

NAME OF THE MEDICINAL PRODUCT

Dupixent 200mg Dupixent 300mg

1. DOSAGE FORMS AND STRENGTHS

DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution available in a :
Single-dose pre-filled syringe with needle shield as:

- Injection: 300 mg/2 mL (150 mg/ml) in a single-dose pre-filled syringe with needle shield
- Injection: 200 mg/1.14 mL (175 mg/ml) in a single-dose pre-filled syringe with needle shield

Single-dose pre-filled pen as:

Injection: 300 mg/2 mL (150 mg/ml)

Injection: 200 mg/1.14 mL (175 mg/ml)

2. THERAPEUTIC INDICATIONS

DUPIXENT is indicated for the following diseases:

2.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis (AD) 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.

2.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

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

2.3 Chronic Rhinosinusitis with Nasal Polyposis

DUPIXENT 300mg is indicated as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

3. DOSAGE AND ADMINISTRATION

3.1 Important Administration Instructions

DUPIXENT is administered by subcutaneous injection.

DUPIXENT is intended for use under the guidance of a healthcare provider. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the “Instructions for Use”.

Use of Pre-filled Pen or Pre-filled Syringe

The DUPIXENT pre-filled pen is for use in adult and pediatric patients aged 12 years and older.

The DUPIXENT pre-filled syringe is for use in adult and pediatric patients aged 6 years and older.

A caregiver or patient 12 years of age and older may inject DUPIXENT using the pre-filled syringe or pre-filled pen. In pediatric patients 12 to 17 years of age, administer DUPIXENT under the supervision of an adult.

In pediatric patients 6 years to 11 years of age, administer DUPIXENT pre-filled syringe by a caregiver.

Administration Instructions

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

For AD 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 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.

The DUPIXENT “Instructions for Use” contains more detailed instructions on the preparation and administration of DUPIXENT.

3.2 Vaccination Prior to Treatment

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT [*see Warnings and Precautions (5.9)*].

3.3 Recommended Dosage for Atopic Dermatitis

Dosing in Adults

The recommended dosage 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).

Dosage in Pediatric Patients 6 Years to 17 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 years to 17 years of age is specified in Table 1.

Table 1: Dosage of DUPIXENT in Pediatric Patients 6 Years to 17 Years of Age with Atopic Dermatitis

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

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. If dupilumab treatment interruption becomes necessary, patients can still be successfully re-treated.

3.4 Recommended Dosage for Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older

The recommended dosage of DUPIXENT for adult and pediatric patients 12 years of age and older is specified in Table 2.

Table 2: Dosage of DUPIXENT in Adult and Pediatric Patients 12 Years and Older with Asthma

Initial Loading Dose	Subsequent Dose
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
or	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyps	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 to 11 years of age is specified in Table 3.

Table 3: Dosage of DUPIXENT in Pediatric Patients 6 to 11 Years of Age with Asthma

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

^a For pediatric patients 6 to 11 years of age with asthma, no initial loading dose is recommended.

For pediatric patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe AD, follow the recommended dosage as per Table 1 which includes an initial loading dose.

3.5 Recommended Dosage for Chronic Rhinosinusitis with Nasal Polyposis

The recommended dose of DUPIXENT for adult patients is 300 mg given every other week.

3.6 Missed doses

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

3.7 Preparation for Use of DUPIXENT

Before injection, remove DUPIXENT from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe or pre-filled pen and 30 minutes for the 200 mg/1.14 mL pre-filled syringe or pre-filled pen) without removing the needle cap. After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

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 or pre-filled pen.

4 CONTRAINDICATIONS

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

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme

have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see *Adverse Reactions* (6.1, 6.2, 6.3)].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis adverse reactions have been reported in clinical trials.

Conjunctivitis and keratitis occurred more frequently in AD subjects who received DUPIXENT compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period [see *Adverse Reactions* 6.1].

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPIXENT group compared to 1% in the placebo group in the 24-week safety pool; these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program [see *Adverse Reactions* (6.1)].

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

Conjunctivitis and keratitis adverse events have also been reported with DUPIXENT in postmarketing settings, predominantly in AD patients. Some patients reported visual disturbances (e.g., blurred vision) associated with conjunctivitis or keratitis.

Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate [see *Adverse Reactions* (6.1)].

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. Healthcare providers 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 subjects who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult subjects who participated in the asthma development program as well as in adult subjects with co-morbid asthma in the CRSwNP 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 Risk Associated with Abrupt 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 healthcare provider. 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 co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Arthralgia

Arthralgia has been reported with the use of DUPIXENT with some patients reporting gait disturbances or decreased mobility associated with joint symptoms; some cases resulted in hospitalization [see *Adverse Reactions (6.1)*]. In postmarketing reports, onset of arthralgia was variable, ranging from days to months after the first dose of DUPIXENT. Some patients' symptoms resolved while continuing treatment with DUPIXENT and other patients recovered or were recovering following discontinuation of DUPIXENT.

Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT.

5.8 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. Adverse reactions of helminth infections (5 cases of enterobiasis and 1 case of ascariasis) were reported in pediatric patients 6 to 11 years old who participated in the pediatric asthma development program [see *Adverse Reactions (6.1)*].

5.9 Vaccinations

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT. Avoid use of live vaccines in patients treated with DUPIXENT. It is unknown if administration of live vaccines during DUPIXENT treatment will impact the safety or effectiveness of these vaccines. Limited data are available regarding coadministration of DUPIXENT with non-live vaccines [see *Clinical Pharmacology* (10.2)].

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Warnings and Precautions* (5.1)]
- Conjunctivitis and Keratitis [see *Warnings and Precautions* (5.2)]
- Arthralgia [see *Warnings and Precautions* (5.7)]

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 SOLO 1, SOLO 2, and CHRONOS) and one dose-ranging trial (AD-1021) evaluated the safety of DUPIXENT in subjects with moderate-to-severe AD. 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 AD.

Trials SOLO 1, SOLO 2, and AD-1021 compared the safety of DUPIXENT monotherapy to placebo through Week 16. CHRONOS compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

AD-1225 is a multicenter, open-label extension (OLE) study which assessed the long-term safety of repeat doses of DUPIXENT (through 148 weeks of treatment) in adults with moderate-to-severe AD who had previously participated in controlled studies of DUPIXENT or had been screened for SOLO 1 or SOLO 2. The safety data in AD-1225 reflect exposure to DUPIXENT in 2677 subjects, including 2254 exposed for at least 52 weeks, 1192 exposed for at least 100 weeks, and 357 exposed for at least 148 weeks. In AD-1225, 99.7% of subjects were exposed to DUPIXENT 300 mg weekly dosing (QW).

Weeks 0 to 16 (SOLO 1, SOLO 2, CHRONOS, and AD-1021):

In DUPIXENT monotherapy trials (SOLO 1, SOLO 2, and AD-1021) 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 4 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 4 : Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	DUPIXENT Monotherapy ^a		DUPIXENT + TCS ^b	
	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 reaction	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 SOLO 1, SOLO 2, and AD-1021.

^b Analysis of CHRONOS 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 (CHRONOS):

In the DUPIXENT with concomitant TCS trial (CHRONOS) 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.

Safety through 148 Weeks (AD-1225)

The long-term safety profile observed in this trial through 148 weeks was generally consistent with the safety profile of DUPIXENT observed in controlled studies.

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 pediatric subjects 12 to 17 years of age with moderate-to-severe AD (AD-1526). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile seen in adults with AD .

The long-term safety of DUPIXENT was assessed in an open-label extension study in pediatric subjects 12 to 17 years of age with moderate-to-severe AD (AD-1434). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in AD-1526. The long-term safety profile of DUPIXENT observed in pediatric subjects 12 to 17 years of age was consistent with that seen in adults with AD .

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 367 pediatric subjects 6 to 11 years of age with severe AD (AD-1652). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adult and pediatric subjects 12 to 17 years of age with AD .

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 368 pediatric subjects 6 to 11 years of age with AD (AD-1434). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe AD at the time of enrollment in AD-1434. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD1652. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 to 11 years of age was consistent with that seen in adult and pediatric subjects 12 to 17 years of age with AD [see *Use in Specific Populations* (7.3)].

Asthma

Adults and Pediatric Subjects 12 Years of Age and Older with Asthma

A total of 2888 adult and pediatric subjects 12 to 17 years of age with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). 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) (DRI12544 and QUEST). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE). The safety population (DRI12544 and QUEST) 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 DRI12544 and QUEST, 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 5 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 DRI12544 and QUEST.

Table 5 : Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Groups in DRI12544 and QUEST and Greater than Placebo (6 Month Safety Pool)

Adverse Reaction	DRI12544 and QUEST		
	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 $\geq 3,000$ 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 Subjects 6 to 11 Years of Age with Asthma

The safety of DUPIXENT was assessed in 405 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma (VOYAGE). The safety profile of DUPIXENT in these subjects through Week 52 was similar to the safety profile from studies in adult and pediatric subjects 12 years of age and older with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 2.2% (6 subjects) in the DUPIXENT group and 0.7% (1 subject) in the placebo group. The majority of cases were enterobiasis, reported in 1.8% (5 subjects) in the DUPIXENT group and none in the placebo group. There was one case of ascariasis in the DUPIXENT group. All helminth infection cases were mild to moderate and subjects recovered with anti-helminth treatment without DUPIXENT treatment discontinuation.

Chronic Rhinosinusitis with Nasal Polyposis

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (SINUS-24 and SINUS-52). The safety pool consisted of data from the first 24 weeks of treatment from both studies.

In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the DUPIXENT 300 mg Q2W group.

Table 6 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 group in SINUS-24 and SINUS-52.

Table 6: Adverse Reactions Occurring in $\geq 1\%$ of the DUPIXENT Group in SINUS-24 and SINUS-52 and Greater than Placebo (24 Week Safety Pool)

Adverse Reaction	SINUS-24 and SINUS-52	
	DUPIXENT 300 mg Q2W N=440 n (%)	Placebo N=282 n (%)
Injection site reactions ^a	28 (6%)	12 (4%)
Conjunctivitis ^b	7 (2%)	2 (1%)
Arthralgia	14 (3%)	5 (2%)
Gastritis	7 (2%)	2 (1%)
Insomnia	6 (1%)	0 (<1%)
Eosinophilia	5 (1%)	1 (<1%)
Toothache	5 (1%)	1 (<1%)

^a Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.

^b Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

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

Specific Adverse Reactions

Conjunctivitis and Keratitis

In adult subjects with AD, conjunctivitis was reported in 10% (34 per 100 subject-years) in the 300 mg Q2W dose group and in 2% of the placebo group (8 per 100 subject-years) during the 16-week treatment period of the monotherapy trials (SOLO 1, SOLO 2, and AD1021). During the 52-week treatment period of concomitant therapy AD trial (CHRONOS), 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). During the long-term OLE trial with data through 148 weeks (AD-1225), conjunctivitis was reported in 20% of the DUPIXENT group (12 per 100 subject-years).

In DUPIXENT AD monotherapy trials (SOLO 1, SOLO 2, and AD-1021) 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 DUPIXENT + topical corticosteroids (TCS) AD trial (CHRONOS), keratitis was reported in 4% of the DUPIXENT + TCS group (4 per 100 subject-years) and in 2% of the placebo + TCS group (2 per 100 subject-years). Conjunctivitis and keratitis occurred more frequently in AD subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. During the long-term OLE trial with data through 148 weeks (AD-1225), keratitis was reported in 3% of the DUPIXENT group (2 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Among subjects with asthma, the frequency of conjunctivitis and keratitis was similar between DUPIXENT and placebo.

In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUPIXENT group compared to 1% in the placebo group in the 24-week safety pool; these subjects recovered.

In the 52-week CRSwNP study (SINUS-52), the frequency of conjunctivitis was 3% in the DUPIXENT subjects and 1% in the placebo subjects; all of these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program [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 AD trials. The rates remained stable through 148 weeks in the long-term OLE trial (AD-1225).

Herpes zoster was reported in <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 AD monotherapy trials. In the 52-week DUPIXENT + TCS AD 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). During the long-term OLE trial with data through 148 weeks (AD-1225), 1.9% of DUPIXENT-treated subjects reported herpes zoster (0.99 per 100 subject-years of follow up).

Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Among CRSwNP subjects there were no reported cases of herpes zoster or eczema herpeticum.

Hypersensitivity Reactions

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

Eosinophils

DUPIXENT-treated subjects with AD, asthma and CRSwNP had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In adult subjects with AD (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively.

In adult and pediatric subjects 12 years of age and older with asthma (DRI12544 and QUEST), the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. In subjects 6 to 11 years of age with asthma (VOYAGE), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/mcL, respectively.

In adult subjects with CRSwNP (SINUS-24 and SINUS-52), the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across the trials for AD, asthma and CRSwNP indications, the incidence of treatment-emergent eosinophilia (≥ 500 cells/mcL) was similar in DUPIXENT and placebo groups.

Treatment-emergent eosinophilia ($\geq 5,000$ cells/mL) was reported in $<3\%$ of DUPIXENT-treated subjects and $<0.5\%$ in placebo-treated subjects (SOLO 1, SOLO 2, and AD-1021; DRI12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52). Blood eosinophil counts declined to near baseline levels during study treatment. In study AD-1539, treatment-emergent eosinophilia ($\geq 5,000$ cells/mL) was reported in 8% of DUPIXENT-treated subjects and 0% in placebo treated subjects [see *Warnings and Precautions* (5.3)].

Cardiovascular

In the 1-year placebo-controlled trial in adult and pediatric subjects 12 years of age and older with asthma (QUEST), 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 AD (CHRONOS), 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.

In the 24-week placebo-controlled trial in subjects with CRSwNP (SINUS-24), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.7%) of the DUPIXENT group and 0 (0.0%) of the placebo group. In the 1-year placebo controlled trial in subjects with CRSwNP (SINUS-52), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

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.

Atopic Dermatitis

Approximately 6% of subjects with AD who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies. Similar results were observed in pediatric subjects 6 to 11 years of age with atopic dermatitis who received DUPIXENT 200 mg Q2W or 300 mg Q4W for 16 weeks.

Approximately 16% of pediatric subjects 12 to 17 years of age with AD who received DUPIXENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to DUPIXENT ;

approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Asthma

Approximately 5% of subjects with asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; 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 asthma who received either DUPIXENT 100 mg Q2W or 200 mg Q2W up to 52 weeks.

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

Chronic Rhinosinusitis with Nasal Polyposis

Approximately 5% of subjects with CRSwNP who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 3% had neutralizing antibodies.

The antibody titers detected in subjects who received DUPIXENT were mostly low. In subjects who received DUPIXENT, development of high titer antibodies to DUPIXENT was associated with lower serum dupilumab concentrations [see *Clinical Pharmacology (10.3)*]. Two adult subjects with AD 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 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of DUPIXENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: angioedema [see *Warnings and Precautions (5.1)*]

Skin and subcutaneous tissue disorders: Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain

6.4 Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form at <https://sideeffects.health.gov.ill>.

7. USE IN SPECIFIC POPULATIONS

7.1 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-4R α) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) (*see Data*).

The 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.

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-4R α 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.

7.2 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.

7.3 Pediatric Use

Atopic Dermatitis

The safety and effectiveness of DUPIXENT have been established in pediatric patients 6 years of age and older with moderate-to-severe AD [see *Clinical studies 12.1*].

Use of DUPIXENT in this age group is supported by data from the following clinical trials:

- AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to severe AD treated with DUPIXENT
- AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe AD treated with DUPIXENT + TCS

Use is also supported by AD-1434, an open-label extension study that enrolled subjects who completed Trials AD-1526 and AD-1652. AD-1434 included 136 adolescents from Trial AD-1434 and 110 children from Trial AD-1652 with moderate atopic dermatitis at enrollment into the extension study. Trial AD-1434 included 64 adolescents from Trial AD-1526 and 72 children from AD-1652 with severe atopic dermatitis at enrollment. No new safety signals were identified in AD-1434 [see *Adverse Reactions (6.1)*].

The safety and efficacy were generally consistent between pediatric and adult patients [see *Adverse Reactions (6.1) and Clinical Studies (12.1)*].

DUPIXENT is not indicated in pediatric patients (<6 years of age) with atopic dermatitis.

Asthma

The safety and effectiveness of DUPIXENT for an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma have been established in pediatric patients 6 years of age and older. Use of DUPIXENT for this indication is supported by evidence from adequate and well controlled studies in adult and pediatric patients 6 years and older [see *Clinical Studies (12.2)*].

Pediatric Subjects 12 to 17 Years of Age:

A total of 107 pediatric subjects 12 to 17 years of age with moderate-to-severe asthma were enrolled in QUEST 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 pediatric subjects 12 to 17 years of age 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 pediatric subjects 12 to 17 years of age than that in adults at the respective dose level which was mainly accounted for by difference in body weight [see *Clinical Pharmacology (10.3)*].

The adverse event profile in pediatric subjects 12 to 17 years of age was generally similar to the adults [see *Adverse Reactions (6.1)*].

Pediatric Subjects 6 to 11 Years of Age:

A total of 408 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma were enrolled in VOYAGE, which evaluated doses of 100 mg Q2W or 200 mg Q2W. Improvement in asthma exacerbations and lung function were demonstrated [see *Clinical Studies (12.2)*]. The effectiveness of DUPIXENT 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W [see *Clinical Pharmacology (10.3)*]. Subjects who completed the treatment period of the VOYAGE study could participate in the open-label extension study (LTS14424). Eighteen subjects (≥ 15 to <30 kg) out of 365 subjects were exposed to 300 mg Q4W in this study, and the safety profile in these eighteen subjects was consistent with that seen in VOYAGE. Additional safety for DUPIXENT 300 mg Q4W is based upon available safety information from the pediatric AD indication [see *Adverse Reactions (6.1)* and *Clinical Pharmacology (10.3)*].

Safety and effectiveness in pediatric patients younger than 6 years of age with asthma have not been established.

CRSwNP

Safety and effectiveness in pediatric patients younger than 18 years of age with CRSwNP have not been established.

7.4 Geriatric Use

Of the 1472 subjects with AD exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Clinical studies of DUPIXENT in AD did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects [see *Clinical Pharmacology (10.3)*].

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.

Of the 440 subjects with CRSwNP exposed to DUPIXENT, a total of 79 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

8. OVERDOSAGE

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.

9. DESCRIPTION

Dupilumab, an interleukin-4 receptor alpha antagonist, is a human monoclonal antibody of the IgG4 subclass that binds to the IL-4R α 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 is provided as a single-dose pre-filled syringe with needle shield or a single-dose pre-filled pen in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg pre-filled syringe or pre-filled pen delivers 300 mg dupilumab in 2 mL which also contains Sucrose (100mg), L-arginine monohydrochloride, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 80, glacial acetic acid, sodium acetate trihydrate, water for injections.

Each 200 mg pre-filled syringe or pre-filled pen delivers 200 mg dupilumab in 1.14 mL which also contains Sucrose (57mg), L-arginine monohydrochloride, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 80, glacial acetic acid, sodium acetate trihydrate, water for injections.

10. CLINICAL PHARMACOLOGY

10.1 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-4R α 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 driven by IL-4 and IL-13 is an important component in the pathogenesis of asthma, AD and CRSwNP. Multiple cell types that express IL-4R α (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-4R α with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. The mechanism of dupilumab action has not been definitively established.

10.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers of inflammation. 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. Reductions in these 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 (DRI12544) and 70% at Week 52 (QUEST). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in DRI12544 and QUEST respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

Antibody Response to Non-Live Vaccines During DUPIXENT Treatment

In a clinical study, adult subjects with AD were treated once weekly for 16 weeks with 300 mg of DUPIXENT (twice the recommended dosing frequency). After 12 weeks of administration, subjects received a Tdap vaccine and a meningococcal polysaccharide vaccine. Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus toxoid and serogroup C meningococcal polysaccharide were similar in DUPIXENT-treated and placebo-treated subjects. Antibody responses to the other active components of both vaccines were not assessed. Antibody responses to other non-live vaccines were also not assessed.

10.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with AD, asthma and CRSwNP.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean \pm 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 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 \pm 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 195 ± 71.7 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 similar between AD, asthma and CRSwNP subjects, 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 QW, 300 mg Q2W, 200 mg Q2W or 300mg Q4W dupilumab, the median times to non-detectable concentration (<78 ng/mL) ranged from 9 to 13 weeks in adults and pediatric subjects 12 to 17 years of age. Population pharmacokinetic analyses indicate the median times to non-detectable concentration are approximately 1.5 times (up to 19 weeks) longer in pediatric subjects 6 to 11 years of age.

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 in adults and in pediatric subjects 6 to 17 years of age .

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

For pediatric subjects 6 to 11 years of age with AD receiving every other week dosing (Q2W) with 200 mg (≥ 30 kg) or every four week dosing (Q4W) with 300 mg (<30 kg), mean \pm 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 pediatric subjects 12 to 17 years of age with asthma were enrolled in QUEST. The mean \pm 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 VOYAGE, dupilumab pharmacokinetics was investigated in 270 subjects with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 pediatric subjects weighing <30 kg) or 200 mg Q2W (for 179 pediatric subjects weighing ≥ 30 kg). The mean \pm 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 pediatric subjects 6 to 11 years of age with body weight of ≥ 15 to <30 kg resulted in predicted steady-state trough concentrations (98.7 ± 41.0 mg/L) and average concentrations higher than the observed trough concentrations and average concentrations of 100 mg Q2W (<30 kg).

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 subjects 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 AD (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%.¹¹

Nonclinical Toxicology

11.1 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-4R α at doses up to 200 mg/kg/week.

12. CLINICAL STUDIES

12.1 Atopic Dermatitis

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled trials (SOLO 1, SOLO 2, and CHRONOS) enrolled a total of 2119 adult subjects 18 years of age and older with moderate-to-severe 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 $\geq 10\%$. 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 (SOLO 1 and SOLO 2), subjects received DUPIXENT or placebo for 16 weeks.

In the concomitant therapy trial (CHRONOS), 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 (SOLO 1, SOLO 2, and CHRONOS)

The results of the DUPIXENT monotherapy trials (SOLO 1 and SOLO 2) and the DUPIXENT with concomitant TCS trial (CHRONOS) are presented in Table 7.

Table 7 : Efficacy Results of DUPIXENT with or without Concomitant TCS at Week 16 (FAS) in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

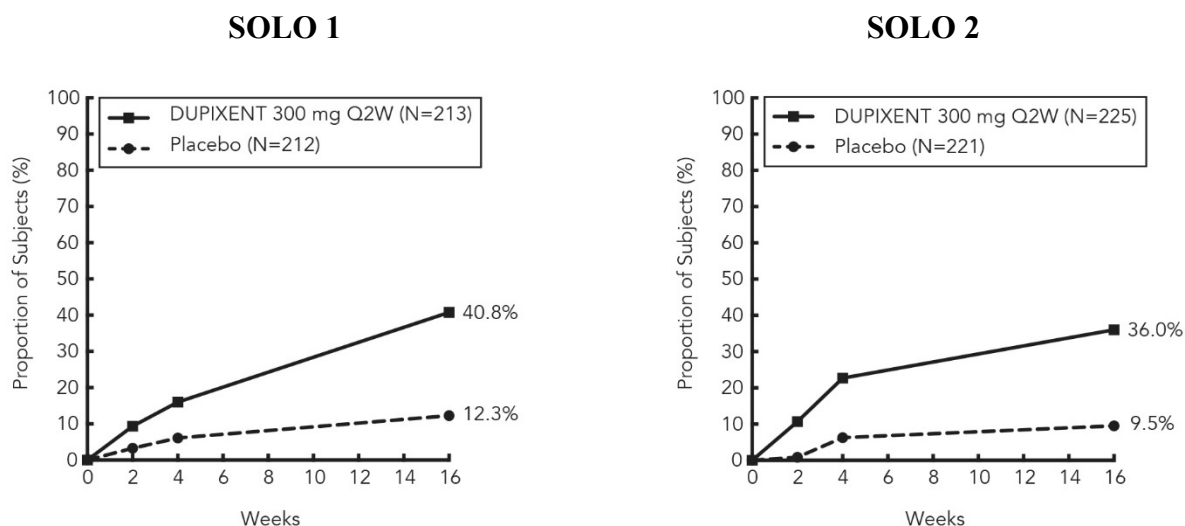
	SOLO 1		SOLO 2		CHRONOS	
	DUPIXENT 300 mg Q2W	Placebo	DUPIXENT 300 mg Q2W	Placebo	DUPIXENT 300 mg Q2W + TCS	Placebo + TCS
Number of subjects randomized (FAS)^a	224	224	233	236	106	315
IGA 0 or 1 ^{b,c}	38%	10%	36%	9%	39%	12%
EASI-75 ^c	51%	15%	44%	12%	69%	23%
EASI-90 ^c	36%	8%	30%	7%	40%	11%
Number of 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 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.

Figure 1: Proportion of Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD with ≥ 4 -point Improvement on the Peak Pruritus NRS in SOLO 1^a and SOLO 2^a Studies (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.

In CHRONOS, 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 (CHRONOS) are presented in Table 8.

Table 8 : Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52 in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

	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 CHRONOS, 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 SOLO 1, SOLO 2, and CHRONOS were generally consistent with the results in the overall study population.

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

Subjects in SOLO 1 and SOLO 2 who had an IGA 0 or 1 with a reduction of ≥ 2 points were re-randomized into SOLO CONTINUE (NCT02395133). SOLO CONTINUE 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.

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

The efficacy of DUPIXENT monotherapy in pediatric subjects 12 to 17 years of age was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1526; ; NCT03054428) in 251 pediatric 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 $\geq 10\%$. 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 AD-1526, 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 AD-1526 are presented in Table 9 .

Table 9 : Efficacy Results of DUPIXENT in AD-1526 at Week 16 (FAS)^a in Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD

	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.

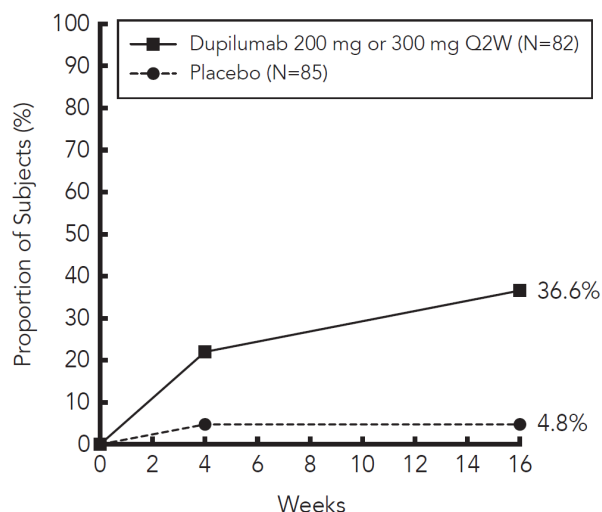
^b Responder was defined as a subject with an IGA 0 or 1 (“clear” or “almost clear”) and a reduction of ≥ 2 points on a 0-4 IGA scale.

^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 Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD with ≥ 4 -point Improvement on the Peak Pruritus NRS in AD-1526^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.

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1652; 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 $\geq 15\%$. 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 AD-1652, 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 10 presents the results by baseline weight strata for the approved dose regimens.

Table 10 : Efficacy Results of DUPIXENT with Concomitant TCS in AD-1652 at Week 16 (FAS)^a in Pediatric Subjects 6 to 11 Years of Age with AD

	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”).

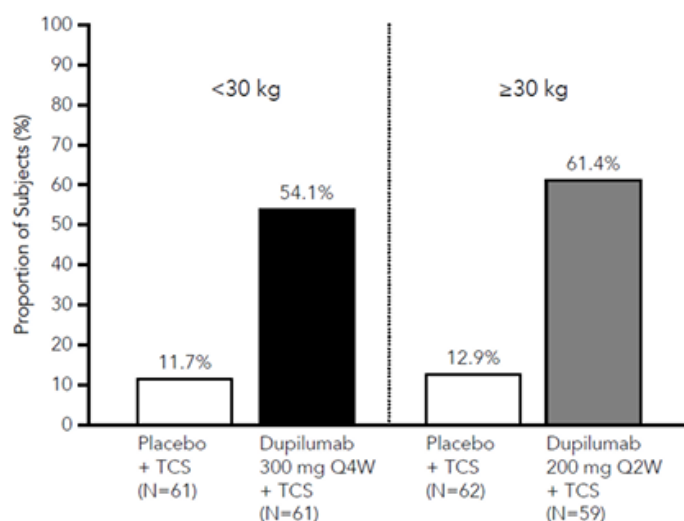
^c Subjects who received rescue treatment or with missing data were considered as non-responders.

^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 6 to 11 Years of Age with AD with ≥ 4 -point Improvement on the Peak Pruritus NRS at Week 16 in AD-1652a (FAS)^b



^aIn 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.

12.2 Asthma

The asthma development program for patients aged 12 years and older included three randomized, double-blind, placebo-controlled, parallel-group, multicenter trials (DRI12544 (NCT01854047), QUEST (NCT02414854), and VENTURE (NCT02528214)) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects. Subjects enrolled in DRI12544 and QUEST 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 VENTURE 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 QUEST and VENTURE 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 VENTURE in which OCS dose was tapered as described below.

DRI12544

DRI12544 was a 24-week dose-ranging study which included 776 adult subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with moderate-to-severe 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 (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

QUEST

QUEST was a 52-week study which included 1902 adult and pediatric subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 pediatric subjects 12 to 17 years of age and 1795 adult subjects with moderate-to-severe 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 pre-bronchodilator 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 subjects with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

VENTURE

VENTURE₂ was a 24-week oral corticosteroid-reduction study in 210 adult and pediatric subjects 15 years of age and older 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 11 below.

Table 11 : Demographics and Baseline Characteristics of Asthma Trials

Parameter	DRI12544 (N=776)	QUEST (N=1902)	VENTURE (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 FEV ₁ (L) at baseline (± SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV ₁ at baseline (%) (± SD)	61 (11)	58 (14)	52 (15)
% Reversibility (± SD)	27 (15)	26 (22)	19 (23)
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)
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)

ICS = inhaled corticosteroid; FEV₁ = Forced expiratory volume in 1 second; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

Exacerbations

DRI12544 and QUEST 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/mL in DRI12544 and the overall population in QUEST), 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 QUEST, 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/mL in DRI12544 and QUEST are shown in Table 12.

Response rates by baseline blood eosinophils for QUEST are shown in Figure 4. Pre-specified subgroup analyses of DRI12544 and QUEST demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In QUEST, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥ 150 cells/mL. In subjects with baseline blood eosinophil count < 150 cells/mL, similar severe exacerbation rates were observed between DUPIXENT and placebo.

In QUEST, 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 12 : Rate of Severe Exacerbations in DRI12544 and QUEST

Trial	Treatment	Baseline Blood EOS ≥ 300 cells/mL (primary analysis population, DRI12544)		
		N	Rate (95% CI)	Rate Ratio (95% CI)
DRI12544	DUPIXENT 200 mg Q2W	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)
	DUPIXENT 300 mg Q2W	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)
	Placebo	68	1.04 (0.57, 1.90)	
QUEST	DUPIXENT 200 mg Q2W	264	0.37 (0.29, 0.48)	0.34 (0.24, 0.48)
	Placebo	148	1.08 (0.85, 1.38)	
	DUPIXENT 300 mg Q2W	277	0.40 (0.32, 0.51)	0.33 (0.23, 0.45)
	Placebo	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 Subjects with Moderate-to-Severe Asthma (QUEST)

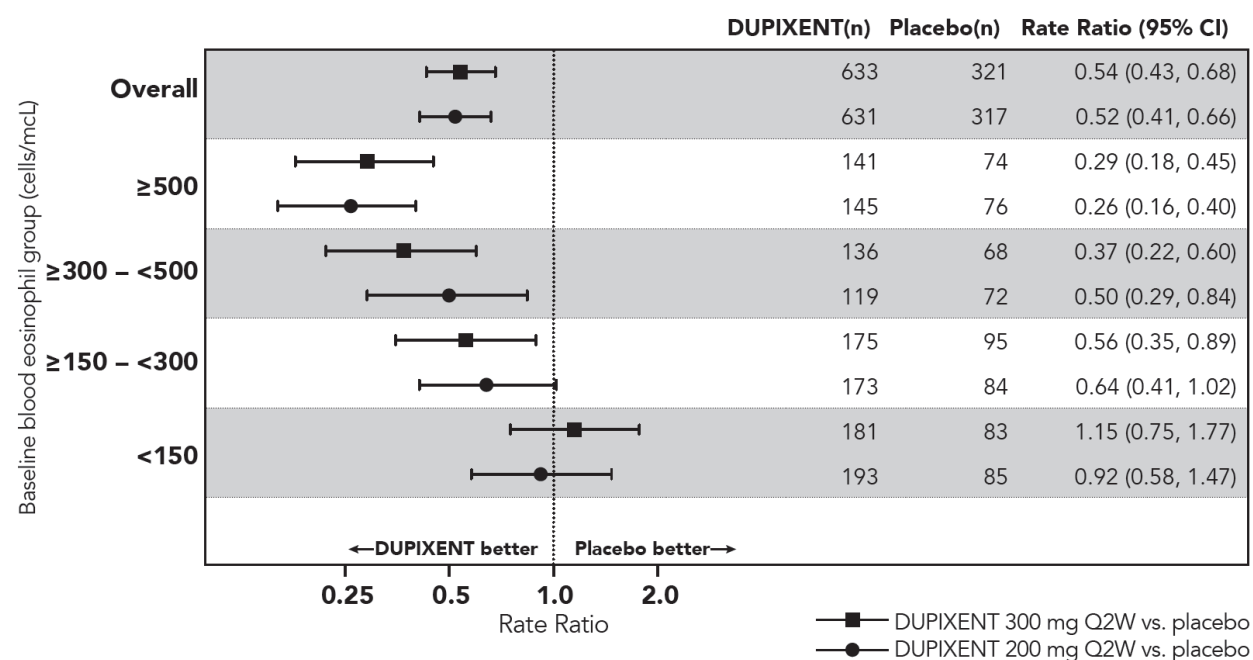
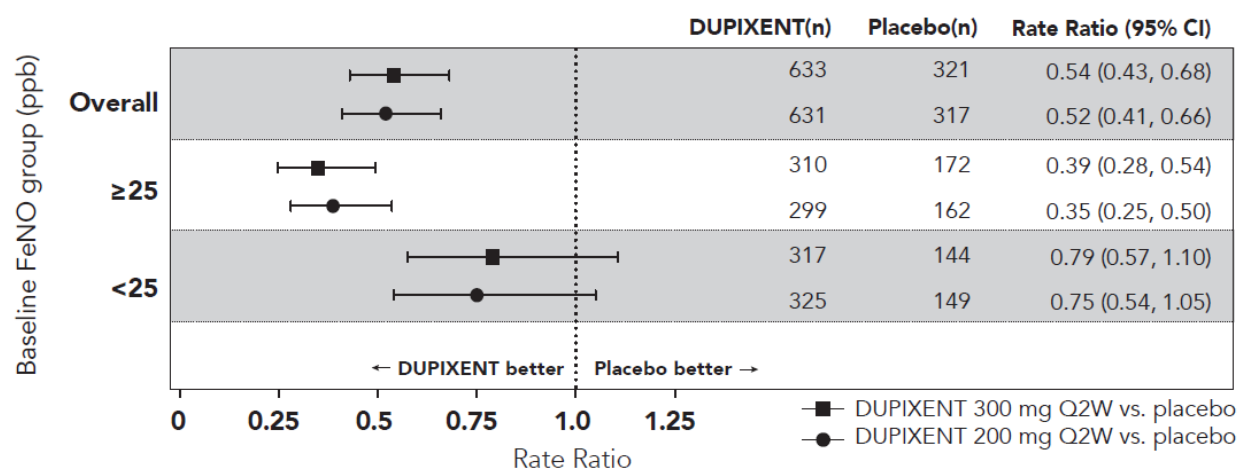
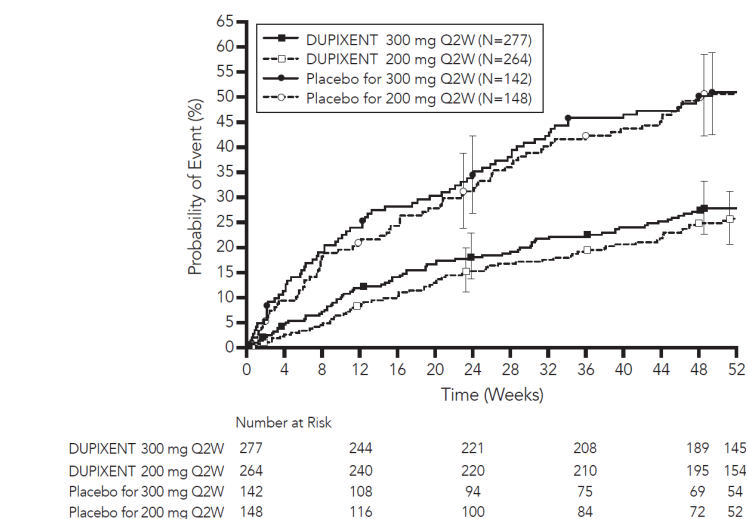


Figure 5: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline FeNO Group (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)



The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in QUEST (Figure 6).

Figure 6: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥ 300 cells/mcL (QUEST)^a



^a At the time of the database lock, not all subjects had completed Week 52

Lung Function

Significant increases in pre-bronchodilator FEV₁ were observed at Week 12 for DRI12544 and QUEST in the primary analysis populations (subjects with baseline blood eosinophil count of ≥ 300 cells/mcL in DRI12544 and the overall population in QUEST). In the overall population in QUEST, 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 DRI12544 and QUEST are shown in Table 13.

Improvements in FEV₁ by baseline blood eosinophils and baseline FeNO for QUEST are shown in Figure 7 and 8, respectively. Subgroup analysis of DRI12544 and QUEST demonstrated greater improvement in subjects with higher baseline blood eosinophils (≥ 150 cells/mcL) or FeNO (≥ 25 ppb). In subjects with baseline blood eosinophil count < 150 cells/mcL and FeNO < 25 ppb, similar differences in FEV₁ were observed between DUPIXENT and placebo.

Mean changes in FEV₁ over time in QUEST are shown in Figure 9.

Table 13 : Mean Change from Baseline and Difference vs Placebo in Pre-Bronchodilator FEV₁ at Week 12 in Subjects with Moderate-to-Severe Asthma (DRI12544 and QUEST)

Trial	Treatment	Baseline Blood EOS ≥ 300 cells/mcL (primary analysis population, DRI12544)		
		N	LS Mean Change from baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544	DUPIXENT 200 mg Q2W	65	0.43 (25.9)	0.26 (0.11, 0.40)
	DUPIXENT 300 mg Q2W	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	68	0.18 (10.2)	
QUEST	DUPIXENT 200 mg Q2W	264	0.43 (29.0)	0.21 (0.13, 0.29)
	Placebo	148	0.21 (15.6)	
	DUPIXENT 300 mg Q2W	277	0.47 (32.5)	0.24 (0.16, 0.32)
	Placebo	142	0.22 (14.4)	

Figure 7: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV₁ across Baseline Blood Eosinophil Counts (cells/mcL) in Subjects with Moderate-to-Severe Asthma (QUEST)

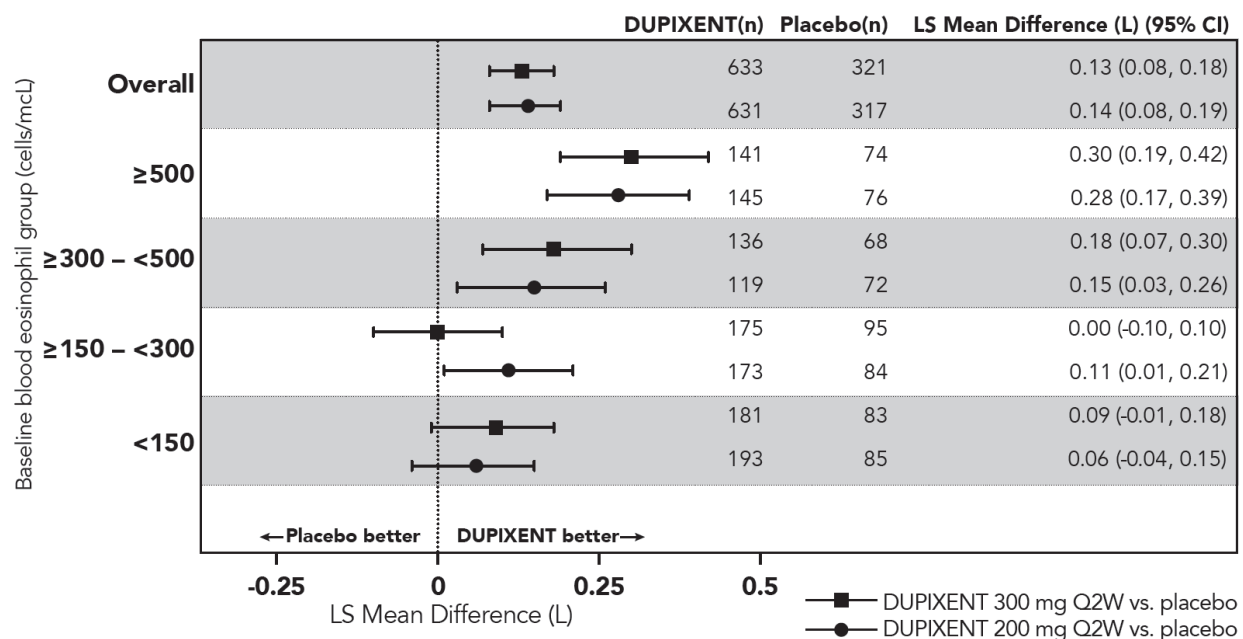


Figure 8: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Prebronchodilator FEV₁ across Baseline FeNO (ppb) in Subjects with Moderate to-Severe Asthma (QUEST)

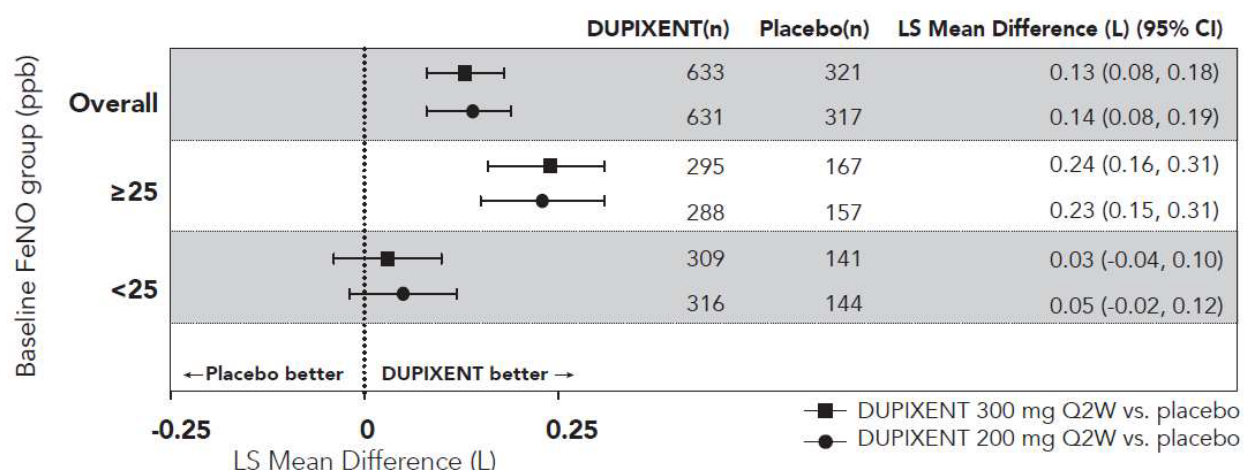
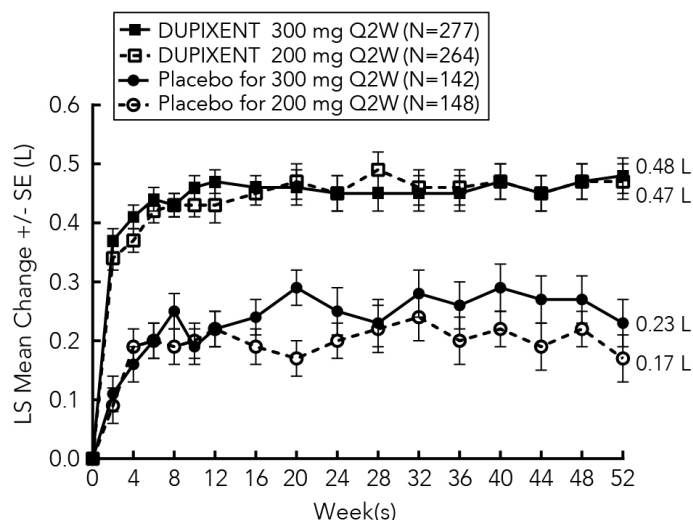


Figure 9: Mean Change from Baseline in Pre-Bronchodilator FEV₁ (L) Over Time in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥300 cells/mcL (QUEST)



Additional Secondary Endpoints

ACQ-5 and AQLQ(S) were assessed in QUEST 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.

Oral Corticosteroid Reduction (VENTURE)

VENTURE 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 VENTURE and showed improvements similar to those in QUEST.

Pediatric Subjects 6 to 11 Years of Age with Asthma

The efficacy and safety of DUPIXENT in pediatric subjects was evaluated in a 52-week multicenter, randomized, double-blind, placebo-controlled study (VOYAGE; NCT02948959) in 408 subjects 6 to 11 years of age, with moderate-to-severe asthma on a medium or high-dose ICS and a second controller medication or high-dose ICS alone. Subjects were required to have a history of 1 or more asthma exacerbation(s) 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 were randomized to DUPIXENT (N=273) or matching placebo (N=135) every other week based on body weight <30 kg (100 mg Q2W) or ≥ 30 kg (200 mg Q2W). The effectiveness of DUPIXENT 300 mg Q4W was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W [see *Pediatric Use (7.3) and Pharmacokinetics (10.3)*].

The primary endpoint was the annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled period. Severe asthma 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. The key secondary endpoint was the change from baseline in pre-bronchodilator FEV₁ percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores.

The demographics and baseline characteristics for VOYAGE are provided in Table 14 below.

Table 14: Demographics and Baseline Characteristics for VOYAGE

Parameter	VOYAGE (N=408)
Mean age (years) (SD)	9 (2)
% Female	36
% White	88
Mean body weight (kg)	36
Mean exacerbations in previous year (± SD)	2.4 (2.2)
High dose ICS dose (%)	44
Pre-dose FEV ₁ (L) at baseline (± SD)	1.48 (0.41)
Mean percent predicted FEV ₁ (%) (±SD)	78 (15)
Mean % Reversibility (± SD)	20 (21)
Atopic Medical History % Overall (AD %, AR %)	92 (36, 82)
Mean FeNO ppb (± SD)	28 (24)
% subjects with FeNO ppb ≥20	50
Median total IgE IU/mL (±SD)	792 (1093)
Mean baseline Eosinophil count (± SD) cells/mcL	502 (395)

ICS = inhaled corticosteroid; FEV₁ = Forced expiratory volume in 1 second; AD = atopic dermatitis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

DUPIXENT significantly reduced the annualized rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in populations with an eosinophilic phenotype as indicated by elevated blood eosinophils and/or the population with elevated FeNO. Subgroup analyses for results of DUPIXENT treatment based upon either baseline eosinophil level or baseline FeNO level were similar to the pediatric (12 to 17 years of age) and adult trials and are described for the adult and pediatric (12 to 17 years of age) asthma population above. In subjects with baseline blood eosinophil count <150 cells/mcL and FeNO <20 ppb, similar severe asthma exacerbation rates were observed between DUPIXENT and placebo.

Significant improvements in percent predicted pre-bronchodilator FEV₁ were observed at Week 12. Significant improvements in percent predicted FEV₁ were observed as early as Week 2 and were maintained through Week 52 in VOYAGE (Figure 10).

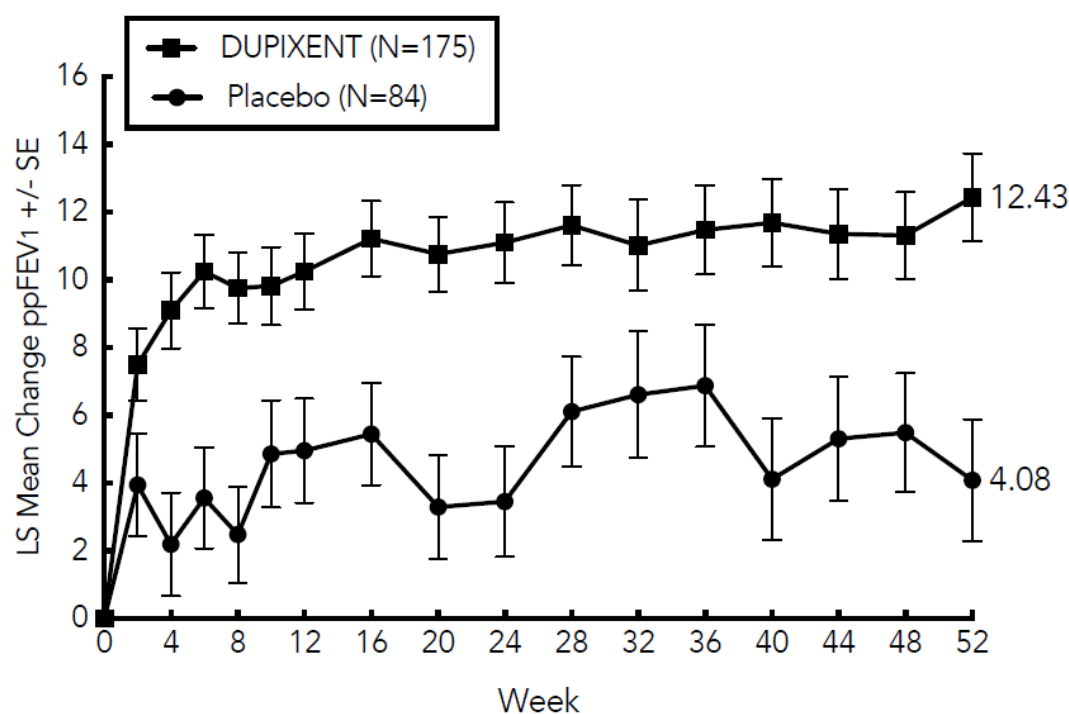
The efficacy results for VOYAGE are presented in Table 15.

Table 15: Efficacy Results of DUPIXENT in VOYAGE

Treatment	EOS ≥ 300 cells/mcL ^a		
Annualized Severe Exacerbations Rate over 52 Weeks			
	N	Rate (95% CI)	Rate Ratio (95% CI)
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥ 30 kg)	175	0.24 (0.16, 0.35)	0.35 (0.22, 0.56)
Placebo	84	0.67 (0.47, 0.95)	
Mean Change from Baseline in Percent Predicted FEV ₁ at Week 12			
	N	LS mean Δ from Baseline	LS mean difference vs. Placebo (95% CI)
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥ 30 kg)	168	10.15	5.32 (1.76, 8.88)
Placebo	80	4.83	

^a This reflects the prespecified primary analysis population for VOYAGE in the United States.

Figure 10: Mean Change from Baseline in Percent Predicted Pre-bronchodilator FEV₁ (L) Over Time in Pediatric Subjects 6 to 11 Years of Age in VOYAGE (Baseline Blood Eosinophils ≥ 300 cells/mcL)



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 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)-IA). In the subgroup of subjects with baseline blood eosinophil count ≥ 300 cells/mcL, DUPIXENT led to a higher proportion of subjects with a response in ACQ-7-IA (80.6% versus 64.3% for placebo) with an OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.0% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

12.3 Chronic Rhinosinusitis with Nasal Polyposis

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454)) in 724 adult subjects 18 years of age and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Subjects with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In SINUS-24, a total of 276 subjects were randomized to receive either 300 mg DUPIXENT (N=143) or placebo (N=133) every other week for 24 weeks. In SINUS-52, 448 subjects were randomized to receive either 300 mg DUPIXENT (N=150) every other week for 52 weeks, 300 mg DUPIXENT (N=145) every other week until Week 24 followed by 300 mg DUPIXENT every 4 weeks until Week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD.

The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central blinded readers, and change from baseline to Week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. For NPS, polyps on each side of the nose were graded on a categorical scale (0=no polyps; 1=small polyps in the middle meatus not reaching below the inferior border of the middle turbinate; 2=polyps reaching below the lower border of the middle turbinate; 3=large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4=large polyps causing complete obstruction of the inferior nasal cavity). The total score was the sum of the right and left scores. Nasal congestion was rated daily by the subjects on a 0 to 3 categorical severity scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

In both studies, key secondary end-points at Week 24 included change from baseline in: LMK sinus CT scan score, daily loss of smell, and 22-item sino-nasal outcome test (SNOT-22). The LMK sinus CT scan score evaluated the opacification of each sinus using a 0 to 2 scale (0=normal; 1=partial opacification; 2=total opacification) deriving a maximum score of 12 per side and a total maximum score of 24 (higher scores indicate more opacification). Loss of smell was scored reflectively by the subject every morning on a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). SNOT-22 includes 22 items assessing symptoms and symptom impact associated with CRSwNP with each item scored from 0 (no problem) to 5 (problem as bad as it can be) with a global score ranging from 0 to 110. SNOT-22 had a 2 week recall period. In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sino-nasal surgery (up to Week 52) were evaluated.

The demographics and baseline characteristics of these 2 trials are provided in Table 16 below.

Table 16 : Demographics and Baseline Characteristics of CRSwNP Trials

Parameter	SINUS-24 (N=276)	SINUS-52 (N=448)
Mean age (years) (SD)	50 (13)	52 (12)
% Male	57	62
Mean CRSwNP duration (years) (SD)	11 (9)	11 (10)
Subjects with ≥ 1 prior surgery (%)	72	58
Subjects with systemic corticosteroid use in the previous 2 years (%)	65	80
Mean Bilateral endoscopic NPS ^a (SD), range 0-8	5.8 (1.3)	6.1 (1.2)
Mean Nasal congestion (NC) score ^a (SD), range 0-3	2.4 (0.6)	2.4 (0.6)
Mean LMK sinus CT total score ^a (SD), range 0-24	19 (4.4)	18 (3.8)
Mean loss of smell score ^a (AM), (SD) range 0-3	2.7 (0.5)	2.8 (0.5)
Mean SNOT-22 total score ^a (SD), range 0-110	49.4 (20.2)	51.9 (20.9)
Mean blood eosinophils (cells/mcL) (SD)	440 (330)	430 (350)
Mean total IgE IU/mL (SD)	212 (276)	240 (342)
Atopic Medical History % Overall	75%	82%
Asthma (%)	58	60
NSAID-ERD (%)	30	27

^aHigher scores indicate greater disease severity

SD = standard deviation; AM = morning; NPS = nasal polyps score; SNOT-22 = 22-item sino-nasal outcome test; NSAID-ERD = asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Clinical Response (SINUS-24 and SINUS-52)

The results for primary endpoints in CRSwNP studies are presented in Table 17 .

Table 17: Results of the Primary Endpoints in CRSwNP Trials

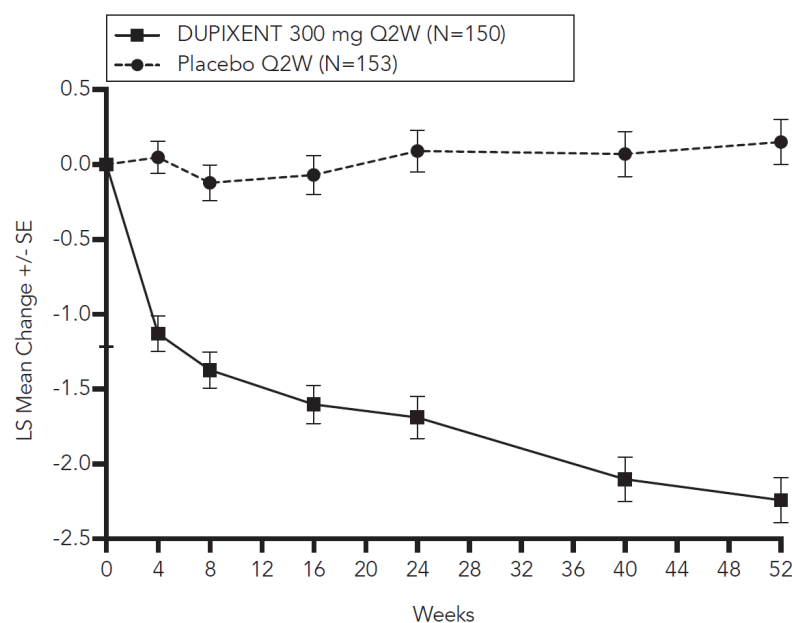
	SINUS-24					SINUS-52				
	Placebo (n=133)		DUIXENT 300 mg Q2W (n=143)		LS mean difference vs. Placebo (95% CI)	Placebo (n=153)		DUIXENT 300 mg Q2W (n=295)		LS mean difference vs. Placebo (95% CI)
Primary Endpoints at Week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change		Baseline mean	LS mean change	Baseline mean	LS mean change	
NPS	5.86	0.17	5.64	-1.89	-2.06 (-2.43, -1.69)	5.96	0.10	6.18	-1.71	-1.80 (-2.10, -1.51)
NC	2.45	-0.45	2.26	-1.34	-0.89 (-1.07, -0.71)	2.38	-0.38	2.46	-1.25	-0.87 (-1.03, -0.71)

A reduction in score indicates improvement.

NPS = nasal polyps score; NC = nasal congestion/obstruction

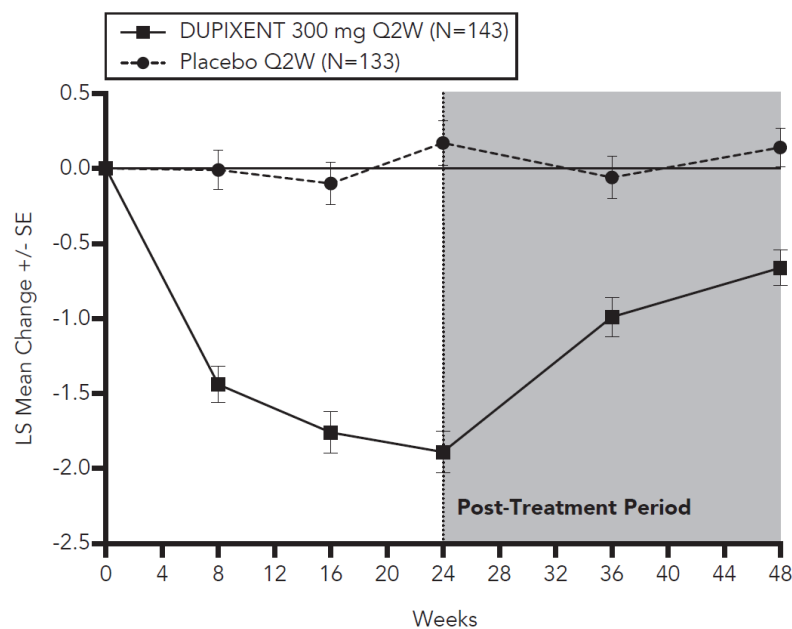
Statistically significant efficacy was observed in SINUS-52 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 11).

Figure 11 : LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 52 in Subjects 18 Years of Age and Older with CRSwNP (SINUS-52 - ITT Population)



Similar results were seen in SINUS-24 at Week 24. In the post-treatment period when subjects were off DUPIXENT, the treatment effect diminished over time (see Figure 12).

Figure 12 : LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 48 in Subjects 18 Years of Age and Older with CRSwNP (SINUS-24 - ITT Population)



At Week 52, the LS mean difference for nasal congestion in the DUPIXENT group versus placebo was -0.98 (95% CI -1.17, -0.79). In both studies, significant improvements in nasal

congestion were observed as early as the first assessment at Week 4. The LS mean difference for nasal congestion at Week 4 in the DUPIXENT group versus placebo was -0.41 (95% CI: -0.52, -0.30) in SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52.

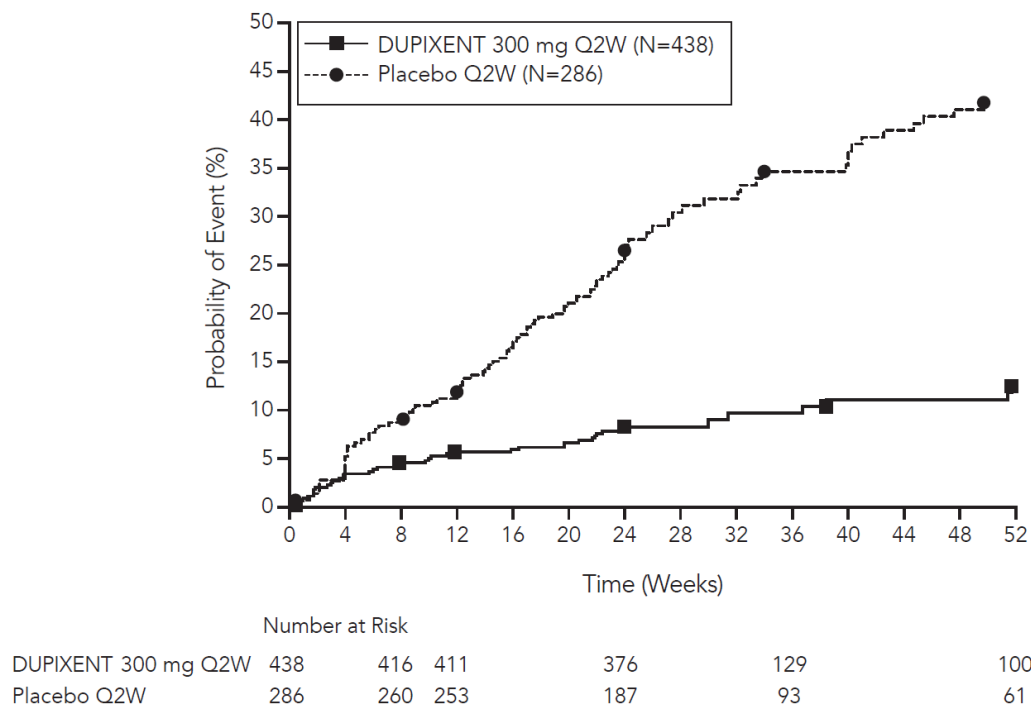
A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in SINUS-24 and -5.13 (95% CI: -5.80, -4.46) in SINUS-52. At Week 52, in SINUS-52 the LS mean difference for LMK sinus CT scan score in the DUPIXENT group versus placebo was -6.94 (95% CI: -7.87, -6.01).

Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.12 (95% CI: -1.31, -0.93) in SINUS-24 and -0.98 (95% CI: -1.15, -0.81) in SINUS-52. At Week 52, the LS mean difference for loss of smell in the DUPIXENT group versus placebo was -1.10 (95% CI: -1.31, -0.89). In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4.

Dupilumab significantly decreased sino-nasal symptoms as measured by SNOT-22 compared to placebo. The LS mean difference for SNOT-22 at Week 24 in the DUPIXENT group versus placebo was -21.12 (95% CI: -25.17, -17.06) in SINUS-24 and -17.36 (95% CI: -20.87, -13.85) in SINUS-24. At Week 52, the LS mean difference in the DUPIXENT group versus placebo was -20.96 (95% CI: -25.03, -16.89).

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with DUPIXENT resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure 13). The proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

Figure 13 : Kaplan Meier Curve for Time to First Systemic Corticosteroid Use and/or Sino-Nasal Surgery During Treatment Period in Subjects 18 Years of Age and Older with CRSwNP (SINUS-24 and SINUS-52 Pooled - ITT Population)



The effects of DUPIXENT on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in subjects with prior surgery and without prior surgery.

In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV₁ were similar to subjects in the asthma program.

13. HOW SUPPLIED/STORAGE AND HANDLING

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 or pre-filled pens.

DUPIXENT is available in cartons containing 2 pre-filled syringes with needle shield or 2 pre-filled pens. Packs of 1/3/6 are also approved. Not all pack sizes may be marketed.

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, DUXIXENT must be used within 14 days or discarded.

Do not expose DUXIXENT to heat or direct sunlight.

Do NOT freeze. Do NOT shake.

The expiry date of the product is indicated on the packaging materials.

MARKETING AUTHORISATION HOLDER

sanofi-aventis Israel ltd. 10 Beni Gaaon St. Netanya

MANUFACTURER

Sanofi Winthrop Industries, France

Revised in October 2022 according to MoH guidelines.