CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761055Orig1s017

Trade Name:	**DUPIXENT**
Generic or Proper Name:	(dupilumab)
Sponsor:	REGENERON PHARMACEUTICALS, INC.
Approval Date:	June 18, 2020

Indication:

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

- For the treatment of patients aged 6 years and older with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.
  DUPIXENT can be used with or without topical corticosteroids.

- 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.

- As an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).
  Limitations of Use
  Not for the relief of acute bronchospasm or status asthmaticus.

CENTER FOR DRUG EVALUATION AND RESEARCH

761055Orig1s017

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s017

APPROVAL LETTER

BLA 761055/S-015
BLA 761055/S-017

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 applications (sBLAs) BLA 761055/S-015, dated and received January 24, 2019, and BLA 761055/S-017, dated and received May 20, 2019, and your amendments, submitted under section 351(a) of the Public Health Service Act for DUPIXENT (dupilumab) injection, for subcutaneous use.

We acknowledge receipt of your major amendment to S-017 dated March 9, 2020, which extended the goal date for this supplement by three months.

Changes Being Effected supplemental biologics application S-015 provides for updating the label with information for patients and prescribers about an enrolling pregnancy exposure registry.

Prior Approval supplemental biologics application S-017 provides for a new 300 mg (150 mg/mL) pre-filled pen presentation.

APPROVAL & LABELING

We have completed our review of these applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

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 FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information,

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

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 *SPL Standard for Content of Labeling Technical Qs and As*.[2]

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).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling and carton and container labeling submitted to S-017 on May 20, 2019, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved BLA 761055/S-017**." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

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,

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

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 Dentistry
Office of Drug Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
  - Instructions for Use
- Carton and Container Labeling

[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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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
06/18/2020 05:11:02 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s017

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, Atopic Dermatitis (1.1)	05/2020
Dosage and Administration (2; 2.4; 2 5)	06/2020
Dosage and Administration, Atopic Dermatitis (2.1; 2.4)	05/2020
Warnings and Precautions (5.2)	05/2020

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

- for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1.1)
- as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)
- as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). (1.3)

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

DOSAGE AND ADMINISTRATION

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

Atopic Dermatitis

Adults

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

Pediatric Patients

Body Weight	Initial Dose	Subsequent Doses[a]
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg Q4W
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg Q2W
60 kg or more	600 mg (two 300 mg injections)	300 mg Q2W

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

Asthma

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

Chronic Rhinosinusitis with Nasal Polyposis

- The recommended dose of DUPIXENT for adult patients is 300 mg given every other week. (2.3)

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)
- Injection: 300 mg/2 mL solution in a single-dose pre-filled pen (3)

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

DRUG INTERACTIONS

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

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

Revised: 06/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DUPIXENT is indicated for the following diseases:

1.1 Atopic Dermatitis

DUPIXENT is indicated for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids.

1.2 Asthma

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

Limitation of Use

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

1.3 Chronic Rhinosinusitis with Nasal Polyposis

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

2 DOSAGE AND ADMINISTRATION

DUPIXENT is administered by subcutaneous injection, either by pre-filled syringe or pre-filled pen. The DUPIXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older.

2.1 Atopic Dermatitis

Dosing in Adults

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

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

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

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

Body Weight	Initial Dose	Subsequent Doses
15 to less than 30 kg	600 mg (two 300 mg injections)	300 mg every 4 weeks (Q4W)
30 to less than 60 kg	400 mg (two 200 mg injections)	200 mg every other week (Q2W)
60 kg or more	600 mg (two 300 mg injections)	300 mg every other week (Q2W)

Concomitant Topical Therapies

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

2.2 Asthma

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

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

2.3 Chronic Rhinosinusitis with Nasal Polyposis

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

2.4 Important Administration Instructions

DUPIXENT is intended for use under the guidance of a healthcare provider. A patient may self-inject DUPIXENT after training in subcutaneous injection technique using the pre-filled syringe or pre-filled pen. The DUPIXENT pre-filled pen is only for use in adults and adolescents aged 12 years and older. In adolescents 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult. Dupixent pre-filled syringe should be given by a caregiver in children 6-11 years of age. Provide proper training to patients and/or caregivers on the preparation and administration of DUPIXENT prior to use according to the "Instructions for Use".

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

For atopic dermatitis and asthma patients taking an 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 an every other week 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.

If an every 4 week 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 administer the dose, starting a new schedule based on this date.

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

2.5 Preparation for Use of DUPIXENT

Before injection, remove DUPIXENT from the refrigerator and allow DUPIXENT to reach room temperature (45 minutes for the 300 mg/2 mL pre-filled syringe or pre-filled pen 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 or pre-filled pen.

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
- Injection: 300 mg/2 mL in a single-dose pre-filled pen

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 or keratitis recovered or were recovering during the treatment period *[see Adverse Reactions (6.1)]*.

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

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

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 were reported in adult patients who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult patients who participated in the asthma development program as well as in adult patients with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Reduction of Corticosteroid Dosage

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

be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

5.6 Patients with Co-morbid Asthma

Advise patients with atopic dermatitis or CRSwNP who have co-morbid asthma 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 co-morbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

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

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

Weeks 0 to 16 (Trials 1 to 4)

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 reaction	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 (12 to 17 Years of Age)

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

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

Week 16 in Trial 6. The long-term safety profile of DUPIXENT observed in adolescents was consistent with that seen in adults with atopic dermatitis.

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

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

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

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 Warnings and Precautions (5.3)]*.

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

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

Chronic Rhinosinusitis with Nasal Polyposis

A total of 722 adult subjects with chronic rhinosinusitis with nasal polyposis (CRSwNP) were evaluated in 2 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (CSNP Trials 1 and 2). The safety pool consisted of data from the first 24 weeks of treatment from both studies.

In the safety pool, the proportion of subjects who discontinued treatment due to adverse events was 5% of the placebo group and 2% of the DUPIXENT 300 mg Q2W group.

Table 4 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in CSNP Trials 1 and 2.

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

Adverse Reaction	CSNP Trials 1 and 2	
	DUPIXENT 300 mg Q2W N=440 n (%)	Placebo N=282 n (%)
Injection site reactions[a]	28 (6%)	12 (4%)
Conjunctivitis[b]	7 (2%)	2 (1%)
Arthralgia	14 (3%)	5 (2%)
Gastritis	7 (2%)	2 (1%)
Insomnia	6 (1%)	0 (<1%)
Eosinophilia	5 (1%)	1 (<1%)
Toothache	5 (1%)	1 (<1%)

[a] Injection site reactions cluster includes injection site reaction, pain, bruising and swelling.
[b] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.

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

Specific Adverse Reactions

Conjunctivitis and Keratitis

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). In DUPIXENT atopic dermatitis monotherapy trials (Trials 1, 2, and 4) through Week 16, keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per

100 subject-years). In the 52-week atopic dermatitis DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial (Trial 3), keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with conjunctivitis or keratitis recovered or were recovering during the treatment period.

Among asthma subjects, the frequency of conjunctivitis was similar between DUPIXENT and placebo. In the 52-week CRSwNP study (CSNP Trial 2), the frequency of conjunctivitis was 3% in the DUPIXENT subjects and 1% in the placebo subjects; all of these subjects recovered. *[see Warnings and Precautions (5.2)]*.

Eczema Herpeticum and Herpes Zoster

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

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

Hypersensitivity Reactions

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

Eosinophils

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

Across all indications, the incidence of treatment-emergent eosinophilia (≥500 cells/mcL) was similar in DUPIXENT and placebo groups. Treatment-emergent eosinophilia ≥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.

In the 24-week placebo controlled trial in subjects with CRSwNP (CSNP Trial 1), cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.7%) of the DUPIXENT group and 0 (0.0%) of the placebo group. In the 1-year placebo controlled trial in subjects with CRSwNP (CSNP Trial 2), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

6.2 Immunogenicity

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

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

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

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

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

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

Two adult subjects who experienced high titer antibody responses developed serum sickness 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 adult 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

Pregnancy Exposure Registry

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

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

Risk Summary

Available data from case reports and case series with DUPIXENT use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Human IgG antibodies are known to cross the placental barrier; therefore, DUPIXENT may be transmitted from the mother to the developing fetus. There are adverse effects on maternal and fetal outcomes associated with asthma in pregnancy (*see Clinical* Considerations). In an enhanced pre- and post-natal developmental study, no adverse developmental effects were observed in offspring born to pregnant monkeys after subcutaneous administration of a homologous antibody against interleukin-4-receptor alpha (IL-4Rα during organogenesis through parturition at doses up to 10-times the maximum recommended human dose (MRHD) (*see Data*). The 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 6 years of age and older with moderate-to-severe atopic dermatitis.

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

Use is also supported by Trial 7, an open-label extension study that enrolled subjects who completed Trials 6 and 8. Trial 7 included 136 adolescents from Trial 6 and 110 children from Trial 8 with moderate atopic dermatitis at enrollment into the extension study. Trial 7 included 64 adolescents from Trial 6 and 72 children from Trial 8 with severe atopic dermatitis at enrollment. No new safety signals were identified in Trial 7 *[see Adverse Reactions (6.1)]*.

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

Asthma

A total of 107 adolescents aged 12 to 17 years with moderate-to-severe asthma were enrolled in AS Trial 2 and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or matching

placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both adolescents and adults. For both the 200 mg and 300 mg Q2W doses, improvements in FEV_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)]*.

CRSwNP

CRSwNP does not normally occur in children. Safety and efficacy in pediatric patients (<18 years of age) with CRSwNP have not been established.

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.

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

10 OVERDOSE

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

11 DESCRIPTION

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

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 either a single-dose pre-filled syringe with needle shield or a single dose pre-filled pen in a siliconized Type-1 clear glass syringe. The needle cap is not made with natural rubber latex.

Each 300 mg pre-filled syringe or pre-filled pen 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, atopic dermatitis, and CRSwNP. Multiple cell types that express IL-4Rα (e.g., mast cells, eosinophils, macrophages, lymphocytes, epithelial cells, goblet cells) and inflammatory mediators (e.g., histamine, 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 decreased certain biomarkers. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. 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, asthma, and CRSwNP.

Absorption

Following an initial subcutaneous (SC) dose of 600 mg, 400 mg, or 300 mg, dupilumab reached peak mean ± SD concentrations (C_{max}) of 70.1±24.1 mcg/mL, 41.8±12.4 mcg/mL, or 30.5±9.39 mcg/mL respectively, by approximately 1 week post dose. Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose and 300 mg dose

either weekly (twice the recommended dosing frequency) or Q2W, or 400 mg starting dose and 200 mg dose Q2W, or 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD steady-state trough concentrations ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W, from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.

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

Distribution

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

Elimination

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

Dose Linearity

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

Weight

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

Age

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

Immunogenicity

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

Specific Populations

Geriatric Patients

In subjects who are 65 years and older, the mean ± SD steady-state trough concentrations of dupilumab were 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.

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

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)

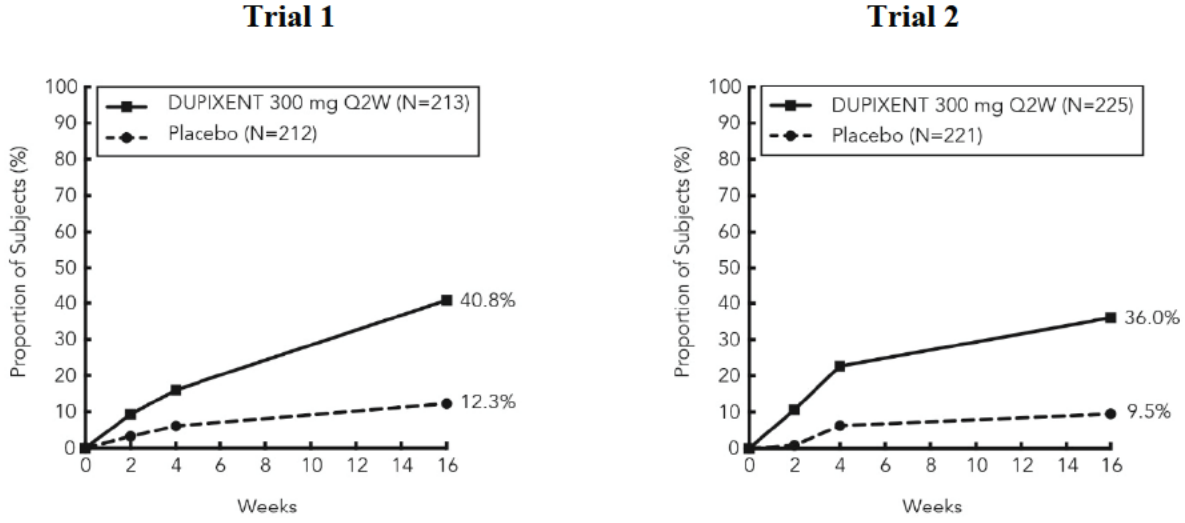
The results of the DUPIXENT monotherapy trials (Trials 1 and 2) and the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 5.

Table 5: 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 6.

Table 6: 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 (12 to 17 Years of Age)

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 7.

Table 7: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)[a]

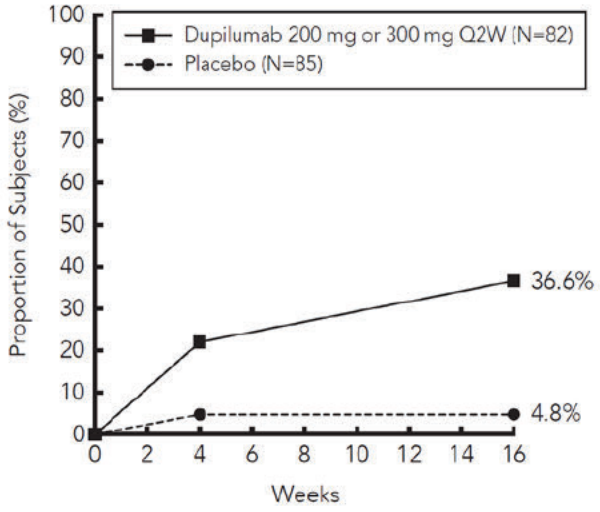
	DUPIXENT[d] 200 mg (<60 kg) or 300 mg (≥60 kg) Q2W N=82[a]	**Placebo N=85[a]**
IGA 0 or 1[b,c]	24%	2%

	DUPIXENT[d] 200 mg (<60 kg) or 300 mg (≥60 kg) Q2W N=82[a]	Placebo N=85[a]
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.

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

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (Trial 8; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; ≥30 kg).

Subjects in the DUPIXENT Q4W + TCS group received an initial dose of 600 mg on Day 1, followed by 300 mg Q4W from Week 4 to Week 12, regardless of weight. Subjects in the

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

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

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

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

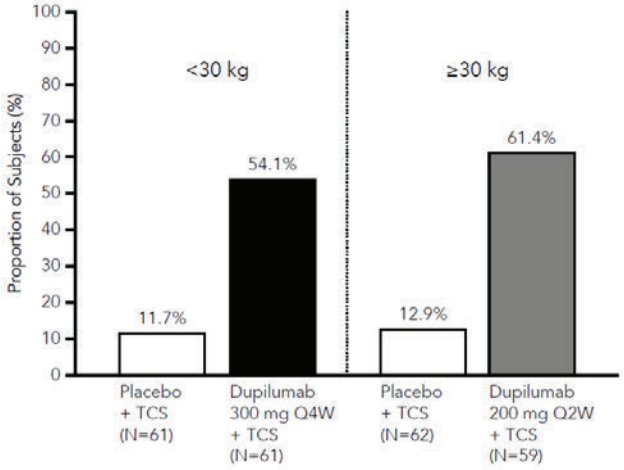
Table 8: Efficacy Results of DUPIXENT with Concomitant TCS in Trial 8 at Week 16 (FAS)[a]

	DUPIXENT 300 mg Q4W[d] + TCS (N=61)	**Placebo + TCS (N=61)**	**DUPIXENT 200 mg Q2W[e] + TCS (N=59)**	**Placebo + TCS (N=62)**
	<30 kg	**<30 kg**	**≥30 kg**	**≥30 kg**
IGA 0 or 1[b,c]	30%	13%	39%	10%
EASI-75[c]	75%	28%	75%	26%
EASI-90[c]	46%	7%	36%	8%
Peak Pruritus NRS (≥4-point improvement)[c]	54%	12%	61%	13%

[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").
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.
[d] At Day 1, subjects received 600 mg of DUPIXENT.
[e] At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUPIXENT.

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

Figure 3: Proportion of Pediatric Subjects with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in Trial 8[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 9 below.

Table 9: 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 10.

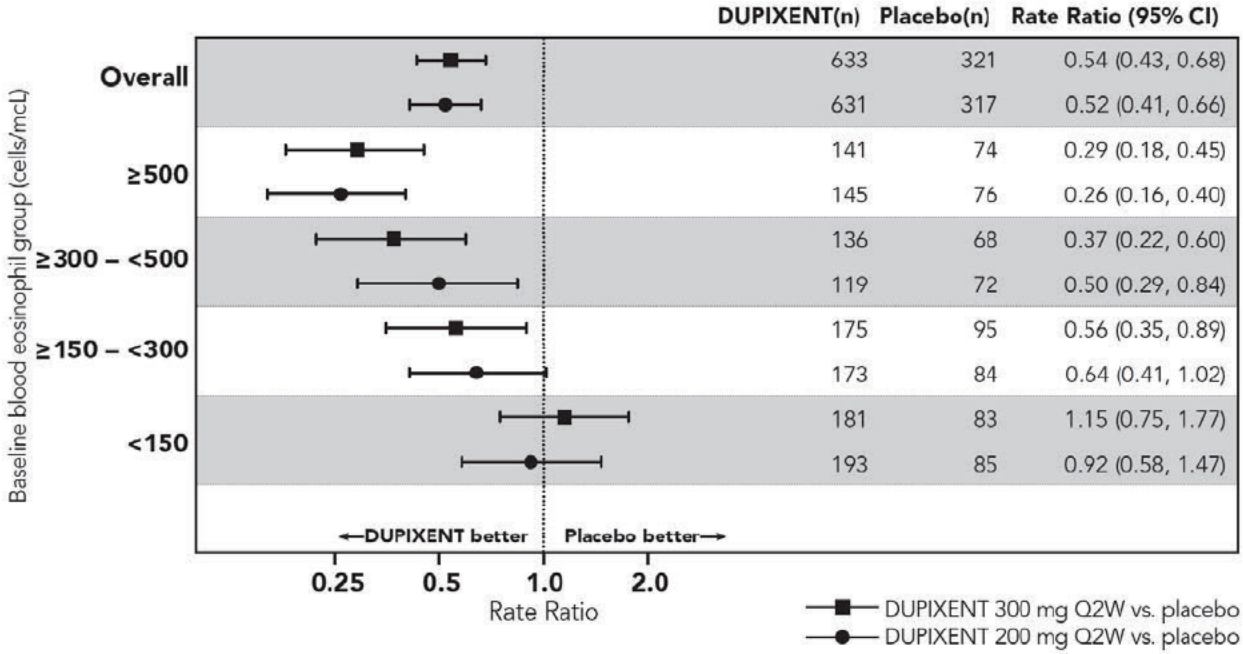
Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 4. Pre-specified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils ≥150 cells/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 10: Rate of Severe Exacerbations in AS Trials 1 and 2

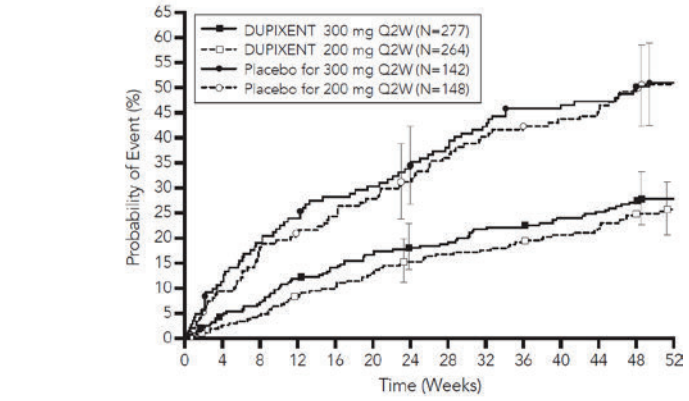
Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)		
		N	Rate (95% CI)	Rate Ratio (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)
	DUPIXENT 300 mg Q2W	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)
	Placebo	68	1.04 (0.57, 1.90)	
AS Trial 2	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 4: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline Blood Eosinophil Count (cells/mcL) in AS Trial 2



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

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



Number at Risk

DUPIXENT 300 mg Q2W	277	244	221	208	189	145
DUPIXENT 200 mg Q2W	264	240	220	210	195	154
Placebo for 300 mg Q2W	142	108	94	75	69	54
Placebo for 200 mg Q2W	148	116	100	84	72	52

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

Lung Function

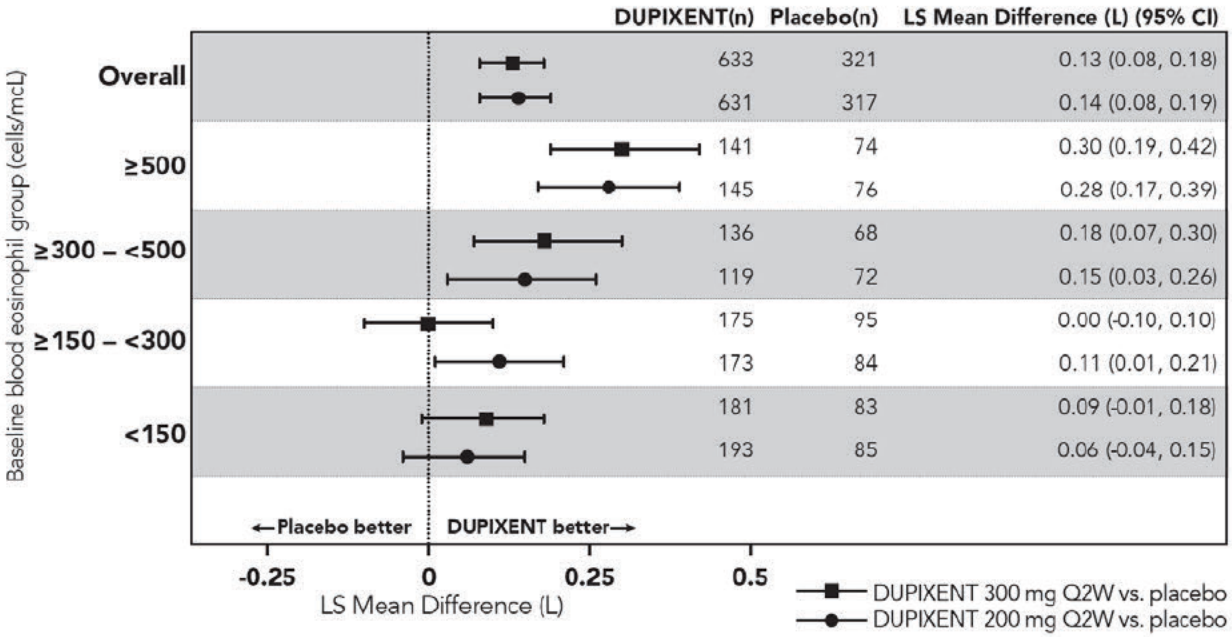
Significant increases in pre-bronchodilator FEV_1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV_1 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 11.

Improvements in FEV_1 by baseline blood eosinophils for AS Trial 2 are shown in Figure 6. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils.

Table 11: Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV_1 at Week 12 in AS Trials 1 and 2

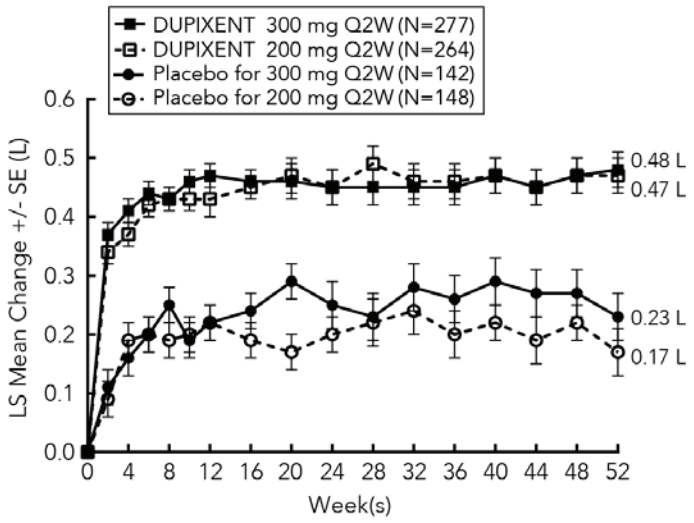
Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)		
		N	LS Mean Change from baseline L (%)	LS Mean Difference vs. placebo (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.43 (25.9)	0.26 (0.11, 0.40)
	DUPIXENT 300 mg Q2W	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	68	0.18 (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 6: 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 7.

Figure 7: 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.

14.3 Chronic Rhinosinusitis with Nasal Polyposis

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) in 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg DUPIXENT (N=143) or placebo (N=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized to receive either 300 mg DUPIXENT (N=150) every other week for 52 weeks, 300 mg DUPIXENT (N=145) every other week until week 24 followed by 300 mg DUPIXENT every 4 weeks until week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD.

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

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

The demographics and baseline characteristics of these 2 trials are provided in Table 12 below.

Table 12: Demographics and Baseline Characteristics of CRSwNP Trials

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

[a] Higher scores indicate greater disease severity
SD = standard deviation; AM = morning; NPS = nasal polyps score; SNOT-22 = 22-item sino-nasal outcome test; NSAID-ERD = asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Clinical Response (CSNP Trial 1 and CSNP Trial 2)

The results for primary endpoints in CRSwNP studies are presented in Table 13.

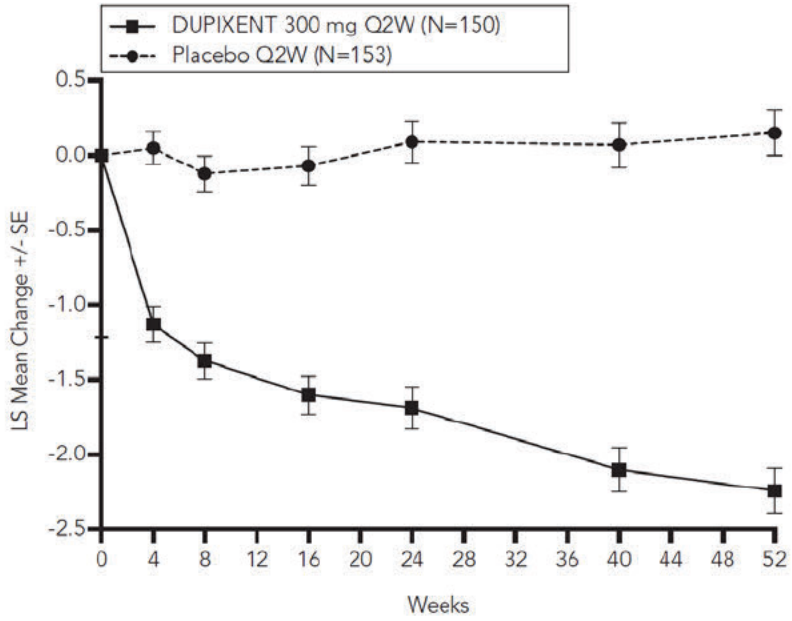
Table 13: Results of the Primary Endpoints in CRSwNP Trials

	CSNP Trial 1					CSNP Trial 2				
	Placebo (n=133)		**DUPIXENT 300 mg Q2W (n=143)**		**LS mean difference vs. Placebo (95% CI)**	**Placebo (n=153)**		**DUPIXENT 300 mg Q2W (n=295)**		**LS mean difference vs. Placebo (95% CI)**
Primary Endpoints at Week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change		Baseline mean	LS mean change	Baseline mean	LS mean change	
NPS	5.86	0.17	5.64	-1.89	-2.06 (-2.43, -1.69)	5.96	0.10	6.18	-1.71	-1.80 (-2.10, -1.51)
NC	2.45	-0.45	2.26	-1.34	-0.89 (-1.07, -0.71)	2.38	-0.38	2.46	-1.25	-0.87 (-1.03, -0.71)

A reduction in score indicates improvement.
NPS = nasal polyps score; NC = nasal congestion/obstruction

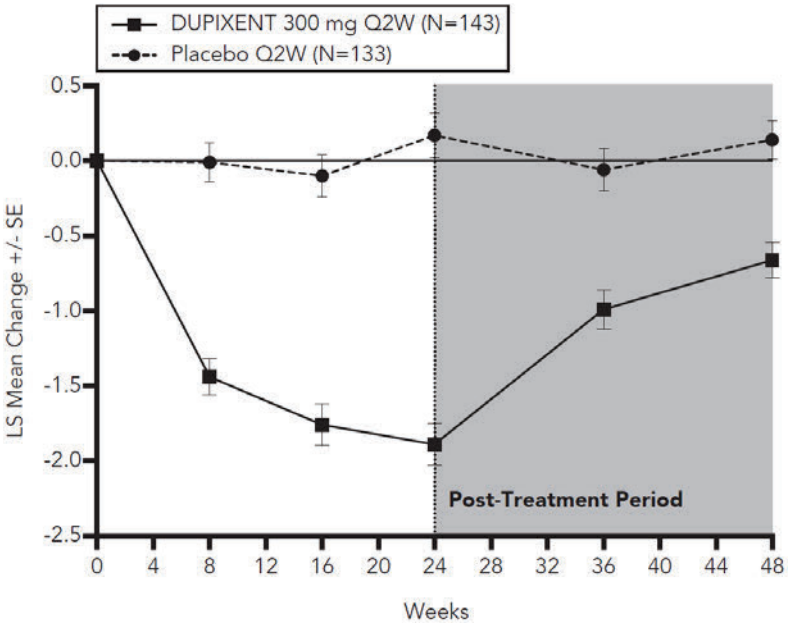
Statistically significant efficacy was observed in CSNP Trial 2 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 8).

Figure 8: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 52 in CSNP Trial 2 - ITT Population



Similar results were seen in CSNP Trial 1 at Week 24. In the post-treatment period when subjects were off DUPIXENT, the treatment effect diminished over time (see Figure 9).

Figure 9: LS Mean Change from Baseline in Bilateral Nasal Polyps Score (NPS) up to Week 48 in CSNP Trial 1 - ITT Population



At Week 52, the LS mean difference for nasal congestion in the DUPIXENT group versus placebo was -0.98 (95% CI -1.17, -0.79). In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. The LS mean difference for nasal congestion at Week 4 in the DUPIXENT group versus placebo was -0.41 (95% CI: -0.52, -0.30) in CSNP Trial 1 and -0.37 (95% CI: -0.46, -0.27) in CSNP Trial 2.

A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in CSNP Trial 1 and -5.13 (95% CI: -5.80, -4.46) in CSNP Trial 2. At Week 52, in CSNP Trial 2 the LS mean difference for LMK sinus CT scan score in the DUPIXENT group versus placebo was -6.94 (95% CI: -7.87, -6.01).

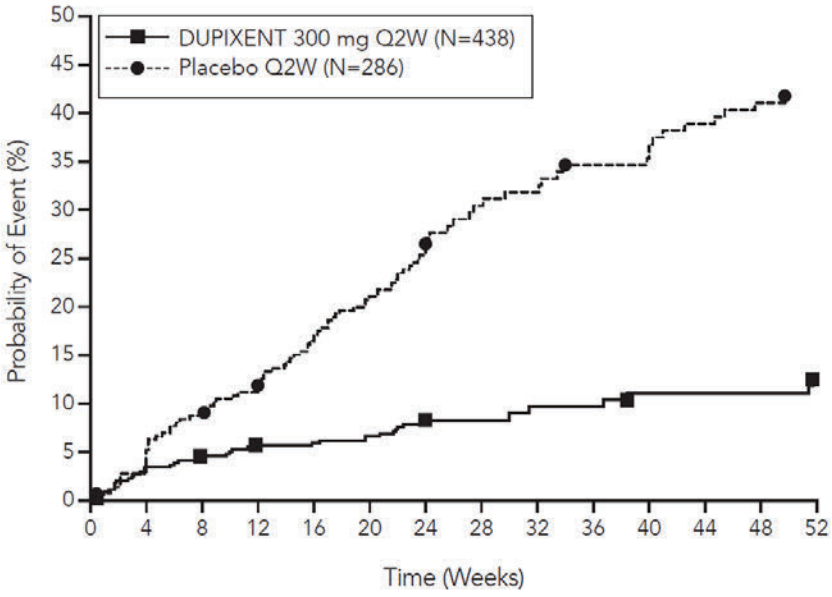
Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.12 (95% CI: -1.31, -0.93) in CSNP Trial 1 and -0.98 (95% CI: -1.15, -0.81) in CSNP Trial 2. At Week 52, the LS mean difference for loss of smell in the DUPIXENT group versus placebo was -1.10 (95% CI -1.31, -0.89). In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4.

Dupilumab significantly decreased sino-nasal symptoms as measured by SNOT-22 compared to placebo. The LS mean difference for SNOT-22 at Week 24 in the DUPIXENT group versus placebo was -21.12 (95% CI: -25.17, -17.06) in CSNP Trial 1 and -17.36 (95% CI: -20.87, -13.85) in CSNP Trial 2. At Week 52, the LS mean difference in the DUPIXENT group versus placebo was -20.96 (95% CI -25.03, -16.89).

In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with DUPIXENT resulted in significant reduction of systemic corticosteroid use and need for sino-nasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35) (see Figure 10). The

proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46).

Figure 10: Kaplan Meier Curve for Time to First Systemic Corticosteroid Use and/or Sino-Nasal Surgery During Treatment Period - ITT population CSNP Trial 1 and CSNP Trial 2 Pooled



Number at Risk						
DUPIXENT 300 mg Q2W	438	416	411	376	129	100
Placebo Q2W	286	260	253	187	93	61

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

In subjects with co-morbid asthma, improvements in pre-bronchodilator FEV_1 were similar to patients in the asthma program.

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 or pre-filled pens. 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). Each pre-filled pen is designed to deliver 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5915-00).

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

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

Pack Size	300 mg/2 mL Pre-filled Pen
Pack of 2 pens	NDC 0024-5915-02

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, DUPIXENT 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 DUPIXENT to heat or direct sunlight.

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

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

Pregnancy Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy. Encourage participation and advise patients about how they may enroll in the registry *[see Use in Specific Populations (8.1)]*.

Administration Instructions

Provide proper training to patients and/or caregivers on proper subcutaneous injection technique, including aseptic technique, and the preparation and administration of DUPIXENT prior to use. Advise patients to follow 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)]*.

Patients with Co-morbid Asthma

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

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

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

What is DUPIXENT?

DUPIXENT is a prescription medicine used:

- to treat people aged 6 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.
- with other medicines for the maintenance treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled.

- DUPIXENT is not used to treat sudden breathing problems.
- DUPIXENT works by blocking two proteins that contribute to a type of inflammation that plays a major role in atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.
- It is not known if DUPIXENT is safe and effective in children with atopic dermatitis under 6 years of age.
- It is not known if DUPIXENT is safe and effective in children with asthma under 12 years of age.
- It is not known if DUPIXENT is safe and effective in children with chronic rhinosinusitis with nasal polyposis under 18 years of age.

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

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

- have eye problems
- have a parasitic (helminth) infection
- are scheduled to receive any vaccinations. You should not receive a “live vaccine” if you are treated with DUPIXENT.
- are pregnant or plan to become pregnant. It is not known whether DUPIXENT will harm your unborn baby.

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

- are breastfeeding or plan to breastfeed. It is not known whether DUPIXENT passes into your breast milk.

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

Especially tell your healthcare provider if you:

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

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

How should I use DUPIXENT?

- **See the detailed “Instructions for Use” that comes with DUPIXENT for information on how to prepare and inject DUPIXENT and how to properly store and throw away (dispose of) used DUPIXENT pre-filled syringes and pre-filled pens.**
- Use DUPIXENT exactly as prescribed by your healthcare provider.
- Your healthcare provider will tell you how much DUPIXENT to inject and how often to inject it.
- DUPIXENT comes as a single-dose pre-filled syringe with needle shield or as a pre-filled pen.
- DUPIXENT is given as an injection under the skin (subcutaneous injection).
- If your healthcare provider decides that you or a caregiver can give the injections of DUPIXENT, you or your caregiver should receive training on the right way to prepare and inject DUPIXENT. **Do not** try to inject DUPIXENT until you have been shown the right way by your healthcare provider. In children 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult. In children younger than 12 years of age, DUPIXENT should be given by a caregiver.
- **If your dose schedule is every other week and you miss a dose of DUPIXENT**: Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.
- **If your dose schedule is every 4 weeks and you miss a dose of DUPIXENT**: Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, start a new every 4 week dose schedule from the time you remember to take your DUPIXENT injection.
- If you inject 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.** 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
- pain in the throat (oropharyngeal pain)
- cold sores in your mouth or on your lips
- high count of a certain white blood cell (eosinophilia)
- trouble sleeping (insomnia)
- toothache
- gastritis
- joint pain (arthralgia)

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 Pharmaceuticals, 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 Information has been approved by the U.S. Food and Drug Administration. Revised: June 2020

Instructions for Use
DUPIXENT® (DU-pix-ent)
(dupilumab)
injection, for subcutaneous use
Single-Dose Pre-filled Pen (300 mg/2 mL)

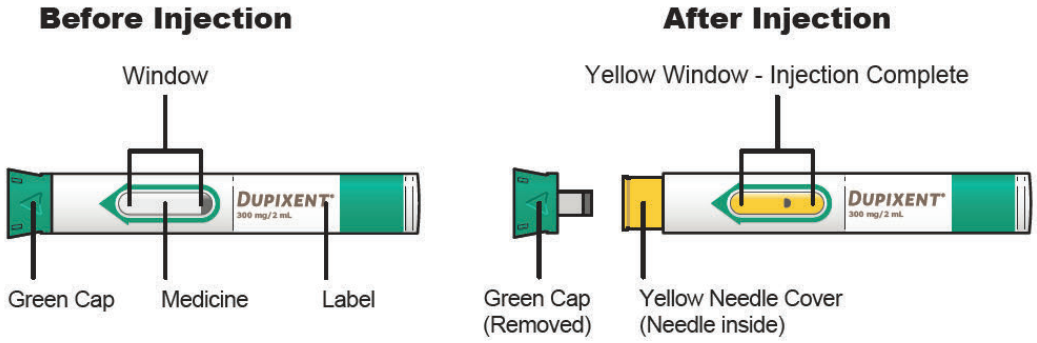
This "Instructions for Use" contains information on how to inject DUPIXENT.

Read this Instructions for Use before using the DUPIXENT Pre-filled Pen. **Do not inject yourself or someone else until you have been shown how to inject DUPIXENT.** 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 for the first time. Keep this Instructions for Use. Call your healthcare provider if you have any questions.

This DUPIXENT Pre-filled Pen is only for use in adults and children aged 12 years and older.

This DUPIXENT Pre-filled Pen is a single-dose device. It contains 300 mg of DUPIXENT for injection under the skin (subcutaneous injection).

The parts of the DUPIXENT Pre-filled Pen are shown below:



Important Information

- Read all of the instructions carefully before using the DUPIXENT Pre-filled Pen.
- Ask your healthcare provider how often you will need to inject the medicine.
- In adolescents 12 years of age and older, it is recommended that DUPIXENT be administered by or under supervision of an adult.
- Choose a different injection site for each injection.
- **Do not** press or touch the Yellow Needle Cover with your fingers.
- **Do not** inject through clothes.
- **Do not** remove the Green Cap until just before you give the injection.
- **Do not** try to put the Green Cap back on the DUPIXENT Pre-filled Pen.
- Throw away (dispose of) the used DUPIXENT Pre-filled Pen right away after use.
- **Do not** re-use a DUPIXENT Pre-filled Pen.

Storing DUPIXENT

- Store unused DUPIXENT Pre-filled Pens in the refrigerator between 36ºF and 46ºF (2ºC and 8ºC).
- Store DUPIXENT Pre-filled Pens in the original carton to protect from light.
- If necessary, you may keep DUPIXENT Pre-filled Pens at room temperature up to 77ºF (25ºC) for up to **14 days**.
- **Do not** store DUPIXENT Pre-filled Pens at room temperature more than 77ºF.
- After removing a DUPIXENT Pre-filled Pen from the refrigerator, it must be used within 14 days or thrown away (disposed of).
- **Do not** shake the DUPIXENT Pre-filled Pen at any time.
- **Do not** heat the DUPIXENT Pre-filled Pen.
- **Do not** freeze the DUPIXENT Pre-filled Pen.
- **Do not** put the DUPIXENT Pre-filled Pen into direct sunlight.
- **Keep DUPIXENT Pre-filled Pens and all medicines out of the reach of children.**

A. Get ready to inject

A1. Gather supplies

Find a clean, flat work surface. Make sure you have the following supplies:

• the DUPIXENT Pre-filled Pen

• 1 alcohol wipe*

• 1 cotton ball or gauze*

• a sharps disposal container* (See Step D)

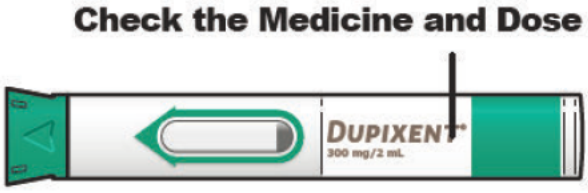
** Items not included in the carton.*

A2. Check the Pen

- **Do not** use the DUPIXENT Pre-filled Pen if it has been damaged.
- **Do not** use the DUPIXENT Pre-filled Pen if the Green Cap is missing or not securely attached.
- **Do not** use the DUPIXENT Pre-filled Pen if the Window is yellow before use.

A3. Look at the Label

- Check to be sure that you have the correct Medicine and dose.



- Check the expiration date.
- ⚠ **Do not use the DUPIXENT Pre-filled Pen if the expiration date has passed.**

A4. Check the Medicine

- Look at the Medicine through the Window: it should be clear and colorless to pale yellow.
- Note: You may see an air bubble, this is normal.
- ⚠ **Do not use the DUPIXENT Pre-filled Pen if the liquid is discolored or cloudy, or if it contains visible flakes or particles.**

A5. Wait 45 minutes	
• Lay the DUPIXENT Pre-filled Pen on a flat surface and let it warm up at room temperature less than 77°F (25°C) for at least 45 minutes. • ⚠ **Do not heat the DUPIXENT Pre-filled Pen in a microwave, hot water or direct sunlight.**	

B. Choose and prepare your injection site

B1. Wash your hands well with soap and water

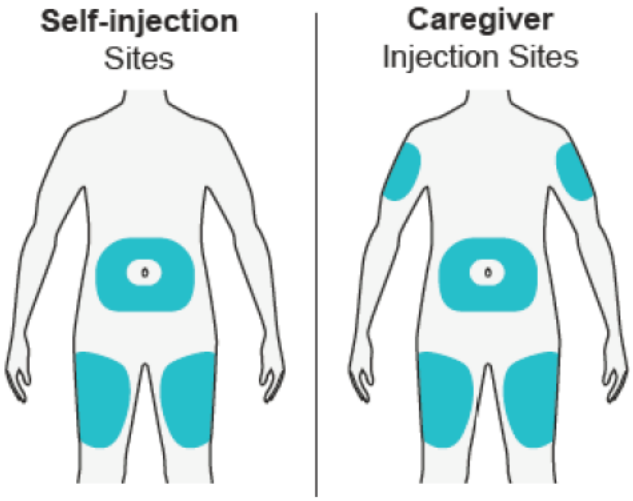
B2. Choose an injection site

- **Thigh**
- **Stomach** except for the 2 inches (5 cm) around your belly button (navel).
- A caregiver can also inject in the outer area of the **upper arm**.

- Choose a different site for each injection.

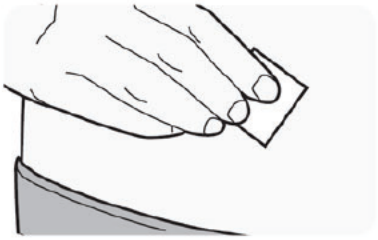
- ⚠ **Do not inject into skin that is tender, damaged, has bruises or scars, or into areas with visible veins.**

- ⚠ **Do not inject through clothes.**



B3. Prepare the injection site

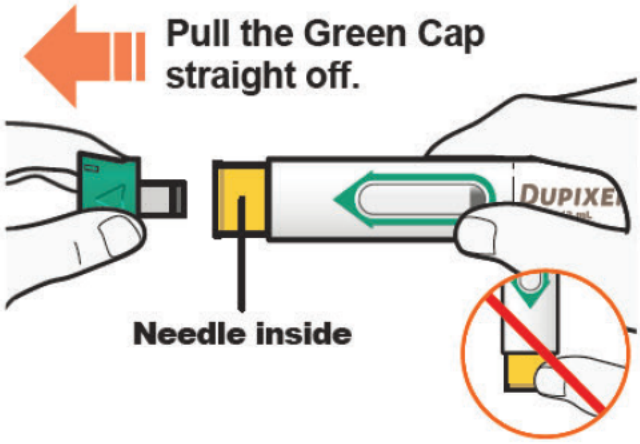
- Clean the injection site with an alcohol wipe.
- Let your skin dry before injecting.
- ⚠ **Do not touch the injection site again or blow on it before the injection.**



C. Give the injection

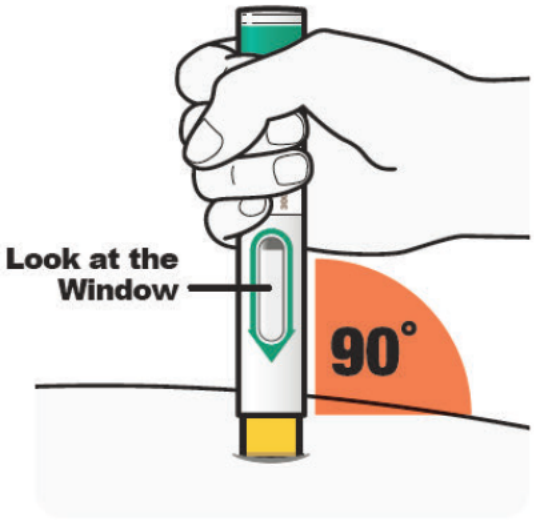
C1. Remove Green Cap

- Remove the Green Cap by pulling it straight off, as shown. **Do not** twist the Green Cap off.
- **Do not** remove the Green Cap until you are ready to inject.
- **Do not** press or touch the Yellow Needle Cover with your fingers. The Needle is inside.
- ⚠ **Do not put the Green Cap back on the DUPIXENT Pre-filled Pen after you have removed it.**

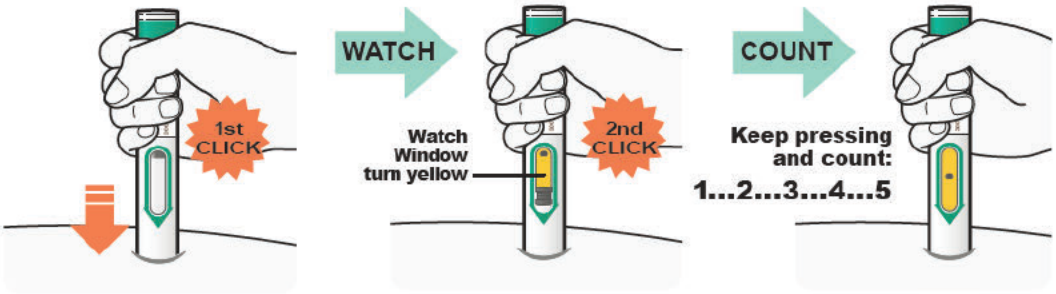


C2. Place

- Hold the DUPIXENT Pre-filled Pen as shown so that you can see the Window. Place the Yellow Needle Cover on your skin.
- Place the Yellow Needle Cover on your skin at approximately a 90-degree angle.



C3. Press down → Watch Window turn fully yellow → Then count to 5



Press and hold the DUPIXENT Pre-filled Pen firmly against your skin **until you cannot see the Yellow Needle Cover**. • There will be a "click" when the injection starts, **and** • The Window will start to turn yellow. • **Keep pressing** the DUPIXENT Pre-filled Pen against your skin.	Keep pressing the DUPIXENT Pre-filled Pen against your skin and watch the window: • The Window will turn completely yellow, **and** • You will hear a **2nd "click"**. • Keep pressing the DUPIXENT Pre-filled Pen against your skin.	Keep pressing the DUPIXENT Pre-filled Pen against your skin and **count to 5 to make sure you get your full dose.**

C4. Remove

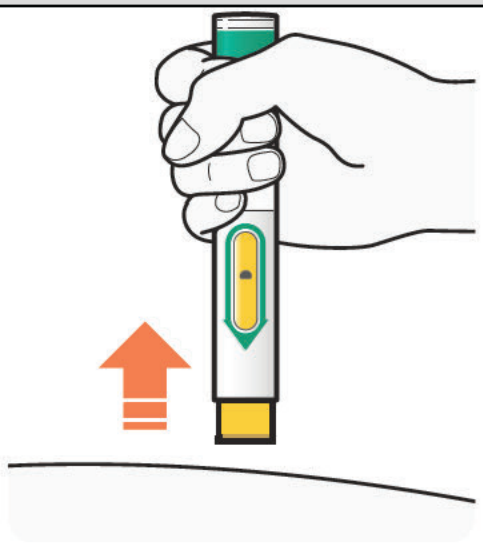
- After you have completed your injection pull straight up to remove DUPIXENT Pre-filled Pen from the skin. The Yellow Needle Cover will cover the needle.

- If you see any blood at the site, lightly dab a cotton ball or gauze pad.

- ⚠ **Do not rub your skin after the injection.**

If the Window does not turn completely Yellow, remove the pen and call your healthcare provider.

- ⚠ **Do not give yourself a second dose without speaking to your healthcare provider.**



D. Dispose of used DUPIXENT Pre-filled Pen

How to Dispose of (throw away) DUPIXENT Pre-filled Pen

Put your used DUPIXENT Pre-filled Pens, and Green Caps in a FDA-cleared sharps disposal container right away after use.

⚠ **Do not dispose of (throw away) DUPIXENT Pre-filled Pens and Green Caps in your household trash.**

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

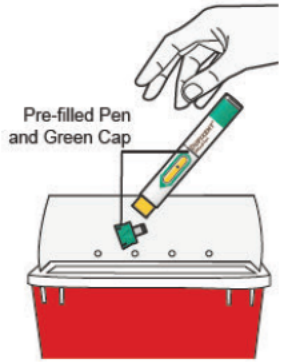
- made of a heavy-duty plastic,
- can be closed with a tightfitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

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 DUPIXENT Pre-filled Pens.

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 Green Cap back on.

Keep your sharps disposal container out of the reach of children.

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

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Tarrytown, NY 10591
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Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)
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Issued: June 2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s017

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

BLA Multidisciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761055/S-017
Priority or Standard	Standard
Submit Date	20 May 2019
Received Date	20 May 2019
PDUFA Goal Date	20 Jun 2020
Division/Office	DDD/OII
Review Completion Date	18 Jun 2020
Established/Proper Name	Dupilumab
Trade Name	DUPIXENT
Pharmacologic Class	Interleukin-4 receptor alpha antagonist
Code name	Not applicable
Applicant	Regeneron Pharmaceuticals, Inc.
Dosage form	Injection, for subcutaneous use
Applicant proposed Dosing Regimen	Not applicable
Applicant Proposed Indication(s)/Population(s)	New presentation - 300 mg (150 mg/mL) autoinjector (prefilled pen).
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Not applicable
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Not applicable
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Not applicable
Recommended Dosing Regimen	Not applicable

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Reviewers of Multidisciplinary Review and Evaluation

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Office of Clinical Pharmacology Reviewer(s)	Luke Oh, PhD
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla, PhD
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Division Director (DDDP)	Kendall A. Marcus, MD

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OPQ-Labeling	Vicky Borders-Hemphill
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OSE/DMEPA	James Schlick, MBA, RPh/Millie Shah, PharmD, BCPS
OSE SRPM	Tri Bui-Nguyen, PhD

DDDP, Division of Dermatology and Dental Products
PLT, Patient Labeling Team
SRPM, Safety Regulatory Project Manager
OPQ, Office of Pharmaceutical Quality
OPDP, Office of Prescription Drug Promotion
OSE, Office of Surveillance and Epidemiology
DMEPA, Division of Medication Error Prevention and Analysis

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Luke Oh, PhD	OCP/DCP III	Section: 6, 14.4	Select one: _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OCP/DCP III	Section: 6, 14.4	Select one: ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Clinical Reviewer	Brenda Carr, MD	OII/DDD	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 14.1, 14.2	Select one: _X_ Authored ___ Approved
	Signature: See DARRTS signature page			
Clinical Team Leader	Snezana Trajkovic, MD	OII/DDD	Sections: 1, 2, 3, 7, 8, 9, 10, 11, 12, 13, 14.1, 14.2	Select one: ___ Authored _X_ Approved
	Signature: See DARRTS signature page			
Division Director (Clinical)	Kendall A. Marcus, MD	OII/DDD	Sections: 1	Select one: ___ Authored _X_ Approved
	Signature: See DARRTS signature page			

Glossary

AD	atopic dermatitis
ADA	antidrug antibody
AI	autoinjector
AUC	area under the concentration-time curve
AUC_{0-14}	area under the concentration-time curve from day 0 to day 14
BA	bioavailability
CI	confidence interval
C_{max}	maximum concentration
C_{trough}	minimum concentration
EASI-75	eczema area and severity index score of 75% improvement
HF	human factor
IGA	investigator global assessment
IL	interleukin
mITT	modified intention to treat
NAb	neutralizing antibody
PFP	prefilled pen
PFS	prefilled syringe
PK	pharmacokinetics
PTC	product technical complaint
PTF	product technical failure
Q2W	once every 2 weeks
SAE	serious adverse event
SAF	safety analysis set
SC	subcutaneous
SOC	system organ class
TEAE	treatment-emergent adverse event

1. Executive Summary

1.1. Product Introduction

Per Section 11 ("Description") of the package insert, "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 is available as:

- Injection: 300 mg/2 mL in a single-dose prefilled syringe (PFS) with needle shield
- Injection: 200 mg/1.14 mL in a single-dose PFS with needle shield

In Supplement S-017 (S-017), the Applicant proposes introduction of a new presentation, a 300 mg/2 mL prefilled pen (PFP). The addition of this presentation would revise the "Dosage Forms and Strengths" section of the package insert to add the following: "Injection: 300 mg/2 mL solution in a single-dose prefilled pen."

The PFP is intended as an alternative to the 300 mg PFS for patients who self-administer treatment or those who have treatment administered by a caregiver. The Applicant describes the device as "a disposable, single dose, button-less, push-activated injector that utilizes a glass syringe as the primary container… (that) contains the same dupilumab drug, same drug formulation, same drug volume, and same primary container closure system as the PFS…(that will deliver) the same amount of dupilumab as the 300 mg PFS."[1]

The PFS has been used across all clinical development programs, and the Applicant intends that the proposed new presentation will be used across indications. The Applicant selected adults and adolescents with atopic dermatitis as the representative population for the study conducted to support approval of the new device, study R668-AD-1607 (1607). According to the study report, the Applicant considered subjects with atopic dermatitis to represent a "worst-case scenario" (relative to other indications), as they "potentially may have more difficulties to use auto-injector device due to their extensive involvement of the skin."[2]

The Applicant also refers to the PFP as the autoinjector, and both acronyms will be applied in this review.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant demonstrated that the relative bioavailability between the PFS and the autoinjector for the 300 mg dose was within the no-effect boundary range of 80% to 125%. See Section 6.

[1] Clinical Overview p. 7
[2] Clinical study report for R668-AD-1607, p. 19.

1.3. Benefit-Risk Assessment

This section is not applicable to this review.**Patient Experience Data**

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

□	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Section 8.1.2
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	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		
	□	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		
	□	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

2.1. Analysis of Condition

See the multidisciplinary review of S-020.

2.2. Analysis of Current Treatment Options

See the multidisciplinary review of S-020.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dupilumab received initial licensure on 03/28/2017 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."

It has subsequently been licensed for the following indications:

- "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" (S-007).
- "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" (S-012).
- "as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis" (S-014).

On 05/26/2020, the atopic dermatitis (AD) indication was extended to allow for the treatment of patients aged 6 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 (S-020).

3.2. Summary of Presubmission/Submission Regulatory Activity

In S-016, the Applicant proposed introduction of a 200 mg autoinjector (AI). However, the Applicant did not provide evidence to support the pharmacokinetic (PK) comparability of the 200 mg AI to the 200 mg prefilled syringe (PFS). The lack of comparability was thought to potentially have been a function of the loss of product during injection procedures, which was related to the device design and the misunderstanding by some subjects of its proper use. This ultimately resulted in some subjects not administering the full intended dose of dupilumab when using the 200 mg AI. The Agency took a complete response action on S-016 on 07/11/2019.

The following summary is based on information from the Division of Medication Error Prevention and Analysis review of S-017, conducted by James Schlick, MBA, RPh:

On 03/03/2020, the Agency advised the Applicant that preliminary review of the human factors (HF) validation study report, submitted in support of the 300 mg prefilled pen (PFP) (S-017), identified use errors with critical tasks that could lead to underdosing and that would require additional risk mitigation measures. In response to a subsequent Information Request, the Applicant indicated that they had not conducted an HF validation study for the 200 mg PFP to address Division of Medication Error Prevention and Analysis concerns regarding the protocol submitted for that study. The Applicant indicated that, instead, they had conducted an HF validation study for the 300 mg PFP that included revised instructions based on Agency comments from the 07/11/2019 complete response letter for S-016 (200 mg PFP), as well as other Agency comments. The Applicant's submission of this report on 03/09/2020 was determined to represent a major amendment, which resulted in an extension of the Prescription Drug User Fee Act date for S-017.

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

4.1. Office of Scientific Investigations

An Office of Scientific Investigations audit was not requested for this supplement.

4.2. Product Quality

Product Quality recommends approval of this supplement.

In this supplement, Regeneron is introducing a new presentation, the 300 mg (150 mg/mL) AI (PFP) for the currently approved indication for the treatment of patients aged 12 years or older with moderate-to-severe AD and as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years or older with an eosinophilic phenotype or with oral corticosteroid-dependent asthma. The 300 mg bulk PFS was reviewed under the original submission approved on 03/28/2017 and under Supplement 13, which was approved on 04/04/2019. In this Supplement 17, Regeneron is introducing an AI pen in which the approved 300 mg PFS is part of the AI assembly. Detailed information was provided, which included information about, but not limited to:

- Manufacturer
- PFP manufacturing process and process control
- PFP specification
- PFP stability

The process validation study for the 300 mg PFP included [redacted] The results of these validation studies, in addition to quality control release testing, analytical characterization, stability and forced degradation studies, show that the dupilumab 300 mg PFP lots manufactured at [redacted] are acceptable from a product-quality perspective (physiochemical and biological properties). The applicant provided sufficient data to support the proposed shelf life of [redacted] at the long-term storage condition of [redacted] This is based on submitted stability results of the 300 mg PFP [redacted] and from those of the approved 300 mg PFS [redacted] Additional supportive stability data were provided and showed that the clinical PFP batch [redacted] was stable for up to [redacted] Both the 300 mg PFP and the approved 300 mg PFS consist of the same bulk PFS.

4.3. Clinical Microbiology

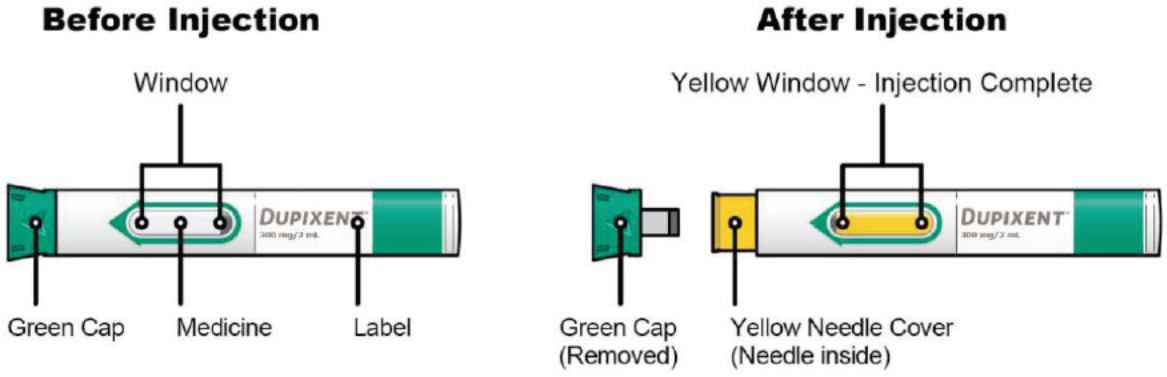
This section is not applicable to the supplement.

4.4. Devices and Companion Diagnostic Issues

The 300 mg PFP is provided fully assembled and is for a single use and is disposable. It is intended to deliver a minimum volume of 2.0 mL of 150 mg/mL dupilumab, with the entire contents providing a 300 mg dose.

Figure 1 depicts the parts of the PFP, as presented in the draft Instructions for Use. The window allows for inspection of the dupilumab content and converts to yellow upon completion of the injection.

Figure 1: DUPIXENT 300 mg Autoinjector[1]



[1] Draft instructions for use

From Mr. Schick's review (p. 12):

The results of the HF validation studies identified failures, close calls, and use difficulties with critical and non-critical tasks. We did not identify areas of improvement in the proposed user interface based upon the root cause analyses. After evaluating the errors for the 300 mg PFP,

we identified that with subsequent injections, users learned to hold the PFP at the injection site to complete a full injection. Thus, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable.

The above assessment reflects consideration of the additional HF validation study that the Applicant submitted on 03/09/2020.

5. Nonclinical Pharmacology/Toxicology

A nonclinical review was not required for this supplement.

6. Clinical Pharmacology

6.1. Executive Summary

Dupilumab (DUPIXENT®) is a human immunoglobulin-G4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signaling by binding to the IL-4 receptor-α subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is indicated 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. Dupilumab can be used with or without topical corticosteroids for the treatment of AD. Dupilumab is also 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. Dupilumab is administered by subcutaneous (SC) injection. The approved dosage regimens for the AD and asthma indications are summarized in Table 1.

Table 1: Approved Dosage Regimens

Atopic dermatitis	Adults: The recommended dose is an initial dose of 600 mg (2 × 300 mg injections), followed by 300 mg given every other week (Q2W). Adolescents: < 60 kg: Initial dose of 400 mg (2 × 200 mg injections) followed by 200 mg Q2W ≥ 60 kg: Initial dose of 600 mg (2 × 300 mg injections) followed by 300 mg Q2W
Asthma	Adults and adolescents (12 years of age and older): Initial dose of 400 mg (2 × 200 mg injections) followed by 200 mg Q2W; or Initial dose of 600 mg (2 × 300 mg injections) followed by 300 mg Q2W

The purpose of this supplemental BLA is to support the introduction of new presentation, the 300 mg (150 mg/mL) PFP (also referred to as an AI). This submission consists of Study R668-AD-1607 (part B; phase 1 actual-use study comparing PK following administration of the 300 mg dose as PFS vs. AI).

6.1.1. Recommendation

From the Clinical Pharmacology perspective, this supplement is acceptable.

6.1.2. PMC/PMR

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant conducted a phase-1b, open-label, randomized, actual-use study of a dupilumab AI device in patients with atopic dermatitis. This study consisted of two parts. In Part A was assessed the relative bioavailability (BA) between 200 mg AI and 200 mg PFS; in Part B was assessed the relative BA between for 300 mg AI and 300 mg PFS. Part A was reviewed by Dr. Xiaohui Li (see review in DARRTS dated 06/05/2019); Part B is the focus of this review.

The total PK results of Part B supports a comparable BA of dupilumab between AI administration and PFS in subjects 12 years of age and older with AD. The 90% confidence interval (CI) of the geometric mean ratios (AI/PFS) for systemic exposure of dupilumab were within the no-effect boundary range of 80% to 125%.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

This supplement supports the acceptability of the use of the 300 mg PFP for dupilumab administration.

Therapeutic Individualization

This supplement does not contain any proposed therapeutic individualizations.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this supplement from a Clinical Pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

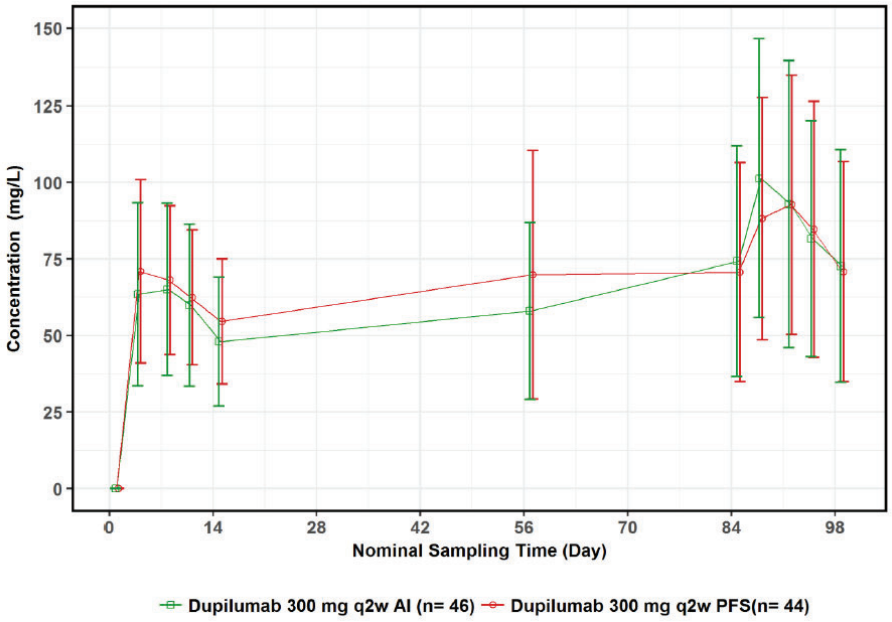
6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Pharmacokinetics

The 90% CI of the geometric mean ratios (AI/PFS) for systemic exposure of dupilumab were within the no-effect boundary range of 80% to 125% on days 1 and 85 (end of treatment),

indicating that the systemic exposure of dupilumab after SC administration using the 300 mg AI is comparable to that using the 300 mg PFS in subjects 12 years of age and older with AD. The serum concentration-versus-time profile, both after a single 600 mg loading dose and following six subsequent 300 mg once every 2 weeks (Q2W) doses, showed that systemic exposure of dupilumab was comparable between the two device groups (Figure 2 and Table 2). The mean ± SD area under the concentration-time curve (AUC) of dupilumab on day 1 was 758 ± 323 day.mg/L and 803 ± 298 day.mg/L for AI and PFS, respectively (Table 2). The mean ± SD maximum concentration (C_{max}) of dupilumab on day 1 was 71.5 ± 29.2 mg/L and 76.6 ± 28.5 mg/L for AI and PFS, respectively (Table 2). The mean AUC and C_{max} of dupilumab were comparable between the AI and PFS groups on day 85 (Figure 2 and Table 2). The geometric mean ratios of AI/PFS for the AUC from day 0 to day 14 (AUC_{0-14}) and C_{max} on day 1 were 0.924 and 0.915, respectively (Table 3). On day 85, the mean ratios for AUC_{0-14} and C_{max} were 1.073 and 1.083, respectively (Table 3).

Figure 2: Mean (± SD) Serum Dupilumab Concentration by Nominal Time and Device in Patients With AD



Abbreviations: AD, atopic dermatitis; AI, autoinjector; n, number of patients; PFS, prefilled syringe; Q2W, once every 2 weeks
Concentrations below the lower limit of quantification were set to zero. A loading dose of 600 mg was administered on day 1.
Source: Figure 2 of study report R668-AD-1607-CP-01V2

Table 2: Mean (± SD) Concentration of Dupilumab in Serum by Nominal Time and Device in Patients With AD

Study Day	Parameter	Treatment	n	Mean	Median	Min	Max	SD	SE	CV	Geometric Mean
Day 1	AUC_{0-14} (mg*day/L)	Dupilumab 300 mg Q2W AI	46	758	778	45.0	1630	323	47.7	42.6	674
		Dupilumab 300 mg Q2W PFS	44	803	794	252	1910	298	44.9	37.1	748
	C_{max} (mg/L)	Dupilumab 300 mg Q2W AI	46	71.5	74.7	4.71	135	29.2	4.31	40.9	64.0
		Dupilumab 300 mg Q2W PFS	44	76.6	75.7	26.8	182	28.5	4.29	37.2	71.6
	C_{trough} (mg/L)	Dupilumab 300 mg Q2W AI	46	48.0	46.3	0.548	98.4	21.0	3.10	43.8	40.8
		Dupilumab 300 mg Q2W PFS	44	54.6	54.5	10.3	98.8	20.4	3.07	37.3	50.1
	t_{max} (Day)	Dupilumab 300 mg Q2W AI	46	--	6.79	2.70	10.9	--	--	--	--
		Dupilumab 300 mg Q2W PFS	44	--	4.48	2.03	14.0	--	--	--	--
Day 85	AUC_{0-14} (mg*day/L)	Dupilumab 300 mg Q2W AI	42	1140	1090	111	2520	588	90.7	51.7	944
		Dupilumab 300 mg Q2W PFS	37	1100	1050	101	2800	595	97.9	54.2	899
	C_{max} (mg/L)	Dupilumab 300 mg Q2W AI	42	107	104	25.5	230	50.7	7.82	47.4	94.2
		Dupilumab 300 mg Q2W PFS	37	100	95.2	20.3	187	45.6	7.50	45.5	88.6
	C_{trough} (mg/L)	Dupilumab 300 mg Q2W AI	42	75.4	71.1	13.7	171	39.8	6.15	52.8	63.8
		Dupilumab 300 mg Q2W PFS	37	70.8	65.1	4.58	137	34.9	5.74	49.3	59.1
	t_{max} (Day)	Dupilumab 300 mg Q2W AI	42	--	4.03	0	13.8	--	--	--	--
		Dupilumab 300 mg Q2W PFS	37	--	5.97	0	11.9	--	--	--	--

Abbreviations: AD, atopic dermatitis; AI, autoinjector; AUC_{0-14}, area under the concentration-time curve from time zero to day 14 (relative to the day in the 'Study Day' column); C_{max}, maximum concentration; C_{trough}, minimum concentration; PFS, prefilled syringe; PK, pharmacokinetics; t_{max}, time to the maximum concentration
Source: Figure 2 of Study report R668-AD-1607-CP-01V2

Table 3: Geometric Mean Ratios (AI/PFS) for PK Parameters of Functional Dupilumab in Patients With AD

Study Day	Parameter	Geometric Mean Ratio	90% Confidence Interval
Day 1	AUC_{0-14} (mg*day/L)	0.924	0.818 -- 1.045
	C_{max} (mg/L)	0.915	0.809 -- 1.034
	C_{trough} (mg/L)	0.840	0.708 -- 0.995
Day 85	AUC_{0-14} (mg*day/L)	1.070	0.859 -- 1.333
	C_{max} (mg/L)	1.083	0.950 -- 1.234
	C_{trough} (mg/L)	1.098	0.934 -- 1.291

Abbreviations: AI, autoinjector; AUC_{0-14}, area under the concentration-time curve from time zero to day 14 (relative to the day in the 'Study Day' column); C_{max}, maximum concentration; C_{trough}, minimum concentration; PFS, prefilled syringe; PK, pharmacokinetics
Source: Table 7 of study report R668-AD-1607-CP-01V2

While the total PK results support the comparable BA of dupilumab between AI and PFS administration, subgroup analyses by injection site suggested that AI injection in the abdomen produced an approximately 30% lower BA following the first injection compared to PFS administered in the abdomen. Further analysis indicated a lower BA in the abdomen only in heavier subjects; i.e., those of body weight greater than 70 kg (Table 4).

Table 4: PK Data by Injection Site and by Body Weight

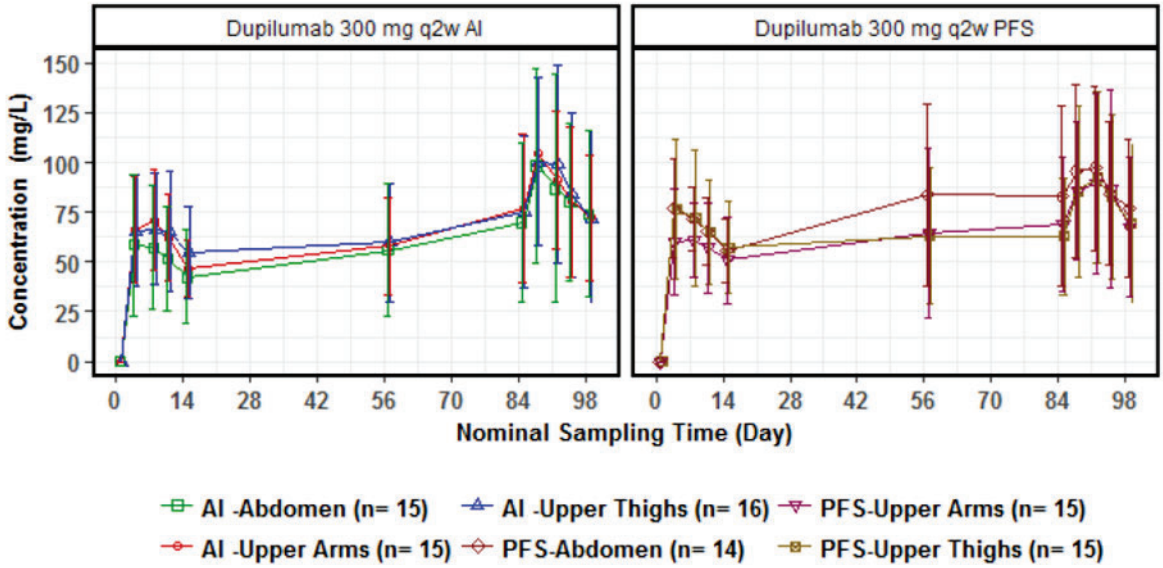
	Dupilumab 300 mg Q2W AI			Dupilumab 300 mg Q2W PFS			AI/PFS ratio		
Day 1- 15	AUC	Cmax	Ctrough	AUC	Cmax	Ctrough	**AUC**	**Cmax**	**Ctrough**
<= 70 kg									
Abdomen (N = 7)	931	91.7	61.4	970.2	92.7	63.2	**0.96**	**0.99**	**0.97**
Upper arms (N = 8)	952.8	88.9	55.3	820.5	75.6	60.4	**1.16**	**1.18**	**0.92**
Upper thighs (N = 7)	898.8	80.3	64.3	1107.3	102.5	71.9	**0.81**	**0.78**	**0.89**
>70 - <100 kg									
Abdomen (N = 6,5)	481.7	42.7	26.5	686.8	63.2	46.9	**0.70**	**0.68**	**0.57**
Upper arms (N = 5)	639.8	64.6	37.9	675	63.4	44.6	**0.95**	**1.02**	**0.85**
Upper thighs (N = 6,5)	797.4	75.8	53.2	702.2	69	53	**1.14**	**1.10**	**1.00**
>= 100 kg									
Abdomen (N = 2)	141	14.8	4.1	699.5	74	43.1	**0.20**	**0.20**	**0.10**
Upper arms (N = 2)	381	37.5	28.2	296.6	30.3	14.3	**1.28**	**1.24**	**1.97**
Upper thighs (N = 3)	407.2	40.4	22.9	373.4	40.9	24	**1.09**	**0.99**	**0.95**
	Dupilumab 300 mg Q2W AI			Dupilumab 300 mg Q2W PFS			AI/PFS ratio		
Day 1- 15	AUC	Cmax	Ctrough	AUC	Cmax	Ctrough	**AUC**	**Cmax**	**Ctrough**
<= 70 kg									
Abdomen (N = 7)	931	91.7	61.4	970.2	92.7	63.2	**0.96**	**0.99**	**0.97**
Upper arms (N = 8)	952.8	88.9	55.3	820.5	75.6	60.4	**1.16**	**1.18**	**0.92**
Upper thighs (N = 7)	898.8	80.3	64.3	1107.3	102.5	71.9	**0.81**	**0.78**	**0.89**
>70 - <100 kg									
Abdomen (N = 6,5)	481.7	42.7	26.5	686.8	63.2	46.9	**0.70**	**0.68**	**0.57**
Upper arms (N = 5)	639.8	64.6	37.9	675	63.4	44.6	**0.95**	**1.02**	**0.85**
Upper thighs (N = 6,5)	797.4	75.8	53.2	702.2	69	53	**1.14**	**1.10**	**1.00**
>= 100 kg									
Abdomen (N = 2)	141	14.8	4.1	699.5	74	43.1	**0.20**	**0.20**	**0.10**
Upper arms (N = 2)	381	37.5	28.2	296.6	30.3	14.3	**1.28**	**1.24**	**1.97**
Upper thighs (N = 3)	407.2	40.4	22.9	373.4	40.9	24	**1.09**	**0.99**	**0.95**

Abbreviations: AI, autoinjector; AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{trough}, minimum concentration; PFS, prefilled syringe; PK, pharmacokinetics; Q2W, once every 2 weeks
Note: There were only two subjects with body weight ≥ 100 kg that injected the drug in the abdomen. One subject has unusually low systemic exposure and the reason for this could not be explained.
Source: Reviewer's analysis

Any real effect of injection site would be expected to be consistent across all body weight ranges and not be restricted to heavier subjects. This indicates that body weight is unlikely to influence systemic exposure and injection site.

For the sake of argument, if we consider possibility of a depot effect in heavier subjects because of fat deposition in the abdomen, then the lower BA following injection in the abdomen should be consistent for both AI and PFS administration. In this case, following drug administration using PFS, the highest BA was observed in the abdomen; the opposite effect was observed when AI was used—the BA was lower in the abdomen compared to other injection sites (Figure 3). These data suggest that the injection site is unlikely to influence the systemic exposure of dupilumab.

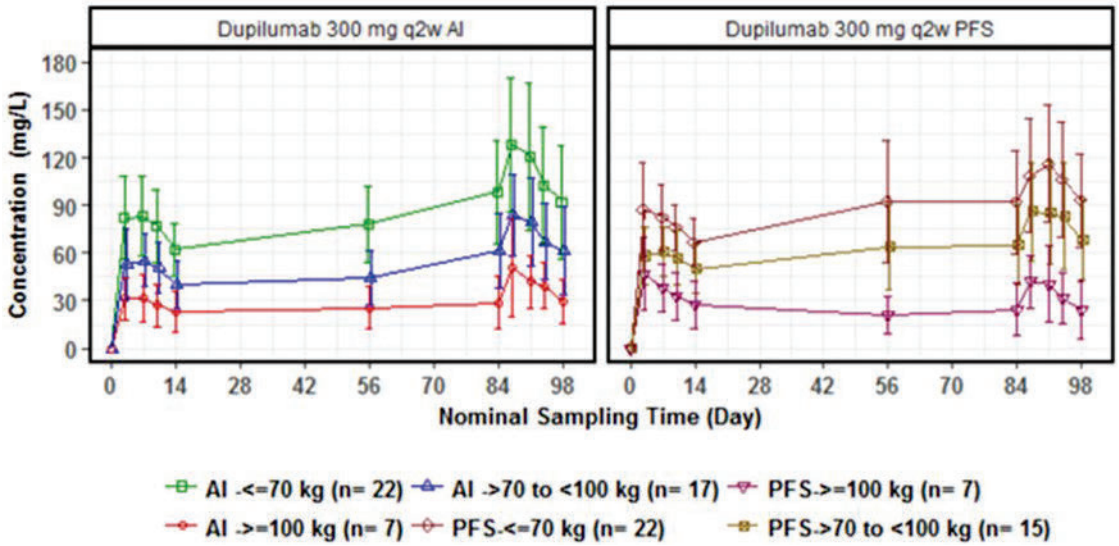
Figure 3: PK Profile of AI and PFS by Injection Site



Abbreviations: AI, autoinjector; PFS, prefilled syringe; PK, pharmacokinetics; q2w, once every 2 weeks
Source: Figure 5 of study report R668-AD-1607-CP-01V2

Furthermore, the Applicant provided additional data to justify the difference in exposure between AI and PFS in the abdomen. The Applicant's data showed an imbalance in the body-weight distribution in subjects who administered the drug into their abdomen; the AI arm included a greater number of heavier subjects compared to the PFS arm. Other injection sites (upper arm and thigh) did not show an apparent imbalance in subject distribution by body weight. Body weight influences systemic exposure—systemic exposure of dupilumab decreases as body weight increases (Figure 4).

Figure 4: Effect of Body Weight on Systemic Exposure of Dupilumab



Abbreviations: AI, autoinjector; PFS, prefilled syringe; PK, pharmacokinetics; q2w, once every 2 weeks
Source: Figure 4 of study report R668-AD-1607-CP-01V2

Based on the above evidence, it appears that the 30% lower BA in the abdomen following AI compared to PFS administration is likely a result of the imbalanced body weight distribution

and high variability in the PK data. This reviewer also notes that the efficacy analysis did not show a difference in clinical outcomes between the two devices, even in subjects that administered the drug in the abdomen. Although the efficacy findings are considered exploratory because of the small number of subjects, different efficacy endpoints, and the open label nature of the study; this reviewer opines that these data also indirectly support the lack of an effect of injection site.

In conclusion, taken as a whole, the evidence suggests that the injection site is unlikely to influence the systemic exposure of dupilumab.

Immunogenicity

SC administration of dupilumab by AI resulted in an antidrug antibody (ADA) response in one subject (1/43, 2.33%). In comparison, the PFS induced an ADA response in six subjects (6/42, 14.3%) (Table 5). Immunogenicity and effect on PK appeared to be similar between the two devices because there was no marked influence on the PK of dupilumab. It should be noted that the number of ADA-positive subjects was too small to draw definitive conclusions in this study.

Table 5: Summary of ADA Category and NAb Status by Device

ADA Category; NAb Status N (%)	Dupilumab 300 mg Q2W		Overall
	AI	PFS	
Total ADA/NAb Patients	43 (100%)	42 (100%)	85 (100%)
Neg/PE; NAb-	42 (97.7%)	36 (85.7%)	78 (91.8%)
Neg/PE; NAb+	0 0	0 0	0 0
TE/TB; NAb-	1 (2.33%)	2 (4.76%)	3 (3.53%)
TE/TB; NAb+	0 0	4 (9.52%)	4 (4.71%)

ADA, antidrug antibody; AI, autoinjector; n, number of patients; NAb-, negative in neutralizing antibody (NAb) assay NAb+, positive by NAb assay; neg, negative; PE, preexisting immunoreactivity; PFS, prefilled syringe; TB, treatment-boosted; TE, treatment emergent
Source: Table 12 of study report R668-AD-1607-CP-01V2

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

The efficacy assessment was considered exploratory because the study was of open label design with the aim of evaluating the actual use of the two devices by humans. Also, the efficacy end point was different from that in the original approved BLA. The proportion of subjects who achieved an eczema area and severity index score of 75% improvement (EASI-75) at week 12 was numerically higher (76.1% vs. 54.5%) with the AI than with the PFS (Table 6). The proportion of subjects who achieved both an IGA score of 0 or 1 and a reduction from baseline of ≥ 2 points at week 12 was numerically higher (39.1% vs. 31.8%) with the AI than with the PFS (Table 6). More details are provided in Section 7 (Clinical Review).

Table 6: Clinical Response Rate—EASI-75 and IGA 0/1 Scores by Device

EASI-75 (≥ 75% improvement from baseline)

	Dupilumab 300mg Q2W	
Visit	Auto-injector (N=46)	Pre-filled Syringe (N=44)
Week 2		
Responder Rate, n(%)	8 (17.4%)	6 (13.6%)
Clopper-Pearson Exact 95% CI	(7.8%, 31.4%)	(5.2%, 27.4%)
Week 8		
Responder Rate, n(%)	27 (58.7%)	24 (54.5%)
Clopper-Pearson Exact 95% CI	(43.2%, 73.0%)	(38.8%, 69.6%)
Week 12		
Responder Rate, n(%)	35 (76.1%)	24 (54.5%)
Clopper-Pearson Exact 95% CI	(61.2%, 87.4%)	(38.8%, 69.6%)

IGA 0/1 and a reduction of ≥ 2 points

	Dupilumab 300mg Q2W	
Visit	Auto-injector (N=46)	Pre-filled Syringe (N=44)
Week 2		
Responder Rate, n(%)	3 (6.5%)	3 (6.8%)
Clopper-Pearson Exact 95% CI	(1.4%, 17.9%)	(1.4%, 18.7%)
Week 8		
Responder Rate, n(%)	15 (32.6%)	15 (34.1%)
Clopper-Pearson Exact 95% CI	(19.5%, 48.0%)	(20.5%, 49.9%)
Week 12		
Responder Rate, n(%)	18 (39.1%)	14 (31.8%)
Clopper-Pearson Exact 95% CI	(25.1%, 54.6%)	(18.6%, 47.6%)

Note: Patient with a missing value at a visit was counted as a non-responder for the visit.
Abbreviations: CI, confidence interval; EASI, eczema area and severity index; IGA, investigator global assessment; n, number of patients; Q2W, once every 2 weeks
Source: Tables 19 and 20 in clinical study report R668-AD-1607 (Part B)

Is the Proposed Dosing Regimen Appropriate for the General Patient Population for which the Indication is Being Sought?

Yes. This supplement is an actual-use study comparing an AI device versus PFS used by subjects with AD and the totality of the data supports use of the AI device.

Is an Alternative Dosing Regimen or Management Strategy Required for Subpopulations based on Intrinsic Patient Factors?

No. An alternative dosing regimen or management strategy for subpopulations is not necessary based on intrinsic factors.

Are there Clinically Relevant Food-Drug or Drug-Drug Interactions, and What is the Appropriate Management Strategy?

Food-drug interactions are not applicable because dupilumab is administered by SC injection. The drug interaction potential for dupilumab with cytochrome P450 substrates is described in Section 12.3 of the dupilumab product labeling. There is no additional drug interaction information in the current sBLA to update the drug interaction potential of dupilumab.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The supplement provides data from one clinical study, R668-AD-1607 (1607) titled, "An Open Label, Randomized, Actual Use Study of Dupilumab Auto-Injector Device in Patients with Atopic Dermatitis" (Part B). The study is described in Section 8.

7.2. Review Strategy

Although Study 1607 was not an efficacy trial, it is discussed in Section 8, in accordance with the format of the template.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. "An Open Label, Randomized, Actual Use Study of Dupilumab Auto-Injector Device in Patients With Atopic Dermatitis" (R668-AD-1607)

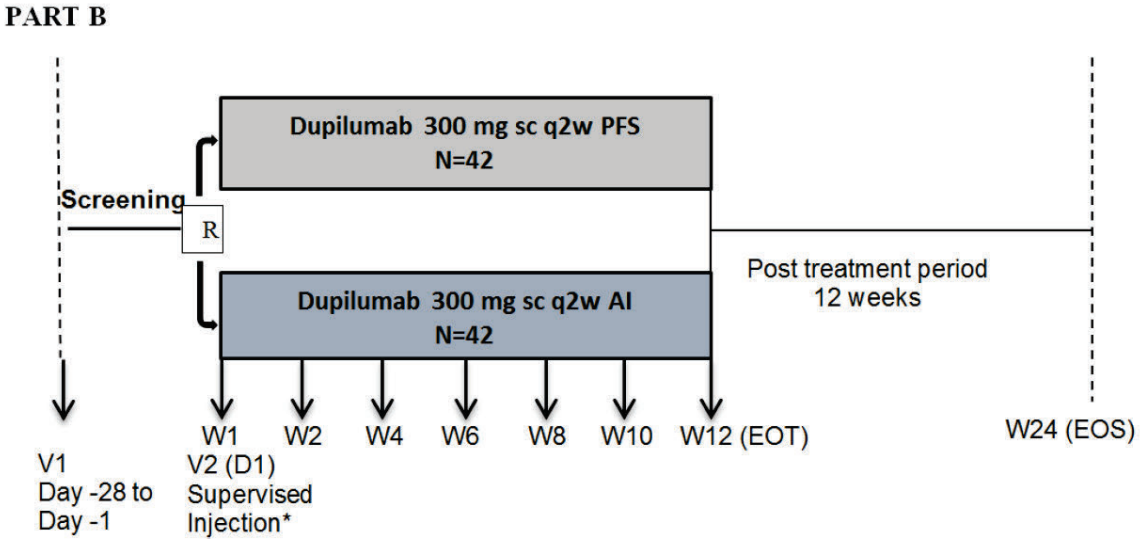
Trial Design

This was a multicenter, randomized, parallel group, open-label study that consisted of a screening period (up to 28 days), a 12-week treatment period, and a 12-week post-treatment follow-up period. The study was conducted in two parts: Part A and Part B (Figure 5).

In Part A, patients with AD were randomized to receive dupilumab 200 mg either by AI device or by PFS, after a loading dose of 400 mg on day 1; the loading dose consisted of two injections. Part A of this study was reviewed under S-016 and will not be further discussed in this review.

In Part B, patients with AD were randomized to receive dupilumab 300 mg either by AI device or by PFS, after a loading dose of 600 mg on day 1. Part B started after enrollment in Part A was completed. S-017 pertains to Part B.

Figure 5: Design of Study R668-AD-1607



Abbreviations: AI, autoinjector; EOS, end of study; EOT, end of treatment; PFS, prefilled syringe; q2w, once every 2 weeks; SC, subcutaneous
* Patients/caregivers were trained at clinical sites for SC injection during visit 2. The injection site was predefined for day 1. R: randomization; stratification by day-1 injection site (abdomen, upper arm ,or thigh)

The primary objective of the study was to collect actual-use data assessing technical performance and user interactions of the dupilumab AI device when used by patients (or caregivers for injections in the upper arm) with AD over a 12-week treatment period.

The secondary objectives of the study were to:

- Assess the types of product technical complaints (PTCs)
- Assess subject satisfaction with the dupilumab AI device
- Compare systemic exposure of dupilumab administered using the AI device versus PFS
- Assess the efficacy of 200 mg and 300 mg dupilumab administered Q2W SC using the AI device and PFS in patients with AD
- Assess the safety of 200 mg and 300 mg dupilumab administered Q2W SC using the AI device and PFS in patients with AD

Study Endpoints

The primary endpoint was the number and type of validated AI device-associated product technical failures (PTFs) during the treatment period divided by the total number of actual injections.

The secondary endpoints are listed below:

- Number and percentage of patients with an AI device-associated PTC
- Number and type of AI device-associated PTCs divided by the 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 PTFs) divided by the total number of actual injections
- Number and percentage of patients with an AI device-associated failure to deliver a dose
- Number and percentage of patients who responded to patient satisfaction questions on the AI device

The other endpoints included the following efficacy assessments:

- Proportion of patients with both IGA 0 to 1 (on a 5-point scale) and a reduction from baseline of ≥ 2 points at week 12
- Proportion of patients with an EASI-75 (≥ 75% improvement from baseline) at week 12

Evaluation of PK parameters was among the other endpoints; see Section 6 of this review.

PTCs were collected if there was any problem associated with either device during drug administration. The investigator also assessed PTCs at each study visit by reviewing the patient's dosing diary and by asking if there were any problems associated with the AI or PFS during drug administration. AI devices and PFS for which a PTC was reported were evaluated by the Applicant following a predefined process to determine the occurrence of a PTF (defined as a PTC that had a validated technical cause) or a failed drug delivery (defined as perceived failure to administer the full dose at a given attempt, excluding PTF).

Statistical Analysis Plan

No formal statistical hypothesis was specified.

The modified intention-to-treat (mITT) population included all randomized patients who received at least one injection of the study drug. All efficacy variables and device-related endpoints were evaluated in the mITT population based on the actual treatment received.

The safety analysis set (SAF) included all randomized patients who received at least one injection of the study drug, and were analyzed as treated. Treatment compliance/administration and all clinical safety variables were summarized based on the SAF.

The PK analysis set included all randomized patients who received any study drug and who had at least one non-missing drug concentration result following the first dose of the study drug. Patients were analyzed according to the actual treatment received.

Protocol Amendments

Revisions under the one protocol amendment appeared to be largely minor edits and clarifications.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant attested that the study was conducted in accordance with the ethical principles that are consistent with the International Council for Harmonisation guidelines for Good Clinical Practices and applicable regulatory requirements.

Financial Disclosure

The Applicant adequately disclosed financial arrangements with clinical investigators. None of the disclosed arrangements raised any questions about the integrity of the data because:

- Patients were randomly assigned to the treatment arms via an interactive voice response system.
- A central clinical team blinded to the treatment arm monitored the quality of the data reported by the investigators and compliance with the protocol.

Patient Disposition

The study was conducted at 30 clinical sites in the United States.

Table 7: Summary of Patient Disposition During the Treatment Period: Reasons for Discontinuation of Study Treatment – Part B – SAF

	Dupilumab 300 mg Q2W		
	Autoinjector (N=46)	Prefilled Syringe (N=44)	Combined (N=90)
Patients in safety analysis set	46 (100%)	44 (100%)	90 (100%)
Patients who completed treatment	43 (93.5%)	40 (90.9%)	83 (92.2%)
Patients withdrawn from treatment	3 (6.5%)	4 (9.1%)	7 (7.8%)
Noncompliance with protocol by the subject	0	0	0
Adverse event	1 (2.2%)	2 (4.5%)	3 (3.3%)
Pregnancy	0	0	0
Lack of efficacy	0	0	0
Decision by the investigator/sponsor	0	0	0
Withdrawal of consent by subject	0	2 (4.5%)	2 (2.2%)
Lost to follow-up	2 (4.3%)	0	2 (2.2%)
Death	0	0	0
Other	0	0	0

Abbreviations: Q2W, once every 2 weeks; SAF, safety analysis set
Source: Table 3 of the study report for Part B of 1607

Protocol Violations/Deviations

Major protocol deviations were varied in type and affected a small number of patients.

Table 8: Summary of Protocol Deviations – Part B – All Randomized Patients

	Dupilumab 300 mg Q2W		
	Autoinjector (N=46)	**Prefilled Syringe (N=45)**	**Combined (N=91)**
Number of protocol deviations	68	60	128
Number of major protocol deviations	6	11	17
Number of minor protocol deviations	62	49	111
Patients with any protocol deviation, n (%)	29 (63.0%)	31 (68.9%)	60 (65.9%)
Patients with any major protocol deviation	6 (13.0%)	9 (20.0%)	15 (16.5%)
Patients with any minor protocol deviation	26 (56.5%)	27 (60.0%)	53 (58.2%)
Type of major protocol deviation			
Procedure not performed[1]	2 (4.3%)	8 (17.8%)	10 (11.0%)
Treatment deviation	2 (4.3%)	1 (2.2%)	3 (3.3%)
Prohibited medications	1 (2.2%)	1 (2.2%)	2 (2.2%)
Visit not performed	1 (2.2%)	0	1 (1.1%)

Abbreviation: Q2W, once every 2 weeks
Source: Table 5 of the study report for Part B of 1607
[1] Procedure not performed considered major protocol violations consisted of patient not receiving injection training; the diary not reviewed with the patient; human immunodeficiency virus, hepatitis screen, or tuberculin test not performed at screening; study drug not administered at a study visit; visit not performed; and early termination visit not performed.

Table of Demographic Characteristics

Table 9 presents the demographics of the study population. The baseline demographic characteristics of the two groups were generally similar. The differences in baseline demographics between the groups would not appear to affect the study results.

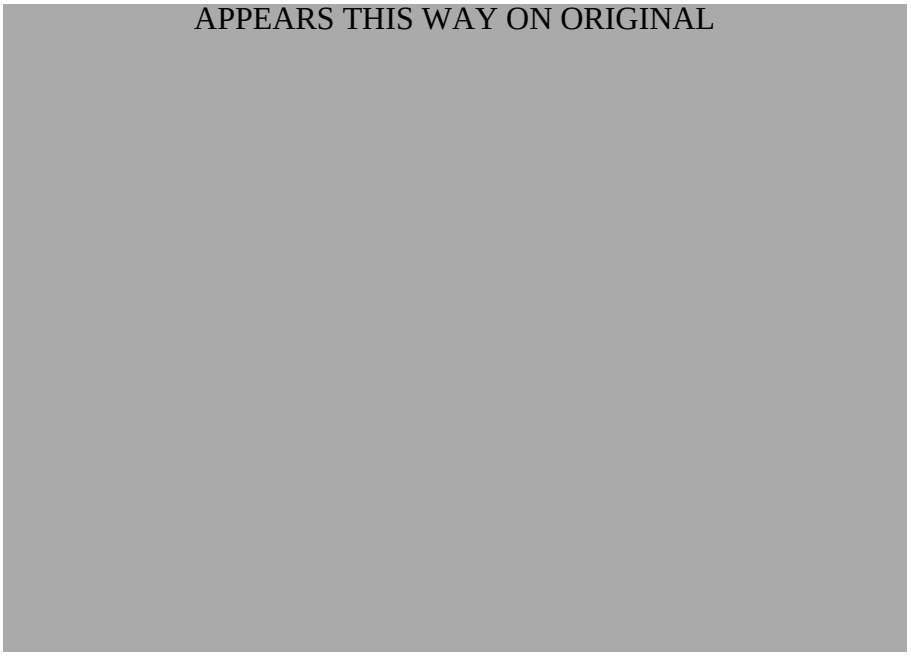


Table 9: Summary of Demographics – Part B – All Randomized Patients

	Dupilumab 300 mg Q2W		
	Autoinjector (N=46)	**Prefilled Syringe (N=45)**	**Combined (N=91)**
n	46	45	91
Mean (SD)	30.7 (18.53)	30.3 (20.17)	30.5 (19.25)
Median	22.0	24.0	22.0
Q1: Q3	16.0: 39.0	15.0: 37.0	16.0: 38.0
Min: max	13: 79	12: 84	12: 84
Age group, n (%)			
< 18 years	15 (32.6%)	17 (37.8%)	32 (35.2%)
≥ 18 to < 40 years	21 (45.7%)	18 (40.0%)	39 (42.9%)
≥ 40 to < 65 years	6 (13.0%)	5 (11.1%)	11 (12.1%)
≥ 65 years	4 (8.7%)	5 (11.1%)	9 (9.9%)
Ethnicity, n (%)			
Not Hispanic or Latino	33 (71.7%)	34 (75.6%)	67 (73.6%)
Hispanic or Latino	13 (28.3%)	11 (24.4%)	24 (26.4%)
Race, n (%)			
White	31 (67.4%)	30 (66.7%)	61 (67.0%)
Black/African-American	8 (17.4%)	11 (24.4%)	19 (20.9%)
Asian	5 (10.9%)	3 (6.7%)	8 (8.8%)
American Indian or Alaska Native	2 (4.3%)	0 (0%)	2 (2.2%)
Other	0 (0%)	1 (2.2%)	1 (1.1%)
Sex, n (%)			
Male	21 (45.7%)	24 (53.3%)	45 (49.5%)
Female	25 (54.3%)	21 (46.7%)	46 (50.5%)
Height (cm)			
Mean (SD)	168.96 (10.651)	167.36 (10.136)	168.17 (10.373)
Median	167.60	167.60	167.60
Q1: Q3	162.50: 177.80	157.60: 175.30	160.50: 176.50
Min: max	147.0: 191.0	143.0: 188.0	143.0: 191.0
Weight (kg)			
Mean (SD)	76.50 (23.405)	74.81 (21.521)	75.66 (22.384)
Median	71.50	71.00	71.00
Q1: Q3	58.00: 90.40	60.00: 82.60	59.00: 87.20
Min: max	40.3: 157.4	40.0: 141.1	40.0: 157.4

Abbreviation: Q, quartile; Q2W, once every 2 weeks
Source: Table 7 of the study report for Part B of 1607

Other Baseline Characteristics (e.g., Disease Characteristics, Important Concomitant Drugs)

The mean baseline disease characteristics were similar in the two groups:

- IGA score: 3.5 in the AI group and 3.4 in the PFS group
- EASI-75: 28 in the AI group and 30 in the PFS group
- Body surface area: 43.0% in the AI group and 45.5% in the PFS group
- Peak weekly averaged pruritus numerical rating scale score: 7.3 in the AI group and 6.9 in the PFS group

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

All subjects were at least 80% compliant with treatment (Table 10).

Table 10: Summary of Treatment Compliance in Part B – SAF

Exposure Characteristic	Dupilumab 300 mg Q2W		
	Autoinjector (N=46)	Prefilled Syringe (N=44)	Combined (N=90)
N	46	44	90
Mean (SD)	99.73 (1.843)	99.72 (1.884)	99.72 (1.853)
Median	100.0	100.0	100.0
Q1: Q3	100.00: 100.00	100.00: 100.00	100.00: 100.00
Min: max	87.5: 100.0	87.5: 100.0	87.5: 100.0
≥ 80%	46 (100%)	44 (100%)	90 (100%)
< 80%	0	0	0

Abbreviation: Q, quartile; Q2W, once every 2 weeks; SAF, safety analysis set
Source: Table 13 of the study report for Part B of 1607

Concomitant Medications

Most patients reported using at least one concomitant medication during the treatment period: 100% in the AI group and 97.7% in the PFS group. Products in the "Corticosteroids, dermatological preparations" category were the most frequently reported by the patients: 95.7% in the AI group and 97.7% in the PFS group. Corticosteroids were the most frequently reported in the "moderately potent (Group II)" category: 89.1% in the AI group and 90.9% in the PFS group.

Efficacy Results – Primary Endpoint

The primary endpoint was the number and type of validated AI device-associated PTFs during the treatment period divided by the total number of actual injections (Table 11).

In the analysis, the Applicant considered the total number of actual injections to include the actual injections and attempted injections that failed because of possible device malfunction and which were reported as PTCs. The Applicant defined PTFs as any PTC that was found to have a technical cause that could be validated.

The Applicant identified no validated PTFs among the 364 injections with the AI or among the 336 injections with the PFS.

Table 11: Device Assessment (Number of Product Technical Failures) in Part B – mITT Population

	Dupilumab 300mg Q2W	
	Auto-injector (N=46)	Pre-filled Syringe (N=44)
Total number of injections taken	362	335
Total number of attempted injections*	2	1
Total number of actual injections (including attempted injections)**	364	336
Product Technical Failure (PTF)		
Total number (%) of patients with PTF	0	0
Total number of PTFs	0	0
Total number of PTFs/Total number of actual injections, 95% CI (%)	0.00% (0.00% - 1.01%)	0.00% (0.00% - 1.10%)

Abbreviations: CI, confidence interval; mITT, modified intention to treat; Q2W, once every 2 weeks
Source: Table 15 of the study report for Part B of 1607
* Total number of attempted injections was defined as injections that failed due to possible device malfunction. Details regarding the attempted injections are provided in Table 17.
** Total number of actual injections was defined as injections taken, including attempted injections that failed due to possible device malfunction and which were reported as a PTC. All devices and associated PTCs were adjudicated for PTFs.
Note: The loading dose, which consisted of two injections, for the same patient was counted as separate study drug administration. The percentage of patients with PTF was calculated using the number of patients in each treatment group as denominator. The 95% CI for the event rate was calculated using Clopper-Pearson exact method.

Data Quality and Integrity

No issues with the data quality or integrity were identified.

Efficacy Results – Secondary and Other Relevant Endpoints

PTCs were reported by the patients and assessed by the investigators after discussion with the patients and by review of the patients' diaries. Six PTCs were reported by five patients (Table 12):

- Three (6.5%) patients in the AI group reported four PTCs
- Two (4.5%) patients in the PFS group reported two PTCs

No patient-reported PTCs were assessed as PTFs.

Table 12: Summary of Device Assessment (Product Technical Complaints) in Part B – mITT Population

	Dupilumab 300mg Q2W	
	Auto-injector (N=46)	Pre-filled Syringe (N=44)
Total number of actual injections (including attempted injections)*	364	336
Product Technical Complaint (PTC)		
Total number (%) of patients with PTCs	3 (6.5%)	2 (4.5%)
Total number of PTCs	4	2
Device did not deliver any drug	1	1
Other	3	1
Total number of PTCs/Total number of actual injections* 95% CI (%)	1.10% (0.30% - 2.80%)	0.60% (0.07% - 2.14%)
Device did not deliver any drug	0.28% (0.01% - 1.53%)	0.30% (0.01% - 1.65%)
Other	0.83% (0.17% - 2.40%)	0.30% (0.01% - 1.65%)

Abbreviations: CI, confidence interval; mITT, modified intention to treat; Q2W, once every 2 weeks
Source: Table 16 of the study report for Part B of 1607
* Total number of actual injections was defined as injections taken and including attempted injections that failed due to possible device malfunction and reported as a PTC.

PTCs in the AI Group

The other complaints in the AI group included:

- Delivering the medication without pressure being applied
- Removing the device too soon
- Medication spilling out because the patient did not wait for the second click of the AI

The "delivering medication without pressure being applied" complaint occurred at a study site as a staff member was attempting to administer the study drug to subject (b) (6) The complaint was described as follows: "Staff removed cap from AI and AI just clicked and started dispensing the medication. No pressure was put on the AI top." The Applicant evaluated the mechanics of the AI and syringe and found no defect; on that basis, the Applicant concluded that this apparent spontaneous discharge of study medication was not a PTF. However, the Applicant did not provide a theory for the seemingly spontaneous activation of the AI.

The same subject (subject (b) (6) also reported a complaint of "device did not deliver any drug." This event was from a home injection. However, from Table 17 of the study report, it appears that the complaint may have been recorded as "delayed expelling of IP from auto-injector - defective device," which seems somewhat different than "did not deliver any drug." In any event, investigations identified no "deficiencies related to the complaint description."

PTCs in the PFS Group

Although subject (b) (6) reported that the "device did not deliver any drug," drug was released when the needle was removed from under the skin. Investigation did not result in identification of the root cause of this complaint.

The 'other' complaint in the PFS group was a bent needle.

Efficacy Endpoints

Study 1607 was not intended to be an efficacy study. The outcomes for IGA 0 or 1 and EASI-75 are included in the Clinical Studies section of the approved dupilumab label. The outcomes for those endpoints from Study 1607 are listed in Table 13. The outcomes for both endpoints at week 12 were higher in the AI group compared to the PFS group.

The IGA outcomes for the AI in Study 1607 were similar to those in the dupilumab label for adults. For the PFS, the IGA outcomes were lower compared to those in the label (Table 14). The EASI 75 scores for the AI in Study 1607 were higher compared to those in the label for this endpoint. For the PFS, the EASI-75 scores varied compared to those in the label (Table 14).

Table 13: Proportion of Patients Achieving Both an IGA Score of 0 or 1 and a Reduction From Baseline of ≥ 2 Points at Week 12 and Proportion of Patients Achieving an EASI-75

Responder Rate	Dupilumab 300 mg Q2W	
	Autoinjector (N=46)	Prefilled Syringe (N=44)
IGA Success at week 12[1]	18 (39.1%)	14 (31.8%)
EASI-75 at week 12	35 (76.1%)	24 (54.5%)

Abbreviations: EASI-75, eczema area and severity index score of a 75% improvement; IGA, investigator global assessment; Q2W, once every 2 weeks
Source: Tables 19 and 20 of the study report for Part B of 1607
[1] IGA Success is defined as achieving both an IGA score of 0 or 1 and a reduction from baseline of ≥ 2 points at week 12

Table 14: Labeled Efficacy Results of DUPIXENT With/Without Concomitant TCS at Week 16 (SAF)

	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%

Abbreviations: EASI, eczema area and severity index; SAF, safety analysis set; IGA, investigator global assessment; Q2W, every 2 weeks; TCS, topical corticosteroid
Source: Table 4 from the DUPIXENT package insert

The peak pruritus numerical rating scale (≥ 4-point improvement) outcomes are also included in the dupilumab label. However, the Applicant did not evaluate this endpoint in Study 1607.

Dose/Dose Response

This section is not applicable to this review.

Durability of Response

This section is not applicable to this review.

Persistence of Effect

This section is not applicable to this review.

Efficacy Results – Secondary or Exploratory COA (PRO) Endpoints

This section is not applicable to this review.

Additional Analyses Conducted on the Individual Trial

This section is not applicable to this review.

Integrated Review of Effectiveness

This section is not applicable to this review.

8.1.3. Assessment of Efficacy Across Trials

This section is not applicable to this review.

8.1.4. Integrated Assessment of Effectiveness

This section is not applicable to this review.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety data from Part B of Study 1607 were reviewed. The SAF included all randomized patients who received at least one injection of the study drug and were analyzed as treated.

8.2.2. Review of the Safety Database

Overall Exposure

The mean number of injections was similar in the two groups: 7.9 (0.45) in the AI group and 7.6 (1.15) in the PFS group. The mean duration of exposure was generally similar in the two groups: 96.8 (± 6.19) days in the AI group and 93.8 (± 15.61) days in the PFS group.

Adequacy of the Safety Database

The safety database was adequate for the purposes of this supplement.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The data integrity and submission quality appeared adequate.

Categorization of Adverse Events

The investigator (or designee) recorded all adverse events that occurred from the time the informed consent was signed until the end of the study.

Routine Clinical Tests

Routine clinical tests included hematology, chemistry, and pregnancy testing.

8.2.4. Safety Results

Deaths

No deaths occurred in the study.

Serious Adverse Events

No serious adverse events (SAEs) occurred during the treatment period. Two patients experienced SAEs after withdrawing from the study:

- A 65-year-old male in the AI group experienced a cerebrovascular accident 31 days after his last dose of the study drug. His medical history included hyperlipidemia, tobacco use, previous cerebrovascular accident, benign essential hypertension, and chronic ischemic heart disease. The outcome for the SAE was reported as “recovering/resolving.”
- A 72-year-old male in the PFS group reported mycosis fungoides 27 days after his last dose of the study drug and 10 days after withdrawing consent. The outcome of the SAE was reported as “not recovered/not resolved.”

It does not appear that either of these events is likely to be related to the study treatment.

Dropouts and/or Discontinuations Due to Adverse Effects

Few subjects discontinued the study drug because of treatment-emergent adverse events (TEAEs) (Table 15).

Table 15: Summary of TEAEs Leading to Permanent Study Drug Discontinuation During the Treatment Period by SOC and Preferred Term in Part B – SAF

Primary SOC Preferred Term	Dupilumab 300 mg Q2W		
	AI (N=46)	PFS (N=44)	Combined (N=90)
Number of TEAEs leading to study drug discontinuation	1	4	5
Patients with at least one TEAE leading to study drug discontinuation	1 (2.2%)	2 (4.5%)	3 (3.3%)
General disorders and administration site conditions	0	1 (2.3%)	1 (1.1%)
Injection site rash	0	1 (2.3%)	1 (1.1%)
Oedema peripheral	0	1 (2.3%)	1 (1.1%)
Infections and infestations	0	1 (2.3%)	1 (1.1%)
Conjunctivitis	0	1 (2.3%)	1 (1.1%)
Musculoskeletal and connective tissue disorders	0	1 (2.3%)	1 (1.1%)
Arthralgia	0	1 (2.3%)	1 (1.1%)
Skin and subcutaneous tissue disorders	1 (2.2%)	0	1 (1.1%)
Dermatitis atopic	1 (2.2%)	0	1 (1.1%)

Abbreviations: AI, autoinjector; PFS, prefilled syringe; Q2W, once every 2 weeks; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event
Source: Table 30 of the study report for Part B of 1607

Significant Treatment-Emergent Adverse Events

No severe TEAEs were reported in either group.

Adverse Events of Special Interest

The protocol defined adverse events of special interest as anaphylactic reactions or acute allergic reactions that required immediate treatment; systemic or extensive hypersensitivity reactions; severe injection site reactions that lasted more than 24 hours; severe infection (SAE, required parenteral antimicrobial therapy or oral antimicrobial therapy for more than 2 weeks, parasitic, or opportunistic); suicidal behavior; serious or severe conjunctivitis; and serious or severe blepharitis.

Four adverse events of special interest were reported, all in the PFS group (9.1%):

- A 20-year-old male in the PFS group experienced keratitis (keratoconjunctivitis of the left eye) on day 64. His medical history included allergic rhinitis, peanut allergy, and asthma. The event was reported as recovered/resolved on day 168.
- A 12-year-old male experienced mild swelling of the face on day 63. His medical history included environmental allergies, seasonal allergic rhinitis, and asthma. The study drug was interrupted. The event was resolved on study day 73. He resumed the study drug, and the final dose was administered on day 80.
- A 63-year-old female experienced mild-severity conjunctivitis (bilateral) on day 17. Her medical history included multiple food allergies and nasal polyps. She was withdrawn from the study drug on day 36. The event was not recovered/not resolved.
- A 16-year-old male experienced mild urticaria (intermittent hives) on day 35. His medical history included hives and pruritis. He continued to receive the study drug according to the schedule. The event was reported as recovered/resolved.

Treatment-Emergent Adverse Events and Adverse Reactions

Overall, a larger number of TEAEs was reported in the PFS group: 15 (32.6%) in the AI group and 23 (52.3%) in the PFS group. TEAEs in the Infections and Infestations system organ class (SOC) were the most commonly reported, with a noticeably higher frequency in the PFS group: 1 (2.2%) in the AI group and 12 (27.3%) in the PFS group. See Table 16.

Pharyngitis streptococcal and viral upper respiratory tract infection were the only events reported more than once: two reports each in the PFS group. The only TEAE of this SOC reported in the AI group was upper respiratory tract infection. The only other TEAEs reported more than once were diarrhoea and cough (two reports each). Injection site reactions occurred at a similar frequency in the two groups. There was no apparent pattern in the occurrence of TEAEs.

Table 16: Summary of TEAEs During the Treatment Period by SOC and PT in Part B – SAF

Primary SOC PT (MedDRA ver. 20.0)	Dupilumab 300 mg Q2W		
	Autoinjector (N=46)	Prefilled Syringe (N=44)	Combined (N=90)
Patients with at least one TEAE	15 (32.6%)	23 (52.3%)	38 (42.2%)
Infections and infestations	**1 (2.2%)**	**12 (27.3%)**	**13 (14.4%)**
Pharyngitis streptococcal	0	2 (4.5%)	2 (2.2%)
Viral upper respiratory tract infection	0	2 (4.5%)	2 (2.2%)
Acute sinusitis	0	1 (2.3%)	1 (1.1%)
Conjunctivitis	0	1 (2.3%)	1 (1.1%)
Folliculitis	0	1 (2.3%)	1 (1.1%)
Fungal skin infection	0	1 (2.3%)	1 (1.1%)
Localised infection	0	1 (2.3%)	1 (1.1%)
Respiratory tract infection	0	1 (2.3%)	1 (1.1%)
Sinusitis	0	1 (2.3%)	1 (1.1%)
Staphylococcal skin infection	0	1 (2.3%)	1 (1.1%)
Tinea pedis	0	1 (2.3%)	1 (1.1%)
Upper respiratory tract infection	1 (2.2%)	0	1 (1.1%)
Gastrointestinal disorders	**4 (8.7%)**	**3 (6.8%)**	**7 (7.8%)**
Diarrhoea	0	2 (4.5%)	2 (2.2%)
Food poisoning	2 (4.3%)	0	2 (2.2%)
Gastrooesophageal reflux disease	0	1 (2.3%)	1 (1.1%)
Impaired gastric emptying	1 (2.2%)	0	1 (1.1%)
Nausea	1 (2.2%)	0	1 (1.1%)
Skin and subcutaneous tissue disorders	**3 (6.5%)**	**4 (9.1%)**	**7 (7.8%)**
Dermatitis atopic	2 (4.3%)	0	2 (2.2%)
Diffuse alopecia	0	1 (2.3%)	1 (1.1%)
Eczema	0	1 (2.3%)	1 (1.1%)
Hyperhidrosis	0	1 (2.3%)	1 (1.1%)
Pityriasis rosea	1 (2.2%)	0	1 (1.1%)
Swelling face	0	1 (2.3%)	1 (1.1%)
Urticaria	0	1 (2.3%)	1 (1.1%)
Eye disorders	**2 (4.3%)**	**4 (9.1%)**	**6 (6.7%)**
Blepharitis	0	1 (2.3%)	1 (1.1%)
Conjunctival haemorrhage	1 (2.2%)	0	1 (1.1%)
Dry eye	1 (2.2%)	0	1 (1.1%)
Eye allergy	0	1 (2.3%)	1 (1.1%)
Eye discharge	0	1 (2.3%)	1 (1.1%)

Primary SOC PT (MedDRA ver. 20.0)	Dupilumab 300 mg Q2W		
	Autoinjector (N=46)	Prefilled Syringe (N=44)	Combined (N=90)
Eye irritation	0	1 (2.3%)	1 (1.1%)
Eye pain	0	1 (2.3%)	1 (1.1%)
Keratitis	0	1 (2.3%)	1 (1.1%)
General disorders and administration site conditions	**3 (6.5%)**	**3 (6.8%)**	**6 (6.7%)**
Injection site induration	1 (2.2%)	1 (2.3%)	2 (2.2%)
Influenza-like illness	0	1 (2.3%)	1 (1.1%)
Injection site erythema	1 (2.2%)	0	1 (1.1%)
Injection site oedema	1 (2.2%)	0	1 (1.1%)
Injection site rash	0	1 (2.3%)	1 (1.1%)
Injection site reaction	0	1 (2.3%)	1 (1.1%)
Injection site urticaria	1 (2.2%)	0	1 (1.1%)
Oedema peripheral	0	1 (2.3%)	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	**1 (2.2%)**	**3 (6.8%)**	**4 (4.4%)**
Cough	0	2 (4.5%)	2 (2.2%)
Oropharyngeal pain	0	1 (2.3%)	1 (1.1%)
Productive cough	0	1 (2.3%)	1 (1.1%)
Rhinorrhoea	0	1 (2.3%)	1 (1.1%)
Upper respiratory tract congestion	1 (2.2%)	0	1 (1.1%)
Injury, poisoning and procedural complications	1 (2.2%)	1 (2.3%)	2 (2.2%)
Arthropod bite	1 (2.2%)	0	1 (1.1%)
Skin abrasion	0	1 (2.3%)	1 (1.1%)
Investigations	**0**	**2 (4.5%)**	**2 (2.2%)**
Alanine aminotransferase increased	0	1 (2.3%)	1 (1.1%)
Eosinophil count increased	0	1 (2.3%)	1 (1.1%)
Musculoskeletal and connective tissue disorders	**1 (2.2%)**	**1 (2.3%)**	**2 (2.2%)**
Arthralgia	0	1(2.3%)	1 (1.1%)
Myalgia	1 (2.2%)	0	1 (1.1%)
Nervous system disorders	**1 (2.2%)**	**1 (2.3%)**	**2 (2.2%)**
Dizziness	1 (2.2%)	1 (2.3%)	2 (2.2%)
Headache	1 (2.2%)	0	1 (1.1%)
Metabolism and nutrition disorders	**1 (2.2%)**	**0**	**1 (1.1%)**
Diabetes mellitus	1 (2.2%)	0	1 (1.1%)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	**0**	**1 (2.3%)**	**1 (1.1%)**
Skin papilloma	0	1 (2.3%)	1 (1.1%)

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; Q2W, once every 2 weeks; SAF, safety analysis set; SOC, system organ class; TEAE, treatment-emergent adverse event
Patients who experienced more than one TEAE were counted only once in each category.
Source: Table 27 of study report for Part B of 1607

Laboratory Findings

The Applicant identified no clinically meaningful trends over time in the values of laboratory parameters. Most subjects had laboratory values within the normal ranges at baseline and at the end of the study (week 24). The results were generally similar in the AI and PFS groups.

Vital Signs

The Applicant identified no clinically meaningful trends in vital signs from baseline and reported that the only clinically meaningful values noted for more than one subject were for systolic blood pressure, diastolic blood pressure, and weight. The overall percentages of clinically meaningful values were generally similar: four subjects (8.7%) in the AI group and five (11.4%) in the PFS group.

Electrocardiogram

The Applicant reported no clinically meaningful trends in the mean or median changes from baseline.

QT

The section is not applicable to this review.

Immunogenicity

See Section 6.3.1.

8.2.5. Analysis of Submission-Specific Safety Issues

This section is not applicable to this review.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

This section is not applicable to this review.

8.2.7. Safety Analyses by Demographic Subgroups

This section is not applicable to this review.

8.2.8. Specific Safety Studies/Clinical Trials

This section is not applicable to this review.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

This section is not applicable to this review.

Human Reproduction and Pregnancy

No pregnancies were reported in the study.

The initial approval letter for the BLA included requirements for the following two postmarketing studies in pregnant subjects:

- 3183-5: A prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small-for-gestational-age births, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.
- 3183-6: Conduct a retrospective cohort study using administrative databases to identify pregnancy outcomes in a cohort of women exposed to dupilumab and a nondupilumab systemic medication or phototherapy exposure cohort. The outcomes will include major congenital malformations, spontaneous abortions, stillbirths, and small-for-gestational-age births. This study may use multiple data sources in order to obtain a sufficient sample size as women with atopic dermatitis are counseled to avoid systemic treatments while trying to conceive and during the course of pregnancy.

The Applicant has initiated both registries.

Supplement 015

The Applicant submitted Supplement 015 (S-015) on 07/08/2019. In S-015, the Applicant indicated that they were updating the label to add information regarding the pregnancy registry to the "Pregnancy" section (8.1), as below:

> Pregnancy Exposure Registry
> There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to DUPIXENT during pregnancy.
>
> Please contact 1-877-311-8972 or go to https://mothertobaby.org/ongoing-study/dupixent/ to enroll in or to obtain information about the registry.

Language will also be added to the Patient Information section, as well as the Patient Package Insert. Labeling negotiations for S-015 were underway as the review of S-017 was being finalized.

Pediatrics and Assessment of Effects on Growth

This section is not applicable to this review.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

This section is not applicable to this review.

Expectations on Safety in the Postmarket Setting

This section is not applicable to this review.

8.2.11. Integrated Assessment of Safety

This section is not applicable to this review.

8.3. Statistical Issues

This section is not applicable to this review.

8.4. Conclusions and Recommendations

The recommendation on the regulatory action for this supplement is approval.

9. Advisory Committee Meeting and Other External Consultations

This section is not applicable to this review.

10. Pediatrics

This section is not applicable to this review.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

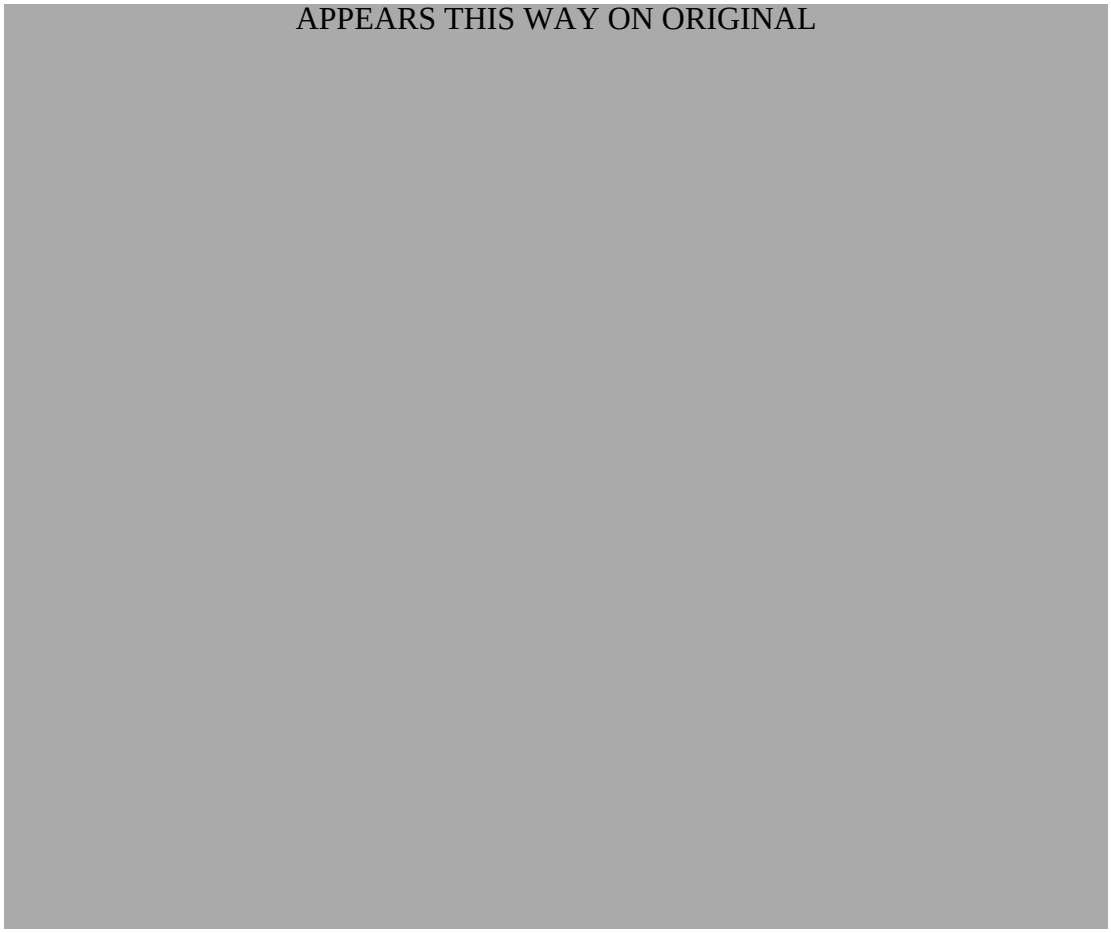
Labeling content was under discussion as the review of S-017 was being finalized.

12. Risk Evaluation and Mitigation Strategies

This section is not applicable to this review.

13. Postmarketing Requirements and Commitment

This section is not applicable to this review.



14. Appendices

14.1. References

None

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): R668-AD-1607

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 30 principal investigators		
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): 14 (12 were principal investigators)		
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: 14 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)

14.3. Nonclinical Pharmacology/Toxicology

Not applicable

14.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Phase 1b Study (R668-AD-1607)

Primary Objective

To collect actual-use data assessing the technical performance and user interactions of the dupilumab autoinjector (AI) device when used by patients (or caregiver for injections in upper arms) with atopic dermatitis (AD) over a 12-week treatment period.

Study Design

Number of subjects (Part B): 90 subjects (≥ 12 years of age) with moderate-to-severe AD. One subject in the prefilled syringe (PFS) group was excluded for reason of "withdrawal by consent." A total of 83/90 (92.2%) subjects in Part B completed treatment through day 99, and 7 (7.8%) subjects withdrew from the treatment as a result of adverse events (AEs) (3 subjects), withdrawal of consent (2 subjects), and loss to follow-up (2 subjects).

Reviewer's comment: *The subjects who withdrew from the study included one subject with atopic dermatitis flare in the AI group, one subject with injection site reaction (erythematous rash right thigh) in the PFS group, and one subject with bilateral conjunctivitis in the PFS group.*

Dose/Dosing Regimen

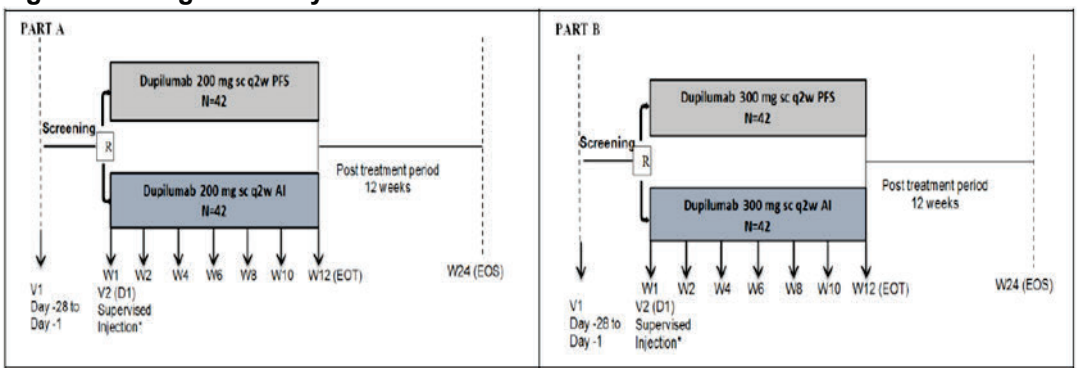
- Dupilumab AI: Each 2 mL single-use AI device delivers 300 mg of dupilumab (approximately 2.0 mL deliverable volume of 150 mg/mL solution) (N=46)
- Dupilumab PFS: Each single-use PFS with snap-off cap delivers 300 mg of dupilumab (approximately 2.0 mL deliverable volume of 150 mg/mL solution) (N=44)

This study consisted of a screening period (up to 38 days), a 12-week treatment period, and a 12-week follow-up period. The study was conducted in two parts: Part A (reviewed in Supplement-16) and Part B (current submission, Supplement-17). A schematic representation of the study design is shown in Figure 6.

In Part B, 84 patients with moderate-to-severe AD were randomized to receive dupilumab 300 mg via an AI device or dupilumab 300 mg via PFS, after a loading dose of 600 mg on day 1. Randomization was stratified by day-1 injection site (abdomen, upper thigh, or upper arm) and by body-weight category (≤ 70 kg, > 70 kg to < 100 kg, or ≥ 100 kg). To ensure balance, a minimum of two and a maximum of seven patients per stratum were enrolled. After the loading dose on day 1, subcutaneous (SC) injection sites were alternated among the four quadrants of the abdomen, the upper thigh, or the upper arm, so that the same site was not injected twice consecutively. All patients who completed the treatment period or prematurely discontinued the study drug had a 12-week follow-up period after the end-of-treatment visit. The duration of the 12-week follow-up period was based on the time expected for the drug level to fall below the lower limit of quantification. Blood samples for assessment of the serum dupilumab level

were collected on days 1 (predose), 4, 8, 11, 15 (predose), 57 (predose), 85 (predose), 88, 92, 95, and 99 or at the time of early termination. Blood samples for evaluation of immunogenicity were collected on days 2, 85, and 169, or at the time of early termination.

Figure 6: Design of Study R668-AD-1607



Abbreviations: AI, autoinjector; EOS, end of study; EOT, end of treatment; PFS, prefilled syringe; q2w, once every 2 weeks; sc, subcutaneous
Source: Figure 1 in the Study R668-AD-1607 protocol

Pharmacokinetic Results

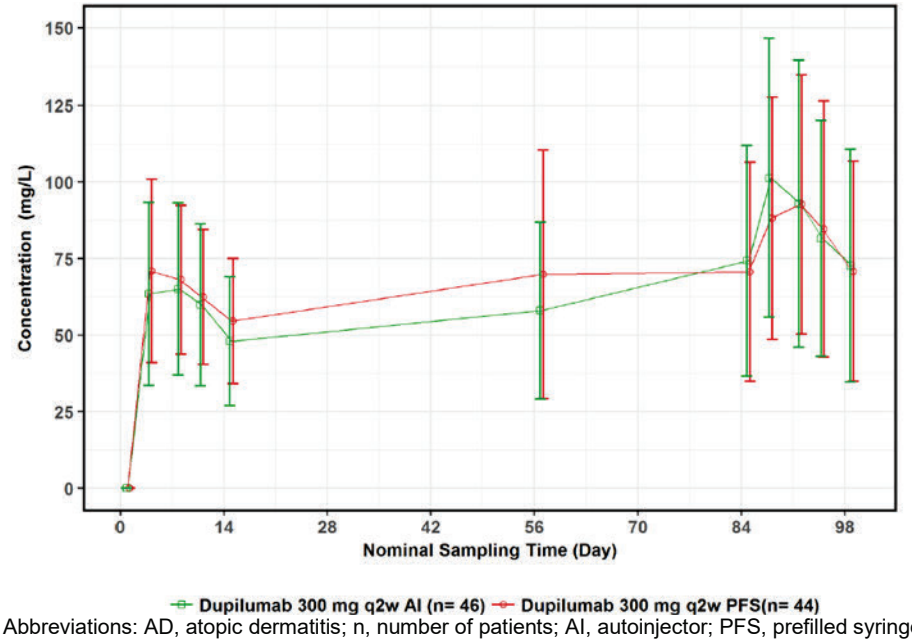
The serum concentration-versus-time profiles after a single 600 mg loading dose and the six subsequent 300 mg every 2 weeks (Q2W) doses showed that systemic exposure of dupilumab was comparable between the two device groups (Figure 7 and Table 17). The mean ± SD area under the concentration-time curve (AUC) of dupilumab on day 1 was 758 ± 323 day.mg/L and 803 ± 298 day.mg/L for AI and PFS, respectively (Table 17). The mean ± SD maximum concentration (C_{max}) of dupilumab on day 1 was 71.5 ± 29.2 mg/L and 76.6 ± 28.5 mg/mL for AI and PFS, respectively (Table 17). The mean AUC and C_{max} values of dupilumab were comparable between the AI and PFS groups on day 85 (Figure 7 and Table 17). The geometric mean ratios of AI/PFS for the area under the concentration-time curve from day zero to 14 (AUC_{0-14}) and C_{max} on day 1 were 0.924 and 0.915, respectively (Table 18). On day 85, the mean ratios for AUC_{0-14} and C_{max} were 1.073 and 1.083, respectively (Table 18). The 90% confidence interval of the ratio of geometric mean (AI/PFS) for AUC_{0-14} and C_{max} were within the no-effect boundary of 80% to 125% on days 1 and 85 (end of treatment).

The Applicant conducted additional analyses of subgroups stratified according to body weight (Table 19). The geometric mean ratios in three subgroups based on body-weight bands (i.e., ≤ 70 kg, > 70 kg to < 100 kg, and ≥ 100 kg) were within the no-effect boundary. This indicates that the systemic dupilumab levels were comparable between the two devices, except in subjects ≥ 100 kg on day 1. The geometric mean ratios of C_{max} and AUC in subjects ≥ 100 kg (heavy) were 0.67 and 0.71, respectively, on day 1 (Table 19), indicating that AI injection in heavy subjects resulted in a lower systemic level of dupilumab than did PFS injection. However, the mean ratios in heavy subjects following multiple administrations on day 85 were within the no-effect boundary.

Additionally, the Applicant compared the mean ratios among subgroups stratified by day-1 injection site. The day-1 injection was a loading dose of 600 mg (2 × 300 mg SC injections with

the AI or the PFS). The mean ratios of C_{max} and AUC in the abdominal-administration subgroup were 0.71 and 0.72, respectively (Table 20). This result indicated that AI injection to abdomen resulted in approximately 30% lower systemic exposure of dupilumab compared to PFS injection in the abdomen. Based on this evidence, it appears that the 30% lower BA in the abdomen following AI compared to PFS administration is likely due to the imbalance in the body-weight distribution and variability in the pharmacokinetics (PK) data between the two groups. It was concluded that the injection site is unlikely to affect systemic exposure (see Section 6.1).

Figure 7: Mean (± SD) Concentration of Dupilumab in Serum by Nominal Time and Device in Patients With AD



Abbreviations: AD, atopic dermatitis; n, number of patients; AI, autoinjector; PFS, prefilled syringe; q2w, once every 2 weeks
Concentrations below the lower limit of quantification were set to zero. A loading dose of 600 mg was administered on day 1.
Source: Figure 2 of study report R668-AD-1607-CP-01V2

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Table 17: Mean (± SD) Concentrations of Dupilumab in Serum by Nominal Time and Device in Patients With AD

Study Day	Parameter	Treatment	n	Mean	Median	Min	Max	SD	SE	CV	Geometric Mean
Day 1	AUC_{0-14} (mg*day/L)	Dupilumab 300 mg Q2W AI	46	758	778	45.0	1630	323	47.7	42.6	674
		Dupilumab 300 mg Q2W PFS	44	803	794	252	1910	298	44.9	37.1	748
	C_{max} (mg/L)	Dupilumab 300 mg Q2W AI	46	71.5	74.7	4.71	135	29.2	4.31	40.9	64.0
		Dupilumab 300 mg Q2W PFS	44	76.6	75.7	26.8	182	28.5	4.29	37.2	71.6
	C_{trough} (mg/L)	Dupilumab 300 mg Q2W AI	46	48.0	46.3	0.548	98.4	21.0	3.10	43.8	40.8
		Dupilumab 300 mg Q2W PFS	44	54.6	54.5	10.3	98.8	20.4	3.07	37.3	50.1
	t_{max} (Day)	Dupilumab 300 mg Q2W AI	46	--	6.79	2.70	10.9	--	--	--	--
		Dupilumab 300 mg Q2W PFS	44	--	4.48	2.03	14.0	--	--	--	--
Day 85	AUC_{0-14} (mg*day/L)	Dupilumab 300 mg Q2W AI	42	1140	1090	111	2520	588	90.7	51.7	944
		Dupilumab 300 mg Q2W PFS	37	1100	1050	101	2800	595	97.9	54.2	899
	C_{max} (mg/L)	Dupilumab 300 mg Q2W AI	42	107	104	25.5	230	50.7	7.82	47.4	94.2
		Dupilumab 300 mg Q2W PFS	37	100	95.2	20.3	187	45.6	7.50	45.5	88.6
	C_{trough} (mg/L)	Dupilumab 300 mg Q2W AI	42	75.4	71.1	13.7	171	39.8	6.15	52.8	63.8
		Dupilumab 300 mg Q2W PFS	37	70.8	65.1	4.58	137	34.9	5.74	49.3	59.1
	t_{max} (Day)	Dupilumab 300 mg Q2W AI	42	--	4.03	0	13.8	--	--	--	--
		Dupilumab 300 mg Q2W PFS	37	--	5.97	0	11.9	--	--	--	--

Abbreviations: AD, atopic dermatitis; AI, autoinjector; AUC_{0-14}, area under the concentration-time curve from time zero to day 14 (relative to the day in the 'Study Day' column) C_{max}, maximum concentration; C_{trough}, minimum concentration; CV, coefficient of variation; PK, pharmacokinetics; PFS, prefilled syringe; SE, standard error; t_{max}, time to the maximum concentration
Source: Figure 2 of study report R668-AD-1607-CP-01V2

Table 18: Geometric Mean Ratios (AI/PFS) for PK Parameters of Functional Dupilumab in AD Patients

Study Day	Parameter	Geometric Mean Ratio	90% Confidence Interval
Day 1	AUC_{0-14} (mg*day/L)	0.924	0.818 -- 1.045
	C_{max} (mg/L)	0.915	0.809 -- 1.034
	C_{trough} (mg/L)	0.840	0.708 -- 0.995
Day 85	AUC_{0-14} (mg*day/L)	1.070	0.859 -- 1.333
	C_{max} (mg/L)	1.083	0.950 -- 1.234
	C_{trough} (mg/L)	1.098	0.934 -- 1.291

Abbreviations: AD, atopic dermatitis; AI, autoinjector; AUC_{0-14}, area under the concentration-time curve from time zero to day 14 (relative to the day in the 'Study Day' column) C_{max}, maximum concentration; C_{trough}, minimum concentration; PK, pharmacokinetics; PFS, prefilled syringe
Source: Table 7 of study report R668-AD-1607-CP-01V2)

Table 19: Geometric Mean Ratios (AI/PFS) for PK Parameters of Dupilumab Stratified by Body Weight in Patients With AD

Study Day	Weight Category	C_{max} (mg/L)	C_{trough} (mg/L)	AUC_{0-14} (mg*day/L)
Day 0	<=70 kg	0.978 (0.817 -- 1.170)	0.926 (0.725 -- 1.183)	0.975 (0.818 -- 1.163)
	>70-<100 kg	0.905 (0.733 -- 1.117)	0.781 (0.586 -- 1.041)	0.908 (0.738 -- 1.116)
	>=100 kg	0.667 (0.485 -- 0.917)	0.607 (0.393 -- 0.936)	0.705 (0.516 -- 0.964)
Day 85	<=70 kg	1.160 (0.927 -- 1.452)	1.080 (0.830 -- 1.406)	1.009 (0.711 -- 1.432)
	>70-<100 kg	0.911 (0.715 -- 1.162)	0.912 (0.686 -- 1.212)	1.093 (0.749 -- 1.595)
	>=100 kg	1.136 (0.785 -- 1.643)	1.467 (0.951 -- 2.265)	0.997 (0.561 -- 1.775)

Abbreviations: AD, atopic dermatitis; AI, autoinjector; AUC_{0-14}, area under the concentration-time curve from time zero to day 14 (relative to the day in the 'Study Day' column) C_{max}, maximum concentration; C_{trough}, minimum concentration; PK, pharmacokinetics; PFS, prefilled syringe
Source: Table 8 of study report R668-AD-1607-CP-01V2

Table 20: Geometric Mean Ratios (AI/PFS) for PK Parameters of Dupilumab Stratified by Day-1 Injection Site in Patients With AD

Study Day	Injection Site	C_{max} (mg/L)	C_{trough} (mg/L)	AUC_{0-14} (mg*day/L)
Day 1	Abdomen	0.711 (0.576 -- 0.877)	0.605 (0.451 -- 0.813)	0.717 (0.580 -- 0.885)
	Upper Arms	1.071 (0.871 -- 1.317)	0.925 (0.692 -- 1.235)	1.039 (0.845 -- 1.279)
	Upper Thighs	0.993 (0.810 -- 1.218)	1.038 (0.780 -- 1.380)	1.046 (0.853 -- 1.283)

Abbreviations: AD, atopic dermatitis; AI, autoinjector; AUC_{0-14}, area under the concentration-time curve from time zero to day 14 (relative to the day in the 'Study Day' column) C_{max}, maximum concentration; C_{trough}, minimum concentration; PK, pharmacokinetics; PFS, prefilled syringe
Source: Table 9 of study report R668-AD-1607-CP-01V2)

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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/

MATTHEW E WHITE
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LUKE Y OH
06/18/2020 03:14:05 PM

CHINMAY SHUKLA
06/18/2020 04:10:16 PM

BRENDA CARR
06/18/2020 04:21:26 PM

SNEZANA TRAJKOVIC
06/18/2020 04:31:45 PM

KENDALL A MARCUS
06/18/2020 05:10:19 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s017

OTHER REVIEW(S)

HUMAN FACTORS RESULTS AND LABEL AND 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:	May 28, 2020
Requesting Office or Division:	Division of Dermatology and Dental Products (DDDP)
Application Type and Number:	BLA 761055/S-17
Product Name and Strength:	Dupixent (dupilumab) Injection 300 mg/2 mL (150 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals
FDA Received Date:	May 20, 2019; October 5, 2019; December 5, 2019; March 9, 2020; March 30, 2020
OSE RCM #:	2019-1090 and 2019-1312
DMEPA Safety Evaluator:	James Schlick, MBA, RPh
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1. REASON FOR REVIEW

We reviewed the human factors (HF) validation study report and proposed labels and labeling submitted under BLA 761055/S-17 for Dupixent (dupilumab) injection. The applicant is seeking licensure for the 300 mg/2 mL single-dose pre-filled pen.

2. REGULATORY HISTORY

Dupixent (dupilumab) injection was approved on March 28, 2017 and is currently approved for

- The treatment of patients 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,
- 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, and
- Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

Dupixent is currently available as a prefilled syringe (PFS) in 300 mg/2 mL and 200 mg/1.14 mL strengths. Regeneron Pharmaceuticals, Inc. previously submitted a human factors validation study results report for the 200 mg/1.14 mL pre-filled pen (PFP) under BLA 761055/S-016 on September 11, 2018. Given the use errors identified in the HF validation study report combined with the findings from clinical pharmacology's review, our evaluation determined that the design of the user-interface did not support the safe and effective use of the product. The Applicant received a Complete Response letter on July 11, 2019 based on clinical pharmacology and human factors validation study concerns.[a]

3. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Request	F

[a] Dixons, S. Complete Response Letter submitted to DARRTS on July 11, 2019. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80504592&_afrRedirect=998958040718743

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Labels and Labeling	G

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

4. OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

HF Validation Study Results Received on May 20, 2019

The 300 mg pre-filled pen (PFP) is similar to the 200 mg PFP in terms of the device, Instructions for Use (IFU), and use tasks. The two products differ in the volume of liquid that is injected (200 mg/1.14 mL vs. 300 mg/2 mL) and warming time to room temperature (30 minutes for 200 mg PFP and 45 minutes for 300 mg PFP). The injection hold time is the same for both PFPs.

Table 2 below provides a comparison and summary of the types of errors seen with critical tasks in the HF validation study results for the 200 mg and 300 mg PFP. DMEPA identified the six tasks in Table 2 as critical for the safe and effective use of the product. Thus, in the table below we focus on these tasks in our comparison between the 200 mg and 300 mg PFP.

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Table 2. Critical Task Errors in 200 mg PFP and 300 mg PFP HF Validation Studies

Critical Tasks	Description of the Task	Errors seen in 200 mg PFP	Errors seen in 300 mg PFP
Task 13 Pick an injection site	Select the appropriate injection sites: Caregiver: Upper arm, stomach, thigh Patient: stomach, thigh	Same use errors with same underlying root cause or lack of adequate information regarding root cause See discussion of residual risk in previous DMEPA review of 200 mg PFP.[b,c]	
Task 14 Clean injection site	Clean the injection site with an alcohol wipe and let skin dry	Same use errors with same underlying root cause or lack of adequate information regarding root cause See discussion of residual risk in previous DMEPA review of 200 mg PFP.[b,c]	
Task 15 Remove cap	Pull cap straight off and do not twist the yellow cap off	Same use errors with same underlying root cause or lack of adequate information regarding root cause See discussion of residual risk in previous DMEPA review of 200 mg PFP.[b,c]	
Task 16 Press needle cover against injection site to activate the injection	Press and hold the pen on the skin at a 90 degree angle and hold the pen so the window can be seen.	User attempted to perform a second injection with the device she used in the first injection due to negative	Users injected at an angle between 45 and 90 degrees due to negative transfer with previous injections.

[b] Patel, M. Human Factors Results and Label Labeling Review for dupilumab BLA 761055/S-16. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 18. RCM No.: 2018-1940 and 2019-495.

[c] Patel, M. Human Factors Results and Label Labeling Review Memorandum for dupilumab BLA 761055/S-16. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 02. RCM No.: 2018-1940-1 and 2019-495-1.

Critical Tasks	Description of the Task	Errors seen in 200 mg PFP	Errors seen in 300 mg PFP
		transfer with another multi-dose injection device. The participant eventually understood that the device is single use. DMEPA analysis: The needle shield locks on the device for both strengths preventing a user to push down and, thus, preventing a user from using the device to give a second injection. The use error seen with the 200 mg PFP may also occur with the 300 mg pen, but we would not anticipate a greater residual risk for the 300 mg pen.	DMEPA analysis: The instructions are the same in this step for both the 200 mg and 300 mg PFP as are the tasks. The use error seen with the 300 mg PFP may also occur with the 200 mg pen, but we anticipate there is similar residual risk when compared to the 200 mg pen, and we do not have further recommendations for changes to the user interface (UI) at this time.
Task 17 Hold PFP firmly against skin until injection is complete	Hold the pen through the first click, second click, and hold for 5 seconds after the second click to ensure the window has turned completely yellow.	Same use errors with same underlying root cause or lack of adequate information regarding root cause See discussion of residual risk in previous DMEPA review of 200 mg PFP.[b,c]	
Task 19 Disposal of PFP and cap	Place PFP and cap in an FDA-cleared sharps disposal container.	Same use errors with same underlying root cause or lack of adequate information regarding root cause See discussion of residual risk in previous DMEPA review of 200 mg PFP.[b,c]	

Table 3 below provides our assessment of the non-critical task errors observed in the 300 mg PFP results, but which did not occur in the 200 mg PFP results.

Table 3. Non-Critical Task Errors in 300 mg PFP

Non-Critical Tasks	Description of the Task	Errors seen in 300 mg PFP and DMEPA Analysis
Task 5 Open Package	Open Package	Users opening the carton from the side rather than using the front tab. All users were able to open the carton without difficulty, did not compromise the device and materials in the carton, and there was no harm to the user. We do not have further recommendations for changes to the user interface (UI) at this time and find this residual risk acceptable.
Task 6 Remove IFU and device from packaging	Remove IFU and device from packaging	Use errors were attributed to negative transfer (familiar with similar products), simulated study environment, and users that do not typically read instructions. None of the users indicated that the IFU was difficult to find in the carton. We do not have further recommendations for changes to the user interface (UI) at this time and find this residual risk acceptable.

Post Mid-Cycle Interaction with the Applicant

We held a teleconference with the Applicant on March 3, 2020 to convey our preliminary findings that the HF validation study demonstrated use errors with critical tasks, which could result in underdosing, and that additional risk mitigations are necessary. After the teleconference discussion, we sent an information request on March 5, 2020 to ask the Applicant if they have HF validation study results incorporating our January 24, 2020 HF protocol recommendations for the 200 mg PFP. The Applicant responded on March 6, 2020 via email that they had not conducted an HF validation study for the 200 mg PFP that incorporated our January 24, 2020 HF protocol comments.[d] Instead, they noted that they had conducted an HF validation study for the 300 mg PFP incorporating

[d] Schlick, J. Human Factor Protocol Review for dupilumab IND 107969. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 24. RCM No.: 2019-2443. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8053a6ed&_afrRedirect=8267673962687943

revised instructions for Task 17, '*Hold PFP firmly against skin until injection is complete'* based on comments from the July 11, 2019 Complete Response letter and comments from the meeting minutes sent on November 4, 2019 under IND 107969.[e,f] We agreed via email to review the HF validation study report referenced in the March 6, 2020 Applicant email, and the study report was received on March 9, 2020.

Analyses of the HF Validation Study Results Report Submitted on March 9, 2020

1. **IFU**

We note the revisions related to Task 17 based on previous recommendations from the Agency. Table 4 includes a comparison of the IFU step that was revised after the first 300 mg PFP HF validation study received on May 20, 2019. We also note other revisions in sections of the IFU to organize information and improve the clarity of the steps in the IFU.

Table 4: IFU Injection Step Comparison (Task 17) Between HF Validation Studies

IFU Tested in the HF Validation Study Report submitted on May 20, 2019	IFU Tested in 300 mg PFP HF Validation Study provided to the BLA on March 9, 2020
(b) (4)	(b) (4)

[e] Dixons, S. Complete Response Letter submitted to DARRTS on July 11, 2019. https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af80504592&_afrRedirect=998958040718743

[f] White, M. Meeting Minutes submitted to DARRTS on November 14, 2019 under IND 107969: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8052811a&_afrRedirect=1450584124732007

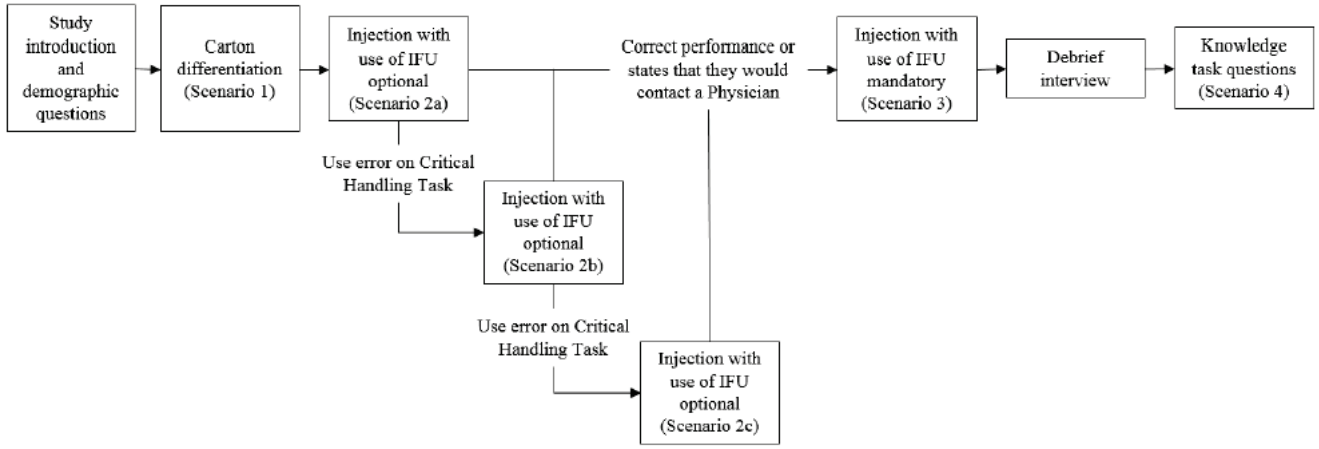
2. Study Methodology

Of note, the Applicant did not submit an HF validation study protocol for our review prior to conducting the study for the 300 mg PFP with the revised IFU. The March 9, 2020 HF validation study methodology includes a pathway where participants who committed a use error on their first attempt (IFU optional) were asked to attempt another injection (IFU optional) to study a learning effect. The Applicant did not include this learning effect methodology in the previous May 20, 2019 HF validation study for the 300 mg PFP. Lastly, we note that the Applicant did not incorporate the user group recommendations from our January 24, 2020 HF validation study protocol recommendations for the 200 mg PFP since the 300 mf PFP study was conducted in December 2019. We sent an information request asking the Applicant to help us understand their rationale that they made the best attempt to ensure the user groups are representative of the intended user groups for this product on March 30, 2020. We acknowledge that the Applicant did not have the benefit of the Agency's latest thinking of user groups for this product before conducting the study as they followed previous agency advice that had been rendered regarding end user groups. Looking in totality at the information that has been submitted, we have determined, in this particular instance, that we have sufficient human factors information to inform our evaluation of the proposed user interface and additional data is not needed at this time.

Table 5 includes a summary of the study methodology for the HF validation study report received March 9, 2020.

Table 5. Study Methodology for Human Factors (HF) Validation Study Received on March 9, 2020

Study Design Elements	Details
Participants	<table><tr><th>User Group (n = x)</th><th>Description</th></tr><tr><td>Adults diagnosed with atopic dermatitis (n=16)</td><td>Injection-experienced using any type of injection device for > 3 months</td></tr><tr><td>Adults diagnosed with atopic dermatitis (n=15)</td><td>Injection-naïve (no experience using an injection device)</td></tr><tr><td>Adults with low literacy (n = 15)</td><td>6th to 8th grade reading level, as determined from assessment with Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) tool (refer to Appendix 1)</td></tr><tr><td>Adolescents (age 12 – 17 years) diagnosed with atopic dermatitis (n = 15)</td><td>No injection experience criteria defined. Any reported experience with injection device was documented.</td></tr><tr><td>HCPs (n = 15)</td><td>Currently licensed Registered Nurses</td></tr></table>

Training	No training was given before Scenario 2 (the IFU was optional), and in Scenario 3, the use of the IFU was mandatory. If an error occurred with a critical task for a participant in Scenario 2, they would be asked to perform another injection (up to 2 times) before moving to Scenario 3 (IFU mandatory).
Test Environment	Typical home environment
Test Overview and Sequence	

3. Reporting of Task Results

The Applicant reported the results of Tasks 15 to 19 (tasks related to injection steps) since this was the focus of the deficiencies communicated to the Applicant in the July 11, 2019 Complete Response letter for the 200 mg PFP. The IFU Tasks 1 to 14 include language and formatting revisions to improve clarity. Based on a previous DMEPA review, we determined that of Tasks 1 to 14, only Tasks 13 and 14 are categorized as critical tasks ('Pick injection site' and 'Clean injection site').[b] See Appendix C.2 for a high-level task sequence for Tasks 1 to 19. We reviewed the IFU revisions that correspond to these tasks (Tasks 13 and 14) and determined they were minor revisions that did not change the residual risk assessed in the previous analyses (see Table 2). Additionally, the knowledge task questions related to these tasks indicated that users could comprehend the IFU for these tasks (99% - 143/144 participants- responded correctly or partially correct for 'Pick injection site' and 98.6% - 74/75 participants- responded correctly or partially correct for 'Clean injection site'). Thus, we find the residual risk acceptable. For tasks 15, 16, 18, and 19, we found the same use errors from previous HF validation studies with the same underlying root cause (see Table 2). Thus, we also find the residual risk

acceptable for these tasks. Below in Table 6 is an assessment of the results for Task 17, which corresponds to the major IFU revision related to lifting up before the injection is complete.

TABLE 6: SUMMARY AND ANALYSES OF ERRORS OBSERVED WITH CRITICAL TASK 17 *'Hold PFP firmly against skin until injection is complete'*.

Tasks	Number of Use Errors	Description of Use Errors	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations
Task 17 *'Hold PFP firmly against skin until injection is complete'.* Scenario 2a – first injection with IFU optional	Use Errors (n=20) 3 Adult Naïve (PN) 3 Adult Experienced (PE) 6 Adult Low Literacy (PL) 6 Adolescent (PA) 2 HCP (N)	14 of the participants lifted up before the second click and 6 lifted up immediately after the second click	**Incorrect Mental Model** (b) (6) – Participant expected to have to loosen their grip in order to hear the second click. **Incorrect Mental Model/IFU Design** (b) (6) (b) (6) Participants expected that the injection time was shorter than it actually was. Based on the review of the data, we could not determine if the participants fully read the injection step in the IFU; therefore, IFU design could not be ruled out as a root cause. On subsequent injections, when participants used the IFU, they self-corrected and delivered complete injections. **Study Artifact** (b) (6) – Participant lifted after the 1st click and indicated that they did not treat the scenario as if they were at home due to being nervous and overwhelmed. **Indeterminate Root Cause** (b) (6) – Participant did not provide additional feedback regarding the injection, but understood what was not done correctly. They lifted the PFP after the 2nd click corresponding to delivery of the labeled dose. **Study Artifact** (b) (6) – Participant acknowledged they would not inject without training but continued with the injection scenarios because of being in the testing situation. **Incorrect Mental Model** (b) (6) - Participant tilted the PFP to look at the window while completing the first injection; the participant completed the subsequent injections correctly. **Negative Transfer** (b) (6) – Participant performance impacted by previous experience with other injection devices.	For the 6 participants that lifted the pen immediately after the second click, the Applicant notes that patients would have received the full dose based on a previous Information Request response[g] For the 14 participants that lifted up before the second click, most users understood they should hold the PFP longer in order to deliver the full labeled dose, as evidenced by the reduction in use errors in subsequent injection scenarios (scenarios 2b and 2c where the IFU was still optional). The one use error that occurred during	We note the potential harm associated with these use errors include incomplete doses. For the 6 participants that lifted the pen immediately after the second click, we agree with the Applicant's assessment that they received the full labeled dose. As for the 14 participants, who lifted the pen before the second click in

[g] Information Request response submitted to DARRTS on December 5, 2019. \\cdsesub1\evsprod\bla761055\0713\m1\us\111-info-amend\qual-info-amend.pdf

				Scenario 2b and 2c that would have resulted in delivery of less than the labeled dose was made by the same person (b) (6) an adult with low literacy who had not fully read the IFU. The participant made the same use errors in Scenario 2a thru 2c. (b) (6) partially lifted the PFP early and the needle cover locked out, but they kept the PFP on the injection pad and watched the window. The injection was incomplete, and they realized they should have held the PFP down longer. However, (b) (6) noted that they did not treat the scenario as if they were at home (study artifact). in Scenario 3 (IFU mandatory), (b) (6) read the IFU, self-corrected, and delivered a complete injection. The one use error that occurred in Scenario 3 (IFU mandatory) that resulted in an incomplete dose occurred with (b) (6) This was the adolescent participant's first injection as	the first scenario, we acknowledge that most participants that experienced the use error were able to successfully administer a complete injection during the second and third injection attempts (Scenario 2b and 2c). Additionally, we note the labeled sub-tasks for this step and related images stating to hold down firmly for 15 seconds and wait for a second click. Furthermore, we contacted our clinical colleagues to obtain their input on the clinical significance of an underdose, and our clinical team states this does not raise any safety concerns.

				their parent had delivered the injection in Scenario 2a. (b) (6) lifted up the pen after the first click resulting in a wet injection. The participant immediately recognized the use error. The moderator then gave them an opportunity to deliver another injection, and they delivered a complete injection. Based on this information, The Applicant concluded that through self-correction and use of the IFU, the observed use errors were mitigated.	Therefore, we find the residual risk acceptable. We have no further recommendations at this time.

5. CONCLUSION

The results of the HF validation studies identified failures, close calls, and use difficulties with critical and non-critical tasks. We did not identify areas of improvement in the proposed user interface based upon the root cause analyses. After evaluating the errors for the 300 mg PFP, we identified that with subsequent injections, users learned to hold the PFP at the injection site to complete a full injection. Thus, we agree with the Applicant that no additional mitigation strategies are necessary, and we determined that the residual risk is acceptable. Our evaluation of the proposed label and labeling did not identify any areas of concern and we have no recommendations at this time.

6. APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 7 presents relevant product information for Dupixent received on May 20, 2019 from Regeneron Pharmaceuticals.

<table>
<tr><th colspan="2">Table 7. Relevant Product Information for Dupixent</th></tr>
<tr><td>Initial Approval Date</td><td>September 28, 2017</td></tr>
<tr><td>Proper Name</td><td>Dupilumab</td></tr>
<tr><td>Indication</td><td>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.
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.</td></tr>
<tr><td>Route of Administration</td><td>Subcutaneous</td></tr>
<tr><td>Dosage Form</td><td>Injection</td></tr>
<tr><td>Strength</td><td>200 mg/1.14 mL and 300 mg/2 mL</td></tr>
<tr><td>Dose and Frequency</td><td><u>Atopic Dermatitis:</u>

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.

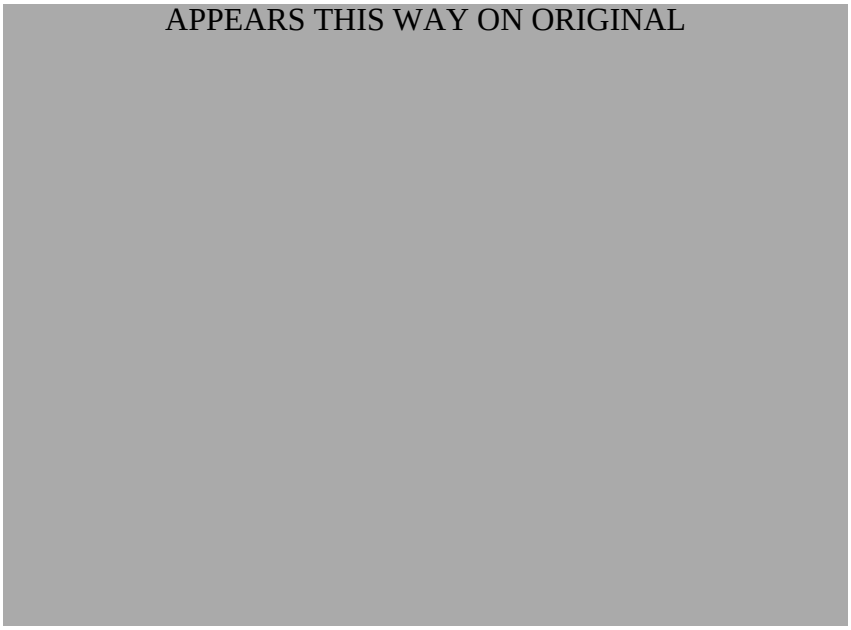
<table>
<tr><th>Body Weight of Patient</th><th>Initial Dose</th><th>Subsequent Doses (every other week)</th></tr>
<tr><td>less than 60 kg</td><td>400 mg (two 200 mg injections)</td><td>200 mg</td></tr>
<tr><td>60 kg or more</td><td>600 mg (two 300 mg injections)</td><td>300 mg</td></tr>
</table>
Adolescents 12 to 17 years of Age:</td></tr>
</table>

<table>
<tr><td></td><td>Asthma:
Adults and adolescents (12 years of age and older):
• initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week or
• 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</td></tr>
<tr><td>How Supplied</td><td>200 mg/1.14 mL and 300 mg/2 mL single-dose pre-filled pens are proposed:

DUPIXENT is available in cartons containing 2 pre-filled syringes with needle shield or 2 pre-filled pens.[36]
<table><tr><th>Pack Size</th><th>300 mg/2 mL Pre-filled Syringe with Needle Shield</th><th>200 mg/1.14 mL Pre-filled Syringe with Needle Shield</th></tr><tr><td>Pack of 2 syringes</td><td>NDC 0024-5914-01</td><td>NDC 0024-5918-01</td></tr></table>
<table><tr><td>Pack Size</td><td>200 mg/1.14 mL Pre-filled Pen</td></tr><tr><td>Pack of 2 pens</td><td>NDC 0024-5919-02</td></tr></table>
<table><tr><td>Pack Size</td><td>300 mg/2 mL Pre-filled Pen</td></tr><tr><td>Pack of 2 pens</td><td>NDC 0024-5915-02</td></tr></table></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>Proposed: Single dose pre-filled pen 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 AND FDA INTERACTIONS WITH APPLICANT

On November 4, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, 'dupilumab'. Our search identified 3 relevant previous reviews and one interaction[h,i,j,k,l,m] and we confirmed that our previous recommendations were implemented.



[h] Patel, M. Human Factor Protocol Review for dupilumab IND 107969. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 09. RCM No.: 2016-2648.

[i] Patel, M. Human Factor Protocol Review Memo for dupilumab IND 107969. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 APR 26. RCM No.: 2016-2648-1.

[j] Patel, M. Human Factors Results and Label Labeling Review for dupilumab BLA 761055/S-16. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 18. RCM No.: 2018-1940 and 2019-495.

[k] Patel, M. Human Factors Results and Label Labeling Review Memorandum for dupilumab BLA 761055/S-16. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUL 02. RCM No.: 2018-1940-1 and 2019-495-1.

[l] White, M. Meeting Minutes submitted to DARRTS on November 14, 2019 under IND 107969: https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8052811a&_afrRedirect=1450584124732007

[m] Schlick, J. Human Factor Protocol Review for dupilumab IND 107969. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JAN 24. RCM No.: 2019-2443

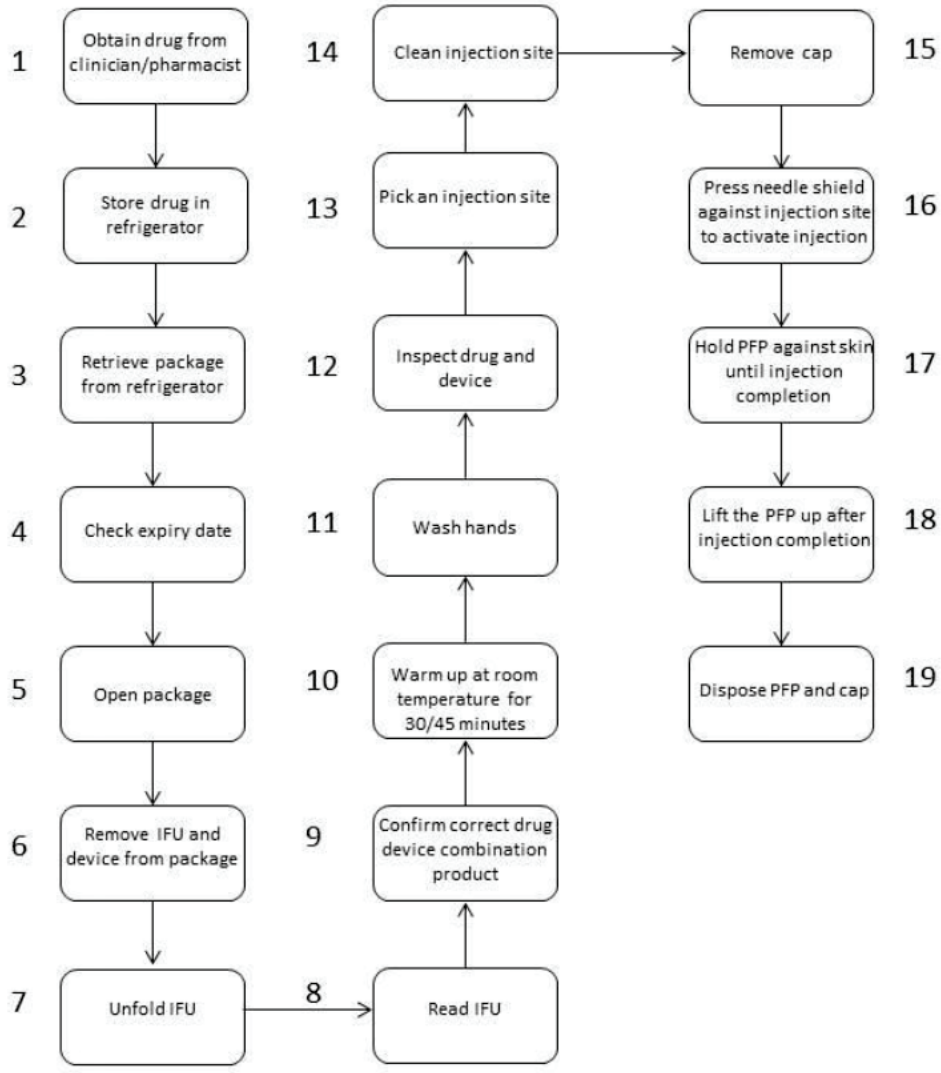
APPENDIX C. HUMAN FACTORS STUDY

C.1 Study Design and Results

Pre-filled Pen Injector Human Factors Validation Study Results Received on May 20, 2019 accessible via:
\\cdsesub1\evsprod\bla761055\0490\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfs\peformance-hfe-design-validation-pfp-300-mg.pdf

Pre-filled Pen Injector Human Factors Validation Study Results Received on March 9, 2020 accessible via:
\\cdsesub1\evsprod\bla761055\0780\m5\53-clin-stud-rep\535-rep-effic-safety-stud\atopicdermatitis\5354-other-stud-rep\hfs\human-factors-summary-pfp-300mg.pdf

C.2 Task Sequence



APPENDIX D. ISMP NEWSLETTERS - N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) - N/A

APPENDIX F. INFORMATION REQUEST

We sent an information request on October 2, 2019 (response received October 7, 2019) where we noted that some users prematurely lifted the pen up when they heard the second click and did not count for 5 seconds after the second click was heard. Additionally, we noted two users lifted the pen after the first click. We asked the Applicant to provide the amount of drug left in the pen at the time of the first and second click for the 300 mg/2 mL pen device. Additionally, we sent an information request on November 22, 2019 (response received December 5, 2019) seeking information on whether the second click is an intentional design feature of the device and the design specifications for the design feature.

The October 7, 2019 Information Request response is accessible via:
\\cdsesub1\evsprod\bla761055\0658\m1\us\111-info-amend\qual-info-amend.pdf

The December 5, 2019 Information Request response is accessible via:
\\cdsesub1\evsprod\bla761055\0713\m1\us\111-info-amend\qual-info-amend.pdf

After our preliminary analysis and teleconference with the Applicant discussing the first HF validation study results (received May 20, 2019), we sent an information request to the Applicant on March 5, 2020 to ask if they had HF validation study results incorporating our January 24, 2020 HF protocol recommendations for the 200 mg PFP. The Applicant responded on March 6, 2020 via email that they had not conducted an HF validation study for the 200 mg PFP that incorporated our January 24, 2020 HF protocol comments. Instead, they noted that they had conducted an HF validation study for the 300 mg PFP incorporating revised instructions for Task 17, *'Hold PFP firmly against skin until injection is complete'.* The Sponsor submitted this HF validation study results report on March 9, 2020 (see Appendix C.1)

The March 5, 2020 Information Request is accessible via:
https://darrts.fda.gov//darrts/faces/ViewDocument?documentId=090140af8054655b&_afrRedirect=8255714210810027

The Applicant did not incorporate the user group recommendations from the January 24, 2020 HF Protocol comments for the 200 mg PFP in the HF validation study received March 9, 2020 due to the fact that the study was conducted in December 2019. We sent an information request (sent on March 23, 2020) asking the Applicant to help us understand their rationale that the user groups used in the March 9, 2020 HF validation study report are an adequate representation of the FDA's current thinking on user groups for this product. The Applicant responded on March 30, 2020 with their rationale.

The March 30, 2020 Information Request response is accessible via \\CDSESUB1\evsprod\bla761055\0800\m1\us\111-info-amend\qual-info-amend.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

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

- Container label received on May 20, 2019
  \\cdsesub1\evsprod\bla761055\0490\m1\us\114-labeling\114a-draft-label\dupixent-300mg2ml-prefilledpen-label.pdf
- Carton labeling received on May 20, 2019
  \\cdsesub1\evsprod\bla761055\0490\m1\us\114-labeling\114a-draft-label\dupixent-300mg2ml-prefilledpen-carton.pdf
- Instructions for Use received on March 9, 2020.

  \\cdsesub1\evsprod\bla761055\0780\m1\us\114-labeling\114a-draft-label\proposed-ifu-300mg.doc
- Prescribing Information (Image not shown) received on May 20, 2019

  \\cdsesub1\evsprod\bla761055\0490\m1\us\114-labeling\114a-draft-label\annotated-uspi-300mg.docx
- Patient Information (Image not shown) received on May 20, 2019

  \\cdsesub1\evsprod\bla761055\0490\m1\us\114-labeling\114a-draft-label\annotated-ppi-300mg.docx

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

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/s/

JAMES H SCHLICK
05/28/2020 12:46:52 PM

MILLIE B SHAH
05/28/2020 01:06:19 PM

QUYNHNHU T NGUYEN
05/28/2020 02:59:31 PM

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

PATIENT LABELING REVIEW

Date:	May 15, 2019
To:	Matthew White Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMP**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
	Review of Patient Labeling: 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-015 and S-017
Applicant:	Regeneron Pharmaceuticals, Inc.

1 INTRODUCTION

On January 24, 2019, Regeneron Pharmaceuticals, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS)- Labeling to their approved Biologics License Application (BLA) 761055/S-015 for DUPIXENT (dupilumab) injection. The Applicant references in their cover letter the Postmarketing Commitment 3183-5 in which they were asked to conduct a prospective, registry-based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to dupilumab during pregnancy to an unexposed control population. As the registry is open for enrollment, with this supplement the Applicant provides updates to the Patient Package Insert (PPI) and Sections 8.1 and 17 of the Prescribing Information (PI) with information for patients and prescribers about the registry in accordance with the December 2014 Pregnancy and Lactation Labeling Rule (PLLR).

On May 20, 2019, Regeneron Pharmaceuticals, Inc. submitted for the Agency's review a PAS- Efficacy to their approved Biologics License Application (BLA) 761055/S-017 for DUPIXENT (dupilumab) injection. With this submission, the Applicant proposes the introduction of a new presentation, the 300 mg (150 mg/ml) auto-injector (pre-filled pen).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Dermatology and Dentistry (DDD) on June 20, 2019, for DMPP and OPDP to review the Applicant's proposed PPI and Instructions for Use (IFU) for DUPIXENT (dupilumab) injection, for subcutaneous use for S-017, and on May 7, 2020 to additionally review the PPI for DUPIXENT (dupilumab) injection for S-015.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be completed.

2 MATERIAL REVIEWED

- Draft DUPIXENT (dupilumab) injection PPI received by DMPP and OPDP on May 7, 2020.
- Draft DUPIXENT (dupilumab) injection IFU received on May 20, 2019 and revised on March 9, 2020, and received by DMPP and OPDP on May 7, 2020.
- Draft DUPIXENT (dupilumab) injection Prescribing Information (PI) received on May 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 7, 2020.
- Approved DUPIXENT (dupilumab) labeling dated June 26, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
05/15/2020 02:52:31 PM

LAURIE J BUONACCORSI
05/15/2020 02:59:05 PM

LASHAWN M GRIFFITHS
05/15/2020 03:03:27 PM

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

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

Memorandum

Date: May 11, 2020

To: Brenda Carr, M.D., Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)

Matthew White, Regulatory Project Manager, (DDD)

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-015,017

In response to DDD's consult requests dated June 20, 2019, and May 7, 2020, OPDP has reviewed the proposed product labeling (PI) and Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the supplemental BLA submissions for Dupixent.

PI and carton and container labeling: OPDP's review of the proposed labeling is based on the draft PI, PPI, IFU, and carton and container labeling received by electronic mail from DDD on May 7, 2020.

We have no comments on the draft PI and carton and container labeling provided below.

PPI and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the PPI and IFU will be sent under separate cover.

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

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/s/

LAURIE J BUONACCORSI
05/11/2020 02:36:14 PM

Benjamin Drosman
Vice President of Regulatory Affairs
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, New York 10591

Dear Mr. Drosman:

The purpose of this letter is to inform you in writing of the outcome of a U.S. Food and Drug Administration (FDA) inspection conducted at Regeneron Pharmaceuticals, Inc. in Tarrytown, New York, United States during January 13 to January 17, 2020 by Michael F. Skelly, Melkamu Getie Kebtie, and Iram Hassan. No objectional conditions or practices were found during the inspection. No response to this letter is necessary.

The FDA conducted this inspection under its Bioresearch Monitoring Program, which includes inspections designed to ensure that data and information submitted to FDA are scientifically valid and reliable. Another objective of the program is to ensure that the rights, welfare, and safety of research subjects are protected during the study of an investigational product.

We appreciate the cooperation you showed to FDA investigators Skelly, Getie Kebtie, and Hassan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please send all correspondence to:

CDER-OSIS-BEQ@fda.hhs.gov

OR

Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
Food and Drug Administration
Building 22, Room 1471
10903 New Hampshire Avenue
Silver Spring, MD 20993

Sincerely,

Seongeun (Julia) Cho
Director
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance
Office of Translational Sciences
Center for Drug Evaluation and Research
United States Food and Drug Administration

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/s/

MELKAMU GETIE KEBTIE
02/23/2020 11:29:38 PM

SEONGEUN CHO
02/24/2020 06:57:29 AM

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: February 19, 2020

TO: Kendall Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Office of New Drugs

FROM: Melkamu Getie-Kebtie, Ph.D., R.Ph.
Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

Michael F. Skelly, Ph.D.
Lead Pharmacologist
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Surveillance inspection of Regeneron Pharmaceuticals, Inc., Tarrytown, NY

1. Inspection Summary

In collaboration with the Office of Regulatory Affairs (ORA), the Office of Study Integrity and Surveillance (OSIS) inspected the analytical portion of study R668-AD-1607 (BLA 761055/S-017, Dupilumab (REGN668)) conducted at Regeneron Pharmaceuticals, Inc., Tarrytown, NY.

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on our review of the inspectional findings, we conclude that data from the audited study are reliable to support a regulatory decision.

2. Inspected Study

Study R668-AD-1607 (BLA 761055/S-017)
"An Open-label, Randomized, Actual Use Study of Dupilumab Auto injector Device in Patients with Atopic Dermatitis"

The following bioanalytical testing conducted under study R668-AD-1607 were audited. All of these testing used ligand binding assay format.

1. Quantitative Measurement of Functional REGN668 in Human Serum
Sample Analysis Period: 7/24/2017 – 3/8/2018

2. Detection of Anti-REGN668 Antibodies in Human Serum
Sample Analysis Period: 7/24/2017 – 3/1/2018

3. Detection of Neutralizing Anti-REGN668 Antibodies in Human Serum
Sample Analysis Period: 10/20/2017 – 2/28/2018

3. Scope of Inspection
ORA Investigator Iram R. Hassan, Ph.D. and OSIS scientists Melkamu Getie-Kebtie, Ph.D., R.Ph. and Michael F. Skelly, Ph.D. audited the analytical portion of the above study at Regeneron Pharmaceuticals, Inc., Tarrytown, NY, from 1/13/2020 to 1/17/2020.

The inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, and sample analysis, and interviews with the firm's management and staff.

There is no bioequivalence inspection history for this site.

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to Regeneron Pharmaceuticals, Inc. However, we discussed the following items with management during the inspection and at close-out.

4.1. Discussion items
1. There was inadequate information from [redacted] (b) (4) which transshipped serum samples from clinical sites to Regeneron. The sample manifest and documents accompanying samples did not clearly explain discrepancies in sample handling histories noted in the manifest. Comments similar to the following were noted for several samples on the manifest: "This sample was originally received for patient [redacted] (b) (6) and has been corrected to patient [redacted] (b) (6)" These comments were noted on nine

manifests reviewed. Regeneron's sample management team was not aware of the identification of the (b) (4) specific patient numbers used on the manifest.

Firm's Response: The firm's management acknowledged this discussion item and agreed to inquire for additional information and clarification from laboratories, which ship samples to Regeneron, if needed. During inspection, the firm received additional information to clarify comments noted on the manifests from (b) (4) and provided them to the inspection team.

OSIS Evaluation: This discussion item was addressed upon review of the additional information provided during inspection. Therefore, the discussion item has no impact on reliability of data from study R668-AD-1607. If implemented, the firm's proposed (b) (4)

2. For the PK assay, the table of repeat analyses in the bioanalytical report R668-AD-1607-BA-01V2 did not include all reanalyzed samples. Samples that were reanalyzed because they were above ULOQ or below LLOQ, due to failed/rejected plates, or replicate samples not meeting %CV acceptance criteria, were not included in the table.

Firm's Response: The firm stated that it is not their practice to include these samples in the table of repeat analysis. They explained that they only report reportable values for all types of repeat analysis, except for samples repeated per written request from the pharmacokineticist due to anomalies in PK profiles. The firm agreed that in the future they will include original and re-assay values, reason for re-assay, and reason for reported values, as recommended in the May 2018 Bioanalytical Method Validation guidance document.

OSIS Evaluation: During inspection we confirmed that all repeat analyses were performed for justifiable reasons. Therefore, the discussion item has no impact on reliability of data from the PK assay in study R668-AD-1607. If implemented, the firm's proposed (b) (4)

5. Conclusion

After review of the inspectional findings, we conclude that data from the audited study (R668-AD-1607) are reliable.

Studies using similar methods conducted between July 2017 and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI – Regeneron Pharmaceuticals, Inc.
Tarrytown, NY
FEI#: 1000521995

cc: OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Kadavil/Choi/Skelly/Au/Getie-Kebtie
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: MG 2/12/2020, 2/13/2020, 2/18/2020, 2/19/2020
Edit: MFS 2/12/2020; SA 2/12/2020, 2/13/2020, 2/18/2020; JC 2/18/2020

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and Surveillance/INSPECTIONS/BE Program/ANALYTICAL/Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA
OSIS File #: BE8633

FACTS: 11941662

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MICHAEL F SKELLY
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STANLEY AU
02/19/2020 09:42:26 AM
Team Lead

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