CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761055Orig1s012

Trade Name:	**DUPIXENT**
Generic or Proper Name:	duplilumab
Sponsor:	**Regeneron Pharmaceuticals, Inc**
Approval Date:	03/11/2019
Indication:	DUPIXENT is an interleukin-4 receptor alpha antagonist indicated: • for the treatment of patients aged 12 years and older with moderate-tosevere atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. • as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitation of Use Not for the relief of acute bronchospasm or status asthmaticus

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761055/S-012

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Elisa Babilonia, PhD
Associate Director, Regulatory Affairs
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Dear Dr. Babilonia:

Please refer to your Supplemental Biologics License Application (sBLA), dated and received September 11, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for DUPIXENT (dupilumab) injection, for subcutaneous use.

This Prior Approval supplemental biologics application proposes a new patient population: patients 12 to less than18 years of age with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical to the enclosed labeling (text for the Prescribing Information, Patient Package Insert, and Instructions for Use) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that you have fulfilled the pediatric study requirement for ages 12 to less than 18 years for this application.

FULFILLMENT OF POSTMARKETING REQUIREMENT

We have reviewed your submission and conclude that the following requirement was fulfilled.

3183-2 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in subjects 12 years to less than 18 years of age with moderate to severe atopic dermatitis.

We remind you that there are postmarketing requirements and a postmarketing commitment listed in the March 28, 2017 approval letter that are still open. There are postmarketing requirements listed in the October 19, 2018 supplement approval letter that are still open.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the Prescribing Information to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

If you have any questions, call Matthew White, Senior Regulatory Project Manager, at (301) 796-4997.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Prescribing Information
Patient Package Insert
Instructions for Use

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

KENDALL A MARCUS
03/11/2019 02:51:14 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

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, Asthma (1.2)	10/2018
Indications and Usage, Atopic Dermatitis (1.1)	03/2019
Dosage and Administration, Asthma (2.2; 2.3; 2.4)	10/2018
Dosage and Administration, Atopic Dermatitis (2.1; 2 3; 2.4)	03/2019
Warnings and Precautions (5.1; 5.2; 5.3; 5.4; 5.5; 5.6; 5.7)	10/2018

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

- for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1.1)
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)

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

DOSAGE AND ADMINISTRATION

Administer by subcutaneous injection. (2)

Atopic Dermatitis

Adults

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

Adolescents

Body Weight	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Asthma

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

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

Revised: 03/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Limitation of Use

DUPIXENT is not indicated for the relief of acute bronchospasm or status asthmaticus

2 DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection.

2.1 Atopic Dermatitis

Dosing in Adults

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

Dosing in Adolescents

The recommended dose of DUPIXENT for patients 12 to 17 years of age is specified in Table 1.

Table 1: Dose of DUPIXENT for Subcutaneous Administration in Adolescent Patients

Body Weight	Initial Dose	Subsequent Doses (every other week)
less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

Concomitant Topical Therapies

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

2.2 Asthma

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

- an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
- an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week
- For patients with oral corticosteroids-dependent asthma, or with co-morbid moderate-to-severe atopic dermatitis for which DUPIXENT is indicated, start with an initial dose of 600 mg followed by 300 mg given every other week

2.3 Important Administration Instructions

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the "Instructions for Use".

For the initial 600 mg dose, administer each of the two DUPIXENT 300 mg injections at different injection sites.

For the initial 400 mg dose, administer each of the two DUPIXENT 200 mg injections at different injection sites.

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

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

If a dose is missed, instruct the patient to 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, instruct the patient to wait until the next dose on the original schedule.

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

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

Before injection, remove DUPIXENT pre-filled syringe from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe and 30 minutes for the 200 mg/1.14 mL pre-filled syringe) without removing the needle cap.

Inspect DUPIXENT visually for particulate matter and discoloration prior to administration. DUPIXENT is a clear to slightly opalescent, colorless to pale yellow solution. Do not use if the liquid contains visible particulate matter, is discolored or cloudy (other than clear to slightly opalescent, colorless to pale yellow). DUPIXENT does not contain preservatives; therefore, discard any unused product remaining in the pre-filled syringe.

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*.

Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period. Among asthma subjects the frequency of keratitis was similar between DUPIXENT and placebo *[see Adverse Reactions (6.1)]*.

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

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious systemic eosinophilia sometimes presenting with clinical features of eosinophilic pneumonia or vasculitis consistent with eosinophilic granulomatosis with polyangiitis, conditions which are often treated with systemic corticosteroid therapy. These events may be associated with the reduction of oral corticosteroid therapy. Physicians should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the

asthma development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

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

5.6 Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatments without consultation with their physicians.

5.7 Parasitic (Helminth) Infections

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

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (Trials 1, 2, and 3) and one dose-ranging trial (Trial 4) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were white, 24% were Asian, and 6% were black; in terms of comorbid conditions,

48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

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

Trials 1, 2, and 4 compared the safety of DUPIXENT monotherapy to placebo through Week 16. Trial 3 compared the safety of DUPIXENT + TCS to placebo + TCS through Week 52.

Weeks 0 to 16 (Trials 1 to 4):

In DUPIXENT monotherapy trials (Trials 1, 2, and 4) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups.

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in 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 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

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

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

Safety through Week 52 (Trial 3):

In the DUPIXENT with concomitant TCS trial (Trial 3) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% in DUPIXENT 300 mg

Q2W + TCS group and 7.6% in the placebo + TCS group. Two subjects discontinued DUPIXENT 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.

Adolescents with Atopic Dermatitis

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

The long-term safety of DUPIXENT was assessed in an open-label extension study in subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (Trial 7). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile observed at Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) 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 AS Trials 1 and 2, 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 3 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 Asthma Trials 1 and 2.

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

Adverse Reaction	AS Trials 1 and 2		
	DUPIXENT 200 mg Q2W N=779 n (%)	DUPIXENT 300 mg Q2W N=788 n (%)	Placebo N=792 n (%)
Injection site reactions[a]	111 (14%)	144 (18%)	50 (6%)
Oropharyngeal pain	13 (2%)	19 (2%)	7 (1%)
Eosinophilia[b]	17 (2%)	16 (2%)	2 (<1%)

[a] Injection site reactions cluster includes erythema, edema, pruritus, pain, and inflammation

[b] Eosinophilia = blood eosinophils ≥ 3,000 cells/mcL, or deemed by the investigator to be an adverse event. None met the criteria for serious eosinophilic conditions *[see Section 5.3 Warnings and Precautions]*

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

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

Specific Adverse Reactions

Conjunctivitis

During the 52-week treatment period of concomitant therapy atopic dermatitis trial (Trial 3), conjunctivitis was reported in 16% of the DUPIXENT 300 mg Q2W + TCS group (20 per 100 subject-years) and in 9% of the placebo + TCS group (10 per 100 subject-years). Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo *[see Warnings and Precautions (5.2)]*.

Eczema Herpeticum and Herpes Zoster

The rate of eczema herpeticum was similar in the placebo and DUPIXENT groups in the atopic dermatitis trials.

Herpes zoster was reported in <0.1% of the DUPIXENT groups (<1 per 100 subject-years) and in <1% of the placebo group (1 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + TCS atopic dermatitis trial, herpes zoster was reported in 1% of the DUPIXENT + TCS group (1 per 100 subject-years) and 2% of the placebo + TCS group (2 per 100 subject-years). Among asthma subjects the frequency of herpes zoster was similar between DUPIXENT and placebo.

Hypersensitivity Reactions

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

Eosinophils

DUPIXENT-treated subjects had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. In subjects with atopic dermatitis, the mean and

median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL respectively. In subjects with asthma, the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL respectively. The incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia (≥5,000 cells/mcL) was reported in <2% of DUPIXENT-treated patients and <0.5% in placebo-treated patients. Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular

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

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

6.2 Immunogenicity

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

Approximately 6% of subjects with atopic dermatitis or asthma who received DUPIXENT 300 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 2% exhibited persistent ADA responses, and approximately 2% had neutralizing antibodies.

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

Approximately 5% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

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

Approximately 4% of adolescent subjects with atopic dermatitis in the placebo group were positive for antibodies to DUPIXENT; approximately 1% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

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

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

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

Immune responses to vaccination were assessed in a study in which subjects with atopic dermatitis were treated once weekly for 16 weeks with 300 mg of dupilumab (twice the recommended dosing frequency). After 12 weeks of DUPIXENT administration, subjects were vaccinated with a Tdap vaccine (Adacel®) and a meningococcal polysaccharide vaccine (Menomune®). Antibody responses to tetanus toxoid and serogroup C meningococcal polysaccharide were assessed 4 weeks later. Antibody responses to both tetanus vaccine and meningococcal polysaccharide vaccine were similar in dupilumab-treated and placebo-treated subjects. Immune responses to the other active components of the Adacel and Menomune vaccines were not assessed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

In an enhanced pre- and post-natal development toxicity study, pregnant cynomolgus monkeys were administered weekly subcutaneous doses of homologous antibody against IL-4Rα up to 10 times the MRHD (on a mg/kg basis of 100 mg/kg/week) from the beginning of organogenesis to parturition. No treatment-related adverse effects on 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 efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults *[see Adverse Reactions (6.1) and Clinical Studies (14.2)]*. Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate to severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_1 (LS mean change from baseline at Week 12) were observed (0.36 L and 0.27 L, respectively). For the 200 mg Q2W dose, subjects had a reduction in the rate of severe exacerbations that was consistent with adults. Safety and efficacy in pediatric patients (<12 years of age) with asthma have not been established. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3)]*.

The adverse event profile in adolescents was generally similar to the adults *[see Adverse Reactions (6.1)]*.

8.5 Geriatric Use

Of the 1472 subjects with atopic dermatitis exposed to DUPIXENT in a dose-ranging study and placebo-controlled trials, 67 subjects were 65 years or older. Although no differences in safety or efficacy were observed between older and younger subjects, the number of subjects aged 65 and over is not sufficient to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

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

10 OVERDOSE

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

11 DESCRIPTION

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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

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

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment markedly decreased fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin in asthma subjects relative to placebo. These reductions in biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (AS Trial 1) and 70% at Week 52 (AS Trial 2). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in AS Trials 1 and 2 respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

12.3 Pharmacokinetics

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

Absorption

Following an initial subcutaneous (SC) dose of 600 mg or 400 mg, dupilumab reached peak mean ± SD concentrations (C_{max}) of 70.1±24.1 mcg/mL or 41.8±12.4 mcg/mL, respectively, by approximately 1 week post dose.

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose either weekly (twice the recommended dosing frequency) or Q2W, or 400 mg starting dose and 200 mg dose Q2W. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 79.9±41.4 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.

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

Distribution

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

Elimination

The metabolic pathway of dupilumab has not been characterized. As a human monoclonal IgG4 antibody, dupilumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. After the last steady-state dose of

300 mg Q2W, 300 mg QW, or 200 mg Q2W dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10-11, 13, and 9 weeks, respectively.

Dose Linearity

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

Weight

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

Age

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

Immunogenicity

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

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean ±SD steady-state trough concentrations of dupilumab were 69.4±31.4 mcg/mL 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 adolescents 12 to 17 years of age with atopic dermatitis receiving every other week dosing (Q2W) with either 200 mg (<60 kg) or 300 mg (≥60 kg), the mean±SD steady-state trough concentration of dupilumab was 54.5±27.0 mcg/mL.

Asthma

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

Renal or Hepatic Impairment

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

Drug Interaction Studies

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

Cytochrome P450 Substrates

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

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

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

In the concomitant therapy trial (Trial 3), subjects received DUPIXENT or placebo with concomitant topical corticosteroids (TCS) and as needed topical calcineurin inhibitors for problem areas only, such as the face, neck, intertriginous and genital areas for 52 weeks.

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

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

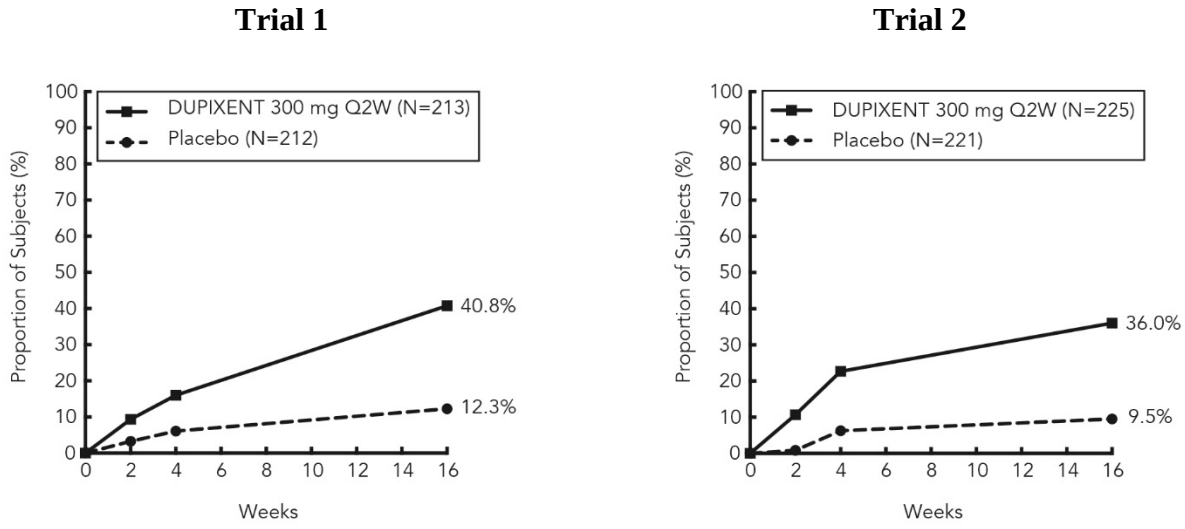
The results of the DUPIXENT monotherapy trials (Trials 1 and 2) and the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 4.

Table 4: Efficacy Results of DUPIXENT With or Without Concomitant TCS at Week 16 (FAS)

	Trial 1		Trial 2		Trial 3	
	DUPIXENT 300 mg Q2W	**Placebo**	**DUPIXENT 300 mg Q2W**	**Placebo**	**DUPIXENT 300 mg Q2W + TCS**	**Placebo + TCS**
Number of subjects randomized (FAS)[a]	224	224	233	236	106	315
IGA 0 or 1[b,c]	38%	10%	36%	9%	39%	12%
EASI-75[c]	51%	15%	44%	12%	69%	23%
EASI-90[c]	36%	8%	30%	7%	40%	11%
Number of subjects with baseline Peak Pruritus NRS score ≥4	213	212	225	221	102	299
Peak Pruritus NRS (≥4-point improvement)[c]	41%	12%	36%	10%	59%	20%

[a] Full Analysis Set (FAS) includes all subjects randomized.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

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



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomized.

In Trial 3, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of DUPIXENT IGA 0 or 1 responders at Week 16 remained responders at Week 52) and subjects who were non-responders at Week 16 who later responded to treatment (e.g., 24% of DUPIXENT IGA 0 or 1 non-responders at Week 16 became responders at Week 52). Results of supportive analyses of the 353 subjects in the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 5.

Table 5: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52

	DUPIXENT 300 mg Q2W + TCS	**Placebo + TCS**
Number of Subjects[a]	89	264
Responder[b,c] at Week 16 and 52	22%	7%
Responder at Week 16 but Non-responder at Week 52	20%	7%
Non-responder at Week 16 and Responder at Week 52	13%	6%
Non-responder at Week 16 and 52	44%	80%
Overall Responder[b,c] Rate at Week 52	36%	13%

[a] In Trial 3, of the 421 randomized and treated subjects, 68 subjects (16%) had not been on study for 52 weeks at the time of data analysis.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.

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

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

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

Adolescents with Atopic Dermatitis

The efficacy and safety of DUPIXENT monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 6; NCT03054428) in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD defined by an IGA score ≥3 (scale of 0 to 4), an EASI score ≥16 (scale of 0 to 72), and a minimum BSA involvement of ≥10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication.

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

In Trial 6, the mean age was 14.5 years, the median weight was 59.4 kg, 41% of subjects were female, 63% were White, 15% were Asian, and 12% were Black. At baseline 46% of subjects had an IGA score of 3 (moderate AD), 54% had an IGA score of 4 (severe AD), the mean BSA involvement was 57%, and 42% had received prior systemic immunosuppressants. Also, at baseline the mean EASI score was 36, and the weekly averaged Peak Pruritus NRS was 8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 66% had allergic rhinitis, 54% had asthma, and 61% had food allergies.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

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

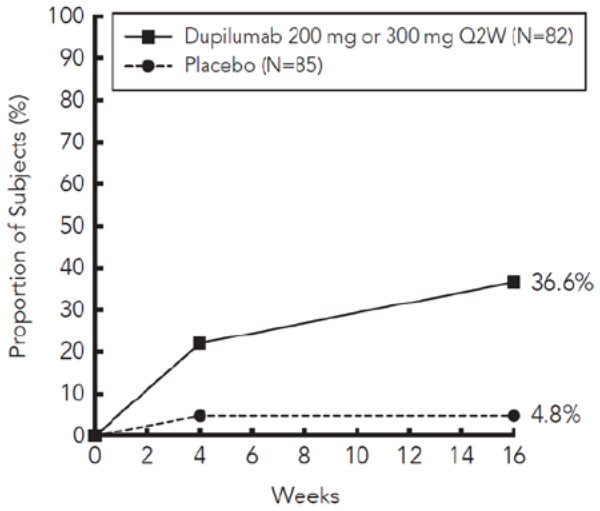
Table 6: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)[a]

	DUPIXENT[d] 200 mg (<60 kg) or 300 mg (≥60 kg) Q2W N=82[a]	Placebo N=85[a]
IGA 0 or 1[b,c]	24%	2%
EASI-75[c]	42%	8%
EASI-90[c]	23%	2%
Peak Pruritus NRS (≥4-point improvement)[c]	37%	5%

[a] Full Analysis Set (FAS) includes all subjects randomized.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear") and a reduction of ≥2 points on a 0-4 IGA scale.
[c] Subjects who received rescue treatment or with missing data were considered as non-responders (59% and 21% in the placebo and DUPIXENT arms, respectively).
[d] At Week 0, subjects received 400 mg (baseline weight <60 kg) or 600 mg (baseline weight ≥60 kg) of DUPIXENT.

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

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



[a] In the primary analyses of the efficacy endpoints, subjects who received rescue treatment or with missing data were considered non-responders.
[b] Full Analysis Set (FAS) includes all subjects randomized.

14.2 Asthma

The asthma development program included three randomized, double-blind, placebo-controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the

treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of >1500 cells/mcL (<1.3%) were excluded. DUPIXENT was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below.

AS Trial 1

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with moderate to severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) DUPIXENT every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) DUPIXENT every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV_1 (L) in subjects with baseline blood eosinophils ≥300 cells/mcL. Other endpoints included percent change from baseline in FEV_1 and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (≥300 cells/mcL and <300 cells/mcL). Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2

AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 adolescent and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) DUPIXENT Q2W (or matching placebo for either 200 mg [N=317] or 300 mg [N=321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV_1 at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV_1 in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

AS Trial 3

AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg DUPIXENT (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their existing asthma medicine during the study; however their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary

endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores.

The demographics and baseline characteristics of these 3 trials are provided in Table 7 below.

Table 7: Demographics and Baseline Characteristics of Asthma Trials

Parameter	Trial 1 (N=776)	Trial 2 (N=1902)	Trial 3 (N=210)
Mean age (years) (SD)	49 (13)	48 (15)	51 (13)
% Female	63	63	61
% White	78	83	94
Duration of Asthma (years), mean (± SD)	22 (15)	21 (15)	20 (14)
Never smoked (%)	77	81	81
Mean exacerbations in previous year (± SD)	2.2 (2.1)	2.1 (2.2)	2.1 (2.2)
High dose ICS use (%)	50	52	89
Pre-dose FEV_1 (L) at baseline (± SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%) (± SD)	61 (11)	58 (14)	52 (15)
% Reversibility (± SD)	27 (15)	26 (22)	19 (23)
Atopic Medical History % Overall (AD %, NP %, AR %)	73 (8, 11, 62)	78 (10, 13, 69)	72 (8, 21, 56)
Mean FeNO ppb (± SD)	39 (35)	35 (33)	38 (31)
Mean total IgE IU/mL (± SD)	435 (754)	432 (747)	431 (776)
Mean baseline blood Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)

ICS = inhaled corticosteroid; FEV_1 = Forced expiratory volume in 1 second; AD = atopic dermatitis; NP = nasal polyposis; AR = allergic rhinitis; FeNO = fraction of exhaled nitric oxide

Exacerbations

AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either DUPIXENT 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥ 300 cells/mcL in AS Trials 1 and 2 are shown in Table 8.

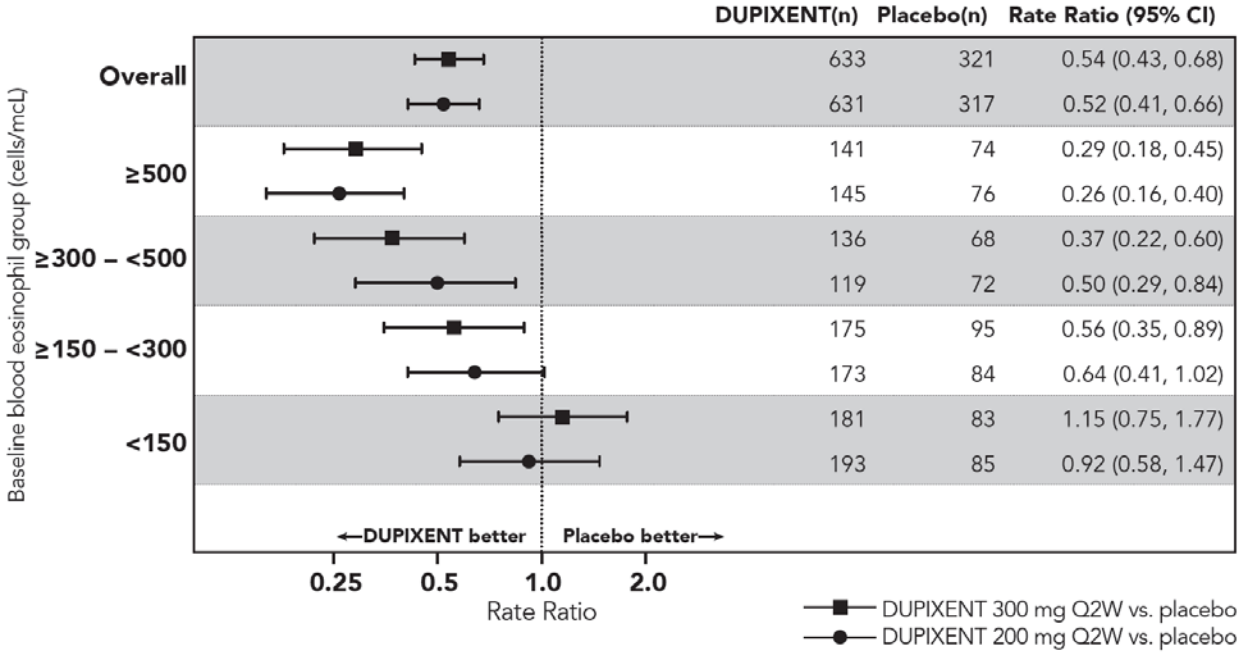
Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 3. Prespecified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥ 150 cells/mcL. In subjects with baseline blood eosinophil count < 150 cells/mcL, similar severe exacerbation rates were observed between DUPIXENT and placebo.

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

Table 8: Rate of Severe Exacerbations in AS Trials 1 and 2

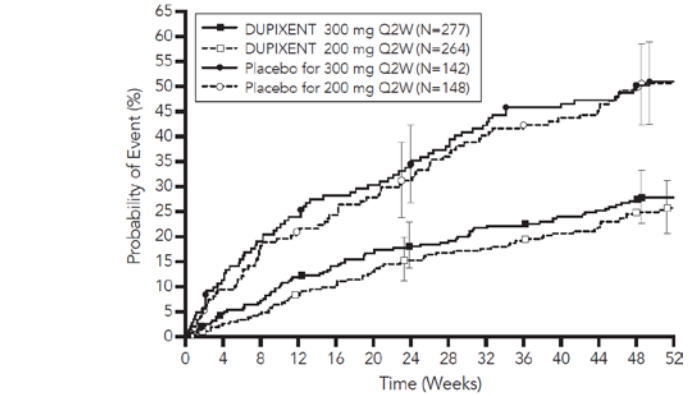
Trial	**Treatment**	**Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)**		
		N	**Rate (95% CI)**	**Rate Ratio (95% CI)**
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)
	DUPIXENT 300 mg Q2W	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)
	Placebo	68	1.04 (0.57, 1.90)	
AS Trial 2	DUPIXENT 200 mg Q2W	264	0.37 (0.29, 0.48)	0.34 (0.24, 0.48)
	Placebo	148	1.08 (0.85, 1.38)	
	DUPIXENT 300 mg Q2W	277	0.40 (0.32, 0.51)	0.33 (0.23, 0.45)
	Placebo	142	1.24 (0.97, 1.57)	

Figure 3: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline Blood Eosinophil Count (cells/mcL) in AS Trial 2



The time to first exacerbation was longer for the subjects receiving DUPIXENT compared to placebo in AS Trial 2 (Figure 4).

Figure 4: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Baseline Blood Eosinophils ≥ 300 cells/mcL (AS Trial 2)[a]



[a] At the time of the database lock, not all patients had completed Week 52

Lung Function

Significant increases in pre-bronchodilator FEV_1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥ 300

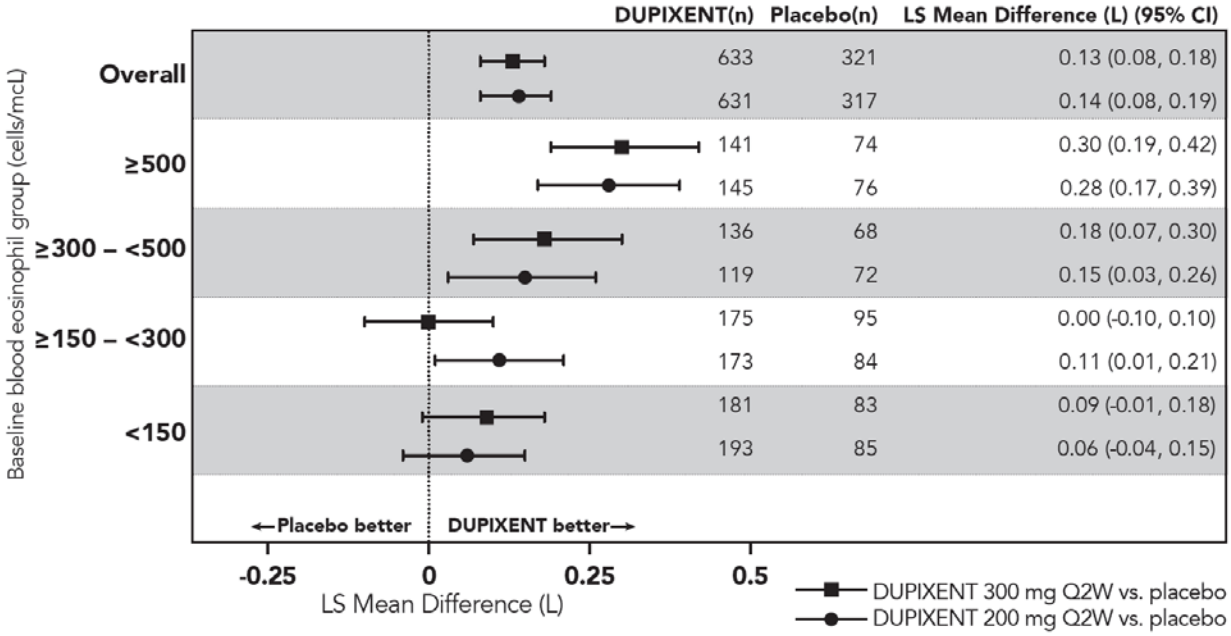
cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV_1 LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for DUPIXENT 200 mg Q2W and 300 mg Q2W, respectively. Results in subjects with baseline blood eosinophil counts ≥ 300 cells/mcL in AS Trials 1 and 2 are shown in Table 9.

Improvements in FEV_1 by baseline blood eosinophils for AS Trial 2 are shown in Figure 5. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Table 9: Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV_1 at Week 12 in AS Trials 1 and 2

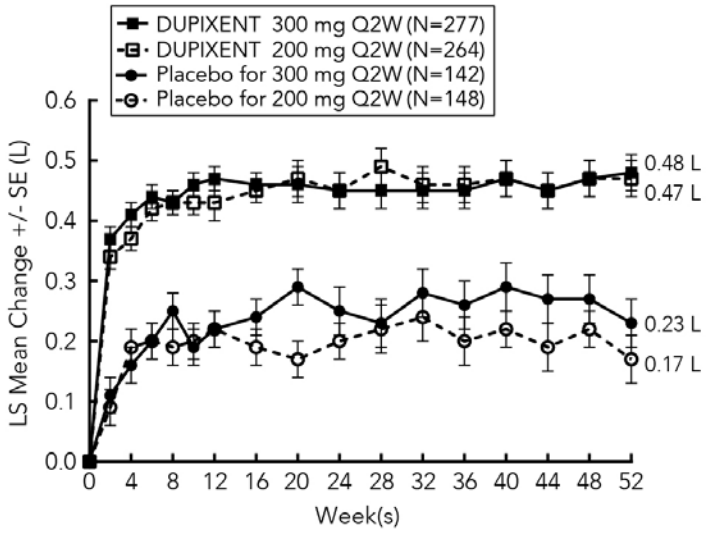
Trial	**Treatment**	**Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)**		
		N	**LS Mean Change from baseline L (%)**	**LS Mean Difference vs. placebo (95% CI)**
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.43 (25.9)	0.26 (0.11, 0.40)
	DUPIXENT 300 mg Q2W	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	68	0.18 (10.2)	
AS Trial 2	DUPIXENT 200 mg Q2W	264	0.43 (29.0)	0.21 (0.13, 0.29)
	Placebo	148	0.21 (15.6)	
	DUPIXENT 300 mg Q2W	277	0.47 (32.5)	0.24 (0.16, 0.32)
	Placebo	142	0.22 (14.4)	

Figure 5: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-Bronchodilator FEV_1 across Baseline Blood Eosinophil Counts (cells/mcL) in AS Trial 2



Mean changes in FEV_1 over time in AS Trial 2 are shown in Figure 6.

Figure 6: Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time in Subjects with Baseline Blood Eosinophils ≥300 cells/mcL (AS Trial 2)



Additional Secondary Endpoints

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

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

Oral Corticosteroid Reduction (AS Trial 3)

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

Compared with placebo, subjects receiving DUPIXENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The mean percent reduction in daily OCS dose from baseline was 70% (median 100%) in subjects receiving DUPIXENT (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 (80%) subjects receiving DUPIXENT compared to 57 (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Weeks 24 was 72% for DUPIXENT and 37% for placebo (odds ratio 4.48 95% CI: 2.39, 8.39). A total of 54 (52%) subjects receiving DUPIXENT 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 DUPIXENT compared with those receiving placebo (annualized rate 0.65 and 1.60 for the DUPIXENT and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV_1 from baseline to Week 24 was greater in subjects receiving DUPIXENT compared with those receiving placebo (LS mean difference for DUPIXENT versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels. The ACQ-5 and AQLQ(S) were also assessed in AS Trial 3 and showed improvements similar to those in AS Trial 2.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

DUPIXENT (dupilumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield. Each pre-filled syringe with needle shield is designed to deliver either 300 mg of DUPIXENT in 2 mL (NDC 0024-5914-00) or 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00).

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

16.2 Storage and Handling

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

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

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

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

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

Advise the patients and/or caregivers to read the FDA-approved patient labeling (Patient Information and Instructions for Use) before the patient starts using DUPIXENT and each time the prescription is renewed as there may be new information they need to know.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow sharps disposal recommendations *[see 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 physician. Inform patients that reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy *[see Warnings and Precautions(5.5)]*.

Atopic Dermatitis Patients with Comorbid Asthma

Advise atopic dermatitis patients with comorbid asthma not to adjust or stop their asthma treatment without talking to their physicians *[see Warnings and Precautions (5.6)]*.

REGENERON SANOFI GENZYME

Manufactured by:

Regeneron Pharmaceuticals, Inc.

Tarrytown, NY 10591

U.S. License No. 1760

Marketed by:

sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

DUPIXENT® is a registered trademark of Sanofi Biotechnology

Revised: March 2019

Patient Information
DUPIXENT® (DU-pix'-ent)
(dupilumab)
injection, for subcutaneous use

What is DUPIXENT?

DUPIXENT is a prescription medicine used:

- to treat people aged 12 years and older with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. DUPIXENT can be used with or without topical corticosteroids.
- with other asthma medicines for the **maintenance treatment of moderate-to-severe asthma** in people aged 12 years 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.

- DUPIXENT works by blocking two proteins that contribute to a type of inflammation that plays a major role in atopic dermatitis and asthma.
- DUPIXENT is not used to treat sudden breathing problems
- It is not known if DUPIXENT is safe and effective in children with atopic dermatitis under 12 years of age.
- It is not known if DUPIXENT is safe and effective in children with asthma under 12 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 (if you also have atopic dermatitis).
- have a parasitic (helminth) infection.
- are taking oral, topical, or inhaled corticosteroid medicines. **Do not** stop taking your corticosteroid medicines unless instructed by your healthcare provider. This may cause other symptoms that were controlled by the corticosteroid medicine to come back.
- are scheduled to receive any vaccinations. You should not receive a "live vaccine" if you are treated with DUPIXENT.
- are pregnant or plan to become pregnant. It is not known whether DUPIXENT will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known whether DUPIXENT passes into your breast milk.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. If you have asthma and are taking asthma medicines, do not change or stop your asthma medicine without talking to your healthcare provider.

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.**
- Use DUPIXENT exactly as prescribed by your healthcare provider.
- DUPIXENT comes as a single-dose pre-filled syringe with needle shield.
- 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 adolescents 12 years of age and older, it is recommended that DUPIXENT be administered by or under supervision of an adult.
- If you miss a dose of DUPIXENT, give the injection within 7 days from the missed dose, then continue with the original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.
- If you inject more DUPIXENT than prescribed, call your healthcare provider right away.
- 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 (hypersensitivity), including a severe reaction known as anaphylaxis.** Stop using DUPIXENT and tell your healthcare provider or get emergency help right away if you get any of the following symptoms:
  - breathing problems
  - fever
  - general ill feeling
  - swollen lymph nodes
  - swelling of the face, mouth, and tongue
  - hives
  - itching
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - joint pain
  - skin rash

- **Eye problems.** If you have atopic dermatitis, tell your healthcare provider if you have any new or worsening eye problems, including eye pain or changes in vision.
- **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
  - shortness of breath
  - persistent fever
  - chest pain
  - a feeling of pins and needles or numbness of your arms or legs

The most common side effects of DUPIXENT include:

- injection site reactions
- eye and eyelid inflammation, including redness, swelling, and itching (if you also have atopic dermatitis)
- pain in the throat (oropharyngeal pain)
- cold sores in your mouth or on your lips

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

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

What are the ingredients in DUPIXENT?
Active ingredient: dupilumab
Inactive ingredients: L-arginine hydrochloride, L-histidine, polysorbate 80, sodium acetate, sucrose, and water for injection.

REGENERON SANOFI GENZYME

Manufactured by: Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591 U.S. License No. 1760
Marketed by: sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and Regeneron Pharmaceu icals, Inc. (Tarrytown, NY 10591)

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

This Patient Informa ion has been approved by the U.S. Food and Drug Administration. Issued: March 2019

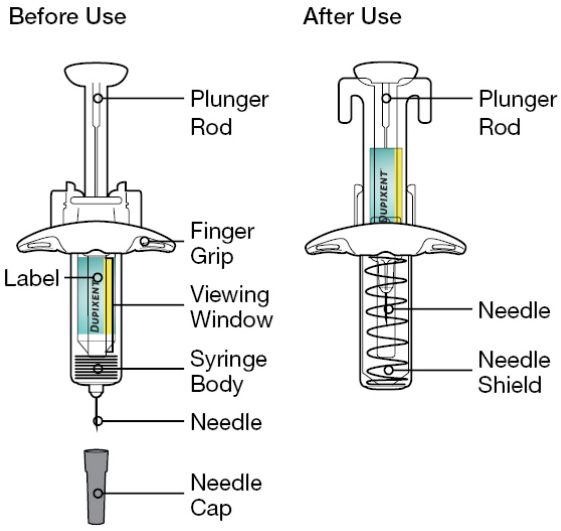
Instructions for Use

DUPIXENT® (DU-pix'-ent)
(dupilumab)
injection, for subcutaneous use
Single-Dose Pre-filled Syringe with Needle Shield

Read this Instructions for Use before using the DUPIXENT Pre-filled Syringe. **Do not inject yourself or someone else until you have been shown how to inject DUPIXENT.** In adolescents 12 years of age and older, it is recommended that DUPIXENT be administered by or under supervision of an adult. Your healthcare provider can show you or your caregiver how to prepare and inject a dose of DUPIXENT before you try to do it yourself the first time. Keep these instructions for future use. Call your healthcare provider if you have any questions.

This device is a **Single-Dose** Pre-filled Syringe (called "DUPIXENT Syringe" in these instructions). It contains 300 mg of DUPIXENT for injection under the skin (subcutaneous injection).

The parts of the DUPIXENT Syringe are shown below:



Important Information	
• Read all of the instructions carefully before using the DUPIXENT Syringe. • Ask your healthcare provider how often you will need to inject the medicine. • Rotate the injection site each time you inject. • **Do not** use the DUPIXENT Syringe if it has been dropped on a hard surface or damaged. • **Do not** use the DUPIXENT Syringe if the Needle Cap is missing or not securely attached. • **Do not** touch the Plunger Rod until you are ready to inject. • **Do not** inject through clothes. • **Do not** get rid of any air bubble in the DUPIXENT Syringe.	• To reduce the risk of accidental needle sticks, each pre-filled syringe has a Needle Shield that is automatically activated to cover the needle after you have given your injection. • **Do not** pull back on the Plunger Rod at any time. • **Do not** remove the Needle Cap until just before you give the injection. • Throw away (dispose of) the used DUPIXENT Single-Dose Pre-filled Syringe right away after use. See "Step 13: Dispose" below. • **Do not re-use a DUPIXENT Single-Dose Pre-filled Syringe**.
How should I store DUPIXENT? • **Keep DUPIXENT Syringes and all medicines out of the reach of children.** • Store DUPIXENT Syringes in the refrigerator between 36ºF and 46ºF (2ºC and 8ºC).	

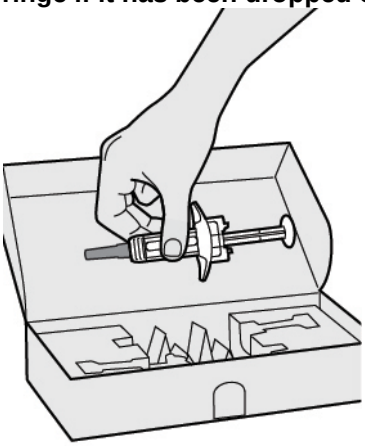
- Store DUPIXENT Syringes in the original carton to protect them from light.
- DUPIXENT Syringes can be stored at room temperature up to 77°F (25°C) up to 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.
- **Do not** shake the DUPIXENT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

Step 1: Remove

Remove the DUPIXENT Syringe from the carton by holding the middle of the Syringe Body.

Do not pull off the Needle Cap until you are ready to inject.

Do not use the DUPIXENT Syringe if it has been dropped on a hard surface or damaged.

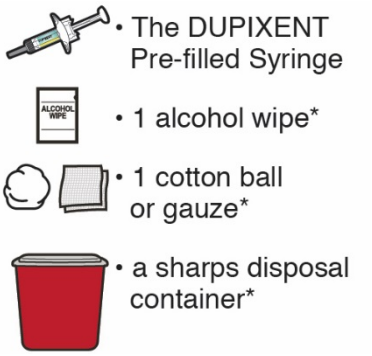


Step 2: Prepare

Ensure you have the following:

- the DUPIXENT Pre-filled Syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a sharps disposal container* (See Step 13)

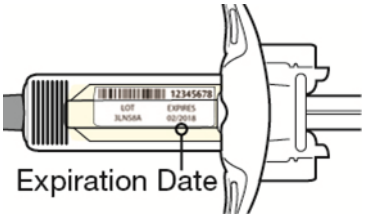
**Items not included in the carton*



Step 3: Check
When you receive your DUPIXENT Syringes, always check to see that:

- you have the correct medicine and dose.
- the expiration date on the Single-Dose Pre-filled Syringe has not passed.

Do not use the DUPIXENT Syringe if the expiration date has passed.



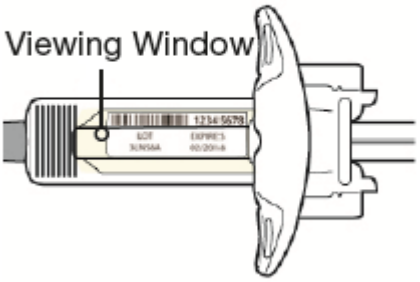
Step 4: Inspect

Look at the medicine through the Viewing Window on the DUPIXENT Syringe:

Check to see if the liquid is clear and colorless to pale yellow.

Note: You may see an air bubble, this is normal.

Do not use the DUPIXENT Syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.



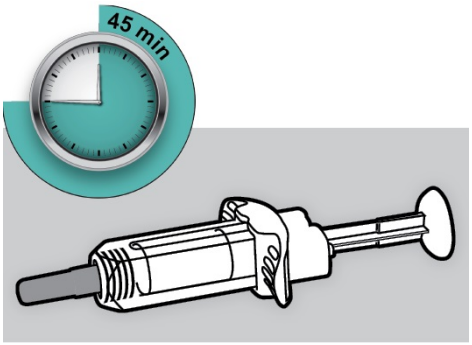
Step 5: Wait 45 minutes

Lay the DUPIXENT Syringe on a flat surface and let it naturally warm to room temperature for at least 45 minutes.

Do not heat the DUPIXENT Syringe.

Do not put the DUPIXENT Syringe into direct sunlight.

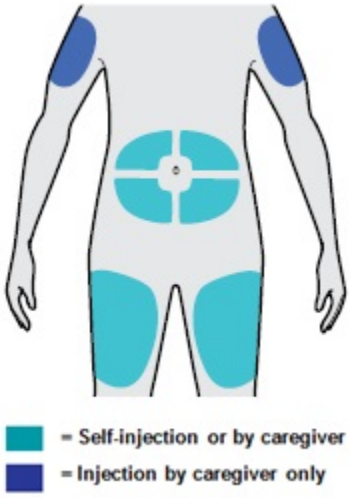
Do not keep DUPIXENT Syringes at room temperature for more than 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.



Step 6: Choose your injection site

- You can inject into your thigh or stomach, except for the 2 inches (5 cm) around your belly button (navel).
- If a caregiver injects your dose, they can also use the outer area of the upper arm.
- Choose a different site each time you inject DUPIXENT.

Do not inject into skin that is tender, damaged, bruised or scarred.



Step 7: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

Do not touch the injection site again or blow on it before the injection.

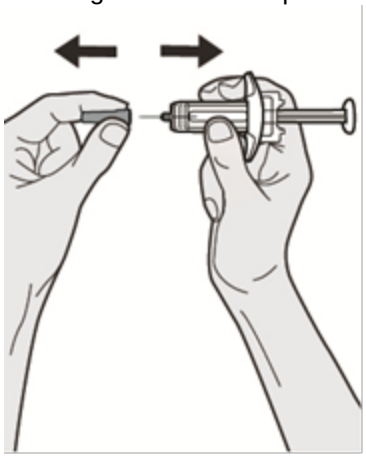
Step 8: Remove Needle Cap

Hold the DUPIXENT Syringe in the middle of the Syringe Body with the Needle pointing away from you and pull off the Needle Cap.

Do not put the Needle Cap back on.

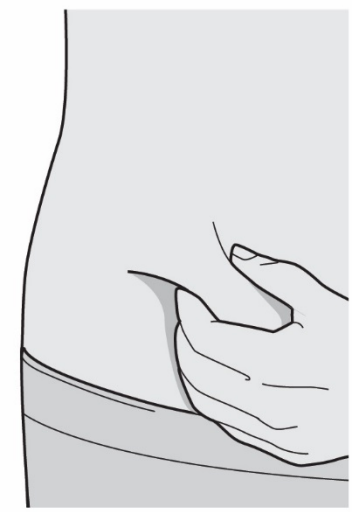
Do not touch the Needle.

Inject your medicine right away after removing the Needle Cap.



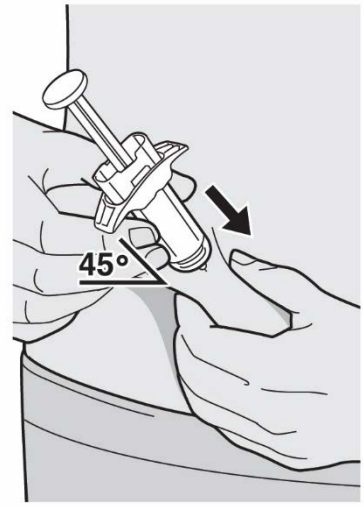
Step 9: Pinch

Pinch a fold of skin at the injection site (thigh or stomach, except 2 inches around your belly button, or outer area of the upper arm if injected by your caregiver). The figure below shows an example of pinching a fold of skin on your stomach.



Step 10: Insert

Insert the Needle completely into the fold of the skin at about a 45º angle.



Step 11: Push

Relax the pinch.

Push the Plunger Rod down slowly and steadily as far as it will go until the DUPIXENT Syringe is empty.

Note: You will feel some resistance. This is normal.

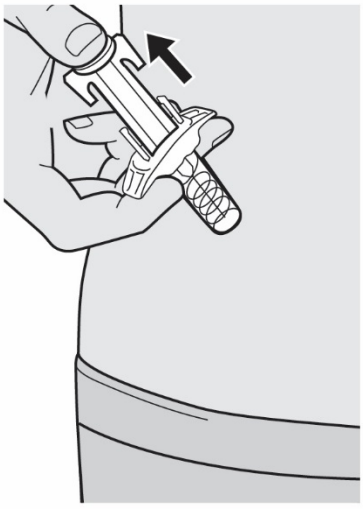
Step 12: Release and Remove

Lift your thumb to release the Plunger Rod until the Needle is covered by the Needle Shield and then remove the Syringe from the injection site.

Lightly press a cotton ball or gauze on the injection site if you see any blood.

Do not put the Needle Cap back on.

Do not rub your skin after the injection.



Step 13: Dispose

Put your used Needles, DUPIXENT Syringes, and Needle Caps in a FDA-cleared sharps disposal container right away after use.

Do not dispose of (throw away) Needles, DUPIXENT Syringes, and Needle Caps in your household trash.

If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:

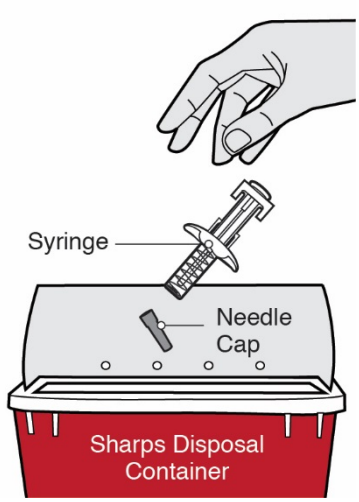
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used Needles and Syringes.

For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal

Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Do not put the Needle Cap back on.



This Instructions for Use has been approved by the U.S. Food and Drug Administration.

REGENERON SANOFI GENZYME

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

Marketed by:
sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

Issue Date: March 2019

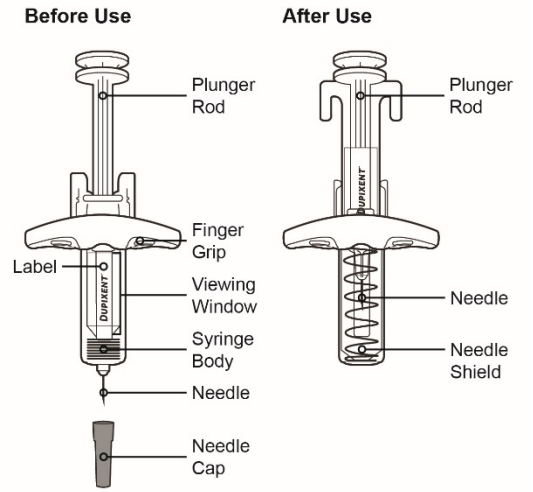
Instructions for Use

DUPIXENT® (DU-pix'-ent)
(dupilumab)
injection, for subcutaneous use
Single-Dose Pre-filled Syringe with Needle Shield

Read this Instructions for Use before using the DUPIXENT Pre-filled Syringe. **Do not inject yourself or someone else until you have been shown how to inject DUPIXENT.** In adolescents 12 years of age and older, it is recommended that DUPIXENT be administered by or under supervision of an adult. Your healthcare provider can show you or your caregiver how to prepare and inject a dose of DUPIXENT before you try to do it yourself the first time. Keep these instructions for future use. Call your healthcare provider if you have any questions.

This device is a **Single-Dose** Pre-filled Syringe (called "DUPIXENT Syringe" in these instructions). It contains 200 mg of DUPIXENT for injection under the skin (subcutaneous injection).

The parts of the DUPIXENT Syringe are shown below:



Important Information	
• Read all of the instructions carefully before using the DUPIXENT Syringe. • Ask your healthcare provider how often you will need to inject the medicine. • Rotate the injection site each time you inject. • **Do not** use the DUPIXENT Syringe if it has been dropped on a hard surface or damaged. • **Do not** use the DUPIXENT Syringe if the Needle Cap is missing or not securely attached. • **Do not** touch the Plunger Rod until you are ready to inject. • **Do not** inject through clothes. • **Do not** get rid of any air bubble in the DUPIXENT Syringe.	• To reduce the risk of accidental needle sticks, each pre-filled syringe has a Needle Shield that is automatically activated to cover the needle after you have given your injection. • **Do not** pull back on the Plunger Rod at any time. • **Do not** remove the Needle Cap until just before you give the injection. • Throw away (dispose of) the used DUPIXENT Single-Dose Pre-filled Syringe right away after use. See "Step 13: Dispose" below. • **Do not re-use a DUPIXENT Single-Dose Pre-filled Syringe**.
How should I store DUPIXENT? • **Keep DUPIXENT Syringes and all medicines out of the reach of children.** • Store DUPIXENT Syringes in the refrigerator between 36ºF and 46ºF (2ºC and 8ºC). • Store DUPIXENT Syringes in the original carton to protect them from light.	

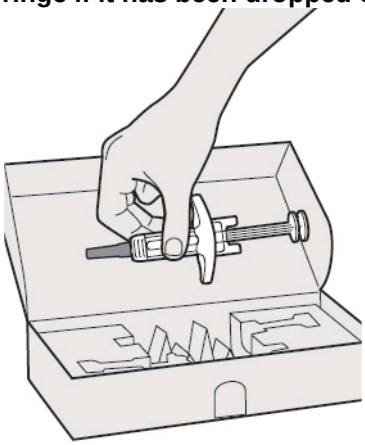
- DUPIXENT Syringes can be stored at room temperature up to 77°F (25°C) up to 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.
- **Do not** shake the DUPIXENT Syringe.
- **Do not** heat the DUPIXENT Syringe.
- **Do not** freeze the DUPIXENT Syringe.
- **Do not** put the DUPIXENT Syringe into direct sunlight.

Step 1: Remove

Remove the DUPIXENT Syringe from the carton by holding the middle of the Syringe Body.

Do not pull off the Needle Cap until you are ready to inject.

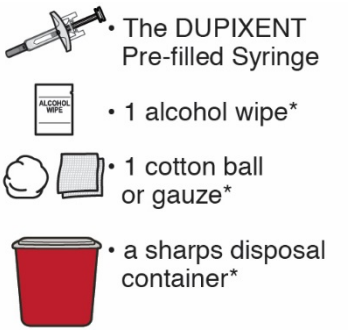
Do not use the DUPIXENT Syringe if it has been dropped on a hard surface or damaged.



Step 2: Prepare

Ensure you have the following:
- the DUPIXENT Pre-filled Syringe
- 1 alcohol wipe*
- 1 cotton ball or gauze*
- a sharps disposal container* (See Step 13)

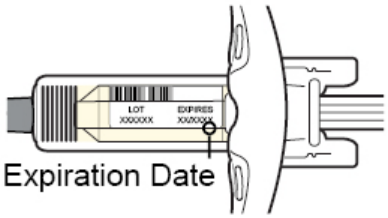
**Items not included in the carton*



Step 3: Check
When you receive your DUPIXENT Syringes, always check to see that:

- you have the correct medicine and dose.
- the expiration date on the Single-Dose Pre-filled Syringe has not passed.

Do not use the DUPIXENT Syringe if the expiration date has passed.



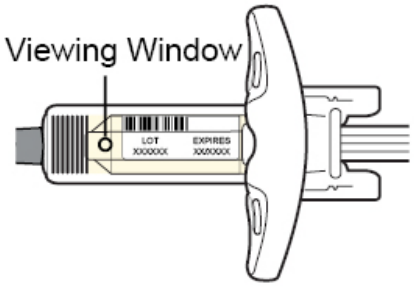
Step 4: Inspect

Look at the medicine through the Viewing Window on the DUPIXENT Syringe:

Check to see if the liquid is clear and colorless to pale yellow.

Note: You may see an air bubble, this is normal.

Do not use the DUPIXENT Syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.



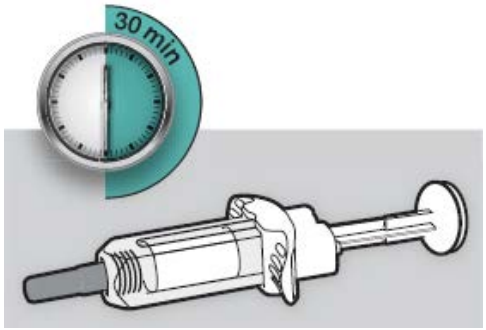
Step 5: Wait 30 minutes

Lay the DUPIXENT Syringe on a flat surface and let it naturally warm to room temperature for at least 30 minutes.

Do not heat the DUPIXENT Syringe.

Do not put the DUPIXENT Syringe into direct sunlight.

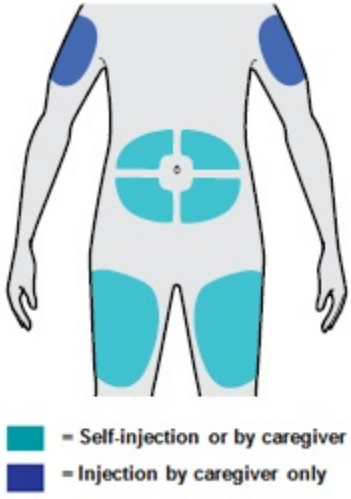
Do not keep DUPIXENT Syringes at room temperature for more than 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.



Step 6: Choose your injection site

- You can inject into your thigh or stomach, except for the 2 inches (5 cm) around your belly button (navel).
- If a caregiver injects your dose, they can also use the outer area of the upper arm.
- Choose a different site each time you inject DUPIXENT.

Do not inject into skin that is tender, damaged, bruised or scarred.



Step 7: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

Do not touch the injection site again or blow on it before the injection.

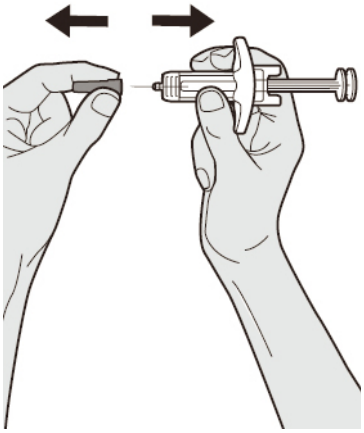
Step 8: Remove Needle Cap

Hold the DUPIXENT Syringe in the middle of the Syringe Body with the Needle pointing away from you and pull off the Needle Cap.

Do not put the Needle Cap back on.

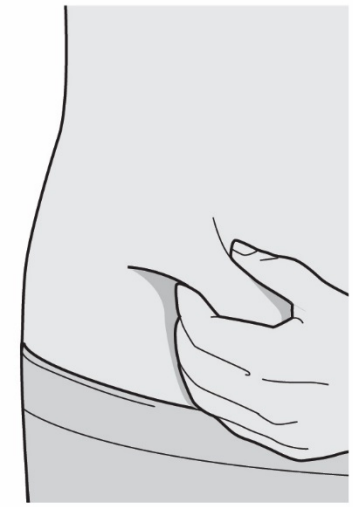
Do not touch the Needle.

Inject your medicine right away after removing the Needle Cap.



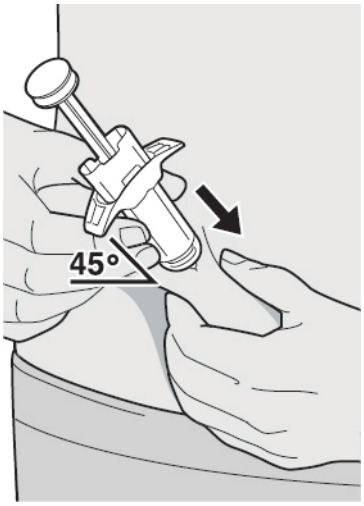
Step 9: Pinch

Pinch a fold of skin at the injection site (thigh or stomach, except 2 inches around your belly button, or outer area of the upper arm if injected by your caregiver). The figure below shows an example of pinching a fold of skin on your stomach.



Step 10: Insert

Insert the Needle completely into the fold of the skin at about a 45º angle.

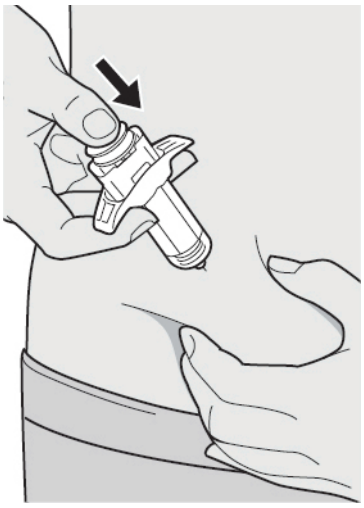


Step 11: Push

Relax the pinch.

Push the Plunger Rod down slowly and steadily as far as it will go until the DUPIXENT Syringe is empty.

Note: You will feel some resistance. This is normal.



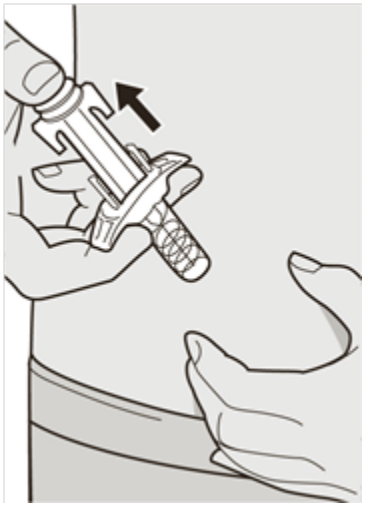
Step 12: Release and Remove

Lift your thumb to release the Plunger Rod until the Needle is covered by the Needle Shield and then remove the Syringe from the injection site.

Lightly press a cotton ball or gauze on the injection site if you see any blood.

Do not put the Needle Cap back on.

Do not rub your skin after the injection.



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- made of a heavy-duty plastic,
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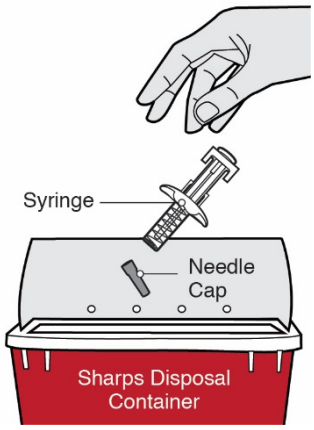
Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Do not put the Needle Cap back on.



This Instructions for Use has been approved by the U.S. Food and Drug Administration.

REGENERON SANOFI GENZYME

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

Marketed by:
sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

Issue Date: March 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s012

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sBLA
Application Number(s)	761055/S-012
Priority or Standard	Priority
Submit Date(s)	September 11, 2018
Received Date(s)	September 11, 2018
PDUFA Goal Date	March 11, 2019
Division/Office	DDDP/ODE III
Review Completion Date	See DARRTS signature page
Established Name	DUPIXENT
Trade Name	Dupilumab
Pharmacologic Class	interleukin inhibitor
Code name	Not applicable
Applicant	Regeneron Pharmaceuticals, Inc.
Formulation(s)	Solution
Dosing Regimen	less than 60 kg: 400 mg then 200 mg every other week 60 kg or more: 600 mg then 300 mg every other week
Applicant Proposed Indication(s)/Population(s)	treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable

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Reviewers Team and Signature Approval Section

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Clinical Pharmacology Reviewer	Xiaohui (Michelle) Li, PhD	OCP/DCP III	Sections: 6, 13.4	**Select one:** __X__ Authored ____ Acknowledged ____ Approved
	Signature: See DARRTS signature page			
Clinical Pharmacology Team Leader	Jie (Jack) Wang, PhD	OCP/DCP III	Sections: 6, 13.4	**Select one:** ____ Authored ____ Acknowledged __X__ Approved
	Signature: See DARRTS signature page			
Pharmacometrics Reviewer	Youwei Bi, PhD	OCP/DPM	Sections: 6, 13.4	**Select one:** __X__ Authored ____ Acknowledged ____ Approved
	Signature: See DARRTS signature page			
Pharmacometrics Team Leader	Jiang Liu, PhD	OCP/DPM	Sections: 6, 13.4	**Select one:** ____ Authored ____ Acknowledged __X__ Approved
	Signature: See DARRTS signature page			
Biostatistics Reviewer	Carin Kim, PhD	OTS/OB/DBIII	Sections: 7.1, 7.2, 7.4	**Select one:** __X__ Authored ____ Acknowledged ____ Approved
	Signature: See DARRTS signature page			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Biostatistics Team Leader	Mohamed Alosh, PhD	OTS/OB/DBIII	Sections: 7.1, 7.2, 7.4	**Select one:** ____ Authored ____ Acknowledged __X__ Approved
	Signature: See DARRTS signature page			
OB Division Director (DBIII)	Laura Lee Johnson, PhD	OTS/OB/DBIII	Sections: 7.1, 7.2, 7.4	**Select one:** ____ Authored ____ Acknowledged __X__ Approved
	Signature: See DARRTS signature page			
Clinical Reviewer	Brenda Carr, MD	ODE III/DDDP	Sections: 1.1, 1.2, 1.3, 1.4, 2, 3, 4.1, 7.3, 7.4, 8, 9, 10, 11, 12, 13.1, 13.2	**Select one:** __X__ Authored ____ Acknowledged ____ Approved
	Signature: See DARRTS signature page			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ ACKNOWLEDGED/ APPROVED	AUTHORED/ ACKNOWLEDGED/ APPROVED
Clinical Team Leader	Snezana Trajkovic, MD	ODE III/DDDP	Sections: 1.1, 1.2, 1.3, 1.4, 2, 3, 4.1, 7.3, 7.4, 8, 9, 10, 11, 12, 13.1, 13.2	**Select one:** ____ Authored ____ Acknowledged __X__ Approved
	Signature: See DARRTS signature page			
Signatory	Kendall A. Marcus, MD	ODE III/DDDP	Section: 1	**Select one:** ____ Authored ____ Acknowledged __X__ Approved
	Signature: See DARRTS signature page			

Additional Reviewers of Application

DDS	Tatiana Oussova, MD, MPH
COA	Selena Daniels, PharmD, MS/Elektra Papadopoulos, MD
OPDP	Laurie Buonaccorsi, PharmD/Matthew Falter, PharmD
PLT	Maria Nguyen, MSHS, BSN, RN/Sharon R. Mills, BSN, RN, CCRP/LaShawn Griffiths, MSHS-PH, BSN, RN
OSI	Cheryl Grandinetti, PharmD/Phillip Kronstein, MD
OSE - SRPM	Tri Bui-Nguyen, PhD
OSE/DMEPA	Madhuri Patel, PharmD/Teresa McMillan, PharmD

COA = Clinical Outcomes Assessment
DDS = Deputy Director for Safety
DMEPA = Division of Medication Error Prevention and Analysis
FOS = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
SRPM = Safety Regulatory Project Manager

Glossary

AKC	atopic keratoconjunctivitis
AD	atopic dermatitis
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse events of special interest
ANCOVA	analysis of covariance
BLA	biologics license application
BSA	body surface area
CMQ	customized MedDRA query
EASI	Eczema Area and Severity Index
ECG	electrocardiogram
E-R	exposure-response
IGA	Investigator's Global Assessment
IL	interleukin
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
NRS	numeric rating scale
OLE	open-label extension
PCSV	potentially clinically significant values
PK	pharmacokinetics
popPK	population pharmacokinetics
PPS	per protocol set
PY	patient years
QW	once weekly
Q2W	every 2 weeks
Q4W	every 4 weeks
SAE	serious adverse event
sBLA	supplemental biologics license application
SC	subcutaneous
SOC	system organ class
SS	steady-state
SU	safety update
TCS	topical corticosteroids
TCI	topical calcineurin inhibitors
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Dupilumab is a recombinant human immunoglobulin-G4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha (IL-4Rα) sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor, and both IL-4 and IL-13 signaling through the Type II receptor. It belongs to the pharmacologic class of immunomodulators, IL inhibitors.

Dupilumab is marketed under the proprietary name DUPIXENT® and is licensed for the following indications:

- Treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
- It can be used with or without topical corticosteroids (TCS).
- As an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

Also see Section 3.1.

The supplemental biologics license application (sBLA) proposes expansion of the AD indication to allow for the "treatment of patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable." The proposed new indication would allow use of concomitant TCS, as is the case for adults. TCIs may also be used, but should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas.

Table 1. Recommended Dosing of Dupilumab for Adolescent Patients (12 to 17 Years of Age)

Body Weight	Initial Dose	Subsequent Doses (every other week)
Less than 60 kg	400 mg (two 200 mg injections)	200 mg
60 kg or more	600 mg (two 300 mg injections)	300 mg

1.2. Conclusions on the Substantial Evidence of Effectiveness

To establish the effectiveness of dupilumab in the treatment of moderate-to-severe AD in adolescent subjects, the Applicant submitted results from a single randomized,

multicenter, placebo-controlled phase 3 trial that evaluated two dosing frequencies: every 2 weeks (Q2W) and every 4 weeks (Q4W).

The trial randomized 251 adolescent subjects (12 to <18 years of age) with moderate-to-severe AD defined as having an Investigator's Global Assessment (IGA) score of at least 3 (moderate), Eczema Area and Severity Index (EASI) ≥12, and Body Surface Area (BSA) ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with at least 2-grade improvement from baseline, at week 16.

Both dupilumab Q2W and Q4W dosing regimens were statistically superior to placebo (p-values <0.001) for the primary and secondary efficacy endpoints at week 16. However, efficacy outcomes were higher for the Q2W regimen. The proportion of responders for the primary endpoint was 24% in the Q2W group and 18% in the Q4W group.

The Applicant provided substantial evidence of effectiveness of dupilumab for treatment of adolescent patients (12 to 17 years of age) with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dupilumab is a recombinant human immunoglobulin-G4 monoclonal antibody that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4 receptor alpha sub-unit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is marketed under the proprietary name “Dupixent” and is licensed for the following indications:

- treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. It can be used with or without TCS.
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

The Applicant proposes expansion of the AD indication to allow for the “treatment of patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.”

To establish the effectiveness of dupilumab in the treatment of moderate-to-severe AD in adolescent subjects, the Applicant submitted results from a single randomized, multicenter, placebo-controlled phase 3 trial that evaluated two dosing frequencies: every 2 weeks (Q2W) and every 4 weeks (Q4W). The trial randomized 251 adolescent subjects (12 to <18 years of age) with moderate-to- severe AD defined as having IGA score of at least 3 (moderate), EASI ≥12, and BSA ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with at least 2-grade improvement from baseline, at week 16. Both dupilumab Q2W and Q4W were statistically superior to placebo (p-values <0.001) for the primary and the secondary efficacy endpoints at week 16. However, efficacy outcomes were higher for the Q2W regimen.

The safety database was comprised of 322 adolescent subjects (12 to 17 years of age) with moderate-to-severe AD who had received at least one dose of dupilumab by data cut-point for the sBLA. No deaths occurred in the development program. The single subject who experienced a serious adverse event (SAE) in the primary safety group was in the placebo group (the event was appendicitis). Of the four subjects who experienced SAEs in the open-label extension (OLE) study, only one experienced an event (injection site cellulitis) where a relationship to treatment was reasonably possible. However, there was no information to implicate dupilumab itself in the occurrence of this event; it could have been related entirely to injection procedures. One subject experienced a treatment-emergent AE (TEAE) that led to permanent discontinuation of study treatment in the pivotal and OLE studies. That

subject was in the placebo group and was withdrawn due to worsening of AD. In the primary safety group, all severe TEAEs of AD occurred in the dupilumab Q4W group. This could be interpreted as potential supportive evidence for the more frequent Q2W dosing regimen. Generally, the safety profiles between the Q4W and Q2W regimens were similar. The most-commonly reported TEAEs were upper respiratory tract infection and nasopharyngitis. Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo, consistent with the known safety profile for dupilumab in the adult AD population. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The patterns of occurrence and course of conjunctivitis and keratitis events in dupilumab-treated adolescents were similar to what was seen in and labeled for adults with AD.

The Applicant comprehensively evaluated the safety of dupilumab in subjects 12 to17 years of age with moderate-to-severe AD. Safety assessments in the program were appropriate for the study population and indication and for what is known about the safety profile of dupilumab. The data allowed for adequate characterization of the safety of dupilumab in the target population of adolescent subjects. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD.

The medical officer concludes that the Applicant has established that the benefits of dupilumab for treatment of patients 12 to 17 years of age with moderate-to-severe AD, whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable, outweigh its risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. The hazard ratio for onset of AD in adolescence (12 to 17 years) has been reported as 2.04 (95% CI 1.66-2.49) compared to age of onset younger than 2 years. The prevalence of AD in individuals 13 to 17 years of age in the United States has been reported as 8.6%. • AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In adolescents, the presentation is similar to that in adults and is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck, volar aspects of the wrists. AD may be generalized. Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.	While AD is not a life-threatening condition, it may be serious. It may significantly impact the quality of life not only of the patient, but also of family members. The intense pruritus may disrupt sleep, which can have carryover effects of tiredness during the day. The dysfunctional skin barrier, further compromised from scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. Affected individuals may experience depression and other psychiatric associations, including impaired psychosocial functioning, social isolation, and social embarrassment. A longitudinal cohort study conducted in adolescents and adults with AD found that patients may be at increased risk for major depression, depressive disorders and anxiety disorders. Patients with AD have been found to have an increased risk of suicidal ideation and suicide attempts compared with individuals without AD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• For the Applicant's target population, the only available FDA-approved systemic treatment is corticosteroids. The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern with their use in children and adolescents is the risk of decreased linear growth during treatment. Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including adolescents. Its drawbacks include a potentially time-intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. • Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil. The reported effectiveness for the products varies from "efficacious" (cyclosporine) to "inconsistent" (mycophenolate mofetil). Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).	The medical need of adolescents with moderate-to-severe AD is not currently being adequately met by available therapies. Approval of dupilumab would represent an important addition to the treatment options for adolescents with moderate-to-severe AD that is not manageable by topical therapies. Approved or licensed treatment options are extremely limited for this population. In the medical officer's opinion, dupilumab would considerably advance the state of the treatment armamentarium for these patients. It would represent the first systemic product approved or licensed for treatment of AD in this population since corticosteroids. Dupilumab would represent a safe and effective alternative to corticosteroids, the only approved systemic treatment for this indication and a treatment that is generally not recommended for treatment of AD. Additionally, dupilumab would represent a safe and effective alternative to the several systemic immunomodulating agents that are used off-label for treatment of this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• To establish the effectiveness of dupilumab in the treatment of moderate-to-severe AD in adolescent subjects, the Applicant submitted results from a single randomized, multicenter, placebo-controlled phase 3 trial that evaluated two dosing every 2 weeks (Q2W) and every 4 weeks (Q4W). The trial randomized 251 adolescent subjects (12 to <18 years of age) with moderate-to-severe AD, defined as an IGA score of at least 3 (moderate), EASI ≥12, and BSA ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with at least 2-grade improvement from baseline, at week 16. Both dupilumab Q2W and Q4W were statistically superior to placebo (p-values <0.001) for the primary and the secondary efficacy endpoints at week 16. However, efficacy outcomes were higher for the Q2W regimen. The proportion of responders for the primary endpoint was 24% in the Q2W group and 18% in the Q4W group.	The medical officer concludes that the submitted evidence has met the evidentiary standard for providing substantial evidence of effectiveness. The Applicant has established that dupilumab is effective for treatment of the target AD population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	• The Applicant comprehensively evaluated the safety of dupilumab in subjects 12 to 17 years of age with moderate-to- severe AD. Safety assessments in the program were appropriate for the study population and indication and for what is known about the safety profile of dupilumab. The data allowed for adequate characterization of the safety of dupilumab in the target population of adolescent subjects. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD. The most-commonly reported TEAEs were upper respiratory tract infection and nasopharyngitis. Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The patterns of occurrence and course of conjunctivitis and keratitis events in dupilumab-treated adolescents were similar to what was seen in and labeled for adults with AD.	The size of the safety database and the scope of the safety analyses were sufficient to characterize the safety profile of dupilumab in the target population. The safety evaluation identified no new signals or concerns; the safety profile in adolescents was similar to that observed in adults with AD. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• No serious safety concerns were identified that might require risk management beyond labeling and routine pharmacovigilance. No serious safety concerns were identified that warranted consideration of a Risk Evaluation and Mitigation Strategy. • AD occurs most commonly in children, and the safety and efficacy of dupilumab for treatment of AD in children have not been established. The Applicant has an Agreed Initial Pediatric Study Plan which covers cohorts down to 6 months of age. These required pediatric assessments are detailed in the approval letter for the original BLA submission. The study in adolescents is the first completed study of those required pediatric assessments. • Pediatric studies are waived for subjects younger than 6 months because study of these subjects would be impossible or highly impractical to conduct, since dupilumab is being developed for the treatment of moderate-to-severe AD in pediatric patients who are not adequately controlled with, or who are intolerant to TCS medications, and it would be impractical to make this determination in patients younger than 6 months of age.	Information from the ongoing OLE study, along with product labeling and routine pharmacovigilance activities should serve as adequate risk mitigation strategies.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO)	Section 7.2.6
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 7.2.4
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

Analysis of Condition

AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years.[1] The hazard ratio for onset of AD in adolescence (12 to 17 years) has been reported as 2.04 (95% CI 1.66-2.49) compared to age of onset younger than 2 years.[2] Shaw et al. reported the prevalence of AD in individuals 13 to 17 years of age in the United States to be 8.6%.[3] For 10 to 30% of individuals, AD persists into the adult years, and, for a smaller proportion of subjects, the disease initially presents in adulthood.[1] A population-based study found a prevalence of 3.2% for AD in adults in the United States.[4]

AD is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy). In adolescents, the presentation is similar to that in adults and is particularly characterized by lichenified plaques in flexural regions of the extremities (antecubital and popliteal) and that may also involve the neck and volar aspects of the wrists. AD may be generalized.

Common comorbidities include asthma, allergic rhinitis/rhinoconjunctivitis, and food allergies.[1,2] Comorbidities involving the eyes include atopic keratoconjunctivitis (AKC),[2] a chronic, intensely pruritic, allergic disease that is most often seen in adults with AD.[5] Onset of AKC is typically in late adolescence or early adulthood.[5] Patients with AD often experience sleep disturbance, largely attributable to the associated extreme pruritus. During disease flares, approximately 80% of patients may experience disturbed sleep,[1] and the disruption in sleep could have carryover effects to disrupt school performance. Sleep disturbance in the AD patient may also disrupt the sleep of family members.[1] The

[1] Eichenfield LF et al., 2014, Guidelines of care for the management of atopic dermatitis Section 1. Diagnosis and assessment of atopic dermatitis, J Am Acad Dermatol, 70(2):338-51.
[2] Weston WL and W. Howe, 2019, Atopic dermatitis (eczema): Pathogenesis, clinical manifestations, and diagnosis of atopic dermatitis. Dellavalle RP, Levy ML, Fowler J, eds. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on February 10, 2019).
[3] Shaw TE et al, 2011, Eczema prevalence in the United States: Data from the 2003 National Survey of Children's Health, J Invest Dermatol., 131:67–73.
[4] Silverberg JI and Hanifin JM, 2013, Adult eczema prevalence and associations with asthma and other health and demographic factors: A US population–based study, J Allergy Clin Immunol, 132:1132-8.
[5] Hamrah P and Dana R. Atopic keratoconjunctivitis. Trobe J, ed. UpToDate. Waltham, MA: UpToDate Inc. http://www.uptodate.com (Accessed on February 11, 2019).

disease may also have impact on mood, and affected individuals may experience depression and also impaired psychosocial functioning, social isolation, and social embarrassment.[1,2,6] A longitudinal cohort study conducted in adolescents and adults with AD found that patients with AD may be at increased risk for major depression, depressive disorders, and anxiety disorders.[2] Patients with AD have been found to have an increased risk of suicidal ideation and suicide attempts compared with individuals without AD.[2]

Patients with AD are predisposed to colonization or infection by microbes, particularly *Staphylococcus aureus* and herpes simplex virus. The susceptibility to *S. aureus* is related to multiple factors, including the abnormal skin barrier function and the production of serine proteases that degrade the skin barrier.[7]

The most common laboratory finding is an elevated IgE.[1] Approximately 80% of the AD population has elevated IgE and/or shows immediate skin test positivity to allergens. However, 20% of patients show no IgE to tested food or inhalant allergens. Some patients with severe AD have normal IgE levels. Additionally, increased allergen-specific IgE is found in 55% of the general population in the United States. Thus, this finding is nonspecific.[1]

The pathogenesis involves a complex interplay of genetic, immunological and environmental factors that result in abnormal skin barrier function and immune system dysfunction. Irregularities in the terminal differentiation of the epidermal epithelium lead to a faulty stratum corneum, which permits the penetration of environmental allergens.[7] The exposure to allergens may ultimately result in systemic sensitization and may predispose AD patients to other conditions, such as asthma and food allergies.[7]

Acute AD is associated with cytokines produced by T helper 2-type cells (as well as other T-cell subsets and immune elements).[7] These cytokines are thought to play an important role in the inflammatory response of the skin, and IL-4 and IL-13 may have distinct functional roles in T helper 2-type cells inflammation.[8] IL-4 has been shown to stimulate IgE production from B cells.[9] IL-13 expression correlates with disease severity and flares.[7] IL-4 mediates its biological activity via binding to IL-4Rα. IL-13 receptor alpha 1 (IL-13Rα1) may then be recruited to form a signaling complex. IL-13 mediates its biological activity via binding to IL-13Rα1 and subsequent recruitment of IL-4Rα,

[6] Drucker AM et al, 2017, The burden of atopic dermatitis: summary of a report for the National Eczema Association, J Invest Dermatol, 137(1):26-30.
[7] Leung DYM, Guttman-Yassky E, 2014, Deciphering the complexities of atopic dermatitis: Shifting paradigms in treatment approaches, J Allergy Clin Immunol, 134(4):769-79.
[8] Bao K and Reinhardt RL, 2015, The differential expression of IL-4 and IL-13 and its impact on type-2 Immunity, Cytokine, 75(1):25-37.
[9] May RD and Fung M, 2015, Strategies targeting the IL-4/IL-13 axes in disease, Cytokine, 75(1):89-116.

forming a signaling complex.[9] IL-4 and IL-13 reside on chromosome 5q23-31, among a grouping of genes related to development of allergic diseases.[9] Dupilumab inhibits IL-4 and IL-13 by blocking the shared IL-4 receptor alpha (IL-4Rα) subunit.[10]

2.2. Analysis of Current Treatment Options

FDA-approved or -licensed treatments for AD fall in the categories of corticosteroids (topical and systemic), calcineurin inhibitors (topical), phosphodiesterase-4 inhibitors (topical), and IL-4 receptor antagonist (dupilumab).

Prior to the licensure of dupilumab, corticosteroids were the only systemically-administered products that were FDA-approved for treatment of an AD indication in any age group. Corticosteroids are available for treatment of AD by various routes of administration, including topical, oral, and parenteral. Although their use may result in rapid improvement, the AD commonly recurs with worse severity on discontinuation of the systemic corticosteroids (rebound). For this reason and because of the potential for adverse effects, the American Academy of Dermatology recommends that systemic steroids generally be avoided in the treatment of AD because potential risks generally outweigh the benefits.[11] Potential adverse effects include reversible hypothalamic-pituitary-adrenal axis suppression with the potential for glucocorticoid insufficiency, hyperglycemia and other endocrine effects. A particular concern in children and adolescents is the risk of decreased linear growth during treatment.[11] Labels for systemic corticosteroids do not specify any limitations on the age of indication.

TCS represent the cornerstone of anti-inflammatory treatment of AD in all age groups.[12] Numerous TCS, in various dosage forms and potencies, are available for treatment of AD, and some are specifically indicated for pediatric use. For example, fluticasone propionate lotion, 0.05%, a medium potency TCS, is indicated for relief of the inflammatory and pruritic manifestations of AD in patients 3 months of age and older. According to product labels, TCS may be sufficiently absorbed to lead to systemic adverse effects. Additionally, pediatric patients may be more susceptible to systemic toxicity doses due to their larger skin surface to body mass ratios. Labeled potential local adverse effects include skin atrophy, striae, telangiectasias, and hypopigmentation.

[10] DUPIXENT package insert.
[11] Sidbury R et al, 2014, Guidelines of care for the management of atopic dermatitis. Section 3. Management and treatment with phototherapy and systemic agents, J Am Acad Dermatol, 71(2):327-49.
[12] Eichenfeld et al, Guidelines of care for the management of atopic dermatitis. Section 2. Management and treatment with topical therapies, J Am Acad Dermatol, 2014; 71(1):116-32.

The topical calcineurin inhibitors (TCI), tacrolimus ointment and pimecrolimus cream, are also indicated for treatment of AD in pediatric patients (2 years and older): tacrolimus for moderate-to-severe AD and pimecrolimus for mild-to-moderate AD. However, both are labeled for second-line, short-term use when other topical prescription treatments have failed or are inadvisable. The calcineurin inhibitors carry boxed warnings advising that the safety of their long-term use has not been established. More specifically, the boxed warnings describe that rare cases of malignancy (e.g., skin and lymphoma) have been reported in patients treated with TCIs; a causal relationship has not been established.

Crisaborole ointment, 2%, a phosphodiesterase-4 inhibitor, is approved for treatment of AD in pediatric patients (2 years of age and older). However, the product is indicated for a somewhat different AD population (mild-to-moderate AD) than the target population for dupilumab (moderate-to-severe AD).

Phototherapy (UVA and UVB) is considered safe and effective treatment for AD patients who are candidates for systemic therapy, including adolescents.[11] However, phototherapy may require frequent in-office visits (e.g., several times a week) and time missed from school (and, also, possibly from work for caregivers). Risks from phototherapy may vary according to the type of phototherapy and may include actinic damage, sunburn-like reactions (erythema, tenderness, pruritus), skin cancer (nonmelanoma and melanoma), and cataracts.[11] However, long-term risks from phototherapy treatment of AD in children have not been evaluated.[11]

Nonpharmacologic care is critical to AD management and includes attention to bathing practices and the regular use of moisturizers, which are available in several delivery systems, such as creams, ointments, oils, and lotions.[12] Moisturizers are directed at the xerosis and transepidermal water loss that are central elements of the disease.[12] They may also relieve pruritus, lessen erythema and fissuring, and improve lichenification. Moisturizers themselves may be the principle treatment for mild disease. Although, there are no standardized or universal recommendations regarding the use of moisturizers, repeated application of generous amounts is thought to be important and required, irrespective of the severity of disease.[12] The use of moisturizers during maintenance may stave off flares and may lessen the amounts of pharmacologic agents needed to control disease.[12]

Systemic immunomodulating agents products that are used off-label to treat AD, including in pediatric patients, include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.[11] The reported effectiveness for the products varies from “efficacious” (cyclosporine) to “inconsistent” (mycophenolate mofetil).[11] Similarly, the safety profiles vary, although each product carries the potential for significant adverse effects, and all of these product labels include boxed warnings. A small sampling of labeled risks includes nephrotoxicity (cyclosporine), cytopenias (azathioprine), hepatotoxicity (methotrexate), and embryofetal toxicity (mycophenolate mofetil).

Dupilumab is currently indicated for use in adults with AD. The Applicant proposes broadening use of dupilumab to allow for the treatment of adolescent patients who have failed topical therapies or when those therapies are inadvisable. Specifically, the Applicant proposes dupilumab for "patients 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable." FDA-approved treatment options are extremely limited for this patient population, consisting only of systemic corticosteroids; their limitations have been discussed above.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dupilumab was licensed "for the treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable" on 03/28/2017.

On 12/20/2017, the Applicant submitted supplemental BLA (sBLA)-007 which proposed dupilumab as "an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, including those with or without an eosinophilic phenotype." That sBLA was approved by the Division of Pulmonary and Rheumatology Products on 10/19/2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant has an Agreed initial Pediatric Study Plan, with the letter of agreement dated 11/10/2015. The Agreed initial Pediatric Study Plan covers pediatric age cohorts down to 6 months.

Two of the studies that were conducted under the adolescent development program are required pediatric assessments as per the approval letter for the original BLA (approval date: 03/28/2017):

3183-2 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in subjects 12 years to less than 18 years of age with moderate to severe AD.

3183-3 Conduct an open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe AD.

The open-label study is ongoing; the Applicant submitted analyses of data only pertaining to subjects ≥12 to <18 years in the sBLA.

The Applicant was granted Breakthrough Therapy designation of dupilumab for the treatment of moderate to severe AD in pediatric patients 12 to <18 years of age who are not adequately controlled with, or who are intolerant to topical medication on 10/14/2016.

See Section 9 of this review for additional information regarding the required pediatric assessments.

4 Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Study R668-AD-1526, entitled "A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥12 to <18 years of age with moderate-to-severe atopic dermatitis" was the pivotal study. It is considered a covered clinical study requiring financial disclosure as per 21 Code of Federal Regulations 54.2(e).

(b) (6) The sites were chosen primarily based on the number of enrolled subjects, positive treatment effects, reported financial disclosures, and no prior inspectional history.

(b) (6)

(b) (6) was paid $97,849 as part of the Applicant's speaker programs. (b) (6)

(b) (6)

(b) (6) was paid $144,584 for "consulting services," not otherwise specified. (b) (6)

(b) (6)

The medical officer concludes that the inspection findings (b) (6) do not affect overall subject safety or efficacy considerations.

4.2. Product Quality

In this submission, the Applicant provided no new product quality information. Therefore, section 4.2 is not applicable.

4.3. Clinical Microbiology

Section 4.3 is not applicable to this submission.

4.4. Devices and Companion Diagnostic Issues

Section 4.4 is not applicable to this submission.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In this submission, the Applicant provided no new nonclinical information. Therefore, sections 5.2, 5.3, 5.4, and 5.5 are not applicable to this review.

5.2. Referenced NDAs, BLAs, DMFs

5.3. Pharmacology

5.4. ADME/PK

5.5. Toxicology

6 Clinical Pharmacology

6.1. Executive Summary

Dupilumab (DUPIXENT) is a human immunoglobulin-G4 monoclonal antibody that inhibits IL-4 and IL-13 signaling by binding to the IL-4 receptor alpha (IL-4Rα) subunit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab was approved on March 28, 2017 for the treatment of adult patients 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 TCS. Dupilumab is administered by subcutaneous (SC) injection. The approved recommended dosing regimen is an initial dose of 600 mg, followed by 300 mg given every other week (Q2W).

In this sBLA, the Applicant has proposed to extend the currently approved age range for the AD indication to include adolescent patients ≥12 to <18 years of age. The Applicant has proposed body weight-tiered dosing regimens in adolescent AD patients:

- For adolescent AD patients weighing <60 kg: an initial dose of 400 mg (two 200 mg injections), following by 200 mg Q2W
- For adolescent patients weighing ≥60 kg: an initial dose of 600 mg (two 300 mg injections), following by 300 mg Q2W

The Applicant has submitted efficacy, safety, and pharmacokinetics (PK) data from phase 3 trial R668-AD-1526 to support the proposed indication and dosing regimens in adolescent AD patients. PK results from phase 1, phase 2, and OLE phase 3 trials (i.e., R668-AD-1607, R668-AD-1412, and R668-AD-1434, respectively) were also provided to support clinical pharmacology information of the sBLA.

6.1.1. Recommendation

From a Clinical Pharmacology standpoint, this sBLA is acceptable to support the approval of DUPIXENT (dupilumab) for the treatment of moderate-to-severe AD in adolescent patients.

6.1.2. Postmarketing Requirement and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Pharmacokinetics

In adolescents ≥12 to <18 years of age with AD who received Q2W dosing with either 200 mg (<60 kg) or 300 mg (≥60 kg) in phase 3 trial R668-AD-1526, the mean ± SD steady-state (SS) trough concentration of dupilumab was 54.5±27.0 mcg/mL.

Immunogenicity

In adolescents ≥12 to <18 years of age with AD who received Q2W dosing with either 200 mg (<60 kg) or 300 mg (≥60 kg) in phase 3 trial R668-AD-1526, the incidence for treatment emergent anti-drug antibodies (ADA) was 16% (13/81). Among the 13 ADA positive subjects, two subjects had persistent ADA. The incidence for neutralizing ADAs was 4.9%. The number of subjects was too small to draw a definitive conclusion on the clinical impact of immunogenicity, although there was no evidence of a clear correlation between ADA formation and PK or efficacy.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The efficacy and PK results in phase 3 trial R668-AD-1526 overall support the acceptability of the proposed body weight-tiered dosing regimens (200 mg/300 mg Q2W) in adolescent AD patients: for patients weighing <60 kg, an initial dose of 400 mg followed by 200 mg Q2W; for patients weighing ≥60 kg, an initial dose of 600 mg followed by 300 mg Q2W.

6.2.2.2. Therapeutic Individualization

Therapeutic individualization based on intrinsic and extrinsic factors is not necessary. Body weight has been identified a significant covariate on dupilumab PK; dupilumab

concentrations were lower in subjects with higher body weight at a given dose. At the proposed body weight-tiered dosing regimens, dupilumab concentrations were similar between subjects (<60 kg) receiving 200 mg Q2W and subjects (≥60 kg) receiving 300 mg Q2W.

6.2.2.3. Outstanding Issues

There are no outstanding issues that would preclude the approval of dupilumab for the treatment of AD in adolescent subjects from a Clinical Pharmacology's perspective.

6.3. Comprehensive Clinical Pharmacology Review

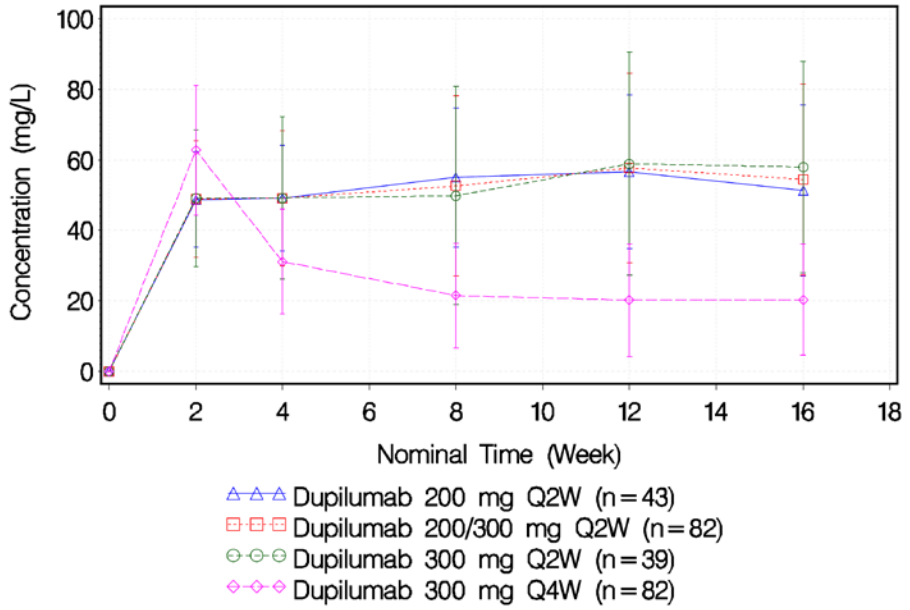
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetics

The PK of dupilumab has been previously characterized in heathy subjects, adult AD patients, and adolescent and adult asthma patients. Dupilumab exhibited nonlinear target-mediated PK with exposure increasing in a greater than dose-proportional manner.

The serum concentrations observed in study R668-AD-1526 are shown in Figure 1. The PK results showed that the SS concentrations were achieved by week 12 across the tested dosing regimens. At week 16, the mean ± SD trough concentrations of dupilumab were 54.5±27.0 mcg/mL and 19.8±15.9 mcg/mL for the 200 mg/300 mg Q2W and 300 mg Q4W dosing regimens, respectively.

Figure 1. Mean ± SD Trough Serum Dupilumab Concentrations in Trial R668-AD-1526



PK samples for assessment of serum dupilumab concentrations were collected on days 1, 15, 29, 57, 85 and 197 in study R668-AD-1526. Serum dupilumab concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA). The ELISA assay has a lower limit of quantitation (LLOQ) of 0.078 mcg/mL. See Clinical Pharmacology review for the original BLA 761055 for more details regarding the performance of the PK assay.
Source: Figure 1, Summary of Clinical Pharmacology Studies

Immunogenicity

The immunogenicity incidences in phase 3 trial R668-AD-1526 are summarized in Table 2. The incidences for treatment emergent ADA were 16% (13/81) and 20.7% (17/82) for the 200 mg/300 mg Q2W and 300 mg Q4W dosing regimens, respectively. The incidences for neutralizing ADAs were 4.9% and 4.9% for the 200 mg/300 mg Q2W and 300 mg Q4W dosing regimens, respectively.

Table 2. Immunogenicity Incidences for Anti-Drug Antibodies (ADA) in Phase 3 Trial R668-AD-1526

		Dupilumab			
	Placebo	300 mg Q4W	200 mg/300 mg Q2W	200 mg Q2W	300 mg Q2W
Number of evaluable subjects (N)	85	82	81	42	39
Treatment-emergent ADA n (%)	3 (3.5%)	17 (20.7%)	13 (16.0%)	5 (11.9%)	8 (20.5%)
Persistent ADA n (%)	1 (1.2%)	2 (2.4%)	2 (2.5%)	1 (2.4%)	1 (2.6%)

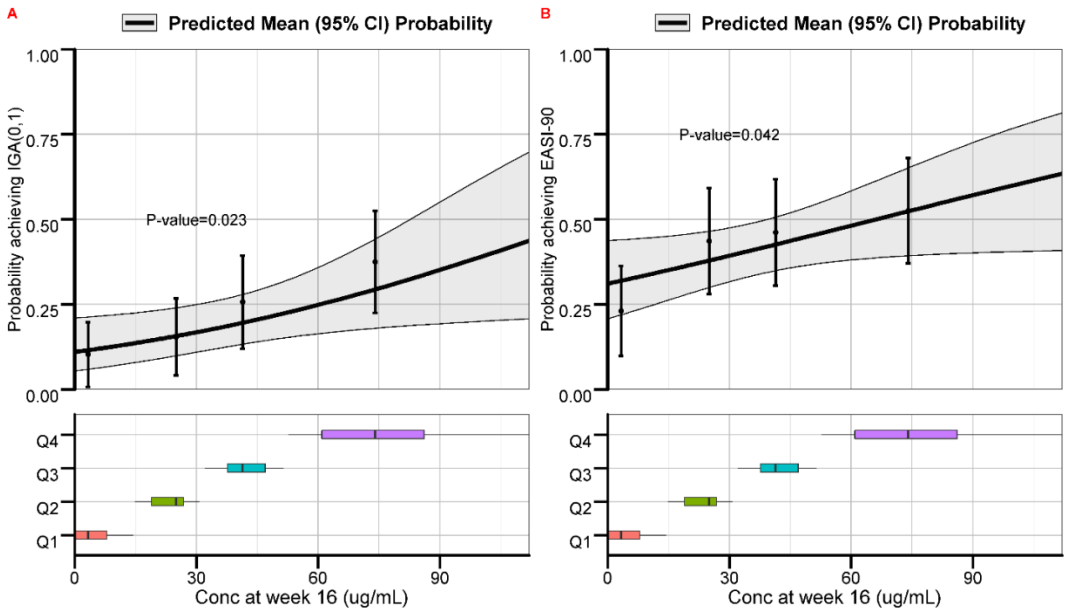
Immunogenicity samples were collected on days 1, 29, 113, and 197. Treatment emergent-ADA was defined as a negative or missing result at baseline with at least one positive postbaseline result in the ADA assay. Persistent ADA was defined as a positive result in the ADA assay detected in at least two consecutive postbaseline samples separated by at least 12-week post baseline period, with no ADA-negative results in-between, regardless of any missing sample.
Source: Table 5, Summary of Clinical of Pharmacology Studies.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

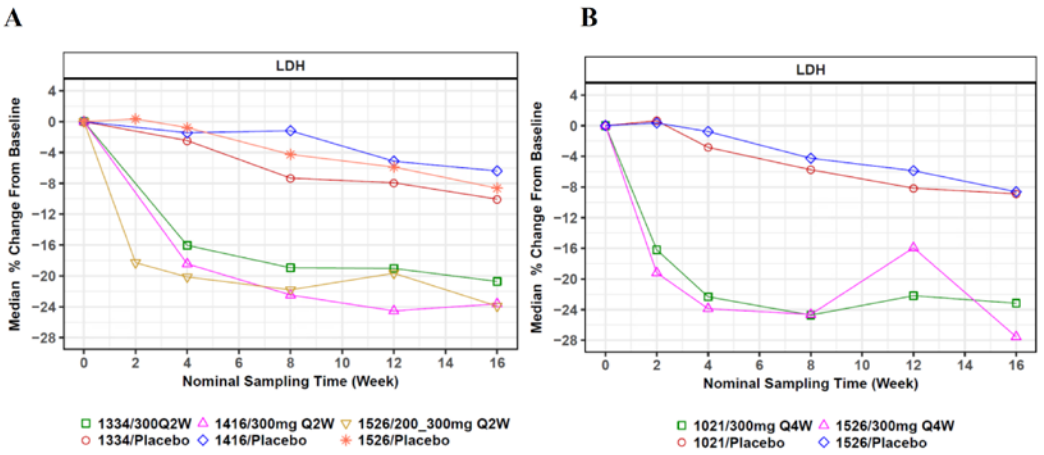
Yes, the overall efficacy data from the phase 3 trial R668-AD-1526 provide evidence that dupilumab is effective for the treatment of adolescent AD patients. See Section 7 of this multi-discipline review for details of the study design and efficacy results of the phase 3 trial. The exposure-response (E-R) relationships for efficacy provide supportive evidence of effectiveness (Figure 2). The E-R relationship revealed increasing drug effects with increasing dupilumab trough concentration in serum. The pharmacodynamic data on lactate dehydrogenase (LDH) reduction also provide supportive evidence of effectiveness (Figure 3).

Figure 2. Logistic Regression Relating Probability of Patients Achieving an (0,1) IGA Score (Panel A) or EASI-75 (Panel B) With Dupilumab Trough Concentrations at Week 16 in Adolescent Patients With Moderate-to-Severe



Among 157 adolescent patients included in the E-R analysis, the percentage of patients achieving an IGA score of 0 or 1 or a 75% reduction in EASI score was higher in quartiles of higher dupilumab concentrations. The logistic regression analysis also identified dupilumab concentration at week 16 and disease severity (baseline EASI total score) as significant covariates on both IGA (0,1) and EASI-75.
Mean regression line—black, confidence area around regression line—grey. The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (black circles) and confidence intervals (black vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Reviewer's Analysis to confirm Figure 11 and Figure 12 in Applicant's Summary of Clinical Pharmacology Studies

Figure 3. Median Percentage Change From Baseline in Lactate Dehydrogenase Following Dupilumab Treatment in Adolescent and Adult Subjects With AD



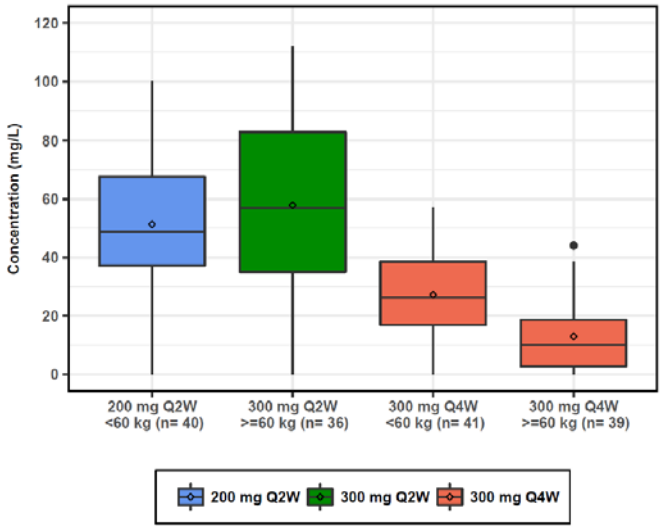
Panel A: Q2W versus placebo; Panel B, Q4W versus placebo across studies R668-AD-1021 (adults), 1334 (adults), 1416 (adults) and 1526 (adolescents). See Clinical Pharmacology review for original BLA 761055 for additional information regarding pharmacodynamic effect of dupilumab in adult AD patients.
Source: Figure 8, Applicant's Summary of Clinical Pharmacology Studies

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the efficacy and safety data from phase 3 trial R668-AD-1526 overall support that the proposed body weight-tiered dosing regimens are appropriate for the general adolescent AD patient population. See Section 7 of this multi-discipline review for details of the study design and efficacy/safety results of the phase 3 trial. The PK and E-R relationship analysis results further supported the proposed body weight-tiered 200 mg/300 mg Q2W regimens.

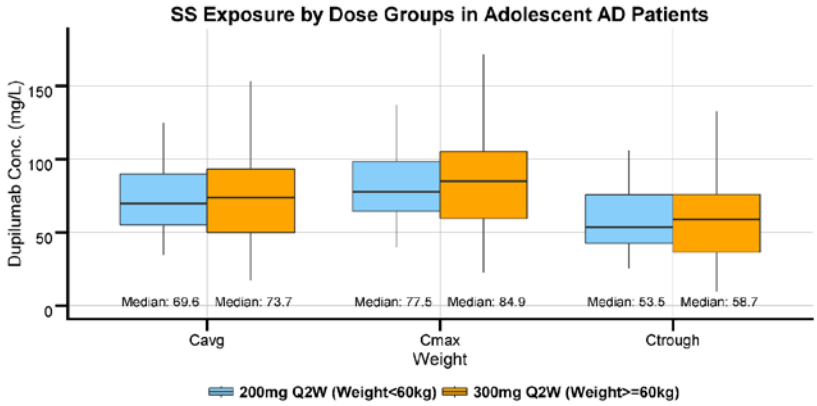
- In the phase 3 trial R668-AD-1526, adolescents <60 kg receiving 200 mg Q2W regimen and adolescents ≥60 kg receiving 300 mg Q2W regimen achieved similar dupilumab concentrations at week 16 (Figure 4). Population PK analysis results also suggest that the weight-tiered 200 mg/300 mg Q2W regimens provide similar SS exposures for average, peak and trough dupilumab concentrations between the two body weight groups (Figure 5).
- Dupilumab concentrations in adolescent AD patients receiving the 200 mg/300 mg Q2W dosing regimens were similar to the concentrations in adult AD patients receiving the approved 300 mg Q2W dosing regimen (Figure 6).
- A positive E-R relationship for efficacy was observed in adolescent AD patients treated with dupilumab (Figure 2).
- The most commonly reported AE observed in the adolescent pivotal study R668-AD-1526 was conjunctivitis. The percentage of patients developing conjunctivitis appears to be similar with increasing rank order of quartiles of dupilumab trough concentrations, indicating a lack of E-R relationship for conjunctivitis (Figure 7).

Figure 4. Concentrations of Dupilumab (mg/L) at Week 16 vs. Body Weight (kg) by Dose Group in Adolescent Patients With Moderate-to-Severe AD (R668-AD-1526)



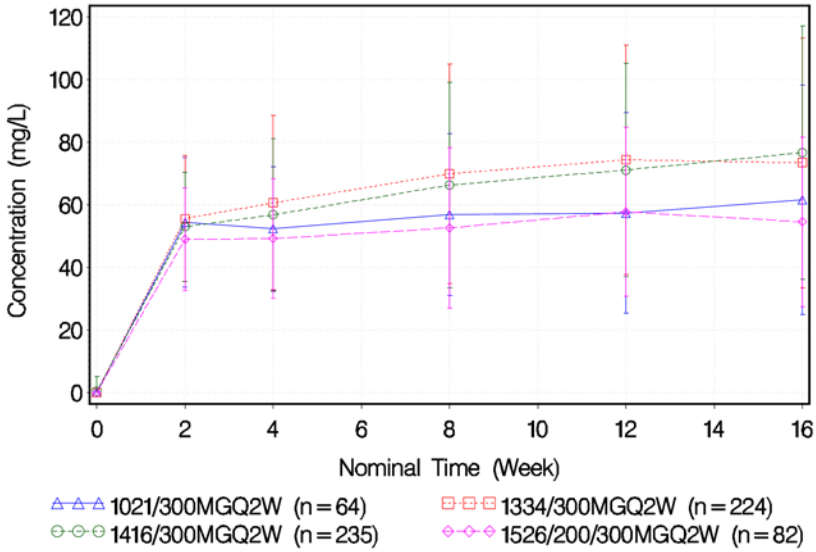
Source: Figure 7 in Applicant's Summary of Clinical Pharmacology Studies

Figure 5. Boxplot of Predicted Dupilumab Exposures at Steady-State (at 26th Dose)



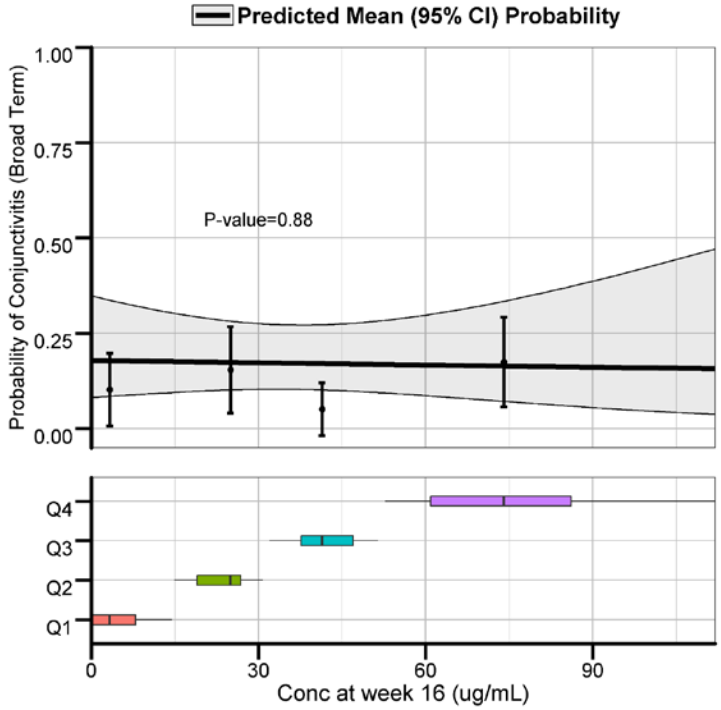
Dupilumab concentrations were predicted based on the post hoc PK parameters from 162 adolescent AD patients.
Source: Reviewer's Analysis based on Applicant's final adolescent PK model

Figure 6. Cross-Study Comparison of Mean ± SD Serum Dupilumab Concentrations in Adolescent and Adult AD patients



Adolescent AD patients received the 200 mg/300 mg Q2W dosing regimens. Adult AD patients received 300 mg Q2W dosing regimens.
Source: Figure 3, Summary of Clinical Pharmacology Studies

Figure 7. Logistic Regression Relating Probability of Developing Conjunctivitis (Broad Term) With Dupilumab Trough Concentrations at Week 16 in Adolescent Patients With Moderate-to-Severe AD



Mean regression line—black, confidence area around regression line—grey. The p-value represents the statistical significance of the inclination of the regression line. Means of response variables (black circles) and confidence intervals (black vertical lines) around the means are presented in the figures by quartile of exposure.
Source: Reviewer's Analysis to confirm Figure 13 in Applicant's Summary of Clinical Pharmacology Studies

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No, an alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors. Population PK identified body weight as a significant covariate on dupilumab PK; however, because the recommended body weight-tiered 200 mg/300 mg Q2W dosing regimens achieved similar exposure in adolescent AD patients across the two body weight groups, a further dose adjustment based on weight is not needed.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-drug interactions are not applicable as dupilumab is administered by SC injection. Drug interaction potential for dupilumab with CYP450 substrates is described in Section 12.3 of dupilumab product labeling. There is no additional drug interaction information in the current sBLA to update the drug interaction potential for dupilumab.

7 Statistical and Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

Table 3. Listing of Clinical Trials Relevant to This sBLA

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1412	Open-label, ascending dose, sequential cohort	-For dose cohort 1: 2 mg/kg at day 1 as single dose in Part A, then weekly at day 1 to week 3 in Part B as repeat doses -For dose cohort 2: 4 mg/kg at day 1 as a single dose in Part A, then weekly at day 1 to week 3 in Part B as repeat doses	**Primary Objective:** To characterize the PK profiles of dupilumab in pediatric AD patients aged ≥6 to <18 years. **Secondary Endpoints:** -Incidence of treatment emergent adverse events (TEAEs) -Percent change from baseline in Eczema Area and Severity Index (EASI) -Percent change from baseline in SCORing Atopic Dermatitis (SCORAD) score -Percent change from baseline in Pruritus Numerical Rating Scale (NRS) -Percentage of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 -Change from baseline in % body surface area (BSA) affected by AD	The study included Part A (including a single-dose treatment followed by an 8-week semi-dense PK sampling period), and Part B (including a 4-week repeat dose treatment period [4 weekly doses] followed by an 8-week follow-up period)	78	Pediatric subjects with moderate-to-severe AD (for adolescents aged ≥12 to <18 years at the time of baseline) or severe AD (for children aged ≥6 to <12 years at the time of baseline) that was not adequately controlled with topical medications

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1526	Randomized, double-blind, placebo controlled	-Dupilumab every 2 weeks (Q2W) treatment group: 200 mg Q2W (patients <60 kg), following an initial or 300 mg Q2W (patients ≥60 kg), following an initial loading dose of 600 mg -Dupilumab every 4 weeks (Q4W) treatment group: 300 mg Q4W, irrespective of weight, following an initial 600 mg loading dose -Placebo group	**Primary Endpoint:** -The proportion of subjects with IGA 0 or 1 at week 16 was the primary endpoint for the U.S. **Key Secondary Endpoints:** -Proportion of subjects with EASI-75 (≥75% improvement from baseline) at week 16 (this was a co-primary endpoint ex-U.S.) -Percent change in EASI score from baseline to week 16 -Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS -Proportion of subjects with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline to week 16 - Proportion of subjects with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16	16 weeks treatment/12 weeks follow-up	251	Pediatric subjects (aged ≥12 to <18 years at the time of baseline) with moderate-to-severe AD that could not be adequately controlled with topical AD medications or for whom topical treatment was medically inadvisable

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1434	Open label extension study	Based on protocol amendment 1, all subjects at the time of enrollment started on a dose regimen of 300 mg Q4W. The dose was up-titrated in case of inadequate clinical response at week 16 as follows: -Subjects weighing ≥60 kg: 300 mg Q2W -Subjects weighing <60 kg: 200 mg Q2W Note: Prior to amendment 1, subjects from study R668-AD-1412 received weight-based dosing regimens of 2 mg/kg or 4 mg/kg.	**Primary Endpoint:** -The incidence and rate of treatment-emergent adverse events (TEAEs) from baseline through the last study visit. **Secondary Endpoints:** -Incidence of treatment-emergent serious adverse events (SAEs) from baseline through the last study visit -Incidence of TEAEs of special interest from baseline through the last study visit -Proportion of subjects with an IGA score of 0 or 1 (clear or almost clear) at all in clinic visits postbaseline -Proportion of subjects with Eczema Area and Severity Index (EASI)-75 (≥75% reduction in EASI from baseline of parent study) response at all in-clinic visits postbaseline -Change and percent change from baseline in EASI at all in-clinic visits postbaseline -Change from baseline in body surface area (BSA) affected by AD at all in-clinic visits postbaseline -Percent change from baseline in SCORAD at all in-clinic visits postbaseline -Change from baseline in Children's Dermatology Life Quality Index (CDLQI) for patients ≥4 years of age at all in-clinic visits postbaseline in which the assessments are planned to be performed	The study will be conducted until regulatory approval of the product for the age group of the subject in his/her geographic region, and a 12-week follow-up period.	275	pediatric subjects with AD, aged ≥6 months to <18 years at the time of screening

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population
R668-AD-1607 Part A	Open-label, randomized, actual use autoinjector (AI) study	200 mg Q2W, after a loading dose of 400 mg	**Primary Endpoint:** -The number and type of validated AI device associated product technical failures (PTFs) during the treatment period divided by total number of actual injections. **Secondary Endpoints:** -Number and percentage of patients with an AI device-associated PTF -Number and type of AI device associated PTCs divided by total number of actual injections -Number and percentage of patients with an AI device-associated PTC -Number and type of AI device associated failed drug deliveries (defined as patient failure to administer the full dose at a given attempt, excluding PTF) divided by total number of actual injections -Number and percentage of patients with an AI device-associated failure to deliver dose -Number and percentage of patients with response to patient satisfaction questions with the AI device	12 weeks treatment/12 weeks follow up	85 (67 adults, and 18 adolescents)	Subjects with moderate-to-severe AD ≥12 years of age

7.1.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of dupilumab for the proposed indication included final study reports submitted by the Applicant, datasets (Study Data Tabulation Model and Analysis Data Model). This application was submitted in electronic common technical document format and entirely electronic. The electronic submission including protocols, statistical analysis plans, clinical study reports, SAS transport datasets in Study Data Tabulation Modal, and Analysis Data Model format were in the following network path:

Original submission: \\cdsesub1\evsprod\bla761055\0300\m5\datasets\r668-ad-1526

Data and Analysis Quality

In general, the data submitted by the Applicant to support the efficacy and safety of dupilumab for the proposed indication appeared adequate.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

7.2.1. Study Design and Endpoints

The Applicant conducted a single phase 3 trial (R668-AD-1526) to support the application.

The key inclusion criteria that defined the study population were similar to those of the adult trials. The inclusion criteria included:

- Male or female subjects 12 to <18 years of age with moderate to severe AD that could not be adequately controlled with topical AD medications or for whom topical treatment was medically inadvisable (e.g., intolerance, other important side effects or safety risks). Moderate to severe AD was defined as the following:
  - IGA score ≥3 at screening and baseline
  - EASI ≥16
  - Baseline Pruritus Numeric Rating Scale (NRS) average score for maximum itch intensity ≥4
  - BSA of AD involvement ≥10%

The Sponsor's IGA scale is shown below.

Table 4. Investigator's Global Assessment Disease Severity Scale and Definitions

IGA: Disease Severity Scale and Definitions of the scoring:

Score	Investigator's Global Assessment (IGA) Standard Definitions	Investigator's Global Assessment (IGA): Proposed Morphological Descriptors
0 = Clear	No inflammatory signs of atopic dermatitis	No inflammatory signs of atopic dermatitis
1 = Almost clear	Just perceptible erythema, and just perceptible papulation/infiltration	Barely perceptible erythema and/or minimal lesion elevation (papulation/infiltration)
2 = Mild disease	Mild erythema and mild papulation/infiltration	Visibly detectable, light pink erythema and very slight elevation (papulation/infiltration)
3 = Moderate disease	Moderate erythema and moderate papulation/infiltration	Dull red, clearly distinguishable erythema; clearly perceptible elevation (papulation/infiltration), but not extensive
4 = Severe disease	Severe erythema and severe papulation/infiltration	Deep/dark red erythema; marked and extensive elevation (papulation/infiltration)

The EASI is shown below.

Table 5. Eczema Area and Severity Index

The definitions of the scoring signs of EASI are given below:

Erythema	**(E)**
0 – None	
1 – Mild	Faintly detectable erythema: very light pink
2 – Moderate	Dull red, clearly distinguishable
3 – Severe	Deep / dark red
Infiltration / Papulation	**(I)**
0 – None	
1 – Mild	Barely perceptible elevation
2 – Moderate	Clearly perceptible elevation but not extensive
3 – Severe	Marked and extensive elevation
Excoriations	**(Ex)**
0 – None	
1 – Mild	Scant evidence of excoriations with no signs of deeper skin damage (erosion, crust)
2 – Moderate	Several linear marks of skin with some showing evidence of deeper skin injury (erosion, crust)
3 – Severe	Many erosive or crusty lesions
Lichenification	**(L)**
0 – None	
1 – Mild	Slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2 – Moderate	Definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern
3 – Severe	Thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern

Scoring

Line	Area	Erythema	Infiltration	Excoriations	Lichenification	Area of Involvement	Multiplier	Score
1	Head/Neck	(_____ +	_____ +	_____ +	_____)	X _____	X 0.1	
2	Trunk	(_____ +	_____ +	_____ +	_____)	X _____	X 0.3	
3	Upper Extremities	(_____ +	_____ +	_____ +	_____)	X _____	X 0.2	
4	Lower Extremities	(_____ +	_____ +	_____ +	_____)	X _____	X 0.4	

The protocol specified the following exclusion criteria:

- Subjects treated with a systemic investigational drug before the baseline visit
- Subjects treated with a topical investigational agent within 4 weeks or within 5 half-lives, whichever was longer, before the baseline visit
- Subjects treated with TCS or TCIs within 2 weeks before the baseline visit
- Subjects that used any of the following treatments within 4 weeks before the baseline visit (immunosuppressive/immunomodulating drugs, phototherapy for AD)
- Body weight <30 kg at baseline

Using the Interactive Voice Response System/Interactive Web Response System, a total of 251 subjects were randomized to one of the following groups in a 1:1:1 ratio:

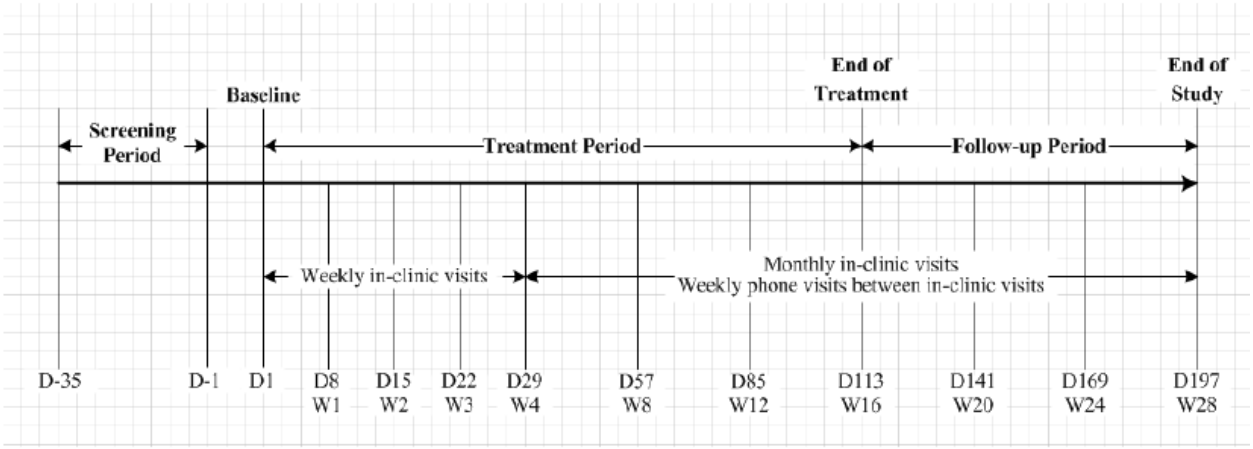
- Dupilumab every 2 weeks (Q2W) group:
  - 200 mg Q2W for subjects <60 kg (loading dose of 400 mg) or
  - 300 mg Q2W for subjects ≥60 kg (loading dose of 600 mg)
- Dupilumab every 4 weeks (Q4W) group:
  - 300 mg Q4W (loading dose of 600 mg), irrespective of weight
- Placebo
  - Subjects <60 kg will receive placebo matching 200 mg dupilumab
  - Subjects ≥60 kg will receive placebo matching 300 mg dupilumab

Note that in the phase 3 trials for the adult subjects with moderate to severe AD, dupilumab 300 mg QW and Q2W were evaluated against placebo, and based on a benefit-risk assessment, dupilumab 300 mg Q2W was approved for the indication.

The protocol specified that randomization would be stratified by baseline weight group (<60 kg and ≥60 kg) and baseline disease severity (moderate [IGA=3] versus severe [IGA=4] on the IGA).

Visits occurred weekly for the first 4 weeks, and then every 4 weeks thereafter until week 16. Follow-up visits occurred on weeks 20, 24 and 28. The following diagram is the Sponsor's study flow diagram:

Figure 8. Study Flow Diagram



D = study day; W = study week

Source: Sponsor's protocol (page 39)

Study drug was provided in prefilled glass syringes for subcutaneous administration, and the injection sites of the study drug were alternated among the different quadrants of the abdomen, upper thighs, and upper arms so that the same site was not injected for 2 consecutive weeks. In order to maintain blinding, subjects received an injection Q2W from day 1 to week 14, and placebo injections were given at the weeks dupilumab was not given. The study staff administered the first of the two injections required for the loading dose, and the subject or the caregiver administered the second injection required for the loading dose under the supervision of the clinic staff. For weeks 2 and 4, study drug was administered under the supervision of the clinic staff in-clinic, and during the weeks in which no in-clinic visit was scheduled, subjects/caregivers had the option to administer study drug outside the study site or visit the clinic to be administered by a study staff.

All enrolled subjects were required to apply moisturizers twice daily for at least 7 days before randomization and continued throughout the study. The protocol specified that to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of nonlesional skin designated for such assessments for at least 8 hours before each clinic visit.

Rescue treatments, if medically necessary to control intolerable AD symptoms, were provided to subjects at the discretion of the investigator. The protocol specified that investigators were encouraged to consider rescue with topical treatment (e.g., medium/high potency TCS), and escalate to systemic medications only for subjects who did not respond adequately after at least 7 days of topical treatment. The protocol specified that TCIs were permitted for use for rescue, alone or in combination with TCS, but the use of TCIs was reserved for problem areas only. Note that the protocol specified that if rescue treatment was used, the subject was specified as a nonresponder from the time the rescue treatment was used.

As in the adult pivotal trials, the protocol-specified the primary endpoint was the proportion of subjects with IGA 0 or 1 at week 16.

The protocol-specified testing the primary and the secondary endpoints in the order shown in Table 6. Previously, in an advice letter dated 4/14/2016, the Agency stated that while EASI 75 endpoint can be considered to be clinically meaningful, a mere percent change in the EASI score might not translate to a clinically meaningful difference. Similarly, the Agency stated that a mere percent change in peak pruritus NRS might not translate to a clinically meaningful difference. In response, the Sponsor stated (SDN 826; stamp date: 5/10/2017) that "the evaluation of these endpoints is of scientific interest and may be object of publications. In addition, results of this study will support regulatory submission worldwide, and different regulatory requirements may apply in different geographical regions." Note that all endpoints in the table below except for the EASI 50, the percent change in weekly average of daily peak pruritus NRS, and the percent change in EASI score were also assessed in the adult pivotal trials and were included in the approved labeling of dupilumab 300 mg Q2W.

Table 6. Testing Hierarchy of Endpoints

	Week 16	**Dupilumab Q2W vs. Placebo**	**Dupilumab Q4W vs. Placebo**
Primary	IGA 0 or 1	1	9
Secondary	EASI 75	2	10
	Percent change in EASI score[(1)]	3	11
	Percent change in weekly average of daily peak pruritus NRS[(2)]	4	12
	Peak pruritus NRS ≥3[(3)]	5	13
	Peak pruritus NRS ≥4[(4)]	6	14
	EASI 50	7	15
	EASI 90	8	16

Source: Reviewer Table; (1), (2) The Sponsor stated that the endpoint is of scientific interest and may be object of publications. (3) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥3 from baseline to week 16; (4) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥4 from baseline to week 16

7.2.2. Statistical Methodologies

The primary efficacy analysis set was the full analysis set defined as all randomized subjects. The protocol specified that the per protocol set (PPS) included all subjects in the full analysis set except for those that are excluded because of major efficacy-related protocol violations. The criteria of major efficacy-related protocol deviation were the following:

- Patients who were randomized more than once
- Any major violations of efficacy-related entry criteria
- Patients who received <80% of the scheduled doses during the study treatment period

For the PPS in this trial, the Sponsor excluded 11 subjects (4%), eight of whom had inadequate compliance to study drug, and three of whom violated the entry criteria.

For the analysis of the primary and the binary secondary endpoints, the protocol specified using the Cochran Mantel Haenszel test stratified by baseline disease severity (IGA 3 or 4) and baseline weight group (≤60 kg versus >60 kg). The protocol specified testing the endpoints in the hierarchical order listed in Table 6 to control the Type I error rate (two-sided, α=0.05). For the analysis of the continuous secondary endpoints, the protocol specified using analysis of covariance (ANCOVA) with baseline measurement as covariate and the treatment, baseline disease severity (IGA 3 or 4) and baseline weight group (≤60 kg versus >60 kg) as fixed factors.

For handling of missing data, the protocol specified that subjects that used rescue medication or that withdrew from the study would be considered as a nonresponder. As sensitivity analyses for handling missing data for the primary and binary secondary endpoints, the protocol specified using the last observation carried forward and using the observed data only. For continuous secondary endpoints, the protocol specified using the multiple imputation with ANCOVA as the primary imputation method, and as sensitivity analyses, the Sponsor proposed ANCOVA model with last observation carried forward, and ANCOVA model with all observed data regardless of rescue use.

7.2.3. Subject Disposition, Demographics, and Baseline Disease Characteristics

The study randomized a total of 251 subjects. Approximately 92% of the subjects completed the study treatment at week 16, and the proportion of subjects that did not complete the study treatment was highest in the placebo group (i.e., nine out of 20 subjects that did not complete the study received placebo). The Applicant reported that six of the nine placebo subjects that did not complete 16 weeks of treatment were due to lack of efficacy. Given that the rate of missing data is low (8%) and that nine of the 20 discontinued subjects were either due to lack of efficacy or due to AEs, the impact of the imputation method on efficacy would be minimal.

Table 7. Subject Disposition

	Dupilumab		**Placebo**
	Q2W (1) N=82	Q4W N=84	N=85
Completed week 16	76 (93%)	79 (94%)	76 (89%)
Adverse events	2	0	1
Lack of efficacy	0	0	6
Protocol deviation	0	2	0
Other	4	3	2

Source: Reviewer Table (1) 200 mg for subjects <60 kg, 300 mg for subjects ≥60 kg

Table 8 presents the baseline demographics for this study. The baseline demographics were generally balanced across the treatment arms. Approximately 59% of the subjects were male, and 63% were white. The average age of the randomized subjects was about 14.5 years and the average weight at baseline was about 65 kg. According to the Applicant, 43% of the subjects were classified as being overweight (Body Mass Index ≥85% for age and gender).

Table 8. Baseline Demographics

	Dupilumab		**Placebo**
	Q2W[(1)] N=82	Q4W N=84	N=85
Sex			
Male	43 (52%)	52 (62%)	53 (62%)
Female	39 (48%)	32 (38%)	32 (38%)
Age			
Mean	14.5	14.4	14.5
SD	1.74	1.59	1.78
Range	12–17	12–17	12–17
Race			
White	54 (66%)	48 (57%)	55 (66%)
Black	7 (9%)	15 (18%)	8 (9%)
Asian	12 (14%)	13 (14%)	13 (15%)
*Other**	9 (11%)	9 (11%)	8 (10%)
Weight (kg)			
Mean	65.6	65.8	64.4
SD	24.5	20.1	21.5
Median	58.1	59.8	58.9
Range	32-174	38.2-122.60	31.0-148.2
BMI			
<85% of population	46 (56%)	47 (56%)	49 (58%)
≥85% of population	36 (44%)	37 (44%)	36 (42%)

Source: Reviewer Table (1) 200 mg for <60 kg, 300 mg for ≥60 kg

The baseline disease severity was generally balanced across the treatment arms. Approximately 46% of the subjects had IGA of 3 at baseline, and the mean EASI (SD) score at baseline was 35.5 (14.2). For the peak pruritus NRS, the average NRS score was about 7.5, and all but two randomized subjects had NRS ≥4 at baseline.

Table 9. Baseline Disease Severity

	Dupilumab		Placebo
	Q2W [(1)] N=82	Q4W N=84	N=85
IGA			
3	39 (48%)	38 (45%)	39 (46%)
4	43 (52%)	46 (55%)	46 (54%)
EASI			
Mean	35.3	35.8	35.5
SD	13.8	14.8	31.7
Median	32.5	33.5	14.0
Range	16-71	16-71	16-71
Peak pruritus NRS			
Mean	7.5	7.5	7.7
SD	1.5	1.8	1.6
Median	7.6	8.0	8
Range	4-10	2-10	4-10
NRS ≥4 at baseline	82 (100%)	83 (99%)	84 (99%)

Source: Reviewer Table (1) 200 mg for subjects <60 kg, 300 mg for subjects ≥60 kg

7.2.4. Results for the Primary and Secondary Efficacy Endpoints

Table 10 presents the results for the primary and secondary efficacy endpoints at week 16. Both dupilumab Q2W and Q4W were superior to placebo for all primary and secondary endpoints in the table below (p<0.001).

Table 10. Efficacy Results at Week 16 (Full Analysis Set)

	Dupilumab		Placebo
	Q2W[(1)] N=82	Q4W N=84	N=85
IGA 0 or 1 (primary)	20 (24%)	15 (18%)	2 (2%)
EASI 75	34 (42%)	32 (38%)	7 (8%)
Percent change in EASI score[(2)]	-65.9 (4.0)	-64.8 (4.5)	-23.6 (5.5)
Percent change in weekly average of daily peak pruritus NRS[(2)]	-47.9 (3.4)	-45.5 (3.5)	-19.0 (4.1)
Peak pruritus NRS ≥3[(3)]	40/82 (49%)	32/83 (39%)	8/85 (9%)
Peak pruritus NRS ≥4[(4)]	30/82 (37%)	22/83 (27%)	4/84 (5%)
EASI 50	50 (61%)	46 (55%)	11 (13%)
EASI 90	19 (23%)	16 (19%)	2 (2%)

Source: Reviewer Table; Full Analysis Set (FAS defined as all randomized subjects: Missing data or subjects using rescue treated as nonresponders. Analyzed using CMH test stratified by baseline IGA disease severity and baseline weight group (<60 kg versus ≥60 kg); (1) Subjects <60 kg received 200 mg Q2W; Subjects ≥60 kg received 300 mg Q2W; (2) The Sponsor stated that the endpoint is of scientific interest and may be object of publications; Least Squares (LS) mean and Standard Error (SE) from ANCOVA model with baseline as covariate and treatment, baseline IGA disease severity and baseline weight group (<60 kg versus ≥60 kg) as fixed factors; (3) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥3 from baseline to week 16; (4) Proportion of subjects with improvement of weekly average of daily peak pruritus NRS ≥4 from baseline to week 16

With only 11 subjects (4%) excluded from the PPS, the efficacy results using the PPS yielded similar results to those using the full analysis set. The analysis of the primary endpoint (IGA 0 or 1 at week 16) using the PPS were 25% (20/79), 18% (14/77), and 2% (2/84) for the dupilumab Q2W, Q4W, and placebo, respectively.

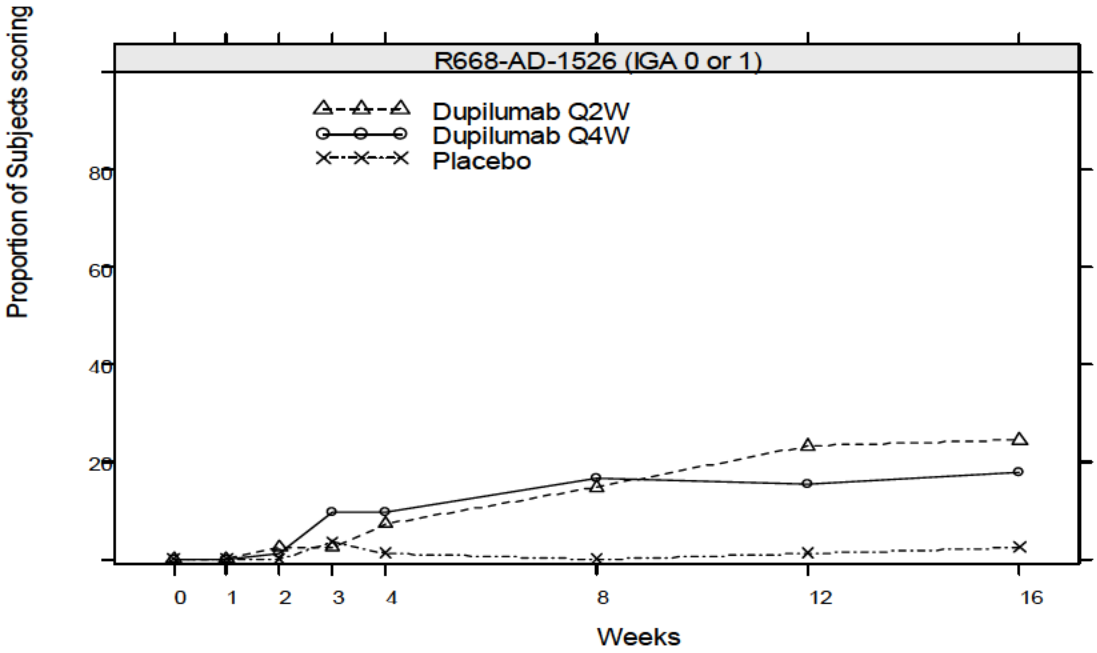
7.2.5. Patient Reported Outcomes (PROs)

The protocols specified secondary efficacy endpoints based on an 11-point NRS. The results are presented in the table above.

7.2.6. Efficacy Over Time

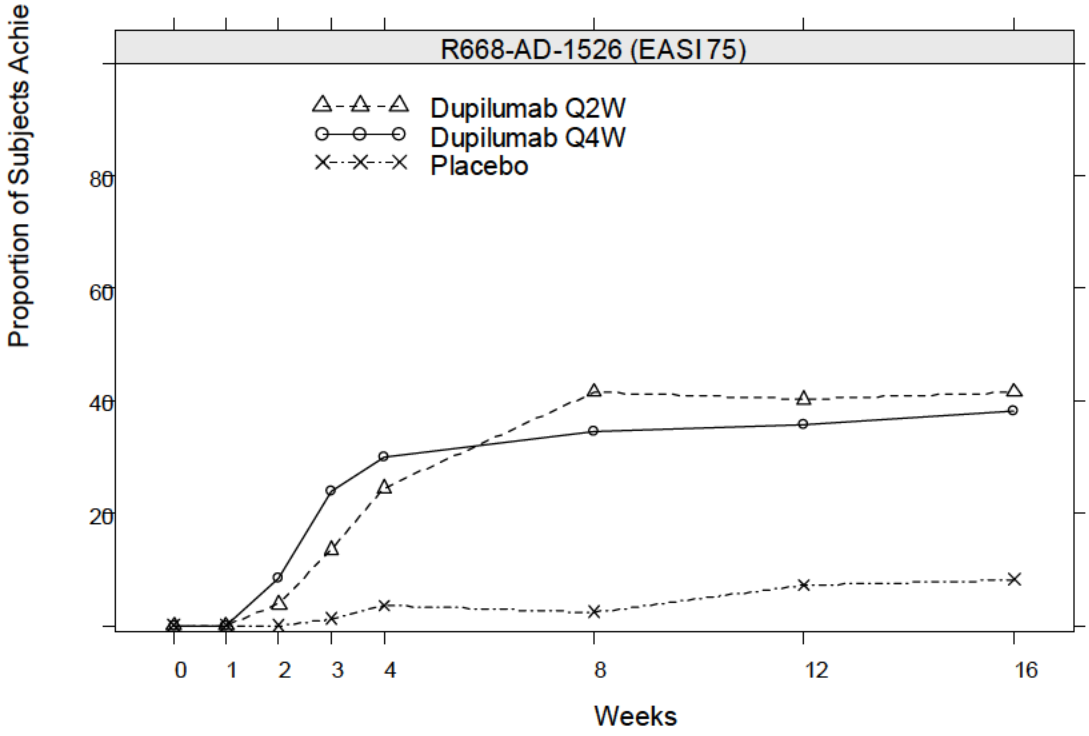
Figure 9 presents the results for IGA 0 or 1 through week 16. Figure 10 presents the results for EASI 75 through week 16.

Figure 9. Results for IGA of 0 or 1 Through Week 16



Source: reviewer figures; Full Analysis Set (FAS) defined as all randomized subjects; Missing data and subjects that used rescue were imputed using nonresponders.

Figure 10. Results for EASI 75 Through Week 16



Source: reviewer figures; Full Analysis Set (FAS) defined as all randomized subjects; Missing data and subjects that used rescue were imputed using nonresponders.

7.2.7. Findings in Special/Subgroup Populations

7.2.7.1. Sex, Race, Age, Weight, Baseline Disease Severity

Table 11 presents the results for the primary efficacy endpoint of IGA score of 0 or 1 at week 16 by sex, age (<15 versus ≥15 to <17 years), race (white, black or African American, Asian, other), weight (<60 kg versus ≥60 kg), and baseline IGA severity. As the number of subjects is small for the subgroups, it would be difficult to draw any meaningful conclusions.

Table 11. Proportion of Subjects With IGA 0 or 1 at Week 16 by Age, Sex, Race, Weight, and by Baseline IGA Severity

	Dupilumab		Placebo
IGA 0 or 1 at week 16	Q2W [(1)] N=82	Q4W N=84	N=85
Age			
<15	12/43 (28%)	7/45 (16%)	0/41 (0%)
≥15 to <17	8/39 (21%)	8/39 (21%)	2/44 (5%)
Sex			
Male	13/43 (30%)	8/52 (15%)	2/53 (4%)
Female	7/39 (18%)	7/32 (22%)	0/32 (0%)
Race			
White	13/54 (24%)	11/55 (20%)	1/48 (2%)
Black	4/7 (57%)	2/8 (25%)	1/15 (7%)
Asian	2/12 (17%)	2/13 (15%)	0/13 (0%)
Other	1/7 (14%)	0/8 (0%)	0/6 (0%)
Weight			
<60 kg	13/43 (30%)	7/42 (17%)	1/43 (2%)
≥60 kg	7/39 (18%)	8/42 (19%)	1/42 (2%)
Baseline IGA			
3	12/39 (31%)	13/38 (34%)	1/39 (3%)
4	8/43 (19%)	2/46 (4%)	1/46 (2%)

Source: Reviewer table; (1) subjects <60 kg received 200 mg Q2W; subjects ≥60 kg received 300 mg Q2W.

7.2.7.2. Rescue Medication

The protocol specified that investigators were encouraged to consider rescue initially with topical treatment (e.g., medium/high potency TCS), and to escalate to systemic medications only for subjects who did not respond adequately after at least 7 days of topical treatment. Note that the protocol specified that if rescue treatment was used, the subject was specified as a nonresponder from the time the rescue treatment was used.

Table 12 shows that the proportion of subjects who used at least one rescue medications. Rescue medication use was higher in the placebo group (59%) compared to the dupilumab Q2W (21%) and Q4W (33%) group. The most common use of rescue medication was corticosteroids.

Table 12. Proportion of Subjects With Rescue Medication Use

	Dupilumab		Placebo
	Q2W [(1)] N=82	Q4W N=83	N=85
≥1 Rescue	17 (21%)	27 (33%)	50 (59%)
Corticosteroids	14 (17%)	26 (31%)	47 (55%)
Other dermatological preparations	3 (4%)	1 (1%)	7 (8%)
Corticosteroids for systemic use	2 (2%)	0	5 (6%)
Immunosuppressants	0	0	3 (4%)

Source: Reviewer Table; Safety Analysis Set

7.3. Review of Safety

Safety Review Approach

The Applicant provided safety data from adolescents exposed to dupilumab in four studies. These constituted the adolescent development program for AD. The number of subjects presented below reflects only the adolescents, in those studies that also enrolled other age groups:

- Study R668-AD-1526 (1526): Phase 3, randomized, double-blind, placebo-controlled, pivotal study; 16-week dosing period; n=165
- Study R668-AD-1607 (1607): Phase 1, open-label, prefilled pen (also known as the autoinjector) study; 12-week dosing period; adolescents in Part A n=18
- Study R668-AD-1412 (1412): Phase 2a, open-label, PK study; single dose followed by 4-week repeat dose treatment; adolescents n=40
- Study R668-AD-1434 (1434): Phase 3, ongoing, OLE, long-term safety study; adolescents n=275 (as of the cutoff for the sBLA; April 21, 2018)

Study 1526 was the only one that exclusively enrolled adolescents. Also, study 1526 was the only monotherapy study; the other three studies allowed concomitant topical therapies e.g., TCS, TCI.

Subjects from studies 1526, 1607, and 1412 could be “rolled over” into study 1434, a long-term treatment study into which all pediatric subjects (irrespective of age) may ultimately be enrolled.

Study 1526 provided for the primary safety data. The safety review will focus on the primary safety data (study 1526) and the supportive safety data from the OLE (study 1434). Only SAEs will be discussed from studies 1412 and 1607. The supplement did not include pooled data for an integrated safety assessment, due to the differing designs of the four studies.

Across the development program, the Applicant analyzed the safety data according to three periods, with each period being defined differently for each study:

- Treatment period
- Follow-up period
- Overall study (consisted of the treatment period and the follow-up periods).

Study 1526 (pivotal)

See Section 7.2.1 for discussion of the study design. The treatment period was 16 weeks; the follow-up period was 12 weeks.

Study 1434 (OLE)

This study enrolls pediatric subjects (≥6 months to <18 years at screening) with moderate-to-severe AD and who had completed a prior dupilumab clinical study across the pediatric development program. The OLE treatment period for a particular pediatric age group (≥6 months to ≤6 years, 6 years to <12 years, and 12 years to <18 years) will continue up to the time when dupilumab is approved for treatment of AD for the age group of the subject in his/her geographic region, or until the company decides not to continue development of dupilumab for treatment of AD in that particular age group and/or overall pediatric population. In addition, if adequate efficacy and safety is demonstrated in future development in a particular age group with AD, the company may then transition subjects from the OLE in this age group in certain geographic regions to some other mechanism to continue to receive drug up to the time of approval. The primary endpoint is the incidence and rate of TEAEs from baseline through the last study visit.

Under the original protocol, subjects ≥12 years to <18 years old received weight-based dosing of 2 mg/kg once weekly (QW) or 4 mg/kg QW, which was the dosing regimen from the parent study (PK), 1412. Protocol Amendment 1 modified the dosing to a fixed-dose regimen of 300 mg Q4W, which was one of the regimens in the parent study (pivotal), 1526. Further, the amendment allowed for up-titration to 200 mg Q2W for subjects <60 kg or 300 mg Q2W for those ≥60 kg, in the face of an inadequate clinical response, defined as failure to achieve an IGA score of 0 or 1 (disease severity of “almost clear,” or “clear”) for at least 16 weeks from the date of initiation of treatment with the 300 mg Q4W regimen.

Safety procedures in this study include the assessment of vital signs, body weight and height, physical examination, laboratory testing (hematology, serum chemistry, urinalysis, and pregnancy testing), ophthalmology examination for subjects who experience adverse events of special interest (AESI) related to eye disorders (any type of conjunctivitis or blepharitis [severe or serious or lasting ≥4 weeks]).

Pharmacokinetic and antibody procedures involve the measurement of dupilumab concentrations and collection of serum samples for ADA assessment.

7.3.2. Review of the Safety Database

Overall Exposure

The Applicant defined the safety analysis set as subjects who received at least one dose of study treatment. Subjects were analyzed according to treatment received.

Table 13. Number of Adolescent Subjects Included in the Safety Analysis Set*

Parent Study ID Number	Number of Adolescents Treated in the Parent Study	Number of Adolescents Patients Who Rolled Over to the OLE Study (R668-AD-1434)	Number of Adolescents Exposed to Dupilumab (in the Parent Study or the OLE Study, R668-AD-1434)
R668-AD-1526	250[a]	201	234[b]
R668-AD-1412			
≥12 to <18 years of age	40	33	40
≥6 to <12 years of age[c]	3[c]	3	3
R668-AD-1607 Part A	18	11	18
R668-AD-1607 Part B[d]	27	27	27
Total	338	275	322

*Source: Table 1 of the Summary of Clinical Safety
a The number of subjects randomized and included in the full analysis set (FAS) was 251; one subject randomized to the dupilumab 300 mg Q4W group did not receive study treatment and was not included in the safety analysis set (SAF).
b 16 subjects in the placebo group withdrew from R668-AD-1526 and did not enter the OLE study
c Subjects who were enrolled as children in parent study and reached adolescence (12 years of age) before or at the time of screening for entry in the OLE study by the time of the data cut for this application
d Data from study R668-AD-1607 Part B (300 mg PFP portion, not complete as of data cutoff for this application) are not discussed in this application, however, the 27 adolescents from Part B who entered the OLE study R668-AD-1434 are included in the OLE analysis dataset (not complete as of data cutoff for this application).

A total of 322 adolescent subjects (12 to 17 years of age) with moderate-to-severe AD had received at least one dose of dupilumab by data cut-point for the sBLA (April 21, 2018), with durations of exposure as follows:

- 246 (76.4%) subjects had completed at least 16 weeks of treatment
- 35 (10.9%) subjects had completed at least 52 weeks of treatment
- 27 (8.4%) subjects had completed at least 104 weeks of treatment

Table 14 below presents a summary of study drug administration and duration of treatment in the adolescent program.

Table 14. Summary of Study Drug Administration (Cumulative) and Duration of Treatment in Adolescent Subjects From All Studies—SAF

	Dupilumab					
Exposure Characteristics	**2 mg/kg QW (N = 21)**	**4 mg/kg QW (N = 22)**	**300 mg Q4W (N = 284)**	**200 mg Q2W (N = 99)**	**300 mg Q2W (N = 89)**	**All Combined [3] (N = 322)**
Number of treated patients [1]	21	22	284	99	89	322
Number of study doses administered						
Mean (SD)	74.4 (39.53)	73.0 (34.61)	5.0 (4.12)	8.5 (4.88)	8.0 (5.30)	19.1 (27.00)
Q1	56.0	58.0	1.0	5.0	3.0	6.0
Median	93.0	81.0	4.0	9.0	9.0	11.0
Q3	108.0	100.0	9.0	9.0	11.0	15.0
Min-Max	5:109	1:109	1:18	1:23	1:22	1:113
Number of doses administered, cumulative, n (%)						
≥1	21 (100%)	22 (100%)	284(100%)	99 (100%)	89 (100%)	322 (100%)
≥4	21 (100%)	21 (95.5%)	148 (52.1%)	83 (83.8%)	66 (74.2%)	282 (87.6%)
≥8	17 (81.0%)	19 (86.4%)	80 (28.2%)	68 (68.7%)	49 (55.1%)	233 (72.4%)
≥12	17 (81.0%)	19 (86.4%)	25 (8.8%)	17 (17.2%)	20 (22.5%)	144 (44.7%)
≥16	17 (81.0%)	19 (86.4%)	1 (0.4%)	10 (10.1%)	9 (10.1%)	80 (24.8%)
≥24	17 (81.0%)	18 (81.8%)	0	0	0	36 (11.2%)
≥48	16 (76.2)	18 (81.8%)	0	0	0	34 (10.6%)
≥52	16 (76.2)	18 (81.8%)	0	0	0	34 (10.6%)
≥76	14 (66.7%)	15 (68.2%)	0	0	0	29 (9.0%)
≥100	8 (38.1%)	6 (27.3%)	0	0	0	17 (5.3%)
≥124	0	0	0	0	0	0
≥148	0	0	0	0	0	0

Exposure Characteristics	Dupilumab					
	2 mg/kg QW (N = 21)	4 mg/kg QW (N = 22)	300 mg Q4W (N = 284)	200 mg Q2W (N = 99)	300 mg Q2W (N = 89)	All Combined [3] (N = 322)
Summary of treatment duration [2] (weeks)						
n	21	22	284	99	89	322
Mean (SD)	75.4 (39.91)	75.4 (35.74)	14.4 (9.52)	16.0 (9.34)	15.4 (10.03)	32.0 (28.73)
Q1	57.1	58.0	4.1	10.0	7.6	16.0
Median	93.3	90.6	15.9	15.9	15.9	24.0
Q3	108.7	101.3	20.1	18.0	20.1	36.3
Min-Max	5:109	1:109	2:52	2:44	2:42	1:125
Treatment duration [2] (weeks) cumulative, n (%)						
≥1 week	21 (100%)	22 (100%)	284 (100%)	99 (100%)	89 (100%)	322 (100%)
≥4 weeks	21 (100%)	21 (95.5%)	271 (95.4%)	94 (94.9%)	75 (84.3%)	320 (99.4%)
≥8 weeks	17 (81.0%)	19 (86.4%)	193 (68.0%)	80 (80.8%)	65 (73.0%)	295 (91.6%)
≥12 weeks	17 (81.0%)	19 (86.4%)	168 (59.2%)	71 (71.7%)	55 (61.8%)	272 (84.5%)
≥16 weeks	17 (81.0%)	19 (86.4%)	137 (48.2%)	47 (47.5%)	44 (49.4%)	246 (76.4%)
≥26 weeks	17 (81.0%)	18 (81.8%)	34 (12.0%)	13 (13.1%)	16 (18.0%)	141 (43.8%)
≥39 weeks	16 (76.2%)	18 (81.8%)	4 (1.4%)	5 (5.1%)	2 (2.2%)	73 (22.7%)
≥52 weeks	16 (76.2%)	18 (81.8%)	1 (0.4%)	0	0	35 (10.9%) [4]
≥78 weeks	14 (66.7%)	15 (68.2%)	0	0	0	29 (9.0%)
≥104 weeks	7 (33.3%)	4 (18.2%)	0	0	0	27 (8.4%)
≥130 weeks	0	0	0	0	0	0

*Source: Table 5 of the Summary of Clinical Safety
[1] Including a total of four studies: R668-AD-1526, R668-AD-1412, R668-AD-1607 (Part A), and R668-AD-1434.
[2] Treatment duration is calculated as sum of treatment duration to dupilumab for each dose regimen in each individual study.
[3] Subjects received at least one dupilumab dose in one of the studies were included in this column and counted only once. The duration of treatment exposure to dupilumab dose for a patient who entered study R668-AD-1434 was calculated as the sum of duration of treatment exposure to dupilumab in the previous study plus duration of treatment exposure to dupilumab in the OLE study. The 322 subjects include all subjects who received at least one dose of dupilumab in either the parent study or the OLE study: 234 patients from R668-AD-1526 (16 subjects in the placebo group did not rollover to the OLE study), 43 subjects from R668-AD-1412 (40 adolescent subjects and three subjects who turned 12 years of age at the time rolling over to the OLE study), 18 adolescent subjects from Part A of R668-AD-1607 and 27 adolescent subjects from Part B of R668-AD-1607.
[4] These are 34 subjects from parent study R668-AD-1412 and one subject from parent study R668-AD-1526 who all rolled over in OLE study R668-AD-1434.
Abbreviations: OLE, open-label extension; Q1, first quartile; Q3, third quartile; QW, once weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set; SD, standard deviation.

Study 1526 (pivotal)

Because the weight-based dosing resulted in similar systemic exposures across the span of adolescents, the Applicant pooled the data from the 200 mg Q2W and 300 mg Q2W treatment groups.

Treatment exposures were generally similar across treatment groups.

Table 15. Summary of Study Drug Administration and Treatment Exposure in Study R668-AD-1526–SAF*

		Dupilumab		
	Placebo (N=85)	300 mg Q4W (N=83)	200 mg or 300 mg Q2W (N=82)	Combined (N=165)
Number of study drug doses administered				
Mean (SD)	8.5 (1.48)	8.7 (1.34)	8.7 (1.06)	8.7 (1.20)
Median	9.0	9.0	9.0	9.0
Minimum : Maximum	2 : 9	2 : 9	4 : 9	2 : 9
Overall treatment exposure (days)				
Mean (SD)	105.9 (21.49)	108.5 (18.66)	108.9 (15.49)	108.7 (17.11)
Median	112.0	112.0	112.0	112.0
Minimum : Maximum	14 : 146	14 : 119	42 : 154	14 : 154

*Source: Table 2 of Summary of Clinical Safety
Abbreviations: Q2W, every 2 weeks; Q4W, every 4 weeks; SAF, safety analysis set; SD, standard deviation.

Study 1434 (OLE)

A total of 69 subjects enrolled in the OLE study had received placebo in their parent study. At data cutoff for the sBLA, 275 adolescent subjects were enrolled, and their exposures were as follows:

- 152 subjects had been exposed to dupilumab for 16 weeks
- 34 subjects had been exposed for ≥52 weeks
- 22 subjects had been exposed for ≥104 weeks

Table 16. Summary of Treatment Exposure to Dupilumab for Subjects in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)*

Exposure Characteristics	Exposure to Dupilumab for All Patients in OLE Total (N=275)
Overall Treatment exposure (Weeks)	
n	275
Mean (SD)	26.44 (30.366)
Q1	8.00
Median	16.57
Q3	28.00
Min : Max	4.0 : 120.1
Number (%) of patients with overall treatment exposure (weeks) cumulatively	
≥1 Week	275 (100%)
≥4 Weeks	275 (100%)
≥16 Weeks	152 (55.3%)
≥26 Weeks	80 (29.1%)
≥52 Weeks	34 (12.4%)
≥78 Weeks	29 (10.5%)
≥ 104 Weeks	22 (8.0%)
≥ 130 Weeks	0
Number (%) of patients with treatment exposure with Q4W (weeks) cumulatively	
≥1 Week	268 (97.5%)
≥4 Weeks	250 (90.9%)
≥16 Weeks	80 (29.1%)
≥ 26 Weeks	11 (4.0%)
≥52 Weeks	0
≥78 Weeks	0
Number (%) of patients with treatment exposure with Q2W (weeks) cumulatively	
≥1 Week	126 (45.8%)
≥4 Weeks	103 (37.5%)
≥16 Weeks	36 (13.1%)
≥ 26 Weeks	8 (2.9%)
≥52 Weeks	0
≥78 Weeks	0

*Source: Table 24 of study report for 1434
Abbreviations: Min, minimum; Max, maximum; SD, standard deviation; Q1, quartile 1; Q3, quartile 3

Relevant Characteristics of the Safety Population

See Section 7.2.3 for tables of baseline demographic and disease characteristics for this study.

Baseline demographic and disease characteristics were generally similar across treatment arms. Most subjects (84.9%) had their AD diagnosed before the age of 5 years, and the mean (SD) duration of disease was 12.2 (3.20) years. Most subjects had a history or allergic rhinitis (65.6%), food allergy (60.8%), and/or asthma (53.6%). A higher proportion of subjects (24.8%) in the dupilumab combined group had a history of allergic conjunctivitis compared to the placebo group (18.8%).

All subjects had received at least one prior medication. By therapeutic class, the most commonly used prior medications were dermatological preparations of corticosteroids (96.0%), antihistamines for systemic use (76.8%), drugs for obstructive airway disease (52.8%), and emollients and protectives (49.6%).

In this study, 95% of subjects reported an inadequate response to topicals, 28% had received systemic corticosteroids for AD treatment, and 21% had received systemic nonsteroidal immunosuppressants: azathioprine (1%), cyclosporine (13%), methotrexate (10%), and mycophenolate (1%).

Table 17 suggests that some subjects had a history of treatment with both systemic corticosteroids and systemic nonsteroidal immunosuppressants. Most subjects (67%) who took cyclosporine took it for more than 3 months and, a poor response was the most common reason for discontinuing cyclosporine (54%). All of this suggests a population with refractory disease at baseline.

Table 17. Summary of Prior Use of Systemic Corticosteroid and Systemic Non-Steroidal Immunosuppressant Medications for AD in Study 1526–SAF*

		Dupilumab			
	Placebo (N=85)	300 mg Q4W (N=83)	200 mg or 300 mg Q2W (N=82)	Combined (N=165)	Total (N=250)
Patients receiving prior systemic corticosteroids and/or systemic non-steroidal immunosuppressants, n (%)	33 (38.8%)	38 (45.8%)	35 (42.7%)	73 (44.2%)	106 (42.4%)
Patients receiving prior systemic corticosteroids	21 (24.7%)	27 (32.5%)	21 (25.6%)	48 (29.1%)	69 (27.6%)
Patients receiving prior systemic non-steroidal immunosuppressants	17 (20.0%)	15 (18.1%)	20 (24.4%)	35 (21.2%)	52 (20.8%)
Azathioprine	1 (1.2%)	1 (1.2%)	0	1 (0.6%)	2 (0.8%)
Cyclosporine	12 (14.1%)	6 (7.2%)	14 (17.1%)	20 (12.1%)	32 (12.8%)
Methotrexate	6 (7.1%)	10 (12.0%)	10 (12.2%)	20 (12.1%)	26 (10.4%)
Mycophenolate	0	1 (1.2%)	2 (2.4%)	3 (1.8%)	3 (1.2%)

*Source: Table 11 of the study report for 1526

Adequacy of Safety Database

The safety database was adequate in size and extent of exposures (concentrations and duration) to assess the safety of dupilumab in subjects 12 to <18 years with moderate-to-severe AD, under conditions of intended use.

7.3.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data integrity and submission quality were adequate.

Categorization of Adverse Events

The Applicant coded AEs from the time of informed consent signature and then at each visit until the end of the study. The Applicant coded and classified all AEs according to the primary system organ class (SOC), high-level term, and preferred term according to the Medical Dictionary for Regulatory Activities (MedDRA). Version 20.1 was used for studies 1526 and 1434.

For study 1526, the Applicant separately summarized the number and proportion of subjects with TEAEs for the 16-week treatment period, the 12-week post-treatment follow-up period, and the overall study (treatment period + follow-up period).

For study 1434, the Applicant summarized all TEAEs during the study period. The Applicant also calculated and summarized the number of events per 100 subject-years and number of subjects with at least one event per 100 subject-years (exposure-adjusted incidence rate [EAIR]) for overall TEAEs, severe TEAEs, treatment-related TEAEs, severe treatment-related TEAEs, SAEs, AEs leading to discontinuation, and AESIs. These calculations were adjusted for the duration of the TEAE period.

AESIs

AESIs were mostly defined based on the safety profile from evaluation of dupilumab in adults. The following events were designated as AESIs in studies 1526 and 1434 and required expedited reporting (within 24 hours) by the investigator to the Applicant:

- Anaphylactic reactions
- Systemic or severe hypersensitivity reactions
- Malignancy (except in situ carcinoma of the cervix, nonmetastatic squamous or basal cell carcinoma of the skin)
- Helminthic infections
- Suicide-related events
- Any type of conjunctivitis or blepharitis (severe or serious)
- Keratitis

The medical officer's review of the original BLA submission provides some information regarding the designation of "suicide-related events" as an AESI. From p. 152 of that review (review dated 03/27/2017):

> The FDA requested that Suicidal Behavior (Suicidal Ideation, Suicide Attempt and Completed Suicide) be included as an AESI. The Agency made this request in the preBLA communication; however, the rationale was not stated in the communication.

Routine Clinical Tests

The schedule of testing varied according to the study and was specified in the respective statistical analysis plan for each study. Laboratory testing generally included clinical chemistry, hematology, and urinalysis evaluations.

7.3.4. Safety Results

Deaths

No deaths occurred in the adolescent AD program.

Serious Adverse Events

Study 1526 (pivotal)

One SAE was reported in this study, and it occurred in a subject in the placebo group during the treatment period:

- A 13-year-old male experienced appendicitis.

Study 1434 (OLE)

A total of four SAEs occurred in adolescents through the cutoff point (1.5%; 2.9 patients per 100 patient years [nP/100 PY]). Information pertaining to these SAEs is presented below:

- *Injection Site Cellulitis*. A 16-year-old black female experienced pain and swelling at the injection site (abdomen) on day 35 (5 days after second dose of study drug). Pain and swelling worsened eventuating in presentation to the emergency department, and she was hospitalized the same day. Treatment included intravenous antibiotics. She recovered and continued in the study as planned.
- *Ankle fracture*. A 12-year-old white female fractured her ankle in a tobogganing accident.
- *Patent ductus arteriosus*. A 17-year-old white female was hospitalized for a closure procedure (initial procedure done in childhood was unsuccessful).

- *Food allergy*. A 17-year-old white male with a history of allergy to eggs experienced an "acute allergic reaction" after ingesting mayonnaise (contained eggs). He was treated in the emergency department and continued in the study as planned.

SAEs in studies 1412 and 1607 part A

In study 1412, two subjects experienced two SAEs each:

- A 17-year-old male experienced "dermatitis infected" and "palpitations." He was taking salbutamol for asthma. One day after receiving one dose of dupilumab (2 mg/kg) he experienced palpitations ≤120 seconds. He experienced several episodes over the subsequent 2 to 3 days, with resolution (without treatment) after approximately 4 days. Study treatment was not interrupted. This subject was also hospitalized after the fifth dose of dupilumab for "infected AD." He was treated and recovered. He had completed study treatment at the time of this event.
- A 13-year-old white female experienced "dermatitis infected" and "Staphylococcal skin infection" 7 weeks after one injection of dupilumab (4 mg/kg). She was hospitalized and treated with oral antibiotics; the event resolved. No action was taken with study drug.

In study 1607 Part A, two subjects experienced SAEs; both subjects were older than 18 years of age, and high-level details are presented below:

- A 60-year-old male experienced lymphadenopathy. He had a history of "swollen lymph nodes." He was hospitalized for a severe disease flare accompanied by fever, chills, and "sweats." Evaluation revealed widespread lymphadenopathy. The narrative indicates that he was "worked up" for lymphoma. Lymph node biopsies revealed "no morphologic evidence of lymphoma." Ultimately, the lymphadenopathy "regressed."
- A 63-year-old male experienced sepsis. History included obesity, type 2 diabetes mellitus, and prostate cancer. On the day of his 3rd study treatment, he experienced symptoms considered to be suggestive of "blood infection" and was hospitalized. He was treated with intravenous antibiotics and also underwent several investigations while hospitalized. The narrative is somewhat complex and convoluted. Ultimately, however, he recovered from the event.

Dropouts and/or Discontinuations Due to Adverse Effects

Study 1526 (pivotal)

One subject (1.2%) experienced a TEAE that led to permanent discontinuation of study treatment: a 17-year-old black male in the placebo group was withdrawn from treatment on day 19 due to worsening of AD.

Study 1434 (OLE)

No AEs led to permanent discontinuation or withdrawal of study treatment in this study.

Significant Adverse Events

Severe TEAEs in study 1526 (pivotal)

A total of six subjects reported eight severe TEAEs during the treatment period. A subject was only counted once if the subject experienced the event more than once.

The only severe AE that was reported by more than one subject during the treatment period was “Dermatitis atopic.” Two subjects reported this event (1.2%), both of whom were in the dupilumab Q4W group. The remaining five events and the treatment group in which they occurred were:

- Biliary colic in the 300 mg Q4W
- Food allergy; jaw fracture in the 200 mg or 300 mg Q2W
- Lymphadenitis; appendicitis in the placebo group

One severe event was reported during the follow-up period: “Dermatitis atopic” in the dupilumab Q4W group.

It may be noteworthy that all of the severe TEAEs of AD reported over the course of the study occurred in the dupilumab Q4W group. This could be interpreted as potential supportive evidence for the Q2W dosing frequency.

Severe TEAEs in study 1434 (OLE)

A total of seven subjects (2.5%) experienced TEAEs that were reported as severe: AD exacerbation or worsening (two subjects; 0.7%), and one subject each (0.4%) experienced severe diarrhea, bone fracture, pain in extremity, patent ductus arteriosus, and allergic conjunctivitis (the case of conjunctivitis is discussed below with the AESIs).

AESIs in study 1526 (pivotal)

Three AESIs were reported during the treatment period, all of which occurred in dupilumab treatment groups:

- *Keratitis*. A 12-year-old white female (Q4W group; stratum <60 kg) experienced “bilateral viral keratoconjunctivitis” on day 12, which was 11 days after her baseline dose of 300 mg received on day 1. She was evaluated by an ophthalmologist and prescribed tobramycin-dexamethasone eye drops. Dosing of study treatment was not interrupted. She was considered to have recovered from the event on day 67 and received her final dose of study treatment on day 99. The investigator graded the event as “mild.” She was reported to have a history of allergic keratoconjunctivitis.

- *Suicidal behavior*. A 15-year-old Asian male (300 mg Q2W) experienced “suicidal ideation–passive” (verbatim term) on day 26. His most recent dose of dupilumab had been on day 13. On day 26, he reported daily thoughts of suicide, without accompanying plans for commission of the act. He had a history of depression and of a suicide attempt, prior to entry into the study. He had been on fluoxetine but had been off of it since the last 3 months prior to this episode. A diagnosis of depression with passive suicidal ideation was made. The subject was restarted on fluoxetine in the context of a comprehensive management plan for his depression. Study treatment was not altered, and he received his last dose on day 97.
- *Food allergy*. A 15-year-old white male (200 mg Q2W) experienced an “allergic reaction to food” on day 30, 17 days after his last dose of dupilumab. He had a history of allergy to dairy, eggs, and peanuts. He experienced “anaphylaxis” after consumption of cheese-flavored chips. Treatment in the emergency department included intramuscular epinephrine, oral diphenhydramine, and intravenous methylprednisolone. The event resolved the same day. Study drug was discontinued as the subject had received methylprednisolone which was a prohibited medication.

AESIs in study 1434 (OLE)

Three AESIs were reported in the OLE study:

- *Food allergy*. This 17-year-old subject has been previously discussed (see discussion of SAEs).
- *Depression*. A 17-year-old white female with a history of depression with suicidal ideation began experiencing depression with suicidal thoughts on day 443 (after 55 doses of study drug). The episode was triggered by her AD (conclusion of investigator). She also had a etonogestrel contraceptive implant, and “depressed mood” is labeled in the Warnings and Precautions section of the label. She was treated with antidepressants, and the event ultimately resolved. She continued in the study as planned.
- *Conjunctivitis allergic*. A 13-year-old white female with a history of allergic conjunctivitis began experiencing itching, burning, and several other eye symptoms on day 31. She also had periorbital and eyelid eczematous lesions. An ophthalmologist diagnosed bilateral AKC; she was treated accordingly. The investigator recorded the event as being “severe” and related to study drug. She was treated and continued in the study as planned.

Treatment Emergent Adverse Events and Adverse Reactions

TEAEs in study 1526 (pivotal)

TEAEs were most often reported in the Infections and Infestations SOC, and the two most commonly-reported events in that SOC were Upper respiratory tract infection and Nasopharyngitis. Conjunctivitis was the third most commonly-reported event in this SOC, and it occurred at higher incidences in the dupilumab groups: placebo-1.2%,

Q4W-3.6%, and Q2W-4.9%. The incidences of Conjunctivitis were similar between dupilumab groups, but slightly higher in the Q2W compared to Q4W. “Dermatitis atopic” occurred at the highest frequency in the placebo group (24.7%) and at similar incidences in the Q4W and Q2W groups (18.1% and 18.3%, respectively). Injection site reactions of various types were generally more common in the Q2W group. Generally, there was no evidence of a dose-response in the occurrence of TEAEs.

TEAEs that occurred in ≥2.0% in a dupilumab group and at a higher incidence than placebo are presented in Table 18. Presentation of events by “≥2%” is reasonable, as the report of a single event in any treatment group made for an incidence of “1.2%.”

Table 18. Treatment-Emergent Adverse Events That Occurred in ≥2.0% in a Dupilumab Group and at a Higher Incidence Than Placebo*

System Organ Class Preferred Term	Placebo (n=85)	Dupilumab	
		300 mg Q4W (n=83)	200 mg or 300 mg Q2W (n=82)
Infections and infestations	37 (43.5%)	38 (45.8%)	34 (41.5%)
Conjunctivitis	1 (1.2%)	3 (3.6%)	4 (4.9%)
Pharyngeal streptococcal	0	4 (4.8%)	2 (2.4%)
Viral upper respiratory tract infection	1 (1.2%)	3 (3.6%)	2 (2.4%)
Herpes simplex	1 (1.2%)	4 (4.8%)	0
Conjunctivitis viral	0	2 (2.4%)	1 (1.2%)
Gastroenteritis viral	1 (1.2%)	0	3 (3.7%)
Bronchitis	0	0	2 (2.4%)
Conjunctivitis bacterial	0	2 (2.4%)	0
Sinusitis bacterial	0	0	2 (2.4%)
Urinary tract infection viral	0	2 (2.4%)	0
Skin and subcutaneous disorders	26 (30.6%)	20 (24.1%)	22 (26.8%)
Rash	0	2 (2.4%)	1 (1.2%)
General disorders and administration site conditions	6 (7.1%)	9 (10.8%)	10 (12.2%)
Injection site pain	1 (1.2%)	1 (1.2%)	3 (3.7%)
Injection site swelling	1 (1.2%)	1 (1.2%)	3 (3.7%)
Malaise	0	3 (3.6%)	0
Fatigue	0	0	2 (2.4%)
Injection site erythema	1 (1.2%)	0	2 (2.4%)
Injection site warmth	0	0	2 (2.4%)
Respiratory, thoracic and mediastinal disorders	13 (15.3%)	9 (10.8%)	6 (7.3%)
Oropharyngeal pain	1 (1.2%)	3 (3.6%)	2 (2.4%)
Gastrointestinal disorders	4 (4.7%)	7 (8.4%)	6 (7.3%)
Nausea	1 (1.2%)	2 (2.4%)	2 (2.4%)
Abdominal pain upper	1 (1.2%)	1 (1.2%)	2 (2.4%)
Eye disorders	7 (8.2%)	6 (7.2%)	6 (7.3%)
Conjunctivitis allergic	3 (3.5%)	4 (4.8%)	3 (3.7%)
Injury, poisoning and procedural complications	2 (2.4%)	3 (3.6%)	9 (11.0%)
Ligament sprain	0	0	2 (2.4%)
Procedural pain	0	0	2 (2.4%)

*Source: Table 57 of study report for 1526

TEAEs in study 1434 (OLE)

In the OLE study, 149 subjects (54.2%) reported TEAEs making for an EAIR of 283.1 nP/100 PY. Similar to study 1526, TEAEs were most often reported in the infections and infestations SOC, and the two most commonly-reported events were nasopharyngitis (13.8%; 17.8 nP/100 PY) and upper respiratory tract infection (8.0%; 33.3 nP/100 PY) (although the order of frequency of these two TEAEs was reversed in study 1526).

Table 19**. Summary of Subjects With Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Reported in ≥2% of Subjects by SOC) in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)***

System Organ Class Preferred Term	Total (N=275) (nP/100PY)	Total (N=275) (nP/PY)
Number of TEAEs	700	700 (493.915)
Patients with at least one TEAE	149 (54.2%)	149/52.6 (283.051)
Infections and infestations	100 (36.4%)	100/79.6 (125.684)
Nasopharyngitis	38 (13.8%)	38/114.2 (33.262)
Upper respiratory tract infection	22 (8.0%)	22/131.3 (16.759)
Influenza	13 (4.7%)	13/136.8 (9.506)
Oral herpes	11 (4.0%)	11/130.3 (8.445)
Tonsillitis	7 (2.5%)	7/134.9 (5.190)
Pharyngitis	6 (2.2%)	6/138.1 (4.344)
Skin and subcutaneous tissue disorders	57 (20.7%)	57/112.3 (50.742)
Dermatitis atopic	39 (14.2%)	39/122.9 (31.738)
Acne	7 (2.5%)	7/135.0 (5.185)
Gastrointestinal disorders	31 (11.3%)	31/115.0 (26.954)
Diarrhoea	8 (2.9%)	8/129.7 (6.170)
Vomiting	8 (2.9%)	8/132.7 (6.028)
Abdominal pain upper	6 (2.2%)	6/137.8 (4.353)
Respiratory, thoracic and mediastinal disorders	23 (8.4%)	23/116.1 (19.806)
Oropharyngeal pain	12 (4.4%)	12/131.2 (9.148)
Cough	7 (2.5%)	7/134.5 (5.205)
Nervous system disorders	21 (7.6%)	21/123.4 (17.022)
Headache	16 (5.8%)	16/126.0 (12.702)
Injury, poisoning and procedural complications [1]	20 (7.3%)	20/123.8 (16.149)
General disorders and administration site conditions	18 (6.5%)	18/124.2 (14.495)
Pyrexia	6 (2.2%)	6/134.4 (4.464)
Eye disorders	13 (4.7%)	13/135.3 (9.607)
Conjunctivitis allergic	6 (2.2%)	6/136.4 (4.400)
Musculoskeletal and connective tissue disorders [2]	10 (3.6%)	10/134.3 (7.449)
Psychiatric disorders [3]	9 (3.3%)	9/135.1 (6.661)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) [4]	6 (2.2%)	6/135.3 (4.435)

*Source: Table 27 of study report for 1434; Subjects who experienced more than one TEAE were counted only once in each category. For subjects with event, number of patient years is calculated up to date of the first event; for subjects without event, it corresponds to the length of study observation period.

Laboratory Findings

Study 1526 (pivotal)

Hematology

There were no clinically-meaningful trends or differences between treatment groups in changes or shifts from baseline in any red blood cell parameter during the treatment period. Mean platelet counts remained within the normal range for all treatment groups at each study visit.

The same was generally true of white blood cells (basophils, monocytes, leukocytes, and neutrophils). Regarding eosinophils, mean counts were noted to increase from baseline in the dupilumab groups, peaking at week 8, then trending back towards baseline. A similar trend was seen in the adult program. In the placebo group, mean counts showed a progressive decrease from baseline. The Applicant relates this eosinophil effect to the mechanism of action of dupilumab in blocking IL-4 and IL-3 activity and the resultant impact on eosinophil activity, which ultimately may lead to transient increases in circulating eosinophil counts.

Table 20. Mean and Median Changes From Baseline in Eosinophils–SAF*

		Change from Baseline ($x10^9$/L)							
Treatment	**Visit**	**n**	**Mean**	**SD**	**Min**	**Q1**	**Median**	**Q3**	**Max**
Placebo (N=85)	Week 4	78	-0.080	0.4206	-1.76	-0.280	-0.075	0.130	1.29
	Week 8	76	-0.086	0.4924	-2.42	-0.240	0.010	0.140	1.03
	Week 16	72	-0.092	0.5284	-2.09	-0.275	-0.105	0.125	1.45
	Week 28	2	-0.105	0.0778	-0.16	-0.160	-0.105	-0.050	-0.05
Dupilumab 300 mg Q4W (N=83)	Week 4	79	0.027	0.5248	-1.03	-0.270	-0.050	0.120	2.23
	Week 8	78	0.177	0.7203	-1.11	-0.230	0.000	0.440	2.88
	Week 16	78	-0.094	0.5368	-1.16	-0.420	-0.125	0.080	2.23
	Week 28	3	-0.140	0.1400	-0.30	-0.300	-0.080	-0.040	-0.04
Dupilumab 200 mg or 300 mg Q2W (N=82)	Week 4	81	0.035	0.6412	-1.53	-0.190	-0.030	0.190	4.17
	Week 8	76	0.189	0.8246	-1.57	-0.145	0.025	0.430	3.84
	Week 16	74	0.027	0.8075	-1.97	-0.300	-0.040	0.270	5.23
	Week 28	4	-0.233	0.5160	-1.00	-0.535	-0.005	0.070	0.08
Dupilumab Combined (N=165)	Week 4	160	0.031	0.5848	-1.53	-0.215	-0.040	0.175	4.17
	Week 8	154	0.183	0.7710	-1.57	-0.190	0.015	0.440	3.84
	Week 16	152	-0.035	0.6825	-1.97	-0.310	-0.075	0.200	5.23
	Week 28	7	-0.193	0.3769	-1.00	-0.300	-0.070	0.060	0.08

*Source: Table 62 of study report for 1526.

No subject had relevant hematology test abnormalities that led to treatment discontinuation or to reporting of a SAE. One subject in the dupilumab Q4W group did have a TEAE reported as “Eosinophil count increased.”

Chemistry

Generally, no clinically-meaningful trends in changes or shift from baseline in any treatment group in chemistries (measures of metabolic, renal, liver or liver function or electrolytes or lipids) were noted. No subject had abnormalities in these parameters that led to treatment discontinuation or to reporting of a SAE. However, the following chemistries were reported as TEAEs:

- "Blood creatine phosphokinase increased":
  - Two subjects in the Q4W group (2.4%) and one subject each in the placebo and Q2W groups (1.2% each)
- "Transaminases increased": one subject each in the placebo and Q2W groups (1.2% each)
- "Liver function test increased": one subject in the placebo group (1.2%).

Mean LDH decreased from baseline in all treatment groups during the treatment period, but to a greater extent in the dupilumab groups compared to the placebo group. For all treatment groups, mean LDH values remained in the normal range. These patterns were observed in the adult AD program. The Applicant anticipated these trends, indicating that LDH levels correlate with severity and activity of AD.

Potentially clinically significant values (PCSVs) in chemistries were reported in all treatment groups and in no particular pattern.

Study 1434 (OLE)

The findings in the OLE generally did not reveal any new patterns in hematology parameters or in most white blood cell parameters relative to study 1526. Mean eosinophil counts trended downwards in the OLE. The Applicant theorizes that this may possibly have been due to subjects previous dupilumab exposure. "Eosinophil count increased" is the only parameter that was reported as a TEAE, and there was only one report.

The findings in the OLE generally did not reveal any new patterns in chemistry parameters. Mean LDH values trended towards decrease and remained within normal limits.

Vital Signs

No subject had abnormalities in vital signs that led to treatment discontinuation or to reporting of a SAE. No clinically-significant trends were noted in changes in vital signs in any treatment group. PCSVs were reported in all treatment groups and in no particular pattern. In study 1526, the PCSV of "Respiratory rate" ">20 bpm and <=20 bpm at baseline" was the only PCSV vital sign event that occurred at a higher incidence in the Q2W group (7.3%), compared to the Q4W and placebo groups (4.8% and 1.2%, respectively). In studies 1526 and 1434, the most common PCSV was diastolic

hypertension (>=95th percentile for gender, age and height; baseline <95th percentile and increase from baseline >=10 mmHg). In study 1526, this was reported at similar incidences in the placebo and Q2W groups, 20.0% and 20.7%, respectively (12.0% in the Q4W group). This PCSV was reported in 6.9% of subjects in the OLE study.

Electrocardiograms

The Applicant reported no clinically-meaningful trends in mean or median changes from baseline in electrocardiogram (ECG) parameters in any treatment group. No ECG findings eventuated in permanent discontinuation of study treatment or in the reporting of a SAE.

QT

The Applicant did not conduct a thorough QT study. Per the EOP2 meeting minutes that preceded the phase 3 program in adults and submission of the original BLA: "Monoclonal antibodies do not need to be evaluated in a thorough QT study. Routine ECG monitoring in phase 3 trials should be performed to capture important cardiac effects."

Immunogenicity

The TEAEs profile did not suggest a correlation between ADA positivity and events that might suggest loss of efficacy ("Dermatitis atopic") or in injection site reactions. In study 1526:

- "Dermatitis atopic" was reported in ADA-positive subjects as follows:
  - Q4W 17.6% (in ADA-negative: 20.0%)
  - Q2W 15.4% (in ADA-negative: 19.1%).
- Injection site reactions were reported in ADA-positive subjects as follows:
  - Q4W 11.8% (in ADA-negative: 10.8%)
  - Q2W 7.7% (in ADA-negative: 13.2%).

Also, see Section 6.2.1 of this review.

7.3.5. Analysis of Submission-Specific Safety Issues

Conjunctivitis

The approved package insert includes a Warning and Precaution, entitled "Conjunctivitis and Keratitis," driven by the signal for these events detected in the AD development program in adults.

The Applicant included “Any type of conjunctivitis or blepharitis (severe or serious)” and “Keratitis” among the designated AESIs in studies 1526 (pivotal) and 1434 (OLE). Table 21 below presents all of events of this type that were reported in study 1526.

Conjunctivitis events were more common in the dupilumab groups compared to placebo in study 1526. The OLE did not reveal any difference in the types of eye-related events; the same types of conjunctivitis events were reported in that study. Eye-related findings in studies 1526 and 1434 were similar to those observed in dupilumab-treated subjects in the adult studies in the AD population.

Table 21. Conjunctivitis Events During the Treatment Period in Study 1526 (Pivotal)*

System Organ Class Preferred Term	Placebo (n=85)	Dupilumab	
		300 mg Q4W (n=83)	200 mg or 300 mg Q2W (n=82)
Infections and infestations	37 (43.5%)	38 (45.8%)	34 (41.5%)
Conjunctivitis	1 (1.2%)	3 (3.6%)	4 (4.9%)
Conjunctivitis viral	0	2 (2.4%)	1 (1.2%)
Conjunctivitis bacterial	0	2 (2.4%)	0
Viral keratitis	0	1 (1.2%)	0
Eye disorders	7 (8.2%)	6 (7.2%)	6 (7.3%)
Conjunctivitis allergic	3 (3.5%)	4 (4.8%)	3 (3.7%)

*Sources: Table 8 of the Summary of Clinical Safety and Post text table 7.2.1.1/1 of the study report for 1526

In the OLE, the Applicant further evaluated conjunctivitis by performing a narrow customized MedDRA query (CMQ) containing five terms that included the term “Conjunctivitis.” Additionally, the Applicant conducted a broader CMQ containing 16 terms. This is similar to the approach that the Applicant took in the analysis of the data in the adult program once the signal had been identified. The terms included in each CMQ are listed with the respective tables below.

Summary of narrow CMQ search for conjunctivitis; study 1434 (OLE)

Under this search, 12 subjects (4.4%) reported a conjunctivitis event. The event was graded as severe for one subject (discussed above in Section 7.3.4). However, none of the events was serious, and none resulted in discontinuation of treatment.

Table 22. Number of Subjects With Treatment-Emergent Conjunctivitis by (Narrow CMQ) by Preferred Term in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)*

	Total (N=275)	Total(N=275) nP/PY (nP/100 PY))
Number of TEAEs	22	
Patients with at least one TEAE	12 (4.4%)	12/131.2 (9.149)
Conjunctivitis allergic	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	5 (1.8%)	5/135.8 (3.681)
Conjunctivitis bacterial	2 (0.7%)	2/138.8 (1.441)
Conjunctivitis viral	1 (0.4%)	1/141.5 (0.707)

*Source: Table 31 of the study report for 1434
Search terms for Narrow CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral and atopic keratoconjunctivitis
Subjects who experienced more than one TEAE were counted only once in each category
Abbreviations: CMQ, customized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; nP, number patients with events; TEAE, treatment emergent adverse event

Summary of broad CMQ search for conjunctivitis; study 1434 (OLE)

Under this search, the Applicant identified 16 subjects (5.8%) who experienced a conjunctivitis event.

Table 23. Number of Subjects With Treatment-Emergent Conjunctivitis (Broad CMQ) by Preferred Term in Study 1434–Adolescent ≥12 to <18 Years of Age (SAF)*

Preferred Term MedDRA version 20.1	Total (N=275)	Total (N=275) nP/PY (nP/100 PY)
Number of TEAEs	27	
Patients with at least one TEAE	16 (5.8%)	16/130.7 (12.240)
Conjunctivitis allergic	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	5 (1.8%)	5/135.8 (3.681)
Dry eye	3 (1.1%)	3/141.3 (2.124)
Conjunctivitis bacterial	2 (0.7%)	2/138.8 (1.441)
Conjunctivitis viral	1 (0.4%)	1/141.5 (0.707)
Eye pruritus	1 (0.4%)	1/141.5 (0.707)
Ocular hyperaemia	1 (0.4%)	1/141.5 (0.707)

*Source: Table 30 of study report for 1434
PTs included under Conjunctivitis Broad CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, Dry eye, eye irritation eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperaemia, conjunctival hyperaemia
Subjects who experienced more than one TEAE were counted only once in each category
Abbreviations: CMQ, customized MedDRA query; MedDRA, Medical Dictionary for Regulatory Activities; nP, number of patients with events; TEAE, treatment emergent adverse event.

Conclusion

The pattern of occurrence of conjunctivitis events in adolescents was similar to that seen in the adult program.

7.3.6. Safety Analyses by Demographic Subgroups

Table 24 presents the overall occurrence of TEAEs by subgroups. The number of subjects experiencing TEAEs was generally similar between treatment groups within each subgroup.

Table 24. Number of Subjects With TEAEs in Study 1526 by Subgroups*

	Placebo		Dupilumab			
			300 mg Q4W		200 mg or 300 mg Q2W	
	N (%)	# (%) with TEAEs	N (%)	# (%) with TEAEs	N (%)	# (%) with TEAEs
Age Group (yrs)						
≥12<15	41 (48.2%)	28 (68.3%)	45 (54.2%)	30 (66.7%)	43 (52.4%)	34 (79.1%)
≥15<18	44 (51.8%)	31 (70.5%)	38 (45.8%)	24 (63.2%)	39 (47.6%)	26 (66.7%)
Gender						
Male	53 (62.4%)	37 (69.8%)	51 (61.4%)	32 (62.7%)	43 (52.4%)	29 (67.4%)
Female	32 (37.6%)	22 (68.8%)	32 (38.6%)	22 (68.8%)	39 (47.6%)	31 (79.5%)
Ethnicity						
Not Hispanic or Latino	72 (84.7%)	50 (69.4%)	63 (75.9%)	41 (65.1%)	69 (84.1%)	50 (72.5%)
Hispanic or Latino	13 (15.3%)	9 (69.2%)	20 (24.1%)	13 (65.0%)	13 (15.9%)	10 (76.9%)
Race						
White	48 (56.5%)	34 (70.8%)	55 (66.3%)	37 (67.3%)	54 (65.9%)	40 (74.1%)
Black	15 (17.6%)	8 (53.3%)	8 (9.6%)	4 (50.0%)	7 (8.5%)	4 (57.1%)
Asian	13 (15.3%)	10 (76.9%)	13 (15.7%)	9 (69.2%)	12 (14.6%)	10 83.3%)
Other	6 (7.1%)	5 (83.3%)	7 (8.4%)	4 (57.1%)	7 (8.5%)	4 (57.1%)
Not reported or missing	3 (3.5%)	—	0	—	2 (2.4%)	—
Baseline weight group						
<60 kg	43 (50.6%)	31 (72.1%)	42 (50.6%)	27 (64.3%)	43 (52.4%)	35 (81.4%)
≥60 kg	42 (49.4%)	28 (66.7%)	41 (49.4%)	27 (65.9%)	39 (47.6%)	25 (64.1%)

*Sources: Post-text tables 7.2.1.1/2, 7.2.1.1/3, 7.2.1.1/4, 7.2.1.1/5, 7.2.1.1/6, 7.2.1.1/7 for study 1526

7.3.7. Specific Safety Studies/Clinical Trials

The Applicant did not conduct any specific safety study or clinical trial.

7.3.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported in the adolescent program. Six subjects (2.2%) reported seven events in the "Neoplasms benign, malignant and unspecified (including cysts and polyps)" SOC in the OLE study (1434): skin papilloma (5), hemangioma (1), and melanocytic nevus (1). No events were reported in this SOC in the pivotal study 1526.

Pediatrics and Assessment of Effects on Growth

The Applicant proposes a pediatric indication in the supplement that is the subject of this review. Therefore, this sBLA review pertains to a pediatric assessment. The sBLA did not include an assessment of the effects on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Investigators were instructed to report symptomatic overdose events in the study, and no such events were reported. The approved package insert advises the following in Section 10 ("OVERDOSE"):

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

Regarding abuse potential the Applicant states the following (Section 5.7 of the Summary of Clinical Safety):

> The molecule structure and weight, known mechanism of action, peripheral route of administration, and metabolic pathways of dupilumab do not suggest a potential for central nervous system activity or drug dependence potential, and abuse is unlikely. Nonclinical data did not yield events raising a concern of drug dependence or abuse.

The data (clinical and nonclinical) do not indicate a potential for addiction, abuse, or physical dependency with use of dupilumab.

In the phase 2a PK study, R668-AD-1412, the Applicant evaluated the impact of discontinuation of dupilumab on efficacy parameters. The Applicant observed a trend towards the return of signs and symptoms of AD towards baseline, but not a worsening beyond baseline. Therefore, the data did not indicate a potential for a rebound effect.

Four-Month Safety Update

The four-month safety update (SU) provided updates on the AE data from study 1434 (OLE), the only ongoing study in the adolescent program. The SU covered the period from 04/22/2018 (04/21/2018 was the data cut-point for the sBLA) through 08/15/2018. An additional 25 subjects were included in safety analysis set for the SU relative to the 275 subjects in the safety analysis set in the submission of the supplement, making for a cumulative disposition of 300 subjects by cut-point for the SU. Study 1434 is currently ongoing with 270 subjects at data cut-point for the SU.

Table 25. Study R668-AD-1434: Summary of Subject Disposition–Cumulative Until 15 August 2018, and 21 April 2018 (Adolescents ≥12 to <18 Years of Age)–SAF

	Cumulative until 15 Aug 2018 (data cutoff date for the 4-month SUR)	Cumulative until 21 Apr 2018 (data cutoff for the First-step Analysis for the sBLA)
	Total (N=300)	Total (N=275)
Patients in Safety Analysis Set (SAF)	300 (100%)	275 (100%)
Patients who completed study	5 (1.7%)[1]	1 (0.4%)[2]
Patients ongoing	270 (90.0%)	270 (98.2%)
Patients who discontinued from study with reason	25 (8.3%)	4 (1.5%)
Adverse Event	1 (0.3%)	0
Physician Decision	4 (1.3%)	1 (0.4%)
Lost to Follow-up	1 (0.3%)	1 (0.4%)
Withdrawal by Patient	9 (3.0%)	2 (0.7%)
Lack of Efficacy	8 (2.7%)	0
Death	0	0
Other	2 (0.7%)	0
Patients who completed ≥ Week 16	273 (91.0%)	142 (51.6%)
Patients who completed ≥ Week 24	200 (66.7%)	83 (30.2%)
Patients who completed ≥ Week 26	174 (58.0%)	69 (25.1%)
Patients who completed ≥ Week 52	34 (11.3%)	34 (12.4%)
Patients who completed ≥ Week 78	34 (11.3%)	34 (12.4%)
Patients who completed ≥ Week 104	34 (11.3%)	32 (11.6%)
Patients who completed ≥ Week 156	0	0
Patients who completed ≥ Week 208	0	0
Patients who completed ≥ Week 260	0	0

*Source: Table 2of the Safety Update
[1]Per the protocol, subjects who turned 18 years of age during the study were asked to complete an end of treatment visit for the OLE and subsequently transitioned to commercial dupilumab.

No deaths were reported during the interval.

One subject experienced an SAE:

- *Herpes simplex*. A 13-year-old white female developed perioral vesicles with throat pain on day 864 (after 82 doses of study treatment and 79 days after last dose) with progression to periocular distribution at some point (unstated). She was hospitalized on day 870, where ophthalmological examination documented acute keratoconjunctivitis. She improved rapidly with oral and topical antiviral treatment and eye drops. She was discharged on an unspecified day and continued in the study as planned. Verbatim term: Disseminated Herpes Simplex.

One subject experienced a TEAE that resulted in permanent discontinuation of study treatment:

- *Dermatitis atopic*. A 16-year-old Asian female enrolled with AD graded as moderate: IGA of 3, EASI of 24.6; BSA was 31%. By day 113, her best recorded responses were IGA 3. EASI 15.8. and BSA 22%. On day 176 (7 days after most recent dose), “worsening AD” was recorded. Her IGA remained 3, EASI was 22, and BSA was 36%. She was withdrawn from the study.

Three subjects experienced AESIs:

- *Conjunctivitis viral*. A 15-year-old Asian male was diagnosed with viral conjunctivitis on day 135. He was treated and recovered. Study treatment was interrupted for approximately 2 weeks. He resumed treatment and continued in the study as planned.
- *Suicidal ideation*. A 12-year-old white male with a history of anxiety and insomnia began experiencing suicidal thoughts on day 240 (after 16 doses of study treatment and 15 days after last dose). The event resolved the following day. The investigator related the event to the AD. The subject was also taking sertraline and continued in the study as planned.
- *AKC.* A 14-year-old white male began experiencing eye symptoms on day 213. He was evaluated by an ophthalmologist on an unspecified day and was treated with eye drops. The investigator graded the event as “mild.” He recovered and continued in the study as planned.

In the SU, the most-commonly reported TEAEs continued to be Nasopharyngitis and Upper respiratory tract infection.

Conjunctivitis

Under the narrow CMQ, 25 (8.3%) of subjects reported an event compared with 12 subjects (4.4%) in the original supplement submission.

Table 26. Study R668-AD-1434: Number of Subjects With Treatment-Emergent Narrow CMQ Conjunctivitis by Preferred Term (Cumulative Incidence) (Adolescents ≥12 to <18 Years of Age)–SAF*

Preferred Term MedDRA version 21.1	Cumulative until 15 Aug 2018 (data cutoff date for the 4-month SUR) Total (N=300)		Cumulative until 21 Apr 2018 (data cutoff date for the First-Step Analysis CSR for the sBLA) Total (N=275)	
	nP (nP/N)	nP/PY (nP/100 PY)	nP (nP/N)	nP/PY (nP/100 PY)
Number of TEAEs	40		22	
Patients with at least 1 TEAE	25 (8.3%)	25/211.9 (11.797)	12 (4.4%)	12/131.2 (9.149)
Conjunctivitis allergic	14 (4.7%)	14/219.6 (6.374)	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	9 (3.0%)	9/220.0 (4.090)	5 (1.8%)	5/135.8 (3.681)
Conjunctivitis bacterial	3 (1.0%)	3/224.6 (1.336)	2 (0.7%)	2/138.8 (1.441)
Conjunctivitis viral	2 (0.7%)	2/227.5 (0.879)	1 (0.4%)	1/141.5 (0.707)
Atopic keratoconjunctivitis	1 (0.3%)	1/227.9 (0.439)	0	0

*Source: Table 9 of the Safety Update
PTs included under Conjunctivitis Narrow CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral and atopic keratoconjunctivitis.

Under the broad CMQ, 29 (9.7%) of subjects reported an event compared with 16 subjects (5.8) in the original supplement submission.

Table 27. Study R668-AD-1434: Number of Subjects With Treatment-Emergent Broad CMQ Conjunctivitis by Preferred Term (Cumulative Incidence) (Adolescents ≥12 to <18 Years of Age)–SAF*

Preferred Term	Cumulative until 15 Aug 2018 (data cutoff date for the 4-month SUR) Total (N=300)		Cumulative until 21 Apr 2018 (data cutoff date for the First-Step Analysis CSR for the sBLA) Total (N=275)	
	nP (nP/N)	nP/PY (nP/100 PY)	nP (nP/N)	nP/PY (nP/100 PY)
Number of TEAEs	47		27	
Patients with at least 1 TEAE	29 (9.7%)	29/210.2 (13.793)	16 (5.8%)	16/130.7 (12.240)
Conjunctivitis allergic	14 (4.7%)	14/219.6 (6.374)	6 (2.2%)	6/136.4 (4.400)
Conjunctivitis	9 (3.0%)	9/220.0 (4.090)	5 (1.8%)	5/135.8 (3.681)
Conjunctivitis bacterial	3 (1.0%)	3/224.6 (1.336)	2 (0.7%)	2/138.8 (1.441)
Dry eye	3 (1.0%)	3/226.7 (1.323)	3 (1.1%)	3/141.3 (2.124)
Ocular hyperaemia	3 (1.0%)	3/227.3 (1.320)	1 (0.4%)	1/141.5 (0.707)
Conjunctivitis viral	2 (0.7%)	2/227.5 (0.879)	1 (0.4%)	1/141.5 (0.707)
Atopic keratoconjunctivitis	1 (0.3%)	1/227.9 (0.439)	0	0
Eye pruritus	1 (0.3%)	1/227.6 (0.439)	1 (0.4%)	1/141.5 (0.707)

*Source: Table 11 of the Safety Update
PTs included under Conjunctivitis Broad CMQ were: conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, Dry eye, eye irritation eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperaemia, conjunctival hyperaemia.

The Applicant reported the following outcomes for the 47 events identified under the broad analysis:

- 41 (87.2%) were resolved or resolving,
- 4 (8.5%) did not resolve by SU data cutoff,
- 1 (2.1%) had an unknown outcome, and
- 1 (2.1%) had a missing outcome.

Dupilumab continued to be well tolerated through the cut-point for the SU. The SU identified no new safety signals and raised no new safety concerns.

7.3.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Dupilumab is not currently approved for treatment of AD in patients <18 years of age.

Expectations on Safety in the Postmarket Setting

The data from adolescents provided in this supplement revealed a safety profile similar to that seen in adults. Therefore, based on the available safety data, the expectation is that the postmarketing experience for adolescents may be similar to adults.

7.3.10. Integrated Assessment of Safety

The sBLA did not include pooled data for an integrated safety assessment, due to the differing designs of the four studies that constituted the adolescent AD program. The safety database was comprised of 322 adolescent subjects (12 to 17 years of age) with moderate-to-severe AD who had received at least one dose of dupilumab by data cut-point for the sBLA. The safety review of the application focused on the placebo-controlled data from the pivotal study, 1526 (primary safety data) and the data from the OLE study, 1434 (supportive safety data).

No deaths occurred in the development program, and the incidence of SAEs was low. The single subject who experienced an SAE (appendicitis) in the primary safety group (study 1526), was in the placebo group. Of the four subjects who experienced SAEs in the OLE study (1434), only one experienced an event (injection site cellulitis) where a relationship to treatment was reasonably a consideration. However, there was no information to implicate dupilumab itself in the occurrence of this event; it could have been related entirely to injection procedures. The subject recovered fully and completed the study as planned.

Only one subject experienced a TEAE that led to permanent discontinuation of study treatment in studies 1526 and 1434. That subject was in the placebo group and was withdrawn from treatment due to worsening of AD. In the primary safety group (study 1526), all of the severe TEAEs of AD reported over the course of the study occurred in the dupilumab Q4W group. This could be interpreted as potential supportive evidence for the more frequent Q2W dosing regimen. Generally, the safety profiles between the Q4W and Q2W regimens were similar.

In studies 1526 and 1434, TEAEs were most-commonly reported in the Infections and infestations SOC. The two most frequently-reported events in that SOC in both studies were Upper respiratory tract infection and Nasopharyngitis, both of which are common illnesses in the general population.

Laboratory, vital signs and ECG findings were generally unremarkable or consistent with previous experience with dupilumab (eosinophils) or the disease state (LDH in AD). The safety profile did not suggest a correlation between ADA positivity and events that might suggest loss of efficacy (“Dermatitis atopic”) or in injection site reactions.

Conjunctivitis and Keratitis

“Conjunctivitis and Keratitis” is a Warning and Precautions sub-section in the approved dupilumab package insert, and it was driven by a signal identified in the AD program in adults. In the adolescent program, the Applicant included conjunctivitis and keratitis events among the AESIs, events that required expedited reporting. Additionally, and similar to what was done in the adult program, the Applicant performed CMQs in the OLE study to further evaluate this known signal.

Conjunctivitis events were more common in dupilumab-treated subjects compared to subjects who received placebo in study 1526. The OLE study did not reveal any difference in the types or character of eye-related events with longer-term dupilumab exposure. The incidences of conjunctivitis events under the narrow and broad CMQ analyses were higher in the OLE relative to the pivotal study. No eye disorders were recorded as SAEs. One case of “mild” keratitis was reported in a dupilumab-treated subject in study 1526 (pivotal). The subject was treated and recovered, and dupilumab dosing was not interrupted; the subject completed study treatment. One case of allergic conjunctivitis that occurred in study 1434 (OLE) was graded as “severe.” The subject was treated and continued dupilumab as planned. The experiences of these two subjects are consistent with those described in the label for adults, wherein subjects who experienced conjunctivitis or keratitis recovered or were recovering during dupilumab treatment. Based on review of placebo-controlled data (pivotal study 1526) and long-term data (study 1434), the patterns of occurrence and course of conjunctivitis and keratitis events in adolescents were similar to what was seen in the adult program.

The Applicant adequately evaluated the risk of eye disorders in adolescents. Additionally, the Applicant has adequate measures in place for continued assessment of these events in pediatric subjects in the ongoing, long-term study 1434. This study will ultimately enroll subjects down to 6 months of age, and the protocol specifies procedures for referral to an ophthalmologist and, per the protocol, preferably one with pediatric expertise or cornea and external eye disease subspecialty expertise.

Hypersensitivity

"Hypersensitivity" is labeled in the Warning and Precautions section of the approved package insert, based on the safety data from the AD program in adults. Labeled reactions noted in the adult program included generalized urticaria and serum sickness or serum sickness-like reactions. No systemic hypersensitivity reactions were reported in the adolescent program.

Concomitant Use of Topicals

Study 1526 was the only monotherapy study in the adolescent development program. The other three studies allowed concomitant topical therapies e.g., TCS, TCI. The safety profile of dupilumab when administered as monotherapy was similar to that when it was administered with concomitant topical therapy. Thus, the development program supports the labeling for use of dupilumab "with or without topical corticosteroids" and for the allowance of use of concomitant TCIs ("for problem areas only, such as the face, neck, intertriginous and genital areas") in adolescents.

7.4. Summary and Conclusions

7.4.1. Statistical Issues

There were no major statistical issues affecting the overall conclusion. The amount of missing data was relatively small (approximately 8%) at the primary timepoint, week 16. The results for the primary and secondary efficacy endpoints in Table 10 for both dupilumab dosing regimens (Q2W and Q4W) were statistically significant (p-values <0.001). Approximately 59% of the subjects were male, and 63% were white. The average age was about 14.5 years with an average weight of 65 kg. Due to the limited sample size, it was difficult to draw any meaningful conclusions in the efficacy analysis by subgroups (age, sex, race, weight, baseline disease severity).

7.4.2. Conclusions and Recommendations

To establish the effectiveness of dupilumab in the treatment of moderate to severe AD in adolescent subjects, the Applicant submitted results from a single randomized, multicenter, placebo-controlled phase 3 trial. The trial randomized 251 adolescent subjects (12 to <17 years of age) with moderate to severe AD defined as having IGA score of at least 3 (moderate), EASI ≥12, and BSA ≥10% at baseline. The primary efficacy endpoint was the proportion of subjects achieving an IGA score of 0 or 1, with

at least 2-grade improvement from baseline, at week 16. Both dupilumab Q2W and Q4W were statistically superior to placebo (p-values <0.001) for the primary and the secondary efficacy endpoints at week 16.

The Applicant comprehensively evaluated the safety of dupilumab in 322 subjects 12 to 17 years of age with moderate-to-severe AD. Safety assessments in the program were appropriate for the study population and indication and for what is known about the safety profile of dupilumab. The data allowed for adequate characterization of the safety of dupilumab in the target population of adolescent subjects. The safety evaluation identified no new signals or concerns, and the safety profile in adolescents was similar to that observed in adults with AD. Dupilumab was generally well-tolerated by adolescent subjects (12 to 17 years of age) with moderate-to-severe AD.

Results from the ongoing long-term study (1434) will continue to inform the safety of use of dupilumab in adolescents with moderate to severe AD. Information from this study along with product labeling and routine pharmacovigilance activities should serve as adequate risk mitigation strategies.

The submitted safety data support approval of the sBLA and the proposed expansion of the indication to allow for the “treatment of patients aged 12 years and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.” The data further support labeling for allowance of use of concomitant TCS and TCI.

8 Advisory Committee Meeting and Other External Consultations

This application was not discussed at an Advisory Committee Meeting.

9 Pediatrics

The approval letter for the original BLA (03/28/2017) details the following outstanding required pediatric assessments:

3183-1 Conduct a randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical therapy in subjects 6 years to less than 12 years of age with severe AD.

Final Protocol Submission: 03/18

Study Completion: 06/19

Final Report Submission: 09/19

3183-3 Conduct an open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe AD.

Final Protocol Submission: 04/18

Study Completion: 12/22

Final Report Submission: 03/23

3183-4 Conduct a safety, PK, and efficacy study in subjects 6 months to less than 6 years with severe AD.

Final Protocol Submission: 01/18

Study Completion: 08/21

Final Report Submission: 11/21

The Applicant provided the status of the outstanding pediatric assessments in the Annual Report submitted 05/25/2018 as Sequence 0264:

- The study in subjects 6 years to less than 12 years of age with severe AD (3183-1) is ongoing and "on track."
- The safety, PK, and efficacy study in subjects 6 months to less than 6 years with severe AD (3183-4) is enrolling. However, "the clinical trial authorization was slower than anticipated as several queries were received from the health authorities, all of which were successfully clarified and resolved. The study enrollment is also proving to be slower than anticipated."

The open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe AD (3183-3) is also ongoing. The Applicant provided data from this study for the adolescent population in this supplement (study 1434).

The Agency waived the pediatric study requirement for ages less than 6 months because necessary studies are impossible or highly impracticable. This is because dupilumab is indicated for the treatment of moderate to severe AD in patients whose disease is not adequately controlled with topical prescription therapies or for whom those therapies are not advisable, and it will be impractical to make this determination in patients younger than 6 months of age.

10 Labeling Recommendations

10.1. Prescribing Information

The medical officer has reviewed all labeling. Labeling negotiations were ongoing as this review closed.

10.2. Patient Labeling

11 Risk Evaluation and Mitigation Strategies (REMS)

The medical officer recommends product labeling and routine pharmacovigilance activities as the methods for postmarket risk evaluation and mitigation.

12 Postmarketing Requirements and Commitments

See Section 10.

13 Appendices

13.1. References

See footnotes in Section 2.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study R668-AD-1526 ("A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥12 to <18 years of age, with moderate-to-severe atopic dermatitis")

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 45		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 12		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 12 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

In this submission, the Applicant provided no new nonclinical information. Therefore, section 13.3 is not applicable to this review.

13.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

13.4.1. Individual Study Summary

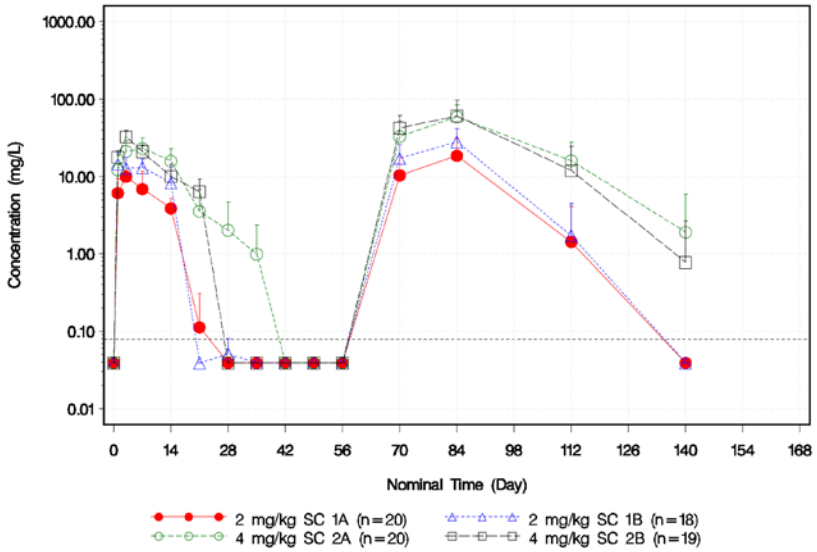
In the current sBLA, the Applicant submitted clinical pharmacology data from four dupilumab clinical trials in adolescent patients with moderate-to-severe AD: R668-AD-1526, R668-AD-1412, R668-AD-1434 and R668-AD-1607. The PK and immunogenicity data for phase 3 study R668-AD-1526 are summarized in Section 6 of this review. Note that it was decided internally that study R668-AD-1607 supporting the approval of the autoinjector presentation will be reviewed in a separate sBLA. This section provides individual study summary for phase 2a study R668-AD-1412 and the OLE phase 3 study R668-AD-1434.

13.4.1.1. Study R668-AD-1412

Study R668-AD-1412 was a phase 2a ascending dose, sequential cohort study of single dose and repeat doses of SC dupilumab in pediatric AD patients ≥6 to <18 years of age. Pediatric AD patients were administered with single dose in Part A followed by four repeated weekly doses of 2 mg/kg (Cohort 1) or 4 mg/kg (Cohort 2) in Part B.

The concentration-time profiles for dupilumab in serum are shown in Figure 11. The maximal concentrations were observed on day 2 through day 8 following a single SC administration. The PK results suggest concentration dependent elimination, consistent with target-mediated drug disposition.

Figure 11. Mean ± SD Serum Dupilumab Concentrations-Time Profiles in Study R668-AD-1412



1A and 2A, adolescents ≥12 to <18 years of age; 1Band 2B, children ≥6 to <12 years of age
Source: Figure 2, PK report for CSR R668-AD-1412

13.4.1.2. Study R668-AD-1434

This summary for study R668-AD-1434 is based on Applicant's individual study summary provided in Section 2.2.4 of the Summary of Clinical Pharmacology Studies.

Study R668-AD-1434 was an ongoing, phase 3, OLE study investigating the long-term safety, efficacy, PK, and immunogenicity of repeat monthly SC doses of dupilumab in pediatric patients with AD who have previously completed a clinical study with dupilumab (i.e., Studies R668-AD-1412, R668-AD-1526, and R668-AD-1607). Pediatric patients who had previously enrolled in prior dupilumab pediatric AD studies were given dupilumab 2 mg/kg QW, 4 mg/kg QW, 300 mg Q4W, or 200/300 Q2W, delivered by PFS. Only results from adolescent patients ≥12 years to <18 years of age were reported in this sBLA.

Patients aged ≥6 years to <18 years were started on a dose regimen of 300 mg Q4W. The dose was up-titrated in case of inadequate clinical response at week 16 to either 300 mg Q2W (for patients weighing ≥60 kg) or 200 mg Q2W (for patients weighing <60 kg). It should be noted that in the original protocol, patients received weight-based dosing of 2 mg/kg or 4 mg/kg; a fixed dose regimen of 300 mg Q4W was implemented with amendment 1.

Patients who rolled over from R668-AD-1412 received weight-based dosing (2 mg/kg QW or 4 mg/kg QW) for a significant duration (median duration of treatment exposure was around 89 weeks), before being switched to a fixed dose (300 mg Q4W). On the

other hand, patients who rolled over from R668-AD-1526 and R668-AD-1607 received a fixed dose from the time they enrolled into the study.

For patients entering from study R668-AD-1412, PK data were summarized through week 48, during which all patients were maintained on either 2 or 4 mg/kg QW. Individual PK and ADA data were presented for as long as week 104. For patients entering from R668-AD-1607 and R668-AD-1526, both summary and individual level data were presented through week 16. Samples for drug concentration assessments for the patients ≥12 years to <18 years were collected on days 1, 113, 365, 533, 729, 1065, 1401, and 1821. Samples for ADA analysis were collected at baseline, and weeks 4, 12, 24, 36, and 48 for patients recruited from parent study R668-AD-1412 and for patients recruited from R668-AD-1607 and R668-AD-1526, samples were collected at baseline and week 16.

PK Results

At the time of the data cut-off for this report, a total of 275 patients aged ≥12 to <18 years from parent studies were included in the study. Adolescent patients receiving a 2 mg/kg QW regimen achieved mean SS trough concentration at week 48 of 73 mcg/mL versus 161 mcg/mL for the 4 mg/kg QW regimen. The mean concentration of dupilumab at week 16 in adolescent patients from parent studies R668-AD-1526 and R668-AD-1607 who received 300 mg Q4W in R668-AD-1434 was 15.9 mcg/mL. In those adolescent patients who were up-titrated to 200 mg/300 mg Q2W due to inadequate response, mean trough concentrations at week 16 was approximately 45 mcg/L.

Immunogenicity Results

The overall incidence of treatment-emergent ADA in R668-AD-1434 was 26.5% and the responses were mostly transient and of low titer. The overall incidence of persistent ADA was 5.9%. Three (2.2%) high titer responses were observed (2 of the patients from study R668-AD-1412 who initially received a 2 mg/kg QW dose and one from study R668-AD-1526). Three (2.2%) moderate responses were observed in patients who received a 4 mg/kg QW regimen from parent study R668-AD-1412. The distribution of dupilumab concentrations for ADA positive patients was generally in the range of concentrations of ADA negative patients with the exception of a few patients with high or moderate ADA titers.

13.4.2.Population PK Analysis

The goal of population PK (popPK) analysis was to develop a popPK model to assess sources of variability (intrinsic and extrinsic covariates) of dupilumab in adolescent subjects with AD. The popPK model included 162 adolescent patients ≥12 years to <18 years of age with moderate to severe AD who were on active dupilumab treatment from

study R668-AD-1526. Among them 43 patients received dupilumab 200 mg Q2W, 37 received dupilumab 300 mg Q2W, and 82 received 300 mg Q4W.

The PK of dupilumab was characterized with a two-compartment model with parallel linear and nonlinear Michaelis-Menten elimination and transit compartments used to describe the absorption of dupilumab (Figure 12). Same model structure had been applied to the previous popPK model in adult AD patients. Population PK of dupilumab were characterized by nonlinear mixed-effects modeling using Monolix version 2018R1 (Lixoft). Parameter estimates of final model with significant covariates were provided in Table 28. Shrinkage was 25.3% and 54.3% for empirical bayes estimates of elimination rate and V2, respectively. There were small and inconsequential numeric differences in popPK parameters between adolescent and adult models. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 13 and Figure 14).

Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of dupilumab in all treatment groups (Figure 15). The final popPK model included statistically significant effects of body weight on apparent volume of distribution and body mass index, ADA and EASI on apparent elimination rate. The covariate coefficients for ADA, body mass index, EASI score, and body weight were similar to those in the adult model (Table 28). The effect of disease activity (EASI score) and ADA on dupilumab exposure is not clinically relevant. Body weight was a statistically significant and clinically relevant covariate on dupilumab exposure. Weight-tiered dosing regimen with a cut-off value of 60 kg was applied in the clinical trial.

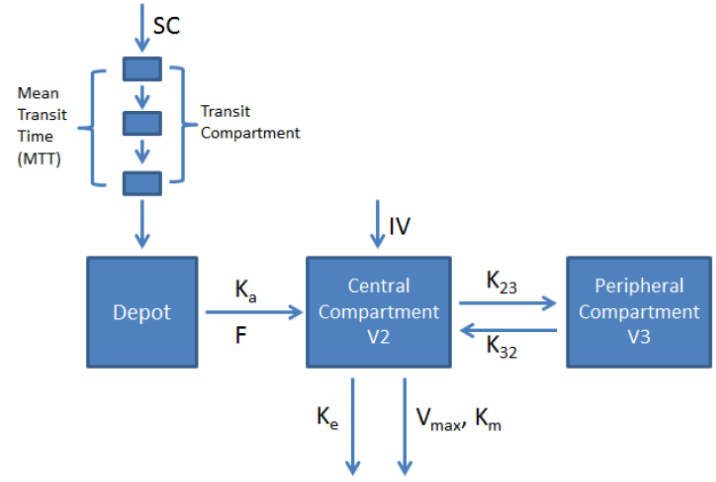
The dupilumab concentration-time profile in 1-year treatment period with the recommended weight-tiered Q2W dosing regimen was predicted based on the post hoc PK parameters in 162 adolescent AD patients from study R668-AD-2526 (Figure 16). The central tendency and variability of dupilumab concentrations were comparable between the two dosing regimens (200 mg Q2W and 300 mg Q2W). In addition, average, trough and maximum concentration at SS (the 26th dose) with the recommended dosing regimen were calculated. The distributions of C_{avg}, C_{trough}, and C_{max} achieved by the two dosing regimens were similar. The difference in median point estimate is within 10%. The SS C_{trough} of dupilumab achieved by the recommended dosing regimen (200/300 mg Q2W) in adolescent AD patients appears to be slightly lower (within 25%) than that in adult AD patients (300 mg Q2W), which is partly due to the difference in body weights between adolescent and adult patients.

Table 28. Parameter Estimates of the Final Model

Parameter Name	Adolescent Covariate Model		Adult Covariate Model	
	Population Estimate (SE)	Bootstrap Median (2.5^{th}, 97.5^{th} percentiles)	Population Estimate (SE)	Bootstrap Median (2.5^{th}, 97.5^{th} percentiles)
PK parameter				
V_2 (L)	2.47 (0.0501)	2.45 (2.34, 2.56)	2.74 (0.021)	2.72 (2.67, 2.78)
k_e (1/d)	0.0520 (0.00188)	0.0504 (0.0338, 0.0560)	0.0477 (0.00078)	0.0477 (0.0457, 0.0498)
V_m (mg/L/d)	1.43 (0.0379)	1.43 (1.25, 1.61)	1.07 (fixed)	---
k_{23} (1/d)	0.211 (fixed)	---	0.211 (fixed)	---
k_{32} (1/d)	0.310 (fixed)	---	0.310 (fixed)	---
k_a (1/d)	0.306 (fixed)	---	0.306 (fixed)	---
MTT (d)	0.105 (fixed)	---	0.105 (fixed)	---
K_m (mg/L)	0.01 (fixed)	---	0.01 (fixed)	---
F (unitless)	0.642 (fixed)	---	0.642 (fixed)	---
Covariates				
V_2 ~ weight	0.755 (0.0517)	0.722 (0.579, 0.845)	0.817 (0.031)	0.805 (0.740, 0.891)
V_2 ~ albumin	---	---	-0.653 (0.072)	-0.679 (-0.829, -0.536)
k_e ~ BMI	0.357 (0.116)	0.367 (0.0244, 0.809)	0.368 (0.053)	0.378 (0.225, 0.521)
k_e ~ ADA	0.193 (0.0566)	0.196 (0.0634, 0.325)	0.164 (0.029)	0.168 (0.103, 0.248)
k_e ~ EASI	0.356 (0.0523)	0.350 (0.237, 0.481)	0.143 (0.021)	0.147 (0.104, 0.198)
k_e ~ race (white)	---	---	-0.123 (0.018)	-0.116 (-0.168, -0.0749)
Omega Matrix				
$\sigma(\eta(V_2))^a$	0.304 (0.0242)	0.309 (0.105, 0.172)	0.206 (0.0068)	0.213 (0.198, 0.231)
$\sigma(\eta(k_e))$	0.140 (0.0145)	0.140 (0.245, 0.351)	0.293 (0.010)	0.306 (0.280, 0.332)
Corr (k_e,V_2)	-0.529 (0.0902)	-0.563	-0.450 (0.035)	-0.502
Residual SD				
σ prop. (CV%)	9.94 (0.602)	10.1 (7.19, 12.2)	12.5 (0.18)	12.3 (0.117, 0.132)
σ add. (mg/L)	2.36 (0.24)	2.33 (1.56, 3.81)	6.06 (0.23)	6.04 (4.85, 7.03)
Derived Parameters[b]				
CL (L/d)	0.128	---	0.131	---
Q (L/d)	0.521	---	0.578	---
V_3 (L)	1.68	---	1.86	---

Source: Table 10, Population PK report

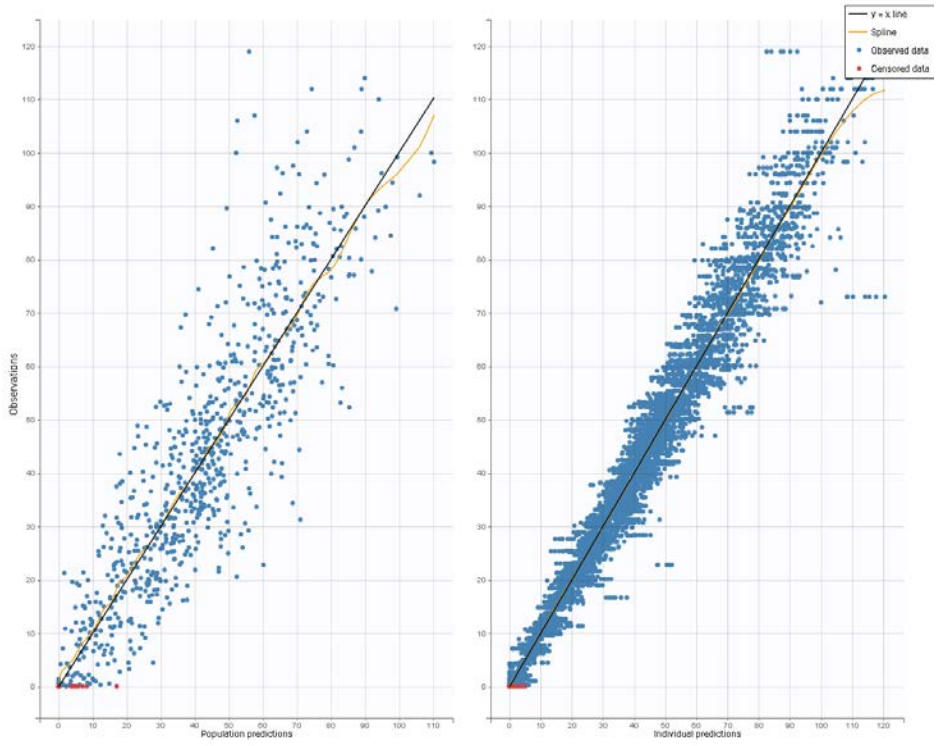
Figure 12. Structural Representation of Model With Parallel Michaelis-Menten and Linear Elimination of Dupilumab



F = Bioavailability; K_a = Absorption rate constant; MTT = Mean transit time; V_2 = Central compartment volume; V_3 = Peripheral compartment volume; k_{23}, k_{32} = Inter-compartmental rate constants; K_e = Elimination rate constant; V_m = Maximum target-mediated rate of elimination; K_m = Michaelis-Menten constant.

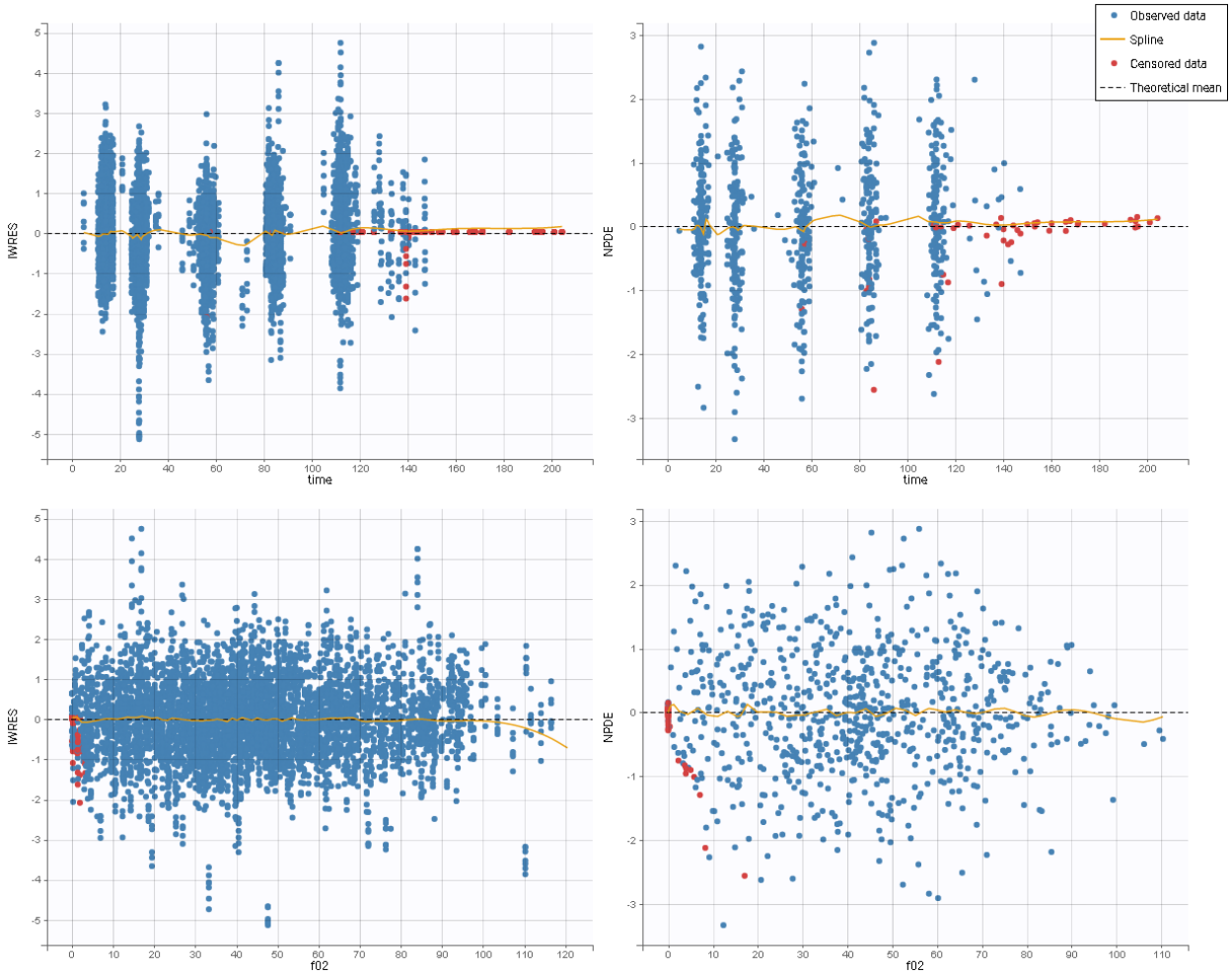
Source: Figure 2, Population PK report

Figure 13. Observed vs. Population and Individual Predicted Concentrations for Final Adolescent Model



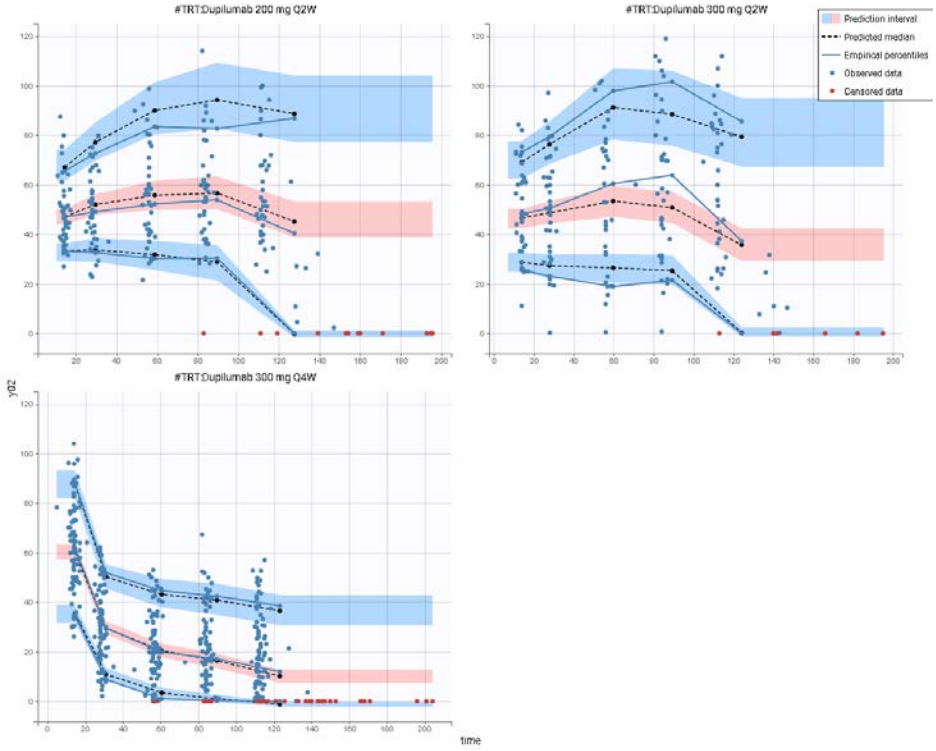
Source: Reviewer's analysis to confirm Figure 11 in Applicant's Population PK report

Figure 14. Scatter Plots of Residuals for Final Adolescent Model



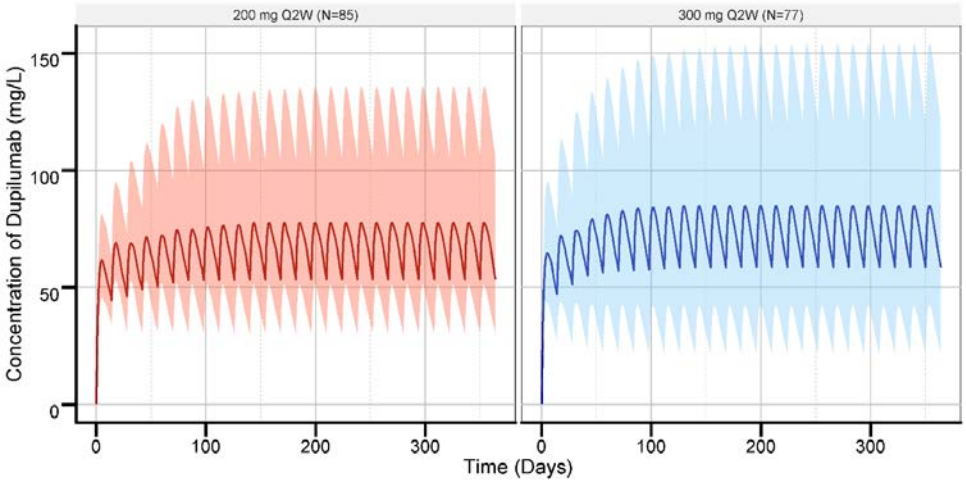
Source: Reviewer's analysis to confirm Figure 12 in Applicant's Population PK report

Figure 15. Visual Predictive Checks for Final Adolescent Model by Treatment vs. Actual Day



Source: Reviewer's analysis to confirm Figure 16 in Applicant's Population PK report

Figure 16. Predicted Dupilumab Concentration-Time Profile Based on Weight-Tiered Q2W Dosing Regimen



Dupilumab concentration was predicted based on post hoc PK parameters from 162 adolescent AD patients.
Solid line: Median. Colored bands: 5th and 95th percentile
Source: Reviewer's analysis based on final adolescent PK model

13.4.3.Dose/Exposure Response Relationships

In study R668-AD-1526, following the initial dosing both dose regimens (200 mg/300 mg Q2W and 300 mg Q4W) showed statistically significant improvement over placebo on both primary and secondary efficacy endpoints. The efficacy responses achieved with the weight-tiered Q2W regimen (adolescents <60 kg receiving 200 mg Q2W and adolescents ≥60 kg receiving 300 mg) were numerically higher to those with the 300 mg Q4W for the majority of efficacy endpoints (Table 29). Within the Q2W dosing regimen, the efficacy responses were observed to be lower in 300 mg Q2W group compared to 200 mg Q2W group despite similar observed dupilumab exposure (Table 30). However, this exploratory comparison is limited by small sample size and could be confounded by unknown baseline predictors.

Exposure-efficacy analyses were conducted in adolescents with moderate-to-severe AD receiving 200 mg Q2W (N=40), 300 mg Q2W (N=36) and 300 mg Q4W (N=81) from study R668-AD-1526. Efficacy endpoints include the co-primary endpoints, percentage of patients achieving an IGA score of 0 or 1 (IGA (0,1)) and reduction of 75% in EASI score from baseline (EASI-75), and the evaluated exposure metric was observed dupilumab concentration at week 16. Among 157 adolescent patients included in the analysis, the percentage of patients achieving an IGA score of 0 or 1 or a 75% reduction in EASI score is higher in quartiles of higher dupilumab concentration. Week 16 dupilumab concentration appears to be positively associated with both the co-primary efficacy endpoints. The final logistic regression model also identified dupilumab concentration at week 16 and disease severity (baseline EASI total score) as significant covariates on both IGA (0,1) and EASI-75 (Figure 2).

Exposure-safety relationship was also evaluated in 157 adolescent patients from study R668-AD-1526. Safety endpoint was conjunctivitis, the most commonly reported adverse drug reaction, and the evaluated exposure metric was observed dupilumab concentration at week 16. Percentage of patients developing conjunctivitis appears to be similar with increasing rank order of quartiles of dupilumab trough concentrations. No evident ER relationship for the probability of developing conjunctivitis was identified in the logistic regression analysis (Figure 7).

Table 29. Overview of Co-Primary and Key Secondary Efficacy Endpoints of Pivotal Study R668-AD-1526

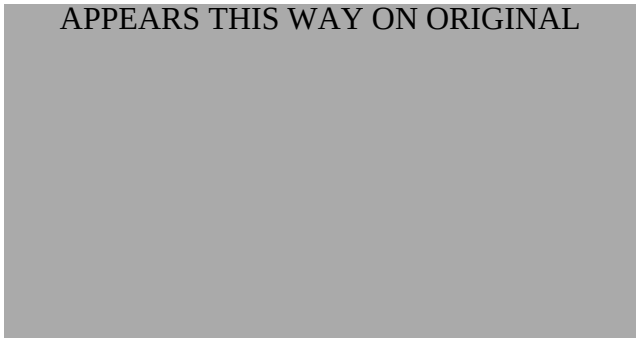
	Placebo	Dupilumab	
	N=85	300 mg Q4W N=84	200/300 mg Q2W N=82
Co-Primary Efficacy Endpoints			
Proportion of patients with IGA 0 to 1 (on a 5-point scale) at week 16			
n (%)[1]	2 (2.4)	15 (17.9)**	20 (24.4)*
Difference vs. placebo (95% CI)		15.5 (6.70, 24.31)	22.0 (12.20, 31.87)
Proportion of patients with EASI-75 (≥75% improvement from baseline) at week 16			
n (%)[1]	7 (8.2)	32 (38.1)*	34 (41.5)*
Difference vs. placebo (95% CI)		29.9 (17.94, 41.78)	33.2 (21.07, 45.39)
Key Secondary Efficacy Endpoints			
Percent change in EASI score from baseline to week 16			
LS mean (SE)[2]	-23.6 (5.49)	-64.8 (4.51)*	-65.9 (3.99)*
Difference vs. placebo (95% CI)		-41.2 (-54.44, -28.02)	-42.3 (-55.60, -29.04)
Percent change from baseline to week 16 in weekly average of daily peak Pruritus NRS			
LS mean (SE)[2]	-19.0 (4.09)	-45.5 (3.54)*	-47.9 (3.43)*
Difference vs. placebo (95% CI)		-26.5 (-37.45, -15.63)	-29.0 (-39.54, -18.38)
Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥3 from baseline to week 16			
n/N1[3] (%)[1]	8/85 (9.4)	32/83 (38.6)*	40/82 (48.8)*
Difference vs. placebo (95% CI)		29.1 (16.97, 41.32)	39.4 (26.90, 51.84)
Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus NRS ≥4 from baseline to week 16			
n/N1[4] (%)[1]	4/84 (4.8)	22/83 (26.5)*	30/82 (36.6)*
Difference vs. placebo (95% CI)		21.7 (11.21, 32.28)	31.8 (20.45, 43.20)

LS = least square; SE = standard error; CI = confidence interval
Source: Table 2, Clinical Overview

Table 30. Overview of Efficacy Endpoints by Treatment and Weight Groups (Study R668-AD-1526)

	200 mg Q2W (<60 kg) (n=40)	300 mg Q2W (>=60 kg) (n=36)	300 mg Q4W (<60 kg) (n=41)	300 mg Q4W (>=60 kg) (n=40)
Proportion of patients with IGA 0 to 1 at week 16	13 (32.5%)	7 (19.4%)	7 (17.1%)	8 (20%)
Proportion of patients with EASI-75 at week 16	20 (50.0%)	13 (36.1%)	18 (43.9%)	14 (35.0%)

Source: Reviewer's analysis based on dataset "adpcef.xpt"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LAURA L JOHNSON
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BRENDA CARR
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SNEZANA TRAJKOVIC
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KENDALL A MARCUS
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s012

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	February 14, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761055/S-012
Product Name and Strength:	Dupixent (dupilumab) Injection 200 mg/1.14 mL (175 mg/mL) 300 mg/2 mL (150 mg/mL) Prefilled Syringe (PFS)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc.
FDA Received Date:	February 11, 2019
OSE RCM #:	2018-1924-1
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (acting):	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

Division of Dermatology and Dental Products (DDDP) requested that we review the revised Prescribing Information (PI), Patient Package Insert (PPI), and Instructions for Use (IFU) for Dupixent (dupilumab) (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

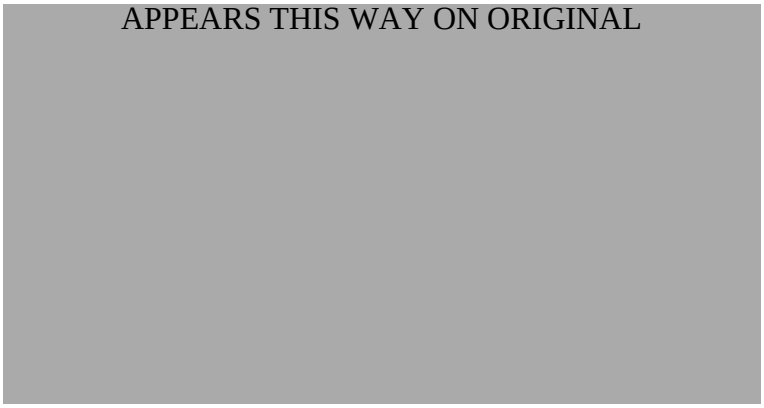
2 CONCLUSION

The revised PI, PPI, and IFU for Dupixent is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Patel, M. Labeling Review for Dupixent (dupilumab) BLA 761055/S-12. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 12. RCM No.: 2018-1924.

APPENDIX A. LABELING RECEIVED ON FEBRUARY 11, 2019

- Prescribing Information (Image not shown) received on February 11, 2019
- Patient Package Insert (Image not shown) received on February 11, 2019
- Instructions for Use (Image not shown) received on February 11, 2019



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/s/

MADHURI R PATEL
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02/14/2019 11:19:37 AM

LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	February 12, 2019
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761055/S-012
Product Name and Strength:	Dupixent (dupilumab) Injection 200 mg/1.14 mL (175 mg/mL) 300 mg/2 mL (150 mg/mL) Prefilled Syringe (PFS)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc.
FDA Received Date:	September 11, 2018 and October 30, 2018
OSE RCM #:	2018-1924
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader (acting):	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

Regeneron Pharmaceuticals, Inc. submitted a supplement for Dupixent (dupilumab) Injection, in order to provide for a new patient population [patients with moderate to severe atopic dermatitis (AD) aged 12 to less than 18 years of age]. Subsequently, the Division of Dermatology and Dental Products (DDDP) requested that we review the proposed Prescribing Information (PI) and Patient Package Insert (PPI) for areas that may lead to medication errors.

2 REGULATORY HISTORY

Dupixent (dupilumab) was approved on March 28, 2017 and is currently approved for the treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Dupixent is currently available as a prefilled syringe in 300 mg/2 mL and 200 mg/1.14 mL strengths.

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We reviewed the proposed revised PI and PPI from a medication error perspective. The currently approved dosage form and strength support the proposed treatment dose in patients 12 to less than 18 years of age. The PPI is acceptable from a medication error perspective. We note the PI can be improve to prevent confusion when using the dosing table.

Tables 2 below includes the identified medication error issues with the submitted labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Division of Dermatology and Dental Products (DDDP)

Prescribing Information			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information			
1.	Use of the symbols "<" and "≥" in the dosing table under the Dosage and Administration section.	The use of symbols could lead to misinterpretation and confusion.	Consider replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion per ISMP's recommendation[a]. For consistency, ensure this dosing table matches the dosing table in the Highlights, which we note does not use these symbols.

5 CONCLUSION

Our evaluation of the proposed labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division.

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 Oct 02]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Dupixent that Regeneron Pharmaceuticals, Inc. submitted on September 11, 2018.

Table 4. Relevant Product Information for Dupixent	
Initial Approval Date	September 28, 2017
Active Ingredient	dupilumab
Indication	Current: Atopic Dermatitis: Treatment of adult patients with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Asthma: Add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Proposed: Treatment of patients aged 12 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	200 mg/1.14 mL (175 mg/mL) 300 mg/2 mL (150 mg/mL)
Dose and Frequency	Current: Atopic Dermatitis: The recommended dose is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week. Asthma: The recommended dose is an initial dose of 400 mg (two 200 mg injections), followed by 200 mg given every other week or is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week. Proposed: Atopic Dermatitis:

<table>
<tr><td></td><td>Adults- The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week.

Adolescents 12 to 17 years of Age-
<table>
<tr><th>Body Weight of Patient</th><th>Initial Dose</th><th>Subsequent Doses (every other week)</th></tr>
<tr><td>less than 60 kg</td><td>400 mg (two 200 mg injections)</td><td>200 mg</td></tr>
<tr><td>60 kg or more</td><td>600 mg (two 300 mg injections)</td><td>300 mg</td></tr>
</table>
</td></tr>
<tr><td>How Supplied</td><td>Pack of 2 prefilled syringes with needle shield</td></tr>
<tr><td>Storage</td><td>Store refrigerated at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light.
If necessary, pre-filled syringes may be kept at room temperature up to 77°F (25°C) for a maximum of 14 days. Do not store above 77°F (25°C). After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded.</td></tr>
<tr><td>Container Closure</td><td>single-dose pre-filled syringe with needle shield in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On February 4, 2019, we searched the L:drive and AIMS using the terms, "dupixent" to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 5 relevant previous reviews[b,c,d,e,f], and we confirmed that our previous recommendations were implemented or considered.

Table 5. Summary of Previous DMEPA Reviews for Dupixent

OSE RCM #	Review Date	Summary of Recommendations
2016-1727 and 2016-2020	March 10, 2017	Recommendations for the Instructions for Use (IFU), carton labels, and container labeling.
2017-1170	August 21, 2017	No recommendations.
2017-1806	October 6, 2017	No further recommendations.
2018-346 and 2018-328	August 22, 2018	Recommendation of color scheme differentiation for new strength.
2018-348-1	September 12, 2018	No further recommendations.

[b] Mena-Grillasca, C. Human Factors, Label and Labeling Review for Dupixent (dupilumab) (BLA 761055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 10. RCM No.: 2016-1727 and 2016-2020.

[c] Mena-Grillasca, C. Human Factors and Labeling Review for Dupixent (dupilumab) (BLA 761055/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 AUG 21. RCM No.: 2017-1170.

[d] Mena-Grillasca, C. Labeling Review Memorandum for Dupixent (dupilumab) (BLA 761055/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 21. RCM No.: 2017-1806.

[e] Owens, L. Human Factors, Label and Labeling Review for Dupixent (dupilumab) (BLA 761055/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 AUG 22. RCM No.: 2018-346 and 2018-348.

[f] Owens, L. Label and Labeling Review Memorandum for Dupixent (dupilumab) (BLA 761055/S-007). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 12. RCM No.: 2018-348-1.

APPENDIX C. ISMP NEWSLETTERS

C.1 Methods

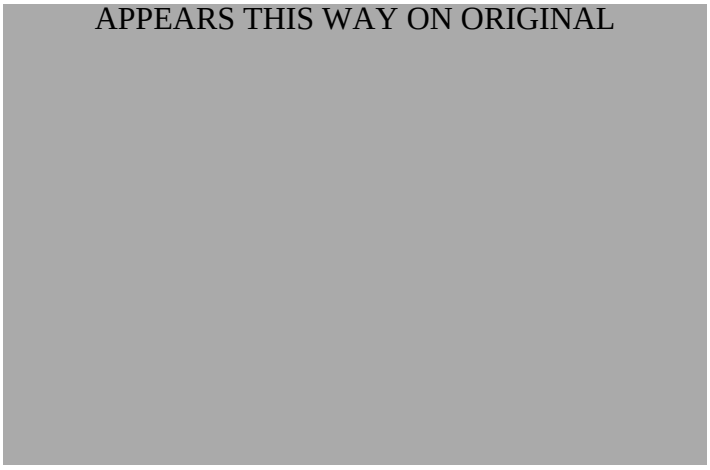
On February 4, 2019, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

Table 6. ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care ISMP Medication Safety Alert Community/Ambulatory Care ISMP Medication Safety Alert Nurse Advise-ERR Long-Term Care Advise-ERR ISMP Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: dupixent

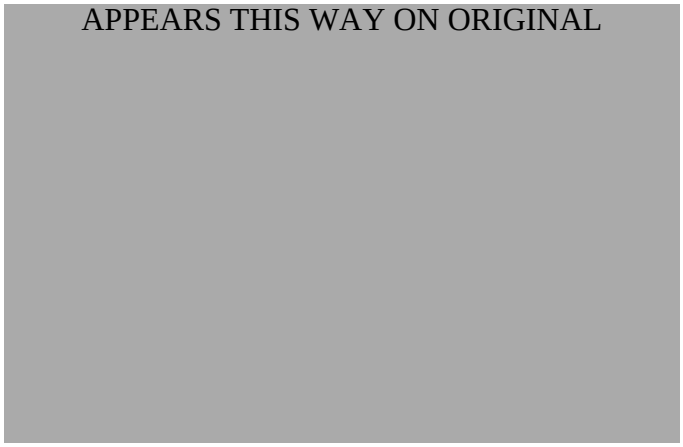
C.2 Results

The search retrieved no relevant articles associated with label and labeling for Dupixent.

APPENDIX D. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A



APPENDIX E. OTHER – N/A

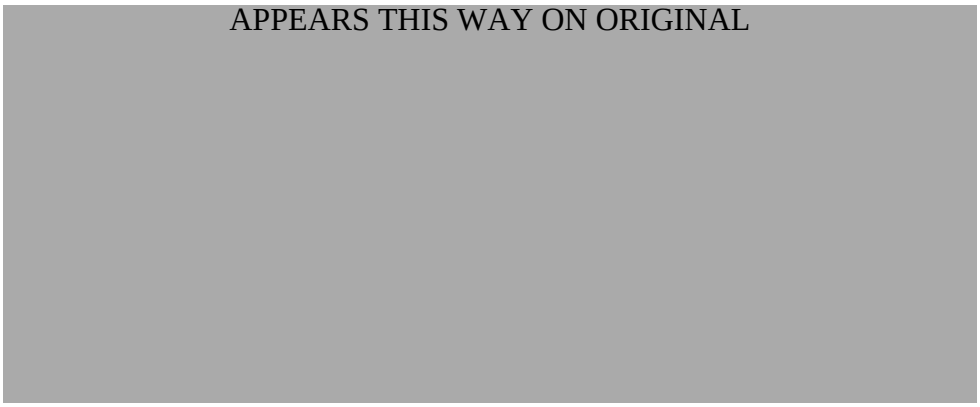


APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error data, we reviewed the following Dupixent labels and labeling submitted by Regeneron Pharmaceuticals, Inc. on October 30, 2018.

- Prescribing Information (Image not shown) received on October 30, 2018
- Patient Package Insert (Image not shown) received on October 30, 2018



[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

MADHURI R PATEL
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TERESA S MCMILLAN
02/13/2019 10:26:30 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	January 24, 2019
To:	Kendal Marcus, MD Director **Division of Dermatology and Dental Products (DDDP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	DMPP Concurrence with submitted: Patient Package Insert (PPI)
Drug Name (established name):	DUPIXENT (dupilumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761055
Supplement Number:	S-012
Applicant:	Regeneron Pharmaceuticals, Inc.

1 INTRODUCTION

On September 11, 2018, Regeneron Pharmaceuticals, Inc., submitted for the Agency's review a Prior Approval Supplement- Efficacy to their approved Biologics License Application (BLA) 761055/S-012 for DUPIXENT (dupilumab) injection. With this supplement, Regeneron Pharmaceuticals, Inc. proposes the following:

- a new patient population: for the treatment of patients ages $\geq$ 12 years to < 18 years with moderate to severe atopic dermatitis.
- a new presentation: 200 mg (175 mg/mL) auto-injector (pre-filled pen)

This memorandum documents the DMPP review and concurrence with the Applicant's proposed PPI for DUPIXENT (dupilumab) injection.

2 MATERIAL REVIEWED

- Draft DUPIXENT (dupilumab) injection PPI received on September 11, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on January 23, 2019.
- Draft DUPIXENT (dupilumab) injection Prescribing Information (PI) received on September 11, 2018, revised by the Review Division throughout the review cycle, and received by DMPP on January 23, 2019.
- Approved DUPIXENT (dupilumab) injection labeling dated October 19, 2018.

3 CONCLUSIONS

We find the Applicant's proposed PPI acceptable as submitted.

4 RECOMMENDATIONS

- Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.
- Upon approval, insert the Month and Year revised at the bottom of the PPI.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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SHARON R MILLS
01/24/2019 01:54:40 PM

LASHAWN M GRIFFITHS
01/24/2019 02:13:41 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 24, 2019

To: Brenda Carr, M.D., Clinical Reviewer,
Division of Dermatology and Dental Products (DDDP)

Matthew White, Regulatory Project Manager, (DDDP)

Barbara Gould, Regulatory Project Manager, (DDDP)

Nancy Xu, Associate Director for Labeling, (DDDP)

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for DUPIXENT® (dupilumab) injection, for subcutaneous use (Dupixent)

BLA: 761055/S-012

In response to DDDP's consult request dated September 12, 2018, OPDP has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI) for the supplemental BLA submission for Dupixent.

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI and PPI received by electronic mail from DDDP on January 22, 2019, and our comments are provided below.

Carton and Container Labeling: OPDP was notified by DDDP that the proposed pre-filled pen would no longer be considered under this supplement (S-012), and therefore, has not reviewed the carton and container labeling submitted by the Sponsor on September 11, 2018, to the electronic document room.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

31 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

LAURIE J BUONACCORSI
01/24/2019 10:06:38 AM

Clinical Inspection Summary

Date	January 2, 2019
From	Cheryl Grandinetti, Pharm.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Matthew White, R.P.M. Brenda Carr, MD, Clinical Reviewer Snezana Trajkovic M.D., Clinical Team Leader Kendall Marcus, M.D., Division Director Division of Dermatology and Dental Products
BLA #	761055/S-012
Applicant	Regeneron Pharmaceuticals, Inc
Drug	Dupixent (dupilumab)
NME	No
Review Priority	Priority
Proposed Indication	Treatment of patients with moderate to severe atopic dermatitis aged 12 to <18 years of age
Consultation Request Date	October 12, 2018
Summary Goal Date	February 8, 2019
Action Goal Date	March 11, 2019
PDUFA Date	March 11, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Cohen and Lockshin were inspected in support of this NDA. At Dr. Lockshin's site, some discrepancies were noted between the source documents at the site and the data line listings provided by the sponsor for a key secondary efficacy measure (i.e., the Eczema Area and Severity Index (EASI) assessment) for three subjects. The data discrepancies were due to transcription errors made by site personnel when entering values from the original paper source document into the electronic data capture system. However, the critical EASI assessments for this secondary efficacy endpoint occurred at Visit 2 (Baseline, Day 1) and Visit 18 (Week 16, end of treatment); therefore, because these data discrepancies occurred only during Visits 3, 4, 8, and 10, they likely do not have an impact on the efficacy results of the study. We defer to the review division whether they wish to correct these EASI assessment values in their database.

Otherwise, the study appears to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final compliance classification of the inspection of Dr. Cohen was No Action Indicated (NAI) and of Dr. Lockshin was Voluntary Action Indicated (VAI).

II. BACKGROUND

Regeneron Pharmaceuticals, Inc submitted this supplemental application in support of the use of dupilumab for the treatment of adolescent subjects, aged 12 years or greater to less than 18 years, with moderate-to-severe atopic dermatitis (AD). The key study supporting this application was Protocol R668-AD-1526, "A randomized, double-blind, placebo-controlled, parallel-group study to investigate the efficacy and safety of dupilumab monotherapy in patients ≥ 12 to < 18 years of age with moderate-to-severe atopic dermatitis."

This was a randomized, double-blind, placebo-controlled, parallel-group study with a primary objective to investigate the efficacy and safety of dupilumab monotherapy in adolescent subjects, aged 12 years to less than 18 years, with moderate-to-severe AD.

Subjects: 251 subjects were enrolled

Sites: 45 sites in North America

Study Initiation and Completion Dates: 21 March 2017 to 5 April 2018.

The study consisted of a screening period of up to 5 weeks, treatment period of 16 weeks, and follow-up of 12 weeks. During the screening period, systemic and topical treatments for AD were washed out, as applicable, according to the eligibility requirements. During the treatment period, subjects who met eligibility criteria at baseline underwent baseline (day 1) assessments and were stratified by baseline weight group (<60 kg and ≥60kg) and baseline disease severity (moderate [IGA=3] vs. severe [IGA=4] AD) and randomized in a 1:1:1 ratio to one the following treatment groups:

- **Dupilumab every two-week (Q2W) treatment group:**
  - Subjects with baseline weight <60 kg received 400 mg loading dose on day 1, followed by dupilumab 200 mg, administered subcutaneously Q2W.
  - Subjects with baseline weight ≥60 kg received 600 mg loading dose on day 1, followed by dupilumab 300 mg administered subcutaneously Q2W.

- **Dupilumab every four-week (Q4W) treatment group:**
  - Subjects received a 600 mg loading dose on day 1, followed by 300 mg dupilumab administered subcutaneously Q4W. To maintain blinding, subjects received placebo injection at the weeks dupilumab was not given.

- **Placebo treatment group:**
  - Subjects received placebo matching dupilumab 200 mg or 300 mg Q2W (including doubling the amount of placebo on day 1 to match the loading dose).
  - In order to maintain blinding for the study, subjects in the <60 kg weight stratum received, in a 1:1 ratio, either placebo matching 200 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose) or placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose).

- In the ≥60 kg weight stratum, subjects randomized to the placebo group received placebo matching 300 mg dupilumab (including doubling the amount of placebo on day 1 to match the loading dose). To maintain blinding, all subjects received an injection Q2W from day 1 to week 14.

The primary efficacy endpoint in the study was the proportion of subjects with Investigator's Global Assessment (IGA) 0 or 1 (on a 5-point scale) at week 16.

Key secondary endpoints included the following:

- Proportion of subjects with Eczema Area and Severity Index (EASI)-75 (≥75% improvement from baseline) at week 16
- Proportion of patients with EASI-90 at week 16
- Proportion of patients with improvement (reduction) of weekly average of daily peak Pruritus Numerical Rating Scale (NRS ≥4) from baseline to week 16

Rationale for Site Selection

The clinical sites were chosen primarily based on the number of enrolled subjects, positive treatment effects, reported financial disclosures, and no prior inspectional history.

III. RESULTS (by site):

Site / Name of CI/ Address	Protocol #/ # of Subjects Enrolled	Inspection Dates	Classification
Site #840033 **David Cohen, MD** 308 Coliseum Drive, Suite 200 Macon, GA 31217 Phone:478-742-2180 Fax:478-745-2623 Email: (b) (6)	R668-AD-1526 Subjects: 10	26-29 Nov 2018	NAI
Site #840016 **Benjamin Lockshin, MD** 15245 Shady Grove Road, Suite 480 Rockville, MD 20850 Phone:301-355-3183 Fax:301-355-3065 Email:blockshin@dermassociates.com	R668-AD-1526 Subjects: 16	29 Oct 2018 to 01 Nov 2018	VAI

Key to Compliance Classifications
NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable

1. David Cohen, M.D

At this site for Protocol R668-AD-1526, 12 subjects were screened and 10 were enrolled, all of whom completed the study. Study and subject source records were reviewed for all 12 subjects. Records reviewed included, but were not limited to, informed consent process and documentation, protocol amendments, FDA 1572s, financial disclosure forms, IRB approvals and correspondence, randomization, case report forms, drug accountability records, adverse event reporting, source records for the primary and secondary efficacy endpoints, sponsor correspondence, and monitoring logs.

There was no evidence of under-reporting of adverse events. All primary and secondary efficacy data points were compared against the data listings provided by the sponsor. No discrepancies were noted.

2. Benjamin Lockshin, M.D.

At this site for Protocol R668-AD-1526, 16 subjects were screened and enrolled, and 15 subjects completed the study. As reported in the Clinical Study Report, one subject did not wish to continue in the trial and withdrew consent. Study and subject source records were reviewed for all 16 subjects. Records reviewed included, but were not limited to, financial disclosure, informed consent procedure and documentation, IRB documentation, randomization, protocol deviations, adverse events, source records for primary and secondary efficacy endpoints, drug accountability, subject study visits, and monitoring logs.

There was no evidence of under-reporting of adverse events. The primary efficacy endpoint and key secondary efficacy endpoint data were compared against the data listings provided by the sponsor. No discrepancies were noted for the primary efficacy endpoint.

Although a Form FDA 483, Inspectional Observations, was not issued at the close of the inspection, after OSI review of the Establishment Inspection Report (EIR), the inspection was classified as VAI for inadequate and/or inaccurate records. Specifically, the following data discrepancies were noted during the inspection for the key secondary endpoints. Of note, the data discrepancies were due to transcription errors made by site personnel when entering values from the original paper source document located at the site into the electronic data capture system.

Subject Number	Study Visit/Date	EASI Assessment -- Raw Data Points	Sponsor Data Listing Submitted to FDA	Source Data at the Clinical Investigation Site
(b) (6)	Visit 3 (Week 1) (b) (6)	Trunk AD severity score	5.4	3.6
	Visit 4 (Week 2) (b) (6)	Head AD severity score	0.40	0.60
	Visit 4 (Week 2) (b) (6)	Lower Extremity AD severity score	1.6	1.4

(b) (6)	Visit 3 (Week 1) (b) (6)	Lower Extremity AD severity score	21.60	48.60
(b) (6)	Visit 10 (Week 8) (b) (6)	Head AD severity score	3.25	3.75
	Visit 10 (Week 8) (b) (6)	Total Score	63.55	64.05

Reviewer's Comment: The data discrepancies observed during the inspection involved the EASI raw data scores, a measure used to assess a key secondary efficacy endpoint. The critical EASI assessments for the secondary efficacy endpoint occurred at Visit 2 (Baseline, Day 1) and Visit 18 (Week 16, end of treatment); therefore, because these data discrepancies occurred during Visits 3, 4, 8, and 10 for the above subjects, they likely do not have an impact on the efficacy results of the study. We defer to the review division whether they wish to correct the above EASI assessment values in their database.

Although, as noted above, no Form FDA 483 was issued for inadequate and inaccurate records, the FDA field investigator discussed this finding with Dr. Lockshin during the closeout meeting. Dr. Lockshin acknowledged these discrepancies and committed to improvements in the future.

{See appended electronic signature page}

Cheryl Grandinetti, Pharm.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

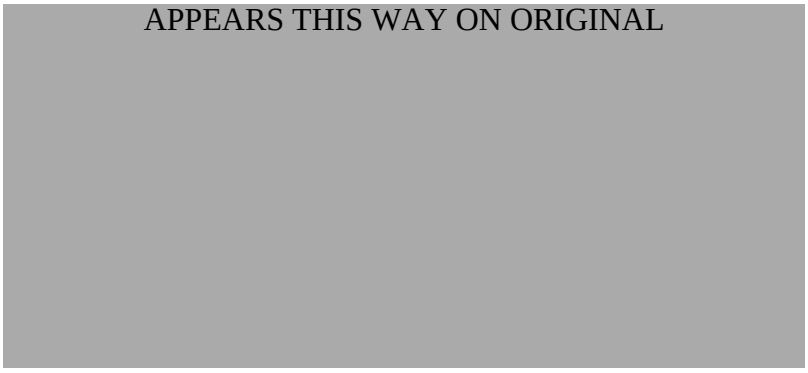
{See appended electronic signature page}

Phillip Kronstein, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm. BLA 761055/S-012
DNP /Project Manager/Matthew White
DNP /Medical Officer/Brenda Carr
DNP/ Clinical Team Leader/Snezana Trajkovic
DNP/Division Director/ Kendall Marcus
OSI/DCCE/Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/Team Leader/Phillip Kronstein
OSI/DCCE/GCP Reviewer/Cheryl Grandinetti
OSI/ GCP Program Analysts/Yolanda Patague
OSI/Database Project Manager/Dana Walters

APPEARS THIS WAY ON ORIGINAL



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