HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DUPIXENT safely and effectively. See full prescribing information for DUPIXENT.

DUPIXENT® (dupilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage, Atopic Dermatitis (1.1) 06/2022
Indications and Usage, Asthma (1.2) 10/2021
Indications and Usage, EoE (1.4) 05/2022
Indications and Usage, PN (1.5) 09/2022
Dosage and Administration, Atopic Dermatitis (2.1; 2.3) 06/2022
Dosage and Administration and Asthma (2.1; 2.2; 2.4; 2.9) 12/2021
Dosage and Administration, EoE (2.6; 2.8) 05/2022
Dosage and Administration, PN (2.7) 09/2022
Warnings and Precautions (5.1; 5.2; 5.7; 5.8; 5.9) 12/2021
Warnings and Precautions (5.2) 05/2022
Warnings and Precautions (5.2) 09/2022

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor antagonist indicated:

Atopic Dermatitis

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

Limitations of Use: Not for the relief of acute bronchospasm or status asthmaticus. (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)

Eosinophilic Esophagitis

for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE). (1.4)

Prurigo Nodularis

for the treatment of adult patients with prurigo nodularis (PN). (1.5)

DOSAGE AND ADMINISTRATION

Atopic Dermatitis

Dosage in Adults (2.3):

Recommended dosage is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W).

Dosage in Pediatric Patients 6 Months to 5 Years of Age (2.3):

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial and Subsequent Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to less than 15 kg</td>
<td>200 mg (one 200 mg injection) every 4 weeks (Q4W)</td>
</tr>
<tr>
<td>15 to less than 30 kg</td>
<td>300 mg (one 300 mg injection) every 4 weeks (Q4W)</td>
</tr>
</tbody>
</table>

Dosage in Pediatric Patients 6 to 11 Years of Age (2.4):

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Dose and Subsequent Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>200 mg every other week (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) every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age (2.4):

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

DOSAGE FORMS AND STRENGTHS

Single-Dose Pre-Filled Syringe with Needle Shield (3):

- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL
- Injection: 100 mg/0.67 mL

Single-Dose Pre-Filled Pen (3):

- Injection: 300 mg/2 mL
- Injection: 200 mg/1.14 mL

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

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

Eosinophilic Esophagitis (incidence ≥2%): injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. (6.1)
Prurigo Nodularis (incidence ≥2%): nasopharyngitis, conjunctivitis, herpes infections, dizziness, myalgia, and diarrhea. (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: 09/2022
Dosage in Pediatric Patients 6 Months to 5 Years of Age
The recommended dosage of DUXPENT for pediatric patients 6 months to 5 years of age is specified in Table 1.

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

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial and Subsequent Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 to less than 15 kg</td>
<td>200 mg (one 200 mg injection) every 4 weeks (Q4W)</td>
</tr>
<tr>
<td>15 to less than 30 kg</td>
<td>300 mg (one 300 mg injection) every 4 weeks (Q4W)</td>
</tr>
</tbody>
</table>

* For pediatric patients 6 months to 5 years of age with AD, no initial loading dose is recommended.

Dosage in Pediatric Patients 6 Years to 17 Years of Age
The recommended dosage of DUXPENT for pediatric patients 6 years to 17 years of age is specified in Table 2.

Table 2: Dosage of DUXPENT in Pediatric Patients 6 Years to 17 Years of Age with Atopic Dermatitis

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial Loading Dose</th>
<th>Subsequent Dosage</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
DUXPENT 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 DUXPENT for adult and pediatric patients 12 years of age and older is specified in Table 3.

Table 3: Dosage of DUXPENT in Adult and Pediatric Patients 12 Years and Older with Asthma

<table>
<thead>
<tr>
<th>Initial Loading Dose</th>
<th>Subsequent Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg (two 200 mg injections)</td>
<td>200 mg every 2 weeks (Q2W)</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 DUXPENT for pediatric patients 6 to 11 years of age is specified in Table 4.

Table 4: Dosage of DUXPENT in Pediatric Patients 6 to 11 Years of Age with Asthma

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Initial and Subsequent Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 to less than 30 kg</td>
<td>100 mg every other week (Q2W)</td>
</tr>
<tr>
<td>≥30 kg</td>
<td>200 mg every other week (Q2W)</td>
</tr>
</tbody>
</table>

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

For pediatric patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe AD, follow the recommended dosage as per Table 2 which includes an initial loading dose [see Dosage and Administration (2.3)].

2.5 Recommended Dosage for Chronic Rhinosinusitis with Nasal Polyposis
The recommended dosage of DUXPENT for adult patients is 300 mg given every other week.

2.6 Recommended Dosage for Eosinophilic Esophagitis
The recommended dosage of DUXPENT for adult and pediatric patients 12 years of age and older, weighing at least 40 kg, is 300 mg given every week (QW).

2.7 Recommended Dosage for Prurigo Nodularis
The recommended dosage of DUXPENT for adult patients is an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week (Q2W).

2.8 Missed Doses
If a weekly dose is missed, administer the dose as soon as possible, and start a new weekly schedule from the date of the last administered dose.

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

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

2.9 Preparation for Use
Before injection, remove DUXPENT from the refrigerator and allow DUXPENT 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, DUXPENT must be used within 14 days or discarded.

Inspect DUXPENT visually for particulate matter and discoloration prior to administration. DUXPENT 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). DUXPENT does not contain preservatives; therefore, discard any unused product remaining in the pre-filled syringe or pre-filled pen.

3 DOSAGE FORMS AND STRENGTHS
DUXPENT is a clear to slightly opalescent, colorless to pale yellow solution in a:

- Single-dose pre-filled syringe with needle shield as:
  - Injection: 300 mg/2 mL
  - Injection: 200 mg/1.14 mL
  - Injection: 100 mg/0.67 mL

4 CONTRAINDICATIONS
DUXPENT is contraindicated in patients who have known hypersensitivity to dupilumab or any excipients of DUXPENT [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 DUXPENT [see Adverse Reactions (6.1, 6.2, 6.3)].

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

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

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

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

Among subjects with EoE, the frequency of conjunctivitis and keratitis was 0% and 0% in the DUXPENT group and 2% and 0% in the placebo group, respectively [see Adverse Reactions (6.1)].

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

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

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

5.3 Eosinophilic Conditions
Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Healthcare providers should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult subjects who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangitis have been reported with DUXPENT 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 DUXPENT 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 A abrupt Reduction of Corticosteroid Dosage

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

5.6 Patients with Co-morbid Asthma

Advise patients with co-morbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Arthralgia

Arthralgia has been reported with the use of DUPIXENT with some patients reporting gait disturbances or decreased mobility associated with joint symptoms; some cases resulted in hospitalization. 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.

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.

5.9 Vaccinations

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT. Avoid use of live vaccines in patients treated with DUPIXENT. It is unknown if administration of live vaccines during DUPIXENT treatment will impact the safety or effectiveness of these vaccines. Limited data are available regarding coadministration of DUPIXENT with non-live vaccines [see Clinical Pharmacology (12.2)].

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (SOLO 1, SOLO 2, and CHRONOS) and one dose-ranging trial (AD-1021) evaluated the safety of DUPIXENT in subjects with moderate-to-severe AD. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were White, 24% were Asian, and 6% were Black; in terms of 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 concurrent topical corticosteroids (TCS).

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

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 16.

AD-1225 is a multicenter, open-label extension (OLE) study which assessed the long-term safety of DUPIXENT in 2677 subjects, including 2254 exposed for at least 52 weeks, 1192 exposed for at least 100 weeks, and 357 exposed for at least 148 weeks. In AD-1225, 59.7% of subjects were exposed to DUPIXENT 300 mg weekly dosing (QW), Weeks 0 to 16 (SOLO 1, SOLO 2, CHRONOS, and AD-1021)

In DUPIXENT monotherapy trials (SOLO 1, SOLO 2, and AD-1021) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups. Table 5 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 5: 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</td>
<td>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>

PA pooled analysis of SOLO 1, SOLO 2, and AD-1021.

b Analysis of CHRONOS where subjects were on background TCS therapy.

c DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.

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

f Keratitis cluster includes keratitis, ulcerative keratitis, allergic keratitis, atopic keratoconjunctivitis, and ophthalmic herpes simplex.

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

Safety through Week 52 (CHRONOS)

In the DUPIXENT with concomitant TCS trial (CHRONOS) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in DUPIXENT 300 mg Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT because of adverse reactions: atopic dermatitis (1 subject) and exfoliative dermatitis (1 subject).

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

Safety through 148 Weeks (AD-1225)

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

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 pediatric subjects 12 to 17 years of age with moderate-to-severe AD (AD-1329). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile seen in adults with AD. The long-term safety of DUPIXENT was assessed in an open-label extension study in pediatric subjects 12 to 17 years of age with moderate-to-severe AD (AD-1434). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in AD-1526. The long-term safety profile of DUPIXENT observed in pediatric subjects 12 to 17 years of age was consistent with that seen in adults with AD.

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

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

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 368 pediatric subjects 6 to 11 years of age with AD (AD-1434). Among subjects who entered this study, 110 (30%) had moderate and 72 (20%) had severe AD at the time of enrollment in AD-1434. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD-1652. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 to 11 years of age was consistent with that seen in adult and pediatric subjects 12 to 17 years of age with AD [see Use in Specific Populations (8.4)].

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

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

The long-term safety of DUPIXENT ± TCS was assessed in an open-label extension study of 222 pediatric subjects 6 months to 5 years of age with AD (AD-1435). The majority of subjects were treated with DUPIXENT 300 mg every 4 weeks. The safety profile of DUPIXENT ± TCS in subjects followed through Week 52 was similar to the safety profile observed through Week 16 in AD-1539. The long-term safety profile of DUPIXENT ± TCS observed in pediatric subjects 6 months to 5 years of age was consistent with that seen in adults and pediatric subjects 6 to 17 years old with AD. In addition, hand-foot-and-mouth
Asthma

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

A total of 2388 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 (DR12544, QUEST, and VENTURE). Of these, 2078 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (DR12544 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 (DR12544 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 DR12544 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 6 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in DR12544 and QUEST.

Table 7 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in SINUS-24 and SINUS-52.

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

Eosinophilic Esophagitis

A total of 239 adult and pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE were evaluated in a randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Parts A and B) and received either DUPIXENT 300 mg QW or placebo [see Clinical Studies (14.4)].

The proportion of subjects who discontinued treatment due to adverse events was 2% of the placebo group and 2% of the DUPIXENT 300 mg QW group.

Table 8 summarizes the adverse reactions that occurred at a rate of at least 2% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in Parts A and B.

The safety profile of DUPIXENT in 72 pediatric subjects 12 to 17 years of age, weighing at least 40 kg, and adults in Parts A and B was similar.

Prurigo Nodularis

A total of 309 adult subjects with prurigo nodularis (PN) were evaluated in two 24-week randomized, double-blind, placebo-controlled, multicenter trials of 24 to 52 weeks duration (PRIME and PRIME2). The safety pool included data from the 24-week treatment and 12-week follow-up periods from both trials.

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

Table 9 summarizes the adverse reactions that occurred at a rate of at least 2% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in PRIME and PRIME2.
Table 9: Adverse Reactions Occurring in ≥2% of the DUXIPENT Group in PRIME and PRIME2 and Greater than Placebo

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>PRIME and PRIME2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis*</td>
<td>8 (5%) N=152</td>
<td>3 (2%) N=157</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>6 (4%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Herpes infection</td>
<td>5 (3%)</td>
<td>0%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5 (3%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (3%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

* Nasopharyngitis includes pharyngitis
** Conjunctivitis includes conjunctivitis and allergic conjunctivitis
** Herpes infection includes oral herpes, genital herpes simplex, herpes zoster and ophthalmic herpes zoster
** Dizziness includes dizziness postural, vertigo and vertigo positional
** Myalgia includes musculoskeletal pain and musculoskeletal chest pain

Eosinophils

DUXIPENT-treated subjects with AD, asthma, and CRSwNP had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. An increase from baseline in blood eosinophil count was not observed in subjects with EoE treated with DUXIPENT as compared to placebo. In adult subjects with AD (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In pediatric subjects <6 years old with AD, the mean and median increases from baseline to week 4 were 476 and 90 cells/mcL, 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/mcL, respectively. In subjects 6 to 11 years of age with asthma (VOYAGE), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/mcL, respectively.

In adult subjects with CRSwNP (SINUS-24 and SINUS-52), the mean and median increases in blood eosinophils from baseline to Week 4 were 9 and 0 cells/mcL, respectively.

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

In the 1-year placebo-controlled trial in subjects with PN (CHRONOS), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.2%) of the DUXIPENT 200 mg Q2W group, 2 (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 AD (CHRONOS), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.9%) of the DUXIPENT + TCS 300 mg Q2W group, 0 (0.0%) of the DUXIPENT + TCS 300 mg QW group, and 1 (0.3%) of the placebo + TCS group.

In the 24-week placebo-controlled trial in subjects with CRSwNP (SINUS-24), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.7%) of the 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.

In the 24-week placebo-controlled trial in subjects with EoE (Parts A and B), 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 characteristics, and the prevalence of the same or similar diseases in the population of the study. For these reasons, comparison of the incidence of antibodies to dupilumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Atopic Dermatitis

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

Approximately 16% of pediatric subjects 12 to 17 years of age with AD who received DUXIPENT 300 mg or 200 mg Q2W for 16 weeks developed antibodies to DUXIPENT; approximately 3% exhibited persistent ADA responses, and approximately 5% had neutralizing antibodies.

Asthma

Approximately 5% of subjects with asthma who received DUXIPENT 300 mg Q2W for 52 weeks developed antibodies to DUXIPENT; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies. Similar results were observed in pediatric subjects 6 to 11 years of age with asthma who received either DUXIPENT 100 mg Q2W or 200 mg Q2W up to 52 weeks.

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

Chronic Rhinosinusitis with Nasal Polyps

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

In subjects with PN (PRIME and PRIME2), the mean and median decrease in blood eosinophils from baseline to Week 4 were 9 and 0 cells/mcL, respectively.

Specific Adverse Reactions

Conjunctivitis and Keratitis

In adult subjects with AD, conjunctivitis was reported in 10% (34 per 100 subject-years) in the 300 mg Q2W dose group and in 2% of the placebo group (8 per 100 subject-years) during the 16-week treatment period of the monotherapy trials (SOLO 1, SOLO 2, and AD-1021). During the 52-week treatment period of concomitant therapy AD 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 AD monotherapy trials (SOLO 1, SOLO 2, and AD-1021) 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 DUXIPENT + topical corticosteroids (TCS) AD 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 AD 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 recovered or were recovering during the treatment period.

Among subjects with asthma, 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 of keratitis reported in the CRSwNP development program [see Warnings and Precautions (5.2)].

Among subjects with EoE, the frequency of conjunctivitis and keratitis was 0% and 0% in the DUXIPENT group and 2% and 0% in the placebo group, respectively.

Among subjects with PN, the frequency of conjunctivitis was 4% in the DUXIPENT group compared to 1% in the placebo group; all of these subjects recovered or were recovering during the treatment period. There were no cases of keratitis reported in the PN development program [see Warnings and Precautions (5.2)].

Eczema Herpeticum and Herpes Zoster

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

Herpes zoster was reported in <1% of the DUXIPENT groups (1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week AD monotherapy trials. In the 52-week DUXIPENT + TCS AD 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), 19% of DUXIPENT-treated subjects reported herpes zoster (0.09 per 100 subject-years of follow up). Among asthmatics subjects the frequency of herpes zoster was similar between DUXIPENT and placebo. Among subjects with CRSwNP or EoE there were no reported cases of herpes zoster or eczema herpeticum.

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

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)].
Skin and subcutaneous tissue disorders: Two adult subjects with AD who experienced high titer antibody responses developed use in specific populations

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://mothertobaby.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. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (see clinical Considerations). In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4 receptor alpha (IL-4Rα) during organogenesis through parturition at doses up to 10 times the maximum recommended human dose (MRHD) (see Data).

The background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

In women with poorly or moderately controlled asthma, evidence demonstrates that there is an increased risk of pre eclampsia 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 cynomolgous monkeys were treated weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on embryo-fetal toxicity or malformations, or on morphological, functional, or immunological development were observed in the infants from birth through 6 months of age.

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Atopic Dermatitis

The safety and effectiveness of DUPIXENT have been established in pediatric patients 6 months of age and older with moderate-to-severe AD [see Clinical Studies (14.1)].

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

• AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to-severe AD treated with DUPIXENT
• AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe AD treated with DUPIXENT + TCS
• AD-1539 which included 161 pediatric subjects 6 months to 5 years of age with moderate-to-severe AD treated with DUPIXENT + TCS
• AD-1434, an open-label extension study that enrolled 275 pediatric subjects 12 to 17 years of age treated with DUPIXENT, 368 pediatric subjects 6 to 11 years of age treated with DUPIXENT + TCS, and 180 pediatric subjects 6 months to 5 years of age treated with DUPIXENT + TCS

The safety and effectiveness were generally consistent between pediatric and adult patients [see Adverse Reactions (6.1) and Clinical Studies (14.1)]. In addition, hand-foot-and-mouth disease was reported in 9 (5%) pediatric subjects and skin papilloma was reported in 1 (0.6%) pediatric subjects 6 months to 5 years of age treated with DUPIXENT + TCS in AD-1434. These cases did not lead to study drug discontinuation. [see Adverse Reactions (6.1)].

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

Asthma

The safety and effectiveness of DUPIXENT for an add-on maintenance treatment in patients with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma have been established in pediatric patients 6 years of age and older. Use of DUPIXENT for this indication is supported by evidence from adequate and well-controlled studies in adult and pediatric patients 6 years and older [see Clinical Studies (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) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) QW. 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 QW doses, improvements in FEV₁ (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg QW 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 QW. Improvement in asthma exacerbations and lung function were demonstrated [see Clinical Studies (14.2)]. The effectiveness of DUPIXENT 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q4W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W [see Clinical Pharmacology (12.3)]. Subjects who completed the treatment period of the VOYAGE study could participate in the open-label extension study (LTS14434). Eight people (6 to <15 years of age) treated with DUPIXENT 300 mg Q4W in this study, and the safety profile in these eighteen subjects was consistent with that seen in VOYAGE. Additional safety for DUPIXENT 300 mg Q4W is based upon available safety information from the pediatric AD indication [see Adverse Reactions (6.1), Clinical Pharmacology (12.3)].

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

CRSwNP

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

EoE

The safety and effectiveness of DUPIXENT for the treatment of EoE have been established in pediatric patients 12 years of age and older, weighing at least 40 kg. Use of DUPIXENT in this population is supported by an adequate and well-controlled study in adults (Parts A and B) which included 72 pediatric patients 12 to 17 years of age, weighing at least 40 kg, and additional pharmacokinetic data. The safety and effectiveness in adults and pediatric patients were similar [see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.3)].

The safety and effectiveness of DUPIXENT for the treatment of EoE in pediatric patients less than 12 years of age and weighing less than 40 kg have not been established.

Prurigo Nodularis

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

8.5 Geriatric Use

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

Of the 1477 subjects with asthma exposed to DUPIXENT, a total of 240 subjects were 65 years or older. Efficacy and safety in this age group was similar to the overall study population.

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

Clinical studies of DUPIXENT in EoE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.
The bioavailability of dupilumab following a SC dose is similar between AD, asthma, Q2W. administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered for 300 mg administered Q2W, from 173±75.9 mcg/mL to 195±71.7 mcg/mL for 300 mg steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD dose and 300 mg dose either weekly or Q2W, or 400 mg starting dose and 200 mg dose or 30.5±9.39 mcg/mL, respectively, by approximately 1 week post dose. Steady-state and PN.

Antibody responses to the other active components of both serogroup C meningococcal polysaccharide were similar in DUPIXENT-treated and placebo-treated subjects. Antibody responses to both tetanus toxoid and Dupilumab, an interleukin-4 receptor alpha antagonist, is a human monoclonal antibody vaccine. Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus toxoid and certain biomarkers of inflammation. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. Reductions in these biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (DR12544) and 70% at Week 52 (QUEST). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in DR12544 and QUEST, respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb. Antibody Response to Non-Live Vaccines During DUPIXENT Treatment

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

12.3 Pharmacokinetics

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

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± SD concentrations (C_{max}) of 70.1±24.1 mcg/mL, 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 daily dose for 4 months. Steady-state trough concentrations were 173±75.9 mcg/mL to 195±71.7 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 195±71.7 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 195±71.7 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.

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

Distribution

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

Elimination

The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of 300 mg QW, 300 mg Q2W, 200 mg Q2W, 300 mg Q4W, or 200 mg Q4W, the estimated median time-to-non-detectable concentration (<78 ng/mL) ranged from 9 to 13 weeks in adults and pediatric subjects 12 to 17 years of age. Population pharmacokinetic analyses indicate the median times to non-detectable concentration are approximately 1.5 times (up to 19 weeks) and 2.5 times (up to 32 weeks) longer in pediatric subjects 6 to 11 years of age and pediatric subjects 6 months to 5 years of age, respectively.

Dose Linearity

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

Weight

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

Age

Based on population pharmacokinetic analysis, age did not affect dupilumab clearance in adults and in pediatric subjects 6 to 17 years of age. In pediatric subjects 6 months to 5 years of age, clearance increased with age.

Immunogenicity

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

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean ± SD steady-state trough concentrations of dupilumab were 69.6±31.4 mcg/mL and 166±62.3 mcg/mL, respectively, for 300 mg administered Q2W and weekly, and 39.7±21.7 mcg/mL for 200 mg administered Q2W.

Pediatric Patients

Atopic Dermatitis

For pediatric subjects 12 to 17 years of age with AD receiving every other week dosing (Q2W) with either 200 mg (<50 kg) or 300 mg (≥50 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 AD receiving every other week dosing (Q2W) with 300 mg (≥15 to <30 kg) or 200 mg (≥15 to <15 kg), the mean ± SD steady-state trough concentration was 86.0±34.6 mcg/mL and 98.7±33.2 mcg/mL, respectively.

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

Asthma

A total of 107 pediatric subjects 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/L) and average concentrations higher than the observed trough concentrations and average concentrations of 100 mg Q2W (≥30 kg).

Eosinophilic Esophagitis

In a clinical study (Parts A and B), dupilumab pharmacokinetics were investigated in 35 pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE, receiving 300 mg QW. The mean ± SD steady-state trough concentration of dupilumab was 227 ± 98.3 mcg/mL.

Drug Interaction Studies

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

Cytochrome P450 Substrates

The effects of dupilumab on the pharmacokinetics of midazolam (metabolized by CYP3A4), warfarin (metabolized by CYP2C9), omeprazole (metabolized by CYP2C19), metoprolol (metabolized by CYP2D6), and caffeine (metabolized by CYP1A2) were evaluated in a study with 12-13 evaluable subjects with AD (a SC loading dose of 600 mg followed by 300 mg SC weekly for six weeks). No clinically significant changes in AUC were observed. The largest effect was observed for metoprolol (CYP2D6) with an increase in AUC of 29%.
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-4Rx 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 (NCT02277743), SOLO 2 (NCT02277769), and CHRONOS (NCT02260986)) enrolled a total of 2119 adult subjects 18 years of age and older with moderate-to-severe AD not adequately controlled by topical medication(s). Disease severity was defined by an Investigator’s Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥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 DUXIPENT group received subcutaneous injections of DUXIPENT 600 mg at Week 0, followed by 300 mg every other week (Q2W). In the monotherapy trials (SOLO 1 and SOLO 2), subjects received DUXIPENT or placebo for 16 weeks.

In the concomitant therapy trial (CHRONOS), subjects received DUXIPENT 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 a reduction of ≥4 points on a 0-4 IGA scale.

Clinical Response at Week 16

Subjects in SOLO 1 and SOLO 2 who had an IGA 0 or 1 with a reduction of ≥2 points on a 0-4 IGA scale at Week 16 (FAS) in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

The results of the DUXIPENT monotherapy trials (SOLO 1 and SOLO 2) and the DUXIPENT with concomitant TCS trials (CHRONOS) are presented in Table 10.

Table 10: Efficacy Results of DUXIPENT with or without Concomitant TCS at Week 16 (FAS) in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

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<td>38%</td>
<td>10%</td>
<td>36%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>39%</td>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EASI-75c</td>
<td>51%</td>
<td>15%</td>
<td>44%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>69%</td>
<td>23%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EASI-90c</td>
<td>36%</td>
<td>8%</td>
<td>30%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>40%</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with baseline Peak</td>
<td>213</td>
<td>212</td>
<td>225</td>
<td>221</td>
</tr>
<tr>
<td>Pruritus NRS score</td>
<td></td>
<td></td>
<td>102</td>
<td>299</td>
</tr>
<tr>
<td>≥4</td>
<td>41%</td>
<td>12%</td>
<td>36%</td>
<td>10%</td>
</tr>
<tr>
<td>Peak Pruritus NRS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(≥4-point improvement)d</td>
<td>59%</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>10%</td>
<td>20%</td>
<td></td>
<td></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 non-responders.

d In CHRONOS, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUXIPENT 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 DUXIPENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUUXIPENT with concomitant TCS trial (CHRONOS) are presented in Table 11.

Table 11: Efficacy Results (IGA 0 or 1) of DUXIPENT with Concomitant TCS at Week 16 and 52 in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

<table>
<thead>
<tr>
<th></th>
<th>DUUXIPENT 300 mg Q2W + TCS</th>
<th>Placebo + TCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Subjectsa</td>
<td>89</td>
<td>264</td>
</tr>
<tr>
<td>Responderb,c at Week 16 and 52</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Non-responder at Week 16 and 52</td>
<td>20%</td>
<td>6%</td>
</tr>
<tr>
<td>Non-responder at Week 16 and 52</td>
<td>13%</td>
<td>6%</td>
</tr>
<tr>
<td>Overall Responderb,c Rate at Week 52</td>
<td>36%</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

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

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

In CHRONOS, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUXIPENT 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 DUXIPENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUXIPENT with concomitant TCS trial (CHRONOS) are presented in Table 11.

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)
The efficacy results at Week 16 for AD-1526 are presented in Table 12.

<table>
<thead>
<tr>
<th>Table 12: Efficacy Results of DUPIXENT in AD-1526 at Week 16 (FAS) in Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DUPIXENT</strong> 200 mg (&lt;60 kg) or 300 mg (≥60 kg) Q2W N=82</td>
</tr>
<tr>
<td>IGA 0 or 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>EASI-75&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>EASI-90&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peak Pruritus NRS (&gt;4-point improvement)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

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

<sup>c</sup> Subjects who received rescue treatment or with missing data were considered as non-responders (59% and 21% in the placebo and DUPIXENT arms, respectively).

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

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

Figure 2: Proportion of Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD with ≥4-point Improvement on the Peak Pruritus NRS in AD-1526<sup>a</sup> (FAS)<sup>b</sup>

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

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

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1652; NCT03349184) 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 ≥25%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; ≥30 kg).

Subjects in the DUPIXENT Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12, regardless of weight. Subjects in the DUPIXENT Q4W + TCS group with baseline weight of <30 kg received an initial dose of 200 mg on Day 1, followed by 100 mg Q2W from Week 2 to Week 14, and subjects with baseline weight of ≥30 kg received an initial dose of 400 mg on Day 1, followed by 200 mg Q2W from Week 2 to Week 14. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In AD-1652, the mean age was 8.5 years, the median weight was 23.8 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 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).

The efficacy results at Week 16 for AD-1526 are presented in Table 12.

<table>
<thead>
<tr>
<th>Table 12: Efficacy Results of DUPIXENT in AD-1526 at Week 16 (FAS) in Pediatric Subjects 6 to 11 Years of Age with AD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DUPIXENT</strong> 300 mg Q4W + TCS (N=61)</td>
</tr>
<tr>
<td>IGA 0 or 1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>EASI-75&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>EASI-90&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Peak Pruritus NRS (&gt;4-point improvement)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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

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

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

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

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

Figure 3: Proportion of Pediatric Subjects 6 to 11 Years of Age with AD with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in AD-1652<sup>a</sup> (FAS)<sup>b</sup>

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

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

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

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1539; NCT03346434) in 162 subjects 6 months to 5 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (≥25 to <15 kg and ≥15 to <30 kg).

Subjects in the DUPIXENT Q4W + TCS group with baseline weight of ≥25 to <15 kg received an initial dose of 200 mg on Day 1, followed by 200 mg Q4W from Week 4 to Week 12, and subjects with baseline weight of ≥15 to <30 kg received an initial dose of 200 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders.

In AD-1539, the mean age was 3.8 years, the median weight was 16.5 kg, 39% of subjects were female, 69% were White, 19% were Black, and 6% were Asian. At baseline, the mean BSA involvement was 58%, and 29% of subjects had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 34.1, and the weekly average...
of daily worst scratch/itch score was 7.6 on a scale of 0-10. Overall, 81.4% of subjects had at least one co-morbid allergic condition; 68.3% had food allergies, 52.8% had other allergies, 44.1% had allergic rhinitis, and 25.5% had asthma. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Worst Scratch/Itch NRS (≥4-point improvement).

The efficacy results at Week 16 for AD-1539 are presented in Table 14.

Table 14: Efficacy Results of DUXIPENT with Concomitant TCS in AD-1539 at Week 16 (FAS) in Pediatric Subjects 6 Months to 5 Years of Age with Moderate-to-Severe AD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DUXIPENT + TCS</th>
<th>Placebo + TCS</th>
<th>Difference vs. Placebo (% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGA 0 or 1</td>
<td>28% (N=83)</td>
<td>4% (N=79)</td>
<td>24% (13%, 34%)</td>
</tr>
<tr>
<td>EASI-75</td>
<td>53%</td>
<td>11%</td>
<td>42% (29%, 55%)</td>
</tr>
<tr>
<td>EASI-90</td>
<td>25%</td>
<td>3%</td>
<td>23% (12%, 33%)</td>
</tr>
<tr>
<td>Worst Scratch/Itch NRS (≥4-point improvement)</td>
<td>48%</td>
<td>9%</td>
<td>39% (26%, 52%)</td>
</tr>
</tbody>
</table>

CI = confidence interval

Table 15: 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)</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)</td>
<td>22 (15)</td>
<td>21 (15)</td>
<td>20 (14)</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 (8, 21, 56)</td>
</tr>
<tr>
<td>Mean FeNO ppb (≥ SD)</td>
<td>39 (35)</td>
<td>35 (33)</td>
<td>38 (31)</td>
</tr>
<tr>
<td>Mean total IgE IU/mL (≥ SD)</td>
<td>435 (754)</td>
<td>432 (747)</td>
<td>431 (776)</td>
</tr>
<tr>
<td>Mean baseline blood eosinophil count (≥ SD) cells/mL</td>
<td>350 (430)</td>
<td>360 (370)</td>
<td>350 (310)</td>
</tr>
</tbody>
</table>

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

Exacerbations

DRI12544 and QUEST evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥300 cells/mL), the frequency of severe exacerbations in subjects exposed to DUXIPENT was significantly lower compared to placebo (28% vs. 33%, p<0.05). The rate of severe exacerbations was lower in subjects with higher baseline blood eosinophil count (≥400 cells/mL) compared to those with lower baseline blood eosinophil count (≥200 cells/mL).

In QUEST, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits during treatment period and responder rate in the ACO-Q and AQLQ(S) scores were compared between DUXIPENT and placebo. In QUEST, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits was lower in subjects exposed to DUXIPENT compared to placebo (0.67 vs. 1.00, p<0.05).

In VENTURE, the estimated rate ratio of exacerbations leading to hospitalizations and/or emergency room visits was lower in subjects exposed to DUXIPENT compared to placebo (0.63 vs. 1.00, p<0.05).
Table 16: Rate of Severe Exacerbations in DRI12544 and QUEST

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Baseline Blood EOS ≥300 cells/mcL (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></td>
<td>65</td>
<td>0.30 (0.13, 0.68)</td>
<td>0.29 (0.11, 0.76)</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td></td>
<td>64</td>
<td>0.20 (0.08, 0.52)</td>
<td>0.19 (0.07, 0.56)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>68</td>
<td>1.04 (0.57, 1.90)</td>
<td></td>
</tr>
<tr>
<td>QUEST</td>
<td>DUPIXENT 200 mg Q2W</td>
<td></td>
<td>264</td>
<td>0.37 (0.29, 0.48)</td>
<td>0.34 (0.24, 0.48)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>148</td>
<td>1.08 (0.85, 1.38)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td></td>
<td>277</td>
<td>0.40 (0.32, 0.51)</td>
<td>0.33 (0.23, 0.45)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>142</td>
<td>1.24 (0.97, 1.57)</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 Subjects with Moderate-to-Severe Asthma (QUEST)

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

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

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

Figure 7: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV₁, across Baseline Blood Eosinophil Counts (cells/mcL) in Subjects with Moderate-to-Severe Asthma (DRI12544 and QUEST)

Figure 8: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV₁, across Baseline FeNO (ppb) in Subjects with Moderate-to-Severe Asthma (DRI12544 and QUEST)

Lung Function

Significant increases in pre-bronchodilator FEV₁ were observed at Week 12 for DRI12544 and QUEST in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in DRI12544 and the overall population in QUEST). In the overall population in QUEST, the FEV₁ LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥300 cells/mcL in DRI12544 and QUEST are shown in Table 17.

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

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

Table 17: 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/mcL (primary analysis population, DRI12544)</th>
<th>N</th>
<th>LS Mean Change from baseline L (%); LS Mean Difference vs. placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRI12544</td>
<td>DUPIXENT 200 mg Q2W</td>
<td></td>
<td>65</td>
<td>0.43 (25.9); 0.26 (0.11, 0.40)</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td></td>
<td>64</td>
<td>0.39 (25.8); 0.21 (0.06, 0.36)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>68</td>
<td>0.18 (10.2)</td>
</tr>
<tr>
<td>QUEST</td>
<td>DUPIXENT 200 mg Q2W</td>
<td></td>
<td>264</td>
<td>0.43 (29.0); 0.21 (0.13, 0.29)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>148</td>
<td>0.21 (15.6)</td>
</tr>
<tr>
<td></td>
<td>DUPIXENT 300 mg Q2W</td>
<td></td>
<td>277</td>
<td>0.47 (32.5); 0.24 (0.16, 0.32)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td></td>
<td>142</td>
<td>0.22 (14.4)</td>
</tr>
</tbody>
</table>

* At the time of the database lock, not all subjects had completed Week 52.
Additional Secondary Endpoints

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

- The ACQ-5 responder rate for DUPERIXT 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, 2.11) and 62% vs 57% placebo (odds ratio 1.33; 95% CI: 0.98, 1.81), respectively.

- The ACQ-5 responder rate for DUPERIXT 200 mg and 300 mg Q2W in subjects with baseline blood eosinophils ≥300 cells/ml was 75% vs 67% placebo (odds ratio: 1.46; 95% CI: 0.90, 2.35) and 71% vs 64% placebo (odds ratio: 1.39; 95% CI: 0.88, 2.19), respectively; and the AQLQ(S) responder rates were 71% vs 55% placebo (odds ratio: 2.02; 95% CI: 1.24, 3.21) and 65% vs 52% placebo (odds ratio: 1.79; 95% CI: 1.13, 2.65), respectively.

Oral Corticosteroid Reduction (VENTURE)

VENTURE evaluated the effect of DUPERIXT on the reduction of 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 DUPERIXT. The primary endpoint was the percent reduction from baseline of the oral corticosteroid dose at Week 24 while maintaining asthma control.

Compared with placebo, subjects receiving DUPERIXT 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 DUPERIXT (95% CI: 60%, 80%) compared to 42% (median 50%) in subjects receiving placebo (95% CI: 33%, 51%). Reductions of 50% or higher in the OCS dose were observed in 82 (90%) subjects receiving DUPERIXT compared to 57 (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Week 24 was 72% for DUPERIXT and 37% for placebo (odds ratio 4.48 95% CI: 2.39, 8.39). A total of 54 (52%) subjects receiving DUPERIXT 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 DUPERIXT compared with those receiving placebo (annualized rate 0.65 and 1.60 for the DUPERIXT 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 DUPERIXT compared with those receiving placebo (LS mean difference for DUPERIXT versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels. The ACQ-5 and AQLQ(S) were also assessed in VENTURE and showed improvements similar to those in QUEST.

Pediatric Subjects 6 to 11 Years of Age with Asthma

The efficacy and safety of DUPERIXT in pediatric subjects was evaluated in a 52-week multicenter, randomized, double-blind, placebo-controlled study (VOYAGE; NCT02948959) in 408 subjects 6 to 11 years of age, with moderate-to-severe asthma on a medium or high-dose ICS and a second controller medication or high-dose ICS alone. Subjects were required to have a history of 1 or more asthma exacerbation(s) that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects were randomized to DUPERIXT (N=273) or matching placebo (N=135) every other week based on body weight (<30 kg) (100 mg Q2W), ≥30 kg but <50 kg) (200 mg Q2W) or ≥50 kg) (300 mg Q2W). The effectiveness of DUPERIXT 300 mg Q2W 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 compared to 100 mg Q2W and 200 mg Q2W.

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

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454)) in 724 adult subjects 18 years of age and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Subjects with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator’s discretion. In SINUS-24, a total of 276 subjects were randomized to receive either 300 mg DURPIXENT (N=143) or placebo (N=133) every other week for 24 weeks. In SINUS-52, 448 subjects were randomized to receive either 300 mg DURPIXENT (N=150) every other week for 52 weeks, 300 mg DURPIXENT (N=145) every other week until Week 24 followed by 300 mg DURPIXENT 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 polyposis score (NPS; 0-9 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 scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms).

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

The demographics and baseline characteristics of these 2 trials are provided in Table 20 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 (8)</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/μL) (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>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 polyposis 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 21.

<table>
<thead>
<tr>
<th>Primary Endpoints at Week 24</th>
<th>Placebo (n=133)</th>
<th>DURPIXENT 300 mg Q2W (n=143)</th>
<th>LS mean difference vs. Placebo (95% CI)</th>
<th>Placebo (n=153)</th>
<th>DURPIXENT 300 mg Q2W (n=295)</th>
<th>LS mean difference vs. Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NPS</strong></td>
<td>Baseline mean</td>
<td>5.86</td>
<td>5.64</td>
<td>-0.22 (-2.62, 1.19)</td>
<td>5.96</td>
<td>6.18</td>
</tr>
<tr>
<td>LS mean change</td>
<td>0.17</td>
<td>-1.89</td>
<td>-0.22 (-2.62, 1.19)</td>
<td>0.10</td>
<td>1.17</td>
<td>-0.22 (-1.73, 1.29)</td>
</tr>
<tr>
<td><strong>NC</strong></td>
<td>Baseline mean</td>
<td>2.45</td>
<td>2.26</td>
<td>-0.19 (-0.69, 0.32)</td>
<td>2.38</td>
<td>2.46</td>
</tr>
<tr>
<td>LS mean change</td>
<td>-0.45</td>
<td>-1.34</td>
<td>-0.19 (-0.69, 0.32)</td>
<td>-0.38</td>
<td>-1.25</td>
<td>-0.08 (-0.58, 0.41)</td>
</tr>
</tbody>
</table>

A reduction in score indicates improvement.

NPS = nasal polyps score; NC = nasal congestion/obstruction
Statistically significant efficacy was observed in SINUS-52 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 11).

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

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

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

At Week 52, the LS mean difference for nasal congestion in the DUXIPENT 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 DUXIPENT group versus placebo was 0.41 (95% CI: -0.52, -0.30) in SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52. A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUXIPENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in SINUS-24 and -5.13 (95% CI: -5.80, -4.46) in SINUS-52. At Week 52, in SINUS-52 the LS mean difference for LMK sinus CT scan score in the DUXIPENT 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 DUXIPENT group versus placebo was -1.12 (95% CI: -1.31, -0.93) in SINUS-24 and -0.98 (95% CI: -1.15, -0.81) in SINUS-52. At Week 52, the LS mean difference for loss of smell in the DUXIPENT 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.

**Table 22: Efficacy Results of DUPIXENT at Week 24 in Subjects 12 Years of Age and Older with EoE (Parts A and B)**

<table>
<thead>
<tr>
<th>Co-primary Endpoints</th>
<th>Part A</th>
<th>Part B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤5 eos/hpf), n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUXIPENT 300 mg QW</td>
<td>25 (59.5)</td>
<td>57.0 (40.9, 73.1)</td>
</tr>
<tr>
<td>Placebo</td>
<td>2 (5.1)</td>
<td>47 (58.8)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>53.5 (41.2, 65.8)</td>
</tr>
<tr>
<td>Absolute change from baseline in DSQ score (0-84), LS mean (SE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DUXIPENT 300 mg QW</td>
<td>-21.9 (2.5)</td>
<td>-12.3 (-19.1, -5.5)</td>
</tr>
<tr>
<td>Placebo</td>
<td>-9.6 (2.8)</td>
<td>-23.8 (1.9)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>-13.9 (1.9)</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td>-9.9 (-14.8, -5.0)</td>
</tr>
</tbody>
</table>

a Total biweekly DSQ scores range from 0 to 84; higher scores indicate greater frequency and severity of dysphagia.

b For histological remission, the difference in percentages is estimated using the Cochran Mantel Haenszel method, adjusting for randomization stratification factors. For absolute change in DSQ score, the LS mean changes, standard errors, and differences are estimated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as covariates.

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

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

14.4 Eosinophilic Esophagitis

A single randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Parts A and B), was conducted in adult and pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE (NCT03633617). In both parts, subjects were randomized to receive 300 mg DUXIPENT every week or placebo. Eligible subjects had ≥15 intraepithelial eosinophils per high-power field (eos/hpf) following a treatment course of a proton pump inhibitor (PPI) either prior to or during the screening period and symptoms of dysphagia as measured by the Dysphagia Symptom Questionnaire (DSQ). At baseline, 43% of subjects in Part A and 37% of subjects in Part B had a history of prior esophageal dilations.

Demographics and baseline characteristics were similar in Parts A and B. A total of 81 subjects (61 adults and 20 pediatric subjects) were enrolled in Part A and 159 subjects (107 adults and 52 pediatric subjects) were enrolled in Part B. The mean age in years was 32 years (range 13 to 62 years) in Part A and 28 years (range 12 to 66 years) in Part B. The majority of subjects were male (80% in Part A and 88% in Part B) and White (96% in Part A and 90% in Part B). The mean baseline DSQ score (SD) was 53.6 (12.4) in Part A and 37.2 (10.7) in Part B.

The coprimary efficacy endpoints in Parts A and B were the (1) proportion of subjects achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤5 eos/hpf at Week 24; and (2) the absolute change in the subject-reported DSQ score from baseline to Week 24. Efficacy results for Parts A and B are presented in Table 22.
In Parts A and B, a greater proportion of subjects randomized to DUXIPENT achieved histological remission (peak esophageal intraepithelial eosinophil count ≤5 eos/hpf) compared to placebo. Treatment with DUXIPENT also resulted in a significant improvement in LS mean change in DSQ score compared to placebo at Week 24. The results of the anchor-based analyses that incorporated the subjects’ perspectives indicated that the observed improvement in dysphagia from Parts A and B is meaningful within-subject improvement.

14.5 Prurigo Nodularis

The prurigo nodularis (PN) disease program included two 24-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (PRIME (NCT04183335) and PRIME 2 (NCT04202679)) in 311 adult subjects 18 years of age and older with prurigo nodularis (PN-S) (≥4 points on a scale of 0 to 10) and greater than or equal to 20 nodular lesions. PRIME and PRIME 2 assessed the effect of DUXIPENT on pruritus improvement as well as its effect on PN lesions.

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

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

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

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

The efficacy results for PRIME and PRIME2 are presented in Table 23 and Figures 14, 15, 16, and 17.

### Table 23: Efficacy Results of DUXIPENT in PRIME and PRIME 2

<table>
<thead>
<tr>
<th></th>
<th>PRIME</th>
<th>PRIME 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=76)</td>
<td>DUPIXENT 300 mg Q2W (N=75)</td>
</tr>
<tr>
<td>Proportion of subjects with both an improvement (reduction) in WI-NRS by ≥4 points from baseline to Week 24b</td>
<td>9.2%</td>
<td>38.7%</td>
</tr>
<tr>
<td>Proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 24b</td>
<td>18.4%</td>
<td>60.0%</td>
</tr>
<tr>
<td>Proportion of subjects with IGA PN-S 0 or 1 at Week 24b</td>
<td>18.4%</td>
<td>48.0%</td>
</tr>
<tr>
<td>Proportion of subjects with improvement (reduction) in WI-NRS by ≥4 points from baseline at Week 12b</td>
<td>15.8%a</td>
<td>44.0%a</td>
</tr>
</tbody>
</table>

a Not adjusted for multiplicity in PRIME.

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

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

### 16 HOW SUPPLIED/STORAGE AND HANDLING

**How Supplied**

DUXIPENT (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:
- 200 mg of DUXIPENT in 1.14 mL solution (NDC 0024-5918-00)
- 300 mg of DUXIPENT in 2 mL solution (NDC 0024-5914-00)

The pre-filled pen is designed to deliver:
- 100 mg of DUXIPENT in 0.67 mL solution (NDC 0024-5911-00)
- 200 mg of DUXIPENT in 1.14 mL solution (NDC 0024-5919-00)

### Figures

**Figure 14:** Proportion of Adult Subjects with PN with Both WI-NRS ≥4-point Improvement and IGA PN-S 0 or 1 Over Time in PRIME and PRIME 2

**Figure 15:** Proportion of Adult Subjects with WI-NRS ≥4-point Improvement Over Time in PRIME and PRIME 2

**Figure 16:** Proportion of Adult Subjects with IGA PN-S 0 or 1 Over Time in PRIME and PRIME 2
DUPIXENT 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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pack Size</th>
<th>300 mg/2 mL Pre-filled Pen</th>
<th>200 mg/1.14 mL Pre-filled Pen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pack of 2 pens</td>
<td>NDC 0024-5915-02</td>
<td>NDC 0024-5919-02</td>
</tr>
</tbody>
</table>

Storage and Handling

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

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

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

Do not expose DUPIXENT 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 DUPIXENT 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 DUPIXENT prior to use. Advise patients to follow sharp disposal recommendations [see Dosage and Administration (2.1) and Instructions for Use].

Hypersensitivity

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

 Conjunctivitis and Keratitis

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

Eosinophilic Conditions

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

Not for Acute Asthma Symptoms or Deteriorating Disease

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

Reduction in Corticosteroid Dosage

Inform patients to not discontinue systemic 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

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

Arthralgia

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

Parasitic (Helminth) Infections

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

Vaccinations

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

**DUPIXENT® (DU-pix-ent) (dupilumab)**

**Injection, for subcutaneous use**

### What is DUPIXENT?

DUPIXENT is a prescription medicine used:
- to treat adults and children 6 months of age and older with moderate-to-severe eczema (atopic dermatitis or AD) 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.
- is not used to treat sudden breathing problems.
- to treat adults and children 12 years of age and older, who weigh at least 88 pounds (40 kg), with eosinophilic esophagitis (EoE).
- to treat adults with prurigo nodularis (PN).

DUPIXENT works by blocking two proteins that contribute to a type of inflammation that plays a major role in atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and prurigo nodularis.

It is not known if DUPIXENT is safe and effective in children with atopic dermatitis under 6 months of age.

It is not known if DUPIXENT is safe and effective in children with 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.

It is not known if DUPIXENT is safe and effective in children with eosinophilic esophagitis under 12 years of age and who weigh at least 88 pounds (40 kg).

It is not known if DUPIXENT is safe and effective in children with prurigo nodularis 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.

**Pregnancy Exposure Registry.** There is a pregnancy exposure registry for women who use DUPIXENT during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Your healthcare provider can enroll you in this registry. You may also enroll yourself or get more information about the registry by calling 1-877-311-8972 or going to https://mothertobaby.org/ongoing-study/dupixent/.

- 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, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis 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 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 months 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 week and you miss a dose of DUPIXENT:** Give the DUPIXENT injection as soon as possible and start a new every week dose schedule from the time you remember to take your DUPIXENT injection.
- **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.
What are the possible side effects of DUPIXENT?

DUPIXENT can cause serious side effects, including:

- **Allergic reactions.** DUPIXENT can cause allergic reactions that can sometimes be severe. Stop using DUPIXENT and tell your healthcare provider or get emergency help right away if you get any of the following signs or symptoms:
  - breathing problems or wheezing
  - fast pulse
  - fever
  - general ill feeling
  - swollen lymph nodes
  - allergic reactions. DUPIXENT can cause allergic reactions that can sometimes be severe. Stop using DUPIXENT and tell your healthcare provider or get emergency help right away if you get any of the following signs or symptoms:
  - breathing problems or wheezing
  - fast pulse
  - fever
  - general ill feeling
  - swollen lymph nodes
  - skin rash

- **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
- upper respiratory tract infections
- eye and eyelid inflammation, including redness, swelling, and itching, sometimes with blurred vision
- herpes virus infections
- common cold symptoms (nasopharyngitis)
- cold sores in your mouth or on your lips
- high count of a certain white blood cell (eosinophilia)
- dizziness
- muscle pain
- diarrhea
- pain in the throat (oropharyngeal pain)
- gastritis
- joint pain (arthralgia)
- trouble sleeping (insomnia)
- toothache
- 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.

How should I store DUPIXENT?

- Store DUPIXENT in the refrigerator at 36°F to 46°F (2°C to 8°C).
- Store DUPIXENT in the original carton to protect from light.
- DUPIXENT can be stored at room temperature up to 77°F (25°C) up to 14 days. Throw away (dispose of) any DUPIXENT that has been left at room temperature for longer than 14 days.
- Do not heat or put DUPIXENT into direct sunlight.
- Do not freeze. Do not shake.

Keep DUPIXENT and all medicines out of the reach of children.

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.

**REGENERON sanofi**

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License No. 1760
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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.

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