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

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DUPIXENT is indicated for the following diseases:

1.1 Atopic Dermatitis

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

1.2 Asthma

DUPIXENT is indicated in adults and adolescents 12 years and older as an add on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO). DUPIXENT is indicated as maintenance therapy for oral corticosteroid-dependent asthma.

1.3 Chronic Rhinosinusitis with Nasal Polyposis

DUPIXENT is indicated as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control.

1.4 Prurigo Nodularis

DUPIXENT is indicated for the treatment of adult patients with moderate to severe prurigo nodularis (PN) 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 DOSAGE AND ADMINISTRATION

2.1 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 Syringe

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

A caregiver or patient 12 years of age and older may inject DUPIXENT using the pre-filled syringe.

In pediatric patients 12 to 17 years of age, administer DUPIXENT under the supervision of an adult.

In pediatric patients 6 months to less than 12 years of age, administer DUPIXENT by a caregiver.

Administration Instructions

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

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

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

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

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

2.2 Vaccination Prior to Treatment

Live and live attenuated vaccines should not be given concurrently with dupilumab as clinical safety and efficacy has not been established. Immune responses to TdaP vaccine and meningococcal polysaccharide vaccine were assessed, see section 5.9. It is recommended that patients should be brought up to date with live and live attenuated immunisations in agreement with current immunisation guidelines prior to treatment with dupilumab.

2.3 Recommended Dosage for Atopic Dermatitis

Dosage in Adults

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

Dosage in Pediatric Patients 6 Months to 5 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 months to 5 years of age is specified in Table 1.

Table 1: Dosage of DUPIXENT in Pediatric Patients 6 Months to 5 Years of Age with Atopic Dermatitis

Body Weight	Initial[a] and Subsequent Dosage
5 to less than 15 kg	200 mg (one 200 mg injection) every 4 weeks (Q4W)
15 to less than 30 kg	300 mg (one 300 mg injection) every 4 weeks (Q4W)

[a] For pediatric patients 6 months to 5 years of age with atopic dermatitis, no initial loading dose is recommended.

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

The recommended dose of DUPIXENT for patients 6 to 17 years of age is specified in Table 2.

Table 2: Dose of DUPIXENT in Pediatric Patients 6 to 17 Years of Age with Atopic Dermatitis

Body Weight	Initial Loading Dose	Subsequent Dosage
15 to less than 30 kg	600 mg (two 300 mg injection)	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.

2.4 Recommended Dosage for Asthma

The recommended dosage of DUPIXENT for adults and adolescents 12 years of age and older is:

- An initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week administered as subcutaneous injection.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis, an initial dose of 600 mg (two 300 mg injections), followed by 300 mg every other week administered as subcutaneous injection.

Patients receiving concomitant oral corticosteroids may reduce their steroid dose once clinical improvement with dupilumab has occurred. Steroid reductions should be accomplished gradually.

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

2.5 Recommended Dosage for Chronic Rhinosinusitis with Nasal Polyposis

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

2.6 Recommended Dosage for Prurigo Nodularis

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). DUPIXENT can be used with or without topical corticosteroids.

2.7 Missed Doses

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

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

2.8 Preparation for Use

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 and 30 minutes for the 200 mg/1.14 mL pre-filled syringe) 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.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including 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 atopic dermatitis 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)]*.

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

In subjects with PN, the frequency of conjunctivitis was 4% in the DUPIXENT group compared to 1% in the placebo group; these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN development program [*see Adverse Reactions (6.1)*].

Conjunctivitis and keratitis adverse events have also been reported with DUPIXENT in postmarketing settings, predominantly in atopic dermatitis 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 Eosinopilic 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. Heatlthcare 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 physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.6 Patients with Co-morbid Asthma

Advise patients with 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 antihelminth treatment, discontinue treatment with DUPIXENT until the infection resolves. [*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 during treatment 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 (12.2)]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Warnings and Precautions (5.1)]*
- Conjunctivitis and Keratitis *[see Warnings and Precautions (5.2)]*
- 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 (SOLO 1, SOLO 2, and CHRONOS) and one dose-ranging trial (AD-1021) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis.

The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

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

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) trial which assessed the long-term safety of repeat doses of DUPIXENT through 260 weeks of treatment in adults with moderate-to-severe AD who had previously participated in controlled trials of DUPIXENT or had been screened for SOLO 1 or SOLO 2.

The safety data in AD-1225 reflect exposure to DUPIXENT 200 mg QW, 300 mg QW and 300 mg Q2W in 2677 subjects, including 2254 exposed for at least 52 weeks, 1224 exposed for at least 100 weeks, 561 exposed for at least 148 weeks and 179 exposed for at least 260 weeks.

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

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

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

[a] pooled analysis of 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 260 Weeks (AD-1225)

The long-term safety profile observed in this trial through 260 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 atopic dermatitis (AD-1526). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile from studies in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (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 atopic dermatitis.

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 11years of age with severe atopic dermatitis (AD-1652). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adults and pediatric subjects 12 to 17 years of age with atopic dermatitis.

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 atopic dermatitis (AD-1434). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe atopic dermatitis 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 AD-1652.

The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 to 11 years of age was consistent with that seenin adults and pediatric subjects 12 to 17 years of age with atopic dermatitis [*see Use in Specific Populations (8.4)*].

Pediatric Subjects 6 Months to 5 Years of Age with Atopic Dermatitis

The safety of DUPIXENT with concomitant TCS was assessed in a trial of 161 pediatric subjects 6 months to 5 years of age with moderate-to-severe atopic dermatitis (AD-1539). The safety profile of DUPIXENT + TCS in these subjects through Week 16 was similar to the safety profile from trials in adults and pediatric subjects 6 to 17 years of age with atopic dermatitis.

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 180 pediatric subjects 6 months to 5 years of age with atopic dermatitis (AD-1434). The majority of subjects were treated with DUPIXENT 300 mg every 4 weeks. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD-1539. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 months to 5 years of age was consistent with that seen in adults and pediatric subjects 6 to 17 years old with atopic dermatitis. In addition, hand-foot-and-mouth disease was reported in 9 (5%) pediatric subjects and skin papilloma was reported in 4 (2%) pediatric subjects treated with DUPIXENT ± TCS. These cases did not lead to study drug discontinuation *[see Use in Specific Populations (8.4)]*.

Atopic Dermatitis with Hand and/or Foot Involvement

The safety of DUPIXENT was assessed in a 16-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (Liberty-AD-HAFT) in 133 adult and pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement *[see Clinical Studies (14)]*. In this trial 67 subjects received DUPIXENT, and 66 subjects received placebo. DUPIXENT-treated subjects received the recommended dosage based on their age and body weight *[see Dosage and Administration (2.3)]*. The safety profile of DUPIXENT in these subjects through Week 16 was consistent with the safety profile from studies in adult and pediatric subjects 6 months of age and older with moderate-to-severe AD.

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 DRI2544 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 4 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in DRI12544 and QUEST.

Table 4: Adverse Reactions Occurring in ≥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 ≥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.

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 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 group in SINUS-24 and SINUS-52.

Table 5: Adverse Reactions Occurring in ≥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.

Prurigo Nodularis

A total of 309 adult subjects with prurigo nodularis (PN) were evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter trials (PRIME and PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both trials.

The proportion of subjects who discontinued treatment due to adverse events was 3% of the placebo group and 0% of the DUPIXENT 300 mg Q2W group.

The safety population had a mean age of 49 years; 65% of subjects were female, 56% were White, 34% were Asian, and 6% were Black or African American. Subjects with co-morbid conditions included 43% of subjects with a history of atopy (defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy), 8% of subjects with a history of hypothyroidism and 9% of subjects with a history of diabetes mellitus type 2.

Table 6 summarizes the adverse reactions that occurred at a rate of at least 2% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in PRIME and PRIME2.

Table 6: Adverse Reactions Occurring in ≥2% of the DUPIXENT Group in PRIME and PRIME2 and Greater than Placebo

Adverse Reaction	PRIME and PRIME2	
	DUPIXENT 300 mg Q2W N=152 n (%)	Placebo N=157 n (%)
Nasopharyngitis[a]	8 (5%)	3 (2%)
Conjunctivitis[b]	6 (4%)	2 (1%)
Herpes Infection[c]	5 (3%)	0%
Dizziness[d]	5 (3%)	2 (1%)
Myalgia[e]	5 (3%)	2 (1%)
Diarrhea	4 (3%)	1 (1%)

[a] Nasopharyngitis includes pharyngitis
[b] Conjunctivitis includes conjunctivitis and allergic conjunctivitis
[c] Herpes infection includes oral herpes, genital herpes simplex, herpes zoster and ophthalmic herpes zoster
[d] Dizziness includes dizziness postural, vertigo and vertigo positional
[e] Myalgia includes musculoskeletal pain and musculoskeletal chest pain

Specific Adverse Reactions

Conjunctivitis and Keratitis

In adult subjects with atopic dermatitis, 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 AD-1021). During the 52-week treatment period of concomitant therapy atopic dermatitis 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 260 weeks (AD-1225), conjunctivitis was reported in 21% of the DUPIXENT group (12 per 100 subject-years).

In DUPIXENT atopic dermatitis 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 atopic dermatitis DUPIXENT +

topical corticosteroids (TCS) atopic dermatitis 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 atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. During the long-term OLE trial with data through 260 weeks (AD-1225), keratitis was reported in 3% of the DUPIXENT group (1 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

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

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)]*.

Among subjects with PN, the frequency of conjunctivitis was 4% in the DUPIXENT group compared to 1% in the placebo group; all of these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN 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 atopic dermatitis trial. The rates remained stable through 260 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 atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). During the long-term OLE trial with data through 260 weeks (AD-1225), 2.0% of DUPIXENT-treated subjects reported herpes zoster (0.94 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.

Among subjects with PN, herpes zoster and ophthalmic herpes zoster were each reported in <1% of the DUPIXENT group (1 per 100 subject-years) and 0% of the placebo group.

Hypersensitivity Reactions

Hypersensitivity reactions were reported in <1% of DUPIXENT-treated subjects. These included anaphylaxis, serum sickness or serum sickness-like reaction, 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 atopic dermatitis, asthma, and CRSwNP had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo.

In adult subjects with atopic dermatitis 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 pediatric subjects <6 years old with atopic dermatitis, the mean and median increases from baseline to Week 4 were 478 and 90 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 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.

In subjects with PN (PRIME and PRIME2), the mean and median decrease in blood eosinophils from baseline to Week 4 were 9 and 10 cells/mcL, respectively.

Across the trials for atopic dermatitis, asthma and CRSwNP indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. In the trials for the PN indication, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was lower in DUPIXENT than in the placebo group.

Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <3% of DUPIXENT-treated subjects and <0.5% in placebo-treated subjects. Blood eosinophil counts declined to near baseline or remained below baseline levels (PRIME and PRIME2) during study treatment *[see Warnings and Precautions (5.3)]*.

In study AD-1539, treatment-emergent eosinophilia (≥5,000 cells/mcL) 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 atopic dermatitis (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 atopic dermatitis 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 months to 11 years of age with atopic dermatitis who received DUPIXENT 200 mg Q2W, 200mg Q4W or 300 mg Q4W.

Approximately 16% of pediatric subjects 12 to 17 years of age with atopic dermatitis 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.

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.

Prurigo Nodularis

Approximately 8% of subjects with PN who received DUPIXENT 300 mg Q2W for 24 weeks developed antibodies to DUPIXENT; approximately 1% 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 (12.3)*].

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

6.3 Post Marketing Experience

The following adverse reactions have been identified during postapproval 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (see Clinical Considerations). In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) *[see Data]*. The background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryofetal toxicity or malformations, or on morphological,

functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 6 months of age and older with moderate-to-severe atopic dermatitis, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable *[see Clinical Studies (14.1)]*.

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 atopic dermatitis. Of the 251 subjects, 82 were treated with DUPIXENT 200 mg Q2W (<60 kg) or 300 mg Q2W (≥60 kg) and 85 were treated with matching placebo
- AD-1652 which included 367 pediatric subject 6 to 11 years of age with severe atopic dermatitis. Of the 367 subjects, 120 were treated with DUPIXENT 300 mg Q4W + TCS (15 to <30 kg) or 200 mg Q2W + TCS (≥30 kg) and 123 were treated with matching placebo + TCS
- AD-1539 which included 162 pediatric subjects 6 months to 5 years of age with moderate-tosevere atopic dermatitis. Of the 162 subjects, 83 were treated with DUPIXENT 200 mg Q4W + TCS (5 to <15 kg) or 300 mg Q4W + TCS (15 to <30 kg) and 79 subjects were assigned to be treated with matching placebo + TCS
- AD-1434, an open-label extension study that enrolled 275 pediatric subjects 12 to 17 years of age treated with DUPIXENT ± TCS, 368 pediatric subjects 6 to 11 years of age treated with DUPIXENT ± TCS, and 180 pediatric subjects 6 months to 5 years of age treated with DUPIXENT ± TCS
- Liberty-AD-HAFT which included 27 pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement treated with DUPIXENT (N=14) or matching placebo (N=13)

The safety and efficacy were generally consistent between pediatric and adult patients [*see Adverse Reactions (6.1) and Clinical Studies (14.2)*]. In addition, hand-foot-and-mouth disease was reported in 9 (5%) pediatric subjects and skin papilloma was reported in 4 (2%) pediatric subjects 6 months to 5 years of age treated with DUPIXENT ± TCS in AD-1434. These cases did not lead to study drug discontinuation *[see Adverse Reactions (6.1)]*.

Safety and efficacy in pediatric patients younger than 6 months of age with atopic dermatitis have not been established.

Asthma

A total of 107 pediatric subjects aged 12 to 17 years 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. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. 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 (12.3)]*.

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

CRSwNP

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

Prurigo Nodularis

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

8.5 Geriatric Use

Of the 1539 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 70 subjects were 65 years or older. Clinical trials of DUPIXENT in atopic dermatitis did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

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

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.

Of the 152 subjects with PN exposed to DUPIXENT, a total of 37 were 65 years or older including 8 subjects 75 years or older. Clinical trials did not include a sufficient number of subjects 65 years of age and older to determine whether they respond differently from younger adult subjects.

10 OVERDOSE

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

11 DESCRIPTION

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

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

DUPIXENT (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUPIXENT is provided as a single-dose pre-filled syringe with needle shield in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

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

Each 200 mg pre-filled syringe delivers 200 mg dupilumab in 1.14 mL which also contains L-arginine hydrochloride (12 mg), L-histidine (3.5 mg), polysorbate 80 (2.3 mg), sodium acetate (1.2 mg), sucrose (57 mg), and water for injection, pH 5.9.

12 CLINICAL PHARMACOLOGY

Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH05.

12.1 Mechanism of Action

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

Inflammation driven by IL-4 and IL-13 is an important component in the pathogenesis of asthma, atopic dermatitis, CRSwNP, and PN. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines, chemokines) are involved in inflammation.

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

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. These reductions in biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent

reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (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 atopic dermatitis 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

12.3 Pharmacokinetics

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

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg or 300 mg, dupilumab reached peak mean ±SD concentrations (C_{max}) of 70.1±24.1 mcg/mL or 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 ±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, CRSwNP, and PN 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 Q2W, 200 mg Q2W, 300mg Q4W or 200mg 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) and 2.5 times (up to 32 weeks) longer in pediatric subjects 6 to 11 years of age and pediatric subjects 6 months to 5 years of age, respectively.

Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. The systemic exposure increased by 30-fold when the dose increased 8-fold following a single dose of dupilumab from 75 mg to 600 mg (i.e., 0.25-times to 2-times the recommended dose).

Weight

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

Age

Based on population pharmacokinetic analysis, age did not affect dupilumab clearance in adults and in pediatric subjects 6 to 17 years of age. In pediatric subjects from 6 months to 5 years of age, clearance increased with 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 ±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 atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean±SD steady-state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

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

For pediatric subjects 6 months to 5 years of age with atopic dermatitis receiving every four week dosing (Q4W) with 300 mg (≥15 to <30 kg) or 200 mg (≥5 to <15 kg), the mean ± SD steady-state trough concentration was 110±42.8 mcg/mL and 109±50.8 mcg/mL, respectively.

Asthma

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

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 atopic dermatitis (a SC loading dose of 600 mg followed by 300 mg SC weekly for six weeks). No clinically significant changes in AUC were observed. The largest effect was observed for metoprolol (CYP2D6) with an increase in AUC of 29%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled trials (SOLO1, SOLO 2, and CHRONOS; NCT02277743, NCT02277769, and NCT02260986 respectively) enrolled a total of 2119 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were white, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged peak pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (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)

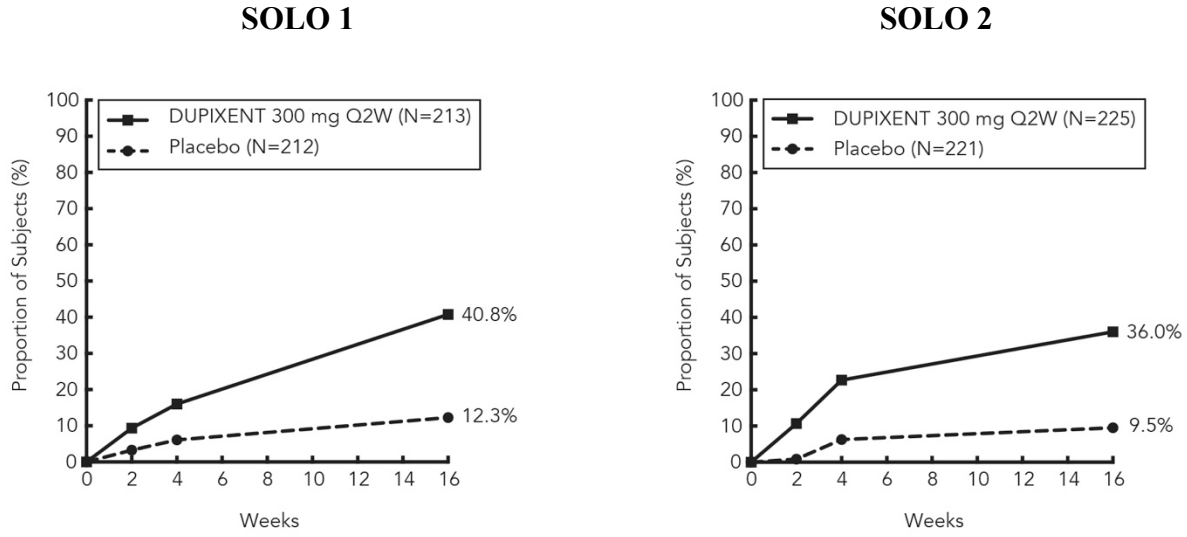
The results of the DUPIXENT monotherapy trials (SOLO 1 and SOLO 2) and the DUPIXENT with concomitant TCS trial (CHRONOS) are presented in Table 7.

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 IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

Figure 1: Proportion of 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 SOLO2[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 IGA 0 or 1 ("clear" or "almost clear") with a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

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 and safety 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 ≥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] 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.

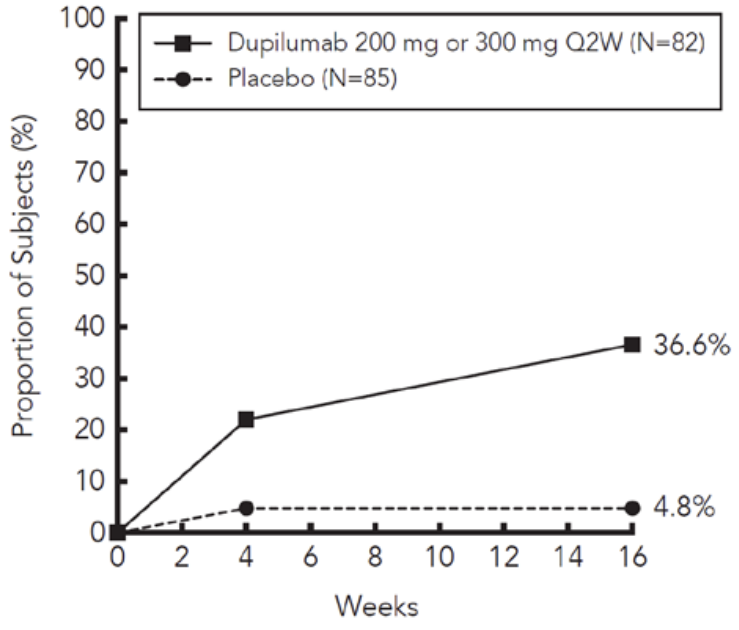
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.

[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 ≥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.

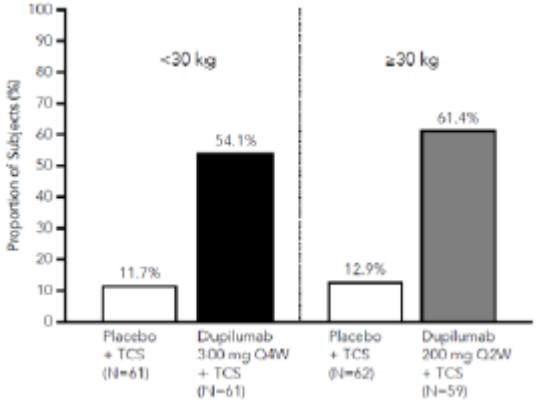
Table 10: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1652 at Week 16 (FAS)[a] Pediatric Subjects 6 to 11 Years of Age with AD

	DUPIXENT 300 mg Q4W[d] + TCS (N=61)	**Placebo + TCS (N=61)**	**DUPIXENT 200 mg Q2W[e] + TCS (N=59)**	**Placebo + TCS (N=62)**
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-1652[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 Months to 5 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-1539; NCT03346434) in 162 subjects 6 months to 5 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (≥5 to <15 kg and ≥15 to <30 kg).

Subjects in the DUPIXENT Q4W + TCS group with baseline weight of ≥5 to <15 kg received an initial dose of 200 mg on Day 1, followed by 200 mg Q4W from Week 4 to Week 12, and subjects with baseline weight of ≥15 to <30 kg received an initial dose of 300 mg on Day 1, followed by 300mg Q4W from Week 4 to Week 12. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.
In AD-1539, the mean age was 3.8 years, the median weight was 16.5 kg, 39% of subjects were female, 69% were White, 19% were Black, and 6% were Asian. At baseline, the mean BSA involvement was 58%, and 29% of subjects had received prior systemic immunosuppressants.
Also, at baseline the mean EASI score was 34.1, and the weekly average of daily worst scratch/itch score was 7.6 on a scale of 0-10. Overall, 81.4% of subjects had at least one comorbid allergic condition; 68.3% had food allergies, 52.8% had other allergies, 44.1% had allergic rhinitis, and 25.5% 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 Worst Scratch/Itch NRS (≥4-point improvement). The efficacy results at Week 16 for AD-1539 are presented in Table 11.

Table 11: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1539 at Week 16 (FAS)[a] in Pediatric Subjects 6 Months to 5 Years of Age with Moderate-to-Severe AD

	DUPIXENT + TCS 200 mg (5 to <15 kg) or 300 mg (15 to <30 kg) Q4W[d] (N=83)[a]	**Placebo + TCS (N=79)[a]**	**Difference vs. Placebo (95 % CI)**
IGA 0 or 1[b,c]	28%	4%	24% (13%, 34%)
EASI-75[c]	53%	11%	42% (29%, 55%)
EASI-90[c]	25%	3%	23% (12%, 33%)
Worst Scratch/Itch NRS (≥4-point improvement)[c]	48%	9%	39% (26%, 52%)

CI = confidence interval

[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 (63% and 19% in the placebo and DUPIXENT arms, respectively) or with missing data were considered as non-responders.

[d] At Day 1, subjects received 200 mg (5 to <15kg) or 300 mg (15 to <30 kg) of DUPIXENT.

Atopic Dermatitis with Hand and/or Foot Involvement

The efficacy and safety of DUPIXENT was evaluated in a 16-week, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial (Liberty-AD-HAFT; NCT04417894) in 133 adult and pediatric subjects 12 to 17 years of age with atopic dermatitis with moderate-to-severe hand and/or foot involvement, defined by an established diagnosis of atopic dermatitis and screening to rule out irritant and allergic contact dermatitis through history and appropriate patch testing, and by an IGA (hand and foot) score ≥3 (scale of 0 to 4) and a hand and foot Peak Pruritus Numeric Rating Scale (NRS) score for maximum itch intensity ≥4 (scale of 0 to 10). Fifty-three (53) percent (N=70/133) of the subjects also had moderate-to-severe AD outside of the hands or feet (IGA global ≥3). Eligible subjects had previous inadequate response or intolerance to treatment of hand and/or foot dermatitis with topical AD medications. In this trial 67 subjects received DUPIXENT, and 66 subjects received placebo. DUPIXENT-treated subjects received the recommended dosage based on their age and body weight *[see Dosage and Administration (2.2)]*. Subjects were not allowed concomitant use of topical treatments for AD on the hands and feet during the trial, but were allowed the use of topical treatments for AD on other parts of the body with certain restrictions.

In Liberty-AD-HAFT, 38% of subjects were male, 80% were White, 13% were Asian, and 5% were Black or African American. For ethnicity, 4% were identified as Hispanic or Latino and 96% were identified as not Hispanic or Latino. Seventy-two (72) percent (N=96/133) of subjects had a baseline IGA (hand and foot) score of 3 (atopic dermatitis with moderate hand and/or foot involvement), and

28% (N=37/133) of subjects had a baseline IGA (hand and foot) score of 4 (atopic dermatitis with severe hand and/or foot involvement). The baseline weekly averaged hand and foot Peak Pruritus NRS score was 7.1.

The primary endpoint was the proportion of subjects with an IGA hand and foot score of 0 (clear) or 1 (almost clear) at Week 16. The key secondary endpoint was reduction of itch as measured by the hand and foot Peak Pruritus NRS (≥4-point improvement).

The efficacy results at Week 16 for Liberty-AD-HAFT are presented in Table 12.

Table 12: Efficacy Results of DUPIXENT in Liberty-AD-HAFT at Week 16 (FAS)[a] in Adult and Pediatric Subjects 12 to 17 Years of Age with AD with Moderate-to-Severe Hand and/or Foot Involvement

	DUPIXENT 200/300 mg Q2W[d] (N=67)[a]	Placebo (N=66)[a]	Difference vs. Placebo (95 % CI)
IGA (hand and foot) 0 or 1[b,c]	40%	17%	24% (9%, 38%)
Improvement (reduction) of weekly averaged hand and foot Peak Pruritus NRS ≥4[c]	52%	14%	39% (24%, 53%)

CI = confidence interval

[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 (21% and 3% in the placebo and DUPIXENT arms, respectively) or with missing data were considered as non-responders.

[d] Adults received a loading dose of DUPIXENT 600 mg SC followed by 300 mg SC Q2W. Pediatric subjects 12 to 17 years of age received a loading dose of DUPIXENT 600 mg SC followed by 300 mg SC Q2W (for body weight ≥60 kg) or a loading dose of DUPIXENT 400 mg SC followed by 200 mg SC Q2W (for body weight <60 kg).

14.2 Asthma

The asthma development program included three randomized, double-blind, placebo-controlled, parallel-group, multi-center studies (DRI12544, QUEST, and VENTURE) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older).

Subjects enrolled in DRI12544 and QUEST studies 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 study entry. Subjects enrolled in VENTURE study required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s).

The effects of DUPIXENT treatment discontinuation on severe exacerbations and FEV1 were assessed in the DRI12544 study during the 16-week follow-up period. Subjects in both the overall and the baseline blood eosinophil count of ≥ 300 cells/mcL populations experienced a gradual return to baseline asthma status, with no evidence of rebound effect.

In all 3 studies, subjects were enrolled without requiring a minimum baseline blood eosinophil or other Type 2 biomarker (e.g. FeNO or IgE) level.

In the QUEST and VENTURE studies, subjects with baseline 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 study in which OCS dose was tapered as described below.

DRI12544 study
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 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 change from baseline to Week 12 in FEV1 (L). 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 mean change from baseline and responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

EFC13579 (QUEST) study
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 controller medications.

Subjects requiring a third controller were allowed to participate in this study. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) DUPIXENT every other week (or matching placebo for either 200 mg [N = 317] or 300 mg [N= 321] every other week) 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 overall population (unrestricted by minimum baseline eosinophils or other Type 2 biomarkers).

Additional secondary endpoints included exacerbation rates and FEV1 in subjects with different baseline levels of eosinophils as well as mean change from baseline and responder rates in the ACQ-5 and AQLQ(S) scores.

EFC13691 (VENTURE) study

VENTURE 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 every other week 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 which was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The OCS reduction was performed according to algorithm specified in the protocol.

The primary endpoint was the percent reduction of oral corticosteroid dose at Week 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline eosinophils or other Type 2 biomarkers). The key secondary endpoints were the proportion of subjects achieving a reduction of 50% or greater in their OCS dose compared with baseline and proportion of subjects achieving a reduction of OCS dose to <5 mg/day at Week 24 while maintaining asthma control.
Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and mean change from baseline and responder rate in the ACQ-5 and AQLQ(S) scores.

The demographics and baseline characteristics of these 3 studies are provided in Table 13 below.

Table 13: Demographics and Baseline Characteristics of Asthma Trials

Parameter	DRI12544 (n = 776)	QUEST (n = 1902)	VENTURE (n=210)
Mean age (years) (SD)	48.6 (13.0)	47.9 (15.3)	51.3 (12.6)
% Female	63.1	62.9	60.5
% White	78.2	82.9	93.8
Body Mass Index ≥30 kg/ m2 (%)	40.2	39.5	41.4
Duration of Asthma (years), mean (± SD)	22.03 (15.42)	20.94 (15.36)	19.95 (13.90)
Never smoked, (%)	77.4	80.7	80.5
Mean exacerbations in previous year (± SD)	2.17 (2.14)	2.09 (2.15)	2.09 (2.16)
High dose ICS use* (%)	49.5	51.5	88.6
Pre-dose FEV1 (L) at baseline (± SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV1 at baseline (%) (±SD)	60.77 (10.72)	58.43 (13.52)	52.18 (15.18)
% Reversibility (± SD)	26.85 (15.43)	26.29 (21.73)	19.47 (23.25)
Mean ACQ-5 score (± SD)	2.74 (0.81)	2.76 (0.77)	2.50 (1.16)
Mean AQLQ score (± SD)	4.02 (1.09)	4.29 (1.05)	4.35 (1.17)
Atopic Medical History % Overall (AD %, NP %, AR %)	72.9 (8.0, 10.6, 61.7)	77.7 (10.3, 12.7, 68.6)	72.4 (7.6, 21.0, 55.7)

Parameter	DRI12544 (n = 776)	QUEST (n = 1902)	VENTURE (n=210)
Mean FeNO ppb (± SD)	39.10 (35.09)	34.97 (32.85)	37.61 (31.38)
% patients with FeNO ppb			
≥25	49.9	49.6	54.3
≥50	21.6	20.5	25.2
Mean total IgE IU/mL (± SD)	435.05 (753.88)	432.40 (746.66)	430.58 (775.96)
Mean baseline Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)
% patients with EOS			
≥ 150 cells/mcL	77.8	71.4	71.4
≥ 300 cells/mcL	41.9	43.7	42.4

ICS = inhaled corticosteroid; LABA = Long-acting beta2-agonist; FEV1 = Forced expiratory volume in 1 second; ACQ-5 = Asthma Control Questionnaire-5; AQLQs = Asthma Quality of Life Questionnaire, Standardized Version; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide; EOS = blood eosinophil

* High dose ICS was defined as > 500 mcg fluticasone equivalent per day.

Exacerbations

DRI12544, QUEST, and VENTURE studies evaluated the frequency of severe asthma exacerbations.

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.

For subjects on maintenance corticosteroids, an asthma exacerbation was defined as a temporary increase in oral corticosteroid dose for at least 3 days.

In the overall population, subjects receiving either DUPIXENT 200 mg or 300 mg every other week had significant reductions in the rate of severe asthma exacerbations compared to placebo (see Table 14).

In the pooled analysis of the DRI12544 and QUEST studies, the rate of severe exacerbations leading to hospitalizations and/or emergency room visits was reduced by 25.5% and 46.9% with DUPIXENT 200 mg or 300 mg every other week, respectively.

Table 14: Rate of Severe Exacerbations in DRI12544, QUEST, and VENTURE (Overall Population[a])

Study	Treatment (N)	Exacerbations per Year		Percent Reduction
		Rate (95% CI)	Rate Ratio (95%CI)	
All Severe Exacerbations				
DRI12544	Dupixent 200 mg Q2W (n= 150)	0.27 (0.16, 0.46)	0.30 (0.16, 0.57)	70%
	Dupixent 300 mg Q2W (n = 157)	0.27 (0.16, 0.45)	0.30 (0.16, 0.55)	70%
	Placebo (n = 158)	0.90 (0.62, 1.30)		
QUEST	Dupixent 200 mg Q2W (n= 631)	0.46 (0.39, 0.53)	0.52 (0.41, 0.66)	48%
	Placebo (n = 317)	0.87 (0.72, 1.05)		
	Dupixent 300 mg Q2W	0.52 (0.45, 0.61)	0.54 (0.43, 0.68)	46%
	Placebo (n = 321)	0.97 (0.81, 1.16)		
VENTURE[b]	Dupixent 300 mg Q2W (n = 103)	0.65 (0.44, 0.96)	0.41 (0.26, 0.63)	59%
	Placebo (n = 107)	1.60 (1.25, 2.04)		

a Overall population is unrestricted by minimum baseline eosinophils or other Type 2 biomarkers
b OCS withdrawal study

Prespecified subgroup analyses of DRI12544, QUEST, and VENTURE studies demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline levels of markers for Type 2 inflammation such as eosinophil level and FeNO.

Prespecified 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/mcL. In subjects with baseline blood eosinophil count < 150 cells/mcL, similar severe exacerbation rates were observed between DUPIXENT and placebo.

In all studies, when compared to placebo greater reductions in severe exacerbations were also seen in subjects with baseline FeNO ≥25 ppb.

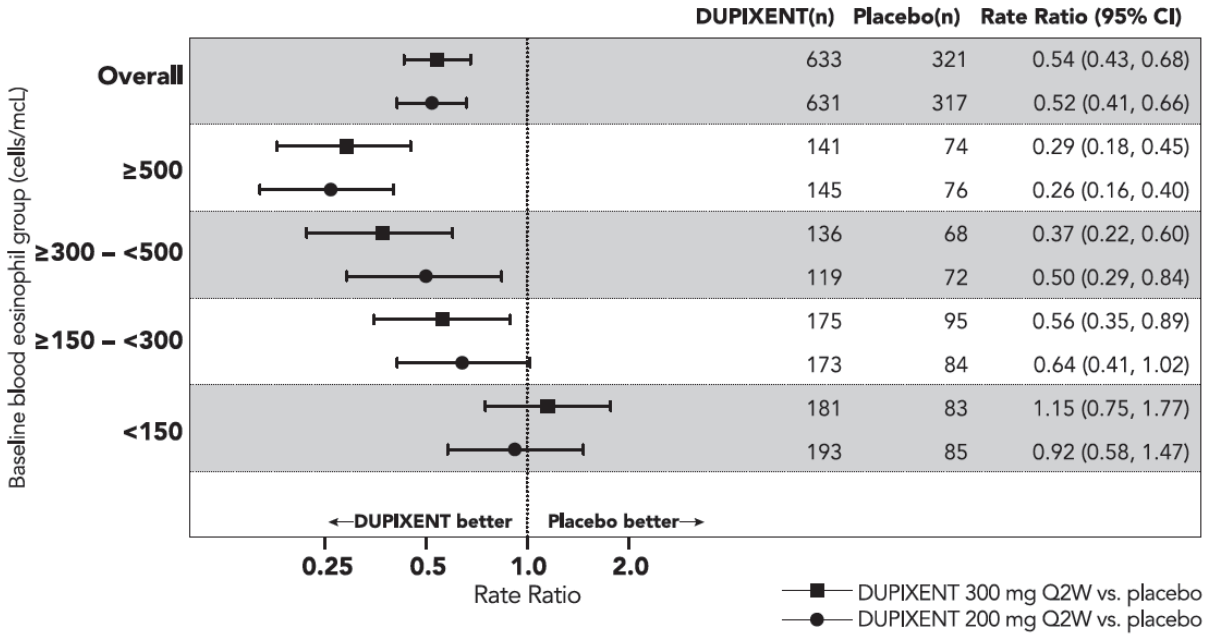
In the QUEST study, subjects receiving medium dose ICS showed a similar reduction in rate of severe asthma exacerbations compared to subjects receiving high dose ICS.

Table 15: Rate of Severe Exacerbations in DRI12544, QUEST, and VENTURE by Subgroups

Study	Treatment	Baseline Blood EOS							
		≥150 cells/mcL				≥300 cells/mcL			
		Exacerbations per Year			Percent Reduction	Exacerbations per Year			Percent Reduction
		N	Rate (95% CI)	Rate Ratio (95%CI)		N	Rate (95% CI)	Rate Ratio (95%CI)	
All Severe Exacerbations									
DRI12544	Dupixent 200 mg Q2W	120	0.29 (0.16, 0.53)	0.28 (0.14, 0.55)	72%	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)	71%
	Dupixent 300 mg Q2W	129	0.28 (0.158, 0.496)	0.27 (0.14, 0.52)	73%	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)	81%
	Placebo	127	1.05 (0.69, 1.60)			68	1.04 (0.57, 1.90)		
QUEST	Dupixent 200 mg Q2W	437	0.45 (0.37, 0.54)	0.44 (0.34,0.58)	56%	264	0.37 (0.29, 0.48)	0.34 (0.24,0.48)	66%
	Placebo	232	1.01 (0.81, 1.25)			148	1.081 (0.846, 1.382)		
	Dupixent 300 mg Q2W	452	0.43 (0.36, 0.53)	0.40 (0.31,0.53)	60%	277	0.40 (0.32, 0.51)	0.33 (0.23,0.45)	67%
	Placebo	237	1.08 (0.88, 1.33)			142	1.24 (0.97, 1.57)		
VENTURE[a]	Duixent 300 mg Q2W	69	0.64 (0.43, 0.97)	0.42 (0.25, 0.69)	58%	48	0.50 (0.26, 0.98)	0.29 (0.14,0.60)	71%
	Placebo	81	1.54 (1.14. 2.07)			41	1.74 (1.20, 2.53)		

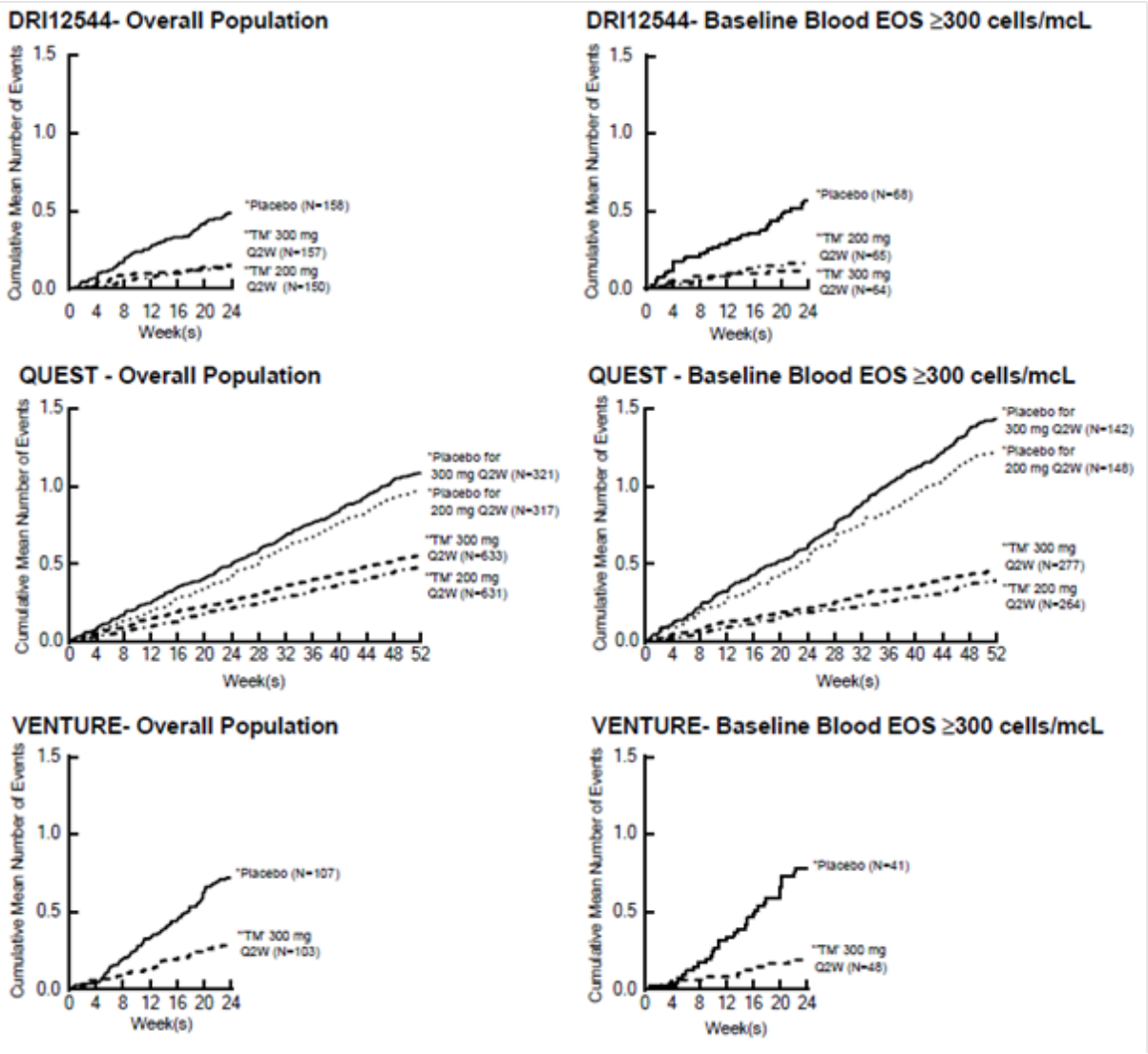
a OCS withdrawal trial

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



The cumulative mean number of severe exacerbation events in DRI12544, QUEST, and VENTURE studies (Overall Population and Baseline Eosinophils ≥300 cells/mcL) during the 24- or 52-week treatment period is shown in Figure 5.

Figure 5: Cumulative Mean Function for the Number of Severe Exacerbation Events During 24-or 52-week Treatment Period (Overall Populationa and Baseline Eosinophils ≥ 300 cells/mcL)



aOverall population is unrestricted by minimum baseline eosinophils or other Type 2 biomarkers

Over the course of the studies, subjects in both DUPIXENT dose groups had lower cumulative number of events compared with subjects in their respective placebo groups.

Lung Function

Significant increases in pre-bronchodilator FEV1 were observed at week 12 for DRI12544 and QUEST trials in the primary analysis populations (subjects with baseline blood eosinophil count of ≥ 300 cells/mcL in DRI12544 and the overall population in the QUEST trial.
Subgroup analysis of DRI12544, QUEST, and VENTURE studies demonstrated that subjects with baseline blood eosinophil count of ≥150 and ≥300 cells/mcL showed greater improvement in FEV1 compared with the overall population (Table 16).

Clinically meaningful improvements in FEV1 were observed in subjects with baseline eosinophils <300 cell/mcL, although less than in the population with baseline blood eosinophil count ≥300 cells/mcL. Magnitude of effect was directly correlated with baseline eosinophil counts at all baseline eosinophil levels studied.

In the QUEST study, compared to placebo, greater improvements in FEV1 were also seen in subjects with FeNO ≥25 and ≥ 50 ppb.

Improvement in FEV1 was similar whether subjects were receiving medium dose ICS, high dose ICS, or OCS.

Table 16: Mean Change from Baseline in Pre-Bronchodilator FEV1 at Week 12 in DRI12544 and QUEST and Week 24 in VENTURE (Overall Population[a] and Baseline Blood Eosinophil Levels ≥150 and ≥300 cells/mcL)

Study	Treatment	Overall Population[a]			Baseline Blood EOS					
					≥150 cells/mcL			≥300 cells/mcL		
		N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544	Dupixent 200 mg Q2W	150	0.31 (18.0)	0.20 (0.11, 0.28)	108	0.32 (18.25)	0.23 (0.13, 0.33)	65	0.43 (25.9)	0.26 (0.11, 0.40)
	Dupixent 300 mg Q2W	157	0.28 (17.8)	0.16 (0.08, 0.25)	120	0.26 (17.1)	0.18 (0.08, 0.27)	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	158	0.12 (6.1)		102	0.09 (4.36)		68	0.18 (10.2)	
QUEST	Dupixent 200 mg Q2W	631	0.32 (21.3)	0.14 (0.08, 0.19)	425	0.36 (23.6)	0.17 (0.11, 0.23)	264	0.43 (29.0)	0.21 (0.13, 0.29)
	Placebo	317	0.18 (12.1)		224	0.18 (12.4)		148	0.21 (15.6)	
	Dupixent 300 mg Q2W	633	0.34 (23.1)	0.13 (0.08, 0.18)	434	0.37 (25.3)	0.15 (0.09, 0.21)	277	0.47 (32.5)	0.24 (0.16, 0.32)
	Placebo	321	0.21 (13.7)		229	0.22 (14.2)		142	0.22 (14.4)	
VENTURE[b]	Dupixent 300 mg Q2W	103	0.22 (19.9)	0.22 (0.09, 0.34)	76	0.32 (26.0)	0.22 (0.06, 0.38)	48	0.44 (35.1)	0.32 (0.10, 0.54)
	Placebo	107	0.01 (4.8)		66	0.06 (9.1)		41	0.12 (10.5)	

Study	Treatment	Overall Population[a]			Baseline Blood EOS					
					≥150 cells/mcL			≥300 cells/mcL		
		N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS Mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)	N	LS mean Δ From baseline L (%)	LS Mean Difference vs. placebo (95% CI)

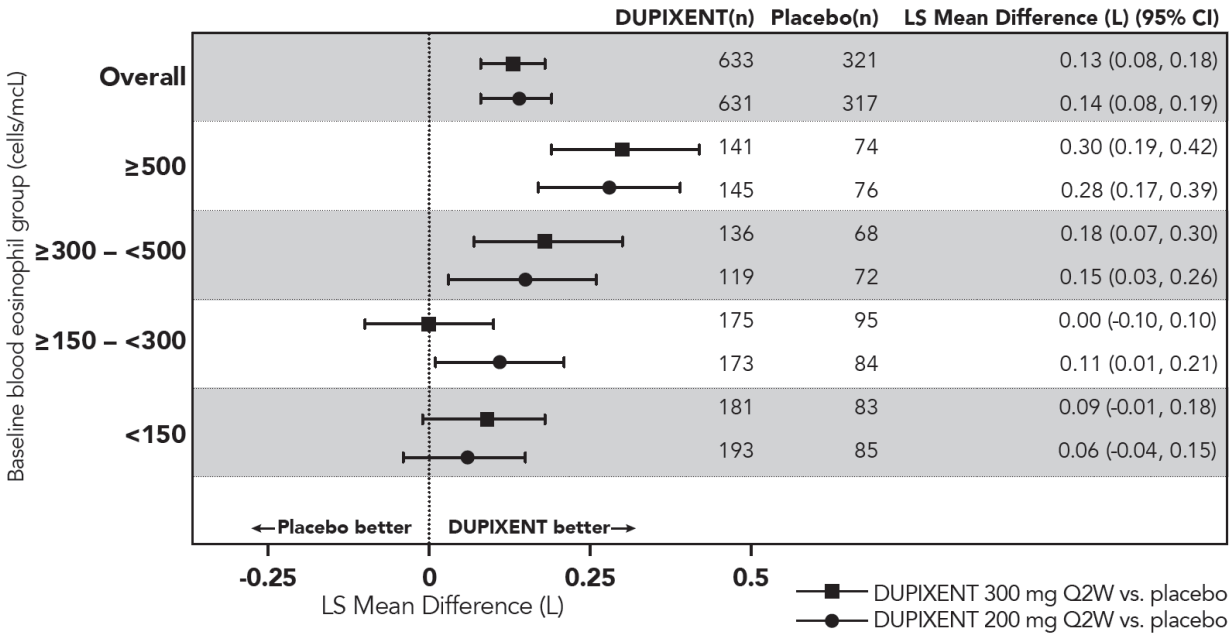
[a] Overall population is unrestricted by minimum baseline eosinophils or other Type 2 biomarkers
[b] For VENTURE, the OCS withdrawal study, change from baseline in pre-brochodilator FEV1 at week 24 was reported to allow time for OCS reduction to reach optimization

Table 17: Mean Change from Baseline in Pre-Bronchodilator FEV1 at Week 12 and Week 52 in QUEST by Baseline FeNO Subgroups

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

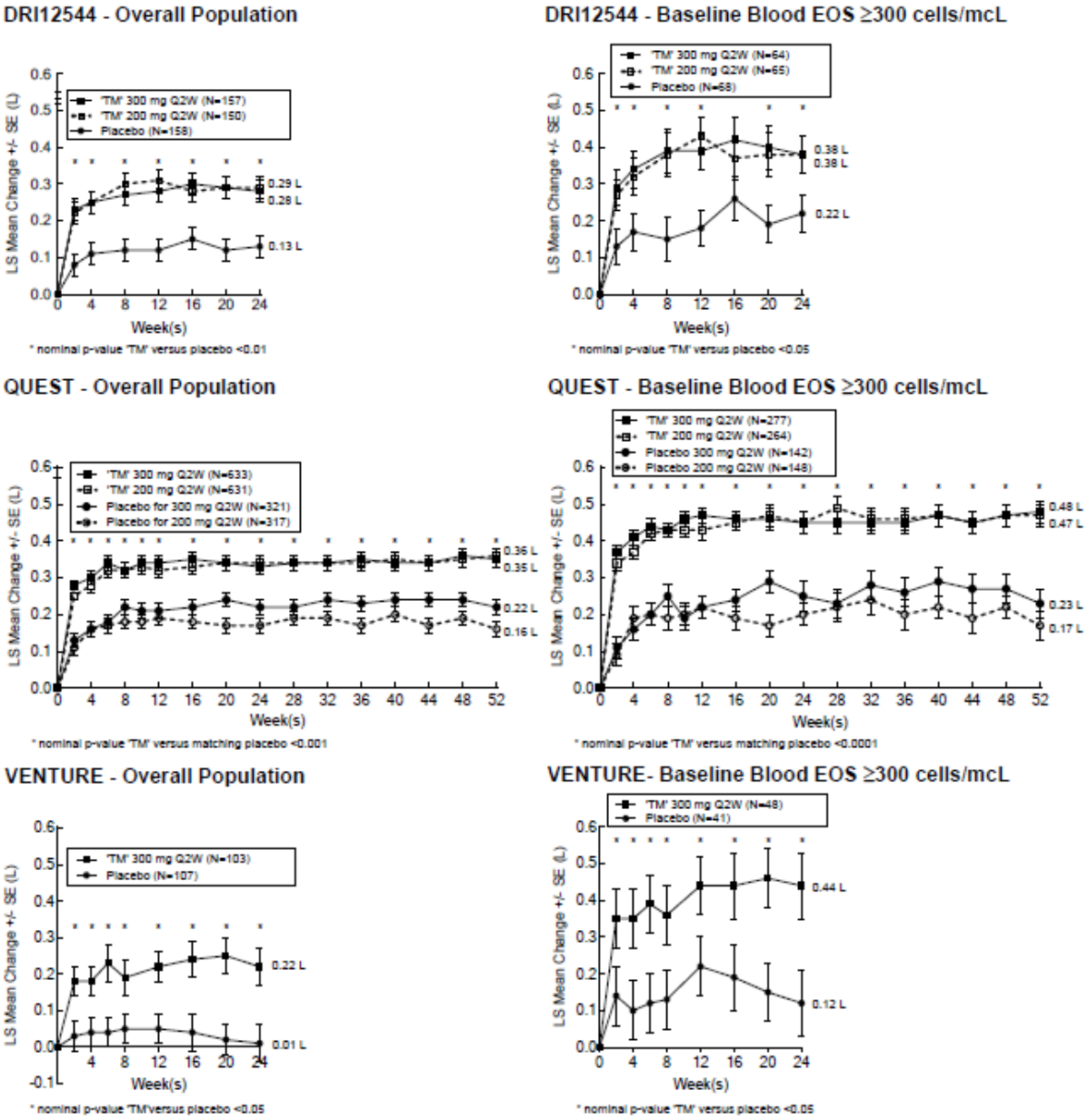
[a] p-value < 0.0001

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



Significant improvements in FEV1 were observed as early as Week 2 (DRI12544, QUEST, and VENTURE) following the first dose of DUPIXENT for both the 200 mg and 300 mg dose strengths and were maintained through Week 24 (DRI12544 and VENTURE) and Week 52 (QUEST) (Figure 6).

Figure 7: Mean Change from Baseline in Pre-Bronchodilator FEV1 (L) Over Time (Overall Populationa and Baseline Eosinophils ≥ 300 cells/mcL)



a Overall population is unrestricted by minimum baseline eosinophils or other Type 2 biomarkers.

Additional Secondary Endpoints

ACQ-5 and AQLQ(S) were analysed at both a cohort level (mean change from baseline) and an individual-level (responder analyses) at 24 weeks (DRI12544) and at 52 weeks (QUEST).

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)). Improvements in ACQ-5 and AQLQ(S) were observed as early as Week 2 and maintained for 24 weeks in DRI12544 study and 52 weeks in QUEST study.
Similar results were observed in the VENTURE Study. In asthma subjects with comorbid upper airway disease DUPIXENT treatment also reduced upper airway symptoms.

Subjects with asthma and comorbid chronic rhinosinusitis (CRS) with or without nasal polyposis, and/or comorbid allergic rhinitis (AR), reported their health-related quality of life on disease-specific questionnaires; the 22-Item Sino Nasal Outcome Test (SNOT-22) for CRS subjects and Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ (S)+ 12) for AR subjects. Mean change from baseline in total scores on SNOT-22 and RQLQ(S)+12 were pre-specified endpoints in these subpopulations. Improvements in SNOT-22 and RQLQ(S)+12 total score were observed with DUPIXENT compared to placebo as early as week 12 and sustained over 52 weeks.

Oral Corticosteroid Reduction (VENTURE)

The Venture study evaluated the effect of DUPIXENT on reducing the use of maintenance oral corticosteroids. The baseline mean oral corticosteroid use was 11.75 mg in the placebo group and 10.75 mg in the group receiving Dupixent.

Compared with placebo, subjects receiving DUPIXENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control.

The results for primary and secondary endpoints of the VENTURE study are presented in the Table 18.

Table 18: Results of the Primary and Secondary Endpoints in VENTURE (Overall Population)

	Overall population	
	Dupixent 300 mg N=103	Placebo N=107
Primary endpoint (week 24)		
Percent reduction in OCS from baseline		
Mean overall percent reduction from baseline (%)	70.1	41.9
Difference (% [95 % CI])(Dupixent vs. placebo)	28.2 (15.81, 40.67)	
Secondary endpoint (week 24)		
Proportion of patients achieving a reduction ≥ 50% OCS dose from base line	79.6	53.3
Proportion of patients achieving a reduction of OCS dose to <5 mg/day	69	33
Odds ratio (95% CI)	4.48 (2.39, 8.39)	

	Overall population

14.3 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 subjects aged 18 years 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 19 below.

Table 19: 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

[a] Higher 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 20.

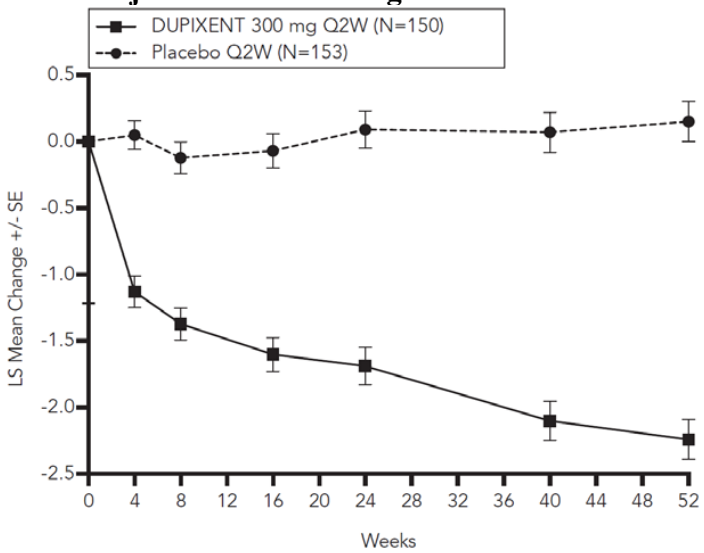
Table 20: Results of the Primary Endpoints in CRSwNP Trials

	SINUS-24					SINUS-52				
	Placebo (n=133)		**DUPIXENT 300 mg Q2W (n=143)**		**LS mean difference vs. Placebo (95% CI)**	**Placebo (n=153)**		**DUPIXENT 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

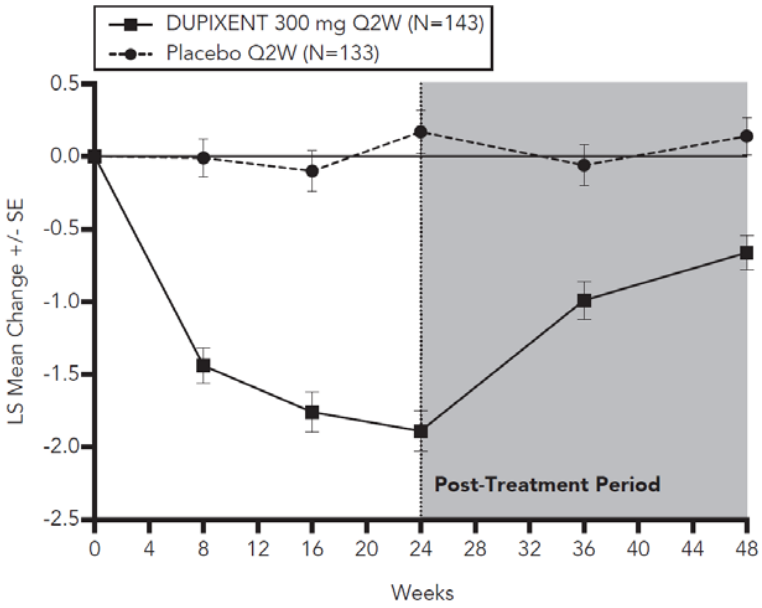
Statistically significant efficacy was observed in SINUS-52 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 8).

Figure 8: 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 at Week 24. In the post-treatment period when subjects were off DUPIXENT, the treatment effect diminished over time (see Figure 9).

Figure 9: 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).

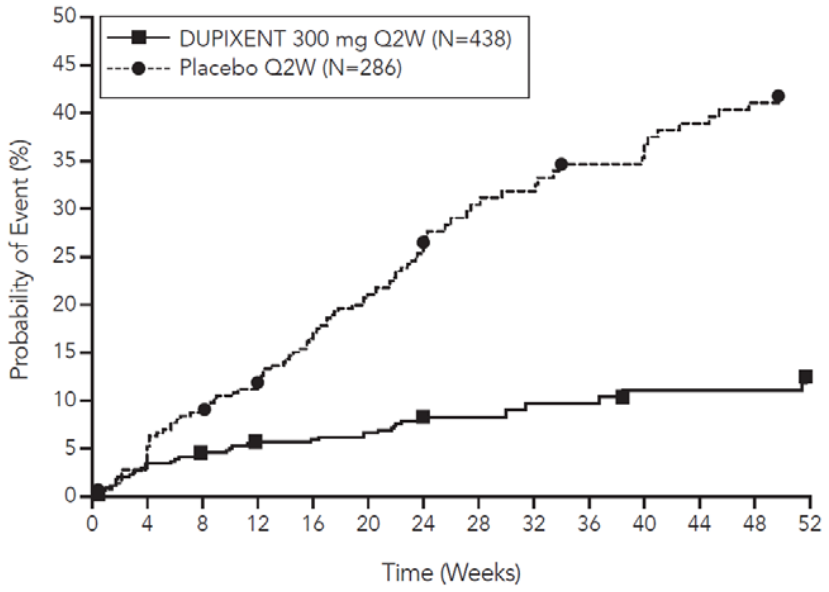
Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.12 (95% CI: -1.31, -0.93) in SINUS-24 and -0.98 (95% CI: -1.15, -0.81) in SINUS-52. At Week 52, the LS mean difference for loss of smell 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-52. 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 10). 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 10: 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)



Number at Risk

DUPIXENT 300 mg Q2W	438	416	411	376	129	100
Placebo Q2W	286	260	253	187	93	61

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.

14.4 Prurigo Nodularis

The prurigo nodularis (PN) development program included two 24-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (PRIME (NCT04183335) and PRIME 2 (NCT04202679)) in 311 adult subjects 18 years of age and older with pruritus (WI-NRS ≥ 7 on a scale of 0 to 10) and greater than or equal to 20 nodular lesions. PRIME and PRIME2 assessed the effect of DUPIXENT on pruritus improvement as well as its effect on PN lesions.

In these two trials, subjects received either subcutaneous DUPIXENT 600 mg (two 300 mg injections) on day 1, followed by 300 mg once every other week (Q2W) for 24 weeks, or matching placebo.

In these trials, the mean age was 49.5 years, the median weight was 71 kg, 65% of subjects were female, 57% were White, 6% were Black, and 34% were Asian. At baseline, the mean Worst Itch-Numeric Rating Scale (WI-NRS) was 8.5, 66% had 20 to 100 nodules (moderate), and 34% had greater than 100 nodules (severe). Eleven percent (11%) of subjects were taking stable doses of antidepressants at baseline and were instructed to continue taking these medications during the trial. Forty-three percent (43%) had a history of atopy (defined as having a medical history of AD, allergic rhinitis/rhinoconjunctivitis, asthma, or food allergy).

The WI-NRS is comprised of a single item, rated on a scale from 0 ("no itch") to 10 ("worst imaginable itch"). Subjects were asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale. The Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) is a scale that measures the approximate number of nodules using a 5-point scale from 0 (clear) to 4 (severe).

Efficacy was assessed with the proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points, the proportion of subjects with IGA PN-S 0 or 1 (the equivalent of 0-5 nodules), and the proportion of subjects who achieved a response in both WI-NRS and IGA PN-S per the criteria described above.

The efficacy results for PRIME and PRIME2 are presented in Table 21 and Figures 11, 12 and 13.

Table 21: Efficacy Results of DUPIXENT in PRIME and PRIME2

	PRIME			**PRIME2**		
	Placebo (N=76)	**DUPIXENT 300 mg Q2W (N=75)**	**Difference (95% CI) for DUPIXENT vs. Placebo**	**Placebo (N=82)**	**DUPIXENT 300 mg Q2W (N=78)**	**Difference (95% CI) for DUPIXENT vs. Placebo**
Proportion of subjects with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24 and an IGA PN-S 0 or 1 at Week 24[b]	9.2%	38.7%	29.6% (16.4, 42.8)	8.5%	32.1%	25.5% (13.1, 37.9)
Proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24[b]	18.4%	60.0%	42.7% (27.8, 57.7)	19.5%	57.7%	42.6% (29.1, 56.1)
Proportion of subjects with IGA PN-S 0 or 1 at Week 24[b]	18.4%	48.0%	28.3% (13.4, 43.2)	15.9%	44.9%	30.8% (16.4, 45.2)

Proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12[b]	15.8%[a]	44.0%[a]	29.2% (14.5, 43.8)[a]	22.0%	37.2%	16.8% (2.3, 31.2)

[a] Not adjusted for multiplicity in PRIME.

[b] Subjects who received rescue treatment earlier or had missing data were considered as non-responders.

Figure 11: Proportion of Adult Subjects with PN with Both WI-NRS ≥4-point Improvement and IGA PN-S 0 or 1 Over Time in PRIME and PRIME2

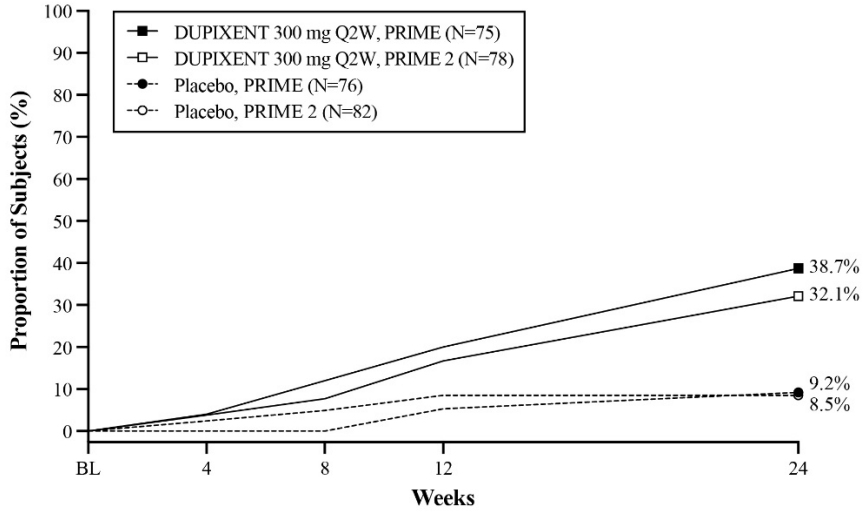


Figure 12: Proportion of Adult Subjects with PN with WI-NRS ≥4-point Improvement Over Time in PRIME and PRIME2

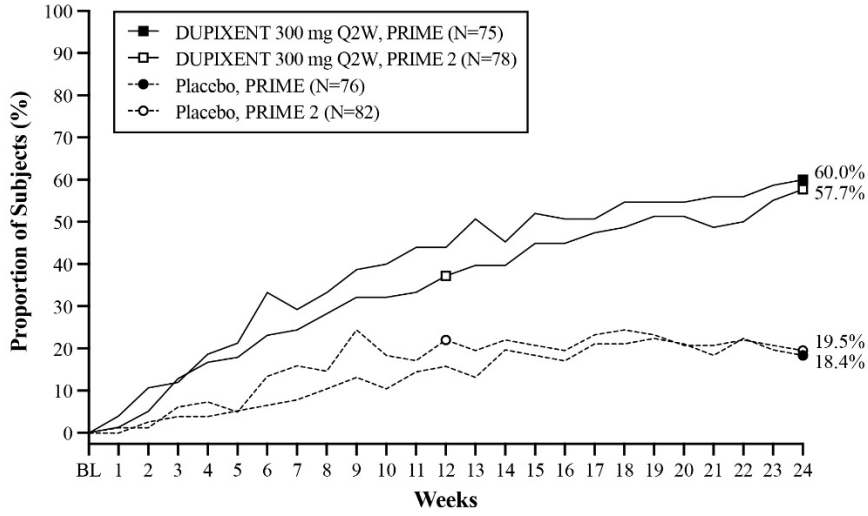
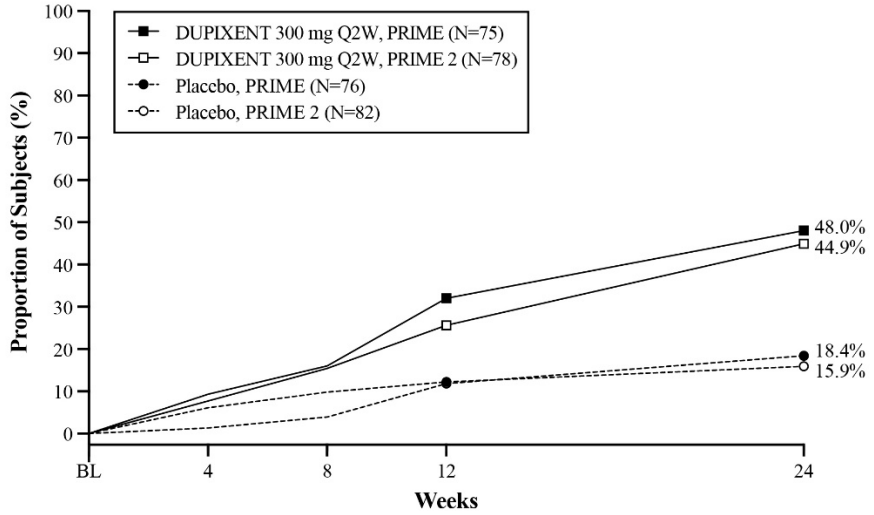


Figure 13: Proportion of Adult Subjects with IGA PN-S 0 or 1 Over Time in PRIME and PRIME 2



The efficacy data did not show differential treatment effect across demographic subgroups.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPIXENT (dupilumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield. Each pre-filled syringe with needle shield is designed to deliver 300 mg of DUPIXENT in 2 mL solution or 200 mg of DUPIXENT in 1.14 mL solution.

DUPIXENT 300 mg /2 mL pre-filled syringe is available in cartons containing 2 pre-filled syringes with needle shield.

DUPIXENT 200 mg /1.14 mL pre-filled syringe is available in cartons containing 2 pre-filled syringes with needle shield.

16.2 Storage and Handling

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

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

If necessary, pre-filled syringes may be kept at room temperature up to 25°C (77°F) for a maximum of 14 days. Do not store above 25°C (77°F). After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

Do not expose the syringe to heat or direct sunlight.

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

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the Instructions for Use.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations *[see Dosage and Administration (2.1) and Instructions for Use]*.

Hypersensitivity

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

Conjunctivitis and Keratitis

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

Eosinophilic Conditions

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

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

Reduction in Corticosteroid Dosage

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

Patients with Co-morbid Asthma

Advise patients with co-morbid asthma not to adjust or stop their asthma treatment without talking to their healthcare providers *[see Warnings and Precautions (5.6)]*.

Arthralgia

Advise patients to report new onset or worsening joint symptoms to their healthcare provider [*see Warnings and Precautions (5.7)*].

Parasitic (Helminth) Infections

Advise patients to notify their healthcare provider if they present with clinical features consistent with helminthic infection [*see Warnings and Precautions (5.8)*].

Vaccinations

Advise patients that vaccination with live vaccines is not recommended immediately prior to and while they are receiving DUPIXENT. Instruct patients to inform their healthcare provider that they are taking DUPIXENT prior to a potential vaccination [*see Warnings and Precautions (5.9)*].

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