Indications and Usage, Atopic Dermatitis (1.1) 05/2020
Indications and Usage, CRSwNP (1.3) 06/2019
Dosage and Administration, Atopic Dermatitis (2.1; 2.4) 06/2020
Dosage and Administration, CRSwNP (2.3; 2.4) 06/2019
Warnings and Precautions (5.2; 5.3; 5.6) 06/2019
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 asthma whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without oral 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 (CRSwNP). (1.3)

Limitation of Use

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

**DOSE AND ADMINISTRATION**

Administer by subcutaneous injection. (2)

**Atopic Dermatitis**

**Adults**

- The recommended dose 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)

**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 helmint infections before initiating therapy with DUPIXENT. If patients become infected while receiving treatment with DUPIXENT and do not respond to anti-helmint 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 herps, keratitis, eye pruritus, other herps 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: 05/2020
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 or
- 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 Polyposis

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. 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 or under the supervision of an adult. Dupixent pre-filled syringe should be given for patients who do not understand the instructions for use.

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

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is 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.

1.2 Asthma

DUPIXENT is indicated 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.

1.3 Chronic Rhinosinusitis with Nasal Polypsis

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

2 dosage and administration

DUPIXENT is administered by subcutaneous injection.

2.1 Atopic Dermatitis

Dosing in Adults

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

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

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

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

<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 every 4 weeks (Q4W)</td>
</tr>
<tr>
<td>30 to less than 60 kg</td>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg every other week (Q2W)</td>
</tr>
<tr>
<td>60 kg or more</td>
<td>500 mg (two 300 mg injections)</td>
<td>300 mg every other week (Q2W)</td>
</tr>
</tbody>
</table>

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.

2.5 Preparation for Use of DUPIXENT Pre-filled Syringe with Needle Shield

Before injection, remove DUPIXENT pre-filled syringe from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 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.

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 generalized urticaria, rash, erythema nodosum and serum sickness or serum sickness-like reactions, were reported in less than 1% of subjects who received DUPIXENT in clinical trials. Two subjects in the atopic dermatitis development program experienced anaphylaxis [see Adverse Reactions (6.2)]. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see Adverse Reactions (6.1, 6.2)].

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. 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 period; these subjects recovered. There were no cases of keratitis reported in the CRSwNP development program [see Adverse Reactions (6.1)].

Advise patients to report new onset or worsening eye symptoms to their healthcare provider.

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neurologic presentation in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients 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 Reduction of Corticosteroid Dosage
Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of therapy with DUPIXENT. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.6 Patients with Co-morbid Asthma
Advise patients with atopic dermatitis or CRSwNP who have co-morbid asthma 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)]

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

Weeks 0 to 16 (Trials 1 to 4):
In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups. Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with 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 2: 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>N=529 n (%)</td>
<td>N=517 n (%)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>51 (10)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>51 (10)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Blepharitis</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>20 (4)</td>
<td>8 (2)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
<tr>
<td>Eye pruritus</td>
<td>3 (1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Other herpes simplex virus infection</td>
<td>10 (2)</td>
<td>6 (1)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (&lt;1)</td>
<td>0</td>
</tr>
</tbody>
</table>

As 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 epithelial herpes simplex.

Other herpes simplex virus infection cluster includes herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection, but excludes eczema herpeticum.

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

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

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

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

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

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

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

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

### Table 3: Adverse Reactions Occurring in ≥1% of the DUPIXENT Groups in Asthma Trials 1 and 2 and Greater Than Placebo (6 Month Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT 200 mg Q2W</th>
<th>AS Trials 1 and 2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
<td>50 (6%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
<td>7 (1%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
<td>2 (&lt;1%)</td>
</tr>
</tbody>
</table>

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 Polyps

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.
### Inclusion Criteria

- Serum sickness reaction
- Serum sickness-like reaction
- Generalized urticaria
- Eosinophils
- Precautions (5.1), and Adverse Reactions (6.2).

### Study Treatment

- The incidence of treatment-emergent eosinophilia (≥ 500 cells/µL) was reported in 1% of the placebo + TCS group.

### Cardiovascular Thromboembolic Events

- 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.

### Precautions

- During the 52-week treatment period of concomitant therapy for atopic dermatitis (Trials 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W group and 0 (0.0%) of the placebo group.

### Adverse Reactions

- Across all indications, the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/µL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/µL respectively. In subjects with atopic dermatitis, the mean and median increases in blood eosinophils from baseline to Week 4 were 150 and 50 cells/µL respectively.

### 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)).

### Eosinophilia

- 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/µL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/µL respectively. In subjects with CRSwNP, the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/µL respectively.

### Cardiovascular

- In the 24-week placebo controlled trial in subjects with CRSwNP (CSNpT 2), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

### Immuneogenicity

- 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 formation and 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.

#### Data

- Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo. In the 52-week CRSwNP study (CSNpT 2), 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 (5.2)].

#### Table 4: Adverse Reactions Occurring in ≥1% of the DUPIXENT Group in CRSwNP Trials 1 and 2 and Greater than Placebo (24 Week Safety Pool)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUPIXENT 300 mg Q2W</th>
<th>Placebo N=282</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>28 (6%)</td>
<td>12 (4%)</td>
</tr>
<tr>
<td>Conjunctivitisb</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>14 (3%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>7 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (1%)</td>
<td>0 (&lt;1%)</td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>5 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (1%)</td>
<td>1 (&lt;1%)</td>
</tr>
</tbody>
</table>

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.

### Pregnancy

- There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during 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.

### Use in Specific Populations

- Eosinophilia: in the 24-week placebo controlled trial in subjects with CRSwNP (CSNpT 2), the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20% respectively.

- Cardiovascular: in the 24-week placebo controlled trial in subjects with CRSwNP (CSNpT 2), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.
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-4R and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation is an important component in the pathogenesis of asthma, 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., IL-4, IL-13, eotaxin, 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 Pharmacokinetics
The pharmacokinetics of dupilumab is similar in subjects with atopic dermatitis, asthma, and CRSwNP.

Absorption
Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± SD concentrations (Cmax) 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 0.2±0.3 mcg/mL to 0.2±0.35 mcg/mL for 300 mg administered Q2W, from 0.2±0.35 mcg/mL to 0.2±0.35 mcg/mL for 300 mg administered Q2W, from 0.2±0.35 mcg/mL to 0.2±0.35 mcg/mL for 300 mg administered Q2W, from 0.2±0.35 mcg/mL to 0.2±0.35 mcg/mL for 300 mg administered Q2W, and from 0.2±0.35 mcg/mL to 0.2±0.35 mcg/mL for 300 mg administered Q2W.

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

10 OVERDOSE
There is no specific treatment for DUPLEX treatment overdose. In the event of overdose, 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.

DUPLEX (dupilumab) Injection is supplied as a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for subcutaneous injection. DUPLEX 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 200 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 (40 mg), sodium acetate (2 mg), sucrose (100 mg), and water for injection, pH 5.9.
Clinical Response at Week 16 (Trials 1, 2, and 3)

At baseline, 59% of subjects (FAS) had an IGA score of 0 or 1 (clear or 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 assessed by a Numerical Rating Scale (NRS) of 7 on a scale of 0-10.

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At baseline, 59% of subjects (FAS) had an IGA score of 0 or 1 (clear or 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 assessed by a Numerical Rating Scale (NRS) of 7 on a scale of 0-10.

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), 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-4Ra.

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 ≥4 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥72 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 46% 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>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Placebo</td>
<td>Placebo</td>
</tr>
<tr>
<td>Placebo</td>
<td>224</td>
<td>224</td>
</tr>
<tr>
<td>Placebo</td>
<td>38%</td>
<td>10%</td>
</tr>
<tr>
<td>Placebo</td>
<td>51%</td>
<td>15%</td>
</tr>
<tr>
<td>Placebo</td>
<td>36%</td>
<td>8%</td>
</tr>
<tr>
<td>Placebo</td>
<td>213</td>
<td>212</td>
</tr>
<tr>
<td>Placebo</td>
<td>41%</td>
<td>12%</td>
</tr>
</tbody>
</table>

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.

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.

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.
The efficacy results at Week 16 for Trial 6 are presented in Table 7. A greater proportion of subjects randomized to DUXIPENT achieved an improvement in the Peak Pruritus NRS compared to placebo (defined as ≥4-point improvement at Week 4). See Figure 2.

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

<table>
<thead>
<tr>
<th></th>
<th>DUXIPENT</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg Q2W + TCS</td>
<td>Placebo + TCS</td>
</tr>
<tr>
<td>Number of Subjects(^a)</td>
<td>89</td>
<td>264</td>
</tr>
<tr>
<td>Responder(^a) 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 and 52</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Overall Responder(^b-c) Rate at Week 52</td>
<td>36%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

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

The efficacy and safety of DUXIPENT monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 6; NCT03354428) in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10\%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.

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

In Trial 6, the median 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; 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).

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

Table 7: Efficacy Results of DUXIPENT in Trial 6 at Week 16 (FAS)\(^d\)

<table>
<thead>
<tr>
<th></th>
<th>DUXIPENT(^d)</th>
<th>Placebo N=85(^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg (≥60 kg) or 300 mg (≥60 kg) Q2W N=82(^f)</td>
<td>Placebo N=85(^g)</td>
</tr>
<tr>
<td>IGA 0 or 1(^h) (^i)</td>
<td>24%</td>
<td>2%</td>
</tr>
<tr>
<td>EASI-75(^k)</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>EASI-90(^l)</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)(^m)</td>
<td>37%</td>
<td>5%</td>
</tr>
</tbody>
</table>

\(^d\) Full Analysis Set (FAS) includes all subjects randomized.

\(^e\) 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.

\(^f\) Subjects who received rescue treatment or with missing data were considered as non-responders (59\% and 21\% in the placebo and DUXIPENT arms, respectively).

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

\(^h\) Responders were defined with an IGA 0 or 1 (“clear” or “almost clear”).

\(^i\) Subjects who received rescue treatment or with missing data were considered as non-responders.

\(^k\) At Day 1, subjects received 600 mg of DUXIPENT.

\(^l\) At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUXIPENT.

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

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

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

\(^b\) Full Analysis Set (FAS) includes all subjects randomized.

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

The efficacy and safety of DUXIPENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 8; NCT03354514) 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 DUXIPENT + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 2 to Week 12, regardless of weight. Subjects in the DUXIPENT Q2W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and subjects with baseline weight of ≥30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from Week 2 to Week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

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

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

Table 8 presents the results by baseline weight strata for the approved dose regimens.

Table 8: Efficacy Results of DUXIPENT with Concomitant TCS in Trial 8 at Week 16 (FAS)\(^f\)

<table>
<thead>
<tr>
<th></th>
<th>DUXIPENT 300 mg Q4W(^f) + TCS (N=61)</th>
<th>Placebo + TCS (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA 0 or 1(^h) (^i)</td>
<td>30%</td>
<td>13%</td>
</tr>
<tr>
<td>EASI-75(^k)</td>
<td>75%</td>
<td>28%</td>
</tr>
<tr>
<td>EASI-90(^l)</td>
<td>46%</td>
<td>7%</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)(^m)</td>
<td>54%</td>
<td>12%</td>
</tr>
</tbody>
</table>

\(^f\) Full Analysis Set (FAS) includes all subjects randomized.

\(^h\) Responders were defined with an IGA 0 or 1 (“clear” or “almost clear”).

\(^i\) Subjects who received rescue treatment or with missing data were considered as non-responders.

\(^k\) At Day 1, subjects received 600 mg of DUXIPENT.

\(^l\) At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUXIPENT.

A greater proportion of subjects randomized to DUXIPENT + TCS achieved an improvement in the Peak Pruritus NRS compared to placebo (defined as ≥4-point improvement at Week 16). See Figure 3.
The asthma development program included three randomized, double-blind, placebo-controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of >1500 cells/mL (≥1.3%) were excluded. DUPIXENT was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) DUPIXENT every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) DUPIXENT every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV1 (L) in subjects with baseline blood eosinophils ≥300 cells/mL. 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/mL and <300 cells/mL). Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2

AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 adolescent and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a medium or high-dose inhaled corticosteroid plus a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=363) or 300 mg (N=363) DUPIXENT Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV1, at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV1 in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3

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

The demographics and baseline characteristics of these 3 trials are provided in Table 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 (± SD)</td>
<td>27 (15)</td>
<td>26 (22)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall (AD %, NP %, AR %)</td>
<td>73 (8, 11, 62)</td>
<td>78 (10, 13, 69)</td>
<td>72 (7, 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 DUPIXENT 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.67 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mL in 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 eosinophils ≥150 cells/mL. In subjects with baseline blood eosinophil count <150 cells/mL, similar severe exacerbation rates were observed between DUPIXENT and placebo.

In AS Trial 2, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits versus placebo was 0.53 (95% CI: 0.28, 1.03) and 0.74 (95% CI: 0.32, 1.70) with DUPIXENT 200 mg or 300 mg Q2W, respectively.
Table 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>
<th>N</th>
<th>Rate (95% CI)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
<td>0.30 (0.13, 0.68)</td>
<td>0.29 (0.11, 0.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
<td>0.20 (0.08, 0.52)</td>
<td>0.19 (0.07, 0.56)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
<td>1.04 (0.57, 1.90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
<td>0.37 (0.29, 0.48)</td>
<td>0.34 (0.24, 0.48)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>148</td>
<td>1.08 (0.85, 1.38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</td>
<td>0.40 (0.32, 0.51)</td>
<td>0.33 (0.23, 0.45)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
<td>1.24 (0.97, 1.57)</td>
<td></td>
<td></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)*

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>
<th>N</th>
<th>LS Mean Change from baseline L (%): Placebo vs DUPIXENT (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Trial 1</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
<td>0.43 (25.9)</td>
<td>0.26 (0.11, 0.40)</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>64</td>
<td>0.39 (25.8)</td>
<td>0.21 (0.06, 0.36)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
<td>0.18 (10.2)</td>
<td></td>
</tr>
<tr>
<td>AS Trial 2</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
<td>0.43 (29.0)</td>
<td>0.21 (0.13, 0.29)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>148</td>
<td>0.21 (15.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>277</td>
<td>0.47 (32.5)</td>
<td>0.24 (0.16, 0.32)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
<td>0.22 (14.4)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

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: 1.06, 2.00) and 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 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mcL in AS Trials 1 and 2 are shown in Table 11.

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

* At the time of the database lock, not all patients had completed Week 52
Oral Corticosteroid Reduction (AS Trial 3)

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

Compared with placebo, subjects receiving DUXPENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The mean percent reduction in daily OCS dose from baseline was 70% (median 100%) in subjects receiving DUPIXENT compared to 50% (median 50%) in subjects receiving placebo (95% CI: 33%, 51%). Reductions of 50% or higher in the OCS dose were observed in 82% (80%) subjects receiving DUXPENT compared to 57% (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Weeks 24 was 72% for DUXPENT and 37% for placebo (95% CI: 2.99, 8.39). A total of 54 (52%) subjects receiving DUXPENT versus 31 (29%) subjects in the placebo group had a 100% reduction in their OCS dose.

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

14.3 Chronic Rhinosinusitis with Nasal Polyps

The chronic rhinosinusitis with nasal polyposis (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 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. Patients 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 CSNP Trial 1, 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 CSNP Trial 2, 448 subjects were randomized to receive either 300 mg DUPIXENT and placebo (N=229) or placebo alone every other week for 52 weeks.

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

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 CSNP 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 (0.6)</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/mL) (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

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 (CSNP Trial 1 and CSNP Trial 2)
The results for primary endpoints in CRSwNP studies are presented in Table 13.

### 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></td>
<td>Placebo (n=133)</td>
<td>DUPIXENT 300 mg Q2W (n=143)</td>
</tr>
<tr>
<td>Scores Baseline mean</td>
<td>5.86</td>
<td>5.64</td>
</tr>
<tr>
<td>LS mean change</td>
<td>0.17</td>
<td>-1.34</td>
</tr>
<tr>
<td>NC</td>
<td>5.86</td>
<td>-1.89</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>
</tbody>
</table>

* 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
Statistically significant efficacy was observed in CSNP Trial 2 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 CSNP Trial 2 - ITT Population

![Figure 8](image)

Similar results were seen 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

![Figure 9](image)

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 4 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.

Duliplumab 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 DUPLEXENT 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).

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPLEXENT (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 either 300 mg of DUPLEXENT in 2 mL (NDC 0024-5914-00) or 200 mg of DUPLEXENT in 1.14 mL solution (NDC 0024-5918-00).

DUPLEXENT is available in cartons containing 2 pre-filled syringes with needle shield.

Pack Size | 300 mg/2 mL Pre-filled Syringe with Needle Shield | 200 mg/1.14 mL Pre-filled Syringe with Needle Shield
---|---|---
Pack of 2 syringes | NDC 0024-5914-01 | NDC 0024-5918-01

16.2 Storage and Handling

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

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

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

Do not expose the pre-filled syringe to heat or direct sunlight.

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPLEXENT during pregnancy. Encourage participation in the registry. [see USE IN SPECIFIC POPULATIONS (8.1)].

Administration Instructions

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

Hypersensitivity

Advise patients to discontinue DUPLEXENT 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 DUPLEXENT 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 DUPLEXENT [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)].