DUPIXENT® (dupilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage, Atopic Dermatitis (1.1) 05/2020
Dosage and Administration (2; 2.4; 2.5) 06/2020
Dosage and Administration, Atopic Dermatitis (2.1; 2.4) 05/2020
Warnings and Precautions (5.2) 05/2020

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:
• for the treatment of patients aged 6 years 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. (1.1)
• as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)
• as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSsNP). (1.3)

Limitation of Use
Not for the relief of acute bronchospasm or status asthmaticus. (1.2)

DOSE AND ADMINISTRATION

Administer by subcutaneous injection. The DUPIXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older. (1.2)

Atopic Dermatitis

Adults
• The recommended dose of DUPIXENT is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week (Q2W). (2.1)

Pediatric Patients

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Dose</th>
<th>Subsequent Doses*</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg Q4W</td>
</tr>
<tr>
<td>30 to less than 60 kg</td>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg Q2W</td>
</tr>
<tr>
<td>60 kg or more</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg Q2W</td>
</tr>
</tbody>
</table>

* Q2W – every other week; Q4W – every 4 weeks

Asthma
• The recommended dose of DUPIXENT for adults and adolescents (12 years of age and older) is:
  • an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
  • an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
  • for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week. (2.2)

Chronic Rhinosinusitis with Nasal Polyposis
• The recommended dose of DUPIXENT for adult patients is 300 mg given every other week. (2.3)

DOSE FORMS AND STRENGTHS

Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield. (3)
Injection: 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield. (3)
Injection: 300 mg/2 mL solution in a single-dose pre-filled pen. (3)

CONTRAINDICATIONS

Known hypersensitivity to DUPIXENT or any of its excipients. (4)

WARNINGS AND PRECAUTIONS

• Hypersensitivity: Hypersensitivity reactions (urticaria, rash, erythema nodosum, anaphylaxis, and serum sickness) have occurred after administration of DUPIXENT. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)
• Conjunctivitis and Keratitis: Patients should report new onset or worsening eye symptoms to their healthcare provider. (5.2)
• Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)
• Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)
• Parasitic (Helminth) Infections: Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves. (5.7)

ADVERSE REACTIONS

Atopic Dermatitis: Most common adverse reactions (incidence ≥1%) are injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye prunus, other herpes simplex virus infection, and dry eye. (6.1)
Asthma: Most common adverse reactions (incidence ≥1%) are injection site reactions, oropharyngeal pain, and eosinophilia. (6.1)
Chronic Rhinosinusitis with Nasal Polyposis: Most common adverse reactions (incidence ≥1%) are injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Regeneron at 1-844-387-4936 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Live Vaccines: Avoid use of live vaccines with DUPIXENT. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 OVERDOSE
10 DESCRIPTION
11 CLINICAL PHARMACOLOGY
12 PHARMACOKINETICS

5.6 Patients with Co-morbid Asthma
5.7 Parasitic (Helminth) Infections
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Immunogenicity
7 DRUG INTERACTIONS
7.1 Live Vaccines
7.2 Non-Live Vaccines
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
Concomitant Topical Therapies

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

2.2 Asthma

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

- an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
- an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week

for patients with oral corticosteroids-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week.

2.3 Chronic Rhinosinusitis with Nasal Polyps

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

2.4 Important Administration Instructions

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe. The DUPIXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older. In adolescents 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult. DUPIXENT pre-filled syringe should be given by a caregiver in children 6-11 years of age.

Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the "Instructions for Use".
5.5 Reduction of CorticosteroidDosage

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

5.6 Patients with Co-morbid Asthma

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

5.7 Parasitic (Helminth) Infections

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

Treat patients with pre-existing helminth infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helminth treatment, discontinue treatment with DUPIXENT until the infection resolves.

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)]
- Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and giant papillary conjunctivitis.

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

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

A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis. Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4) and Week 52 (Trial 3)

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy group, 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: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT Monotherapy</th>
<th>DUPIXENT + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Placebo + TCS</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>51 (10)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>51 (10)</td>
<td>10 (9)</td>
</tr>
<tr>
<td>Bлеpharitis</td>
<td>2 (1)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection</td>
<td>10 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

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

5.5.2 Injections

Adverse reactions due to injections were generally mild to moderate in intensity. 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.

5.8 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 (CSNP Trials 1 and 2). The safety profile 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 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 CSNP Trials 1 and 2.
specific adverse reactions

Conjunctivitis and Keratitis

During the 52-week period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 8% of the placebo + TCS group (10 per 100 subject-years). In DUPIXENT atopic dermatitis monotherapy trials (Trials 1, 2, and 4) through Week 16, keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years). In the 52-week atopic dermatitis monotherapy trial (DUPIXENT + TCS, atopic dermatitis trial [Trial 3]), keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo. In the 52-week CRSwNP study (CSNP Trial 1), the frequency of conjunctivitis was 3% in the DUPIXENT subjects and 1% in the placebo subjects; all of these subjects recovered [see Warnings and Precautions (5.1)].

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials. Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo. Among CRSwNP subjects there were no reported cases of herpes zoster or eczema herpeticum.

Hypersensitivity Reactions

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

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. In subjects with CRSwNP, the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥500 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during the study treatment period [see Warnings and Precautions (5.2)].

Cardiovascular

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

In the 1-year placebo controlled trial in subjects with atopic dermatitis (Trial 3), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUPIXENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUPIXENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

In the 24-week placebo controlled trial in subjects with CRSwNP (CSNP Trial 1), 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 (CSNP Trial 2), 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.

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

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

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

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

6.3 Drug Interactions

In the 1-year placebo controlled trial in subjects with CRSwNP, there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.
In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

### 2.8 Lactation

#### Risk Summary

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

### 8.4 Pediatric Use

#### Aptom Dermatitis

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

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

#### Use is also supported by Trial 7, an open-label extension study that enrolled subjects who completed Trials 6 and 8. Trial 7 included 138 adolescents from Trial 6 and 110 children from Trial 8 with moderate to severe atopic dermatitis at enrollment. Trial 7 included 64 adolescents from Trial 6 and 72 children from Trial 8 with severe atopic dermatitis at enrollment. No new safety signals were identified in Trial 7 [see Adverse Reactions (6.1)].

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

#### Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV<sub>1</sub> (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 adolescent patients than that in adults at the respective dose level which was mainly accounted for by the reduced body mass and renal function in adolescents.

#### Risk Summary

Asthma have not been established. Dupilumab exposure was higher in adolescent patients [see Adverse Reactions (6.1)].

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

### 8.5 Geriatric Use

#### 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.

### 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. It is a recombinant IgG4 kappa monoclonal antibody. Dupilumab is a subcutaneous injection.

#### dupilumab (dupilumab) injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. INJECTION is provided as a single-dose pre-filled syringe without needle shield or a single dose pre-filled pen in a siliconized Type-1 glass clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg pre-filled syringe delivers 200 mg dupilumab in 1.14 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.

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type 1 receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation is an important component in the pathogenesis of asthma, atopic dermatitis, and CRSwNP. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, leukotrienes, cytokines, chemokines) are involved in inflammation. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE; however, the mechanism of dupilumab action in asthma has not been definitively established.

#### 12.2 Pharmacodynamics

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

#### The bioavailability of dupilumab following a SC dose is similar between AD, asthma, and CRSwNP.

#### Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± SD concentrations ([C<sub>peak</sub>]) of 70.1±24.1 mcg/mL, 41.8±12.4 mcg/mL, or 30.5±9.39 mcg/mL respectively, by approximately 1 week post dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or Q2W, or 400 mg starting dose and 200 mg dose Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mcg/mL for 200 mg administered Q2W.

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

### Distribution

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

#### Elimination

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

#### Dose Linearity

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

#### Weight

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

#### Age

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

### Immunogenicity

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

#### Specific Populations

#### Geriatric Patients

In subjects who are 65 years and older, the mean ± SD steady-state trough concentrations of dupilumab were 69.4±31.4 mcg/mL, 196±23.4 mcg/mL, and 155±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

Aptom Dermatitis

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

For children 6 to 11 years of age with atopic dermatitis receiving every other week dosing (Q2W) with 200 mg (<30 kg) or every four week dosing (Q4W) with 300 mg (>30 kg), mean ± SD steady-state trough concentration was 86.0±34.6 mcg/mL and 98.7±33.2 mcg/mL respectively.
Clinical Response at Week 16 (Trials 1, 2, and 3)

Week 16 was defined by at least a 4-point improvement in the Peak Pruritus NRS from baseline to Week 16 (improvement of at least 75% in EASI score from baseline), and reduction in itch as the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point reduction in AD problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

Renal or Hepatic Impairment

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

Drug Interaction Studies

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

Cytochrome P450 Substrates

The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), 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%. A total of 107 adolescents aged 12 to 17 years with asthma were enrolled in AS Trial 2. The mean ± SD steady-state trough concentrations of dupilumab were 107±51.6 mcg/mL and 46.7±26.9 mcg/mL, respectively, for 300 mg or 200 mg administered Q2W.

Asthma

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

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

In all three trials, subjects in the DUPIXENT group received subcutaneous injections of DUPIXENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (Trials 1 and 2), subjects received DUPIXENT or placebo for 16 weeks. In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

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

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

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

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

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUPIXENT 300 mg Q2W</td>
<td>Placebo</td>
<td>DUPIXENT 300 mg Q2W</td>
</tr>
<tr>
<td>Number of subjects randomized (FAS)</td>
<td>224</td>
<td>224</td>
</tr>
<tr>
<td>IGA 0 or 1 ‡</td>
<td>38%</td>
<td>10%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>51%</td>
<td>15%</td>
</tr>
<tr>
<td>EASI-90</td>
<td>36%</td>
<td>8%</td>
</tr>
<tr>
<td>Number of subjects with baseline Peak Pruritus NRS score ≥4</td>
<td>213</td>
<td>212</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)</td>
<td>41%</td>
<td>12%</td>
</tr>
</tbody>
</table>

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 ≥5 points on a 0-4 IGA scale.
c Subjects who received rescue treatment or with missing data were considered as non-responders.

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

In Trial 3, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUPIXENT IGA 0 or 1 responders at Week 16 remained responders at Week 52) and subjects who were non-responders at Week 16 who later responded to treatment (e.g., 24% of DUPIXENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 6.
The efficacy results at Week 16 for Trial 6 are presented in Table 7.

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

<table>
<thead>
<tr>
<th></th>
<th>DUPIXENT 300 mg Q2W + TCS</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjects</td>
<td>89</td>
<td>264</td>
</tr>
<tr>
<td>Responder&lt;sup&gt;a&lt;/sup&gt; at Week 16 and 52</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Responder at Week 16 but Non-responder at Week 52</td>
<td>20%</td>
<td>7%</td>
</tr>
<tr>
<td>Non-responder at Week 16 but Responder at Week 52</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-responder at Week 16 and Non-responder at Week 52</td>
<td>44%</td>
<td>80%</td>
</tr>
<tr>
<td>Overall Responder&lt;sup&gt;a-c&lt;/sup&gt; Rate at Week 52</td>
<td>36%</td>
<td>13%</td>
</tr>
</tbody>
</table>

<sup>a</sup> In Trial 3, of the 421 randomized and treated subjects, 68 subjects (16%) had not been on study for 52 weeks at the time of data analysis.

<sup>b</sup> 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.

<sup>c</sup> Subjects who received rescue treatment or with missing data were considered as non-responders.

### Treatment Effects

The efficacy and safety of DUPIXENT monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 6; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of ≤1 (clear), the mean BSA involvement was 57%, and 42% had received prior systemic non-steroidal immunosuppressants (including biologics) in Trials 1, 2, and 3 were generally consistent with the results in the overall study population.

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

Subjects in the DUPIXENT group with baseline weight <60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg Q2W for 16 weeks. Subjects with baseline weight ≥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.

At Week 0, subjects received 400 mg (baseline weight <60 kg) or 600 mg (baseline weight ≥60 kg) of DUPIXENT.

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

### Figure 2: Proportion of Adolescent Subjects with ≥4-point Improvement on the Peak Pruritus NRS in Trial 6<sup>a</sup> (FAS)

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo</th>
<th>DUPIXENT 300 mg Q2W + TCS</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>96%</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>92%</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>4</td>
<td>88%</td>
<td>86%</td>
<td>84%</td>
</tr>
<tr>
<td>6</td>
<td>84%</td>
<td>82%</td>
<td>80%</td>
</tr>
<tr>
<td>8</td>
<td>80%</td>
<td>78%</td>
<td>76%</td>
</tr>
<tr>
<td>10</td>
<td>76%</td>
<td>74%</td>
<td>72%</td>
</tr>
<tr>
<td>12</td>
<td>72%</td>
<td>70%</td>
<td>68%</td>
</tr>
<tr>
<td>14</td>
<td>68%</td>
<td>66%</td>
<td>64%</td>
</tr>
<tr>
<td>16</td>
<td>64%</td>
<td>62%</td>
<td>60%</td>
</tr>
</tbody>
</table>

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

### Table 7: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)<sup>d</sup>

<table>
<thead>
<tr>
<th></th>
<th>DUPIXENT&lt;sup&gt;e&lt;/sup&gt;</th>
<th>Placebo&lt;sup&gt;f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA 0 or 1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>EASI-75&lt;sup&gt;d&lt;/sup&gt;</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>EASI-90&lt;sup&gt;d&lt;/sup&gt;</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>37%</td>
<td>5%</td>
</tr>
</tbody>
</table>

<sup>e</sup> Full Analysis Set (FAS) includes all subjects randomized.

<sup>f</sup> Responders were 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.

<sup>g</sup> Subjects who received rescue treatment or with missing data were considered as non-responders.

<sup>d</sup> At Day 1, subjects received 600 mg 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.

### Table 8: Efficacy Results of DUPIXENT with Concomitant TCS in Trial 8 at Week 18 (FAS)<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>DUPIXENT 300 mg Q2W + TCS (N=61)</th>
<th>Placebo + TCS (N=61)</th>
<th>DUPIXENT 200 mg Q2W + TCS (N=59)</th>
<th>Placebo + TCS (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 kg</td>
<td>30%</td>
<td>13%</td>
<td>39%</td>
<td>10%</td>
</tr>
<tr>
<td>EASI-75</td>
<td>75%</td>
<td>28%</td>
<td>75%</td>
<td>26%</td>
</tr>
<tr>
<td>EASI-90</td>
<td>46%</td>
<td>7%</td>
<td>36%</td>
<td>8%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>54%</td>
<td>12%</td>
<td>61%</td>
<td>13%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Full Analysis Set (FAS) includes all subjects randomized.

<sup>b</sup> Responders were defined as a subject with an IGA 0 or 1 (“clear” or “almost clear”).

<sup>c</sup> Subjects who received rescue treatment or with missing data were considered as non-responders.

<sup>d</sup> At Day 1, subjects received 600 mg of DUPIXENT.

<sup>e</sup> At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUPIXENT.

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*Note: The text continues with additional information not shown here.*
The demographics and baseline characteristics of these 3 trials are provided in Table 9 below.

Table 9: Demographics and Baseline Characteristics of Asthma Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Trial 1 (N=776)</th>
<th>Trial 2 (N=1902)</th>
<th>Trial 3 (N=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>49 (13)</td>
<td>48 (15)</td>
<td>51 (13)</td>
</tr>
<tr>
<td>% Female</td>
<td>63</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>% White</td>
<td>78</td>
<td>83</td>
<td>94</td>
</tr>
<tr>
<td>Duration of Asthma (years), mean (± SD)</td>
<td>22 (15)</td>
<td>21 (15)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Never smoked (%)</td>
<td>77</td>
<td>81</td>
<td>81</td>
</tr>
<tr>
<td>Mean exacerbations in previous year (± SD)</td>
<td>2.2 (2.1)</td>
<td>2.1 (2.2)</td>
<td>2.1 (2.2)</td>
</tr>
<tr>
<td>High dose ICS use (%)</td>
<td>50</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>Pre-dose FEV1 (L) at baseline (± SD)</td>
<td>1.84 (0.54)</td>
<td>1.78 (0.60)</td>
<td>1.58 (0.57)</td>
</tr>
<tr>
<td>Mean percent predicted FEV1 at baseline (%) (± SD)</td>
<td>61 (11)</td>
<td>58 (14)</td>
<td>52 (15)</td>
</tr>
<tr>
<td>% Reversibility (%)</td>
<td>27 (15)</td>
<td>26 (22)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall</td>
<td>73 (8, 11, 62)</td>
<td>78 (10, 13, 69)</td>
<td>72 (8, 21, 56)</td>
</tr>
<tr>
<td>Mean FeNO ppb (± SD)</td>
<td>39 (35)</td>
<td>35 (33)</td>
<td>38 (31)</td>
</tr>
<tr>
<td>Mean total IgE (IU/mL) (± SD)</td>
<td>435 (754)</td>
<td>432 (747)</td>
<td>431 (776)</td>
</tr>
<tr>
<td>Mean baseline blood eosinophil count (± SD) cells/mL</td>
<td>350 (430)</td>
<td>360 (370)</td>
<td>350 (310)</td>
</tr>
</tbody>
</table>

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

Exacerbations

AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥300 cells/mL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either DUXIPENT 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for DUXIPENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for DUXIPENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mL in AS Trials 1 and 2 are shown in Table 10.

Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 4. Pre-specified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophil levels ≥150 cells/mL in subjects with baseline blood eosinophil counts <150 cells/mL, similar severe exacerbation rates were observed between DUXIPENT and placebo.

In AS Trial 2, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits versus placebo was 0.53 (95% CI: 0.28, 1.03) and 0.74 (95% CI: 0.32, 1.70) with DUXIPENT 200 mg or 300 mg Q2W, respectively.
Table 10: Rate of Severe Exacerbations in AS Trials 1 and 2

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
</tr>
</tbody>
</table>

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

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

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

The mean change in FEV1 over time in AS Trial 2 are shown in Figure 7.

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

Additional Secondary Endpoints

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

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

Lung Function

Significant increases in pre-bronchodilator FEV1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV1 LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and DUPIXENT 300 mg Q2W, respectively, in subjects with baseline blood eosinophil counts ≥300 cells/mcL in AS Trials 1 and 2 are shown in Table 11. Improvements in FEV1 by baseline blood eosinophils for AS Trial 2 are shown in Figure 6. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N</td>
</tr>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
</tr>
</tbody>
</table>

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

Mean changes in FEV1 over time in AS Trial 2 are shown in Figure 7.
14.3 Chronic Rhinosinusitis with Nasal Polyps

The chronic rhinosinusitis with nasal polyps (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background systemic corticosteroids. The primary endpoint was a 100% reduction in their OCS dose.

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 patient 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 12 below.

**Table 12: Demographics and Baseline Characteristics of CRSwNP Trials**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CSNP Trial 1 (N=276)</th>
<th>CSNP Trial 2 (N=448)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>50 (13)</td>
<td>52 (12)</td>
</tr>
<tr>
<td>% Male</td>
<td>57</td>
<td>62</td>
</tr>
<tr>
<td>Mean CRSwNP duration (years) (SD)</td>
<td>11 (9)</td>
<td>11 (10)</td>
</tr>
<tr>
<td>Patients with ≥ 1 prior surgery (%)</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Patients with systemic corticosteroid use in the previous 2 years (%)</td>
<td>65</td>
<td>80</td>
</tr>
<tr>
<td>Mean Bilateral endoscopic NPS* (SD), range 0-8</td>
<td>5.8 (1.3)</td>
<td>6.1 (1.2)</td>
</tr>
<tr>
<td>Mean Nasal congestion (NC) score† (SD), range 0-3</td>
<td>2.4 (0.8)</td>
<td>2.4 (0.6)</td>
</tr>
<tr>
<td>Mean LMK sinus CT total score* (SD), range 0-24</td>
<td>19 (4.4)</td>
<td>18 (3.8)</td>
</tr>
<tr>
<td>Mean loss of smell score* (AM), range 0-3</td>
<td>2.7 (0.5)</td>
<td>2.8 (0.5)</td>
</tr>
<tr>
<td>Mean SNOT-22 total score* (SD), range 0-110</td>
<td>49.4 (20.2)</td>
<td>51.9 (20.9)</td>
</tr>
<tr>
<td>Mean blood eosinophils (cells/mcL) (SD)</td>
<td>440 (330)</td>
<td>430 (350)</td>
</tr>
<tr>
<td>Mean total IgE IU/mL (SD)</td>
<td>212 (276)</td>
<td>240 (342)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall</td>
<td>75</td>
<td>82</td>
</tr>
<tr>
<td>Asthma (%)</td>
<td>58</td>
<td>60</td>
</tr>
<tr>
<td>NSAID-ERD (%)</td>
<td>30</td>
<td>27</td>
</tr>
</tbody>
</table>

* Higher scores indicate greater disease severity

**Table 13: Results of the Primary Endpoints in CRSwNP Trials**

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>CSNP Trial 1</th>
<th>CSNP Trial 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong> (n=133)</td>
<td><strong>DUPIXENT 300 mg Q2W (n=143)</strong></td>
<td><strong>Placebo</strong> (n=153)</td>
</tr>
<tr>
<td><strong>NSP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>5.86</td>
<td>5.96</td>
</tr>
<tr>
<td>LS mean change vs. Placebo (95% CI)</td>
<td>-2.06 (-2.43, -1.69)</td>
<td>2.38 (-0.38, 4.16)</td>
</tr>
<tr>
<td><strong>NC</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline mean</td>
<td>2.45</td>
<td>2.26</td>
</tr>
<tr>
<td>LS mean change</td>
<td>-0.89 (-1.07, -0.71)</td>
<td>-1.25 (-1.30, -1.20)</td>
</tr>
</tbody>
</table>

A reduction in score indicates improvement.

NPS = nasal polyps score; NC = nasal congestion/obstruction.
Similarly, carried out in CSNP Trial 1 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 CSNP Trial 1 - 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 CSNP Trial 1 and -0.37 (95% CI: -0.46, -0.27) in CSNP Trial 2.

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 CSNP Trial 1 and -5.13 (95% CI: -5.80, -4.46) in CSNP Trial 2. At Week 52, in CSNP Trial 2 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 CSNP Trial 1 and -0.98 (95% CI: -1.15, -0.81) in CSNP Trial 2. 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 CSNP Trial 1 and -17.36 (95% CI: -20.87, -13.85) in CSNP Trial 2. 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).
Conjunctivitis and Keratitis
Advise patients to consult their healthcare provider if new onset or worsening eye symptoms develop [see Warnings and Precautions (5.2)].

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

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

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

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