DUPIXENT® (dupilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

**RECENT MAJOR CHANGES**

| Indications and Usage, Asthma (1.2) | 10/2021 |
| Dosage and Administration (2.1; 2.2; 2.4; 2.7) | 12/2021 |
| Warnings and Precautions (5.1; 5.2; 5.7; 5.8; 5.9) | 12/2021 |

**INDICATIONS AND USAGE**

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

**Atopic Dermatitis**
- for the treatment of adult and pediatric 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)

**Asthma**
- as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)

**Chronic Rhinosinusitis with Nasal Polyps**
- as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). (1.3)

**DOSAGE AND ADMINISTRATION**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Loading Dose</th>
<th>Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥30 kg</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg every 4 weeks (Q4W)</td>
</tr>
<tr>
<td>15 to less than 30 kg</td>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg every other week (Q2W)</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>

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

**Dosage in Pediatric Patients 6 to 11 Years of Age**

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Dose and Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 to less than 30 kg</td>
<td>100 mg every other week (Q2W)</td>
</tr>
<tr>
<td>30 kg or more</td>
<td>300 mg every four weeks (Q4W)</td>
</tr>
</tbody>
</table>

For pediatric patients 6 to 11 years old with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per Table 1 which includes an initial loading dose. (2.3, 2.4)

**Chronic Rhinosinusitis with Nasal Polyposis**
- Recommended dosage for adult patients is 300 mg given every other week. (2.5)

**DOSAGE FORMS AND STRENGTHS**

- Injection: 300 mg/2 mL solution in a single-dose pre-filled pen. (3)
- 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 pen. (3)
- Injection: 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield. (3)
- Injection: 100 mg/0.67 mL solution in a single-dose pre-filled syringe with needle shield. (3)

**CONTRAINDICATIONS**

Known hypersensitivity to dupilumab or any excipients in DUPIXENT. (4)

**WARNINGS AND PRECAUTIONS**

- Hypersensitivity: Hypersensitivity reactions including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme have occurred. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)
- Conjunctivitis and Keratitis: Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination, as appropriate. (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 DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)
- Arthralgia: Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT. (5.7)
- Parasitic (Helminth) Infections: Treat pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving DUPIXENT and do not respond to anti-helminth treatment, discontinue DUPIXENT until the infection resolves. (5.8)
- Vaccinations: Avoid use of live vaccines. (5.9)

**ADVERSE REACTIONS**

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

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

Revised: 12/2021
2.2 Vaccination Prior to Treatment
Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT [see Warnings and Precautions (5.9)].

2.3 Recommended Dosage for Atopic Dermatitis

Dosage in Adults

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

Dosage in Pediatric Patients 6 to 17 Years of Age

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

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

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Loading 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>600 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.

2.4 Recommended Dosage for Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older

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

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

<table>
<thead>
<tr>
<th>Initial Loading Dose</th>
<th>Subsequent Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg every 2 weeks (Q2W)</td>
</tr>
<tr>
<td>or</td>
<td></td>
</tr>
<tr>
<td>600 mg (two 300 mg injections)</td>
<td>300 mg every 2 weeks (Q2W)</td>
</tr>
</tbody>
</table>

Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyposis

600 mg (two 300 mg injections) 300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 to 11 years of age is specified in Table 3.
Table 3: Dosage of DUPIXENT in Pediatric Patients 6 to 11 Years of Age with Asthma

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial* and Subsequent Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>Injection: 100 mg/0.67 mL in a single-dose pre-filled pen</td>
</tr>
<tr>
<td>or 300 mg every 4 weeks (Q4W)</td>
<td>Injection: 300 mg/2 mL in a single-dose pre-filled pen</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>Injection: 200 mg/1.14 mL in a single-dose pre-filled syringe</td>
</tr>
</tbody>
</table>

* For pediatric patients (6 to 11 years of age) with asthma, no initial loading dose is recommended.

2.6 Mislid Doses

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

2.7 Preparation for Use

Before injection, remove DUPIXENT from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe or pre-filled pen, 30 minutes for the 200 mg/1.14 mL pre-filled syringe or pre-filled pen, and 100 mg/0.67 mL pre-filled syringe) without removing the needle cap. After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.

Inspect DUPIXENT visually for particulate matter and discoloration prior to administration. DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution available as:

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, serum sickness or serum sickness-like reactions, angioedema, generalized urticaria, rash, erythema nodosum, and erythema multiforme have been reported. If a clinically significant hypersensitivity reaction occurs, institute appropriate therapy and discontinue DUPIXENT [see Adverse Reactions (6.1, 6.2, 6.3)].

5.2 Conjunctivitis and Keratitis

 Conjunctivitis and keratitis adverse reactions have been reported in clinical trials. Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT compared to those who received placebo. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period [see Adverse Reactions (6.1)].

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

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

Conjunctivitis and keratitis adverse events have also been reported with DUPIXENT in postmarketing settings, predominantly in atopic dermatitis patients. Some patients reported visual disturbances (e.g. blurred vision) associated with conjunctivitis or keratitis. Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination for patients who develop conjunctivitis that does not resolve following standard treatment or signs and symptoms suggestive of keratitis, as appropriate [see Adverse Reactions (6.1)].

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious eosinophilic conditions such as eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Healthcare providers should be alert to vascular rash, worsening pulmonary symptoms, cardiac complications, and/or neuro-opathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult subjects who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult subjects who participated in the asthma development program as well as in adult subjects with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Risk Associated with Abru pt Reduction of Corticosteroid Dosage

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

5.6 Patients with Co-morbid Asthma

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

5.7 Arthralgia

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

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

5.8 Parasitic (Helminth) Infections

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (SOLO 1, SOLO 2, and CHRONOS) and one dose-finding trial (AD-1021) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were White, 24% were Asian, and 6% were Black. In terms of co-morbid conditions, 46% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS). A total of 739 subjects were treated with DUPIXENT for at least 1 year in the development program for moderate-to-severe atopic dermatitis.

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

AD-1225 is a multicenter, open-label extension (OLE) study which assessed the long-term safety of repeat doses of DUPIXENT (through 148 weeks of treatment) in adults with moderate-to-severe AD who had previously participated in controlled studies of DUPIXENT or had been screened for SOLO 1 or SOLO 2. The safety data in AD-1225 reflect exposure to DUPIXENT in 2677 subjects, including 2254 exposed for at least 52 weeks, 1128 exposed for at least 112 weeks, 357 exposed for at least 148 weeks. In AD-1225, 99.7% of subjects were exposed to DUPIXENT 300 mg weekly dosing (QW).
Adulthood and Pediatric Subjects 12 Years of Age and Older with Asthma

A total of 2888 adult and pediatric subjects 12 to 17 years of age with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (DRI12544, QUEST, and VENTURE). Of these, 2678 had a history of 1 or more exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (DRI12544 and QUEST). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (VENTURE). The safety population (DRI12544 and QUEST) was 12-87 years of age, of which 63% were female, and 82% were White. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In DRI12544 and QUEST, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 5 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in DRI12544 and QUEST.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DRI12544 and QUEST</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=779 n (%)</td>
<td>N=788 n (%)</td>
<td>N=792 n (%)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>111 (14%)</td>
<td>144 (18%)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (2%)</td>
<td>19 (2%)</td>
</tr>
<tr>
<td>Eosinophiliaab</td>
<td>17 (2%)</td>
<td>16 (2%)</td>
</tr>
</tbody>
</table>

a Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation.
b Eosinophilia = blood eosinophils ≥3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions [see Warnings and Precautions (6.3)].

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

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

Pediatric Subjects 6 to 11 Years of Age with Asthma

The safety of DUPIXENT was assessed in 405 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma (VOYAGE). The safety profile of DUPIXENT in these subjects through Week 52 was similar to the safety profile from studies in adult and pediatric subjects 12 years of age and older with moderate-to-severe asthma with the addition of helminth infections. Helminth infections were reported in 2.2% (6 subjects) in the DRI12544 group and 0.7% (1 subject) in the placebo group. The majority of cases were enterobiasis, reported in 1.8% (5 subjects) in the DUPIXENT group and none in the placebo group. There was one case of ascariasis in the DUPIXENT group. All helminth infection cases were mild to moderate and subjects recovered with anti-helminth treatment without DUPIXENT treatment discontinuation.

### Chronic Rhinosinusitis with Nasal Polyposis

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

In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the DUPIXENT 300 mg Q2W group. The long-term safety of DUPIXENT was assessed in an open-label extension study in 368 pediatric subjects 6 to 11 years of age with atopic dermatitis (AD-1652). The long-term safety of DUPIXENT in pediatric subjects 6 to 11 years of age was consistent with that seen in adult and pediatric subjects 12 to 17 years of age with atopic dermatitis [see Use in Specific Populations (8.4)].

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SINUS-24 and SINUS-52</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=440 n (%)</td>
<td>N=282 n (%)</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>28 (6%)</td>
</tr>
<tr>
<td>Conjunctivitisab</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Arthralgias</td>
<td>14 (3%)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (1%)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>DUXIPENT 300 mg Q2W</th>
<th>Placebo</th>
<th>N=440</th>
<th>n (%)</th>
<th>N=228</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eosinophilia</td>
<td>5 (1%)</td>
<td></td>
<td>1 (&lt;1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toothache</td>
<td>5 (1%)</td>
<td></td>
<td>1 (&lt;1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

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

Specific Adverse Reactions

**Conjunctivitis and Keratitis**

In adult subjects with atopic dermatitis, conjunctivitis was reported in 10% (34 per 100 subject-years) in the 300 mg Q2W dose group and in 2% of the placebo group (8 per 100 subject-years) during the 16-week treatment period of the monotherapy trials (SOLO 1, SOLO 2, and AD-1021). During the 52-week treatment period of concomitant therapy atopic dermatitis trial (CHRONOS), conjunctivitis was reported in 16% of the DUXIPENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). During the long-term OLE trial with data through 148 weeks (AD-1225), conjunctivitis was reported in 20% of the DUXIPENT group (12 per 100 subject-years).

In DUXIPENT atopic dermatitis monotherapy trials (SOLO 1, SOLO 2, and AD-1021) and through Week 16, keratitis was reported in <1% of the DUXIPENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years). In the 52-week atopic dermatitis DUXIPENT + topical corticosteroids (TCS) atopic dermatitis trial (CHRONOS), keratitis was reported in 4% of the DUXIPENT + TCS group (4 per 100 subject-years) and in 2% of the placebo + TCS group (2 per 100 subject-years). Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUXIPENT. Conjunctivitis was the most frequently reported eye disorder. During the long-term OLE trial with data through 148 weeks (AD-1225), keratitis was reported in 3% of the DUXIPENT group (2 per 100 subject-years). Most subjects with conjunctivitis or keratitis were recovering during the treatment period.

Among asthma subjects, the frequency of conjunctivitis and keratitis was similar between DUXIPENT and placebo. In subjects with CRSwNP, the frequency of conjunctivitis was 2% in the DUXIPENT group compared to 1% in the placebo group in the 24-week safety pool; these subjects recovered.

In the 52-week CRSwNP study (SINUS-52), the frequency of conjunctivitis was 3% in the DUXIPENT subjects and 1% in the placebo subjects; all of these subjects recovered. There were no cases reported in the CRSwNP development program [see Warnings and Precautions (5.2)].

**Eczema Herpeticum and Herpes Zoster**

The rate of eczema herpeticum was similar in the placebo and DUXIPENT groups in the atopic dermatitis trials. The rates remained stable through 148 weeks in the long-term OLE trial (AD-1225).

Herpes zoster was reported in <1% of the DUXIPENT 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 DUXIPENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUXIPENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). During the long-term OLE trial with data through 148 weeks (AD-1225), 1.9% of DUXIPENT-treated subjects reported herpes zoster (0.99 per 100 subject-years of follow-up). Among asthma subjects, the frequency of herpes zoster was similar between DUXIPENT 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 DUXIPENT-treated subjects. These included anaphylaxis, serum sickness or serum sickness-like reactions, generalized urticaria, rash, erythema nodosum, and erythema multiforme [see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)].

**Eosinophilia**

DUXIPENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 0 were 100 cells/mL, respectively. In adult and pediatric subjects 12 years of age and older with asthma (DR12544 and QUEST), the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mL, respectively. In subjects 6 to 11 years of age with asthma (VOYAGE), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/mL, respectively. In subjects with CRSwNP (SINUS-24 and SINUS-52), the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mL, respectively.

Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mL) was similar in DUXIPENT and placebo groups. Treatment-emergent eosinophilia (≥500 cells/mL) was reported in <3% of DUXIPENT-treated subjects and <0.5% in placebo-treated subjects (SOLO 1, SOLO 2, and AD-1021; DR12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52). Blood eosinophil counts declined to near baseline levels during study treatment [see Warnings and Precautions (5.3)].

**Cardiovascular**

In the 1-year placebo controlled trial in adult and pediatric subjects 12 years of age and older with asthma (QUEST), cardiovascular thromboembolic events (cardiovascular death, non-fatal myocardial infarction, and non-fatal strokes) were reported in 1 (0.2%) of the DUXIPENT 200 mg Q2W group, 4 (0.6%) of the DUXIPENT 300 mg Q2W group, and 2 (0.3%) of the placebo group.

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

**6.2 Immunogenicity**

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

Approximately 5% of subjects with atopic dermatitis, asthma, or CRSwNP who received DUXIPENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibody results. In pediatric subjects 6 to 11 years of age with atopic dermatitis who received DUXIPENT 200 mg Q2W or 300 mg Q4W for 16 weeks and pediatric subjects 6 to 11 years of age with asthma who received DUXIPENT 100 mg Q2W or 200 mg Q2W for 52 weeks.

Approximately 16% of pediatric subjects 12 to 17 years of age with asthmatic dermatitis who detect and INXIPENT 500 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 DUXIPENT 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4% exhibited persistent ADA responses, and approximately 4% had neutralizing antibodies.

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

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

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

**8 USE IN SPECIFIC POPULATIONS**

**8.1 Pregnancy**

**Pregnancy Exposure Registry**

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

Healthcare providers and patients may call 1-877-311-8972 or go to https://mothersbaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

**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. In pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis through parturition all doses up to 10-times the maximum recommended human dose (MRHD) [see Data].

The background risk of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. The level of asthma control should be closely monitored in pregnant women and treatment adjusted as necessary to maintain optimal control.

### Data

**Animal Data**

In an enhanced pre and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rx up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis through parturition. No treatment-related signs of adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

### 8.2 Lactation

**Risk Summary**

There are no data on the presence of dupilumab in human milk, the effects on the breastfed infant, or the effects on milk production. Maternal IgG is known to be present in human milk. 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 DUPINX and any potential adverse effects on the breastfed child from DUPINX or from the underlying maternal condition.

### 8.4 Pediatric Use

**Atopic Dermatitis**

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

Use of DUPINX in this age group is supported by AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis and AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe atopic dermatitis.

The safety and effectiveness were generally consistent between pediatric and adult patients [see Adverse Reactions (6.1) and Clinical Studies (14.1)].

Use is also supported by AD-1434, an open-label extension study that enrolled subjects who completed AD-1526 and AD-1652. AD-1434 included 136 pediatric subjects 12 to 17 years of age from AD-1526 and 110 pediatric subjects 6 to 11 years of age from AD-1652 with moderate atopic dermatitis at enrollment into the extension study. AD-1434 included 64 pediatric subjects 12 to 17 years of age from AD-1526 and 72 pediatric subjects 6 to 11 years of age from AD-1652 with severe atopic dermatitis at enrollment. No new safety signals were identified in AD-1434 [see Adverse Reactions (6.1)].

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

**Asthma**

The safety and effectiveness of DUPINX in an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma have been established in pediatric patients 6 years of age and older. Use of DUPINX for this indication is supported by evidence from adequate and well-controlled studies in adult and pediatric patients 6 years and older [see Clinical Studies (14.2)].

**Pediatric Subjects 12 to 17 Years of Age:**

A total of 107 pediatric subjects 12 to 17 years of age with moderate-to-severe asthma were enrolled in QUEST and received either 200 mg (N=21) or 300 mg (N=18) DUPINX (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both pediatric subjects 12 to 17 years of age and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV1, (mL change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Dupilumab exposure was higher in pediatric subjects 12 to 17 years of age than that in adults at the respective dose level which was mainly accounted for by difference in body weight [see Clinical Pharmacology (12.3)].

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

**Pediatric Subjects 6 to 11 Years of Age:**

A total of 408 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma were enrolled in VOYAGE, which evaluated doses of 100 mg Q2W or 200 mg Q2W. Improvement in asthma exacerbations and lung function were demonstrated [see Clinical Studies (14.2)]. The effectiveness of DUPINX 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure in pediatric patients 6 to 11 years of age with moderate-to-severe asthma. Additional safety for DUPINX 300 mg Q4W is based upon available safety information from the pediatric atopic dermatitis indication [see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)].

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

### CRSwNP

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

### 8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPINX in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Clinical studies of DUPINX in atopic dermatitis did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects [see Clinical Pharmacology (12.3)].

Of the 197 subjects with asthma exposed to DUPINX, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group were similar to the overall study population.

Of the 440 subjects with CRSwNP exposed to DUPINX, 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 OVERDOSAGE

There is no specific treatment for DUPINX overdose. In the event of overdose, contact Poison Control (1-800-222-1222) for the latest recommendations and 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-4Rx 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.

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

### 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-4Rx subunit shared by the IL-4Rx and IL-13Rx receptor complexes. Dupilumab inhibits IL-4 signaling via the Type 2 receptor and both IL-4 and IL-13 signaling through the Type II receptor.

Inflammation driven by IL-4 and IL-13 is an important component in the pathogenesis of asthma, atopic dermatitis, and CRSwNP. Multiple cell types that express IL-4Rx (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines, chemokines) contribute to inflammation. Blocking IL-4Rx with dupilumab inhibits IL-4 and IL-13 cytokine-induced inflammatory responses, including the release of proinflammatory cytokines, chemokines, nitric oxide, and IgE. The mechanism of dupilumab action 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 of inflammation. In asthma subjects, fractional exhaled nitric oxide (FeNO) was decreased, circulating concentrations of eosinophil-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. Reductions in these biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (DRH12544) and 70% at Week 52 (QUEST). For FeNO, the median percent reduction from baseline was 82% at Week 2 and 88% in QUEST and 50% to 60% across all dose groups. The magnitude of effect was similar in the overall safety population, the median NO level decreased to 29 ppb.

**Antibody Response to Non-Live Vaccines During DUPINX Treatment**

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

#### 12.3 Pharmacokinetics

The pharmacokinetics of dupilumab is similar in subjects with atopic dermatitis, asthma, 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 26.5±8.7 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 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 subjects, ranging between 61% and 64%.

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

Elimination
The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg Q2W, 300 mg QW, 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 89.4±31.4 mcg/mL and 166±62.3 mcg/mL, respectively, for 300 mg administered Q2W and weekly, and 39.7±17.1 mcg/mL for 200 mg administered Q2W.

Pediatric Patients
Atopic Dermatitis
For pediatric subjects 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<30 kg) or 300 mg (>30 kg), the mean ± SD steady-state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

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

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

In VOYAGE, dupilumab pharmacokinetics was investigated in 270 subjects with moderate-to-severe asthma following subcutaneous administration of either 100 mg Q2W (for 91 pediatric subjects weighing <30 kg) or 200 mg Q2W (for 179 pediatric subjects weighing >30 kg). The mean ± SD steady-state trough concentration was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in pediatric subjects 6 to 11 years of age with body weight of <15 to <30 kg resulted in predicted steady-state trough concentrations (98.7±41.0 mcg/mL) and average concentrations higher than the observed trough concentrations and average concentrations of 100 mg Q2W (<30 kg).

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

Cytochrome P450 Substrates
The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), metoprolol (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in a study with 12-13 evaluable subjects with atopic dermatitis (a SC loading dose of 600 mg followed by 300 mg SC weekly for six weeks). No clinically significant changes in AUC were observed. The largest effect was observed for metoprolol (CYP2D6) with an increase in AUC of 29%.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of dupilumab.

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

14 CLINICAL STUDIES
14.1 Atopic Dermatitis
Adults with Atopic Dermatitis
Three randomized, double-blind, placebo-controlled trials (SOLO 1 (NCT 02277743), SOLO 2 (NCT02277769), and CHRONOS (NCT01859988)) enrolled a total of 2119 adult subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator’s Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were White, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged Peak Pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

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

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

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

Clinical Response at Week 16 (SOLO 1, SOLO 2, and CHRONOS)
The results of the DUPIXENT monotherapy trials (SOLO 1 and SOLO 2) and the DUPIXENT with concomitant TCS trial (CHRONOS) are presented in Table 7.

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

<table>
<thead>
<tr>
<th></th>
<th>SOLO 1</th>
<th>SOLO 2</th>
<th>CHRONOS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td>Placebo</td>
<td>DUPIXENT 300 mg Q2W</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo 300 mg Q2W</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
</tr>
<tr>
<td>Number of subjects randomized (FAS)</td>
<td>224</td>
<td>224</td>
<td>233</td>
</tr>
<tr>
<td>IGA 0 or 1b,c</td>
<td>38%</td>
<td>10%</td>
<td>36%</td>
</tr>
<tr>
<td>EASI-75c</td>
<td>51%</td>
<td>15%</td>
<td>44%</td>
</tr>
<tr>
<td>EASI-90c</td>
<td>36%</td>
<td>8%</td>
<td>30%</td>
</tr>
<tr>
<td>Number of subjects with baseline Peak Pruritus NRS score ≥4</td>
<td>213</td>
<td>212</td>
<td>225</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)d</td>
<td>41%</td>
<td>12%</td>
<td>36%</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 ≥2 points on a 0-4 IGA scale.

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

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

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

In CHRONOS, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of...
The efficacy results at Week 16 for AD-1526 are presented in Table 9.

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

<table>
<thead>
<tr>
<th></th>
<th>DUXIPENT*</th>
<th>Placebo N=85</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean EASI Score</strong></td>
<td>200 mg (&lt;60 kg) 300 mg (&gt;60 kg) Q2W N=85</td>
<td>200 mg (&lt;60 kg) 300 mg (&gt;60 kg) Q2W N=82</td>
</tr>
<tr>
<td>PGA 0 or 1 (clear)</td>
<td>23%</td>
<td>2%</td>
</tr>
<tr>
<td>PGA 75% or 90%</td>
<td>42%</td>
<td>8%</td>
</tr>
<tr>
<td>PGA 75% or 90%</td>
<td>23%</td>
<td>2%</td>
</tr>
</tbody>
</table>

* In CHRONOS, the 421 randomized and treated subjects, 88 subjects (16%) had not been on study for 52 weeks at the time of data analysis.

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

The efficacy and safety of DUXIPENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1526; NCT03054428) in 251 pediatric subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.

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

In AD-1526, the mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 66% were White, 15% were Asian, and 12% were Black. At baseline, 60% 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 average Peak Pruritus NRS was 8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 54% had asthma, and 61% had food allergies.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-80 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥2-point improvement).

The efficacy results at Week 16 for AD-1526 are presented in Table 9.
In the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

VENTURE

VENTURE was a 24-week oral corticosteroid-reduction study in 210 adult and pediatric subjects 15 years of age and older with asthma who required daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg DUPIXENT (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their existing asthma medicine during the study; however, their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

The demographics and baseline characteristics of these 3 trials are provided in Table 11 below.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DUPIXENT 300 mg Q2W + TCS (N=61)</th>
<th>Placebo + TCS (N=61)</th>
<th>DUPIXENT 200 mg Q2W + TCS (N=58)</th>
<th>Placebo + TCS (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 at baseline (%)</td>
<td>11.7 ± 15</td>
<td>12.9 ± 15</td>
<td>11.9 ± 15</td>
<td>12.0 ± 15</td>
</tr>
<tr>
<td>Peak Pruritus NRS (≥4-point improvement)b</td>
<td>54%</td>
<td>12%</td>
<td>61%</td>
<td>13%</td>
</tr>
</tbody>
</table>

### Table 11: Demographics and Baseline Characteristics of Asthma Trials

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DRI12544 (N=776)</th>
<th>QUEST (N=1902)</th>
<th>VENTURE (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>2.2 (2.1)</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 (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 (U/mL) (± SD)</td>
<td>435 (754)</td>
<td>432 (747)</td>
<td>431 (776)</td>
</tr>
<tr>
<td>Mean baseline 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 polyps; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide.
Response rates by baseline blood eosinophils and baseline FeNO for QUEST are shown for the overall population in Figure 4 and Figure 5, respectively. Elevation of FeNO can be a marker of the eosinophilic asthma phenotype when supported by clinical data. Pre-specified subgroup analyses of DRI12544 and QUEST demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels (≥150 cells/mL) or FeNO (≥25 ppb). In QUEST, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophil count ≥150 cells/mL and FeNO <25 ppb, similar severe exacerbation rates were observed between DUXIPENT and placebo.

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

Table 12: Rate of Severe Exacerbations in DRI12544 and QUEST

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Baseline Blood EOS ≥300 cells/mL (primary analysis population, DRI12544)</th>
<th>N</th>
<th>Rate (95% CI)</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRI12544</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>QUEST</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>

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

Lung Function

Significant increases in pre-bronchodilator FEV₁, were observed at Week 12 for DRI12544 and QUEST in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mL in DRI12544 and the overall population in QUEST). In the overall population in QUEST, the FEV₁ LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mL in DRI12544 and QUEST are shown in Table 13.

Improvements in FEV₁ were observed in subjects with baseline blood eosinophil counts ≥150 cells/mL or FeNO ≥25 ppb. In subjects with baseline blood eosinophil count <150 cells/mL and FeNO <25 ppb, similar differences in FEV₁ were observed between DUXIPENT and placebo.

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

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

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Baseline Blood EOS ≥300 cells/mL (primary analysis population, DRI12544)</th>
<th>N</th>
<th>LS Mean Change from baseline</th>
<th>LS Mean Difference vs. placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRI12544</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>65</td>
<td>0.43 (25.9)</td>
<td>0.26 (0.11, 0.40)</td>
<td></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>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>68</td>
<td>0.18 (10.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QUEST</td>
<td>DUPIXENT 200 mg Q2W</td>
<td>264</td>
<td>0.43 (29.0)</td>
<td>0.21 (0.13, 0.29)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>148</td>
<td>0.21 (15.6)</td>
<td></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>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>142</td>
<td>0.22 (14.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The time to first exacerbation was longer for the subjects receiving DUXIPENT compared to placebo in QUEST (Figure 6).
for the treatment of asthma in the year prior to trial entry. Subjects were randomized to DUXIPENT (N=273) or matching placebo (N=135) every other week based on body weight ≥30 kg (200 mg Q2W) or <30 kg (200 mg Q2W). The effectiveness of DUXIPENT 300 mg Q4W was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W [see Pediatric Use (8.4) and Pharmacokinetics (12.3)].

The primary endpoint was the annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled period. Severe asthma exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. The key secondary endpoint was the change from baseline in pre-bronchodilator FEV1, percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7 (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores.

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

Table 14: Demographics and Baseline Characteristics for VOYAGE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VOYAGE (N=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years) (SD)</td>
<td>9 (2)</td>
</tr>
<tr>
<td>% Female</td>
<td>36</td>
</tr>
<tr>
<td>% White</td>
<td>88</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>36</td>
</tr>
<tr>
<td>Mean exacerbations in previous year (± SD)</td>
<td>2.4 (2.2)</td>
</tr>
<tr>
<td>High dose ICS dose (%)</td>
<td>44</td>
</tr>
<tr>
<td>Pre-dose FEV1 (L) at baseline (± SD)</td>
<td>1.48 (0.41)</td>
</tr>
<tr>
<td>Mean percent predicted FEV1, (%) (±SD)</td>
<td>78 (15)</td>
</tr>
<tr>
<td>Mean % Reversibility (± SD)</td>
<td>20 (21)</td>
</tr>
<tr>
<td>Atopic Medical History % Overall (AD %, AR %)</td>
<td>92 (36, 82)</td>
</tr>
<tr>
<td>Mean FeNO ppb (± SD)</td>
<td>28 (24)</td>
</tr>
<tr>
<td>% subjects with FeNO ppb ≥20</td>
<td>50</td>
</tr>
<tr>
<td>Median total IgE IU/mL (±SD)</td>
<td>792 (1093)</td>
</tr>
<tr>
<td>Mean baseline Eosinophil count (±SD) cells/mL</td>
<td>502 (395)</td>
</tr>
</tbody>
</table>

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

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

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

The efficacy results for VOYAGE are presented in Table 15.

Table 15: Efficacy Results of DUXIPENT in VOYAGE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>EOS &gt;300 cells/mL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Severe Exacerbations Rate over 52 Weeks</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>Rate (95% CI)</td>
</tr>
<tr>
<td>DUXIPENT 100 mg Q2W (&lt;30 kg)/200 mg Q2W (&gt;30 kg)</td>
<td>175</td>
</tr>
<tr>
<td>Placebo</td>
<td>84</td>
</tr>
<tr>
<td>Mean Change from Baseline in Percent Predicted FEV1, at Week 12</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>LS mean ∆ from Baseline</td>
</tr>
<tr>
<td>DUXIPENT 100 mg Q2W (&lt;30 kg)/200 mg Q2W (&gt;30 kg)</td>
<td>168</td>
</tr>
<tr>
<td>Placebo</td>
<td>80</td>
</tr>
</tbody>
</table>

* This reflects the prespecified primary analysis population for VOYAGE in the United States.
Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S)-IA). In the subgroup of subjects with baseline blood eosinophil count ≥300 cells/mcL, DUXIPENT led to a higher proportion of subjects with a response in ACQ-7-IA (80.6% versus 64.3% for placebo) with an OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.5% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

14.3 Chronic Rhinosinusitis with Nasal Polyposis

The chronic rhinosinusitis with nasal polyps (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454)) in 724 adult subjects 18 years of age and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Subjects with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator’s discretion. In SINUS-24, a total of 276 subjects were randomized to receive either 300 mg DUXIPENT (N=143) or placebo (N=133) every other week for 24 weeks. In SINUS-52, 448 subjects were randomized to receive either 300 mg DUXIPENT (N=150) every other week for 52 weeks, 300 mg DUXIPENT (N=145) every other week until Week 24 followed by 300 mg DUXIPENT every 4 weeks until Week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 39% had co-morbid asthma, and 28% had NSAID-ERD.

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

In both studies, key secondary end-points at Week 24 included change from baseline: 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 subjectively by the subject each morning on a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). SNOT-22 includes 22 items assessing symptoms and symptom impact associated with CRSwNP with each item scored from 0 (no problem) to 5 (problem as bad as it can be) with a global score ranging from 0 to 110. SNOT-22 had a 2 week recall period. In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sino-nasal surgery (up to Week 52) were evaluated.

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SINUS-24 (N=276)</th>
<th>SINUS-52 (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>Subjects with ≥1 prior surgery (%)</td>
<td>72</td>
<td>58</td>
</tr>
<tr>
<td>Subjects 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), (SD), 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

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

Clinical Response (SINUS-24 and SINUS-52) The results for primary endpoints in CRSwNP studies are presented in Table 17.

<table>
<thead>
<tr>
<th>Placebo</th>
<th>DUXIPENT 300 mg Q2W</th>
</tr>
</thead>
<tbody>
<tr>
<td>SINUS-24 (n=153)</td>
<td>SINUS-52 (n=265)</td>
</tr>
<tr>
<td>LS mean difference vs. Placebo (95% CI)</td>
<td>LS mean difference vs. Placebo (95% CI)</td>
</tr>
<tr>
<td>Primary Endpoints at Week 24</td>
<td></td>
</tr>
<tr>
<td>Scores</td>
<td>Baseline mean</td>
</tr>
<tr>
<td>---------</td>
<td>----------------</td>
</tr>
<tr>
<td>NPS</td>
<td>5.86</td>
</tr>
<tr>
<td>NC</td>
<td>2.45</td>
</tr>
</tbody>
</table>

A reduction in score indicates improvement.

NPS = nasal polyps score; NC = nasal congestion/obstruction
DUPIXENT resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure 13). The proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

DUPIXENT significantly decreased sino-nasal symptoms as measured by SNOT-22 score, with statistically significant efficacy observed in SINUS-24 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 11).

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 -0.51 (95% CI: -0.62, -0.40) in SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52.

A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -5.13 (95% CI: -4.46, -5.80) in SINUS-24 and -5.39 (95% CI: -4.68, -6.09) in SINUS-52. At Week 52, in SINUS-52 the LS mean difference for LMK sinus CT scan score in the DUPIXENT group versus placebo was -6.94 (95% CI: -7.87, -6.01).

Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.12 (95% CI: -1.49, -0.75) in SINUS-24 and -0.98 (95% CI: -1.31, -0.65) in SINUS-52. At Week 52, the LS mean difference for loss of smell in the DUPIXENT group versus placebo was -1.10 (95% CI: -1.51, -0.69). In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4.

Dupilumab significantly decreased sino-nasal symptoms as measured by SNOT-22 compared to placebo. The LS mean difference for SNOT-22 at Week 24 in the DUPIXENT group versus placebo was -21.12 (95% CI: -25.17, -17.06) in SINUS-24 and -17.36 (95% CI: -21.20, -13.52) in SINUS-52. At Week 52, the LS mean difference in the DUPIXENT group versus placebo was -20.96 (95% CI: -25.03, -16.89).

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

The effects of DUPLEXIT on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in subjects with prior surgery and without prior surgery. In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV1, were similar to subjects in the asthma program.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

The pre-filled syringe with needle shield is designed to deliver:
- 300 mg of DUPLEXIT in 2 mL solution (NDC 0024-5914-00)
- 200 mg of DUPLEXIT in 1.14 mL solution (NDC 0024-5918-00)
- 100 mg of DUPLEXIT in 0.67 mL solution (NDC 0024-5911-00)

The pre-filled pen is designed to deliver:
- 300 mg of DUPLEXIT in 2 mL solution (NDC 0024-5915-00)
- 200 mg of DUPLEXIT in 1.14 mL solution (NDC 0024-5919-00)

DUPLEXIT is available in cartons containing 2 pre-filled syringes with needle shield or 2 pre-filled pens.

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>300 mg/2 mL Pre-filled Syringe with Needle Shield</th>
<th>200 mg/1.14 mL Pre-filled Syringe with Needle Shield</th>
<th>100 mg/0.67 mL Pre-filled Syringe with Needle Shield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack of 2 syringes</td>
<td>NDC 0024-5914-01</td>
<td>NDC 0024-5918-01</td>
<td>NDC 0024-5911-02</td>
</tr>
<tr>
<td>Pack of 2 pens</td>
<td>NDC 0024-5915-02</td>
<td>NDC 0024-5919-02</td>
<td></td>
</tr>
</tbody>
</table>

Storage and Handling

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

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. If necessary, DUPLEXIT may be kept at room temperature up to 25°C (77°F) for a maximum of 14 days. Do not store above 25°C (77°F). After removal from the refrigerator, DUPLEXIT must be used within 14 days or discarded.

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 DUPLEXIT during pregnancy. Encourage participation and advise patients about how they may enroll 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 DUPLEXIT prior to use. Advise patients to follow sharps disposal recommendations [see Instructions for Use].
Hypersensitivity
Advertise 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
Advertise patients to consult their healthcare provider if new onset or worsening eye symptoms develop [see Warnings and Precautions (5.2)].

Eosinophilic Conditions
Advertise 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 healthcare provider. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy [see Warnings and Precautions (5.5)].

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

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

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

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

Manufactured by:
Regeneron Pharmaceuticals, Inc.
Tarrytown, NY 10591
U.S. License No. 1760
Marketed by:
sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and
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### What is DUPIXENT?

DUPIXENT® (DU-pix-ent) is a prescription medicine used:

- to treat adults and children 6 years of age and older with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. DUPIXENT can be used with or without topical corticosteroids.
- with other asthma medicines for the maintenance treatment of moderate-to-severe asthma in adults and children 6 years of age and older whose asthma is not controlled with their current asthma medicines. DUPIXENT helps prevent severe asthma attacks (exacerbations) and can improve your breathing. DUPIXENT may also help reduce the amount of oral corticosteroids you need while preventing severe asthma attacks and improving your breathing.
- with other medicines for the maintenance treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled.

- DUPIXENT works by blocking two proteins that contribute to a type of inflammation that plays a major role in atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.
- It is not known if DUPIXENT is safe and effective in children with atopic dermatitis or asthma under 6 years of age.
- It is not known if DUPIXENT is safe and effective in children with chronic rhinosinusitis with nasal polyposis under 18 years of age.

Do not use DUPIXENT if you are allergic to dupilumab or to any of the ingredients in DUPIXENT. See the end of this leaflet for a complete list of ingredients in DUPIXENT.

### Before using DUPIXENT, tell your healthcare provider about all your medical conditions, including if you:

- have eye problems
- have a parasitic (helminth) infection
- are scheduled to receive any vaccinations. You should not receive a “live vaccine” right before and during treatment with DUPIXENT.
- are pregnant or plan to become pregnant. It is not known whether DUPIXENT will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known whether DUPIXENT passes into your breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare provider if you:

- are taking oral, topical, or inhaled corticosteroid medicines
- have asthma and use an asthma medicine
- have atopic dermatitis or CRSwNP, and also have asthma

Do not change or stop your corticosteroid medicine or other asthma medicine without talking to your healthcare provider. This may cause other symptoms that were controlled by the corticosteroid medicine or other asthma medicine to come back.

### How should I use DUPIXENT?

- See the detailed “Instructions for Use” that comes with DUPIXENT for information on how to prepare and inject DUPIXENT and how to properly store and throw away (dispose of) used DUPIXENT pre-filled syringes and pre-filled pens.
- Use DUPIXENT exactly as prescribed by your healthcare provider.
- Your healthcare provider will tell you how much DUPIXENT to inject and how often to inject it.
- DUPIXENT comes as a single-dose pre-filled syringe with needle shield or as a pre-filled pen.
  - The DUPIXENT pre-filled pen is only for use in adults and children 12 years of age and older.
  - The DUPIXENT pre-filled syringe is for use in adults and children 6 years of age and older.
- DUPIXENT is given as an injection under the skin (subcutaneous injection).
- If your healthcare provider decides that you or a caregiver can give the injections of DUPIXENT, you or your caregiver should receive training on the right way to prepare and inject DUPIXENT. Do not try to inject DUPIXENT until you have been shown the right way by your healthcare provider. In children 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult. In children younger than 12 years of age, DUPIXENT should be given by a caregiver.
- **If your dose schedule is every other week and you miss a dose of DUPIXENT**: Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.
- **If your dose schedule is every 4 weeks and you miss a dose of DUPIXENT**: Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, start a new every 4 week dose schedule from the time you remember to take your DUPIXENT injection.
- If you inject too much DUPIXENT (overdose), get medical help or contact a Poison Center expert right away at 1-800-222-1222.
- Your healthcare provider may prescribe other medicines to use with DUPIXENT. Use the other prescribed medicines exactly as your healthcare provider tells you to.

### Instructions for Use

The DUPIXENT pre-filled pen is only for use in adults and children 12 years of age and older.

The DUPIXENT pre-filled pen is only for use in adults and children 12 years of age and older.

See the detailed “Instructions for Use” that comes with DUPIXENT for information on how to prepare and inject DUPIXENT and how to properly store and throw away (dispose of) used DUPIXENT pre-filled syringes and pre-filled pens.
• **Breathing problems or wheezing**
  - Fast pulse
  - Fever
  - General ill feeling
  - Swollen lymph nodes

• **Swelling of the face, lips, mouth, tongue, or throat**
  - Hives
  - Itching
  - Nausea or vomiting

• **Rash or worsening shortness of breath**
  - Chest pain
  - Feeling of pins and needles or numbness of your arms or legs
  - Persistent fever

• **Joint pain**
  - Swelling in your stomach-area

• **Eye problems.** Tell your healthcare provider if you have any new or worsening eye problems, including eye pain or changes in vision, such as blurred vision. Your healthcare provider may send you to an ophthalmologist for an eye exam if needed.

• **Inflammation of your blood vessels.** Rarely, this can happen in people with asthma who receive DUPIXENT. This may happen in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered. It is not known whether this is caused by DUPIXENT. Tell your healthcare provider right away if you have:
  - Rash
  - Worsening shortness of breath
  - Persistent fever

• **Joint aches and pain.** Joint aches and pain can happen in people who use DUPIXENT. Some people have had trouble walking or moving due to their joint symptoms, and in some cases needed to be hospitalized. Tell your healthcare provider about any new or worsening joint symptoms. Your healthcare provider may stop DUPIXENT if you develop joint symptoms.

**The most common side effects of DUPIXENT include:**
- Injection site reactions
- Eye and eyelid inflammation, including redness, swelling, and itching, sometimes with blurred vision
- Pain in the throat (oropharyngeal pain)
- Cold sores in your mouth or on your lips
- High count of a certain white blood cell (eosinophilia)
- Trouble sleeping (insomnia)
- Toothache
- Gastritis
- Joint pain (arthralgia)
- Parasitic (helminth) infections

The following additional side effects have been reported with DUPIXENT:
- Facial rash or redness

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of DUPIXENT. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

**General information about the safe and effective use of DUPIXENT.**

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use DUPIXENT for a condition for which it was not prescribed. Do not give DUPIXENT to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about DUPIXENT that is written for health professionals.

**What are the ingredients in DUPIXENT?**

**Active ingredient:** dupilumab

**Inactive ingredients:** L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, and water for injection.

**REGNERON SANOFI GENZYME**

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For more information about DUPIXENT, go to www.DUPIXENT.com or call 1-844-DUPIXENT (1-844-387-4936).

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: December 2021