if injected by your caregiver). The figure below shows an example of pinching a fold of skin on your stomach.



Step 10: Insert
Insert the Needle completely into the fold of the skin at about a 45º angle.



Step 11: Push
Relax the pinch.
Push the Plunger Rod down slowly and steadily as far as it will go until the DUPIXENT Syringe is empty.
Note: You will feel some resistance. This is normal.

Step 12: Release and Remove

Lift your thumb to release the Plunger Rod until the Needle is covered by the Needle Shield and then remove the Syringe from the injection site.

Lightly press a cotton ball or gauze on the injection site if you see any blood.

⚠ **Do not put the Needle Cap back on.**

⚠ **Do not rub your skin after the injection.**

Step 13: Dispose Put your used Needles, DUPIXENT Syringes and Needle Caps in a sharps disposal container right away after use. **Do not dispose of (throw away) Needles, DUPIXENT Syringes, and Needle Caps in your household trash.**

Do not dispose of (throw away) Needles, DUPIXENT Syringes, and Needle Caps in your household trash.

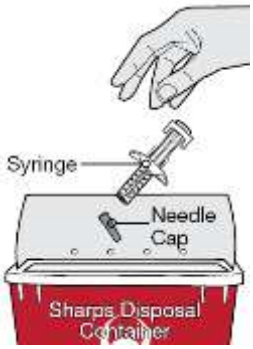
If you do not have a sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic;
- can be closed with a tightfitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used Needles and Syringes.

Do not dispose your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Do not put the Needle Cap back on.



Revision date: December 2019