CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761055Orig1s014

Trade Name:	Dupixent Solution for Injection.
Generic or Proper Name:	dupilumab
Sponsor:	Regeneron Pharmaceuticals, Inc.
Approval Date:	June 26, 2019
Indication:	For the use of dupilumab as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

CENTER FOR DRUG EVALUATION AND RESEARCH

761055Orig1s014

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s014

APPROVAL LETTER

BLA 761055/S-014

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Rd
Tarrytown, NY 10579

Attention: John Huber, Ph.D.
Director, Regulatory Affairs

Dear Dr. Huber:

Please refer to your supplemental biologics license application (sBLA), dated December 24, 2018, received December 26, 2018, and your amendments, submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) Solution for Injection.

This Prior Approval supplemental biologics application provides for the use of dupilumab as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis.

APPROVAL & LABELING

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

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

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, Patient Package Insert, and Instructions for Use) and include the labeling changes proposed in any pending “Changes Being Effected” (CBE) supplements.

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

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).

REQUIRED PEDIATRIC ASSESSMENTS

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

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable, as inadequately controlled chronic rhinosinusitis with nasal polyps occurs very rarely in children.

PROMOTIONAL MATERIALS

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

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

[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.

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *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, 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] For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see FDA.gov.[6]

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 Elaine Sit, Regulatory Project Manager, at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Sally Seymour, MD
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE(S):

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

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf
[6] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm

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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/

SALLY M SEYMOUR
06/26/2019 11:52:24 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s014

<u>LABELING</u>

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)	03/2019
Indications and Usage, Asthma (1.2)	10/2018
Indications and Usage, CRSwNP (1.3)	06/2019
Dosage and Administration, Atopic Dermatitis (2.1; 2.4)	03/2019
Dosage and Administration, Asthma (2.2; 2.4; 2.5)	10/2018
Dosage and Administration, CRSwNP (2.3; 2.4)	06/2019
Warnings and Precautions (5.1; 5.2; 5.3; 5.4; 5.5; 5.6; 5.7)	10/2018
Warnings and Precautions (5.2; 5.6)	06/2019

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

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

DOSAGE AND ADMINISTRATION

Administer by subcutaneous injection. (2)

Atopic Dermatitis

Adults

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

Adolescents

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

Asthma

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

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)

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: 06/2019

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

1.2 Asthma

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

Limitation of Use

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

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.

2.1 Atopic Dermatitis

Dosing in Adults

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

Dosing in Adolescents

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

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

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

Concomitant Topical Therapies

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

2.2 Asthma

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

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

2.3 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. 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 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 a dose is missed, instruct the patient to administer the injection within 7 days from the missed dose and then resume the patient's original schedule. If the missed dose is not administered within 7 days, instruct the patient to wait until the next dose on the original schedule.

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Conjunctivitis and Keratitis

Conjunctivitis and keratitis occurred more frequently in atopic dermatitis subjects who received DUPIXENT. Conjunctivitis was the most frequently reported eye disorder. Most subjects with conjunctivitis recovered or were recovering during the treatment period. Keratitis was reported in <1% of the DUPIXENT group (1 per 100 subject-years) and in 0% of the placebo group (0 per 100 subject-years) in the 16-week atopic dermatitis monotherapy trials. In the 52-week DUPIXENT + topical corticosteroids (TCS) atopic dermatitis trial, keratitis was reported in 4% of the DUPIXENT + TCS group (12 per 100 subject-years) and in 0% of the placebo + TCS group (0 per 100 subject-years). Most subjects with keratitis recovered or were recovering during the treatment period *[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 comorbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

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

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

Weeks 0 to 16 (Trials 1 to 4):

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

Table 2 summarizes the adverse reactions that occurred at a rate of at least 1% in the DUPIXENT 300 mg Q2W monotherapy groups, and in the DUPIXENT + TCS group, all at a higher rate than in their respective comparator groups during the first 16 weeks of treatment.

Table 2: Adverse Reactions Occurring in ≥1% of the DUPIXENT Monotherapy Group or the DUPIXENT + TCS Group in the Atopic Dermatitis Trials through Week 16

Adverse Reaction	DUPIXENT Monotherapy[a]		DUPIXENT + TCS[b]	
	DUPIXENT 300 mg Q2W[c] N=529 n (%)	Placebo N=517 n (%)	DUPIXENT 300 mg Q2W[c] + TCS N=110 n (%)	Placebo + TCS N=315 n (%)
Injection site 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

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

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

Asthma

A total of 2888 adult and adolescent subjects with moderate-to-severe asthma (AS) were evaluated in 3 randomized, placebo-controlled, multicenter trials of 24 to 52 weeks duration (AS Trials 1, 2, and 3). Of these, 2678 had a history of 1 or more severe exacerbations in the year prior to enrollment despite regular use of medium to high-dose inhaled corticosteroids plus an additional controller(s) (AS Trials 1 and 2). A total of 210 subjects with oral corticosteroid-dependent asthma receiving high-dose inhaled corticosteroids plus up to two additional controllers were enrolled (AS Trial 3). The safety population (AS Trials 1 and 2) was 12-87 years of age, of which 63% were female, and 82% were white. DUPIXENT 200 mg or 300 mg was administered subcutaneously Q2W, following an initial dose of 400 mg or 600 mg, respectively.

In AS Trials 1 and 2, the proportion of subjects who discontinued treatment due to adverse events was 4% of the placebo group, 3% of the DUPIXENT 200 mg Q2W group, and 6% of the DUPIXENT 300 mg Q2W group.

Table 3 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator groups in Asthma Trials 1 and 2.

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

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

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

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

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

Approximately 4% of subjects in the placebo groups in the 52-week studies were positive for antibodies to DUPIXENT; approximately 2% exhibited persistent ADA responses, and approximately 1% had neutralizing antibodies.

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

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

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

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

7 DRUG INTERACTIONS

7.1 Live Vaccines

Avoid use of live vaccines in patients treated with DUPIXENT.

7.2 Non-Live Vaccines

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Clinical Considerations

Disease-Associated Maternal and/or Embryo-fetal Risk

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

8.4 Pediatric Use

Atopic Dermatitis

The safety and efficacy of DUPIXENT have been established in pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis. A total of 251 adolescents ages 12 to 17 years old with moderate-to-severe atopic dermatitis were enrolled in Trial 6. The safety and efficacy were generally consistent between adolescents and adults *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. Safety and efficacy in pediatric patients (<12 years of age) with atopic dermatitis have not been established.

Asthma

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

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

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

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

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

Inflammation is an important component in the pathogenesis of asthma, 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.

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)

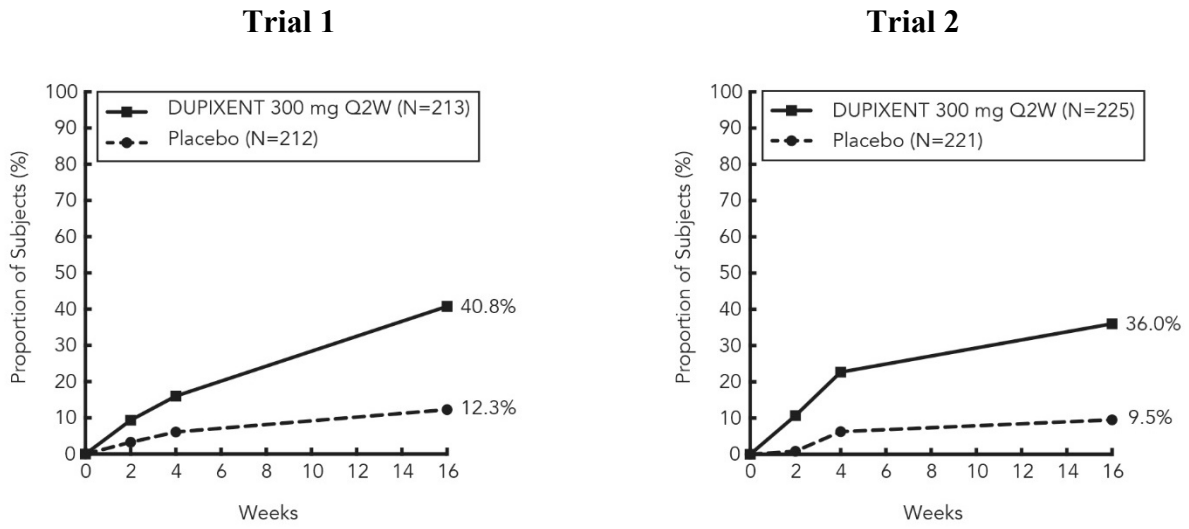
The results of the DUPIXENT monotherapy trials (Trials 1 and 2) and the DUPIXENT with concomitant TCS trial (Trial 3) are presented in Table 5.

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

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.

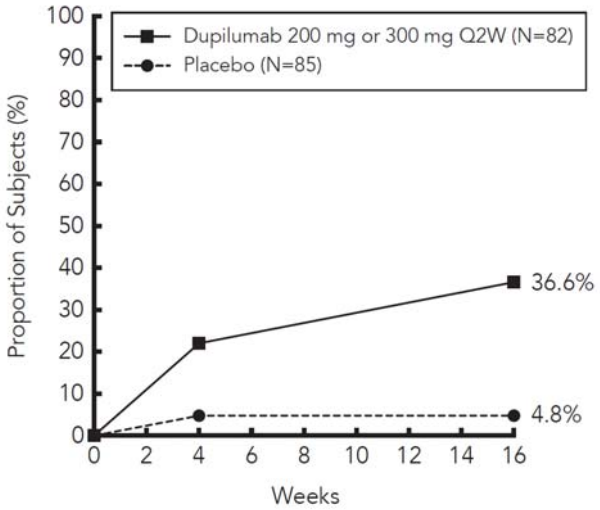
Table 7: Efficacy Results of DUPIXENT in Trial 6 at Week 16 (FAS)[a]

	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%
EASI-75[c]	42%	8%
EASI-90[c]	23%	2%
Peak Pruritus NRS (≥4-point improvement)[c]	37%	5%

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

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

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



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

14.2 Asthma

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

AS Trial 1

AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). DUPIXENT compared with placebo was evaluated in adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N=150) or 300 mg (N=157) DUPIXENT every other week (Q2W) or 200 mg (N=154) or 300 mg (N=157) DUPIXENT every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N=158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV_1 (L) in subjects with baseline blood eosinophils ≥300 cells/mcL. Other endpoints included percent change from baseline in FEV_1 and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled

treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (≥300 cells/mcL and <300 cells/mcL). Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores.

AS Trial 2

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

AS Trial 3

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

The demographics and baseline characteristics of these 3 trials are provided in Table 8 below.

Table 8: 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)

Parameter	Trial 1 (N=776)	Trial 2 (N=1902)	Trial 3 (N=210)
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 9.

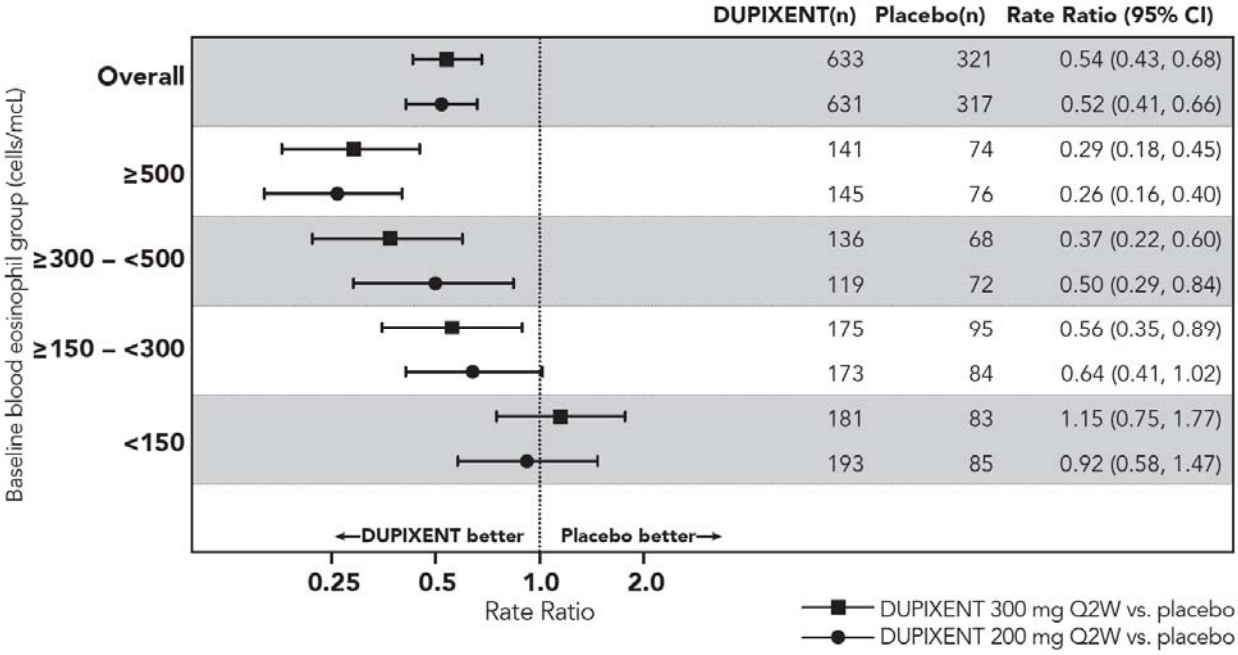
Response rates by baseline blood eosinophils for AS Trial 2 are shown in Figure 3. Pre-specified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations 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 9: Rate of Severe Exacerbations in AS Trials 1 and 2

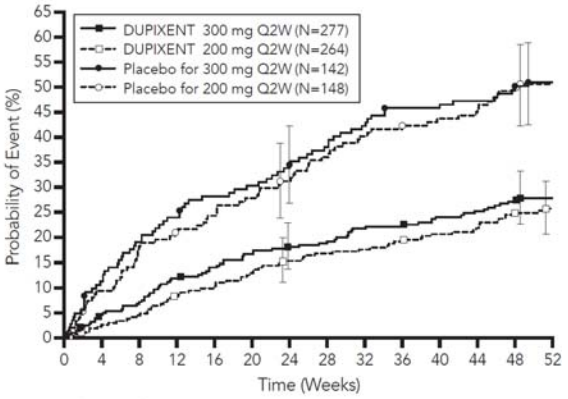
Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)		
		N	Rate (95% CI)	Rate Ratio (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.30 (0.13, 0.68)	0.29 (0.11, 0.76)
	DUPIXENT 300 mg Q2W	64	0.20 (0.08, 0.52)	0.19 (0.07, 0.56)
	Placebo	68	1.04 (0.57, 1.90)	
AS Trial 2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

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



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

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



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

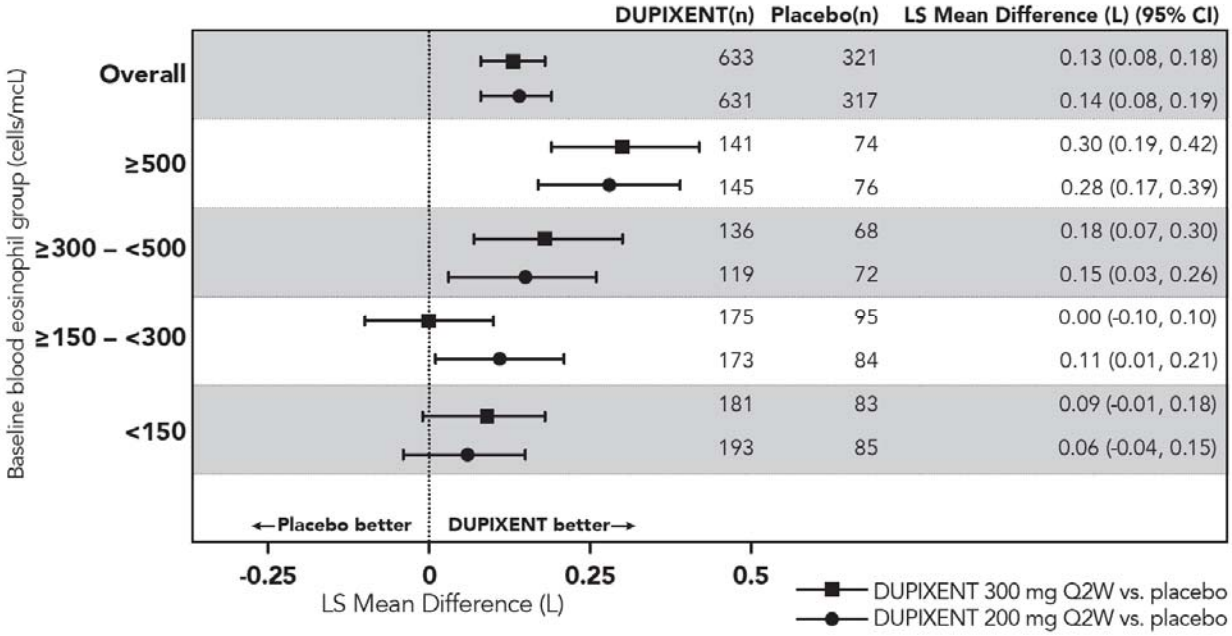
Significant increases in pre-bronchodilator FEV_1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV_1 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 10.

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

Table 10: Mean Change from Baseline and vs Placebo in Pre-Bronchodilator FEV_1 at Week 12 in AS Trials 1 and 2

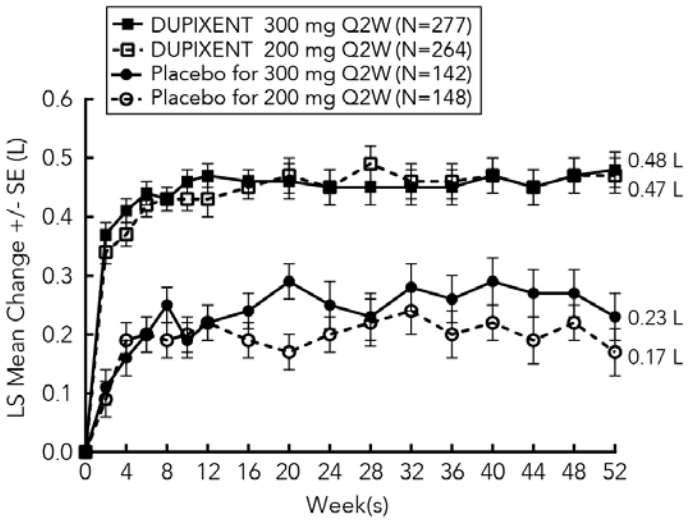
Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, Trial 1)		
		N	LS Mean Change from baseline L (%)	LS Mean Difference vs. placebo (95% CI)
AS Trial 1	DUPIXENT 200 mg Q2W	65	0.43 (25.9)	0.26 (0.11, 0.40)
	DUPIXENT 300 mg Q2W	64	0.39 (25.8)	0.21 (0.06, 0.36)
	Placebo	68	0.18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

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



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

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



Additional Secondary Endpoints

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

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

Oral Corticosteroid Reduction (AS Trial 3)

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

Compared with placebo, subjects receiving DUPIXENT achieved greater reductions in daily maintenance oral corticosteroid dose, while maintaining asthma control. The mean percent reduction in daily OCS dose from baseline was 70% (median 100%) in subjects receiving DUPIXENT (95% CI: 60%, 80%) compared to 42% (median 50%) in subjects receiving placebo (95% CI: 33%, 51%). Reductions of 50% or higher in the OCS dose were observed in 82 (80%) subjects receiving DUPIXENT compared to 57 (53%) in those receiving placebo. The proportion of subjects with a mean final dose less than 5 mg at Weeks 24 was 72% for DUPIXENT and

37% for placebo (odds ratio 4.48 95% CI: 2.39, 8.39). A total of 54 (52%) subjects receiving DUPIXENT versus 31 (29%) subjects in the placebo group had a 100% reduction in their OCS dose.

In this 24-week trial, asthma exacerbations (defined as a temporary increase in oral corticosteroid dose for at least 3 days) were lower in subjects receiving DUPIXENT compared with those receiving placebo (annualized rate 0.65 and 1.60 for the DUPIXENT and placebo group, respectively; rate ratio 0.41 [95% CI 0.26, 0.63]) and improvement in pre-bronchodilator FEV_1 from baseline to Week 24 was greater in subjects receiving DUPIXENT compared with those receiving placebo (LS mean difference for DUPIXENT versus placebo of 0.22 L [95% CI: 0.09 to 0.34 L]). Effects on lung function and on oral steroid and exacerbation reduction were similar irrespective of baseline blood eosinophil levels. The ACQ-5 and AQLQ(S) were also assessed in AS Trial 3 and showed improvements similar to those in AS Trial 2.

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 11 below.

Table 11: 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 12.

Table 12: Results of the Primary Endpoints in CRSwNP Trials

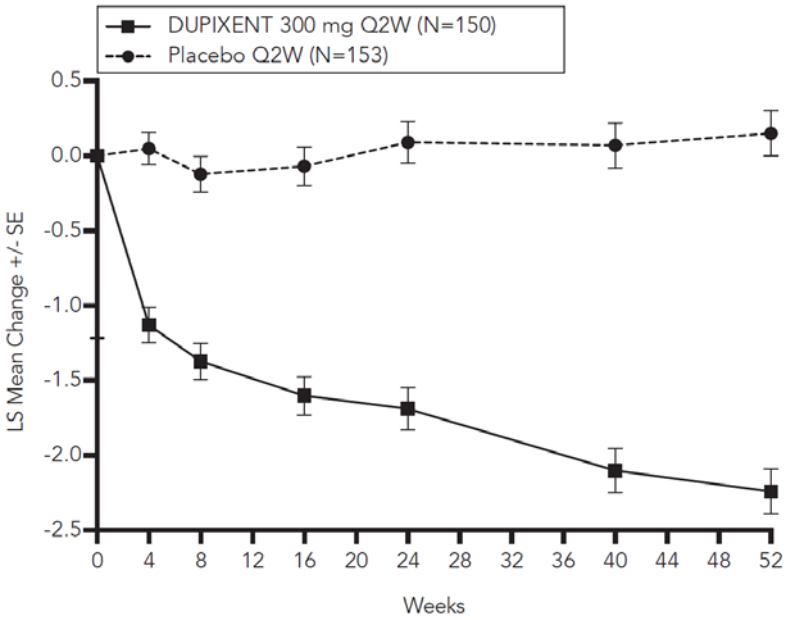
	CSNP Trial 1			**CSNP Trial 2**		
	Placebo (n=133)	**DUPIXENT 300 mg Q2W (n=143)**	**LS mean difference vs. Placebo (95% CI)**	**Placebo (n=153)**	**DUPIXENT 300 mg Q2W (n=295)**	**LS mean difference vs. Placebo (95% CI)**

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

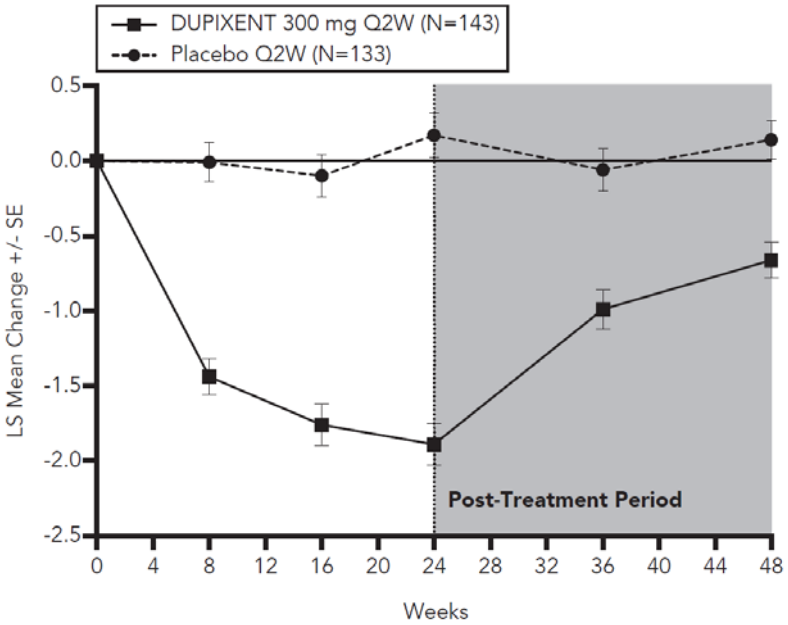
Statistically significant efficacy was observed in CSNP Trial 2 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 7).

Figure 7: 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 8).

Figure 8: 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).

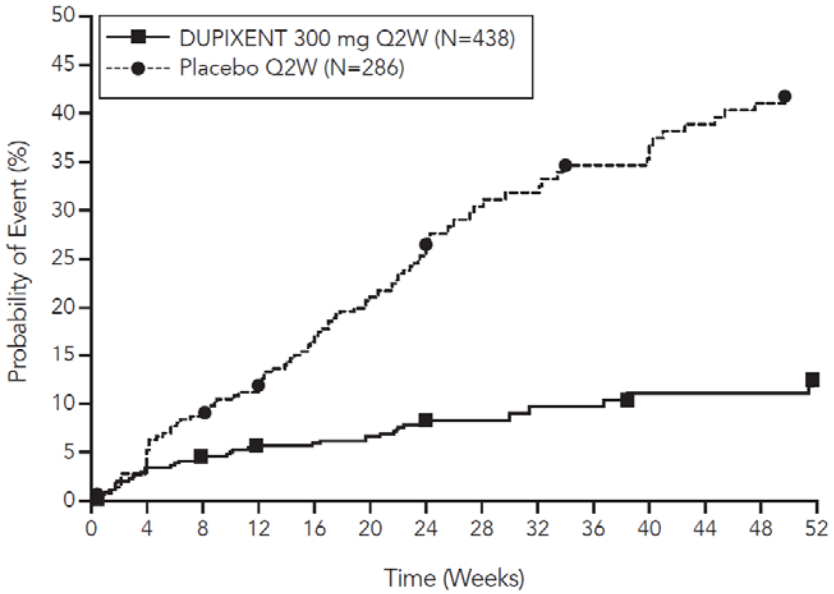
Dupilumab significantly improved the loss of smell compared to placebo. The LS mean difference for loss of smell at Week 24 in the DUPIXENT group versus placebo was -1.12 (95% CI: -1.31, -0.93) in CSNP Trial 1 and -0.98 (95% CI: -1.15, -0.81) in CSNP Trial 2. At Week 52, the LS mean difference for loss 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 9). 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 9: 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. 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).

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

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

16.2 Storage and Handling

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

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

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

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

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

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

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)

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Revised: June 2019

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

What is DUPIXENT?

DUPIXENT is a prescription medicine used:

- to treat people aged 12 years and older with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. DUPIXENT can be used with or without topical corticosteroids.
- with other asthma medicines for the maintenance treatment of moderate-to-severe asthma in people aged 12 years and older whose asthma is not controlled with their current asthma medicines. DUPIXENT helps prevent severe asthma attacks (exacerbations) and can improve your breathing. DUPIXENT may also help reduce the amount of oral corticosteroids you need while preventing severe asthma attacks and improving your breathing.
- with other medicines to treat chronic rhinosinusitis with nasal polyposis in adults whose disease is not controlled.

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

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

How should I use DUPIXENT?

- **See the detailed "Instructions for Use" that comes with DUPIXENT for information on how to prepare and inject DUPIXENT and how to properly store and throw away (dispose of) used DUPIXENT pre-filled syringes.**
- Use DUPIXENT exactly as prescribed by your healthcare provider.
- DUPIXENT comes as a single-dose pre-filled syringe with needle shield.
- DUPIXENT is given as an injection under the skin (subcutaneous injection).
- If your healthcare provider decides that you or a caregiver can give the injections of DUPIXENT, you or your caregiver should receive training on the right way to prepare and inject DUPIXENT. **Do not** try to inject DUPIXENT until you have been shown the right way by your healthcare provider. In children 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult.
- If you miss a dose of DUPIXENT, give the injection within 7 days from the missed dose, then continue with the original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.
- If you inject more DUPIXENT than prescribed, call your healthcare provider right away.
- Your healthcare provider may prescribe other medicines to use with DUPIXENT. Use the other prescribed medicines exactly as your healthcare provider tells you to.

What are the possible side effects of DUPIXENT?

DUPIXENT can cause serious side effects, including:

- **Allergic reactions (hypersensitivity), including a severe reaction known as anaphylaxis.** Stop using DUPIXENT and tell your healthcare provider or get emergency help right away if you get any of the following symptoms:
  - breathing problems
  - fever
  - general ill feeling
  - swollen lymph nodes
  - swelling of the face, mouth, and tongue
  - hives
  - itching
  - fainting, dizziness, feeling lightheaded (low blood pressure)
  - joint pain
  - skin rash

- **Eye problems.** 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
  - chest pain

- shortness of breath
- persistent fever
- 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. Issued: June 2019

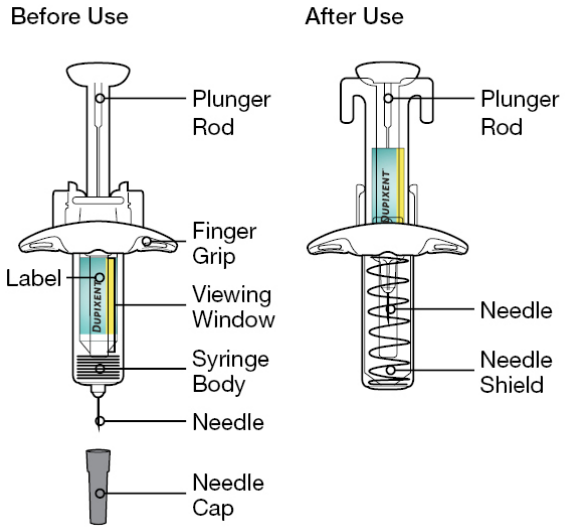
Instructions for Use

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

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

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

The parts of the DUPIXENT Syringe are shown below:



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

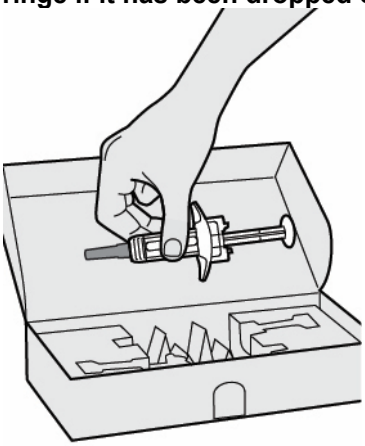
- Store DUPIXENT Syringes in the original carton to protect them from light.
- DUPIXENT Syringes can be stored at room temperature up to 77°F (25°C) up to 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.
- **Do not** shake the DUPIXENT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

Step 1: Remove

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

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

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

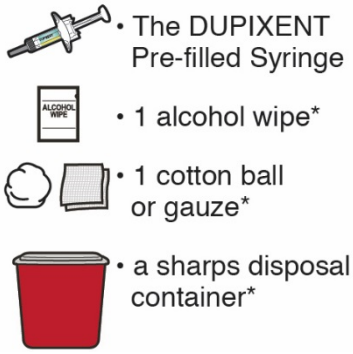


Step 2: Prepare

Ensure you have the following:

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

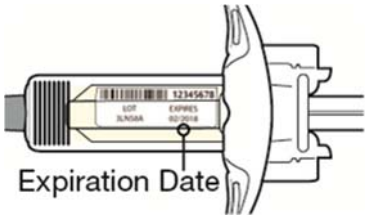
**Items not included in the carton*



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

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

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



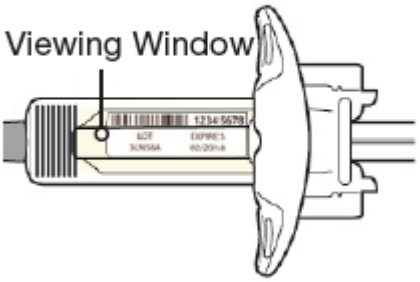
Step 4: Inspect

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

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

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

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



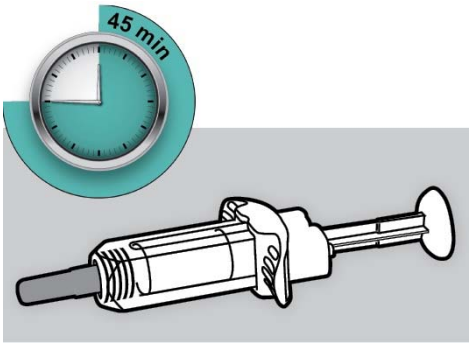
Step 5: Wait 45 minutes

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

Do not heat the DUPIXENT Syringe.

Do not put the DUPIXENT Syringe into direct sunlight.

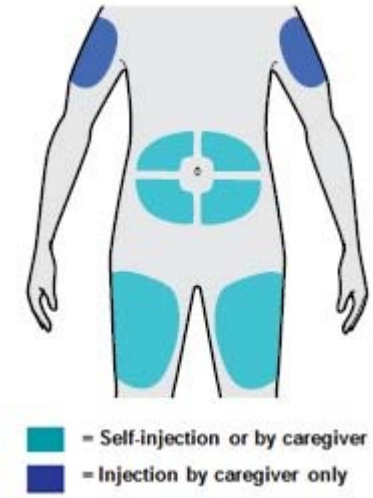
Do not keep DUPIXENT Syringes at room temperature for more than 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.



Step 6: Choose your injection site

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

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



Step 7: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

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

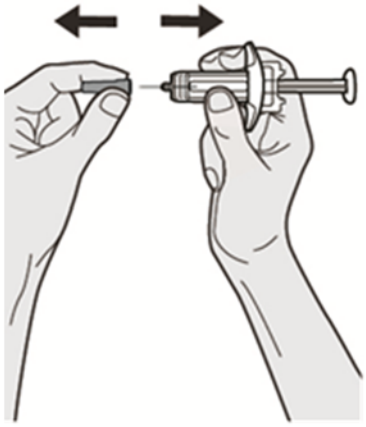
Step 8: Remove Needle Cap

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

Do not put the Needle Cap back on.

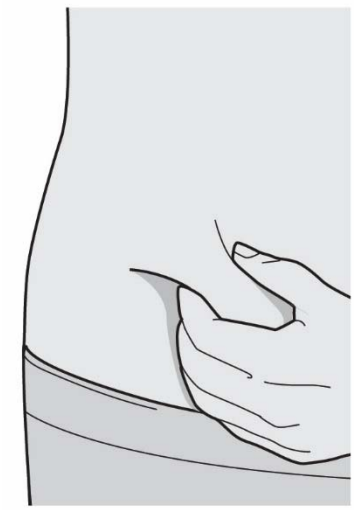
Do not touch the Needle.

Inject your medicine right away after removing the Needle Cap.



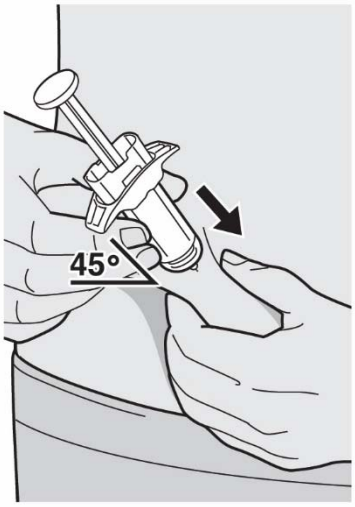
Step 9: Pinch

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



Step 10: Insert

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



Step 11: Push

Relax the pinch.

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

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

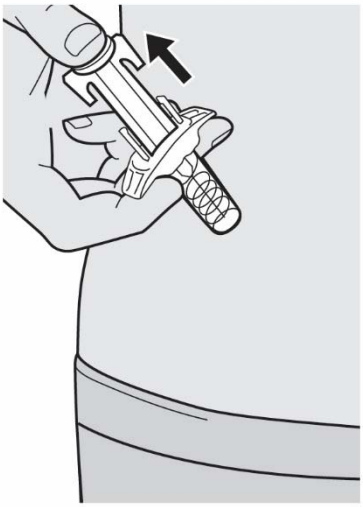
Step 12: Release and Remove

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

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

Do not put the Needle Cap back on.

Do not rub your skin after the injection.



Step 13: Dispose

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

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

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

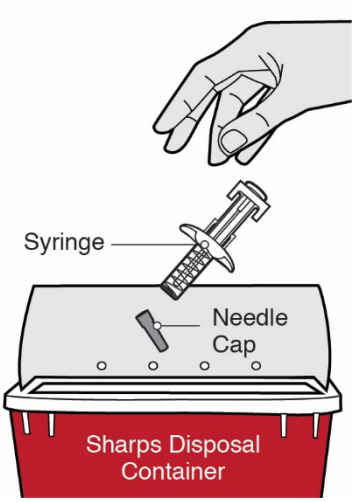
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

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

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

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

Do not put the Needle Cap back on.



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

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

Marketed by:
sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and
Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

Issue Date: March 2019

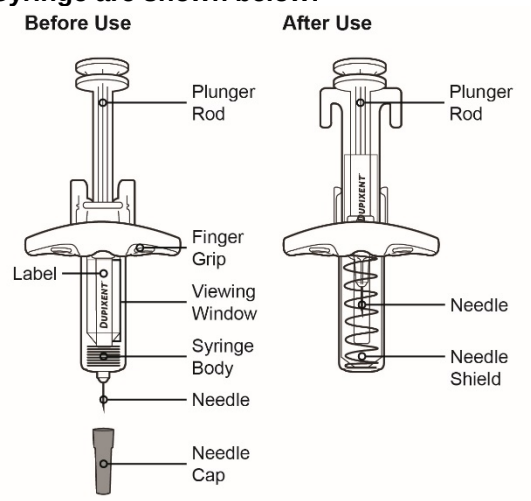
Instructions for Use

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

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

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

The parts of the DUPIXENT Syringe are shown below:



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

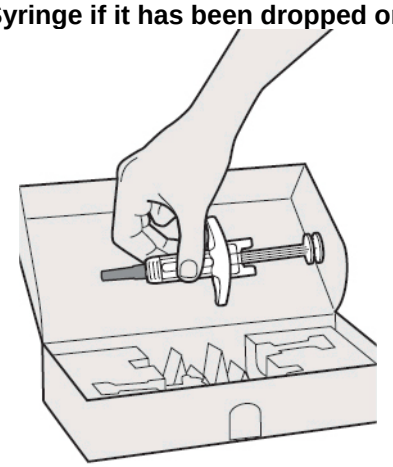
- DUPIXENT Syringes can be stored at room temperature up to 77°F (25°C) up to 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.
- **Do not** shake the DUPIXENT Syringe.
- **Do not** heat the DUPIXENT Syringe.
- **Do not** freeze the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

Step 1: Remove

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

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

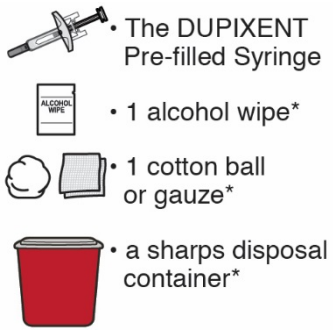
Do not use the DUPIXENT Syringe if it has been dropped on a hard surface or damaged.



Step 2: Prepare

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

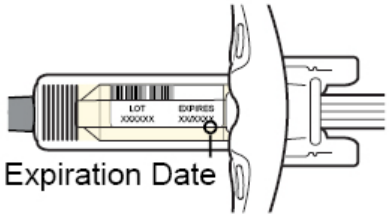
**Items not included in the carton*



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

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

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



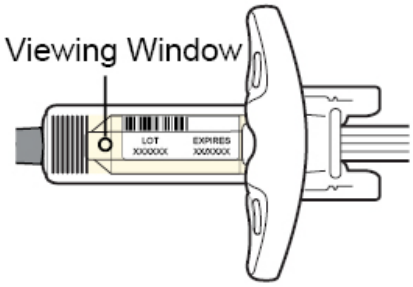
Step 4: Inspect

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

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

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

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



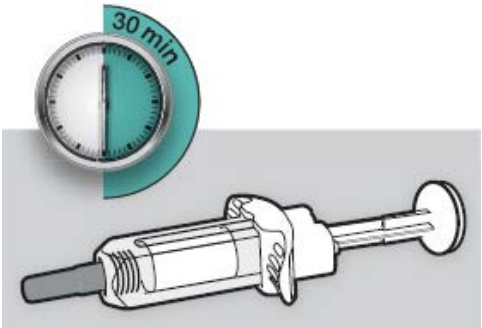
Step 5: Wait 30 minutes

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

Do not heat the DUPIXENT Syringe.

Do not put the DUPIXENT Syringe into direct sunlight.

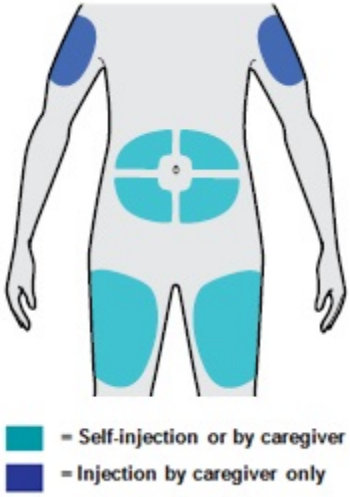
Do not keep DUPIXENT Syringes at room temperature for more than 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.



Step 6: Choose your injection site

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

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



Step 7: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

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

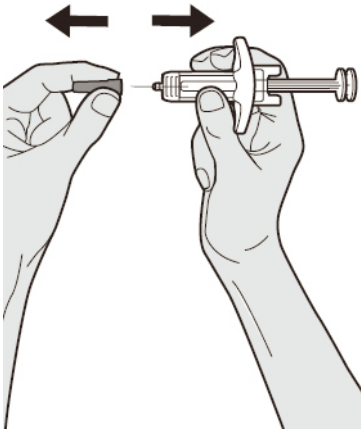
Step 8: Remove Needle Cap

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

Do not put the Needle Cap back on.

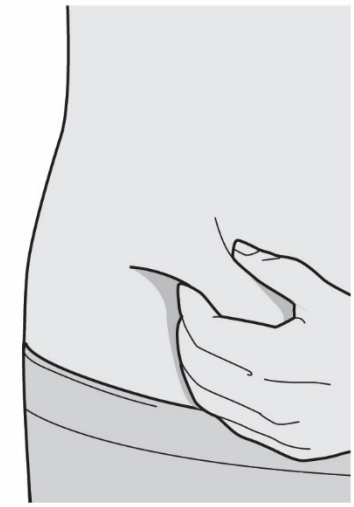
Do not touch the Needle.

Inject your medicine right away after removing the Needle Cap.



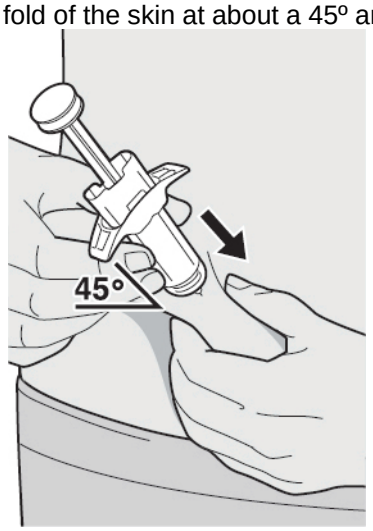
Step 9: Pinch

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



Step 10: Insert

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

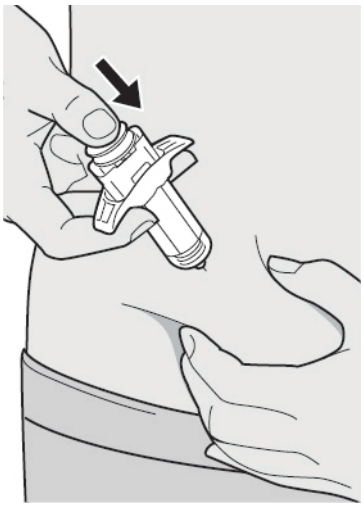


Step 11: Push

Relax the pinch.

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

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



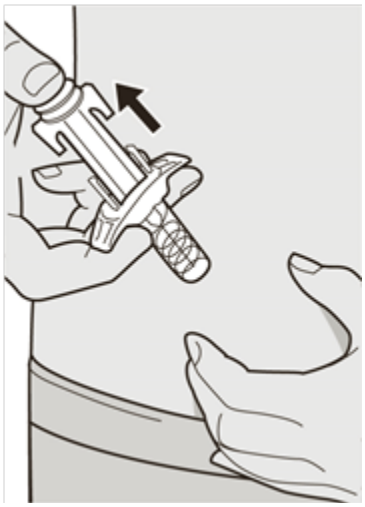
Step 12: Release and Remove

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

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

Do not put the Needle Cap back on.

Do not rub your skin after the injection.



Step 13: Dispose

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

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

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

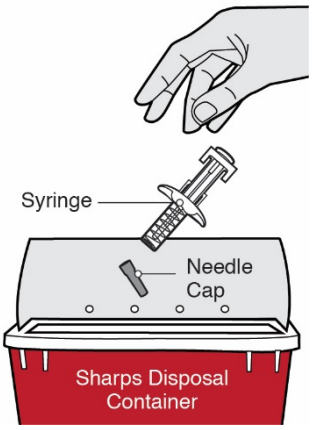
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

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

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

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

Do not put the Needle Cap back on.



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

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Tarrytown, NY 10591
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Issue Date: March 2019

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/s/

SALLY M SEYMOUR
06/26/2019 11:52:24 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s014

MULTI-DISCIPLINE REVIEW

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

NDA/BLA Multi-Disciplinary Review and Evaluation

Application type	Supplemental Biologics Licensing Application
Application number(s)	761055, Supplement-014
Priority or standard	Priority
Submit date(s)	December 26, 2018
Received date(s)	December 26, 2018
PDUFA goal date	June 26, 2019
Division/office	DPARP/ODEII
Review completion date	June 24, 2019
Established/proper name	Dupilumab
(Proposed) trade name	DUPIXENT
Pharmacologic class	Interleukin-4 receptor alpha antagonist
Code name	SAR231893/REGN668
Applicant	Regeneron
Dosage form	Subcutaneous solution for injection
Applicant-proposed dosing regimen	300 mg subcutaneous injection every other week
Applicant-proposed indication(s)/population(s)	Add-on maintenance in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis
Recommendation on regulatory action	Approval

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Reviewers of Multi-Disciplinary Review and Evaluation

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Clinical Reviewer	Rekha Jhamnani
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Statistical Team Leader	Yongman Kim
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OPDP	Kyle Snyder
OSI	Min Lu, Kassa Ayalew
OSE/DMEPA	Lissa Owens/Idalia Rychlik
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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
COA = Clinical Outcome Assessment

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Dipak Pisal, PhD **Signature:** Dipak Pisal -S Digitally signed by ipak Pisal -S DN: c=US o=U.S. Government ou=HHS ou=FDA ou=People cn=Dipak Pisal -S 0.9.2342.19200300.100.1.1=2001808716 Date: 2019.06.25 09:01:44 -04'00'	OCP/DCPII	Section: 6	**Select one:** _X___Authored _X___Approved

BLA Multi-disciplinary Review and Evaluation BLA 761055 S-014
DUPIXENT/dupilumab

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
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Pharmacometrics Reviewer	Junshan Qiu, PhD	OCP/DPM	Section: Appendix	**Select one:** _X___Authored _X___Approved
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Pharmacometrics Team Leader	Jingyu Yu, PhD	OCP/DPM	Section: Appendix	**Select one:** ___ Authored __X_ Approved
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Clinical Reviewer	Rekha Jhamnani, MD	OND/ODEII/DPARP	Sections: 1,2,3,4,7, 8, 9, 10, 11, 12, 13, 15	**Select one:** _X___Authored _X___Approved
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BLA Multi-disciplinary Review and Evaluation BLA 761055 S-014
DUPIXENT/dupilumab

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Miya Paterniti, MD	OND/ODEII/DPARP	Sections: 1-15.2	**Select one:** ___ Authored _X_Approved
	Signature: On behalf of Miya Paterniti, MD Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2019.06.25 18:40:27 -04'00'			
Division Director (Clinical)	Sally Seymour, MD	OND/DPARP	Sections: 1-15	**Select one:** ____Authored _x___Approved
	Signature: Sally M. Seymour -S Digitally signed by Sally M. Seymour -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300222097, cn=Sally M. Seymour -S Date: 2019.06.25 18:41:02 -04'00'			
Statistical Reviewer	Susan Duke, MS	OB/DBII	Sections: 8	**Select one:** _X___Authored _X_Approved
	Signature: Susan P. Duke -S Digitally signed by Susan P. Duke -S DN: c=US o=U.S. Government ou=HHS ou=FDA ou=People cn=Susan P. Duke -S 0.9.2342.19200300.100.1.1=2002454056 Date: 2019.06.25 01:30:36 -04'00'			
Statistical Team Leader	Yongman Kim, PhD	OB/DBII	Sections: 8	**Select one:** ___ Authored _X___Approved
	Signature: Yongman Kim -S Digitally signed by Yongman Kim -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Yongman Kim -S, 0.9.2342.19200300.100.1.1 1300218531 Date 2019.06.25 08 26 09 -04'00'			

Glossary

AD	atopic dermatitis
ADA	antidrug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration-time curve
BLA	biologics license application
BMI	body mass index
CFR	Code of Federal Regulations
CI	confidence interval
CRSwNP	chronic rhinosinusitis with nasal polyps
CSR	clinical study report
CT	computed tomography
C_{trough}	lowest concentration or drug between doses
DHOT	Division of Hematology Oncology Toxicology
ECG	electrocardiogram
EGPA	eosinophilic granulomatosis with polyangiitis
E_{max}	maximal effect of drug at high concentrations
EOS	eosinophil count
ER	exposure-response
FDA	Food and Drug Administration
IMP	investigational medicinal product
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
LMK	Lund-Mackay
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMRM	mixed-effect model for repeated measures
MRI	magnetic resonance imaging
NC	nasal congestion/obstruction
NDA	new drug application
NIMP	noninvestigational medicinal product
NP	nasal polyposis
NPS	nasal polyp score
NSAID	nonsteroidal anti-inflammatory drug
NSAID-ERD	nonsteroidal anti-inflammatory drug-exacerbated respiratory disease
OCS	oral corticosteroid

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamic
PGDM	prostaglandin D2 metabolite
PIND	preinvestigational new drug
PK	pharmacokinetics
PMM	pattern mixture model
PRO	patient reported outcome
PT	preferred term
q2w	once every 2 weeks
q4w	once every 4 weeks
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCS	systemic corticosteroids
SNOT-22	Sino-Nasal Outcome Test
TARC	thymus and activation-regulated chemokine
TSS	total symptom score
UPSIT	University of Pennsylvania smell identification test
WOCF	worst observation carried forward

1. Executive Summary

1.1. Product Introduction

Dupilumab is an interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is proposed as add-on maintenance in adult patients with inadequately controlled (b) (4) chronic rhinosinusitis with nasal polyposis. (b) (4)

The application supports the indication of add-on maintenance in adults with inadequately controlled chronic rhinosinusitis with nasal polyps. (b) (4)

This is the first approval for a chronic rhinosinusitis with nasal polyps indication. Other intranasal steroid products are approved for treatment of nasal polyps, however this is the first systemic and monoclonal antibody proposed for treatment of nasal polyps. For this reason, supported by the study results, we have incorporated the term of chronic rhinosinusitis to acknowledge the overlap and anatomic continguity of these diseases. Further details for the new indication are provided in Section 2.1 Analysis of Condition.

Dupilumab is approved for atopic dermatitis and asthma. Dupilumab was approved in March 2017 for treatment of adult patients with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable dosed as 300 mg subcutaneous (SC) every other week (q2w) with a 600 mg loading dose. The atopic dermatitis indication was expanded to children aged 12 to 18 years old in March 2019. In October 2018, dupilumab was approved for add-on maintenance in moderate-to-severe asthma in patients 12 years old and up with an eosinophilic subtype (200 mg SC q2w with 400 mg loading dose or 300 mg SC q2w with 600 mg loading dose) or oral corticosteroid-dependent asthma (300 mg SC q2w with a 600 mg loading dose).

In July 2015 the Applicant requested (b) (4). At that time, the request was denied because the submitted phase 2 study did not evaluate serious or clinically meaningful disease outcomes (b) (4) With this sBLA submission, the Applicant requested Priority Review. Priority review was granted as two additional phase 3 studies demonstrated significant reductions in the clinically meanginful outcomes of systemic corticosteroid use and nasal polyp surgical intervention.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action from a clinical and statistical perspective is approval of dupilumab 300 mg SC q2w for use as add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps.

To support this application, the Applicant completed a 24- and 52-week safety and efficacy trial in 724 patients with inadequately controlled chronic rhinosinusitis with nasal polyps on background intranasal mometasone furoate. These patients were defined as inadequately controlled due to failing background therapy with intranasal corticosteroid spray, courses of systemic corticosteroid and/or previous nasal polyp surgery. Both trials demonstrated a statistically significant and clinically relevant improvement in endoscopic nasal polyp scores and patient-reported nasal congestion scores. Furthermore, the 24-week trial showed statistically significant reduction in systemic corticosteroid use, and the 52-week trial showed statistically significant reduction in systemic corticosteroid use and nasal polyp surgery. Results from the secondary endpoints of Lund-Mackay (LMK) sinus computed tomography (CT) scan score, loss of smell, and SNOT-22 were supportive of the primary endpoint.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dupilumab is an interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is 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. Dupilumab is also approved 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 the first biologic proposed for a nasal polyp indication. Dupilumab is proposed for the add-on maintenance treatment in adult patients with inadequately controlled (b) (4) chronic rhinosinusitis with nasal polyps. The submission supports modifying the proposed indication to adult patients with inadequately controlled (b) (4) chronic rhinosinusitis with nasal polyps.

The efficacy and safety of dupilumab was evaluated in two well-controlled and adequately designed 24-week and 52-week trials in patients with inadequately controlled chronic rhinosinusitis with nasal polyps on background intranasal mometasone furoate. Both trials demonstrated a statistically significant and clinically relevant improvement in endoscopic nasal polyp scores and patient-reported nasal congestion scores. Furthermore, the 24-week trial showed statistically significant reduction in systemic corticosteroid use, and the 52-week trial showed statistically significant reduction in systemic corticosteroid use and nasal polyp surgery. Results from the secondary endpoints of Lund-Mackay (LMK) sinus computed tomography (CT) scan score, loss of smell, and SNOT-22 were also supportive of the primary endpoint.

The program included an assessment of safety concerns related to immunomodulatory therapy and biologics including cardiovascular events, infections, malignancy, hypersensitivity events, and immunogenicity. In general, the safety profile for chronic rhinosinusitis with nasal polyps was similar to the known safety profile seen in the atopic dermatitis and asthma clinical program. No safety concerns that offset the efficacy benefits provided by dupilumab were identified for the overall population. Injection-site reactions were the most common adverse event and the ocular safety issues seen in the atopic dermatitis program were also seen in chronic rhinosinusitis with nasal polyp patients (but were not seen in the asthma program). There was one major adverse cardiovascular event (MACE) in the 300 mg q2w dose group in EFC14146 which was notable due to the increase in MACE events in the asthma program. No anaphylaxis cases were reported for dupilumab. As per the known safety profile, cases of eosinophilia and eosinophilic granulomatosis with polyangiitis were reported.

This review recommends approval of dupilumab in adults with inadequately controlled nasal polyps at the proposed dose of 300 mg subcutaneous every other week. No safety concerns that would preclude approval were identified in the overall population. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Chronic rhinosinusitis with nasal polyps, primarily an adult condition, manifests as inflammatory outgrowths of the paranasal sinus mucosa	Chronic rhinosinusitis with nasal polyps cause significant morbidity in patients. Many patients

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	bilaterally along the middle and superior meatus. Nasal polyps develop in the setting of chronic mucosal inflammation (chronic rhinosinusitis). Major symptoms include nasal congestion, decreased/loss of smell, and posterior rhinorrhea. Though most patients are treated with intranasal corticosteroids and saline irrigation; many patients require multiple courses of systemic corticosteroids as well as surgery.	require multiple courses of systemic corticosteroids as well as surgery to treat nasal polyps.
Current Treatment Options	Current approved treatment options for nasal polyps include corticosteroid nasal sprays and mometasone furoate sinus implant. There are no currently approved therapies for chronic rhinosinusitis without nasal polyps.	Though many patients are maintained on corticosteroid nasal sprays and saline irrigation, a large percentage of patients require multiple courses of systemic corticosteroids and/or surgical intervention.
Benefit	In two, well-controlled and well-designed studies, dupilumab 300 mg SC q2w demonstrated a statistically significant and clinically relevant improvement in the coprimary endpoints of endoscopic nasal polyp score, patient-reported nasal congestion score, as well as secondary endpoints of systemic corticosteroid use and nasal polyp surgery in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps on background intranasal mometasone furoate. Secondary endpoints of Lund-Mackay (LMK) sinus computed tomography (CT) scan score, loss of smell, and SNOT-22 were also supportive of efficacy.	Dupilumab is a clinically relevant, beneficial treatment, as an add-on to intranasal steroid, for adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps.
Risk and Risk Management	The safety profile for chronic rhinosinusitis with nasal polyps was similar to the known safety profile of dupilumab based on the atopic dermatitis and asthma programs. Injection-site reactions were the most common adverse event and ocular events were also reported.There were no cases of anaphylaxis reported. The safety findings that were seen in the program can be adequately. addressed through labeling and should continue to be followed with routine pharmacovigilance. No risk evaluation and mitigation strategies are proposed.	The program does not demonstrate any safety findings that offset the efficacy findings. The safety profile for chronic rhinosinusitis with nasal polyps was similar to the known safety profile of dupilumab based on the atopic dermatitis and asthma programs.

1.4. 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)	8.1.1
		☐	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

Chronic rhinosinusitis is a term that has evolved within the medical community and literature over time to be used interchangeably with chronic sinusitis, in order to acknowledge the anatomic contiguity between the nasal cavity and paranasal sinuses[1,2,3]. Chronic rhinosinusitis is a disease characterized by inflammation of one or more of the paranasal sinuses. Acute rhinosinusitis (duration of less than 4 weeks) is commonly caused by bacterial invasion of the sinuses. Chronic rhinosinusitis is divided into two subtypes (1) chronic rhinosinusitis with nasal polyps and (2) chronic rhinosinutis without nasal polyps. Symptoms of chronic rhinosinusitis include facial pain or pressure , purulent discharge, and nasal congestion. Chronic rhinosinusitis can be demonstrated on imaging (CT or magnetic resonance imaging (MRI))[3]. There are currently no approved therapies for chronic rhinosinusitis. Standard of care includes saline sprays/washes, intranasal and systemic corticosteroid, and oral antileukotrienes. Surgery is used for refractory cases[3].

Nasal polyps are inflammatory outgrowths of the paranasal sinus mucosa bilaterally along the middle and superior meatus that occur primarily in adults. They develop in the setting of chronic paranasal sinus inflammation[3]. Nasal polyps are characterized by nasal polyp tissue eosinophilia, and in Asian subjects, by nasal polyp tissue neutrophilia[4] . Symptoms of nasal polyps include nasal congestion, decreased/loss of smell, and posterior rhinorrhea. Treatment of nasal polyps includes medical and surgical therapy aimed at either complete elimination of polyps or sufficient reduction in polyp size to alleviate nasal obstruction and associated symptoms[3]. Intranasal steroids (Xhance and Nasonex) and a steroid eluting sinus implant (Sinuva) are approved for the treatment of nasal polyps. Surgical treatment to remove nasal polyps is typically reserved for refractory cases, but recurrence of nasal polyps after surgery occurs in up to 40% of patients[5]. Recurrence for chronic rhinosinusitis without nasal polyps after surgery is less common than for chronic rhinosinusitis with nasal polyps[5.] Nasal polyps cause severe morbidity due to sleep disturbances, headaches, and loss of taste/smell. Several quality-of-life studies in patients with nasal polyps showed impaired quality-of-life scores

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[1] European Academy of Allergy and Clinical Immunology (EAACI), 2007, European Position Paper on Rhinosinusitis and Nasal Polyps.
[2] Joint Task Force on Practice Parameters, 2014, Diagnosis and Management of Rhinosinusitis: a Practice Parameter Update.
[3] American Academy of Otolaryngology Head and Neck Surgery, 2015, Clinical Practice Guideline (Update): Adult Sinusitis.
[4] Stevens WW, et al., 2014, Biology of nasal polyposis, JACI, 133(5):1503-1503.e4.
[5] DeConde AS, et al., 2017, Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis, Laryngoscope, 127(3):550-555.

(decreased general health, emotional function, ability to perform daily activities, sleep quality, and productivity) comparable to congestive heart failure, asthma, and chronic obstructive pulmonary disease[6].

Reviewer comment: The Division met with the Medical Policy and Program Review Council to discuss the indication statement of chronic rhinosinusitis with nasal polyps. Other products (intranasal steroids) are approved for treatment of nasal polyps without the mention of chronic rhinosinusitis. The Division considered including chronic rhinosinusitis as this was the first systemic and monoclonal antibody proposed for treatment of nasal polyps, the inclusion of chronic rhinosinusitis is consistent with medical literature and guidelines, the change in terminology did not change the patient population as all patients would have nasal polyps, and the study results demonstrated evidence of efficacy in endpoints specific to chronic rhinosinusitis such as improved CT sinus scores and chronic rhinosinusitis symptoms.

Since 2007, there has been an change in terminology in the medical literature and guidelines which acknowledges nasal polyps as a subtype of chronic rhinosinusitis. The European Academy of Allergy and Clinical Immunology, in its 2007 position paper, acknowledged that the nose and sinus are a contiguous space and thus described chronic rhinosinusitis as an umbrella term with nasal polyps as a subgroup. In 2014, the Joint Task Force on Allergy Practice Parameters updated its 2005 practice parameter on sinusitis to acknowledge chronic rhinosinusitis as a new term that could be further divided into with and without nasal polyps. The Joint Task Force felt rhinosinusitis could be used interchangeably with the term sinusitis. Treatment algorithms for this disease would depend heavily on whether or not a patient had nasal polyps. The American Academy of Otolaryngology further acknowledges the term chronic rhinosinusitis in its 2015 practice guideline and distinguishes acute versus chronic disease and like others, further divides the disease into with and without nasal polyps due to differences in disease severity and treatment.

The Medical Policy and Program Review Council majority voted in favor of maintaining the Applicant's indication statement and preserving the term chronic rhinosinusitis with nasal polyps as this term includes nasal polyps as well as chronic sinusitis which is an implied coexistent disease with nasal polyps. They also felt this indication should be preserved as the updated medical literature favors the umbrella term of chronic rhinosinusitis with the division of with and without nasal polyps. It was agreed upon that the term "rhino" did not infer rhinitis (inclusion criteria and endpoints did not address patients with chronic rhinitis), but instead acknowledged the anatomic contiguity between the nose and sinus.

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[6] Gliklich RE, Metson R, 1995, The health impact of chronic sinusitis in patients seeking otolaryngologic care, Otolaryngol Head Neck Surg, 113:104-109.

2.2. Analysis of Current Treatment Options

Table 1 contains a summary of treatments relevant to nasal polyps. There are no approved therapies for chronic rhinosinusitis with nasal polyps or chronic rhinosinusitis without nasal polyps; however several intranasal steroid products are approved for treatment of nasal polyps, as shown in Table 1. Several antibiotics have been approved for acute bacterial rhinosinusitis (not listed).

Table 1. Summary of Treatments (b) (4)

Product(s) Name	Relevant Indication	Year of Approval	Dosing/Administration
Mometasone furoate (Nasonex)	(b) (4)	1997	2 sprays (50 mcg) each nostril once or twice daily
Beclomethasone dipropionate (Qnasl)		2012	1 to 2 sprays (42 to 84 mcg) each nostril twice daily
Fluticasone propionate (Xhance)	Nasal polyps ≥18 years of age	2017	1 to 2 sprays (93 mcg) each nostril twice daily
Mometasone furoate implant (SINUVA)	Nasal polyps ≥18 years of age who have had ethmoid sinus surgery	2017	Sinus Implant (1350 mcg mometasone furoate) inserted and then removed after 90 days

3. Regulatory Background

The key regulatory history for prior indications of atopic dermatitis and asthma are summarized in Table 2 and Table 3.

3.1. U.S. Regulatory Actions and Marketing History

Table 2. Summary of Presubmission/Submission Regulatory Activity Atopic Dermatitis

Interaction	Date	Remarks
IND 107969 filed	Jun 30, 2010	RDBPC, MAD safety and PK of subcutaneous dupilumab in moderate-to-severe AD
Granted BDTR	Nov 18, 2014	Dupilumab for treatment of adult patients with moderate-to-severe atopic dermatitis
Agreed iPSP	Nov 10, 2015	Moderate-to-severe AD (12 to <18 years of age) Severe AD (6 to <12 years of age) Severe AD (6 months to <6 years of age)
Granted BTDR	Oct 18, 2016	Treatment of moderate-to-severe (12 to <18 years of age) and severe (6 months to <12 years of age) AD
Approval	Mar 29, 2019	Treatment of moderate-to-severe AD in adult patients
Approval	Mar 11, 2019	Treatment of moderate-to-severe AD 12 to <18 years of age

AD = atopic dermatitis; BDTR = breakthrough designation therapy request; EOP2 = end-of-phase 2; IND = investigational new drug; iPSP = initial pediatric study plan; MAD = multiple ascending dose; PK = pharmacokinetic; RDBPC = randomized, double-blind, placebo-controlled

Table 3. Summary of Presubmission/Submission Regulatory Activity Asthma

Interaction	Date	Remarks
IND 105379 filed	Sep 10, 2009	First-in-human study
Agreed Amended iPSP	March 15, 2017	Deferral <12 years
[redacted]	[redacted]	[redacted] (b) (4)
Approval	Oct 19, 2018	Add-on maintenance moderate-to-severe asthma ≥ 12 years of age with eosinophilic subtype or OCS-dependent

[redacted] (b) (4) IND = investigational new drug; iPSP = initial pediatric study plan; OCS = oral corticosteroid

3.2. Summary of Presubmission/Submission Regulatory Activity

The nasal polyp program was developed under the same IND as asthma (105379) The key regulatory history for the current indication of nasal polyposis is summarized in Table 4.

Table 4. Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
PIND	Oct 11, 2011	(b) (4)
IND 105379 filed		First-in-human study
EOP2	Feb 2, 2015	Two phase 3 studies of 24 and 52 weeks Chronic sinusitis, rhinitis, and nasal polyps are different disease entities
(b) (4)		
Agreed iPSP	Apr 6, 2016	Waived in all <18 years old
Pre-sBLA	Jul 16, 2018	Chronic sinusitis, rhinitis, and nasal polyps are different disease entities Safety data pooling of 24- and 52-week studies deemed acceptable

(b) (4) EOP2 = end of phase 2; IND = investigational new drug; iPSP = initial pediatric study plan; PIND = pre- investigational new drug; sBLA = supplemental biologics license application; SCS= systemic corticosteroid

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 (OSI) consult was requested due to the large clinical development program. Two sites (Dallas, Texas, USA (EFC14146)) and Gent, Belgium (EFC14280)) were recommended for inspection due to high financial disclosure as well as high efficacy and due to death, high enrollment, and high efficacy, respectively. An information request was sent to request subject data listings for all laboratory testing for EFC14280 as well as the nasal endoscopy operational manual. The Applicant provided all subject data listings, laboratory testing data and the nasal endoscopy manual as requested by the Agency. For further details please see review by Dr. Min Lu.

4.2. Product Quality

With this supplement, the Applicant introduced a similar presentation of dupilumab (300 mg/1.14 mL in a single-dose prefilled syringe with a needle shield). The manufacturing of the presentation is similar to the approved processes. The Office of Biotechnology Products recommends approval.

4.3. Clinical Microbiology

No microbiology assessment was required for this application due to prior approvals of dupilumab for other indications.

4.4. Devices and Companion Diagnostic Issues

The dupilumab prefilled syringe is supplied as a ready-to-use, sterile, single-dose, prefilled and disposable glass syringe assembled with a plunger rod and inserted within a safety system preassembled with a finger flange. The device is the same as proposed for atopic dermatitis and asthma.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

In this submission, the Applicant provided no new nonclinical information. Therefore, section 5 is not applicable to this review.

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking the approval of DUPIXENT (dupilumab) as an add-on maintenance treatment in adult patients with inadequately controlled (b) (4) chronic rhinosinusitis with nasal polyposis. The clinical pharmacology information of this supplemental biologics license application (sBLA) consists of pharmacokinetic (PK), pharmacodynamic (PD), and exposure response (ER) data for dupilumab from one phase 2a proof-of-concept study (ACT12340) and two pivotal phase 3 studies (EFC14146 and EFC14280) for treatment periods ranging from 16 weeks to 52 weeks. Population PK analysis using data pooled from phase 2/3 studies conducted in patients with nasal polyposis were also included.

The proposed dosing regimen is 300 mg q2w without a loading dose, although both the atopic dermatitis and asthma programs include loading doses. This proposed dosing regimen has demonstrated clinical efficacy and a tolerable safety profile in patients with nasal polyposis in the two phase 3 trials (see Sections 8.1 and 8.2).

There was no clear dose/exposure response observed, as efficacy appears to reach a plateau with 300 mg q2w-q4w and 300 mg q2w dose. Clinical efficacy of the proposed 300 mg q2w dose was demonstrated in studies EFC14146 and EFC14280. The incidence of safety events was too low to support meaningful ER analysis for safety.

The incidence of treatment-emergent antidrug antibodies (ADA) was generally low in patients with nasal polyposis; 5% and 4% in the 300 mg q2w and combined placebo groups, respectively. The incidence of persistent ADA was 2% and 1.6% in the 300 mg q2w and combined placebo groups, respectively.

The proposed dosing regimen is acceptable (see Section 6.2.2). No dose adjustment is recommended for any intrinsic factors.

Recommendations

The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology 2 (OCP/DCP2) has reviewed the clinical pharmacology information submitted under sBLA 761055 and finds the sBLA approvable.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The following are the major clinical pharmacology findings of the current review:

Dupilumab PK is comparable between healthy subjects, and patients with asthma, atopic dermatitis and nasal polyposis.

In adult patients with nasal polyps, dupilumab is well-absorbed with an estimated SC bioavailability of 62.8%, distributes primarily within the vascular compartment (4.91 L) and exhibits non-linear target-mediated elimination.

Based on Pop PK analysis, the median time to achieve steady state is 16 weeks for 300 mg q2w dosing regimen. After the last dose at steady state, the median time for the serum concentration to fall below the lower limit of quantification is 12 weeks for the 300 mg q2w dosing regimen. When switched from 300 mg q2w to 300 mg q4w at Week 24, a new steady state is achieved in an additional 24 weeks (i.e., 48 weeks from the initiation of dupilumab treatment).

There was no clear dose/exposure response observed, as efficacy appears to reach a plateau with the 300 mg q2w-q4w and 300 mg q2w dose. Clinical efficacy of the proposed 300 mg q2w dose was demonstrated in studies EFC14146 and EFC14280. The incidence of safety events was too low to support meaningful ER analysis for safety.

Body weight is the primary factor responsible for dupilumab PK variability. Other intrinsic factors including age, gender, race/ethnicity, renal function (normal to moderately decreased), lab parameters (albumin), and disease markers do not have a meaningful impact on dupilumab PK. The magnitude of body weight effect on exposure is not likely to yield a clinically meaningful effect on efficacy given the lack of exposure-response relationship. Therefore, no dose adjustment is recommended with respect to the PK covariates.

The incidence of treatment-emergent ADA was 5.2% and 4.4% in the 300 mg q2w and combined placebo groups, respectively. The incidence of persistent ADA was 2% and 1.6% in the 300 mg q2w and combined placebo groups, respectively.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of dupilumab in adult patients with nasal polyposis is 300 mg q2w.

The clinical efficacy of the proposed 300 mg q2w dosing regimen was demonstrated in two pivotal phase 3 studies (EFC14146 and EFC14280, see Sections 8.1 and 8.2). There was no clear dose/exposure response observed as efficacy appears to plateau after 300 mg q2w-q4w and 300 mg q2w dose. Results of the PK/PD analyses are consistent with the efficacy evaluation in patients with NP. Refer to the pharmacometrics review in Appendix 15.2 for details on the population PK and ER analysis.

The incidence of safety events was too low to support meaningful ER analysis for safety. Age was not a significant covariate on dupilumab exposure after adjusting for the effect by body weight. The magnitude of body weight effect on exposure is not likely to yield a clinically meaningful impact on efficacy given the lack of exposure-response relationship. No dose adjustment is recommended with respect to the PK covariates including body weight. Therefore, the 300 mg q2w dosing regimen appears acceptable for the proposed NP indication in adults.

Therapeutic Individualization

Intrinsic factors including body weight, age, gender, race and renal function were not found to have a clinically meaningful effect on dupilumab PK adult patients with NP. Therefore, no dose adjustment is necessary for these factors.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK Characteristics of Dupilumab in Adult Patients with NP following SC Administration

Dupilumab PK has been assessed in healthy subjects, adult patients with atopic dermatitis, and adult and adolescent patients with asthma. For details, see archived clinical pharmacology reviews by Drs. Jie Wang and Dipak Pisal (Reference ID 4030358 and 4319105, respectively).

In this application, PK assessments were performed in phase 2 and phase 3 studies in adult patients with nasal polyposis. Pop PK analyses were conducted with data from studies in healthy subjects and phase 2/3 studies conducted in adult patients with nasal polyposis.

Dupilumab PK was generally comparable between healthy subjects and adult patients with nasal polyposis. In adult patients with nasal polyposis, dupilumab is well-absorbed with an estimated SC bioavailability at 62.8%, distributes primarily within the vascular compartment (4.91 L) and exhibits non-linear target-mediated elimination. After the last dose at the steady state, the median time for the serum concentration to decrease to below the lower limit of quantification is 12 weeks for dupilumab 300 mg q2w.

A Pop PK analysis was conducted using data from one phase 2a study (ACT12340) and two phase 3 studies (EFC141146 and EFC14280) to determine dupilumab PK parameters in adult patients with nasal polyposis and assess the effect of intrinsic and extrinsic factors on

dupilumab PK in the intended patient population. Sparse PK data was collected in adult NP patients in the three studies at pre-dose, during treatment, and follow-up. Based on Pop PK analysis, the median time to reach steady state is 16 weeks for 300 mg q2w. When switched from 300 mg q2w to 300 mg q4w at week 24, a new steady state is achieved in an additional 24 weeks (i.e., 48 weeks from the initiation of dupilumab treatment).

By Pop PK analysis, the estimated clearance (CL) for dupilumab in adult patients with NP was 0.117 L/day (95% CI = (0.115, 0.120)). The PK of dupilumab in adult patients with NP was consistent with that of observed in asthma and atopic dermatitis. The apparent systemic clearance of dupilumab was 0.116 and 0.131 in patients with asthma and atopic dermatitis, respectively. This observation suggested that disease is not a covariate for dupilumab exposure.

Body weight is the primary factor responsible for dupilumab PK variability, whereas other intrinsic factors including age, gender, race/ethnicity, renal function (normal to moderate renal impairment), laboratory parameters (albumin), do not have a meaningful effect on dupilumab PK.

6.3.2. Clinical Pharmacology Questions

Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

This sBLA consists of data from one phase 2a study (ACT12340) and two pivotal phase 3 studies (EFC14146 and EFC14280) for treatment periods ranging from 16 weeks to 52 weeks. Refer to Section 8 for assessment of the primary and secondary endpoints in the two pivotal studies.

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

The proposed dosing regimen is acceptable.

The clinical efficacy of the proposed 300 mg q2w dosing regimen was demonstrated in two pivotal phase 3 studies (EFC14146 and EFC14280, sections 7.2 and 7.3). There was no clear dose/exposure response observed as efficacy appears to plateau at 300 mg Q2W dose. Results of the PK/PD analyses are consistent with the efficacy evaluation in adult patients with NP. Refer to the Pharmacometrics review (Appendix 15.2) for details on the population PK and ER analysis.

Is an Alternative Dosing Regimen or Management Strategy Required for Sub-Populations Based on Intrinsic Patient Factors?

No. The covariates age, gender, race, and renal function were not identified as significant covariates for dupilumab clearance.

Age was not a significant covariate for dupilumab exposure or efficacy after adjusting for the effect by body weight. Dose adjustment in special populations, including renal impaired subjects is not required.

Body Weight

Body weight was identified as a covariate affecting dupilumab clearance and volume of distribution parameters. The CL decreased by 20% and increased by 25% for the <70 kg and >90 kg category, respectively, using >70 to ≤90 kg as the reference. A summary of the impact of body weight on steady state exposure for adult patients with NP is presented by body weight category in Table 5. The 300 mg q2w steady state exposure data is from studies EFC14146 and EFC14280, and 300 mg q2w-q4w steady state exposure data is from study EFC14280.

Table 5. Mean (SD) Dupilumab Steady-State Exposure by Body Weight Category in Adult Patients With NP (Studies EFC14146, and, EFC14280)

	300 mg q2w				300 mg q2–q4w			
Body weight (kg)	N	$AUC_{\tau,ss}$[a] (mg•day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)	N	$AUC_{\tau,ss}$[a] (mg•day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
<70 kg	122	1618 (431)	125 (31.6)	99.6 (28.9)	45	1286 (480)	61.5 (19.1)	27.6 (14.2)
70 to < 90 kg	178	1170 (328)	91.7 (23.9)	70.3 (22.2)	57	934 (367)	46.6 (14.4)	17.9 (10.7)
≥90 kg	120	827 (256)	65.7 (18.8)	48.3 (17.3)	39	511 (256)	29.0 (10.3)	6.73 (7.06)

a) $AUC_{\tau ss}$ represents AUC from week 22 to week 24 for 300 mg q2w dose group, and, AUC from week 48 to week 52 for 300 mg q2w to q4w dose group. .
Note: Descriptive statistics represent the post hoc estimates of steady-state exposure for Studies EFC14146 and EFC14280, in NP patients.(Pop PK analysis report).
AUC = area under the concentration-time curve; C_{max} = maximum concentration; 300 mg q2w = once every 2 weeks; q4w= once every 4 weeks; 300 mg q2w-q4w= 300 mg q2w until Week 24, then 300 mg q4w until Week 52
Source: Summary of Clinical Pharmacology, Table 8, page 42

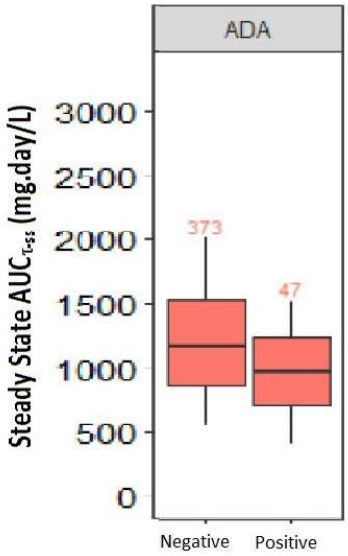
There was no clinically meaningful difference in dupilumab efficacy or safety profiles across the weight categories in adult patients with NP, and therefore no dose adjustment is recommended with regard to body weight.

What Was the Impact of Immunogenicity on Dupilumab Exposure?

An integrated analysis was performed using pooled data from two phase 3 studies (EFC14146 and EFC14280). Overall, 46 of 879 (5.2%) of subjects treated with 300 mg q2w SC and 48 of 1,084 (4.4%) of subjects treated placebo had anti-dupilumab antibodies identified in at least one sample after having received at least one dose. Of all the subjects treated with dupilumab who tested positive for anti-dupilumab antibodies, 16 of 879 (1.8%) patients were positive before dupilumab treatment. The incidence of persistent ADA was 2% (18 of 879) and 1.6 % (17 of 1,084) in 300 mg q2w and combined placebo groups, respectively.

ADA result (considered as positive if positive in at least one time point) was also introduced as a categorical covariate to evaluate its effect on CL, and ADA status did not appear to have an impact on the parameter estimates. The estimates of CL in ADA+ and ADA- subjects are 0.125 L/day and 0.117 L/day, respectively. Accordingly, treatment-emergent ADA positive patients appeared to have lower mean dupilumab exposure compared with that of ADA negative patients (Figure 1).

Figure 1. Impact of Immunogenicity on Pharmacokinetic Exposures in NP Patients Who Received 300 mg q2w of Dupilumab in Two Phase 3 Studies (EFC14146 and EFC14280)



Note: ADA status: negative ADA represents negative ADA at all the time; positive ADA represents positive ADA at any time.
ADA = antidrug antibody; AUC = area under the concentration-time curve; NP = nasal polyposis; q2w = once every 2 weeks
Source: Summary of clinical pharmacology, Figure 8, page 41

There was no clear evidence of lack or loss of efficacy in patients developing low to moderate ADA titers (including neutralizing antibody), and ADA was not a significant covariate for efficacy endpoints in the PK PD analysis. The safety profile in patients with a positive ADA status appeared similar to that of patients with a negative ADA status.

Are the Bioanalytical Methods Properly Validated to Measure PK in Plasma Samples?

Plasma concentration of dupilumab in the NP studies were determined with a validated bioanalytical enzyme-linked immunosorbent assay (ELISA), which was reviewed as part of the original BLA submission for atopic dermatitis. Please refer to the archived clinical pharmacology review by Dr. Jie Wang (Reference ID 4030358).

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6. Listing of Clinical Trials Relevant to This sBLA

Trial Date	Trial Design/ Duration	Regimen/ schedule/ route	N[ϰ]	Population	Primary Endpoints	No. of Centers/ Countries
ACT12340 Aug 2013 - Nov 2014	R, DB, PC phase 2 16 weeks	300 mg qw[γ] Placebo	30 30	Patients with CRSwNP on background therapy with INCS[†]	Nasal polyposis score	14 sites/4 countries (Belgium, Spain, Sweden, United States)
EFC14146 SINUS-24 Dec 2016 – Jul 2018	R, DB, PC phase 3 24 weeks	300 mg q2w Placebo	143 133	Patients with CRSwNP on background therapy with INCS[†] (received/intolerant to systemic steroids within past 2 years and/or prior surgery for nasal polyps)	Nasal polyposis score Nasal congestion score	67 centers/13 countries (Bulgaria, Czechia, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom, United States)
EFC14280 SINUS-52 Nov 2016 – Aug 2018	R, DB, PC phase 3 52 weeks	300 mg q2w 300 mg q2-4w* Placebo	150 145 153	Patients with CRSwNP on background therapy with INCS[†] (received/intolerant to systemic steroids within past 2 years and/or prior surgery for nasal polyps)	Nasal polyposis score Nasal congestion score	117 sites/14 countries (Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan, United States)

γ: with 600 mg loading dose.
ϰ: Randomized population.
†: mometasone furoate 2 sprays in each nostril twice daily, total daily dose 400 micrograms.
* Patients are on q2w until week 24 then switched to q4w until week 52.
R = randomized, DB = double-blind, PC = placebo-controlled, CRSwNP = chronic rhinosinusitis with nasal polyps; INCS = intranasal corticosteroids, q2w = every 2 weeks, q4w = every 4 weeks
Source: ACT 12340 Clinical Study Report (CSR) Synopsis; EFC14146 CSR Synopsis; EFC14280 CSR Synopsis

7.2. Review Strategy

The clinical review consisted of one primary clinical reviewer. This sBLA contained two randomized, placebo-controlled, double-blind studies (24-week: EFC14146 and 52-week: EFC14280) that were evaluated for efficacy and safety. Section 8.1 includes a summary of the protocols, and the efficacy and safety results for each study. The first 24 weeks of the 24- and 52-week studies were pooled for safety, which is discussed in Section 8.2. The sBLA contained an additional study, ACT12340, that will not be a focus of the clinical review, as it was a phase 2 proof-of-cocept trial with a different dosing regimen, primary endpoint, and study population. Study ACT12340 is included in the clinical pharmacology review in Section 6.

The clinical studies included different dosing regimens of 300 mg every other week with no loading dose and SINUS-52 contained an additional arm of patients who were switched to every 4 weeks (q4w) from weeks 24 to 52. Safety data from weeks 24 to 52 was requested from the sponsor and analyzed for any differences from the overall 52-week study.

Data Sources

Data sources in this electronic submission included protocols, clinical study reports, narratives, and SAS transport datasets in legacy format.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. EFC 14146

8.1.1.1. Trial Design

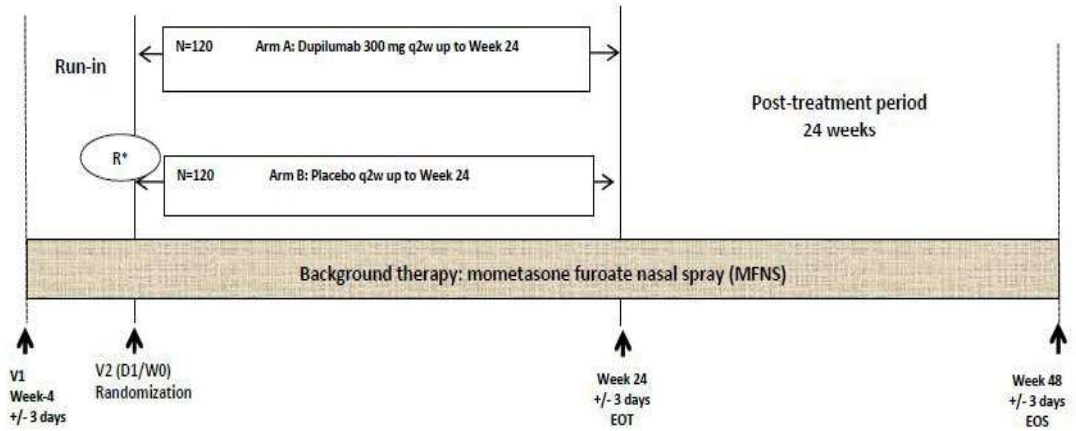
Study EFC14146 was a 24-week, multinational, multicenter, randomized, double-blind, placebo-controlled, phase 3 efficacy and safety study comparing dupilumab 300 mg q2w with placebo in patients with bilateral nasal polyposis on background therapy with intranasal corticosteroids.

The trial consisted of three periods: run-in, treatment, and post-treatment. The run-in period was 4 weeks ±3 days to standardize background intranasal corticosteroids to mometasone furoate 2 actuations (50 micrograms/actuation) in each nostril twice daily for a total daily dose of 400 micrograms, which is the recommended dosage for mometasone furoate for the treatment of nasal polyps (Nasonex (mometasone furoate monohydrate) [package insert]. U.S. Food and Drug Administration website. www.accessdata.fda.gov/spl/data/5a437c69-98bb-46e9-a72f-36a82242b98b/5a437c69-98bb-46e9-a72f-36a82242b98b.xml Revised June 2018. Accessed June 14, 2019). If patients could not tolerate this dose they were allowed to stay on a lower dose of 200 micrograms daily.

In addition to background medication (mometasone furoate nasal spray) and rescue medication (oral corticosteroids), the following concomitant medications were permitted: short term antibiotics (<2 weeks), short and long-acting beta agonists, long-acting muscarinic antagonists, methylxanthines, inhaled corticosteroids, and systemic antihistamines. Leukotriene antagonist/modifiers and allergen immunotherapy were permitted if patients were already on treatment prior to screening. The randomization period was 24 weeks ±3 days where patients were randomized 1:1 to dupilumab 300 mg subcutaneous every 2 weeks or placebo. During the study treatment period and follow-up, the Investigator could consider rescue treatment with nasal lavage (saline and/or systemic antibiotics for up to 2 weeks), oral corticosteroids (prednisone or prednisolone for up to 2 weeks), surgery for polyps. Based on previous experience, 8 weeks of IMP was recommended prior to surgery to allow treatment effect. Patients receiving any rescue other than surgery were to continue IMP unless the Investigator decided otherwise. For patients undergoing surgery for nasal polyps, IMP was to be permanently discontinued. Before starting oral corticosteroids, patients underwent endoscopy and PRO assessments.

The post-treatment period was 24 weeks ±3 days where patients were followed for 24 weeks to evaluate disease recurrence, immunogenicity, and safety after treatment discontinuation. Randomization was stratified by the presence of comorbid asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD), prior nasal polyp surgery, and country.

Figure 2. Study Design for EFC 14146



EOS = end of study; EOT = end of treatment; q2w = once every 2 weeks; V1 = visit 1
Source: CSR EFC14146, Figure 1

A schedule of assessments is provided in Table 7.

Table 7. EFC 14146 Schedule of Assessments

	Run-in	Randomized treatment period								EOT	FU1	FU2 (EOS)
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	**9**	**10**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12,14**	**16**	**18, 20, 22**	**24**	**36**	**48**
Day ±3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**	**D253**	**D337**
Informed consents	X											
Inclusion and exclusion criteria	X	X										
Patient demography	X											
Medical/surgical/medication history	X											
Physical examination	X									X	X	X
Spirometry	X					X		X		X		X
Chest X-ray	X											
Randomization		X										
Treatment:												
IMP: Dupilumab/placebo injection		X	X	X	X	X	X	X	X			
Call IVRS (IWRS) at scheduled and unscheduled visits as needed	X	|----------X----------|								X	X	X
Review IMP and/or NIMP compliance		|----------X----------|								X		
Dispense or download electronic diary for symptoms	|----------X----------|											
NIMP	|----------X----------|											
Record concomitant medication	|----------X----------|											

	Run-in					Randomized treatment period				EOT	FU1	FU2 (EOS)
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	**9**	**10**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12,14**	**16**	**18, 20, 22**	**24**	**36**	**48**
Day ±3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**	**D253**	**D337**
Record planned surgery for NP, SCS use, and other rescue medication use	|----------X----------|											
Efficacy												
Nasal endoscopy	X	X				X		X		X	X	X
CT scan	X									X		X
Smell test (UPSIT)		X	X			X		X		X		X
NPIF	X	|----------DailyAM----------|									X	X
Patient reported outcomes/HRQoL/												
SNOT-22		X				X		X		X	X	X
Visual analog scale (VAS) for rhinosinusitis		X	X	X		X		X		X	X	X
Severity score (0-3) for reduced sense of taste		X	X	X		X		X		X		
EQ-5D		X								X		
SF-36		X										
ACQ-6 in patients with asthma		X				X		X		X		X
Healthcare resource utilization		X				X		X		X		
Safety												
AE/SAE recording (if any)	|----------X----------|											
Vital Signs	X	X				X		X		X	X	X
ECG (local reading)		X								X		
Clinical laboratory testing	X	X						X		X		
Hepatitis B viral load		X								X		
Pregnancy test (for WOCBP)	X	X		X		X	X (W12)	X	X (W20)	X	X	X
Sampling for serum dupilumab concentration		X		X		X		X		X	X	X
Antidrug antibody sampling		X				X		X		X	X	X
Blood biomarkers (TARC, eotaxin-3, periostin)		X										

	Run-in					Randomized treatment period				EOT	FU1	FU2 (EOS)
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**	**9**	**10**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12,14**	**16**	**18, 20, 22**	**24**	**36**	**48**
Day ±3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**	**D253**	**D337**
Serum Total IgE, allergen-specific IgE panel sampling including Staph enterotoxins IgE		X								X		
Spot urine for biomarker sampling (LTE4, PGDM, creatinine)		X								X		
Nasal swabs for microbiome		X								X		
Stored DNA sampling		X										
Stored serum		X								X		
Stored whole blood RNA sampling		X										

ACQ-6 = asthma control questionnaire-6; ADA = antidrug antibodies; AE = adverse event; AM = ante meridiem; CT = computed tomography; D = day; ECG = electrocardiogram; e-CRF = electronic case report form; EOS = end of study; EOT = end of treatment; EQ-5D = European quality of life -5D questionnaire; FEF25-75 = forced expiratory flow to 25% to 75% of forced vital capacity; FEV1 = forced expiratory volume in one second; FU = follow-up; FVC = forced vital capacity; HRQoL = health-related quality of life; IgE = immunoglobulin E; IMP = investigational medicinal product; IVRS = interactive voice response system; IWRS = interactive web response system; LTE4 = leukotriene E4; MFNS = mometasone furoate nasal spray; MRI = magnetic resonance imaging; NC = nasal congestion; NSAID-ERD = nonsteroidal anti-inflammatory drug -exacerbated respiratory disease; NIMP = noninvestigational medicinal product; NP = nasal polyposis; NPIF = nasal peak inspiratory flow; PGDM = prostaglandin D2 metabolite; PK = pharmacokinetic; RDN = randomization; SAE = serious adverse event; SCS = systemic corticosteroids; SF-36 short form 36; SNOT-22 = Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania smell identification test; VAS = visual analog scale; W = week; WBC = white blood cell; WOCBP = women of child bearing potential.

8.1.1.2. Population

Inclusion Criteria

1. Patients with bilateral sino-nasal polyposis despite treatment with systemic corticosteroid within the past 2 years and/or medical contraindication/intolerance to systemic corticosteroid and/or had prior surgery for nasal polyposis at screening
2. Endoscopic bilateral NPS of at least 5 out of 8 (minimum score of 2 in each nasal cavity).
3. Symptoms for at least 8 weeks of nasal congestion/blockade/obstruction with moderate or severe severity (score of 2 or 3) and weekly average severity greater than 1 at randomization AND loss of smell or rhinorrhea

Exclusion Criteria

1. Patients <18 years of age
2. Patients previously treated in dupilumab studies
3. Patient who has taken biologic therapy/systemic immunosuppressant to treat inflammatory/autoimmune disease within 2 months or five half-lives (whichever is longer)
4. Experimental monoclonal antibody five half-lives or 6 months before if half-life unknown
5. Anti-IgE (omalizumab) 130 days prior
6. Patients on leukotriene antagonists/modifiers unless on continuous treatment for 30 days prior
7. Allergen immunotherapy within 3 months prior or planning to begin therapy
8. Intranasal and/or sinus surgery (including polypectomy) 6 months prior or sino-nasal surgery changing lateral wall structure of the nose
9. Concomitant disease making nasal cavity nonevaluable (antrochoanal polyps, septal deviation, acute sinusitis, nasal infection, upper respiratory infection, rhinitis medicamentosa, allergic granulomatous angiitis, granulomatosis with polyangiitis, Young's syndrome, Kartagener's syndrome, cystic fibrosis)
10. Confirmed invasive or expansive fungal rhinosinusitis, or radiologic suspicion
11. Nasal cavity malignant or benign tumors
12. Forced expiratory volume (FEV1) 50% or less of predicted normal
13. Meeting contraindications or warning on National Product labeling for mometasone furoate nasal spray
14. Pregnant, or intent to become pregnant during study, or breast-feeding
15. Women of childbearing potential who do not fulfill: negative serum beta-human chorionic gonadotrophin test at visit 1, established use of contraception (oral/injected/inserted, or implanted hormonal, intrauterine progesterone device, or barrier contraceptive) or female sterilization or postmenopausal status
16. Active parasitic infection (helminths)
17. Human immunodeficiency virus (HIV) or positive screen (anti-HIV1 and HIV-2 antibodies)

18. Any significant past medical history that could interfere with study
19. Known or suspected history of immunosuppression including invasive opportunistic infections (histoplasmosis, listeriosis, coccidiomycosis, pneumocystosis, aspergillosis) or frequent, recurrent, or prolonged infections
20. Active, latent untreated, or history of incompletely treated tuberculosis or nontuberculous mycobacterial infection
21. Acute or chronic infection requiring antibiotic, antiviral, antifungal, antiparasitic, or antiprotozoal treatment within 4 weeks prior or during the run-in period, or significant untreated viral infections 4 weeks prior
22. Live attenuated vaccines 4 weeks prior or planned during the study
23. Active autoimmune disease/immunosuppressive therapy for autoimmune disease or high titer autoantibodies at risk for developing autoimmune disease
24. Malignancy 5 years before, except treated in situ carcinoma of cervix, nonmetastatic squamous or basal cell carcinoma of the skin
25. Known or suspected alcohol and/or drug abuse
26. History of systemic hypersensitivity reaction other than localized injection site reaction to any biologic drug
27. Active hepatitis or positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb) confirmed with hepatitis B virus deoxyribonucleic acid, or positive hepatitis C virus (HCV) antibody confirmed with HCV ribonucleic acid
28. Clinically significant/active underlying hepatobiliary disease, ALT>3 times the upper limit of normal, creatine phosphokinase >10 times the upper limit of normal, platelets <100,000 cells/mm^3, eosinophils >1500 cells/mm^3
29. Noncompliance, inability to meet scheduled visits, administer long-term injections, limiting social/geographical conditions
30. Withdrawal of consent prior to enrollment/randomization

Patients who fail screening due to failure to meet inclusion criteria for weekly average nasal congestion score >1 at visit 2 or those who had an acute illness such as sinusitis, nasal infection, or upper respiratory infection, or took a prohibited treatment can be rescreened once. If laboratory requirements do not meet eligibility criteria, then these laboratory assessments could be repeated at the Investigator's discretion.

8.1.1.3. Endpoints

The study has two coprimary efficacy endpoints: change from baseline in NPS and NC severity at 24 weeks of 300 mg q2wk treatment. For Japan, coprimary endpoints were change from baseline in nasal congestion, NPS, and Lund-Mackay CT sinus scan at week 24.

Secondary efficacy endpoints included change from baseline to Week 24 in:

1. Lund-Mackay (LMK) CT sinus scan score
2. Total symptom score (TSS)
3. University of Pennsylvania smell identification test

4. Loss of smell
5. Sino-Nasal Outcome Test (SNOT-22)
6. Proportion of patients using study treatment receiving systemic corticosteroids and/or plan to undergo surgery for nasal polyps

The coprimary and this group of secondary endpoints were analyzed under multiplicity control with a gatekeeping strategy, in the order as noted above. These primary and multiplicity-controlled secondary endpoints are the focus of this efficacy review (b) (4) .

Biomarkers included eotaxin-3, serum total immunoglobulin E, aeroallergen-specific IgE, serum thymus and activation-regulated chemokine (TARC), serum periostin, and urine leukotriene E4 (LTE4) and prostaglandin D2 (PGDM) metabolites.

Reviewer comment: LTE4 was measured via spot urine which and not a 24-hour collection. The literature supports inaccuracies in spot measures due to significant diurnal variation[7].

8.1.1.4. Efficacy Parameters

<u>Nasal congestion score</u>

Nasal congestion ranged from 0-3, with the 3 being the worst score:

0= no symptoms

1=mild symptoms/easily tolerated

2=moderate symptoms/bothersome but tolerable

3=severe symptoms/interference with daily activities)

Nasal congestion was scored by the patient reflectively over the past 24 hours and recorded every morning in an e-diary. Baseline calculation included an average of 4 or more measurements 7 days prior to randomization. For baseline to end of treatment analysis, 4 weeks average of symptom scores was used.

<u>Nasal polyp score (NPS)</u>

The NPS ranged from 0-8, with 8 being the worst score. Both the left and right sides were scored as follows:

0=no polyps

1=small polyps in middle meatus not reaching below inferior border of middle turbinate

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[7] Asano K, et al., 1995, Diurnal variation of urinary LTE4 and histamine excretion rates in normal subjects and patients with mild-to-moderate asthma. J Allergy Clin Immunol 96(5): 643-651.

2=polyps reaching below lower border of middle turbinate

3=large polyps reaching lower border of inferior turbinate or medial to middle turbinate

4=large polyps completely obstructing inferior nasal cavity.

The total score is the sum of both sides. Trained physicians (2 or more) assessed this score via blinded video recordings of nasal endoscopies. A prespecified adjudication process was performed for disagreements between 2 readings by more than 1 point.

Lund-Mackay (LMK) sinus CT scan score

The LMK score ranged from 0-24, with 24 being the worst score. The LMK score is a validated system for assessing sinus opacification on CT, assessed as follows:

0= normal

1=partial opacification

2=total opacification.

A total of 5 sinuses (maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal) plus the osteometal complex are each graded. The maximum score is 12 per side, or 24 total.

Total symptom score

The total symptom score ranged from 0-9, with 9 being the worst score. The total symptom score was scored by the patient every morning reflectively over 24 hours for 3 symptoms (nasal congestion, decreased/loss of smell, and rhinorrhea), as follows:

0=no symptoms

1=mild symptoms

2=moderate symptoms

3=severe symptoms

University of Pennsylvania Smell Identification Test

The UPSIT is a quantitative test of olfaction ranging from 0-40, with 0 being the worst. Four booklets of 10 odorants each were administered to the patient. Four options describe each odor, from which the patient has to choose the correct odorant. The patients were scored from 0 to 40. A score of 18 was considered anosmia, 19 to 25 as severe microsmia, 26 to 30 as moderate microsmia, 31 to 34 as mild microsmia, and 35 to 40 as normal.

Reviewer comment: Although UPSIT was included as an efficacy measure, we had concerns regarding the UPSIT as it can vary based on cultural background, prior olfactory experience, and gender.[8] For these reasons, we did not include UPSIT results in the label.

Loss of smell score

The loss of smell score ranged from 0-3, with 3 being the worst score. Loss of smell was scored by the patient reflectively every morning as follows:
0=no symptoms
1=mild symptoms
2=moderate symptoms
3=severe symptoms.

SNOT-22

The SNOT-22 ranges from 0-110, with 110 being the worst score. SNOT-22 is a 22-item questionnaire regarding sino-nasal symptoms and the impact of those symptoms. Each of the 22 items is scored from 0 (no problem) to 5 (problem as bad as it can be), with higher scores indicating more severe disease[9].

8.1.1.5. Statistical Analysis Plan

The statistical analysis plan (SAP) for this study was issued on August 14, 2017, with modifications noted based on a protocol amendment approved on May 17, 2017. The Applicant states the SAP was approved prior to database lock and unblinding of the study.

The sample size was chosen to enable an adequate characterization of the difference in efficacy between dupilumab 300 mg q2w and placebo with regard to the two coprimary endpoints, change from baseline in NC and NPS at Week 24. With a sample size of 120 patients per group, the combined power of the two coprimary efficacy endpoints was affirmed by the Applicant to be at least 93% for dupilumab 300 mg q2w group (with alpha =0.05, assuming no negative correlation between the two endpoints). This was confirmed in the statistical review.

Four analysis populations were defined by the Applicant:

- Efficacy population: The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as the randomized population analyzed according to the treatment group allocated by randomization.
- Safety population: The safety population included all patients who received at least one dose or part of a dose of the investigational product, analyzed according to the treatment

[8] Hsieh JW, et al., 2017, PNAS, SMELL-S and SMELL-R: Olfactory tests not influenced by odor-specific insensitivity or prior olfactory experience, 114(43): 11275-11284.
[9] Piccirillo JF, Merritt MG, Richards ML, 2002, Psychometric and clinimetric validity of the 20-item Sino-Nasal Outcome Test (SNOT-20), Otolaryngol Head Neck Surg, 126(1):41-7.

actually received. Patients who were treated without randomization were also to be included in the safety population.

- PK population: The PK population consisted of all patients in the safety population with at least one evaluable functional dupilumab concentration result. Patients were analyzed according to the treatment actually received.
- Anti-drug antibody population: The antidrug antibody (ADA) population consisted of all patients in the safety population with at least one reportable ADA result (either "ADA negative" or "ADA positive") after first dose of the study treatment. Patients were analyzed according to the treatment actually received.

The primary analysis population for the efficacy endpoints was the efficacy population defined above. Therefore, the efficacy analyses were conducted according to the treatment to which they were randomized.

The primary analysis for the coprimary efficacy endpoints were analyzed using a hybrid of the worst observation carried forward (WOCF) and multiple imputation. Data collected after treatment discontinuation were included in the analysis. Imputation methods for patients who undergo surgery for NP or receive systemic corticosteroids (SCS) for any reason, data collected postsurgery (actual date) or post SCS used the worst postbaseline value on or before the time of surgery or SCS to impute Week 24 values (for patients whose postbaseline values are all missing, the baseline was used to impute). For patients who discontinue the treatment without being rescued by surgery or receiving SCS, a multiple imputation approach was used to impute missing Week 24 values.

Each of the imputed complete data were analyzed by fitting an analysis of covariance (ANCOVA) model with treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as factors and the baseline value of the corresponding coprimary endpoint as covariates. Statistical inference obtained from all imputed data was then combined using Rubin's rule.

<u>Sensitivity analyses</u>

For all sensitivity analyses (except for the as-observed analysis) for patients who underwent surgery for NP or received SCS for any reason, data collected postsurgery or post SCS were set to missing.

Mixed-effect model for repeated measures (MMRM) approach was employed. The model included change-from-baseline values up to Week 24 as response variables and factors (fixed effects) for treatment, stratification (comorbid asthma/NSAID-ERD, prior surgery, region), visit, treatment-by-visit interaction, and covariates for NPS/NC baseline value, and baseline-by-visit interaction. No imputation was performed for the MMRM model.

Pattern mixture model with copy increment from placebo was conducted with each of the 2 coprimary efficacy endpoints analyzed with imputed missing values at 24 weeks. This copy increment from placebo implies that when subjects discontinue treatment early, they continue to take advantage of their previous therapy, but they progress in the same way as subjects in the placebo group. The imputed dataset was analyzed by fitting an ANCOVA model that was same as the one in primary analysis.

Tipping point analysis for each of the two coprimary efficacy endpoints was conducted on imputed missing values at 24 weeks with independent penalties for each treatment group to see if the statistical significance was tipped in progressively more implausible clinical scenarios.

An additional as-observed analysis was conducted on the coprimary efficacy endpoints which included all data (including that collected after SCS for any reason and/or treatment discontinuation) but *excluded post NP surgery data*. The data were analyzed in the same ANCOVA model for the primary approach. The statistical reviewer conducted another as-observed analysis that included data for patients rescued via both surgery and SCS.

Reviewer comment: Excluding the post NP surgery data in the additional as-observed analysis was considered reasonable as NP surgery completely removes the NP, compared to SCS which reduces the NP size, but does not completely remove the NP.

Also, a mixed model approach for NC as ordinal response data was conducted after converting to binary response data. Specifically, generalized estimating equation (GEE) model on NC as longitudinal binary response data was conducted.

Secondary analyses

Change from baseline in sinus opacification CT scan score (LMK), total symptom score (TSS), UPSIT score, daily loss of smell, and SNOT-22 at Week 24 were assessed for dupilumab 300 mg q2w compared to placebo. These data were analyzed using the same approach as the coprimary endpoints: a hybrid method of replacing values with WOCF for rescued patients due to surgery or SCS use and multiple imputation for missing data.

Proportion of patients requiring rescue treatment (defined as use of SCS or NP surgery during the treatment period) was derived and analyzed using the Cox proportional hazards model. The decision date of NP surgery or the first SCS intake date was used as the event date, or whichever was earlier if both occurred. Due to the potentially low predicted number of patients requiring rescue treatment, the primary analysis for this endpoint was conducted by pooling both of the pivotal studies. This is reviewed in the integrated analysis section below.

Reviewer comment: The pooling of the primary analysis for NP surgery and SCS use was agreed upon by the Agency due to the low predicted numbers of events and the clinical importance of these endpoints.

Subgroup analyses

Subgroup analyses were conducted to assess the consistency in treatment effects across different subgroup levels for the coprimary efficacy endpoints with respect to: age, gender, region, territory, race, ethnicity, baseline weight, baseline body mass index (BMI), prior NP surgery, asthma comorbidity and/or NSAID-ERD, and SCS use in the prior 2 years.

The primary analysis (adjusted for multiplicity) for the change from baseline in FEV1 in the subpopulation of patients with asthma was conducted by pooling the 2 pivotal CRSwNP studies. Individual study results were also performed.

Based on the dupilumab approval for eosinophilic asthma which did not show efficacy in paitents with low eosinophil counts (< 150 cells/mcL) , we also assessed the primary endpoint

results by level of eosinophils across all patients and several of the individual elements of SNOT-22 related to sinusitis and rhinitis (facial pain, nasal blockage, thick nasal discharge, runny nose and sneezing).

Data collected after treatment discontinuation were included. Data post SCS or NP surgery were set to missing and imputed by WOCF; other missing data were imputed by multiple imputations (MI). Descriptive statistics at Week 24 include patients after WOCF at Week 24, and patients whose Week 24 values were imputed by MI were excluded from the descriptive analysis. Each of the imputed complete data was analyzed by fitting an ANCOVA model with the corresponding baseline value, treatment group, asthma/NSAID-ERD status, prior surgery history, and regions as covariates.

8.1.1.6. Protocol Amendments

One global amendment was made to the study protocol for the purpose of clarification. The following points were included in the amendment dated May 17, 2017:

- Clarification of early treatment discontinuation language
- Retesting dynamic laboratory values during screening
- Analysis changed to systemic corticosteroids from oral corticosteroids
- EQ-5D changed from exploratory endpoint to secondary endpoint
- CT scan administration mandatory unless not approved by local ethics committee or institutional review board
- Intranasal decongestants added to prohibited medications except as needed for nasal endoscopy
- Study procedures can be performed over 3 days as long as visit window respected
- Male birth control no longer required
- Rescue therapy prescribed by investigator not provided by Applicant

8.1.2. Study Results

Compliance With Good Clinical Practices

The study was performed in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Conference on Harmonization guidelines for Good Clinical Practice, all applicable laws, rules, and regulations.

Financial Disclosure

See Appendix 15.1.

8.1.2.1. Disposition

A total of 143 patients were randomized to dupilumab 300 mg q2w and 133 were randomized to placebo (Figure 3). Of the 276 patients randomized in this study, 263 (95%) patients completed study treatments during the randomized treatment period. Twelve (4.3%) patients

discontinued treatment prior to Week 24, and 13 (4.7%) patients discontinued from the 48-week study period. One patient was randomized to dupilumab 300 mg q2w and was not treated. Number and percent of patients for each of the prespecified populations is shown in Table 8.

Table 8. Analysis populations for clinical study EFC14146

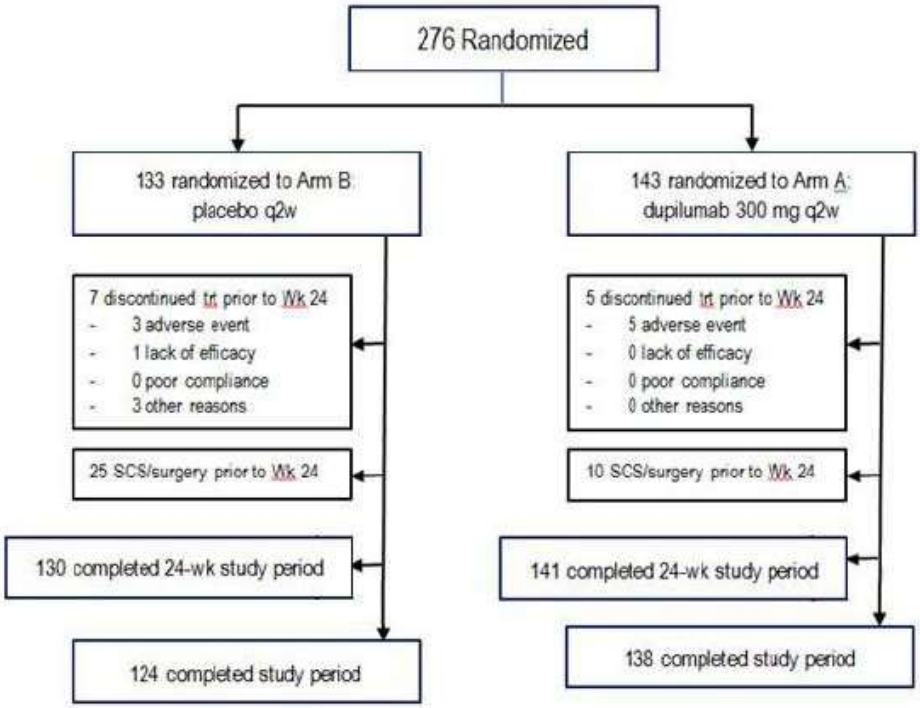
	Placebo (N=133)	Dupilumab 300mg q2w (N=143)	All (N=276)
Randomized population	133 (100%)	143 (100%)	276 (100%)
Efficacy population			
Intent-to-Treat (ITT)	133 (100%)	143 (100%)	276 (100%)
Safety population	132	143	275
PK population	0	142	142
ADA population	132	143	275

Note: For the safety, PK and ADA population, patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment

Source: Clinical study report EFC14146, Table 13

Similar numbers of patients discontinued treatment prior to Week 24 in both arms (seven (5%) in placebo arm, five (3%) in dupilumab arm). Three placebo patients discontinued due to adverse events, one due to lack of efficacy, and three for other reasons. Five dupilumab patients discontinued due to adverse events.

Figure 3. Patient Disposition up to Week 48, Randomized Population



q2w = once every 2 weeks; SCS = systemic corticosteroids
Source: Figure 2, EFC14146 clinical study report

Protocol Violations/Deviations

Overall, 29.4% of dupilumab patients and 42.9% of placebo patients had a deviation. In 21% of dupilumab patients and 33.1% of placebo patients, deviations in schedule of assessments occurred (study visit of phone call outside of visit window). In 7% of dupilumab patients and 9.8% of placebo patients, deviations in investigational medical product management occurred (missed dose, drug administered not per protocol). Critical or major deviations occurred in 3.5% of the dupilumab group and 3% of the placebo group. The most common major deviation that occurred was allowance of a patient to stay in the study after week 24 with a missing nasal congestion score between weeks 21 and 24 (1.4% of dupilumab patients versus 2.3% placebo patients). The second most common type of major deviation was failure to meet the inclusion criteria of ongoing symptoms of 8 weeks or greater prior to randomization (1.4% of dupilumab patients and 0.8% of placebo patients).

Critical protocol deviations potentially impacting safety include laboratory sample not performed at randomization (one dupilumab patient), lack of UPSIT at randomization (one dupilumab patient), and investigational medicinal product (IMP) not permanently discontinued in a patient with opportunistic infection (one patient on placebo).

8.1.2.2. Demographics

Demographics were similar for placebo and active groups, with the largest difference noted in sex, with 53% male in the placebo arm and 61% in the active arm. Overall, there were 57% male and 43% female participants in this study (Table 9).

The mean age was 50.5 years, with minimum age 22 and maximum age 85 years of age; 84% of participants were under 65 years of age. Most participants in this study were white (96%), with nine black (3%) and one Asian (<1%); 2% had Hispanic/Latino ethnicity. There were 63% of participants from Eastern Europe, 37% from Western Countries. The Applicant also characterized region by United States, European Union and rest of world, with 12%, 64%, and 24%, respectively from those regions.

Table 9. Demographic Characteristics of the Primary Efficacy Analysis EFC14146

Demographic Parameters	Placebo Group (N=133) n (%)	Dupilumab 300 mg Group (N=143) n (%)	Total (N=276) n (%)
Sex			
Male	70 (53%)	88 (61%)	158 (57%)
Female	63 (47%)	55 (39%)	118 (43%)
Age			
Mean years (SD)	50.8 (13.2)	50.2 (13.6)	50.5 (13.4)
Median (years)	50.0	52	51
Min, max (years)	22, 85	23, 79	22, 85
Age Group			
<65 years	112 (84%)	121 (85%)	233 (84%)
≥65 years	21 (16%)	22 (15%)	43 (16%)
Race			
White	126 (95%)	138 (97%)	264 (96%)
Black or African American	7 (5%)	2 (1%)	9 (3%)
Asian	0	1 (1%)	1 (<1%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (1%)	1 (<1%)
Other[1]	0	0	0
Ethnicity			
Hispanic or Latino	1 (1%)	5 (3%)	6 (2%)
Not Hispanic or Latino	130 (99%)	138 (97%)	268 (98%)
Region			
Eastern Europe	86 (65%)	87 (61%)	173 (63%)
Western Countries	47 (35%)	56 (39%)	103 (37%)
United States	16 (12%)	18 (13%)	34 (12%)
European Union	85 (64%)	92 (64%)	177 (64%)
Rest of World	32 (24%)	33 (23%)	65 (24%)

SD = standard deviation
Source: Table 14, EFC14146 clinical study report

Other baseline demographics regarding atopic history, nasal polyp history, and history of surgery and systemic corticosteroid use are described below in Tables 10-13.

Table 10. Baseline Nasal Polyposis Characteristics, EFC14146

Characteristic	Placebo N=133	Dupilumab 300 mg q2w N=143	Total N=276
Time since first diagnosis of NP (years)			
N	133	143	276
Mean (SD)	10.77 (8.57)	11.42 (9.69)	11.11 (9.16)
Min	0.2	0.3	0.2
Max	37.5	42.5	42.5
Age of onset of nasal polyposis (years)			
N	133	143	276
Mean (SD)	40.17 (13.07)	38.83 (13.90)	39.48 (13.50)
Min	15.0	11.0	11.0
Max	79.0	73.0	79.0

NP = nasal polyp; q2w = every 2 weeks; SD = standard deviation
Source: Reviewer generated table using CSR EFC14146 Tables 15-19 p. 76-90

Table 11. Surgical History, EFC14146

	Placebo	Dupilumab 300 mg q2w	Total
Number of patients with prior surgery	99 (74.4%)	99 (69.2%)	198 (71.7%)
Number of previous surgeries			
N	99 (74.4%)	99 (69.2%)	198 (71.7%)
Mean (SD)	2.13 (1.50)	2.34 (1.93)	2.24 (1.73)
Min	1	1	1
Max	8	11	11
1	45 (45.5%)	45 (45.5%)	90 (45.5%)
2	25 (25.3%)	21 (21.2%)	46 (23.2%)
≥3	29 (29.3%)	33 (33.3%)	62 (31.3%)

q2w = every 2 weeks; SD = standard deviation
Source: Reviewer generated table using CSR EFC14146 Tables 15-19 p. 76-90

Table 12. SCS Use History, EFC14146

Number of patients with SCS use during the past 2 years	**Placebo**	**Dupilumab 300 mg q2w**	**Total**
	87 (65.4%)	92 (64.3%)	179 (64.9%)
Number of courses of SCS during the past 2 years			
N	87 (65.4%)	92 (64.3%)	179 (64.9%)
Mean (SD)	1.45 (0.85)	1.43 (0.83)	1.44 (0.84)
Min	1.0	1.0	1.0
Max	5.0	6.0	6.0
1	63 (72.4%)	65 (70.7%)	128 (71.5%)
2	13 (14.9%)	18 (19.6%)	31 (17.3%)
3	8 (9.2%)	7 (7.6%)	15 (8.4%)
4	2 (2.3%)	1 (1.1%)	3 (1.7%)
≥5	1 (1.1%)	1 (1.1%)	2 (1.1%)

q2w = every 2 weeks; SCS = systemic corticosteroids; SD = standard deviation
Source: Reviewer generated table using CSR EFC14146 Tables 15-19 p. 76-90

Table 13. Other Medical History and Baseline Scores, EFC14146

Characteristic	Placebo	Dupilumab 300 mg q2w	Total
Epistaxis history			
N	133	143	276
Yes	9 (6.8%)	18 (12.6%)	27 (9.8%)
Ongoing	4 (3.0%)	10 (7.0%)	14 (5.1%)
Rhinosinusitis history (≥2 symptoms 8 weeks prior to screen)*	133 (100%)	141 (98.6%)	274 (99.3%)
Asthma history			
N	133	143	276
Yes	79 (59.4%)	82 (57.3%)	161 (58.3%)
No	54 (40.6%)	61 (42.7%)	115 (41.7%)
NSAID-ERD history**			
N	133	143	276
Yes	38 (28.6%)	46 (32.2%)	84 (30.4%)
No	95 (71.4%)	97 (67.8%)	192 (69.6%)
Allergic rhinitis history			
N	133	143	276
Yes	66 (49.6%)	79 (55.2%)	145 (52.5%)
Ongoing	57 (42.9%)	60 (42%)	117 (42.4%)
Allergic conjunctivitis history			
N	133	143	276
Yes	66 (49.6%)	79 (55.2%)	145 (52.5%)
Ongoing	57 (42.9%)	60 (42.0%)	117 (42.4%)
Baseline nasal polyposis score			
N	132	143	275
Mean (SD)	5.86 (1.31)	5.64 (1.23)	5.75 (1.28)
Min	2	2	2
Max	8	8	8
Baseline Lund-Mackay (LMK) score			
N	129	141	270
Mean (SD)	19.55 (4.26)	18.55 (4.55)	19.03 (4.44)
Min	6	4	4
Max	24	24	24
Baseline SNOT-22 score			
N	131	137	268
Mean (SD)	50.87 (20.22)	48 (20.16)	49.40 (20.20)
Min	10.0	10.0	10.0
Max	107.0	103.0	107.0

NP = nasal polyp; NSAID-ERD = nonsteroidal anti-inflammatory drug-exacerbated respiratory disease; q2w = every 2 weeks; SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test.
*Out of four symptoms: nasal congestion/obstruction, decreased/loss of smell, anterior rhinorrhea, posterior rhinorrhea
**Out of those with NSAID-ERD, 33/38 (86.8%) in placebo group were from medical history, the other 5/38 (13.2%) were from provocational history. In the dupilumab group, 39/46 (84.8%) were from medical history and the remaining 7/46 (15.2%) were from provocational history.
Source: Reviewer generated table using CSR EFC14146 Tables 15-19 p. 76-90

Patients experienced nasal polyps in adulthood and approximately 70% of patients overall underwent prior surgery. Approximately 30% of patients underwent 3 or more prior surgeries, and overall, approximately 65% of patients required systemic corticosteroids in the previous two years, supporting the fact that these patients had inadequately controlled nasal polyps. Patients demonstrated evidence of a history of general atopy (overall 58% had asthma, 53% had allergic rhinitis, and 53% had allergic conjunctivitis). Though approximately 30% of patients overall had a history of NSAID-ERD, the majority of these patients were diagnosed via medical

history, not provocational history. LMK scores demonstrate significant sinusitis burden on CT (overall mean score of 19) and minimum score of 4 or 6 support the fact that all patients had some evidence of sinusitis on imaging.

Other Baseline Characteristics (Important Concomitant Drugs)

Most patients were on twice daily dosing of mometasone furoate nasal spray (92.4%) with only 7.6% using daily dosing. There were less patients in the dupilumab group using rescue saline nasal lavage, systemic antibiotics, short oral corticosteroid course, or surgery for nasal polyps (20.3% versus 35.3% placebo). The most frequently used rescue medication was oral corticosteroids (10.5% dupilumab group versus 22.6% placebo group). Systemic antibiotics were also used as rescue more frequently in the placebo group compared with the dupilumab group (8.4% versus 12.0% placebo group).

Treatment Compliance and Rescue Medication Use

The Investigator or pharmacist kept accurate records of the quantities of IMP and noninvestigational medicinal product (NIMP; mometasone furoate nasal spray) dispensed, used, and unused by each patient. Compliance with both IMP and NIMP was reviewed with the patient at each visit. For IMP, compliance was assessed by inspection of the patient e-diary, and by counting the number of used and unused treatment kits and syringes. For NIMP, compliance with use of mandatory background therapy was verified based on mometasone furoate nasal spray use recorded on the patient electronic diary. Across all treatment groups, mean compliance of IMP was high (>99%). Only 1 patient (0.8%) in the placebo group had a compliance of <80%.

8.1.2.3. Primary Endpoint

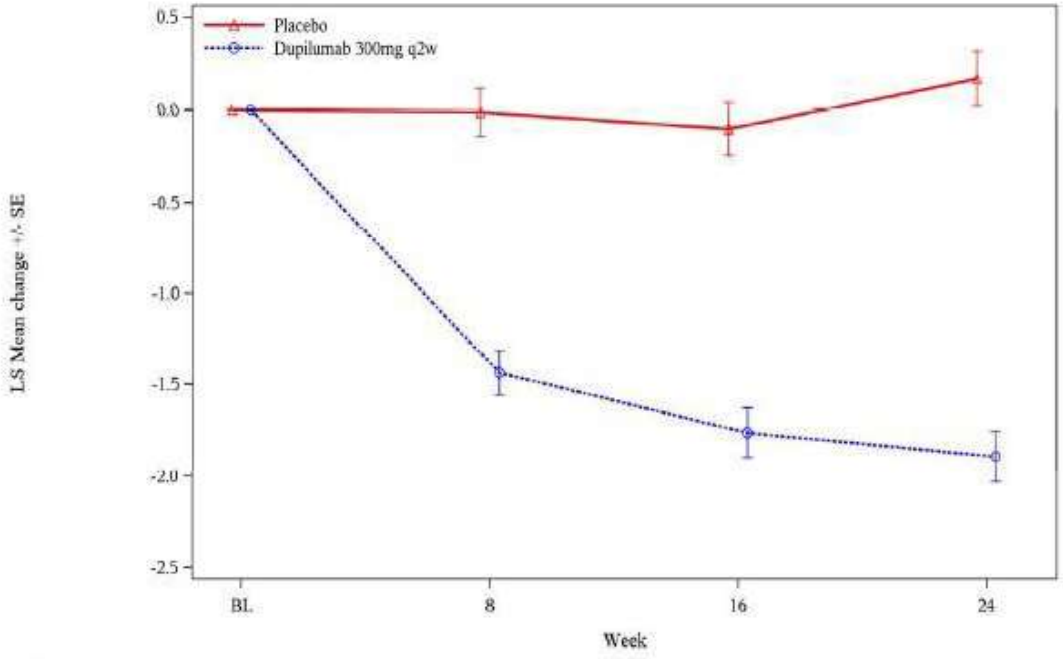
Results for the coprimary efficacy endpoints and multiplicity-controlled secondary endpoints, based on the primary analysis of the ITT Population are displayed in Table 14, and over the course of the 24 weeks in Figure 4 and Figure 5. Coprimary endpoints, NPS and NC, were highly statistically significant: NPS (LS Mean, -2.1; 95% CI: -2.4 to -1.7) and NC (LS Mean, -0.9, 95% CI: -1.1 to -0.7). The effect of dupilumab compared to placebo was seen at the initial postbaseline visit at Week 8.

Table 14. EFC14146: Summary of Primary and Secondary Endpoints in the Multiplicity Testing Procedure (ITT Population)

	Placebo (N=133)			Dupilumab 300mg q2w (N=143)				
	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Absolute Difference for Dupilumab vs. Placebo LS Mean (95% CI)	P Value
Primary endpoints								
Bilateral nasal polyps score (NPS) at Week 24	5.86 (1.31)	5.94 (1.44)	0.17 (0.15)	5.64 (1.23)	3.75 (1.98)	-1.89 (0.14)	-2.06 (-2.43, -1.69)	<.0001
Nasal congestion/obstruction (NC) at Week 24	2.45 (0.55)	1.90 (0.85)	-0.45 (0.07)	2.26 (0.57)	0.94 (0.75)	-1.34 (0.07)	-0.89 (-1.07, -0.71)	<.0001
Key secondary endpoints								
Lund Mackay score (LMK) at Week 24	19.55 (4.26)	18.97 (4.51)	-0.74 (0.37)	18.55 (4.55)	10.89 (4.82)	-8.18 (0.34)	-7.44 (-8.35, -6.53)	<.0001
Total symptom score (TSS) at Week 24	7.28 (1.40)	6.02 (2.02)	-1.17 (0.17)	6.82 (1.35)	3.16 (1.93)	-3.77 (0.16)	-2.61 (-3.04, -2.17)	<.0001
Smell test (UPSIT) at Week 24	14.44 (8.31)	14.56 (8.58)	0.70 (0.71)	14.68 (8.66)	25.39 (9.49)	11.26 (0.67)	10.56 (8.79, 12.34)	<.0001
Loss of smell at Week 24	2.73 (0.51)	2.50 (0.77)	-0.29 (0.07)	2.70 (0.57)	1.35 (0.99)	-1.41 (0.07)	-1.12 (-1.31, -0.93)	<.0001
SNOT-22 at Week 24	50.87 (20.22)	40.49 (23.06)	-9.31 (1.62)	48.00 (20.16)	18.58 (14.92)	-30.43 (1.54)	-21.12 (-25.17, -17.06)	<.0001

Source: EFC14146 Clinical Study Report, Table 24. Results for these parameters replicated by statistical reviewer. ANCOVA model with the baseline value of the corresponding coprimary endpoint, treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgery history, and regions as covariates.

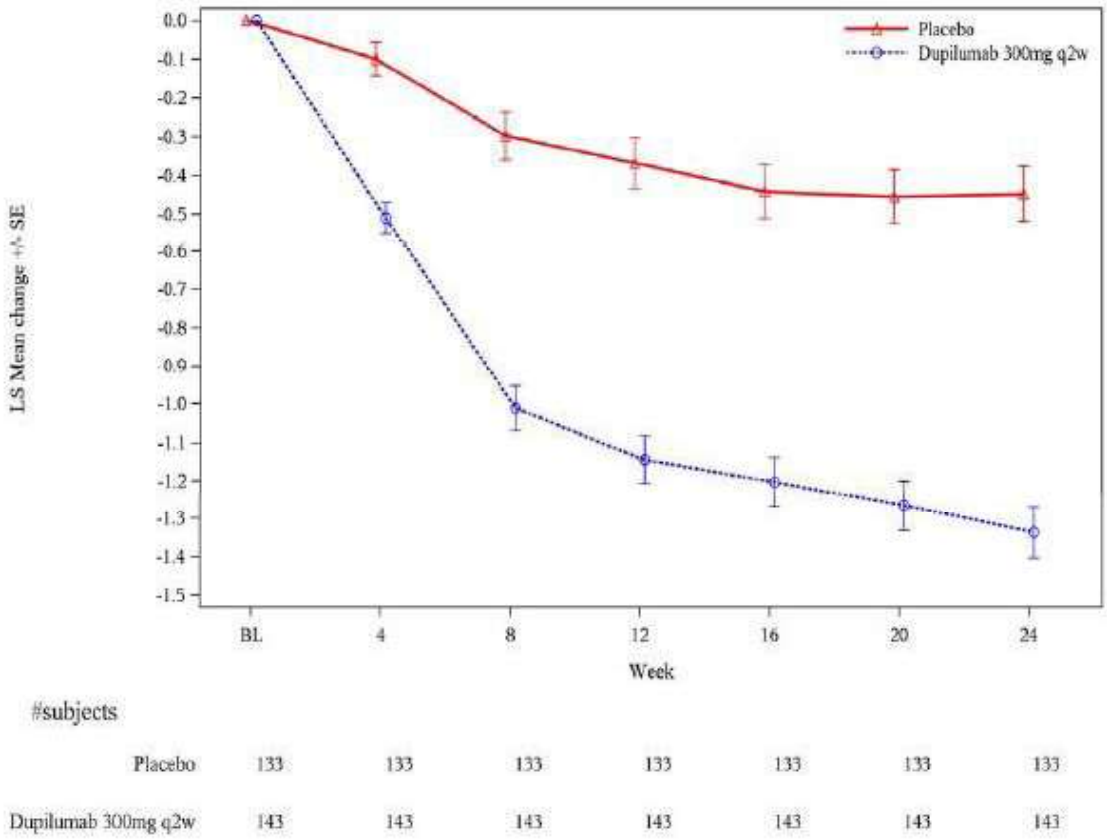
Figure 4. LS Mean Change From Baseline in Bilateral Nasal Polyps Score by Visit to Week 24 (ITT Population)



#subjects				
Placebo	132	132	132	132
Dupilumab 300mg q2w	143	143	143	143

Source: EFC14146 Clinical Study Report, Figure 3

Figure 5. LS Mean Change From Baseline in Nasal Congestion/Obstruction by Month up to Week 24 (ITT Population)



Source: EFC14146 Clinical Study Report, Figure 7

Additional Analyses of the Coprimary Endpoints

The Applicant also analyzed NPS in a responder analysis, evaluating the percent of patients with a change from baseline of ≥1 or ≥2 NPS points at Week 24. A higher percentage of patients had a ≥1 point improvement in NPS in the dupilumab group compared with placebo (65.0% versus 17.3%, odds ratio 9.5 (95% CI 5.3 to 17.0)). Similarly, the proportion of patients showing a ≥2 points improvement in NPS was greater in the dupilumab group compared with placebo (46.2% versus 4.5%, odds ratio 18.6, 95% CI 7.6 to 45.4)). A combined responder analysis relative to baseline (NPS ≥1 point and NC ≥0.5 points) was also conducted. The proportion of patients showing improvement in the combined score in the dupilumab group compared with placebo was 56.6% versus 13.5%, odds ratio 9.05, 95% CI 4.9 to 16.7.

Reviewer comment: The Applicant chose a ≥1 or ≥2 NPS change as a cut-off for their responder analysis; however it's unclear if a change of 1 or 2 on a scale of 8 would represent a clinically meaningful change.

Sensitivity analyses

For all sensitivity analyses (except for the as-observed analysis) for patients who underwent surgery for NP or received SCS for any reason, data collected postsurgery or post SCS were set to worst observation for that patient carried forward.

Results from several alternative analysis approaches for each of the two coprimary efficacy endpoints at 24 weeks had results similar to the primary analysis: MMRM, pattern mixture model with copy increment from placebo, tipping point, and as-observed (Table 15).

An additional as-observed analysis was conducted on the coprimary efficacy endpoints which included all data (including that collected after SCS for any reason and/or treatment discontinuation) but *excluded post NP surgery data*. The data were analyzed with the same ANCOVA model as the primary approach.

Table 15. Summary of Primary and Sensitivity Analyses for Coprimary Endpoints (ITT Population)

Nasal Polyp Score (NPS)	LS Mean Difference	95% CI	P-Value
ANCOVA (Primary)	-2.06	-2.43 to -1.69	<0.0001
MMRM	-2.13	-2.52 to -1.73	<0.0001
PMM	-2.01	-2.41 to -1.61	<0.0001
Tipping point	p-value remained at <0.001 at all shifts in dupilumab, from 0.4 to 4.0 and all shifts in placebo, from -0.4 to -4		
Applicant's as observed[2]	-1.98	-2.35 to -1.61	<0.0001
Stat reviewer's as-observed[3]	-2.01	-2.39 to -1.64	<0.0001
Nasal congestion/obstruction (NC)			
ANCOVA (primary)	-0.89	-1.07 to -0.71	<0.0001
MMRM	-0.88	-1.05 to -0.70	<0.0001
PMM	-0.84	-1.02 to -0.66	<0.0001
Tipping point	p-value remained at <0.001 at all shifts in dupilumab, from 0.4 to 4.0 and all shifts in placebo, from -0.4 to -4		
Applicant's as observed[2]	-0.82	-1.00 to -0.65	<0.0001
Stat reviewer's as-observed[3]	-0.82	-1.00 to -0.64	<0.0001

[1] Model for all analyses included treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgery history, and region
[2] Applicant's as-observed analysis did not use WOCF for steroid rescue but did use WOCF for surgical rescue
[3] Statistical reviewer's as-observed used as-observed (i.e., no WOCF), regardless of steroid or surgical rescue
ANCOVA = Analysis of covariance; CI = confidence interval; MMRM = mixed model for repeated measures; PMM = pattern mixture model with copy increment to placebo

8.1.2.4. Secondary and Other Relevant Endpoints

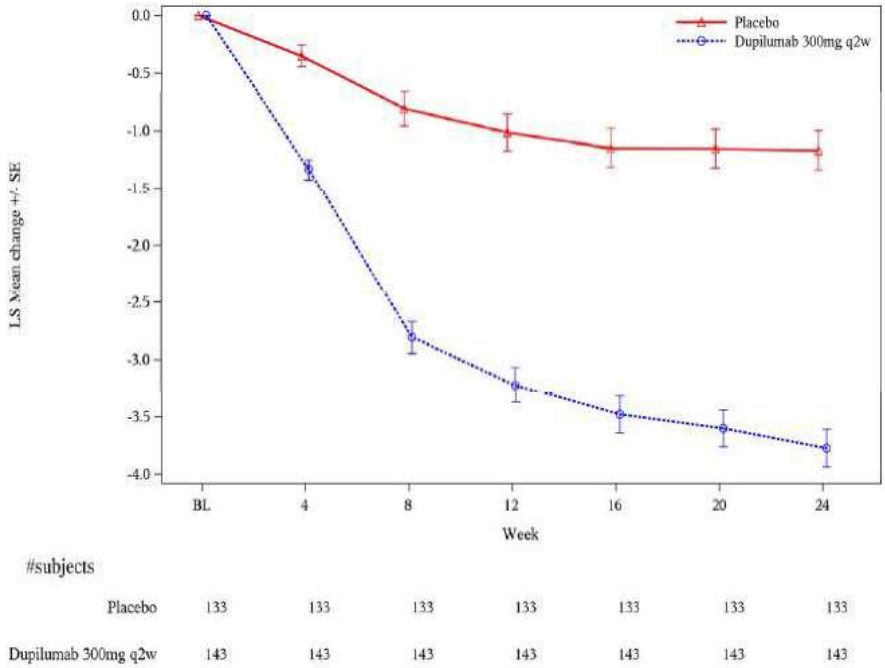
The secondary endpoints tested under a hierarchical multiplicity control (Table 14) began with CT scan/LMK (least squares (LS) mean, -7.4, 95% CI: -8.3 to -6.5); TSS (LS mean, -2.6, 95% CI: -3.0 to -2.2); UPSIT (LS mean, 10.6, 95% CI: 8.9 to 12.3); loss of smell (LS mean, -1.1, 95% CI: -1.3 to -0.9); and SNOT-22 (LS mean, -21.1, 95% CI: -25.2 to -17.1). The identical model and application of data assignment for rescue and missing data was applied to these secondary endpoints. Similar to the coprimary endpoints, each of these secondary endpoints was highly statistically significant.

Dupilumab demonstrated substantial improvements in mean sinus opacification CT scan score (LMK) from baseline to Week 24 on both the left and right sides compared with the placebo

group (LS mean difference versus placebo [95% CI] was -3.56 [-4.06 to -3.06] for the left side and -3.92 [-4.41 to -3.42] for the right side.

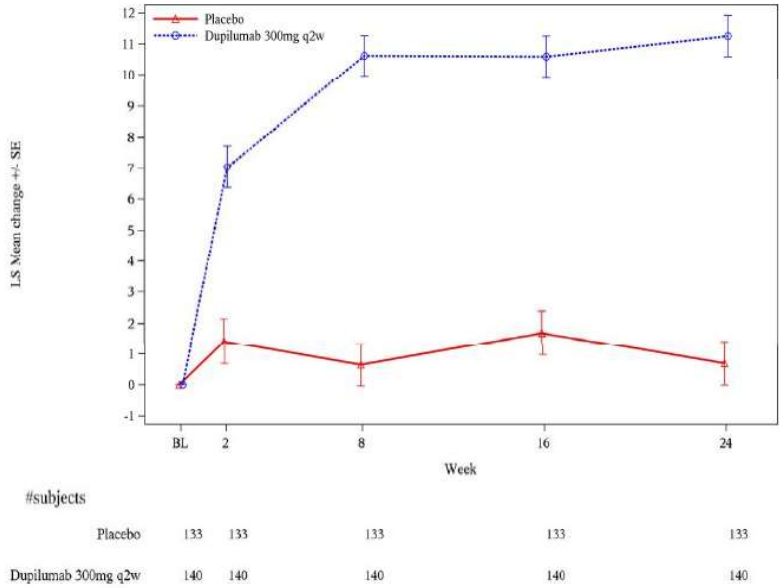
The behavior of dupilumab over time in comparison to placebo is similar across the secondary endpoints of TSS (Figure 6), UPSIT (Figure 7) and daily diary for loss of smell (Figure 8), and SNOT-22 (Figure 9). Significant improvement was observed for each of these measures.

Figure 6. LS Mean Change From Baseline in TSS by Month to Week 24 (ITT Population)



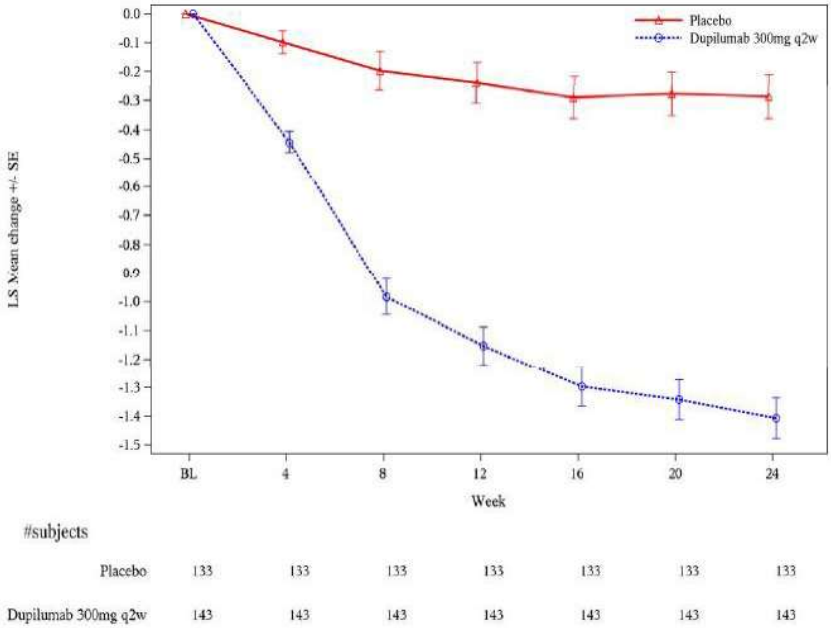
ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; TSS = total symptom score
Source: EFC14146 clinical study report, Figure 14

Figure 7. LS Mean Change From Baseline in UPSIT Score by Visit to Week 24 (ITT Population)



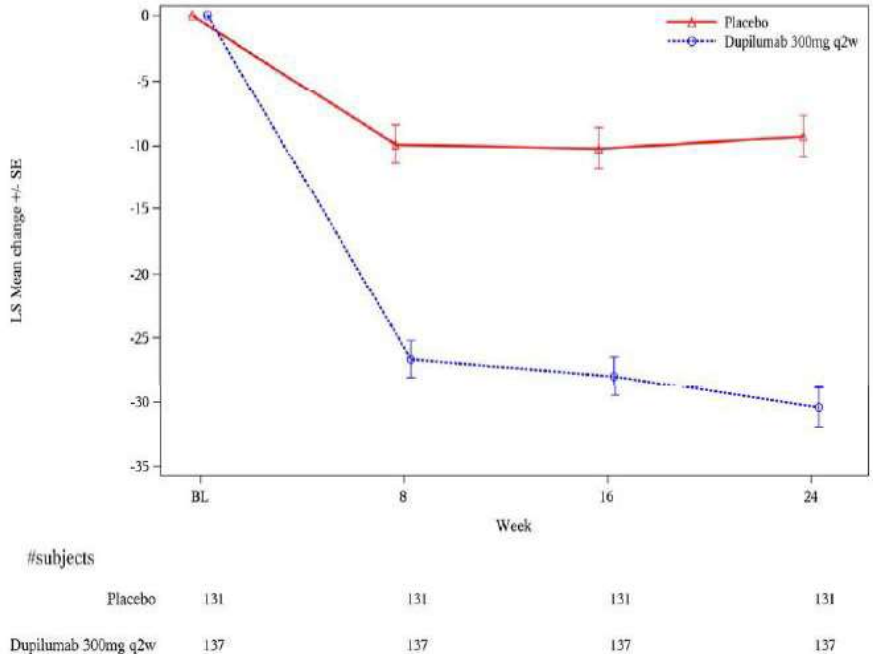
ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; UPSIT = University of Pennsylvania Smell identification test
Source: EFC14146 clinical study report, Figure 16

Figure 8. LS Mean Change From Baseline in Daily Self-Reported Loss of Smell by Month to Week 24 (ITT Population)



ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: EFC14146 clinical study report, Figure 18

Figure 9. LS Mean Change From Baseline in SNOT-22 Total Score by Visit to Week 24 (ITT Population)

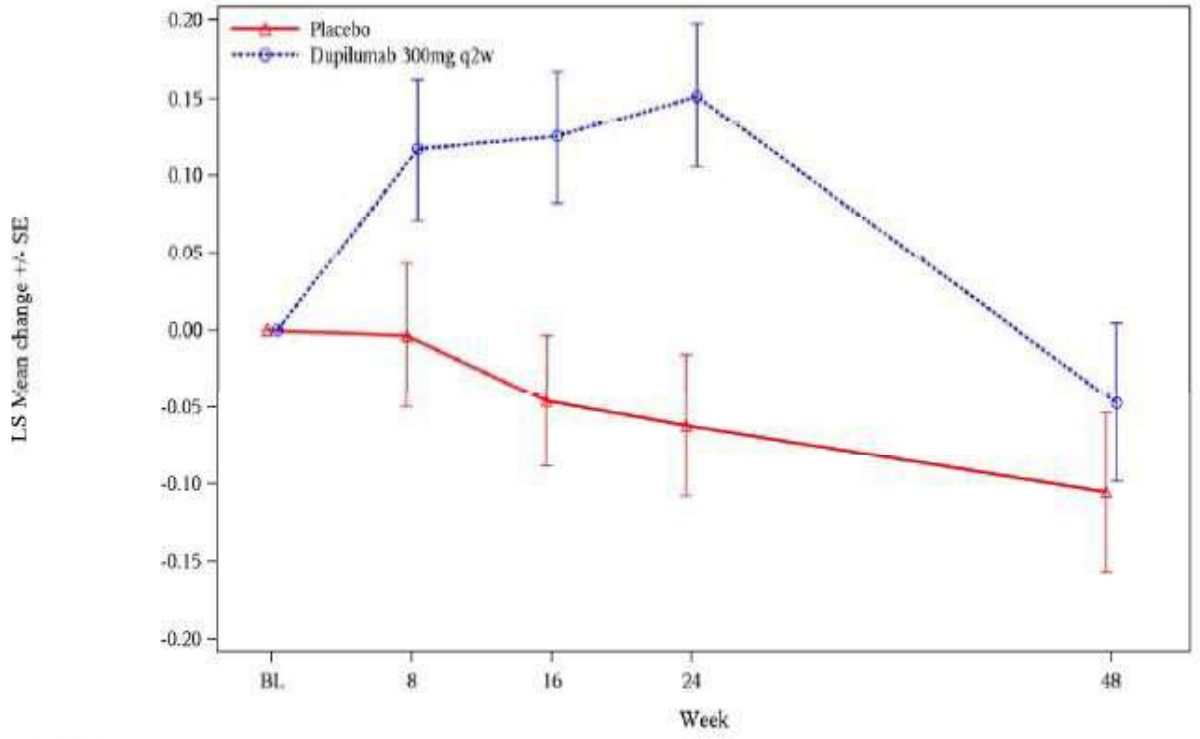


ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; SNOT-22 = Sino-Nasal Outcome Test
Source: EFC14146 clinical study report, Figure 20

Other multiplicity-adjusted endpoints include time to first rescue event (SCS or surgery) and FEV_1 for the subgroup of patients with asthma. These were prespecified as pooled analyses with study EFC14280 and are discussed in the integrated studies section of this review.

Results for the asthma subgroup are also reported here: There was a statistically significant improvement (p=0.0004) in change from baseline for FEV_1 in patients with a history of asthma (76 placebo patients and 80 dupilumab patients). The LS means change from baseline at Week 24 for placebo and dupilumab, respectively, were -0.06L and 0.15L, with an LS mean difference (CI) of 0.21 L (0.10, 0.33). Figure 10 shows FEV1 for this subgroup of patients over the course of 24 week treatment and also at Week 48, demonstrating a positive response to dupilimab that diminished after treatment was completed.

Figure 10. LS mean change from baseline in FEV_1 (L) by visit up to Week 48 for patients with asthma history (ITT Population)



#subjects					
Placebo	79	79	79	79	79
Dupilumab 300mg q2w	82	82	82	82	82

Source: EFC14146 CSR, Figure 31

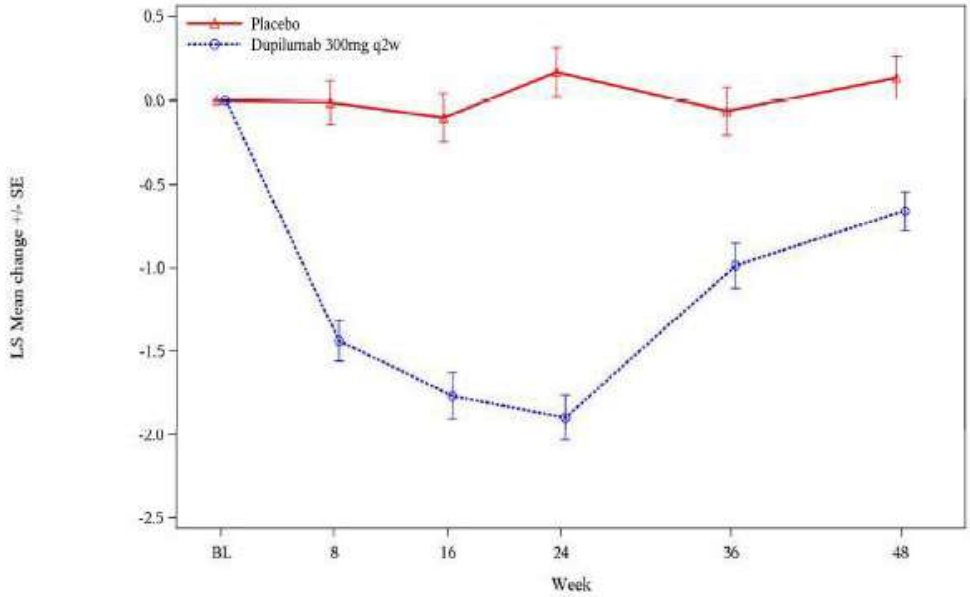
Dose/Dose Response

Only one dose was included in this study, therefore dose response was not assessed.

Persistence of Effect

Behavior of NPS and NC after treatment discontinuation at Week 24 until Week 48 was observed in these coprimary endpoints (Figure 11 and Figure 12) and TSS (Figure 13). Change from baseline in both NPS and NC diminished substantially after discontinuation of dupilumab, however values for active patients remained reduced in comparison to patients administered placebo.

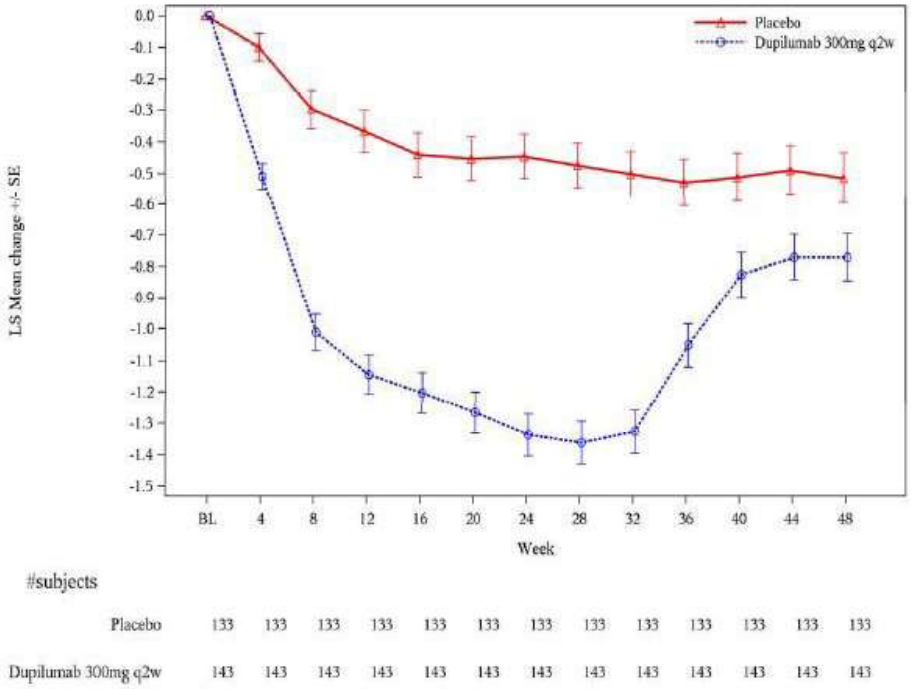
Figure 11. LS Mean Change From Baseline in NPS by Visit up to Week 48 (ITT Population)



#subjects						
Placebo	132	132	132	132	132	132
Dupilumab 300mg q2w	143	143	143	143	143	143

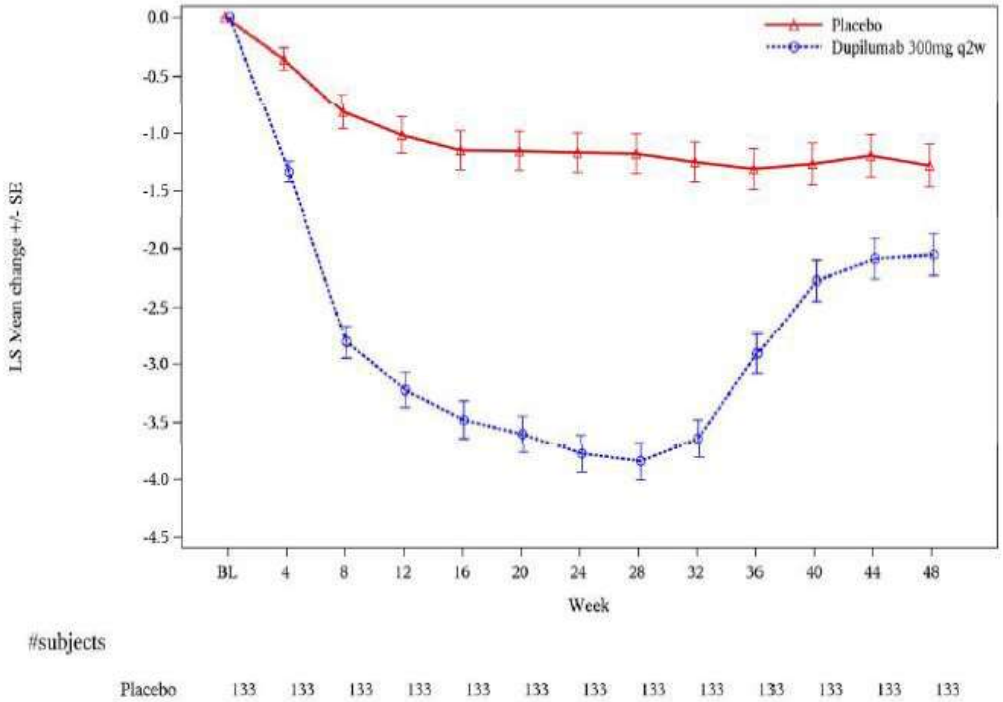
ITT = intention to treat; LS = least squares; NPS = Nasal Polyps Score; q2w = once every 2 weeks
Source: EFC14146 Clinical Study Report, Figure 4

Figure 12. LS Mean Change From Baseline in NC by Month to Week 48 (ITT Population)



ITT = intention to treat; LS = least squares; NC = nasal congestion/obstruction; q2w = once every 2 weeks
Source: EFC14146 Clinical Study Report, Figure 9

Figure 13. LS Mean Change From Baseline in TSS by Month to Week 48 (ITT Population)



ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; TSS = total symptom score
Source: EFC14146 Clinical Study Report, Figure 15

The hierarchical testing plan in the sponsor's Statistical Analysis Plan to control multiplicity stated that results from both trials would be pooled for the proportion of patients who required treatment with SCS or sino-nasal surgery during the treatment period. The same analysis was conducted for EFC14146 alone, and was significantly lower in the dupilumab group compared with the placebo group across the 24-week treatment period (Kaplan-Meier estimate at Week 24 was 7.2% versus 23.3%, hazard ratio and 95% CI of 0.268 [0.131, 0.549]). The individual endpoint of systemic corticosteroid use was also significantly lower in the dupilumab group (2.1%) compared to placebo (15%), hazard ratio and 95% CI of 0.119 (0.035, 0.403).

8.1.2.5. Additional Analyses

A subgroup analysis of the coprimary endpoints using the primary analysis method, ANCOVA, was conducted on patients with baseline eosinophil levels of <150, ≥150 and ≥300 cells/mL (Table 16). We hypothesized that patients with higher baseline eosinophil counts may have a higher mean change from baseline when treated with dupilumab compared to placebo. The mean changes for these two subgroups was slightly higher than the overall population for both coprimary endpoints. Those patients with baseline eosinophil counts < 150 cells/mL had less of a response than the overall population and the other subgroups; however, the point estimate showed a decreased trend and the number of patients with serum eosinophils < 150 cells/mL were too small to make any definitive conclusions.

Table 16. Subgroup Analysis of Coprimary Endpoints, NPS and NC at Week 24, by Baseline Eosinophil Counts (ITT Population) EFC14146

Subgroup	Placebo N, LS Mean (SE)	Dupilumab N, LS Mean (SE)	LS Mean Difference vs. Placebo (95% CI)
NPS at Week 24			
All patients	133, 0.17 (0.15)	143, -1.89 (0.14)	-2.06 (-2.43, -1.69)
Baseline eosinophils <150 cells/mL	16, -0.03 (0.45)	19, -0.63 (0.42)	-0.60 (-1.74, 0.54)
Baseline eosinophils >150 cells/mL	112, 0.19 (0.15)	118, -2.10 (0.14)	-2.29 (-2.68, -1.91)
Baseline eosinophils >300 cells/mL	73, 0.43 (0.21)	83, -2.28 (0.17)	-2.70 (-3.19, -2.22)
NC at Week 24			
All patients	133, -0.45 (0.07)	143, -1.34 (0.07)	-0.89 (-1.07, -0.71)
Baseline eosinophils <150 cells/mL	15, -0.44 (0.82)	19, -0.82 (0.76)	-0.35 (-0.88, 0.18)
Baseline eosinophils >150 cells/mL	115, -0.43 (0.07)	122, -1.42 (0.07)	-0.99 (-1.18, -0.80)
Baseline eosinophils >300 cells/mL	76, -0.41 (0.10)	85, -1.54 (0.08)	-1.13 (-1.36,-0.90)

CI = confidence interval; LS= least squares; NC = nasal congestion/obstruction; NPS = Nasal Polyps Score; SE = standard error
Source: Statistical Reviewer analysis

To support an indication of rhinosinusitis with nasal polyps, the statistical reviewers analyzed the individual components of facial pain (Table 17), nasal blockage (Table 18), thick nasal discharge (Table 19), runny nose (Table 20) and sneezing components (Table 21) from SNOT-22. The identical analysis, handling of missing data and rescue, and population from that used by the Applicant for the primary analysis was used in these analyses.

95% confidence intervals for the difference between dupilumab and placebo for each of these endpoints did not include zero, indicating a similar pattern with the above prespecified efficacy endpoints of statistically significant difference of dupilumab relative to placebo.

Table 17. Change From Baseline in Facial Pain at Week 24 (ITT Population)

Facial Pain (from SNOT-22)	Placebo (N=133)	Dupilumab 300 mg q2w (N=143)
Baseline		
Number	131	137
Mean (SD)	1.34 (1.51)	1.34 (1.37)
Median	1.00	1.00
Q1:Q3	0.00:2.00	0.00:2.00
Min:max	0.0:5.0	0.0:5.0
Week 24		
Number	128	135
Mean (SD)	1.12 (1.47)	0.39 (0.76)
Median	0.00	0.00
Q1:Q3	0.00:2.00	0.00:1.00
Min:max	0.0:5.0	0.0:4.0
Change from baseline		
Number	128	135
Mean (SD)	-0.17 (1.36)	-0.93 (1.22)
Median	0.00	0.00
Q1:Q3	-1.00:0.00	-2.00:0.00
Min:max	-5.0:5.0	-5.0:1.0
LS mean (SE)	-0.17 (0.10)	-0.93 (0.09)
LS mean diff vs. placebo (95% CI) [a]	-0.76 (-1.00, -0.52)	

CI = confidence interval; ITT = intention to treat; LS = least squares; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis

Table 18. Change From Baseline in Nasal Blockage at Week 24 (ITT Population)

Nasal Blockage (SNOT-22)	Placebo (N=133)	Dupilumab 300 mg q2w (N=143)
Baseline		
Number	131	137
Mean (SD)	3.82 (1.00)	3.58 (1.02)
Median	4.00	3.00
Q1:Q3	3.00:5.00	3.00:4.00
Min:max	0.0:5.0	0.0:5.0
Week 24		
Number	128	135
Mean (SD)	3.01 (1.39)	1.25 (1.17)
Median	3.00	1.00
Q1:Q3	2.00:4.00	0.00:2.00
Min:max	0.0:5.0	0.0:5.0
Change from baseline		
Number	128	135
Mean (SD)	-0.81 (1.20)	-2.31 (1.37)
Median	-1.00	-2.00
Q1:Q3	-1.50:0.00	-3.00:-2.00
Min:max	-4.0:2.0	-5.0:1.0
LS mean (SE) [a]	-0.68 (0.11)	-2.35 (0.11)
LS mean diff vs. placebo (95% CI) [a]	-1.67 (-1.95, -1.38)	

CI = confidence interval; ITT = intention to treat; LS = least squares; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis

Table 19. Change From Baseline in Thick Nasal Discharge at Week 24 (ITT Population)

Thick Nasal Discharge (SNOT-22)	Placebo (N=133)	Dupilumab 300 mg q2w (N=143)
Baseline		
Number	131	137
Mean (SD)	3.18 (1.34)	2.96 (1.26)
Median	3.00	3.00
Q1:Q3	2.00:4.00	2.00:4.00
Min:max	0.0:5.0	0.0:5.0
Week 24		
Number	128	135
Mean (SD)	2.52 (1.52)	0.93 (1.08)
Median	3.00	1.00
Q1:Q3	1.00:4.00	0.00:1.00
Min:max	0.0:5.0	0.0:5.0
Change from baseline		
Number	128	135
Mean (SD)	-0.63 (1.25)	-2.01 (1.46)
Median	-1.00	-2.00
Q1:Q3	-1.00:0.00	-3.00:-1.00
Min:max	-4.0:2.0	-5.0:1.0
LS mean (SE) [a]	-0.58 (0.11)	-2.10 (0.11)
LS mean diff vs. placebo (95% CI) [a]	-1.52 (-1.80, -1.23)	

CI = confidence interval; ITT = intention to treat; LS = least squares; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis

Table 20. Change From Baseline in Runny Nose at Week 24 (ITT Population)

Runny Nose (SNOT-22)	Placebo (N=133)	Dupilumab 300 mg q2w (N=143)
Baseline		
Number	131	137
Mean (SD)	3.22 (1.15)	2.85 (1.10)
Median	3.00	3.00
Q1:Q3	3.00:4.00	2.00:4.00
Min:max	0.0:5.0	0.0:5.0
Week 24		
Number	128	135
Mean (SD)	2.45 (1.43)	1.10 (1.03)
Median	2.00	1.00
Q1:Q3	1.00:3.00	0.00:2.00
Min:max	0.0:5.0	0.0:5.0
Change from baseline		
Number	128	135
Mean (SD)	-0.77 (1.25)	-1.75 (1.32)
Median	-1.00	-2.00
Q1:Q3	-2.00:0.00	-3.00:-1.00
Min:max	-4.0:3.0	-5.0:1.0
LS mean (SE) [a]	-0.63 (0.11)	-1.84 (0.11)
LS mean diff vs. placebo (95% CI) [a]	-1.21 (-1.49, -0.93)	

CI = confidence interval; ITT = intention to treat; LS = least squares; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis

Table 21. Change From Baseline in Sneezing at Week 24 (ITT Population)

Sneezing (SNOT-22)	Placebo (N=133)	Dupilumab 300 mg q2w (N=143)
Baseline		
Number	131	137
Mean (SD)	2.21 (1.32)	1.98 (1.29)
Median	2.00	2.00
Q1:Q3	1.00:3.00	1.00:3.00
Min:max	0.0:5.0	0.0:5.0
Week 24		
Number	128	135
Mean (SD)	1.60 (1.31)	0.88 (0.98)
Median	1.00	1.00
Q1:Q3	0.00:3.00	0.00:1.00
Min:max	0.0:5.0	0.0:4.0
Change from baseline		
Number	128	135
Mean (SD)	-0.60 (1.38)	-1.10 (1.35)
Median	-1.00	-1.00
Q1:Q3	-1.00:0.00	-2.00:0.00
Min:max	-5.0:4.0	-5.0:2.0
LS mean (SE) [a]	-0.49 (0.10)	-1.16 (0.10)
LS mean diff vs. placebo (95% CI) [a]	-0.67 (-0.93, -0.41)	

CI = confidence interval; ITT = intention to treat; LS = least squares; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis

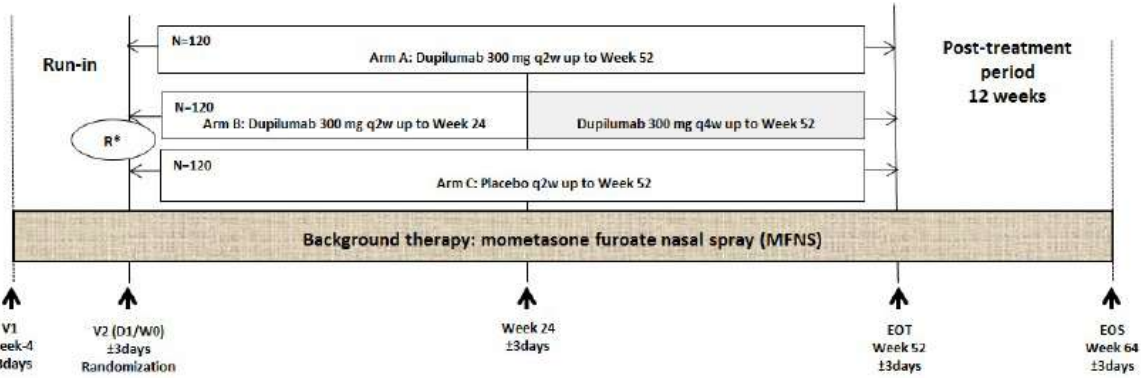
8.1.3. EFC14280

8.1.3.1. Trial Design

EFC14280 is a multinational, multicenter, randomized, double-blind, phase 3 placebo-controlled parallel arm study of dupilumab in patients with bilateral nasal polyposis on background therapy with intranasal corticosteroids. The trial consisted of three periods: run-in, treatment, and post-treatment. The run-in period was identical to EFC14146. In addition to noninvestigational medicinal product (NIMP)s (background medication and rescue medication), the same concomitant medications were permitted as in EFC14146. The randomization period was 52 weeks ±3 days, where patients were randomized 1:1:1 to: (1) dupilumab 300 mg subcutaneous every two weeks, (2) dupilumab 300 mg subcutaneous every 2 weeks until Week 24 then 300 mg subcutaneous every 4 weeks until Week 52, or (3) placebo. During the study treatment period and off follow-up, the Investigator could consider rescue treatment with nasal lavage (saline and/or systemic antibiotics up to 2 weeks), oral corticosteroids (prednisone or prednisolone up to 2 weeks), surgery for polyps. Based on previous experience, 8 weeks of IMP was recommended prior to surgery to allow treatment effect. Patients receiving any rescue other than surgery were to continue IMP unless the Investigator decided otherwise. For patients undergoing surgery for nasal polyps, IMP was to be permanently discontinued. Before starting oral corticosteroids, patients should undergo endoscopy and PRO assessments.

The post-treatment period was 12 weeks ±3 days where patients were followed to evaluate pharmacokinetics, immunogenicity, and safety after discontinuation of investigational medical product. Randomization was stratified by the presence of comorbid asthma, prior nasal polyp surgery, and country (Figure 14).

Figure 14. EFC14280 Study Design



EOS = end of study; EOT = end of treatment; q2w = once every 2 weeks; V1 = visit 1
Source: Clinical study report EFC14280, Figure 1

A schedule of assessments is provided in Table 22.

Table 22. EFC14280 Schedule of Assessments

	Run-in	Randomized treatment period												EOT	EOS
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**		**9**		**10**	**11**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12, 14**	**16**	**18,20, 22**	**24**	**26,28, 30,32, 34,36, 38**	**40**	**42,44, 46,48, 50**	**52**	**64**
Day +/-3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**		**D281**		**D365**	**D449**
Informed consents	X														
Inclusion and exclusion criteria	X	X													
Patient demography	X														
Medical/surgical/medication History	X														
Physical examination	X									X				X	X
Spirometry	X			X				X		X		X		X	
Chest X-ray	X														
Randomization		X													
Treatment:															
IMP: Dupilumab/placebo injection		X	X	X	X	X	X	X	X	X	X	X	X		
Review IMP and/or NIMP compliance		I----------	----------	----------	----------	----------	----------	----------	X----------	----------	----------	----------	----------	I	
Call IVRS (IWRS) at scheduled and unscheduled visits as needed	X	I----------	----------	----------	----------	----------	----------	----------	X----------	----------	----------	----------	I	X	X
Dispense or download electronic diary for symptoms					I----------	----------	----------	----------	----------	----------	----------	X----------	----------	----------	----------
NIMP	I----------	----------	----------	----------	----------	----------	----------	----------	X----------	----------	----------	----------	----------	----------	I
Record concomitant medication	I----------	----------	----------	----------	----------	----------	----------	----------	X----------	----------	----------	----------	----------	----------	I
Record planned surgery for NP, SCS use, and other rescue medication use	I----------	----------	----------	----------	----------	----------	----------	----------	X----------	----------	----------	----------	----------	----------	I
Nasal endoscopy	X	X		X		X		X		X		X		X	X

	Run-in						Randomized treatment period							EOT	EOS
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**		**9**		**10**	**11**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12, 14**	**16**	**18,20, 22**	**24**	**26,28, 30,32, 34,36, 38**	**40**	**42,44, 46,48, 50**	**52**	**64**
Day +/-3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**		**D281**		**D365**	**D449**
CT scan	X									X				X	
Smell test (UPSIT)		X	X	X				X		X				X	
NPIF	X	I----------daily AM up to Week 24----------I									X (W28, W32, W 36)	X	X (W44, W48)	X	
Patient reported outcomes/HRQoL	I----------X ---------- I														
22-item sino-nasal outcome test (SNOT- 22)		X		X		X		X		X		X		X	
Visual analogue scale (VAS) for rhinosinusitis and symptom severity (0-3) for reduced sense of taste		X	X	X		X		X		X		X		X	X
Quality of life (EQ-5D)		X						X		X		X		X	
ACQ-6 in patients with asthma		X		X				X		X		X		X	
Health care resource utilisation		X						X		X		X		X	
Safety															
AE /SAE recording (if any)		I----------X----------I													
Vital signs	X	X		X						X		X		X	X
ECG (local reading)		X												X	
Laboratory Testing															
Clinical laboratory testing	X	X						X		X		X		X	X
Hepatitis B viral load		X						X		X				X	
Pregnancy test (for WOCBP)	X	X		X		X	X (W12)		X (W20)		X (W28, W32, W 36)	X	W48)	X	X
Sampling for serum dupilumab concentration		X	X	X				X		X		X		X	X
Anti-drug antibody sampling		X				X		X		X				X	X

	Run-in						Randomized treatment period							EOT	EOS
VISIT	**1**	**2**	**3**	**4**	**5**	**6**		**7**		**8**		**9**		**10**	**11**
Week	**W-4**	**W0**	**2**	**4**	**6**	**8**	**10,12, 14**	**16**	**18,20, 22**	**24**	**26,28, 30,32, 34,36, 38**	**40**	**42,44, 46,48, 50**	**52**	**64**
Day +/-3 days	**D-28**	**D1**	**D15**	**D29**	**D43**	**D57**		**D113**		**D169**		**D281**		**D365**	**D449**
Blood biomarkers (TARC, eotaxin-3, periostin, serum total IgE)		X								X				X	
Spot urine for biomarker sampling (LTE4 and PGDM and creatinine)	X	X						X		X				X	
Nasal secretion sampling		X						X		X					
Nasal mucosa brushing for RNA and cytology		X								X					
Stored DNA sampling		X													
Stored serum		X								X				X	
Stored whole blood RNA sampling		X													

Abbreviations: ACQ-6 = asthma control questionnaire-6; ADA = antidrug antibodies; AE = adverse event; CT = computerized tomography; D = day; EC = ethics committee; ECG = electrocardiogram; e-CRF = electronic case report form; EOS = end of study; EOT = end of treatment; FEF 25-75 = forced expiratory flow to 25% to 75% of pulmonary volume; FEV1 = forced expiratory volume in one second; FVC = forced volume capacity; FU = follow up; HRQoL = health-related quality of life; IgE = immunoglobulin E; IMP = investigational medicinal product; IRB = institutional review board; IVRS = interactive voice response system; IWRS = interactive web response system; LTE4 = leukotriene E4; MFNS = mometasone furoate nasal spray; MRI = magnetic resonance imaging; NC = nasal congestion; NSAID-ERD = NSAID exacerbated respiratory disease; NIMP = noninvestigational medicinal product; SCS = systemic corticosteroid use; NP = nasal polyposis; NPIF = nasal peak inspiratory flow; PGDM = tetranor metabolite of prostaglandin D2; PK = pharmacokinetic; SAE = serious adverse event; SNOT-22 = sino-nasal outcome test; UPSIT = University of Pennsylvania smell identification test; VAS = visual analog scale; W = week; WBC = white blood cell; WOCBP = women of child bearing potential

8.1.3.2 Population

Inclusion and Exclusion Criteria

The study had the same inclusion and exclusion criteria as EFC14146. Biomarkers were also the same.

8.1.3.3. Study Endpoints

The study had the same coprimary and secondary endpoints as EFC14146.

The coprimary and this group of secondary endpoints were analyzed under multiplicity control with a gatekeeping strategy, identical to study EFC14146 for Week 24 endpoints, plus NPS, NC and SNOT-22 at Week 52 for the dupilumab q2w versus placebo comparison (Table 23).

Table 23. EFC14280 Hierarchical Testing Order for Coprimary and Selected Secondary Endpoints

	Endpoints	Comparison
Coprimary	Change from baseline in bilateral NPS at Week 24	Dupilumab 300 mg q2w (Arm A+B) vs placebo
	Change from baseline in NC at Week 24	
Key secondary[a]	Change from baseline in LMK score at Week 24[b]	Dupilumab 300 mg q2w (Arm A+B) vs placebo
	Change from baseline in TSS at Week 24	
	Change from baseline in smell test (UPSIT) at Week 24	
	Change from baseline in loss of smell daily symptoms at Week 24	
	Change from baseline in SNOT-22 at Week 24	
	Change from baseline in NPS at Week 52	Dupilumab 300 mg q2w (Arm A) vs placebo
	Change from baseline in NC at Week 52	
	Change from baseline in SNOT-22 at Week 52	

a In addition to the key secondary endpoints listed, 2 pre-specified analyses based on pooled data from Study EFC14280 and EFC14146 were included in the hierarchy: Proportion of patients requiring rescue with SCS or NP surgery and FEV_1 at Week 24. The results of the pooled analyses are provided in 2.7.3 Summary of Clinical Efficacy.

b Change from baseline in LMK score is a coprimary endpoint in Japan.

LMK = Lund-Mackay; NC = nasal congestion/obstruction; NPS = Nasal Polyps Score; q2w = once every 2 weeks; SNOT-22 = Sino-Nasal Outcome Test; TSS = total symptom score; UPSIT = University of Pennsylvania smell identification test
Source: CSR EFC14280, Table 5

8.1.3.4. Efficacy Parameters

This study had the same efficacy parameters as EFC14146.

8.1.3.5. Statistical Analysis Plan

The SAP for this study was issued on August 14, 2017. The Applicant states the SAP was approved prior to database lock and unblinding of the study.

The sample size was chosen to enable an adequate characterization of the difference in efficacy between dupilumab 300 mg q2w and placebo with regard to the two coprimary endpoints, changes from baseline in NC and NPS at Week 24. With a sample size of 240 patients for the

active group and 120 patients for placebo, the combined power of the two coprimary efficacy endpoints was affirmed by the Applicant to be at least 98% for dupilumab 300 mg q2w group with alpha =0.05 assuming no negative correlation between the two endpoints.

Four analysis populations were defined by the Applicant, defined in a similar manner to EFC14146. Analysis methods for primary (including sensitivity analyses), secondary and subgroup analyses were also the same as those used in EFC14146. In EFC14280, the analyses were also conducted on change from baseline at Week 52

8.1.3.6. Protocol Amendments

One global amendment was made to the study protocol for the purpose of clarifying and correcting the protocol.

- Assessment of rhinorrhea (anterior/posterior) added following early treatment discontinuation to support total symptom score analysis.
- Permitted 1 retest of dynamic laboratory tests during screening at discretion of Investigator
- Clarified analysis of all patients who used systemic corticosteroids was to include all systemic corticosteroids (not just oral corticosteroid)
- Elevated European quality of life 5D scale (EQ-5D) from exploratory endpoint to secondary efficacy endpoint
- Clarified CT scan was mandatory unless not approved by local ethics committee or institutional review board
- Intranasal decongestants added to list of prohibited medications except as needed for nasal endoscopy procedure
- Permitted study procedures to be performed over 3 days, as long as within visit window
- Deleted requirement for male birth control

8.1.4. Study Results

Compliance With Good Clinical Practices

The study was performed in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Conference on Harmonization guidelines for Good Clinical Practice, all applicable laws, rules, and regulations.

Financial Disclosure

See Appendix 15.1.

8.1.4.1. Disposition

As shown in Figure 15, of the 448 patients randomized (447 patients treated), 418 (93%) completed the first 24 weeks of study treatment. Study treatment discontinuation prior to Week 24 occurred at a lower rate in the dupilumab group compared with the placebo group (10 (3.4%) patients in the dupilumab arm and 19 (12.4%) patients in the placebo arm). Prior to

Week 24, the primary reasons for discontinuation were AEs (10 [6.5%] in the placebo arm, 4 [1.4%] in the dupilumab arm), other reasons (5 [3.3%] in the placebo arm, 5 [1.7%] in the dupilumab arm). The remainder of patients who discontinued study treatment did so for lack of efficacy (three [2.0%] in the placebo arm, one [0.3%] in the dupilumab arm) and poor compliance to protocol (one placebo patient). Patients who discontinued treatment were encouraged to return to the clinic and participate in follow-up assessments. A total of 439 (98.2%), 96.7% placebo patients and 98.6% dupilumab patients, completed the first 24-week study period. Number and percent of patients for each of the prespecified populations is shown in Table 24.

Table 24. Analysis populations for study EFC14280

		Dupilumab		
	Placebo (N=153)	300mg q2w-q4w (N=145)	300mg q2w (N=150)	All (N=448)
Randomized population	153 (100%)	145 (100%)	150 (100%)	448 (100%)
Efficacy population				
Intent-to-Treat (ITT)	153 (100%)	145 (100%)	150 (100%)	448 (100%)
Safety population	150	148	149	447
PK population	0	146	149	295
ADA population	149	148	148	445

Note: For the safety, PK and ADA population, patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment

Source: Table 13, EFC14280 CSR

After Week 24 but prior to Week 52 an additional 20 patients discontinued study treatment (6 [4.0%] and 2 [1.4%] patients in the dupilumab 300 mg q2w and 300 mg q2w-q4w groups, respectively, and 12 [7.8%] patients in the placebo group).

In all, 398 (89%) patients completed 52 weeks of treatment with the study medication, and 428 (96%) patients completed the 52-week study period with or without study medication. Over the 52-week study period, treatment discontinuation rates were lower in the dupilumab groups compared with the placebo group (13 [9%] and 5 [3%] patients in the dupilumab 300 mg q2w and 300 mg q2w-q4w groups, respectively, and 31 [20%] patients in the placebo group).

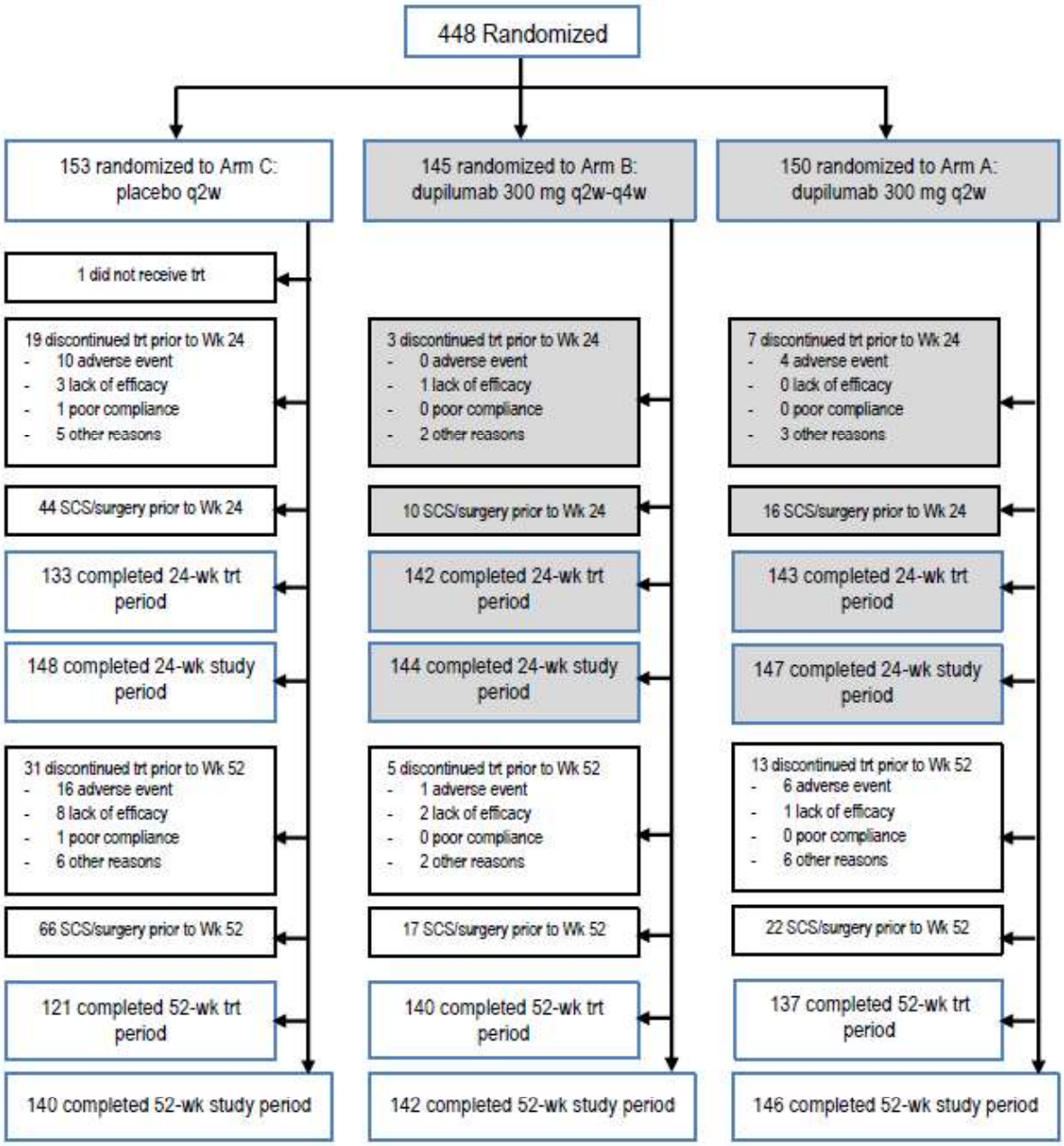
Prior to Week 52, primary reasons for discontinuation were:

- AEs (6 [4%] and 1 [1%] patients in the dupilumab 300 mg q2w and 300 mg q2w-q4w groups, respectively, and 16 [10%] patients in the placebo group)
- Lack of efficacy (1 [1%] and 2 [1%] patients in the dupilumab 300 mg q2w and 300 mg q2w-q4w groups, respectively, and 8 [3%] patients in the placebo group
- Other reasons (6 [4%] and 5 [1%] patients in the dupilumab 300 mg q2w and 300 mg q2w-q4w groups, respectively, and 6 [4%] patients in the placebo group

Reviewer comment: Though treatment discontinuation rates were lower in the dupilumab groups, increased discontinuation in the placebo group was likely driven by surgery as subjects

would discontinue treatment if they underwent surgery. Amongst treatment groups, a similar number of subjects completed the study.

Figure 15. Patient Disposition up to Week 52, Randomized Population, EFC14280



q2w = once every 2 weeks; SCS = systemic corticosteroids; trt = treatment
Source: Response to Agency Request for Information, May 16, 2019, a revision from EFC14280 CSR, Fig 2

Protocol Violations/Deviations

Overall, 39% of dupilumab 300 mg q2w patients, 41% of dupilumab 300 mg q2w-q4w patients and 50% of placebo patients had a deviation. Deviations in schedule of assessments (study visit,

phone call outside of visit window) occurred in 4% and 9% of dupilumab 300 mg q2w and 300 mg q2w-q4w patients, respectively and 7% of placebo patients. Deviations in investigational medical product management occurred (missed dose, drug not administered per protocol) in 18% and 15% of dupilumab 300 mg q2w and 300 mg q2w-q4w patients, respectively and 22% of placebo patients. Critical or major deviations occurred in 3% and 4% of dupilumab 300 mg q2w and 300 mg q2w-q4w subjects, respectively, and 6% of placebo patients. The most common major deviation that occurred was allowance of a patient to stay in the study after Week 24 with a missing nasal congestion score between Weeks 21 and 24 (1% in each of the dupilumab arms and 3% in the placebo arm).

Reviewer comment: As critical or major deviations occurred in ≤ 6% of subjects and themost common major deviation kept patients in the study, these protocol deviations were unlikely to affect the outcome of the study.

8.1.4.2. Demographics

Demographics were similar for placebo and active groups. Overall, there were 62% male and 38% female participants in this study (Table 25).

The mean age was 51.9 years, with minimum age 18 and maximum age 83 years of age. Most (82%) of participants were under 65 years of age. Most participants in this study were white (83%), with 12% Asians, 3% American Indian or Alaska Native, 2% Blacks, <1% other. Twenty-nine percent had Hispanic/Latino ethnicity. There were 49% of participants from Western Countries, 31% from Latin America, 11% from Asia, and 10% from Eastern Europe. The Applicant also characterized region by North America (United States and Canada), European Union and rest of world, with 20%, 19%, and 61%, respectively from those regions.

Table 25. Demographic Characteristics of the Primary Efficacy Analysis EFC14280

Demographic Parameters n (%)	Placebo Group (N=153)	Dupilumab 300 mg q2w-q4w Group (N=145)	Dupilumab 300 mg q2w Group (N=150)	Total (N=448)
Sex				
Male	95 (62.1%)	87 (60.0%)	97 (64.7%)	279 (62.3%)
Female	58 (37.9%)	58 (40.0%)	53 (35.3%)	169 (37.7%)
Age				
Mean years (SD)	51.2	52.3	51.9	51.9
Median (years)	53	53	51	52
Min, max (years)	22, 88	20, 83	18, 81	18, 83
Age Group				
<65 years	129 (84.3%)	113 (77.9%)	125 (83.3%)	367 (81.9%)
≥65 years	24 (15.7%)	33 (22.1%)	25 (16.7%)	81 (18.1%)
Race				
White	128 (83.7%)	120 (82.8%)	124 (82.7%)	372 (83.0%)
Black or African American	3 (2.0%)	2 (1.4%)	2 (1.3%)	7 (1.6%)
Asian	18 (11.8%)	19 (13.1%)	17 (11.3%)	54 (12.1%)
American Indian or Alaska Native	3 (2.0%)	2 (1.4%)	0	12 (2.7%)
Native Hawaiian or other Pacific Islander	0	1 (0.7%)	0	1 (0.2%)
Other	1 (0.7%)	0	0	2 (0.4%)
Ethnicity				
Hispanic or Latino	40 (26.1%)	42 (29.2%)	50 (33.3%)	132 (29.5%)
Not Hispanic or Latino	113 (73.9%)	102 (70.8%)	100 (66.7%)	315 (70.5%)
Region				
Asia	16 (10.5%)	17 (11.7%)	16 (10.7%)	49 (10.9%)
Latin America	44 (28.8%)	44 (30.3%)	49 (32.7%)	137 (30.6%)
East Europe	16 (10.5%)	13 (9.0%)	14 (9.3%)	43 (9.6%)
Western Countries	77 (50.3%)	71 (49.0%)	71 (47.3%)	219 (48.9%)
North America	29 (19.0%)	30 (20.7%)	30 (20.0%)	89 (19.9%)
European Union	30 (19.6%)	29 (20.0%)	28 (18.7%)	87 (19.4%)
Rest of World	94 (61.4%)	86 (59.3%)	92 (61.3%)	272 (60.7%)

q2w = once every 2 weeks; SD = standard deviation
Source: Table 14, EFC14280 clinical study report

Other baseline demographics regarding atopic history, nasal polyp history, and history of surgery and systemic corticosteroid use are described below in Table 26 through Table 29.

Table 26. Baseline Nasal Polyposis Characteristics EFC14280

Characteristic	Placebo N=153	Dupilumab 300 mg q2w-q4w N=145	Dupilumab 300 mg q2w N=150	Total N=448
Time since first diagnosis of NP (years)				
N	151	144	148	443
Mean (SD)	10.88 (9.40)	10.67 (9.12)	11.28 (10.38)	10.94 (9.63)
Min	0.2	0.2	0.1	0.1
Max	42.3	55.1	61.3	61.3
Age of onset of nasal polyposis (years)				
N	151	144	148	443
Mean (SD)	40.97 (14.54)	41.65 (13.87)	40.59 (13.39)	41.06 (13.92)
Min	10.0	7.0	9.0	7.0
Max	75.0	76.0	70.0	76.0

NP = nasal polyposis; q2/4w = every 2 or 4 weeks; SD = standard deviation

Table 27. Surgical History, EFC14280

	Placebo	Dupilumab 300 mg q2w-q4w	Dupilumab 300 mg q2w	Total
Number of patients with prior surgery	88 (57.5%)	85 (58.6%)	88 (58.7%)	261 (58.3%)
Number of previous surgeries				
N	88 (57.5%)	85 (58.6%)	88 (58.7%)	261 (58.3%)
Mean (SD)	1.76 (1.37)	1.54 (1.17)	1.93 (1.57)	1.75 (1.39)
Min	1	1	1	1
Max	8	8	11	11
1	56 (63.6%)	59 (69.4%)	49 (55.7%)	164 (62.8%)
2	14 (15.9%)	17 (20.0%)	17 (19.3%)	48 (18.4%)
≥3	18 (20.5%)	9 (10.6%)	22 (25.0%)	49 (18.8%)

q2/4w = every 2 or 4 weeks; SD = standard deviation

Table 28. SCS Use History, EFC14280

	Placebo	Dupilumab 300 mg q2w-q4w	Dupilumab 300 mg q2w	Total
Number of patients with SCS use during the past 2 years	122 (79.7%)	116 (80.0%)	121 (80.7%)	359 (80.1%)
Number of courses of SCS during the past 2 years				
N	122 (79.7%)	116 (80.0%)	121 (80.7%)	359 (80.1%)
Mean (SD)	1.49 (0.95)	1.72 (1.60)	1.61 (1.37)	1.60 (1.33)
Min	1.0	1.0	1.0	1.0
Max	7.0	12.0	11.0	12.0
1	86 (70.5%)	77 (66.4%)	85 (70.2%)	248 (69.1%)
2	21 (17.2%)	24 (20.7%)	21 (17.4%)	66 (18.4%)
3	9 (7.4%)	7 (6.0%)	6 (5.0%)	22 (6.1%)
4	5 (4.1%)	1 (0.9%)	3 (2.5%)	9 (2.5%)
≥5	1 (0.8%)	7 (6.0%)	6 (5.0%)	14 (3.9%)

SCS = systemic corticosteroids; q2/4w = every 2 or 4 weeks; SD = standard deviation

Table 29. Other Medical History and Baseline Scores, EFC14280

Characteristic	Placebo	Dupilumab 300 mg q2w-q4w	Dupilumab 300 mg q2w	Total
Epistaxis history				
N	153	145	150	448
Yes	36 (23.5%)	26 (17.9%)	23 (15.3%)	85 (19.0%)
Ongoing	10 (12.4%)	13 (9.0%)	13 (8.7%)	45 (10.0%)
Rhinosinusitis history (≥2 symptoms 8 weeks prior to screen)	151 (98.7%)	144 (99.3%)	146 (97.3%)	441 (98.4%)
Asthma history				
N	153	145	150	448
Yes	91 (59.5%)	91 (62.8%)	85 (56.7%)	267 (59.6%)
No	62 (40.5%)	54 (37.2%)	65 (43.3%)	181 (40.4%)
NSAID-ERD history**				
N	153	145	150	448
Yes	44 (28.8%)	41 (28.3%)	35 (23.3%)	120 (26.8%)
No	109 (71.2%)	104 (71.7%)	115 (76.6%)	328 (73.2%)
Allergic rhinitis history				
N	153	145	150	448
Yes	88 (57.5%)	92 (63.4%)	92 (61.3%)	272 (60.7%)
Ongoing	74 (48.4%)	75 (51.7%)	72 (48.0%)	221 (49.3%)
Allergic conjunctivitis history				
N	153	145	150	448
Yes	16 (10.5%)	23 (15.9%)	15 (10.0%)	54 (12.1%)
Ongoing	10 (6.5%)	20 (13.8%)	6 (4.0%)	36 (8.0%)
Baseline nasal polyposis score				
N	152	145	149	446
Mean (SD)	5.96 (1.21)	6.29 (1.20)	6.07 (1.22)	6.10 (1.21)
Min	2	3	1.5	1.5
Max	8	8	8	8
Baseline Lund-Mackay (LMK) score				
N	150	140	149	439
Mean (SD)	17.65 (3.76)	17.81 (3.89)	18.42 (3.61)	17.96 (3.76)
Min	6	4	9	4
Max	24	24	24	24
Baseline SNOT-22 score				
N	152	145	147	444
Mean (SD)	53.48 (21.85)	51.89 (21.05)	50.16 (19.72)	51.86 (20.90)
Min	11.0	8.0	12.0	8.0
Max	110.0	102.0	108.0	110.0

**Out of those with NSAID-ERD, 40/44 (90.9%) in placebo group were from medical history, the other 4/44 (9.1%) were from provocational history. In the dupilumab q2w-q4w group, 34/41 (82.9%) were from medical history and the remaining 7/41 (17.1%) were from provocational history. In the dupilumab q2w group, 32/35 (91.4%) were from medical history and the remaining 3/35 (8.6%) were from provocational history.
NP = nasal polyp; NSAID-ERD = nonsteroidal anti-inflammatory drug exacerbated respiratory disease; q2w = every 2 weeks; q4w = every 4 weeks; SD = standard deviation; SNOT-22 = Sino-Nasal Outcome Test

Similar to EFC14146, patients experienced nasal polyps in adulthood and approximately 60% of patients overall underwent prior surgery. Approximately 19% of patients underwent 3 or more prior surgeries, and overall, approximately 80% of patients required systemic corticosteroids in the previous two years, supporting the fact that these patients had inadequately controlled nasal polyps. Patients demonstrated evidence of a history of general atopy (overall 60% had asthma, 61% had allergic rhinitis, and 12% had allergic conjunctivitis). Though approximately

27% of patients overall had a history of NSAID-ERD, the majority of these patients were diagnosed via medical history, not provocational history. LMK scores demonstrate significant sinusitis burden on CT (overall mean score of 18) and minimum score of 4 support the fact that all patients had some evidence of sinusitis on imaging.

For the 24-week pooled data, the baseline demographics reflected the baseline demographics for Studies EFC14146 and EFC14280.

Other Baseline Characteristics (Important Concomitant Drugs)

Most patients were on twice daily dosing of mometasone furoate nasal spray (84.2%) with only 15.8% using daily dosing. There were less patients in the dupilumab groups using rescue saline nasal lavage, systemic antibiotics, short oral corticosteroid course, or surgery for nasal polyps (13.3% in the q2w group and 15.2% in the q2w-q4w group versus 37.3% placebo). The most frequently used rescue medication was oral corticosteroids (6.7% and 3.4% in the dupilumab groups, respectively, versus 26.1% placebo group). Systemic antibiotics were used as rescue more frequently in the placebo group compared with the dupilumab group (4.7% and 6.9% in the dupilumab groups, respectively versus 13.7% placebo group).

Treatment Compliance and Rescue Medication Use

The Investigator or pharmacist kept accurate records of the quantities of IMP and NIMP (mometasone furoate nasal spray) dispensed, used, and unused by each patient. Compliance with both IMP and NIMP was reviewed with the patient at each visit. For IMP, compliance was assessed by inspection of the patient e-diary, and by counting the number of used and unused treatment kits and syringes. For NIMP, compliance with use of mandatory background therapy was verified based on mometasone furoate nasal spray use recorded on the patient electronic diary. Across all treatment groups, mean compliance with IMP was high (>99%). Only one patient in the Dupilumab 300mg q2w-q4w group had a compliance rate <80%.

8.1.4.3. Primary Endpoint

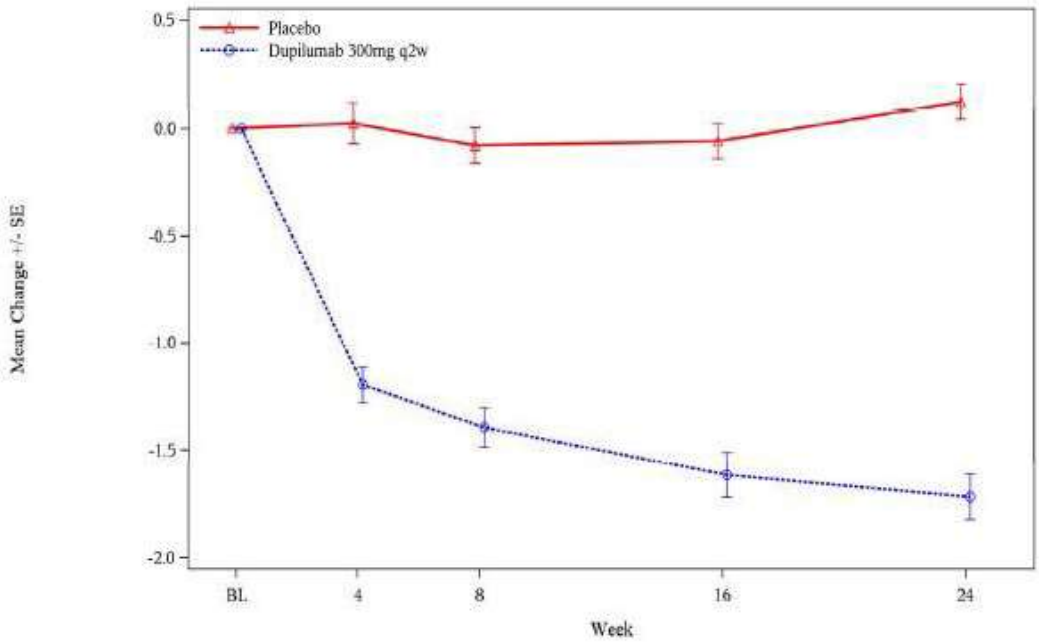
Results for the change from baseline in coprimary efficacy endpoints and multiplicity-controlled secondary endpoints, based on the primary analysis of the ITT population, are displayed in Table 30. These data are displayed over the course of the 24 weeks in Figure 17 and Figure 17. The coprimary endpoints, NPS and NC, were highly statistically significant: NPS (LS mean, -1.8; 95% CI: -2.1 to -1.5) and NC (LS mean, -0.9, 95% CI: -1.0 to -0.7). The effect of dupilumab compared to placebo was seen at the initial postbaseline visit at Week 4.

Table 30. Summary of Primary and Secondary Endpoints in the Multiplicity Testing Procedure EFC14280 (ITT Population)

	Placebo (N=153)			Dupilumab 300mg q2w (N=295)				
	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Baseline Mean (SD)	Week 24 Mean (SD)	Absolute Change from Baseline LS Mean (SE)	Absolute Difference for Dupilumab vs. Placebo LS Mean (95% CI)	P Value
Primary endpoints								
Bilateral nasal polyps score (NPS) at Week 24	5.96 (1.21)	6.09 (1.19)	0.10 (0.14)	6.18 (1.21)	4.46 (1.89)	-1.71 (0.11)	-1.80 (-2.10, -1.51)	<.0001
Nasal congestion/obstruction (NC) at Week 24	2.38 (0.54)	2.02 (0.77)	-0.38 (0.07)	2.46 (0.61)	1.19 (0.90)	-1.25 (0.06)	-0.87 (-1.03, -0.71)	<.0001
Key secondary endpoints								
Lund Mackay score (LMK) at Week 24	17.65 (3.76)	17.73 (3.81)	-0.09 (0.31)	18.12 (3.75)	12.86 (3.87)	-5.21 (0.24)	-5.13 (-5.80, -4.46)	<.0001
Total symptom score (TSS) at Week 24	7.08 (1.38)	6.08 (1.97)	-1.00 (0.20)	7.30 (1.48)	3.77 (2.44)	-3.45 (0.15)	-2.44 (-2.87, -2.02)	<.0001
Smell test (UPSIT) at Week 24	13.78 (8.31)	13.30 (7.96)	-0.81 (0.71)	13.53 (7.88)	23.89 (9.21)	9.71 (0.56)	10.52 (8.98, 12.07)	<.0001
Loss of smell at Week 24	2.72 (0.52)	2.49 (0.79)	-0.23 (0.08)	2.77 (0.53)	1.55 (1.02)	-1.21 (0.06)	-0.98 (-1.15, -0.81)	<.0001
SNOT-22 at Week 24	53.48 (21.85)	42.16 (23.26)	-10.40 (1.61)	51.02 (20.37)	23.89 (18.77)	-27.77 (1.26)	-17.36 (-20.87, -13.85)	<.0001

LS = least squares; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: EFC14280 Clinical Study Report, Table 24, part 1. Results for these parameters replicated by statistical reviewer. ANCOVA model with the baseline value of the corresponding coprimary endpoint, treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory diseasestatus, prior surgery history, and regions as covariates.

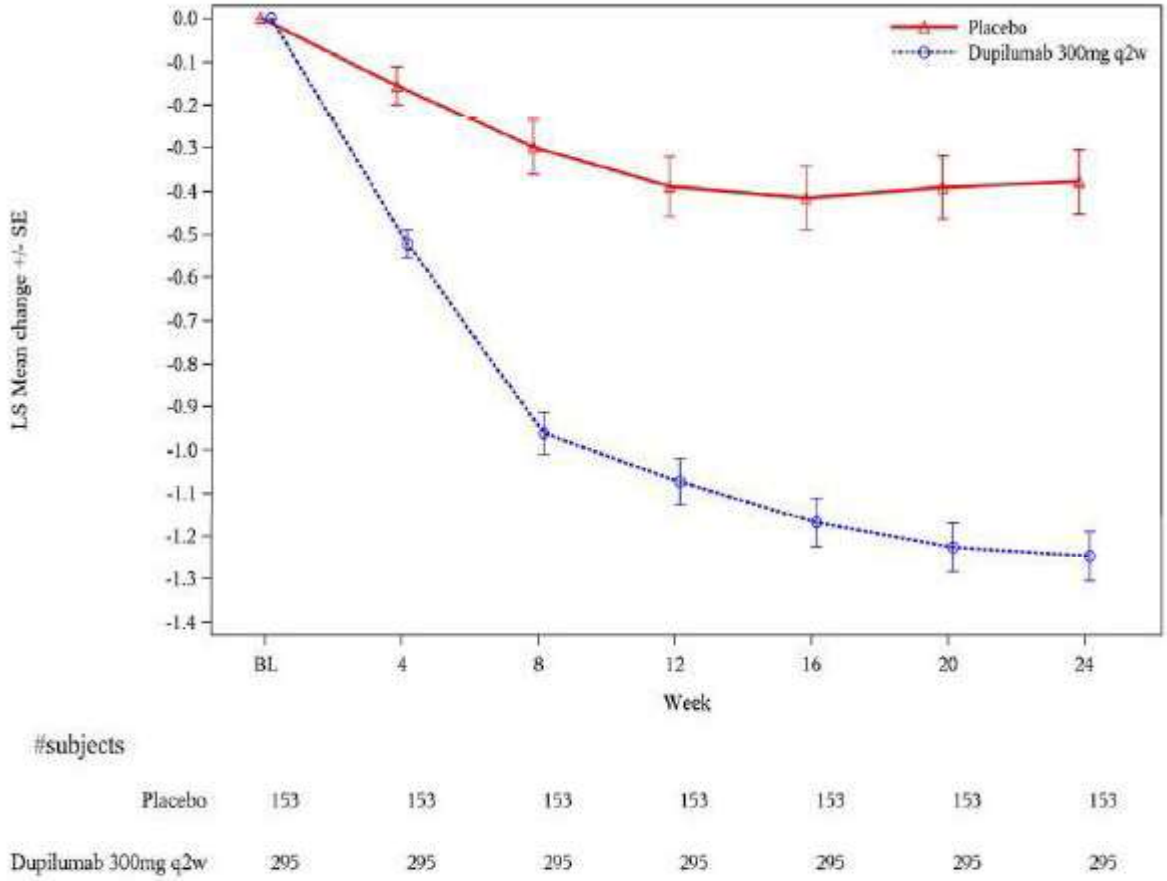
Figure 16. LS Mean Change From Baseline in Bilateral Nasal Polyps Score by Visit to Week 24 (ITT Population) EFC14280



# subjects					
Placebo	152	148	147	146	145
Dupilumab 300mg q2w	294	279	287	277	283

ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; SE = standard error
Source: EFC14280 Clinical Study Report, Figure 3

Figure 17. LS Mean Change From Baseline in Nasal Congestion/Obstruction by Month up to Week 24 (ITT Population) EFC14280



ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; SE = standard error
Source: EFC14280 Clinical Study Report, Figure 8

8.1.4.4. Additional Analyses of the Coprimary Endpoints

As described in the study design for Study EFC14280, the study continued from Week 24 to 52 with the dupilumab arms randomized into two arms, one continuing with the same regimen (q2w) and the other administered q4w. The efficacy for the dupilumab 300 mg q2w treatment arm compared to placebo from for both coprimary endpoints at Week 24 and Week 52 are summarized in Table 31. The treatment difference continued to improve after Week 24 for both NP and NC.

For NPS, the q4w arm improved less than the q2w arm; the placebo arm continued with similar means as at Week 24 (Figure 18).

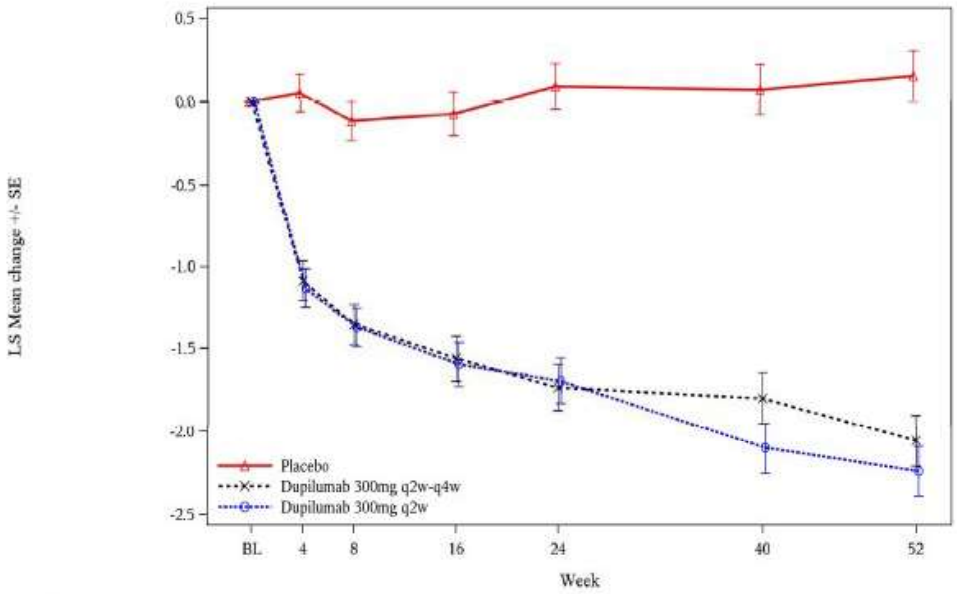
For NC, the dupilumab q2w arm continued to improve after Week 24, with this trend beginning at Week 8. Numerially, the q2w arm improved less than the q4w arm after Week 24; however these differences were not statistically significant. The placebo arm continued with similar means as at Week 24 (Figure 19).

Table 31. Difference in LS Mean Change From Baseline in NPS and NC at Weeks 24 and 52 (ITT Population) EFC14280

Difference for Dupilumab q2w vs. Placebo	Placebo N	Dupilumab q2w N	LS Mean Difference	95% Confidence Interval
NPS				
Week 24	153	295	-1.80	-2.10 to -1.51
Week 52	153	150	-2.40	-2.77 to -2.02
NC				
Week 24	153	295	-0.87	-1.03 to -0.71
Week 52	153	150	-0.98	-1.17 to -0.79

ITT = intention to treat; LS = least squares; NC = nasal congestion/obstruction; NPS = Nasal Polyps Score; q2w = once every 2 weeks
Source: EFC14280 Clinical Study Report, Table 24

Figure 18. LS Mean Change From Baseline in NPS by Visit to Week 52 (ITT Population) EFC14280

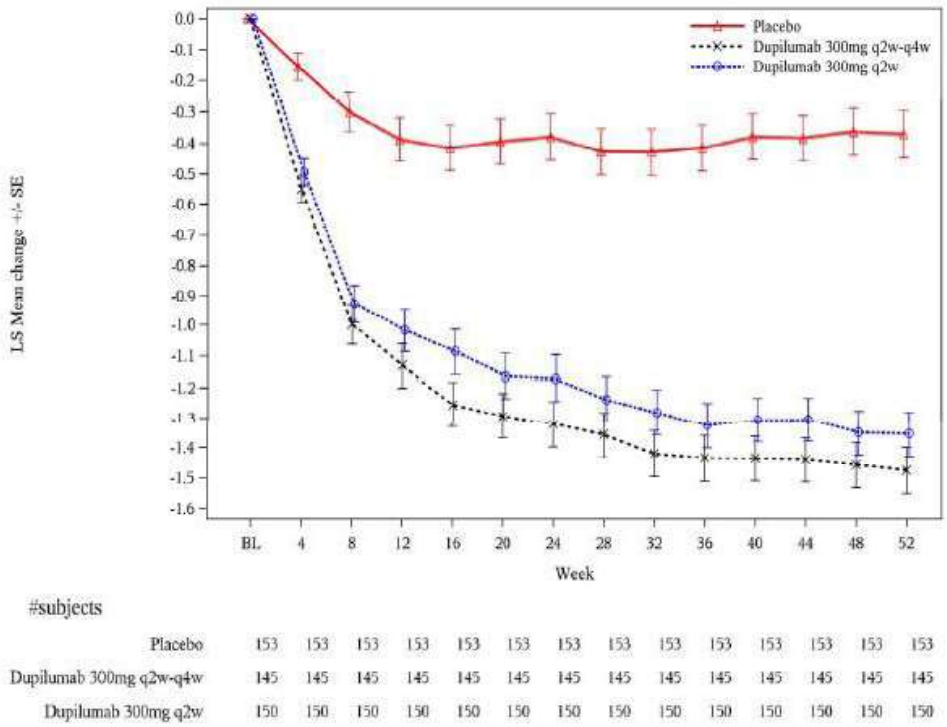


#subjects

Placebo	152	152	152	152	152	152	152
Dupilumab 300mg q2w-q4w	145	145	145	145	145	145	145
Dupilumab 300mg q2w	149	149	149	149	149	149	149

ITT = intention to treat; LS = least squares; NPS = Nasal Polyps Score; q2w = once every 2 weeks; SE = standard error
Source:EFC14280 Clinical Study Report, Figure 4

Figure 19. LS Mean Change From Baseline in NC by Month to Week 52 (ITT Population) EFC14280



ITT = intention to treat; LS = least squares; NC = nasal congestion/obstruction; q2w = once every 2 weeks; SE = standard error
Source:EFC14280 Clinical Study Report, Figure 9

Table 32. Results for Coprimary Endpoints, NPS and NC at Week 24 by Asian and Non-Asian Subgroups (ITT Population) EFC14280

Subgroup	Placebo N, LS Mean (SE)	Dupilumab N, LS Mean (SE)	LS Mean Difference vs. Placebo (95% CI)
NPS at Week 24			
All patients	145, 0.10 (0.14)	283, 1.71 (0.11)	-1.80 (-2.10, -1.51)
Asians	17, 1.16 (0.74)	34, -1.52 (0.69)	-2.68 (-3.84, -1.52)
Non-Asians	128, -0.11 (0.14)	249, -1.62 (0.11)	-1.73 (-2.04, -1.43)
NC at Week 24			
All patients	147, -0.38 (0.07)	289, -1.25 (0.06)	-0.87 (-1.03, -0.71)
Asians	17, -0.31 (0.24)	35, -1.39 (0.23)	-1.07 (-1.47,-0.68)
Non-Asians	130, -0.39 (0.08)	254, -1.23 (0.06)	-0.84 (-1.01, -0.66)

CI = confidence interval; LS = least squares; NC = nasal congestion/obstruction; NPS = Nasal Polyps Score; SE = standard error
Source: Statistical reviewer

We also conducted a post hoc analysis of the coprimary endpoints in Asians, as Asians are known to have neutrophil predominant polyps, whereas non-Asians have eosinophil predominant polyps (Table 32). Because dupilumab is known to act on IL-4 and IL-13, cytokines involved in driving eosinophils, we hypothesized that dupilumab may not be effective in Asian subgroups. The Asian subgroup was small. LS mean differences were higher in this subgroup than the overall means and the non-Asian subgroup for NPS and NC, however because the n was small, it is difficult to interpret the true significance of these results

The Applicant also analyzed NPS in a responder analysis, evaluating the percent of patients with a change from baseline of ≥1 NPS points at Week 24. A higher percentage of patients had a ≥1 point improvement in NPS in the dupilumab group compared with placebo (62.0% versus 10.5%, odds ratio 13.6 (95% CI 7.6 to 24.1)).

A combined responder analysis relative to baseline (NPS ≥1 point and NC ≥ 0.5 points) was also conducted. The proportion of patients showing improvement in the combined score in the dupilumab group compared with placebo was 52.2% versus 5.2%, odds ratio 19.1 (95% CI 9.0 to 40.4.

Sensitivity Analyses

For all sensitivity analyses (except for the as-observed analysis) for patients who underwent surgery for NP or received SCS for any reason, data collected postsurgery or post SCS were set to worst observation for that patient carried forward.

Results from several alternative analysis approaches for each of the two coprimary efficacy endpoints at 24 weeks had results similar to the primary analysis: MMRM, pattern mixture model with copy increment from placebo, tipping point, and as-observed (Table 33).

An additional as-observed analysis was conducted on the coprimary efficacy endpoints which included all data (including that collected after SCS for any reason and/or treatment discontinuation) but *excluded post NP surgery data*. The data were analyzed with the same ANCOVA model as the primary approach.

Table 33. Summary of Primary and Sensitivity Analyses for Coprimary Endpoints (ITT Population) EFC14280

Nasal Polyp Score (NPS)	**LS Mean Difference**	**95% CI**	**P-Value**
ANCOVA (primary)	-1.80	-2.10 to -1.51	<0.0001
MMRM	-1.83	-2.16 to -1.51	<0.0001
PMM	-1.75	-2.08 to -1.42	<0.0001
Tipping point	p-value remained at <0.001 at all shifts in dupilumab, from 0.4 to 4.0 and all shifts in placebo, from -0.4 to -4		
Applicant's as observed[2]	-1.77	-2.07 to -1.47	<0.0001
Stat reviewer's as-observed[3]	-1.69	-2.00 to -1.38	<0.0001
Nasal congestion/obstruction (NC)			
ANCOVA (primary)	-0.87	-1.03 to -0.71	<0.0001
MMRM	-0.82	-0.99 to -0.65	<0.0001
PMM	-0.77	-0.94 to -0.60	<0.0001
Tipping point	p-value remained at <0.001 at all shifts in dupilumab, from 0.4 to 4.0 and all shifts in placebo, from -0.4 to -4		
Applicant's as observed[2]	-0.80	-0.95 to -0.64	<0.0001
Stat reviewer's as-observed[3]	-0.77	-0.93 to -0.61	<0.0001

[1] Model for all analyses included treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgery history, and region
[2] Applicant's as-observed analysis did not use WOCF for steroid rescue but did use WOCF for surgical rescue
[3] Statistical reviewer's as-observed used as-observed (i.e., no WOCF), regardless of steroid or surgical rescue
ANCOVA = Analysis of covariance; MMRM = Mixed model for repeated measures; PMM = Pattern mixture model with copy increment to placebo; LS = least squares; CI = confidence interval

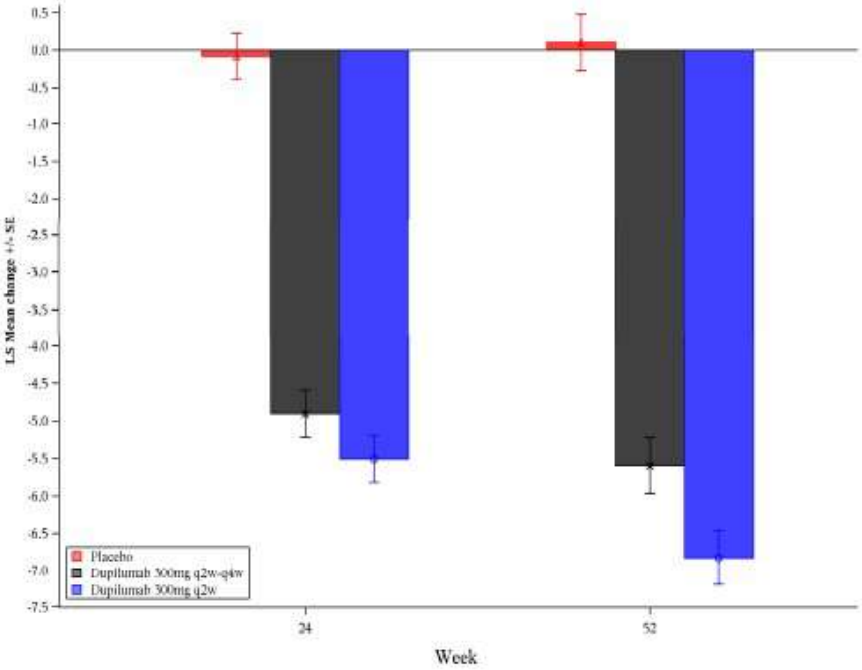
8.1.4.5. Secondary and Other Relevant Endpoints

The secondary endpoints tested under a hierarchical multiplicity control (Table 30) began with CT scan/LMK (LS mean, -5.1, 95% CI: -5.8 to -4.5); TSS (LS mean, -2.4, 95% CI: -2.9 to -2.0); UPSIT (LS mean, 10.5, 95% CI: 9.0 to 12.1); loss of smell (LS mean, -1.0, 95% CI: -1.2 to -0.8); and SNOT-22 (LS mean, -17.4, 95% CI: -20.9 to -13.9). The identical model and application of data assignment for rescue and missing data was applied to these secondary endpoints. Similar to the coprimary endpoints, each of these secondary endpoints were highly statistically significant.

Dupilumab demonstrated improvements in mean sinus opacification CT scan score (LMK) from baseline to Week 24 on both the left and right sides compared with the placebo group (LS mean difference versus placebo [95% CI] was -2.52 [-2.89 to -2.15] for the left side and -2.59 [-2.95 to -2.23] for the right side).

There was a greater improvement in LMK at Week 52 in patients who remained on dupilumab q2w in comparison to those who switched at Week 24 to the dupilumab q4w regimen -6.94 (95% CI: -7.87 to -6.01) and -5.71 (95% CI: -6.64 to -4.77), respectfully (Figure 20).

Figure 20. LS Mean Change From Baseline in LMK Score at Weeks 24 and 52 (ITT Population)



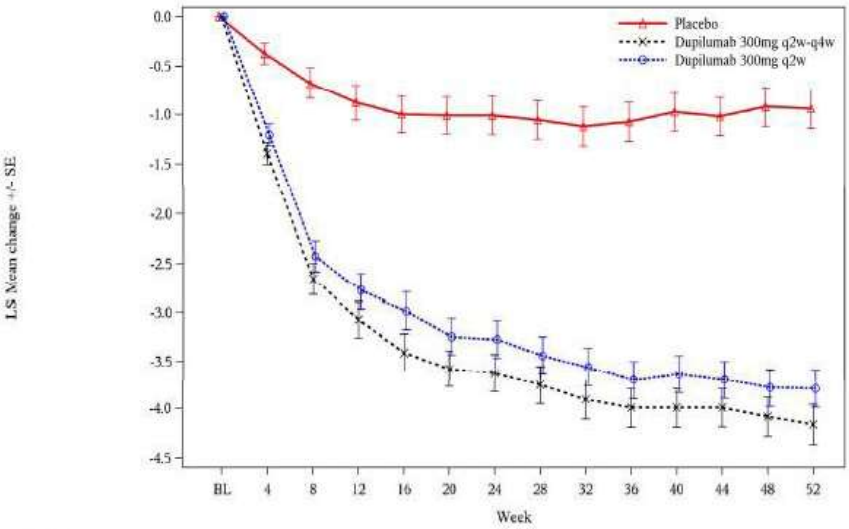
#subjects		
Placebo	150	150
Dupilumab 300mg q2w-q4w	140	140
Dupilumab 300mg q2w	149	149

Source: EFC14280 clinical study report, Figure 15

The behavior of dupilumab over time in comparison to placebo is similar across the secondary endpoints of TSS (Figure 21), UPSIT (Figure 22), daily diary for loss of smell (Figure 23), and SNOT-22 (Figure 24). Daily symptoms of TSS and loss of smell had more pronounced reductions compared to placebo for the q4w regimen than for the q2w regimen. However, this may be an

artifact of the patient population, since the difference in treatment arms begins prior to Week 24 when the study dosing regimen changed.

Figure 21. LS Mean Change From Baseline in TSS by Month to Week 52 (ITT Population) EFC14280

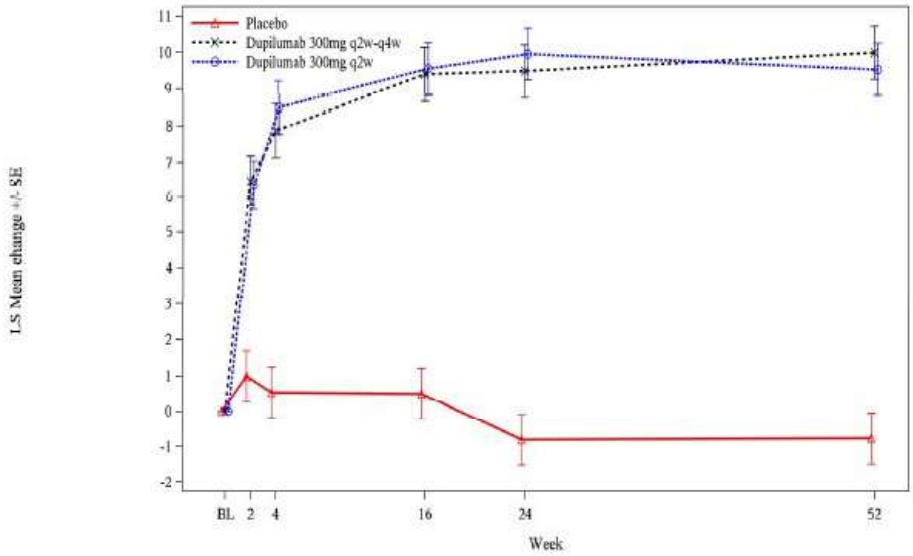


#subjects

	BL	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	153	153	153	153	153	153	153	153	153	153	153	153	153	153
Dupilumab 300mg q2w-q4w	145	145	145	145	145	145	145	145	145	145	145	145	145	145
Dupilumab 300mg q2w	150	150	150	150	150	150	150	150	150	150	150	150	150	150

Source: EFC14280 clinical study report, Figure 18

Figure 22. LS Mean Change From Baseline in UPSIT Score by Visit to Week 52 (ITT Population) EFC14280

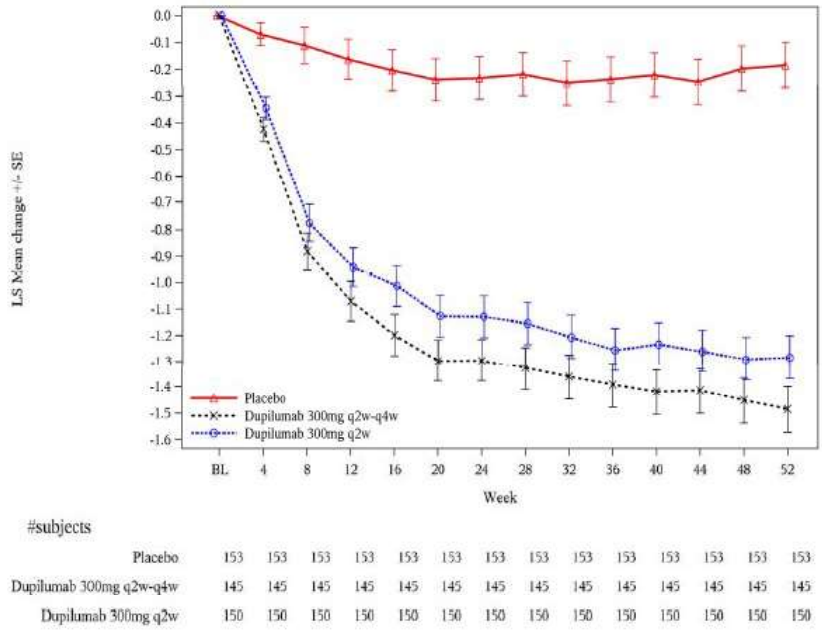


#subjects

	BL	2	4	16	24	52
Placebo	150	150	150	150	150	150
Dupilumab 300mg q2w-q4w	142	142	142	142	142	142
Dupilumab 300mg q2w	145	145	145	145	145	145

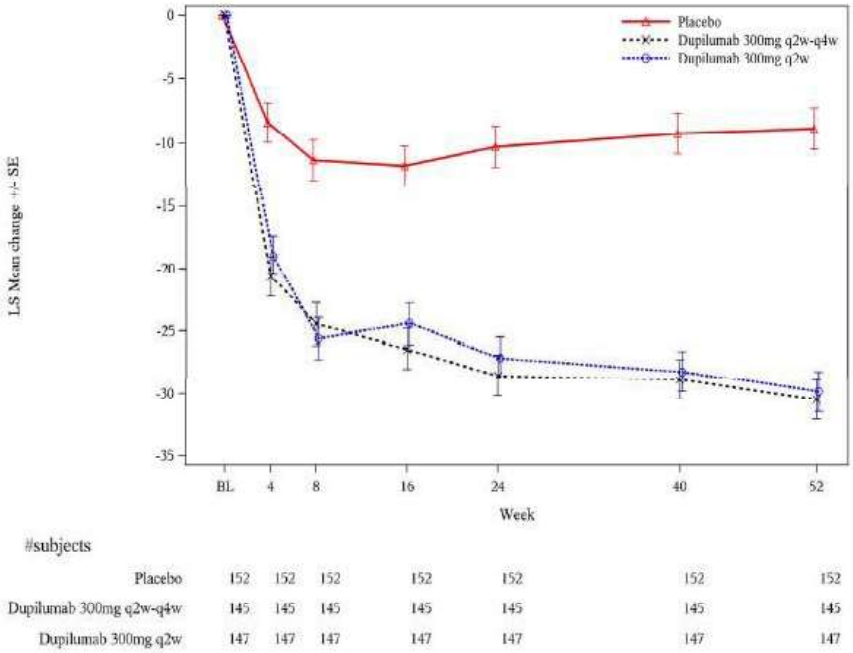
Source: EFC14280 clinical study report, Figure 20

Figure 23. LS Mean Change From Baseline in Daily Self-Reported Loss of Smell by Month to Week 52 (ITT Population) EFC14280



Source: EFC14280 clinical study report, Figure 22

Figure 24. LS Mean Change From Baseline in SNOT-22 Total Score by Visit to Week 52 (ITT Population) EFC14280

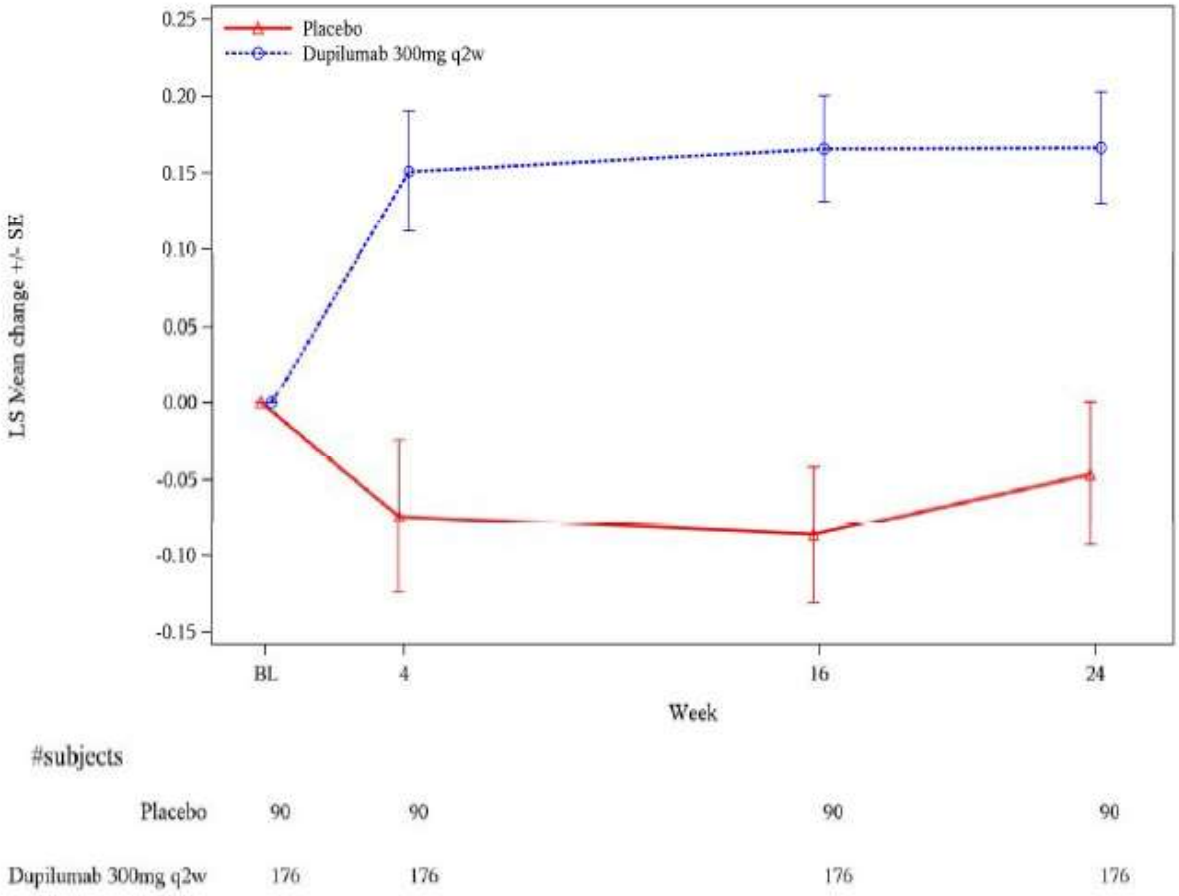


Source: EFC14280 clinical study report, Figure 24

Other multiplicity-adjusted endpoints include time to first rescue event (SCS or surgery) and FEV_1 for the subgroup of patients with asthma. These were prespecified as pooled analyses with EFC14146 and are discussed in the integrated studies section of this review. Results for the asthma subgroup are also reported here: There was a statistically significant improvement

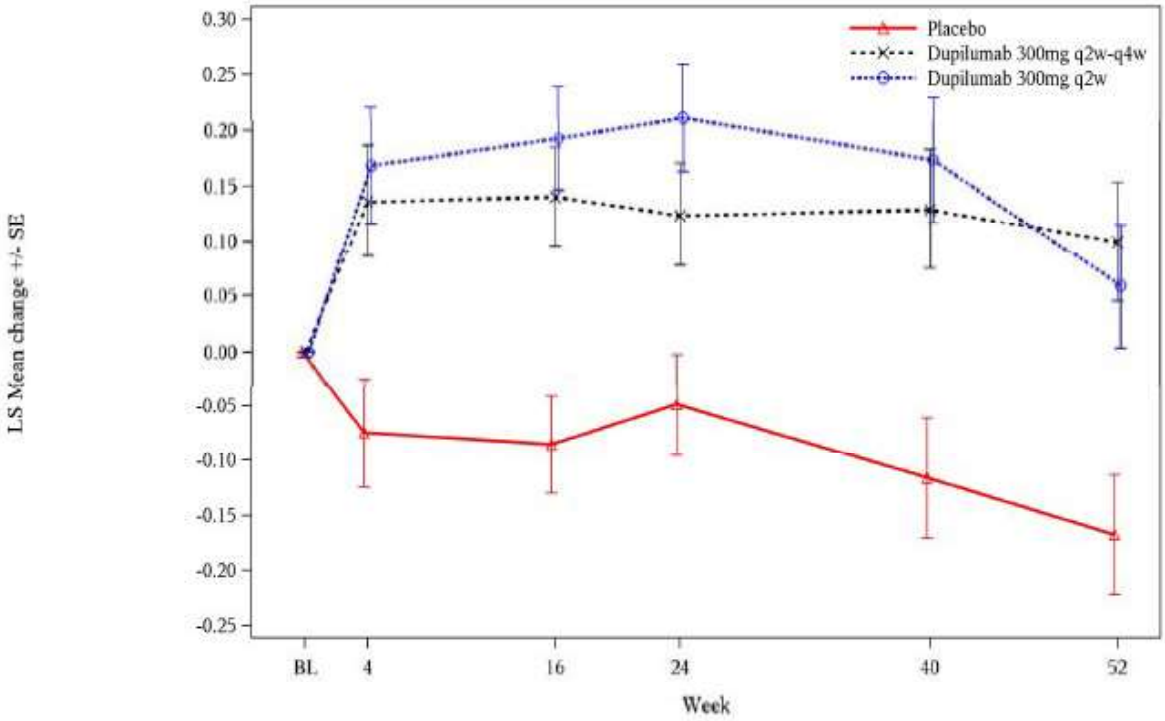
(p=<0.0001) in change from baseline for FEV_1 in patients with a history of asthma (87 placebo patients and 172 dupilumab patients). The LS mean change from baseline at Week 24 for placebo and dupilumab, respectively, were -0.07L and 0.15L, with an LS mean difference (CI) of 0.21 L (0.11, 0.32). Figure 25 shows FEV1 for this subgroup of patients over the course of 24 weeks of treatment.

Figure 25. LS mean change from baseline in FEV_1 (L) by visit up to Week 24 for patients with asthma history (ITT Population) EFC14280



Source: EFC14280 CSR, Fig 36

Figure 26. LS mean change from baseline in FEV1 (L) by visit up to Week 52 for patients with asthma history (ITT Population) EFC14280



#subjects						
Placebo	90	90	90	90	90	90
Dupilumab 300mg q2w-q4w	91	91	91	91	91	91
Dupilumab 300mg q2w	85	85	85	85	85	85

Source: EFC14280 CSR, Fig 37

Figure 26 shows results for this asthma subgroup over the 52-week study period. FEV_1 improvement was somewhat less after 24 weeks when the dosing regimen was changed from q2w to q4w, but was still significantly different from placebo. This further supports the q2w dosing.

The hierarchical testing plan in the sponsor's Statistical Analysis Plan to control multiplicity stated that results from both trials would be pooled for the proportion of patients who required treatment with SCS or sino-nasal surgery during the treatment period. The same analysis was conducted for EFC14280 alone, and was significantly lower in the dupilumab 300 mg q2w group compared with the placebo group across the 52-week treatment period (Kaplan-Meier estimate at Week 52 was 13.1% versus 44.4%, hazard ratio and 95% CI of 0.283 [0.156, 0.364]). The individual endpoint of sino-nasal surgery was also significantly lower in the dupilumab group (0.7%) compared to placebo (8.5%), hazard ratio and 95% CI of 0.106 (0.024, 0.475). As was the individual endpoint of SCS use (26.1% placebo versus 4.1% duplimab, hazard ratio 0.163 and 95% CI (0.085, 0.312).

Dose/Dose Response

See Additional Analyses of the Coprimary Endpoints

Persistence of Effect

Persisitence of effect was not evaluated for Study EFC14280.

Additional Analyses Conducted on the Individual Trial

A subgroup analysis of the coprimary endpoints using the primary analysis method, ANCOVA, was conducted on patients with baseline eosinophil levels of < 150, ≥150 and ≥300 cells/mL (Table 34). We hypothesized that patients with higher baseline eosinophil counts may have a higher mean change from baseline when treated with dupilumab compared to placebo. However, the data did not support this hypothesis. Mean values for these two subgroups was similar to the overall population. The response in patients with eosinophils < 150 cells/mL was numerically lower for both NPS and NC compare to the other overall population and the other subgroups; however, both endpoints were statistically significant.

Table 34. Subgroup Analysis of Coprimary Endpoints, NPS and NC, by Baseline Eosinophil Counts (ITT Population) EFC14280

Subgroup	Placebo N LS Mean (SE)	Dupilumab N LS Mean (SE)	LS Mean Difference vs. Placebo (95% CI)
NPS at Week 24			
All patients	145, 0.10 (0.14)	283, -1.71 (0.11)	-1.80 (-2.10, -1.51)
Baseline eosinophils <150 cells/mL	20, 0.20 (0.27)	45, -1.27 (0.20)	-1.48 (-2.09, -0.86)
Baseline eosinophils ≥150 cells/mL	125, 0.02 (0.15)	237, -1.85 (0.12)	-1.87 (-2.20, -1.54)
Baseline eosinophils >300 cells/mL	91, 0.02 (0.19)	158, -1.77 (0.16)	-1.78 (-2.18, -1.39)
NC at Week 24			
All patients	147, -0.38 (0.07)	289, -1.25 (0.06)	-0.87 (-1.03, -0.71)
Baseline eosinophils <150 cells/mL	20, -0.33 (0.19)	46, -1.05 (0.14)	-0.72 (-1.14, -0.30)
Baseline eosinophils ≥150 cells/mL	129, -0.39 (0.08)	242,-1.29 (0.07)	-0.90 (-1.08, -0.72)
Baseline eosinophils >300 cells/mL	94, -0.46 (0.10)	162,-1.37 (0.08)	-0.91 (-1.12,-0.71)

NPS = nasal polyposis; LS = least squares; SE = standard error; CI = confidence interval; NC = nasal congestion/obstruction
Source: Statistical Reviewer analysis

To support an indication of rhinosinusitis with severe nasal polyps, the statistical reviewers analyzed the individual components of facial pain (Table 35), nasal blockage (Table 36), thick nasal discharge (Table 37), runny nose (Table 38), and sneezing components (Table 39) from SNOT-22. The identical analysis, handling of missing data and rescue, and population from that used by the Applicant for the primary analysis was used in these analyses.

95% confidence intervals for the difference between dupilumab and placebo for each of these endpoints did not include zero, indicating a similar pattern with the above prespecified efficacy endpoints of statistically significant difference of dupilumab relative to placebo.

Table 35. Change From Baseline in Facial Pain at Week 24 (ITT Population) EFC14280

		Dupilumab	
SNOT-22 (Facial Pain)	**Placebo (N=153)**	**300 mg q2w (N=145)**	**300 mg q2w-q4w (N=150)**
Baseline			147
Number	152	145	147
Mean (SD)	1.81 (1.73)	1.66 (1.57)	1.59 (1.54)
Median	1.50	1.00	1.00
Q1:Q3	0.00:3.00	0.00:3.00	0.00:3.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Week 52			143
Number	143	139	143
Mean (SD)	1.47 (1.52)	0.60 (1.07)	0.60 (1.02)
Median	1.00	0.00	0.00
Q1:Q3	0.00:3.00	0.00:1.00	0.00:1.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Change from baseline			143
Number	143	139	143
Mean (SD)	-0.34 (1.37)	-1.09 (1.54)	-1.01 (1.49)
Median	0.00	-1.00	-1.00
Q1:Q3	-1.00:0.00	-2.00:0.00	-2.00:0.00
Min:max	-4.0:4.0	-5.0:3.0	-5.0:3.0
LS mean (SE) [a]	-0.31 (0.10)	-1.12 (0.10)	-1.08 (0.10)
LS mean diff vs. placebo (95% CI) [a]		-0.80 (-1.05, -0.56)	-0.77 (-1.01, -0.52)
P-value vs. placebo [a]		<.0001	<.0001

CI = confidence interval; ITT = intention to treat; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis; Data extracted from SNOT-22

Table 36. Change From Baseline in Nasal Blockage at Week 24 (ITT Population) EFC14280

		Dupilumab	
SNOT-22 (Nasal Blockage)	**Placebo (N=153)**	**300 mg q2w (N=145)**	**300 mg q2w-q4w (N=150)**
Baseline			147
Number	152	145	147
Mean (SD)	3.75 (0.94)	3.82 (0.94)	3.77 (0.99)
Median	4.00	4.00	4.00
Q1:Q3	3.00:4.00	3.00:5.00	3.00:5.00
Min:max	1.0:5.0	1.0:5.0	0.0:5.0
Week 52			143
Number	143	139	143
Mean (SD)	3.10 (1.41)	1.33 (1.30)	1.45 (1.33)
Median	3.00	1.00	1.00
Q1:Q3	2.00:4.00	0.00:2.00	0.00:2.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Change from baseline			143
Number	143	139	143
Mean (SD)	-0.66 (1.38)	-2.52 (1.50)	-2.33 (1.57)
Median	0.00	-3.00	-2.00
Q1:Q3	-2.00:0.00	-4.00:-1.00	-3.00:-1.00
Min:max	-5.0:2.0	-5.0:1.0	-5.0:3.0
LS mean (SE) [a]	-0.71 (0.12)	-2.48 (0.12)	-2.36 (0.12)
LS mean diff vs. placebo (95% CI) [a]		-1.76 (-2.07, -1.46)	-1.65 (-1.96, -1.35)
P-value vs. placebo [a]		<.0001	<.0001

CI = confidence interval; ITT = intention to treat; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis; Data extracted from SNOT-22

Table 37. Change From Baseline in Thick Nasal Discharge at Week 24 (ITT Population) EFC14280

		Dupilumab	
SNOT-22 (Thick Nasal Discharge)	**Placebo (N=153)**	**300 mg q2w (N=145)**	**300 mg q2w-q4w (N=150)**
Baseline			147
Number	152	145	147
Mean (SD)	2.94 (1.36)	3.03 (1.34)	3.14 (1.26)
Median	3.00	3.00	3.00
Q1:Q3	2.00:4.00	2.00:4.00	2.00:4.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Week 52			143
Number	143	139	143
Mean (SD)	2.57 (1.50)	1.00 (1.20)	0.94 (1.23)
Median	3.00	1.00	0.00
Q1:Q3	1.00:4.00	0.00:2.00	0.00:1.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Change from baseline			143
Number	143	139	143
Mean (SD)	-0.36 (1.48)	-2.05 (1.72)	-2.20 (1.54)
Median	0.00	-2.00	-2.00
Q1:Q3	-1.00:0.00	-3.00:-1.00	-4.00:-1.00
Min:max	-5.0:5.0	-5.0:3.0	-5.0:1.0
LS mean (SE) [a]	-0.44 (0.12)	-2.02 (0.12)	-2.14 (0.12)
LS mean diff vs. placebo (95% CI) [a]		-1.58 (-1.87, -1.29)	-1.69 (-1.98, -1.40)
P-value vs. placebo [a]		<.0001	<.0001

CI = confidence interval; ITT = intention to treat; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis; Data extracted from SNOT-22

Table 38. Change From Baseline in Runny Nose at Week 24 (ITT Population) EFC14280

		Dupilumab	
SNOT-22 (Runny Nose)	**Placebo (N=153)**	**300 mg q2w (N=145)**	**300 mg q2w-q4w (N=150)**
Baseline			147
Number	152	145	147
Mean (SD)	3.01 (1.28)	3.23 (1.22)	3.10 (1.19)
Median	3.00	3.00	3.00
Q1:Q3	2.00:4.00	3.00:4.00	2.00:4.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Week 52			143
Number	143	139	143
Mean (SD)	2.52 (1.32)	1.22 (1.23)	1.15 (1.19)
Median	3.00	1.00	1.00
Q1:Q3	2.00:4.00	0.00:2.00	0.00:2.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Change from baseline			143
Number	143	139	143
Mean (SD)	-0.49 (1.34)	-2.04 (1.56)	-1.95 (1.54)
Median	0.00	-2.00	-2.00
Q1:Q3	-1.00:0.00	-3.00:-1.00	-3.00:-1.00
Min:max	-5.0:4.0	-5.0:2.0	-5.0:3.0
LS mean (SE) [a]	-0.61 (0.11)	-1.98 (0.11)	-2.00 (0.11)
LS mean diff vs. placebo (95% CI) [a]		-1.37 (-1.65, -1.10)	-1.39 (-1.66, -1.11)
P-value vs. placebo [a]		<.0001	<.0001

CI = confidence interval; ITT = intention to treat; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis; Data extracted from SNOT-22

Table 39. Change From Baseline in Sneezing at Week 24 (ITT Population) EFC14280

		Dupilumab	
SNOT-22 (Sneezing)	**Placebo (N=153)**	**300 mg q2w (N=145)**	**300 mg q2w-q4w (N=150)**
Baseline			147
Number	152	145	147
Mean (SD)	2.39 (1.23)	2.22 (1.22)	2.21 (1.24)
Median	2.00	2.00	2.00
Q1:Q3	2.00:3.00	1.00:3.00	1.00:3.00
Min:max	0.0:5.0	0.0:5.0	0.0:5.0
Week 52			143
Number	143	139	143
Mean (SD)	1.87 (1.23)	1.16 (1.11)	1.02 (1.04)
Median	2.00	1.00	1.00
Q1:Q3	1.00:3.00	0.00:2.00	0.00:2.00
Min:max	0.0:5.0	0.0:5.0	0.0:3.0
Change from baseline			143
Number	143	139	143
Mean (SD)	-0.52 (1.26)	-1.10 (1.35)	-1.21 (1.46)
Median	0.00	-1.00	-1.00
Q1:Q3	-1.00:0.00	-2.00:0.00	-2.00:0.00
Min:max	-4.0:2.0	-4.0:3.0	-5.0:2.0
LS mean (SE) [a]	-0.49 (0.10)	-1.16 (0.10)	-1.30 (0.10)
LS mean diff vs. placebo (95% CI) [a]		-0.67 (-0.92, -0.43)	-0.81 (-1.05, -0.56)
P-value vs. placebo [a]		<.0001	<.0001

CI = confidence interval; ITT = intention to treat; Q1:Q3 = quartile 1 and quartile 3 values; q2w = once every 2 weeks; SD = standard deviation; SE = standard error; SNOT-22 = Sino-Nasal Outcome Test
Source: Statistical Reviewer analysis; Data extracted from SNOT-22

Integrated Review of Effectiveness

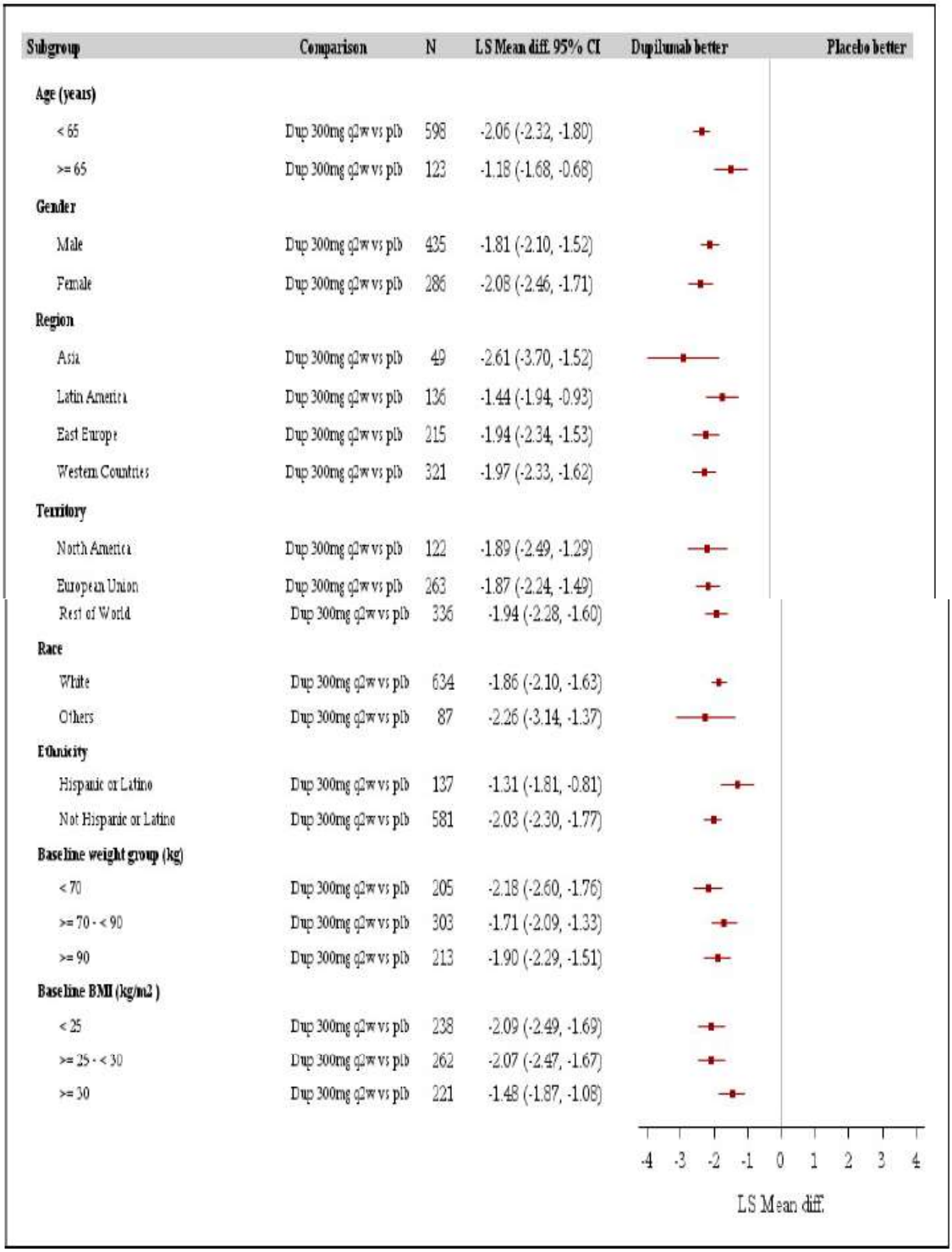
8.1.5. Assessment of Efficacy Across Trials

Review of efficacy assessment across trials was limited to select subgroup analyses on the coprimary endpoints and the prespecified integrated analysis on proportion of patients requiring rescue treatment (defined as use of SCS or NP surgery during the treatment period).

Primary Endpoints

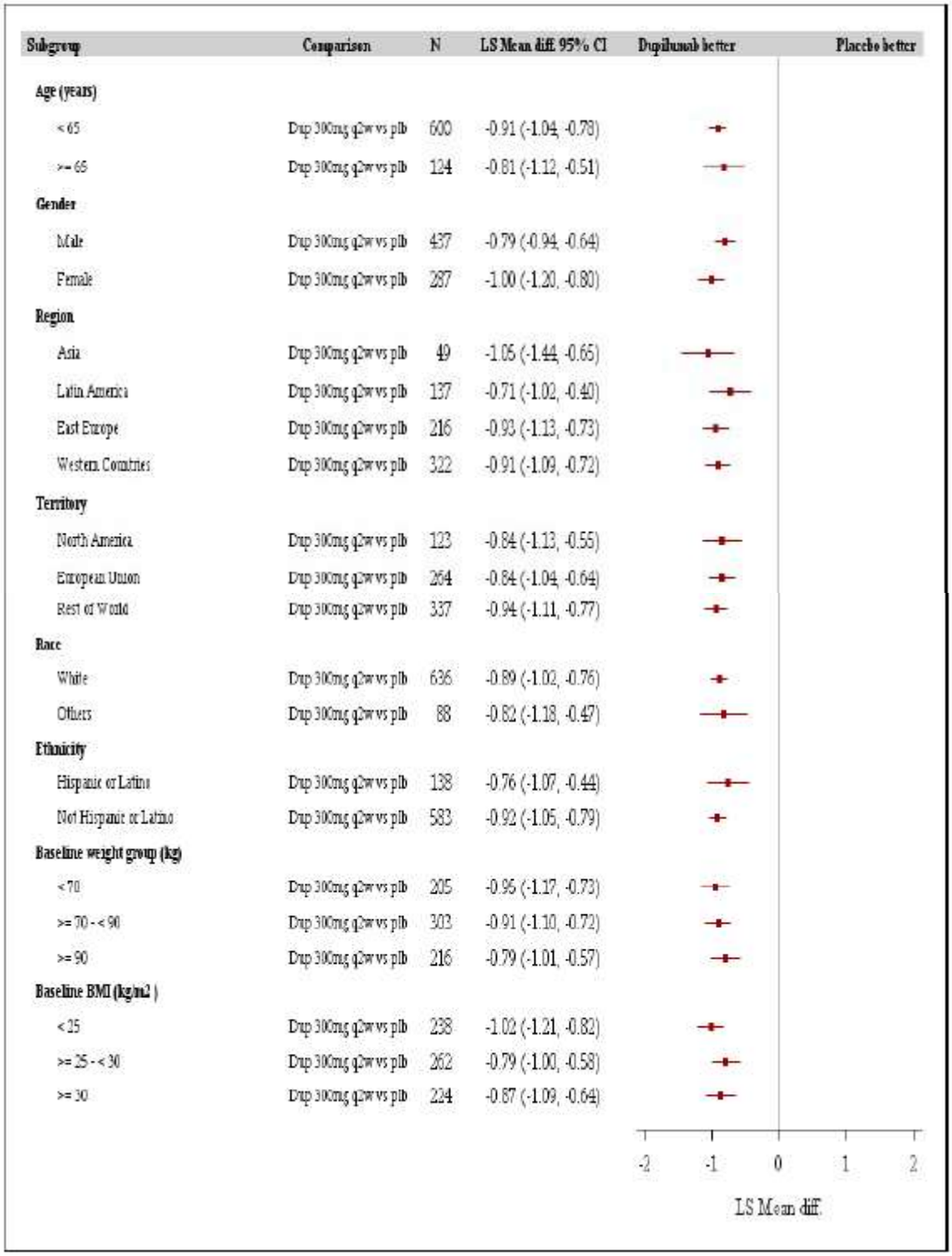
NPS and NC were assessed using the primary analysis method for the subgroups, age, gender, region, territory, race, ethnicity, baseline weight and BMI (Figure 27 and Figure 28). All subgroup means and 95% confidence intervals favored dupilumab over placebo. Those subgroups where dupilumab had a stronger effect on one subgroup over another (as assessed by means and 95% CIs showing a possible trend) for NPS were patients under 65 years of age, Asians and non-Hispanics. For NC there were no clear trends amongst these subgroups. Further research would be needed to know whether these observed trends are real or a statistical anomaly based on the particular patients and randomization schedule of these two trials.

Figure 27. Forest Plot of Treatment Difference on Change From Baseline in NPS at Week 24 (ITT Population, EFC14146 and EFC14280)



Source: Summary of clinical efficacy, Fig 36

Figure 28. Forest Plot of Treatment Difference on Change From Baseline in NC at Week 24 (ITT Population, EFC14146 and EFC14280)



Source: Summary of clinical efficacy, Fig 39

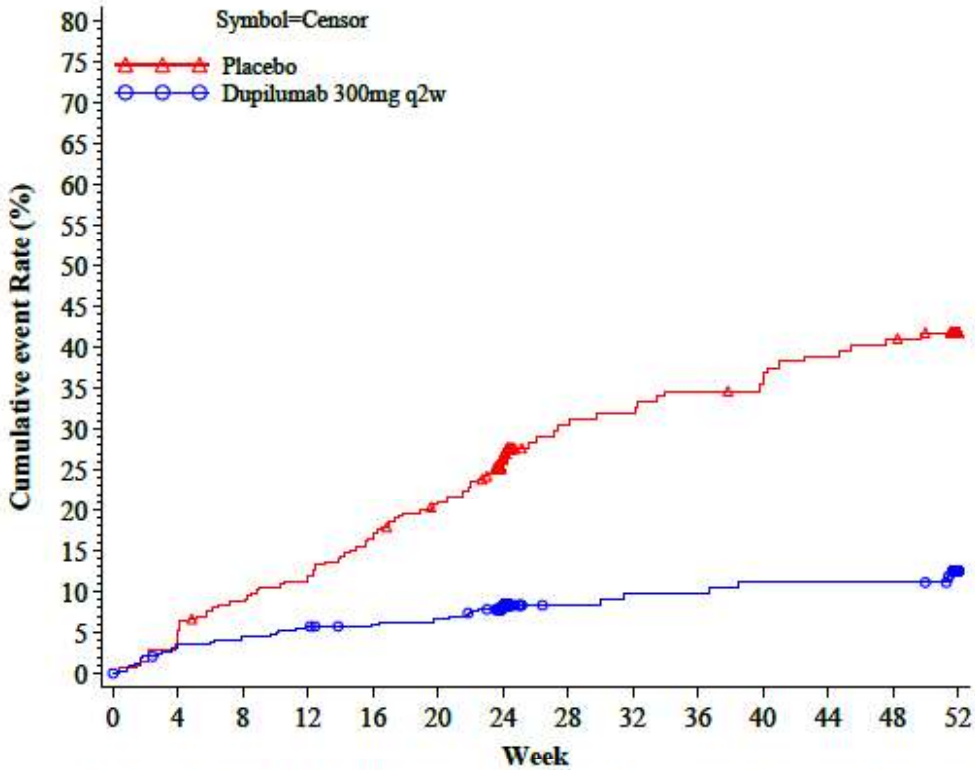
Secondary and Other Endpoints

Analysis for proportion of patients requiring rescue treatment (defined as use of SCS or surgery during the treatment period) used the Cox proportional hazards model using data pooled from EFC14146 and EFC14280, per the Applicant's prespecified analysis.

The Cox model, included the event as the dependent variable, study indicator, treatment group, asthma/NSAID-ERD strata, prior surgery strata, and region (pooled countries) as covariates. Hazard ratio and corresponding 95% CI and p values were estimated for dupilumab 300 mg q2w versus placebo. The Kaplan-Meier method was used to derive the probabilities that a patient would experience events up to Week 52 for 300 mg q2w and placebo. Kaplan-Meier curves were generated.

The proportion of patients who required treatment with SCS or sino-nasal surgery during the treatment period was significantly lower in the pooled dupilumab 300 mg q2w group compared with the pooled placebo group across the 52-week treatment period (Kaplan-Meier estimate at Week 52 was 12.5% versus 41.8%, hazard ratio and 95% CI of 0.243 [0.169, 0.351], and p<0.0001). Results of the companion Kaplan-Meier curve are shown in Figure 29.

Figure 29. Kaplan-Meier Curve for Time to First Rescue Event, SCS or Surgery, During the Treatment Period (ITT Population, EFC14146 and EFC14280)



Number at Risk														
Placebo	286	276	260	253	238	224	187	99	97	93	91	86	83	61
Dupilumab 300mg q2w	438	423	416	411	407	404	376	131	129	129	127	127	127	100

ITT = intention to treat; q2w = once every 2 weeks; SCS = systemic corticosteroids
Source: Summary of clinical efficacy, Fig 8
Note: EFC14146 patients were treated for 24 weeks. One arm of EFC14280 study had patients treated on dupilumab q2w for 24 weeks and another arm treated on this regimen for 52 weeks

8.1.6. Integrated Assessment of Effectiveness

The evidence of effectiveness from the two pivotal studies, EFC14146 and EFC14280, exceeds the statutory evidentiary standard for the coprimary endpoints, NPS and NC, in change from baseline in dupilumab 300 mg q2w treatment relative to placebo at Week 24. The evidence also exceeds the standard for all multiplicity-controlled secondary endpoints (LMK score, TSS, UPSIT, loss of smell, and SNOT-22) at Week 24, and time to first rescue event in a prespecified pooled analysis of both studies. Furthermore, a statistically significant reduction in SCS use was demonstrated in EFC14146 and a statistically significant reduction in SCS use and surgery for nasal polyps was demonstrated in EFC14280.

Results for primary endpoints, NPS and NC, and key secondary endpoints supporting the indication of chronic rhinosinusitis with nasal polyps indication (LMK sinus CT scan score, loss of smell, and SNOT-22) at Week 24 (and for EFC14280, also Week 52) for 300 mg q2w dupilumab demonstrated statistically significant improvement relative to placebo, as shown in Table 40 and Table 41. Time to first rescue event pooled across studies (HR of 0.24; 95% CI: 0.17, 0.35) also support substantial evidence that dupilumab is an effective treatment for nasal polyps.

Total symptom score was not discussed in the label as a secondary endpoint because it included nasal congestion, which was already a coprimary endpoint and loss of smell and rhinorrhea which overlap with a secondary endpoint. UPSIT was not discussed in the label because there are many variations in performance on this objective test based on gender, cultural background, and olfactory experience[10]. Instead, patient reported loss of smell score, performed on a daily basis, was considered to be more clinically meaningful. Table 40 and Table 41 also includes the individual symptoms from SNOT-22 of facial pain/pressure and thick nasal discharge as these were symptoms consistent with chronic rhinosinusitis. In the prescribing information we included the entire SNOT-22 score, which is discussed in more detail in Section 8.1.1.4. LMK CT sinus scan score serves as an objective measure of chronic rhinosinusitis, and though change in LMK CT sinus scan score from baseline has unknown clinical significance, the statistically significant change in this score further support the indication statement. Literature suggests that though the predictive value of LMK CT sinus scan score in symptomatic improvement is controversial, scores may be useful in predicting the extent of surgery that a subject may require.[11]

The 52-week study also included a q4w treatment arm from weeks 24-52. Assessment of the q4w dosing regimen was limited as the new steady state was not achieved until the end of the

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[10] Frank RA, Dulay MF, Niergarth KA, et al., 2004, A comparison of the sniff magnitude test and the UPSIT in children and nonnative English speakers. Physiology and Behavior, 3(81): 475-480.
[11] Hopkins C, Browne JP, Slack R, et al., 2007, The Lund-Mackay staging system for chronic rhinosinusitis: How is it used and what does it predict? Otolaryngology-Head and Neck Surgery, 137:555-561.

study (Week 48). Results showed that q4w dose was not supported as efficacy appeared to reach a plateau with every 2 week dosing, the objective endpoints of NPS and LMK score improved less after the q2w to q4w switch.

Table 40. Results of the Primary and Key Secondary Endpoints From EFC14146 and EFC14280 (ITT Population)

	EFC14146					EFC14280				
	Placebo (n=133)		DUPIXENT 300 mg q2w (n=143)		Difference	Placebo (n=153)		DUPIXENT 300 mg q2w (n=295)		Difference
Primary Endpoints at Week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change	LS mean difference vs. placebo (95%CI)	Baseline Mean	LS mean change	Baseline mean	LS mean change	LS mean difference vs. placebo (95%CI)
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)
Key Secondary Endpoints at Week 24										
Scores	Baseline mean	LS mean change	Baseline mean	LS mean change	LS mean difference vs. placebo (95%CI)	Baseline Mean	LS mean change	Baseline Mean	LS mean change	LS mean difference vs. placebo (95%CI)
LMK sinus CT scan score	19.55	-0.74	18.55	-8.18	-7.44 (-8.35, -6.53)	17.65	-0.09	18.12	-5.21	-5.13 (-5.80, -4.46)
Loss of smell	2.73	-0.29	2.70	-1.41	-1.12 (-1.31, -0.93)	2.72	-0.23	2.77	-1.21	-0.98 (-1.15, -0.81)
Facial pain/ pressure[1]	1.34	-0.17	1.34	-0.93	0.76 (-1.00, -0.52)	1.81	-0.40	1.62	-1.05	-0.66 (-0.87, -0.45)
Thick nasal discharge[1]	3.18	-0.58	2.96	-2.10	-1.52 (-1.80, -1.23)	2.94	-0.58	3.09	-1.88	-1.30 (-1.55, -1.04)

CI = confidence interval; CT = computed tomography; LMK = Lund-Mackay; LS = least squares; NC = nasal congestion/obstruction; NPS = Nasal Polyps Score; q2w = once every 2 weeks
Note: All analyses were performed using analysis of covariance (ANCOVA) with a model that included treatment group, asthma/NSAID-exacerbated respiratory disease (NERD) status, prior surgery history, and region
Source: statistical reviewer

Table 41. Results of Key Secondary Endpoints at Week 52 EFC14280 (ITT Population)

Endpoint	Placebo (n=153)		DUPIXENT 300 mg q2w (n=150)		LS Mean Difference vs. Placebo (95%CI)
	Baseline Mean	LS Mean Change	Baseline Mean	LS Mean Change	
NPS (nasal polyps score) (range 0 to 8)	5.96	0.15	6.07	-2.24	-2.40 (-2.77, -2.02)
NC (nasal congestion/obstruction) score (range 0 to 3)	2.38	-0.37	2.48	-1.35	-0.98 (-1.17, -0.79)
LMK sinus CT scan score (range 0 to 24)	17.65	0.11	18.42	-6.83	-6.94 (-7.87, -6.01)
Loss of smell score (range 0 to 3)	2.72	-0.19	2.81	-1.29	-1.10 (-1.31, -0.89)
Facial pain/ pressure[1]	1.81	-0.31	1.66	-1.12	-0.80 (-1.05, -0.56)
Thick nasal discharge[1]	2.94	-0.44	3.03	-2.02	-1.69 (-1.98, -1.40)

[1] Scores for facial pain/pressure and thick nasal discharge derived from components of SNOT-22
CI = confidence interval; LMK = Lund-Mackay; NC = nasal congestion/obstruction; NPS = Nasal Polyps Score; q2w = once every 2 weeks.
Note: All analyses were performed using ANCOVA with a model that included treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgery history, and region
Source: statistical reviewer

In a pooled analysis of EFC14146 and EFC14280, the change from baseline in both coprimary endpoints demonstrated significant improvement relative to placebo at Week 24 for these demographic subgroups: age, gender, region, territory, race, ethnicity, baseline weight, and BMI (Figure 27 and Figure 28).

In the prospective, multiplicity-adjusted pooled analysis from both studies for patients with a history of asthma, there was a statistically significant improvement (p=<0.0001) in change from baseline for FEV_1 with a (163 placebo patients and 258 dupilumab patients). The LS means for placebo and dupilumab, respectively, were -0.05L and 0.16L, with an LS mean difference (CI) of 0.21 (0.13, 0.29).

A subgroup analysis of the coprimary endpoints using the primary analysis method, ANCOVA, was conducted on patients at Week 24 with baseline eosinophil levels of <150, >150 and >300 cells/mL in both studies. In EFC14146, a trend was observed with higher mean differences in those patients with higher baseline eosinophil levels (Table 16). However, in EFC14280, there was no trend (Table 34); each subgroup had similar results to the overall population.

8.2. Review of Safety

8.2.1. Safety Review Approach

The 24-week safety and efficacy study (EFC14146) and the 52-week safety and efficacy study (EFC14280) were evaluated for safety under each individual protocol in Section 8.2.4. The review tools used to conduct independent reviewer analyses included JMP Clinical, JMP, and the clinical investigator site selection tool. Safety issues identified a priori include anaphylaxis,

hypersensitivity, serious injection site reactions, serious/severe infections, parasitic infections, opportunistic infections, hepatic disorders, malignancy, suicidal behavior, epistaxis, conjunctivitis, eosinophilia, pregnancy, and symptomatic overdose based on potential pharmacologic mechanism of action.

The safety for the 24-week study (EFC14146) and the first 24 weeks of the 52-week study (EFC14280) were pooled as the study populations were similar. The 24-week safety pool is also reviewed in this section.

The q4w dosing regimen was not supported as there were more safety events of sinusitis, nasal polyps, and asthma in subjects after they switched from the q2w to the q4w dosing regimen.

8.2.2. Review of the Safety Database

8.2.2.1. Overall Exposure

Table 42 EFC14280: Overall Exposure (Safety Population)

	Placebo N=150	Dupilumab 300 mg q2w-q4 N=148	Dupilumab 300mg q2w N=149
Duration of study treatment (days)			
Mean (SD)	322.95 (90.24)	356.50 (44.77)	345.64 (67.85)
Min:max	42:377	58:377	14:381
Exposure categories, n (%)			
>0 week	150 (100%)	148 (100%)	149 (100%)
>4 weeks	150 (100%)	148 (100%)	147 (98.7%)
>8 weeks	147 (98%)	148 (100%)	146 (98%)
>12 weeks	146 (97.3%)	145 (98%)	145 (97.3%)
>16 weeks	140 (93.3%)	145 (98%)	143 (96%)
>20 weeks	134 (89.3%)	145 (98%)	143 (96%)
>24 weeks	128 (85.3%)	145 (98%)	141 (94.6%)
>28 weeks	126 (84%)	145 (98%)	139 (93.3%)
>32 weeks	125 (83.3%)	143 (96.6%)	138 (92.6%)
>36 weeks	125 (83.3%)	143 (96.6%)	138 (92.6%)
>40 weeks	124 (82.7%)	143 (96.6%)	138 (92.6%)
>44 weeks	123 (82%)	143 (96.6%)	138 (92.6%)
>48 weeks	120 (80%)	143 (96.6%)	137 (91.9%)
>52 weeks	30 (20%)	42 (28.4%)	41 (27.5%)

q2w = once every 2 weeks; SD = standard deviation
Source: EFC14280 CSR Table 66 p. 204

Table 43 EFC14146 and EFC14280: Overall Exposure (Pooled Safety Population)

	Placebo N=282	Dupilumab 300 mg q2w N=440
Duration of study treatment (days)		
Mean (SD)	162.59 (23.19)	164.42 (19.70)
Min:max	14:168	14:168
Exposure categories, n (%)		
>0 week	282 (100%)	440 (100%)
>4 weeks	280 (99.3%)	437 (99.3%)
>8 weeks	276 (97.9%)	434 (98.6%)
>12 weeks	275 (97.5%)	428 (97.3%)
>16 weeks	267 (94.7%)	426 (96.8%)
>20 weeks	259 (91.8%)	426 (96.8%)
≥24 weeks-3 days	254 (90.1%)	423 (96.1%)

q2w = once every 2 weeks; SD = standard deviation
Source: ISS 1.3.2

Adequacy of the Safety Database

Overall, the safety database is of sufficient size and duration for chronic rhinosinusitis with nasal polyps to assess the safety of the proposed doses of dupilumab given the previous safety support for the approved indications of asthma and atopic dermatitis.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this supplemental BLA. Office of Scientific Investigations audits of site No. 8400001 for Study EFC14146 and site No. 560001 for Study EFC14280 did not reveal any substantial issues related to data integrity.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols. AEs were captured from signing of informed consent through the final follow up visit. Treatment emergent adverse events were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the final follow-up visit. AEs were coded using the MedDRA dictionary version 17.1.

The Applicant's coding of verbatim terms to preferred terms was appropriate. Adverse events of special interest included anaphylactic reactions, hypersensitivity, injection-site reaction (severe), infection (serious/severe), parasitic infection, opportunistic infection, drug-related hepatic disorder, pregnancy, and symptomatic overdose. Other selected AE groups included injection-site reaction, malignancy, suicidal behavior, partner pregnancy, epistaxis, conjunctivitis, and eosinophilia. The Applicant analyzed Standardized MedDRA Queries for anaphylaxis and hypersensitivity events, drug-related hepatic disorders, malignancy or unspecified tumors, and conjunctivitis.

Routine Clinical Tests

Routine clinical testing included complete blood count with differential, electrolytes, metabolic panel, and liver function testing.

8.2.4. Safety Results

8.2.4.1. Deaths

EFC14146

Only one patient in the placebo group died, and this was during the posttreatment period. The patient was a 76-year-old male who had a history of asthma and type 2 diabetes mellitus. Sixteen days prior to receiving the first dose of IMP, the patient was newly diagnosed with hypertension and was placed on Lisinopril. On Day 136 of the study (9 days after his 10th IMP injection), he was diagnosed with a "swollen left leg due to deep vein thrombosis in the left popliteal vein extending into the distal femoral vein." He was placed on oral rivaroxaban with recovery on Day 253. On Day 274, the patient had persistent breathlessness and was switched to beclomethasone/formoterol. He experienced an acute myocardial infarction on Day 277 (122 days after the last dose of investigational medical product (IMP)) and was found dead in his home by emergency services. No autopsy was performed.

EFC14280

One patient in the dupilumab 300 mg q2week-q4week treatment arm died. He was a 78-year-old male with a history of asthma, osteoporosis, and allergic rhinitis who experienced a traumatic intracranial hemorrhage due to an accidental fall from a bike on Day 422 (72 days after the 26th injection of dupilumab). Autopsy was not performed. The event was not related to the IMP per the investigator.

8.2.4.2. Serious Adverse Events

Serious adverse events are summarized in Table 44, Table 45, and Table 46.

Table 44. EFC14146 SAEs > Placebo (Safety Population)

System Organ Class	Preferred Term	Placebo N=132	Dupilumab 300 mg q2w N=143
Subjects reporting SAEs		19 (14.4%)	6 (4.2%)
Cardiac disorders		1 (0.8%)	1 (0.7%)
	Acute MI	0	1 (0.7%)
Reproductive system		0	1 (0.7%)
	Uterine polyp	0	1 (0.7%)
Nervous system disorders		1 (0.8%)	1 (0.7%)
	Carpal tunnel syndrome	0	1 (0.7%)

MI = myocardial infarction; q2w = once every 2 weeks; SAE = serious adverse event
Source: Reviewer generated table in JMP using EFC14146 ADSL and ADAE datasets (TRT01A, TRTEMFL, AESER, PSOCFL, AEDECOD)

There were fewer subjects reporting SAEs in the dupilumab group. The most commonly reported SAEs were nasal polyps and asthma (not listed), with higher rates in placebo compared to the dupilumab treatment group, which is expected. There was one cardiovascular

event of acute myocardial infarction in the treatment group. Because a cardiovascular safety signal was present in the asthma program, this event will be included in the prescribing information. There was also one case of EGPA in the placebo group (0.8%) and one case in the dupilumab group (0.7%) that is not listed in Table 44 above.

Table 45. EFC14280 SAEs > Placebo (Safety Population)

System Organ Class	Preferred Term	Placebo q2w N=150	Dupilumab 300 mg q2-q4w N=148	Dupilumab 300 mg q2w N=149
Subjects reporting SAEs		15 (10%)	10 (6.8%)	8 (5.4%)
Injury, poisoning, procedural complications		3 (2.0%)	3 (2.0%)	1 (7%)
	Femur fracture	0 (0%)	0 (0%)	1 (0.7%)
	Fall	0 (0%)	1 (0.7%)	0 (0%)
	Open globe injury	0 (0%)	1 (0.7%)	0 (0%)
	Traumatic intracranial hemorrhage	0 (0%)	1 (0.7%)	0 (0%)
	Upper limb fracture	0 (0%)	1 (0.7%)	0 (0%)
Respiratory, thoracic, mediastinal disorders		3 (2.0%)	2 (1.4%)	0 (0%)
	Asthmatic crisis	0 (0%)	1 (0.7%)	0 (0%)
Infections and infestations		2 (1.3%)	2 (1.4%)	2 (3%)
	Appendicitis	0 (0%)	0 (0%)	1 (0.7%)
	Infectious pleural effusion	0 (0%)	0 (0%)	1 (0.7%)
	Septic shock	0 (0%)	0 (0%)	1 (0.7%)
	Corneal abscess	0 (0%)	1 (0.7%)	0 (0%)
	Diverticulitis	0 (0%)	1 (0.7%)	0 (0%)
Gastrointestinal disorders		1 (0.7%)	2 (1.4%)	2 (3%)
	Abdominal pain upper	0 (0%)	1 (0.7%)	0 (0%)
	Gastrointestinal angiectasia	0 (0%)	0 (0%)	1 (0.7%)
	Esophageal perforation	0 (0%)	0 (0%)	1 (0.7%)
	Pancreatitis	0 (0%)	1 (0.7%)	0 (0%)
Immune system disorders		0 (0%)	1 (0.7%)	0 (0%)
	EGPA	0 (0%)	1 (0.7%)	0 (0%)
Blood and lymphatic system disorders		0 (0%)	0 (0%)	1 (7%)
	Eosinophilia	0 (0%)	0 (0%)	1 (0.7%)
Eye disorders		0 (0%)	0 (0%)	1 (0.7%)
	Retinal vein thrombosis	0 (0%)	0 (0%)	1 (0.7%)
MSK/connective tissue disorders		0 (0%)	1 (0.7%)	0 (0%)
	Back pain	0 (0%)	1 (0.7%)	0 (0%)
	Osteoarthritis	0 (0%)	0 (0%)	1 (0.7%)
Neoplasms		0 (0%)	0 (0%)	1 (0.7%)
	Nasal neoplasm benign	0 (0%)	0 (0%)	1 (0.7%)

EGPA = eosinophilic granulomatosis with polyangiitis; MSK = musculoskeletal; q2w = once every 2 weeks; q4w = once every 4 weeks; SAE = serious adverse event.
Source: Reviewer generated table in JMP using EFC14280 ADSL and ADAE datasets (TRT01A, TRTEMFL, AESER, PSOCFL, AEDECOD)

Overall, there were fewer subjects reporting SAEs in the dupilumab group. All SAEs in EFC14280 occurred as singular events. The were no notable safety differences in the 52-week study compared to the 24-week study (Table 44). SAEs occurring between weeks 24 and 52 are reflective of SAEs in Table 45.

Table 46. 24-Week Pooled SAEs > Placebo (Safety Population))

System Organ Class	Preferred Term	Placebo N=282	Dupilumab mg q2w N=440
Subjects reporting SAEs		16 (5.7%)	15 (3.4%)
Infections and infestations		3 (1.1%)	3 (0.7%)
	Appendicitis	0 (0%)	1 (0.2%)
	Diverticulitis	0 (0%)	1 (0.2%)
	Infectious pleural effusion	0 (0%)	1 (0.2%)
	Septic shock	0 (0%)	1 (0.2%)
Neoplasms benign, malignant and unspecified		0 (0%)	1 (2%)
	Nasal neoplasm benign	0 (0%)	1 (0.2%)
Blood and lymphatic system disorders		0 (0%)	1 (2%)
	Eosinophilia	0 (0%)	1 (0.2%)
Immune system disorders		0 (0%)	1 (0.2%)
	EGPA	0 (0%)	1 (0.2%)
Nervous system disorders		3 (1.1%)	1 (0.2%)
	Carpal tunnel syndrome	0 (0%)	1 (0.2%)
Eye disorders		1 (0.4%)	1 (0.2%)
	Retinal vein thrombosis	0 (0%)	1 (0.2%)
Cardiac disorders		1 (0.4%)	1 (0.2%)
	Acute myocardial infarction	0 (0%)	1 (0.2%)
Gastrointestinal disorders		1 (0.4%)	3 (0.7%)
	Abdominal pain upper	0 (0%)	1 (0.2%)
	Esophageal perforation	0 (0%)	1 (0.2%)
	Pancreatitis	0 (0%)	1 (0.2%)
MSK and connective tissue disorders		0 (0%)	1 (2%)
	Osteoarthritis	0 (0%)	1 (0.2%)
Reproductive and breast disorders		0 (0%)	1 (2%)
	Uterine polyp	0 (0%)	1 (0.2%)
Injury, poisoning, procedural complications		2 (0.7%)	1 (2%)
	Fall	0 (0%)	1 (0.2%)
	Upper limb fracture	0 (0%)	1 (0.2%)

EGPA = eosinophilic granulomatosis with polyangiitis; MI = myocardial infarction; MSK = musculoskeletal; q2w = once every 2 weeks; SAE = serious adverse event
Source: Reviewer generated table in JMP using integrated safety summary ADSL and ADAE datasets (TRT01A, TRTEMFL, AESER, PSOCFL, AEDECOD)

In the 24-week pooled safety results, there were fewer events occurring in the treatment group when compared to placebo. There was one case of acute myocardial infarction, which is a from EFC14146. There were two cases of EGPA in the dupilumab group, one from EFC14146 and one from EFC14280 (not listed in table above). There was one case of eosinophilia (>3.0 Giga/L) from EFC14280. These are considered to be important SAEs as they were identified as commonly occurring adverse events in the asthma program.

8.2.4.3. Dropouts and/or Discontinuations Due to Adverse Events

Dropouts and/or discontinuations due to adverse events are summarized in Table 47, Table 48, Table 49.

Table 47. EFC14146 AEs Leading to Discontinuation, > Placebo (Safety Population)

Preferred Term	Placebo N=132	Dupilumab 300 mg q2w N=143
Subjects reporting AEs	3 (2.3%)	5 (3.5%)
Nasal polyps	1 (0.8%)	2 (1.4%)
EGPA	0	1 (0.7%)
Psoriatic arthropathy	0	1 (0.7%)
Rheumatic disorder	0	1 (0.7%)

AE = adverse event; EGPA= eosinophilic granulomatosis with polyangiitis; MSK = musculoskeletal; q2w = once every 2 weeks.
Source: CSR EFC14146 Table 60, pg. 188 verified by Reviewer in JMP

There were more events leading to discontinuation in the dupilumab group when compared to placebo. All events occurred as singular events except nasal polyps which lead to discontinuation in two people in the dupilumab group and one person in the placebo group. Psoriatic arthropathy was a reactivation of prior disease in this patient.

Table 48. EFC14280 AEs Leading to Discontinuation, > Placebo (Safety Population)

Preferred Term	Placebo N=150	Dupilumab 300 mg q2-4w N=148	Dupilumab 300 mg q2w N=149
Subjects reporting AEs	17 (11.3%)	2 (1.4%)	6 (4.0%)
Rash macular	0 (0%)	0 (0%)	1 (0.7%)
Arthralgia	0 (0%)	0 (0%)	1 (0.7%)
Lupus-like syndrome	0 (0%)	0 (0%)	1 (0.7%)
Insomnia	0 (0%)	0 (0%)	1 (0.7%)
Confusional state	0 (0%)	1 (0.7%)	0 (0%)
Drug hypersensitivity	0 (0%)	0 (0%)	1 (0.7%)
EGPA	0 (0%)	1 (0.7%)	0 (0%)
Folliculitis	0 (0%)	0 (0%)	1 (0.7%)
Eosinophilia	0 (0%)	0 (0%)	1 (0.7%)
Nasal neoplasm benign	0 (0%)	0 (0%)	1 (0.7%)

AE = adverse event; EGPA = eosinophilic granulomatosis with polyangiitis; MSK = musculoskeletal; q2w = once every 2 weeks; q4w = every 4 weeks.
Source: CSR 14280 Table 72, pg. 218 verified by Reviewer in JMP

In EFC14280 there were fewer events in the dupilumab group leading to discontinuation when compared to placebo. All events occurred as singular events. The were no notable safety differences for AEs leading to discontinuation in the 52-week study compared to the 24-week study (Table 47). AEs leading to discontinuation occurring between weeks 24 and 52 are reflective of SAEs in Table 48.

Table 49. 24-Week Pooled AEs Leading to Discontinuation > Placebo (Safety Population)

Preferred Term	Placebo N=132	Dupilumab 300 mg q2w N=143
Subjects reporting AEs	15 (5.3%)	11 (2.5%)
Folliculitis	0 (0%)	1 (0.2%)
Nasal neoplasm benign	0 (0%)	1 (0.2%)
Eosinophilia	0 (0%)	1 (0.2%)
Drug hypersensitivity	0 (0%)	1 (0.2%)
EGPA	0 (0%)	1 (0.2%)
Insomnia	0 (0%)	1 (0.2%)
Rash macular	0 (0%)	1 (0.2%)
Arthralgia	0 (0%)	1 (0.2%)
Lupus-like syndrome	0 (0%)	1 (0.2%)
Psoriatic arthropathy	0 (0%)	1 (0.2%)
Rheumatic disorder	0 (0%)	1 (0.2%)

AE = adverse event; EGPA = eosinophilic granulomatosis with polyangiitis; q2w = once every 2 weeks
Source: ISS Table 1.4.1.16, pg. 1011 verified by Reviewer in JMP

In the 24-week pooled safety results, there were more adverse events leading to discontinuation in the placebo group when compared to the dupilumab group. Each event occurred as singular events.

8.2.4.4. Common Adverse Events

Common adverse events are summarized in Table 50, Table 51, and Table 52.

Table 50. EFC14146 Common Adverse Events > Placebo (Safety Population)

Preferred Term	Placebo N=132	Dupilumab 300 mg q2w N=143
Subjects reporting AEs	93 (70.5%)	93 (65.0%)
Epistaxis	4 (3%)	11 (7.7%)
Hypertension	3 (2.3%)	5 (3.5%)
Influenza-like illness	3 (2.3%)	5 (3.5%)
Pharyngitis	2 (1.5%)	5 (3.5%)
Arthralgia	3 (2.3%)	4 (2.8%)
Oropharyngeal pain	2 (1.5%)	4 (2.8%)
Musculoskeletal pain	0 (0%)	4 (2.8%)
Dermatitis	1 (0.8%)	3 (2.1%)
Joint swelling	0 (0%)	3 (2.1%)

AE = adverse event; q2w = once every 2 weeks
Source: Reviewer generated table in JMP Clinical

Overall, the number of reported common adverse events were similar between treatment arms. There were more cases of epistaxis in the dupilumab group when compared to placebo, however patients in the placebo group also had epistaxis, and patients at baseline prior to study enrollment also had epistaxisThis reflects that epistaxis is a commonly occurring phenomen in patients with underlying chronic rhinosinusitis with nasal polyps due to underlying inflammation/irritation of the nasal mucosa and possibly intranasal corticosteroid use.

Table 51. EFC14280 Common Adverse Events > Placebo (Safety Population)

Preferred Term	Placebo N=150	Dupilumab 300 mg q2-q4w N=148	Dupilumab 300 mg q2w N=149
Subjects reporting AEs	136 (90.7%)	132 (89.2%)	124 (83.2%)
Oral herpes	1 (0.7%)	4 (2.7%)	1 (0.7%)
Conjunctivitis	1 (0.7%)	2 (1.4%)	3 (2.0%)
Injection site reactions*	5 (3.3%)	17 (11.5%)	9 (6%)
Chest pain	1 (0.7%)	5 (3.4%)	0 (0%)
Pyrexia	1 (0.7%)	3 (2.0%)	2 (1.3%)
Gastritis	3 (2.0%)	6 (4.1%)	3 (2.0%)
GERD	2 (1.3%)	6 (4.1%)	2 (1.3%)
Dyspepsia	0 (0%)	3 (2.0%)	0 (0%)
Arthralgia	2 (1.3%)	11 (7.4%)	7 (4.7%)
Hypertension	2 (1.3%)	6 (4.1%)	6 (4.0%)
Insomnia	0 (0%)	0 (0%)	5 (3.4%)
Fall	2 (1.3%)	4 (2.7%)	1 (0.7%)
Rash	1 (0.7%)	2 (1.4%)	3 (2.0%)

* Includes injection site reaction, swelling, bruising
AE = adverse event; GERD = gastroesophageal reflux disease; q2w = once every 2 weeks; q2-q4w = once every 2-4 weeks
Source: Reviewer generated table in JMP Clinical

Overall, the number of reported common adverse events were similar between treatment arms. There were significantly more injection site reactions in the treatment arms when compared to placebo. There were similar incidents of epistaxis between the treatment and placebo arms in EFC14280 demonstrating that nasal polyp patients experience more epistaxis at baseline. The were no notable safety differences for common AEs in the 52-week study compared to the 24-week study .

For the Week 24-52 week common AEs, there were more adverse events of sinusitis (5% for q2w vs. 9% for q4w), nasal polyps (5% for q2w vs. 10% for q4w), and asthma (4% for q2w vs. 9% for q4w) in subjects who switched from q2w to q4w dosing.

Table 52. 24-Week Pooled Common AEs >1% > Placebo (Safety Population)

Preferred Term	Placebo N=282	Dupilumab 300 mg q2w N=440
Any AE	208 (73.8%)	305 (69.3%)
Injection site reactions*	12 (4.3%)	34 (7.7%)
Cough	9 (3.2%)	15 (3.4%)
Arthralgia	5 (1.8%)	14 (3.2%)
Hypertension	3 (1.1%)	12 (2.7%)
Back pain	7(2.5%)	12 (2.7%)
Influenza	4 (1.4%)	7 (1.6%)
Gastritis	2 (0.7%)	7 (1.6%)
Conjunctivitis	0 (0%)	6 (1.4%)
Oral herpes	2 (0.7%)	6 (1.4%)
Insomnia	0 (0%)	6 (1.4%)
Oropharyngeal pain	3 (1.1%)	6 (1.4%)
Rhinorrhea	2 (0.7%)	6 (1.4%)
GERD	2 (0.7%)	6 (1.4%)
Eosinophilia	1 (0.4%)	5 (1.1%)
Toothache	1 (0.4%)	5 (1.1%)

* Includes injection site reaction, pain, swelling, bruising
AE = adverse event; GERD = gastroesophageal reflux disease; q2w = every 2 weeks
Source: Reviewer generated table in JMP Clinical

Overall, the total number of adverse events was similar across treatment groups. The common adverse events table in the prescribing information differs from this table as it is rounded to the nearest percent for simplicity.

8.2.4.5. Adverse Events of Special Interest

Adverse events of special interest (AESIs) and other selected adverse event groupings are summarized in Table 53, Table 54, Table 55.

Table 53. EFC14146 AESIs > Placebo (Safety Population)

Preferred Term	Placebo N=132	Dupilumab 300 mg q2w N=143
Any AESI	9 (6.8%)	6 (4.2%)
Epistaxis	4 (3%)	11 (7.7%)
Eosinophilia	2 (1.5%)	3 (2.1%)
Conjunctivitis	1 (0.8%)	3 (2.1%)
Hepatic disorder	0 (0%)	1 (0.7%)

AESI = adverse event of special interest; q2w = every two weeks
Source: CSR 14146 p.189 Table 61 verified by Reviewer in JMP

Overall, there were fewer adverse events of special interest in the dupilumab group when compared to placebo. Epistaxis and conjunctivitis occurred much more frequently in the dupilumab group. The cases of conjunctivitis (broad grouping) included two cases of conjunctivitis and one case of blepharitis in the dupilumab group and one case of allergic conjunctivitis in the placebo group. None of the patients with treatment-emergent conjunctivitis had allergic conjunctivitis at baseline. One case of eosinophilia in the dupilumab group progressed to EGPA, the remaining were lab manifestations that self-resolved. The case of drug-related hepatic disorder did not meet Hy's law, it consisted of AST and ALT elevation in a patient that self-resolved.

Table 54. EFC14280 AESIs > Placebo (Safety Population)

Preferred Term	Placebo N=150	Dupilumab 300 mg q2-q4w N=148	Dupilumab 300 mg q2w N=149
Any AESI	13 (8.7%)	7 (4.7%)	8 (5.4%)
Conjunctivitis	2 (1.3%)	7 (4.7%)	5 (3.3%)
Eosinophilia	2 (1.3%)	3 (2.0%)	2 (1.3%)
Serious/severe injection site reaction	0 (0%)	1 (0.7%)	0 (0%)

AESI = adverse event of special interest; q2w = every two weeks; q2-q4w = every 2-4 weeks
Source: CSR 14280 p. 220 Table 73 verified by Reviewer in JMP

Overall, there were fewer adverse events of special interest in the dupilumab arms when compared to placebo. There was more conjunctivitis in the dupilumab arms when compared to placebo. This broad grouping of conjunctivitis includes two cases of conjunctivitis in the placebo group, three in the q2-q4w group, and four in the q2w group. There were also two cases of dry eye in the q2-4w group and one case in the q2w group. There was one case of hyperemia in the q2-4w group and one case of eye discharge in the q2-4w group. Only two patients with treatment-emergent conjunctivitis had allergic conjunctivitis at baseline. Five of the eosinophilia cases were pure laboratory findings. Two cases of eosinophilia were SAEs that resulted in treatment discontinuation. One of these patients had eosinophilia, arthralgia, asthma exacerbation, and insomnia. The second patient progressed to EGPA. AESIs occurring between weeks 24 and 52 are reflective of AESIs in Table 54.

Reviewer comment: In the finalized label, the Applicant chose to focus on the narrow grouping of conjunctivitis (general conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and allergic conjunctivitis). When both dupilumab arms are combined and all percentages are rounded for simplicity, this leads to 3% in the dupilumab group (4+4/148+149) vs. 1% in the placebo group. The Division agreed with this methodology to remain consistent with the other indications.

Table 55. 24-Week Pooled AESIs > Placebo (Safety Population)

Preferred Term	Placebo N=282	Dupilumab 300 mg q2w N=440
Any AESI	11 (3.9%)	12 (2.7%)
Conjunctivitis	1 (0.4%)	12 (2.7%)
Eosinophilia	1 (0.4%)	6 (1.3%)
Hepatic disorder	0 (0%)	3 (0.7%)
EGPA	0 (0%)	1 (0.2%)
Serious/severe injection site reaction	0 (0%)	1 (0.2%)

AESI = adverse event of special interest; EGPA = eosinophilic granulomatosis with polyangiitis; q2w = every two weeks
Source: ISS 1.4.3.1. p. 1054 verified by Reviewer in JMP

Overall, there were fewer AESIs in the dupilumab group when compared to placebo. The broad grouping of conjunctivitis included six cases of conjunctivitis, two cases of dry eye, one case of blepharitis, one case of hyperemia, one case of bacterial conjunctivitis, and one case of eye discharge in the dupilumab group. There was one case of allergic conjunctivitis in the placebo group. The patients with hepatic disorders include the patient with AST/ALT elevation in EFC14146 and additional cases of ALT elevations in two patients which self-resolved.

Reviewer comment: In the finalized label, the Applicant chose to focus on the narrow grouping of conjunctivitis (general conjunctivitis, bacterial conjunctivitis, allergic conjunctivitis, and eye inflammation). When rounded for simplicity, this leads to 2% in the dupilumab group vs. 1% in the placebo group. The Division agreed with this methodology to remain consistent with the other indications.

8.2.4.6. Laboratory Findings

8.2.4.6.1. Liver Function Tests

There were a total of 3 patients with abnormal liver function testing during the entirety of the study:

1. In SINUS-24 one patient experienced AST and ALT elevations on the 9th dose of IMP. ALT was 65 IU/L (normal: 10-40 IU/L), AST was 87 IU/L (normal: 10-43 IU/L), and remaining liver function tests were normal. The patient recovered 7 days after with normalization of all labs.
2. In SINUS-52 one patient in the 300mg q2w-q4w had an increase in ALT. Fourteen days after the 8th dose of IMP, the patient had ALT of 188 IU/L (normal: 10-40 IU/L), AST of 120 IU/L (normal: 10-43 IU/L), and alkaline phosphatase of 120 IU/L (normal: 43-115 IU/L). Bilirubin was normal. The patient was asymptomatic throughout and recovered 6 days after the 9th IMP injection with normalization of all liver function tests.
3. In EFC14280 one patient in the 300mg q2w group had portal hypertensive gastropathy (confirmed by upper endoscopy). Seven days after the 21st dose of IMP, the patient had portal hypertensive gastropathy caused by *Helicobacter pylori.* One week prior to this diagnosis, ALT was 48 IU/L (normal: 10-40 IU/L) and all other liver function test results were normal. He was treated for *Helicobacter pylori* and recovered fully with a normal ALT after treatment.

Changes in liver function testing were rare, asymptomatic, and resolved despite continuing on IMP. No patients had laboratory test abnormalities that met criteria for Hy's law.

8.2.4.6.2. Eosinophilia

Similar to previous programs, eosinophilia and progression to EGPA remains a concern in the nasal polyp program. This may be due to unmasking of EGPA as patients taper off steroids and begin IMP. Cases of eosinophilia were appropriately monitored for symptoms of EGPA, however many of these cases reached a peak eosinophil level and then self-resolved. In subjects with CRSwNP, the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

EFC14146

There were 3 patients in the dupilumab group and 2 patients in the placebo group with eosinophilia. One of these patients in the dupilumab group and one patient in the placebo group progressed to EGPA.

The patient in the dupilumab group that progressed to EGPA received three 5-day courses of prednisone before entering the study and reported lower leg cramping and tingling in her toes one month before IMP. At this time her eosinophil count was 860 cells/mcL (normal: 0-800 cells/mcL). One day prior to IMP symptoms worsened to severe neck and shoulder pain, tingling in all extremities, and paresthesia leading to weakness in the feet and difficulty walking. Eosinophils at this time were 2,420 cells/mcL. One dose of IMP was given and then subsequently discontinued. She was hospitalized and treated with systemic corticosteroids and azathioprine with improvement in symptoms however her last eosinophil count remained elevated at 2,310 cells/mcL.

The other 2 patients in the dupilumab group had asymptomatic increases in eosinophil levels. One of these patients had a baseline eosinophil level of 1610 cells/mcL which increased to 3220 cells/mcL 14 days after the 8th dose of IMP. At the end of study, eosinophil count remained elevated at 2080 cells/mcL. The second patient had an eosinophil cont of 3110 cells/mcL (baseline 2120 cells/mcL), 14 days after the 8th IMP. Eosinophil count was 1730 cells/mcL 34 days after the last IMP.

Reviewer comment: The more commonly used reference range for eosinophil level is 0-300 cells/mcL, ranging to 0-500 cells/mcL. The Applicant notes a reference range of 0-800 cells/mcL in the patient narrative.

EFC14280

Two patients in the placebo group, 3 patients in the dupilumab 300mg q2w-q4w group (with one EGPA case), and 2 patients in the dupilumab 300mg q2w group had eosinophilia.

In the 300mg q2w group, one patient, 2 days after the 7th dose of IMP experienced eosinophilia (8600 cells/mcL from baseline 1470 cells/mcL) associated with arthralgia of all joints, asthma exacerbation, and mild insomnia. Of note the patient was on chronic low dose steroids for one year prior to enrolling in the study and received 6 courses of prednisolone for asthma exacerbations while on study. The patient was treated with oral corticosteroids and pain-relievers and IMP was discontinued 14 days after last IMP. The patient recovered from symptoms with eosinophil count of 530 cells/mcL Giga/L.

The other patient in the 300mg q2w group had eosinophilia of 4780 cells/mcL (baseline 2900 cells/mcL) 13 days after the 8th dose of IMP. The patient was asymptomatic thus IMP was not discontinued and no corrective treatment was given. The last known eosinophil count was 1350 cells/mcL thus eosinophilia had not resolved by time of report.

In the 300mg q2w-q4w group, one female patient on placebo accidentally received one dose of dupilumab 300mg on Day 30. Three hundred and five days after this IMP dose the patient presented with dyspnea, abdominal pain, and eosinophilia of 1570 cells/mcL (baseline 680 cells/mcL) and was diagnosed with EGPA. She received 4 courses of prednisone prior to event

onset for nasal polyps. She was treated with high dose steroids, cyclophosphamide, and IMP was discontinued. By end of study, eosinophil count returned to baseline.

The second patient in the 300mg q2w-q4w group had eosinophilia of 1400 cells/mcL (baseline 580 cells/mcL) 13 days after the 10th dose of IMP which led to temporary interruption of treatment. The patient experienced headache, cough, nausea, and arthralgia which self-resolved. The patient resumed IMP and 33 days after the 11th IMP dose eosinophil count returned to normal (740 cells/mcL). The third patient in the 300mg q2w-q4w had a peak eosinophil count of 3020 cells/mcL (baseline 880 cells/mcL) on the day of 9th IMP. The patient was asymptomatic and eosinophilia resolved 14 days after the 12th IMP (520 cells/mcL).

Vital Signs

Vital sign measurements included blood pressure (mm Hg), heart rate (HR), respiration rate (breaths per minute), body temperature (degrees Celsius), and body weight (kg) prior to IMP at each visit. Height was measured at screening (in cm). There were no notable abnormalities in vital signs except cases of hypertension mentioned in common adverse events tables.

Electrocardiograms

Electrocardiograms (12-lead) were performed at multiple time points to monitor for abnormalities. There were no notable abnormalities in electrocardiograms except for the case of acute myocardial infarction noted in the serious adverse events tables.

Immunogenicity

ADA (anti-drug antibody) formation did not correlate with any safety findings, with no apparent pattern or increase in treatment-emergent adverse event incidence in the ADA-positive patients compared to ADA-negative patients. There was also no apparent temporal relationship between ADA positivity and the occurrence of adverse events.

8.2.5. Analysis of Submission-Specific Safety Issues

No additional safety issues were identified other than the aforementioned.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable

8.2.7. Safety Analyses by Demographic Subgroups

No safety differences were noted in subgroups based on demographics. Though the relative risk ratio (95% CI) for the incidence of AE for dupilumab versus placebo in the 24 week pooled safety population was 1.94 (95% CI 0.94 to 4.01) for Blacks/those of African descent, the n for this number of patients was small (n=6 in dupilumab group) thus no significant conclusion can be made.

8.2.8. Specific Safety Studies/Clinical Trials: 120-Day Safety Update

The 120-day safety update (covering September 29, 2018, to February 28, 2019) included data from subjects in EFC14280, who were still ongoing in the 12-week post-treatment follow-up period for safety at the time of data cut-off (August 29, 2018) for the sBLA filing. There were no notable safety events reported in the 120-day safety update for EFC14280.

The 120-day safety update also included data from the ongoing long-term safety study (LTS12551) in patients with asthma. There were 3 new deaths:

1. 65-year old patient in Spain had pancreatic adenocarcinoma
2. 64-year old patient in the United States died of respiratory failure. One month after her last dose of IMP, she experienced a severe asthma exacerbation in the middle of the night and subsequently died of respiratory failure.
3. 29-year old Chilean female died of tuberculous meningitis 5 months after her last dose of IMP.

There were newly reported safety events in 3 patients in dupilumab studies in other indications.

1. A subject in the pediatric asthma trial EFC14153 (6 to <12 years of age) experienced infection of the lung but recovered.
2. A subject in the pediatric asthma trial EFC14153 reported eosinophilia, headache, and blurred vision. Though eosinophilia resolved, headache and blurred vision was documented as unresolved at the time of the 120-day safety report.
3. Subject in the adult atopic dermatitis trial (R668-AD-1225) was diagnosed with gastroenteritis and recovered.

Overall the newly reported safety events are consistent with safety events identified with the current programs.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No true malignancies were reported in EFC14146 or EFC14280.

Human Reproduction and Pregnancy

No pregnancies occurred in the nasal polyposis trials; a pregnancy registry for the atopic dermatitis indication is in place.

Pediatrics and Assessment of Effects on Growth

Pediatric studies not applicable

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose was defined as administration of at least twice the planned dose during an interval of less than 11 days. In EFC14146, 3 (2.1%) patients in the dupilumab group and 4 (3.0%) patients in the placebo group met criteria for overdose once. In EFC14280, 5 (3.4%) patients in the 300mg q2w group, 12 (8.1%) patients in the dupilumab 300mg q2w-q4w group, and 12 (8.0%) in the placebo group met criteria for overdose at least once, with 2 patients having more than one overdose (1 in 300mg q2w-q4w group and 1 in placebo group). No safety events were reported for these cases of overdose.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

See Section 8.2.8

8.2.11. Integrated Assessment of Safety

Safety analysis was based on a 24-week safety pool of the 300 mg q2w dose from the 24-week safety and efficacy study and the first 24 weeks of the 52-week safety and efficacy study.

For the safety pool, there were two deaths, both in placebo (acute myocardial infarction and traumatic intracranial hemorrhage). There was one major adverse cardiovascular event (acute myocardial infarction) in EFC14146, and this event will be included in the prescribing information.

For the safety pool, 31 (9.1%) patients had an SAE. A lower percentage of subjects reported SAEs in the dupilumab 300 mg q2w group (15 (3.4%)) compared to placebo (16 (5.7%)).

Infection was the most commonly reported SAE, with a lower incidence in the 300 mg q2w dupilumab group (3 (0.7%)) compared placebo (3 (1.1%)). Injection-site reactions were similar between groups in the pooled SAE data. All other SAEs were reported in only one subject. Additional SAEs noted in the full 52-week safety period for EFC14280 were also reported in only one subject. Overall there were no malignancies in the dupilumab groups, only a uterine polyp in one patient in EFC14146.

No additional consistent treatment related safety findings are seen from a review of SAE data from the larger pooling of placebo-controlled trials or review of the data from the individual trials.

For the 24-week safety pool, 26 subjects (7.8%) had AEs leading to discontinuation of investigational product, with 11 subjects (2.5%) on dupilumab. Each event leading to discontinuation occurred only in one person. No additional consistent treatment related safety findings are seen from a review of AEs leading to discontinuation data from the review of the data from the individual trials.

For the 24-week safety pool, the overall common adverse event incidence was similar across treatment groups. The most common adverse event was injection-site reactions, occurring in 34 (7.7%) of subjects on 300 mg q2w of dupilumab and 12 (4.3%) on placebo. Other common

AEs of cough, arthralgia, hypertension, back pain, influenza, gastritis, conjunctivitis, oral herpes, insomnia, oropharyngeal pain, rhinorrhea, GERD, eosinophilia, and toothache were reported at a slightly higher incidence than placebo.

For studies EFC14146 and EFC14280, eosinophilia adverse events were noted in both studies. In EFC14146, three patients (2.1%) reported eosinophilia in the dupilumab group compared to two patients (1.5%) in the placebo group. Two of these cases (one in dupilumab group and one in placebo group) progressed to EGPA. Eosinophils peaked around 16 weeks after the first dose. In EFC14280, two (1.3%) and three (2.0%) of patients had eosinophilia in the dupilumab 300 mg q2w and 300 mg q2w-4w groups respectively. Two patients (1.3%) had eosinophilia in the placebo group. One of the placebo group patients with eosinophilia progressed to EGPA. Eosinophils peaked around 16 weeks after the first dose and returned to baseline by 24 weeks in the 300 mg q2w group and 52 weeks in the 300 mg q2w-q4w group. The prescribing information includes eosinophilia and EGPA to inform prescribers of this risk.

No anaphylaxis events were reported in either study. In the 24-week safety pool, hypersensitivity events occurred less frequently for subjects on dupilumab (four (0.9%)) compared to placebo (five (1.8%)).

Injection site erythema was the most commonly reported injection-site reaction. In the 24-week safety pool, less than 1% of subjects had a serious or severe injection site reaction. In the 24-week safety pool, no subjects discontinued treatment due to injection-site reactions.

The ocular safety issues (conjunctivitis, blepharitis, dry eye, hyperemia) identified in the atopic dermatitis program were also seen in the nasal polyp program. Eczema herpeticum and herpes zoster that were identified in the atopic dermatitis program were not identified in the nasal polyp program.

Safety concerns noted in the atopic dermatitis clinical studies included eczema herpeticum and herpes zoster. This was not noted in the nasal polyposis program. Parasitic infections were not reported in any patients on dupilumab.

No pregnancies were reported in the nasal polyposis clinical studies. A pregnancy registry was included in the atopic dermatitis approval.

No safety differences were noted in the subgroups based on baseline characteristics.

Overall, the safety profile in inadequately controlled nasal polyposis in adults is favorable.

8.3. Statistical Issues

Statistical issues will be described in the context of the efficacy estimand for this development program. An estimand is described by four features:

1. Population of interest: Adult patients with physician diagnosed nasal polyps within the last 2 years, who have nasal polyps with chronic rhinosinusitis, and an inadequate

response to standard of care therapy (which includes at least 8 weeks of intranasal CS and may include systemic CS and/or nasal polyp surgery).

2. Endpoint of interest: Change from baseline in co-primary endpoints, average daily NC, and NPS at Week 24.
3. Measure of intervention effect: Difference in variable means between active and placebo treatment groups at Week 24.
4. How potential intercurrent events were reflected:
    a. Rescue treatment: the patients who had rescue (surgery or systemic corticosteroid treatment) would be considered treatment failures (composite strategy: intercurrent event is taken to be a component of the variable)
    b. Treatment discontinuation: the variables of interest (NC or NPS) values for the patients who did not have rescue are used regardless of whether or not treatment discontinuation occurs (treatment policy strategy: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs)

The estimator is defined as follows:

- Population-level summary for the endpoint: Difference in least squares means between active and placebo treatment groups employing an ANCOVA model consisting of treatment group, asthma/nonsteroidal anti-inflammatory drug-exacerbated respiratory disease status, prior surgery history, and regions as factor variables and baseline value as the covariate.
- How potential intercurrent events are reflected:
    1. Rescue treatment: worst score patient experienced prior to rescue is imputed to Week 24 score
    2. Treatment discontinuation: patients' observed data post discontinuation is used and multiple imputation used to handle missing data

Sensitivity analyses are conducted:

- Analysis models: a) MMRM
- Alternative estimands regarding intercurrent events:
    1. using actual data for patients on SCS
    2. Assumption for missing data used in the primary estimator: tipping point or other analyses in the estimator

Results from the MMRM sensitivity analysis for each of the two coprimary efficacy endpoints at 24 weeks had results similar to the primary analysis. For sensitivity analysis of the two types of intercurrent events, as-observed data for SCS was performed for patients on SCS and tipping point was performed for missing data.

We find this estimand, the corresponding estimator, and sensitivity analysis to be reasonable and appropriate. In all sensitivity analyses, the results remained statistically significant, demonstrating the robustness of dupilumab for patients with nasal polyposis.

Overall, we found the statistical plan and analysis for this submission to be robust.

8.4. Conclusions and Recommendations

In summary, there was evidence of efficacy for dupilumab from the two studies that were reviewed under this supplemental application. Therefore, the overall package provides substantial evidence of efficacy of dupilumab as an add-on maintenance treatment in adult patients with inadequately controlled nasal polyps.

9. Advisory Committee Meeting and Other External Consultations

There were no safety or efficacy concerns requiring an Advisory Committee meeting for dupilumab for nasal polyposis.

10. Pediatrics

A full waiver was requested as studies are impossible or highly impractical (the number of pediatric patients is small). Nasal polyps occur very rarely in children, except for children with cystic fibrosis, who have predominantly neutrophilic polyps. Subjects with cystic fibrosis were excluded from the study[12]. On April 24, 2019, this waiver was brought before PeRC and the committee agreed to a full waiver.

[12] Segal N, Gluk O, Puterman M, 2012, Nasal polyps in the pediatric population. B-ENT 8(4): 265-7.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Section	Proposed Labeling	Approved Labeling	Rationale
Indications and Usage Pharmacodynamics Clinical Studies	(b) (4)		
Indications and Usage	(b) (4)	Interleukin-4 receptor alpha antagonist	As per 21 CFR 201.57(a)(6) if the product is a member of an established pharmacologic class, the statement in Highlights must identify the class.The established pharmacologic class is interleukin-4 receptoralpha receptor antagonist.
Indications and Usage	-Add-on maintenance treatment in adult patients with inadequately controlled (b) (4) chronic rhinosinusitis with nasal polyposis (b) (4)	Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis	-This is the first systemic and monoclonal antibody proposed for treatment of nasal polyps. As discussed in the review, we have incorporated the term of chronic rhinosinusitis to acknowledge the overlap of these diseases and anatomic continguity of the nasal mucosa and paranasal sinuses. (b) (4) (b) (4)

Section	Proposed Labeling	Approved Labeling	Rationale
Dosage	(b) (4)	300mg given every other week	(b) (4)
5	"In subjects with CRSwNP, the frequency of conjunctivitis was (b) (4)% in the DUPIXENT group, compared to (b) (4)% in the placebo group in the 24-week safety pool. (b) (4)	"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	The Applicant chose to focus on (b) (4) grouping of conjunctivitis (conjunctivitis, bacterial conjunctivitis, allergic conjunctivitis, and eye inflammation) to obtain these percentages. (b) (4)
6	In the 52-week CRSwNP study (CSNP Trial 2), the frequency of conjunctivitis was (b) (4)% in the DUPIXENT (b) (4)	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.	This 52-week conjuncitivitis incidence information was corrected based on (b) (4) grouping of conjunctivitis (general conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, and allergic conjunctivitis). (b) (4)
6	(b) (4)		

Section	Proposed Labeling	Approved Labeling	Rationale
6	(b) (4)	Added 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.	The cardiovascular adverse reactions section was updated to include all cardiovascular events that occurred during both trials.
6	(b) (4)	Removed	(b) (4)
6	Immunogenicity	Percentages updated	Percentages updated to reflect accuracy with anti-dupilumab antibody incidence
12			(b) (4)
14	In both studies, key secondary endpoints at Week 24 included change from baseline in: LMK sinus CT scan score, (b) (4) (b) (4) (b) (4) daily loss of smell, and 22-item sino-nasal outcome test (SNOT-22).	(b) (4) -Added loss of smell descriptor	The total symptom score includes symptoms that overlapped between sinusitis, nasal polyps, and rhinitis. One of its symptoms, nasal congestion, was already a co-primary endpoint and other symptoms are included in the SNOT-22. (b) (4) (b) (4) -

Section	Proposed Labeling	Approved Labeling	Rationale
14	(b) (4)	Modified	(b) (4) comment in Section 14 that in those patients with CRSwNP and asthma, the improvement in FEV1 was similar to the asthma studies.
Table 11	Demographics and baseline characteristics		(b) (4)
Table 12			(b) (4) (b) (4)

Section	Proposed Labeling	Approved Labeling	Rationale
14	"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."	Added "with prior surgery and without prior surgery."	Subjects were stratified a priori according to prior surgery (yes/no) and results were consistent in those with and without prior surgery thus the Division agreed to the addition of this statement in the label.

Reviewer comment: Previously the Division did not encourage the use of SNOT-22 in efficacy claims or product labeling due to the fact that it included 22 items with confounding for nasal polyp, sinusitis, and rhinitis symptoms. It also included quality of life mood measures. Symptoms specific to chronic sinusitis (thick nasal discharge, facial/pain and pressure) and nasal polyps were extracted from SNOT-22 and analyzed and proved to be statistically significant. The Clinical Outcome Assessment group was consulted for this sBLA in order to assess the validity of SNOT-22. The Clinical Outcome Assessment group recommended the inclusion of SNOT-22 in the prescribing information as a patient-reported outcome to assess symptoms and symptom impact associated with CRSwNP as the face validity, content validity, and psychometric properties have been supported by literature. For more details see consult review from Dr.Hongling Zhou from May 30, 2019 (DARRTS Reference ID: 4441326).

12. Risk Evaluation and Mitigation Strategies

Not applicable

13. Postmarketing Requirements and Commitment

Not applicable

APPEARS THIS WAY ON ORIGINAL

14. Division Director (Clinical) Comments

Dupilumab is a monoclonal antibody proposed for the indication of add-on maintenance treatment chronic rhinosinusitis with nasal polyps (CRSwNP). Dupilumab targets the IL-4Rα subunit, which is shared by the IL-4 and IL-13 receptor complexes, and therefore, inhibits IL-4 and IL-13 signaling. Dupilumab was approved in March 2017 for adult patients with atopic dermatitis and in October 2018 for treatment of moderate-to-severe asthma in patients 12 years old and older with an eosinophilic subtype or oral corticosteroid-dependent asthma.

Current therapies for nasal polyps include intranasal steroids as well as use of mometasone furoate sinus implants. Many patients require treatment with courses of systemic corticosteroids and some patients require nasal polyp surgery. Nasal polyps can cause significant morbidity due to sleep disturbances, headaches, and loss of smell.

The nasal polyp program consists of 2 pivotal clinical trials: a 24 week and a 52 week efficacy and safety trial in a total of 724 patients with inadequately controlled CRSwNP on background intranasal mometasone furoate. The clinical trials were adequate and well-controlled. The sponsor chose to study a single dose of 300mg SC q2w in both clinical trials. In the 52 week trial, in addition to the dupilumab 300mg SC q2w dose, there was an additional treatment arm that was 300mg SC q2w from week 0 to 24 then 300mg SC q4w from week 24 to week 52. Unlike with the asthma program, there is was no loading dose. Both clinical trials demonstrated a statistically significant improvement in endoscopic nasal polyp scores and nasal congestion in patients treated with dupilumab compared to placebo. Pooled analysis of both clinical trials showed a reduction in systemic corticosteroid use and nasal polyp surgery in patients treated with dupilumab compared to placebo. Results from the secondary endpoints of LMK sinus CT scan score, loss of smell, and SNOT-22 were supportive of the efficacy of dupilumab in this patient population.

The safety of dupilumab was adequately assessed in the nasal polyp development program. In addition, safety data are available from the atopic dermatitis and asthma program. Injection site reactions were the most common AE. The ocular safety issues seen in the atopic dermatitis program were not identified in the asthma studies, but a few cases were noted in the nasal polyp program. Overall, the safety data are consistent with the existing safety data from the atopic dermatitis and asthma programs and do not raise safety concerns that outweigh the benefits of dupilumab for the treatment of patients with nasal polyp.

The overall benefit risk assessment of dupilumab is favorable for the add-on maintenance treatment of CRSwNP. Dupilumab is the first biologic therapy proposed for the treatment of patients with nasal polyps.
The indication statement is important to discuss as this would be the first product approved for patients with CRSwNP. The Division considers chronic sinusitis, allergic rhinitis, and nasal polyps as different regulatory pathways. Each indication would require enrollment of the appropriate patient population and assessment of the relevant endpoints (e.g. rhinitis - total nasal symptom score; chronic sinusitis – symptoms [congestion, facial pain/pressure, purulent discharge] and imaging of sinuses; nasal polyps – nasal polyp score and congestion). Depending

on the development program, sponsors can pursue the individual indications. However, there has been an evolution of terminology with respect to nasal polyps in the academic community and medical literature. As discussed in Section 2.1, chronic rhinosinusitis is now considered an umbrella term acknowledging the nose and sinus are a contiguous space. Presence of nasal polyps is considered as a subgroup of chronic rhinosinusitis. Thus, there are patients with chronic rhinosinusitis with nasal polyps and patients with chronic rhinosinusitis without nasal polyps.

The Division has previously approved intranasal steroids and mometasone drug eluting stent for the treatment of nasal polyps (without any language regarding chronic rhinosinusitis). The dupilumab program supports the CRSwNP indication. As discussed in the review, patients enrolled in the dupilumab clinical trials not only had nasal polyps, but also had evidence of chronic sinusitis per CT sinus scores as well as chronic rhinosinusitis symptoms (congestion, facial pain/pressure, nasal discharge). Results from the clinical program showed treatment with dupilumab improved not only nasal polyp size and symptoms, but also improved LMK sinus CT scan scores, and symptoms of chronic rhinosinusitis (congestion, facial pain, nasal discharge). The indication CRSwNP is distinct from chronic rhinosinusitis (or chronic sinusitis) without nasal polyps. Dupilumab has not been studied in patients with chronic rhinosinusitis without nasal polyps.

Studies in pediatric patients are waived given that CRSwNP is not common in children.

The Division and sponsor have agreed upon labeling. The review teams recommend approval of this sBLA and I concur.

15. Appendices

15.1. Financial Disclosure

- The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this new drug application (NDA). Details of the financial disclosure are outlined below.
- The Applicant submitted Food and Drug Administration (FDA) Form 3454 (3/16) certifying investigators and their spouses/dependents were in compliance with 21 Code of Federal Regulations (CFR) Part 54.
- The five investigators disclosed their financial interests/arrangements and implemented appropriate actions to protect the studies from potential bias.

Covered Clinical Study (Name and/or Number): EFC14146, EFC14280

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 858		
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): 5		
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: 1 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: _____		
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)

15.2. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.2.1. Pharmacometrics Review

15.2.1.1. Population PK Analysis

15.2.1.1.1. Introduction

Population pharmacokinetic analysis of dupilumab used pooled data from Studies ACT12340, EFC14146 and EFC14280 in patients with nasal polyps (NP).

The main objectives of this analysis were the following:

1. To confirm and apply dupilumab global base population pharmacokinetic model in NP patients;
2. To assess the influence of intrinsic and extrinsic factors on dupilumab pharmacokinetics in NP patients;
3. To predict individual dupilumab exposure in NP patients.

15.2.1.2. Model Development

15.2.1.2.1. Data

The study design, study population, and timing of blood samples varied among the three clinical studies. Brief descriptions of the studies along with the timing of the blood samples for each study are presented in Table 56.

The final data file for analysis contained 2,580 PK observations from 466 NP subjects.
Table 57 provides summary statistics of the baseline demographic covariates in the analysis dataset.

Table 56. Summary of Studies with PK Sampling Included in Population PK Analysis

Phase	Study	Dupilumab Dose Regimens	Duration of Treatment	Population	PK Sampling	N[a]	Status at Time of Analysis
2	ACT12340	Subcutaneous (SC) : 300 mg qw with a loading dose of 600 mg at Day 1	16 weeks	patients with bilateral nasal polyposis and chronic symptoms of sinusitis	Sparse sampling[b]	30	Completed
3	EFC14146	SC : Arm A: 300 mg q2w[d]	24 weeks	Patients with bilateral nasal polyposis on a background therapy with intranasal corticosteeroids	Sparse sampling[c]	141	Ongoing[d]
3	EFC14280	SC : Arm A: 300 mg q2w until Week 52; Arm B: 300 mg q2w until Week 24, then 300 mg q4w until Week 52	52 weeks	Patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids	Sparse sampling[e]	294	Ongoing[f]

Abbreviation: N: number of patients included in this Pop PK analysis; qw: every week; q2w: every two weeks.
a. The total number of NP patients included this Pop PK analysis is 465.
b. In study ACT12340, scheduled PK sampling at baseline, trough (predose) at Weeks 2, 4, 8, 12 and 16 during treatment, and at Weeks 20, 24, 28 and 32 during safety follow-up period.
c. In study EFC14146, scheduled PK sampling at baseline, trough (predose) at Weeks 4, 8, 16, and 24 during treatment, and at Weeks 36 and 48 during safety follow-up period.
d. In study EFC14146, up to a PK data cut-off date of Feb 12, 2018, PK data from N=135 (96%), 4 (3%), and 0 (0%) at Weeks 24, 36, and 48, respectively.
e. In study EFC14280, scheduled PK sampling at baseline, trough (predose) at Weeks 2, 4, 16, 24, 40 and 52 during treatment, and at Weeks 64 during safety follow-up period.
f. In study EFC14280, up to a PK data cut-off date of Feb 12, 2018, data from approximately N=270 (92%), 68 (23%) and 4 (1%) at Weeks 24, 40, and 52, respectively.

Source: Applicant's Population PK report POH0611, Table 1

Table 57. Summary of Baseline Demographic Covariates for Analysis

Covariate candidates	ACT12340			EFC14146			EFC14280			Total		
	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)	N	Mean (SD)	Median (min – max)
Weight (kg)	30	84.5 (16.6)	83.0 (55.2 – 126)	141	81.6 (18.0)	79.4 (38.0 – 130)	294	79.7 (17.9)	78.8 (39.4 – 150)	465	80.6 (17.9)	79.0 (38.0 – 150)
Age (Year)	30	48.0 (9.84)	48.7 (25.6 – 63.1)	141	50.8 (13.7)	52.4 (23.2 – 79.7)	294	52.7 (12.3)	52.3 (19.1 – 83.3)	465	51.8 (12.7)	52.0 (19.1 – 83.3)
CLCR (mL/min)	29[a]	119 (34.0)	109 (65.3 – 189)	141	124 (36.3)	116 (56.1 – 233)	294	128 (45.7)	121 (35.9 – 329)	464	127 (42.3)	120 (35.9 – 329)
CLCRN (mL/min/1.73 m2)	29[a]	103 (24.2)	97.2 (66.8 – 153)	141	110 (26.3)	108 (60.7 – 182)	294	116 (34.9)	110 (34.3 – 303)	464	114 (32.1)	109 (34.3 – 303)
Albumin (g/L)	30	42.7 (2.40)	42.0 (38.0 – 47.0)	141	46.1 (2.81)	46.0 (39.0 – 54.0)	294	45.0 (2.87)	45.0 (37.0 – 53.0)	465	45.2 (2.93)	45.0 (37.0 – 54.0)
EoS (cells/mm3)	30	406 (236)	355 (110 – 1190)	141	425 (313)	340 (0 – 2110)	294	423 (349)	330 (20.0 – 2900)	465	422 (332)	340 (0 – 2900)
NPS	30	5.87 (1.01)	6.0 (3.0 – 8.0)	141	5.65 (1.24)	5.50 (2.0 – 8.0)	294	6.18 (1.21)	6.0 (1.5 – 8.0)	465	6.00 (1.23)	6.00 (1.50 – 8.00)
NC	30	1.66 (0.73)	1.57 (0.6 – 3.0)	141	2.26 (0.58)	2.0 (1.0 – 3.0)	294	2.47 (0.59)	2.71 (0 – 3.0)	465	2.35 (0.63)	2.29 (0– 3.00)

Abbreviation: CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by BSA; EoS: eosinophil; NC:nasal congestion; NPS:nasal polyp score. N: subject number; SD: standard deviation.
a.One patient from study ACT12340 with missing information for CLCR and CLCRN was excluded from the summary. In the Pop PK analysis, the missing CLCR and CLCRN values for this patient were imputed using population median of CLCR and CLCRN.

Source: Applicant's Population PK report POH0611, Table 4

Table 58. Additional Baseline Demographic Covariates for Analysis

Covariate candidates	Subgroup	Act12340 N (%)	EFC14146 N (%)	EFC14280 N (%)	Total N (%)
Gender	Male	18 (60%)	87 (61.7%)	183 (62.2%)	288 (61.9%)
	Female	12 (40%)	54 (38.3%)	111 (37.8%)	177 (38.0%)
Race[a]	Caucasian	29 (96.7%)	136 (96.4%)	243 (82.7%)	408 (87.7%)
	Black	1 (3.3%)	2 (1.4%)	4 (1.4%)	7 (1.5%)
	Asian	0 (0%)	1 (0.7%)	36 (12.2%)	37 (8.0%)
	Other	0 (0%)	1 (0.7%)	10 (3.4%)	11 (2.4%)
	Missing	0 (0%)	1 (0.7%)	1 (0.3%)	2 (0.4%)
Stationary ADA	Negative	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	Pre-existing	7 (23.3%)	1 (0.7%)	8 (2.7%)	16 (3.4%)
	Treatment-emergent	3 (10%)	3 (2.1%)	12 (4.1%)	18 (3.9%)
	Treatment-boosted	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Stationary ADA	Non-positive	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	Positive	10 (33.3%)	4 (2.8%)	20 (6.8%)	34 (7.3%)
Stationary ADA	Negative ADA	20 (66.7%)	137 (97.2%)	274 (93.2%)	431 (92.7%)
	0< titers <1000	7 (23.3%)	4 (2.8%)	17 (5.8%)	28 (6.0%)
	1000<= titers <=10000	3 (10%)	0 (0%)	0 (0%)	3 (0.6%)
	titers >10000	0 (0%)	0 (0%)	3 (1.0%)	3 (0.6%)
UPSIT[b]	Normal loss of smell	0 (0%)	4 (2.8%)	5 (1.7%)	9 (1.9%)
	Mild hyposmia	0 (0%)	8 (5.7%)	11 (3.7%)	19 (4.1%)
	Moderate hyposmia	0 (0%)	9 (6.4%)	15 (5.1%)	24 (5.2%)
	Severe hyposmia	0 (0%)	15 (10.6%)	28 (9.5%)	43 (9.2%)
	Anosmia	30 (100%)	100 (70.9%)	218 (74.1%)	348 (74.8%)
	Missing	0 (0%)	5 (3.5%)	17 (5.8%)	22 (4.7%)
ASTH	With	16 (53.3%)	80 (56.7%)	176 (59.9%)	272 (58.5%)
	Without	14 (46.7%)	61 (43.3%)	118 (40.1%)	193 (41.5%)
INCS	Once a day	2 (6.7%)	10 (7.1%)	58 (19.7%)	70 (15.1%)
	Twice a day	28 (93.3%)	131 (92.9%)	236 (80.3%)	395 (85.0%)
ANTIH	With	4 (13.3%)	11 (7.8%)	49 (16.7%)	64 (13.8%)
	Without	26 (86.7%)	130 (92.2%)	245 (83.3%)	401 (86.2%)
OCS	With	1 (3.3%)	87 (61.7%)	225 (76.5%)	313 (67.3%)
	Without	29 (96.7%)	54 (38.3%)	69 (23.5%)	152 (32.7%)
ALLE	With	0 (0%)	2 (1.4%)	8 (2.7%)	10 (2.15%)
	Without	30 (100%)	139 (98.6%)	286 (97.3%)	455 (97.85%)

Abbreviation: ADA: anti-drug antibody; ALLE: allergen immunotherapy; ANTIH: systemic antihistamines; ASTH: patients with comorbid asthma; INCS: intranasal corticosteroid spray; OCS: oral corticosteroids; UPSIT: university of Pennsylvania smell identification test.
a. Two patients from studies EFC14146 and EFC14280 had missing information for race. In Pop PK analysis, the missing race values those patients were imputed using the categorical value of the majority population.
b. Five patients from study EFC14146 and 17 patients form EFC14280 had missing information for UPSIT. In Pop PK analysis, the missing UPSIT values for those patients were imputed using the categorical value of the majority population.
Source: Applicant's Population PK report POH0611, Table 5

PK Model

The final model was a two-compartment model with a first order absorption and parallel linear and nonlinear elimination, with body weight as a covariate.

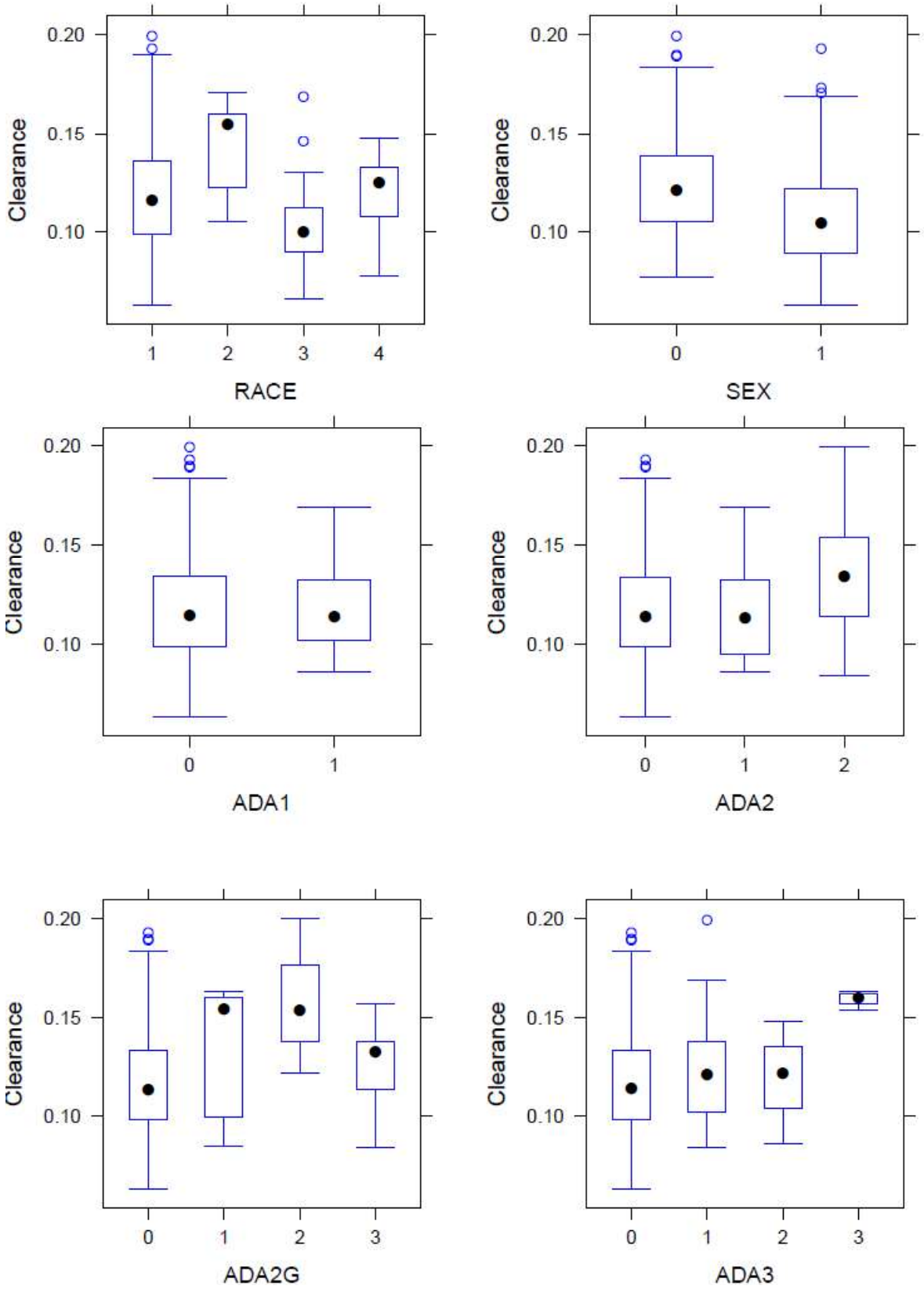
Inter-individual variability for log-transformed PK parameters was modeled assuming a normal distribution for patient level random effects. Residual variability was tested as additive, proportional or both on the dependent variable. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit such as a decrease in the minimum objective function value, accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate Analysis

Selected covariates, including demographics (gender, age, and race), baseline lab parameters (creatinine clearance and albumin), baseline biomarkers (eosinophil [EOS]), disease severity (nasal polyp score [NPS], nasal congestion [NC], University of Pennsylvania smell identification test [UPSIT]), and immunogenicity, were assessed at both screening and stepwise forward selection/backward elimination steps.

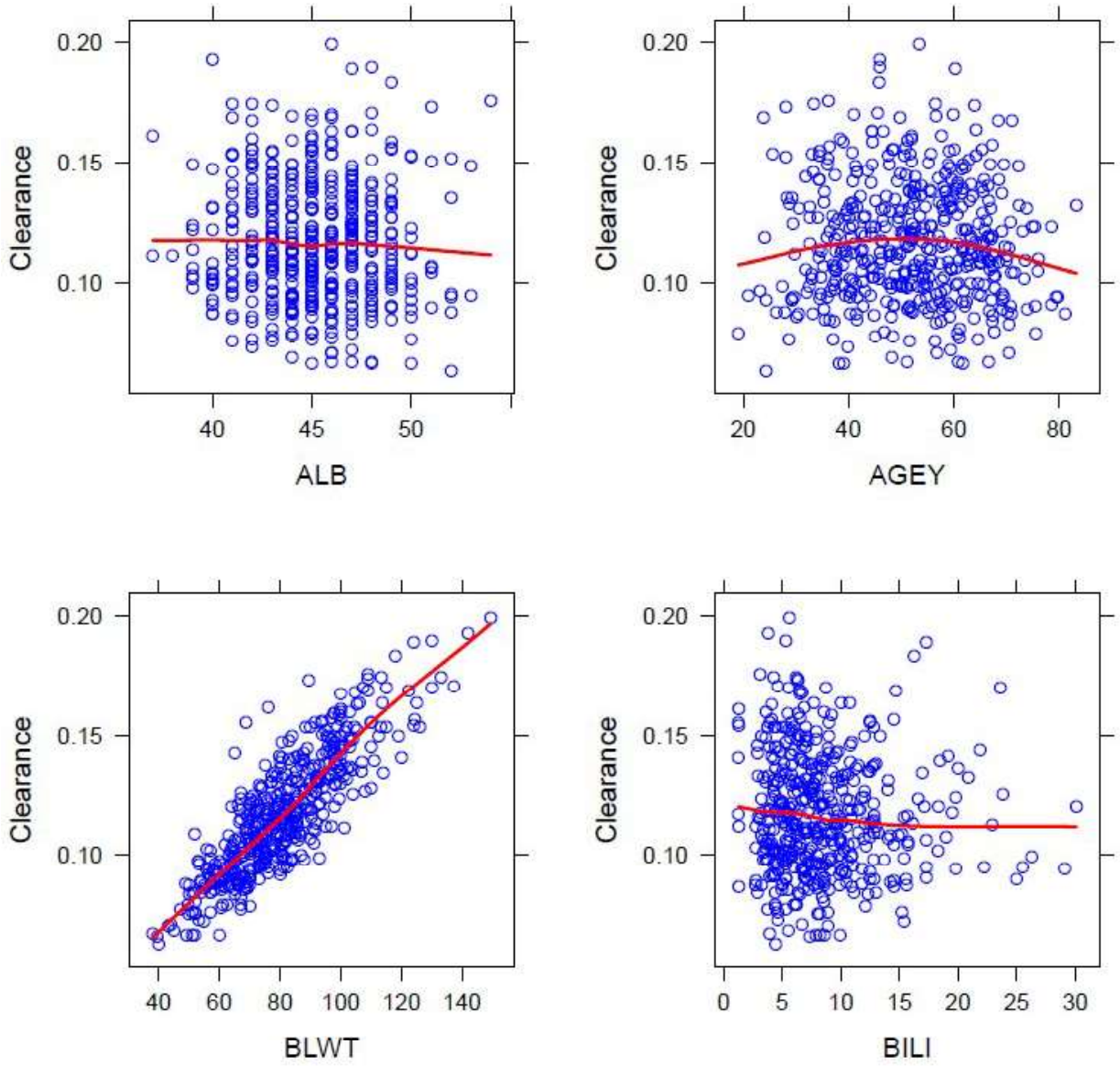
The reviewer's analysis of covariates' effect on PK was similar to that of the Applicant. The effects of covariates including demographics (gender, age, and race), baseline lab parameters (creatinine clearance and albumin), baseline biomarkers (EOS), disease severity (NPS, NC, UPSIT), and immunogenicity on PK parameters are illustrated in Figure 30 to Figure 33.

Figure 30. Covariate Effects on PK Parameters: Race, Sex, and Immunogenicity



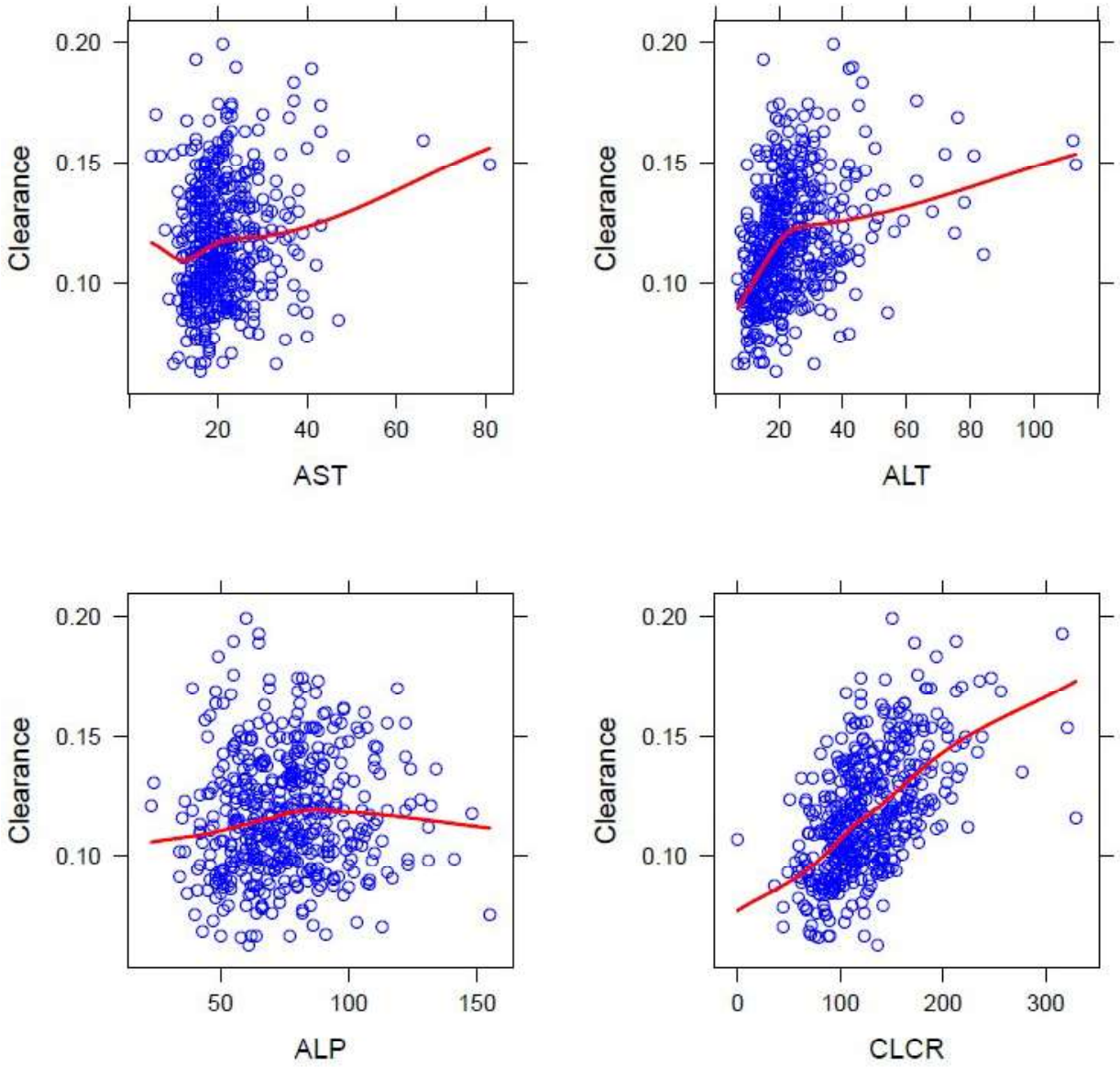
ADA = antidrug antibody

Figure 31. Covariate Effects on PK Parameters: Albumin, Age, Body Weight, and Bilirubin



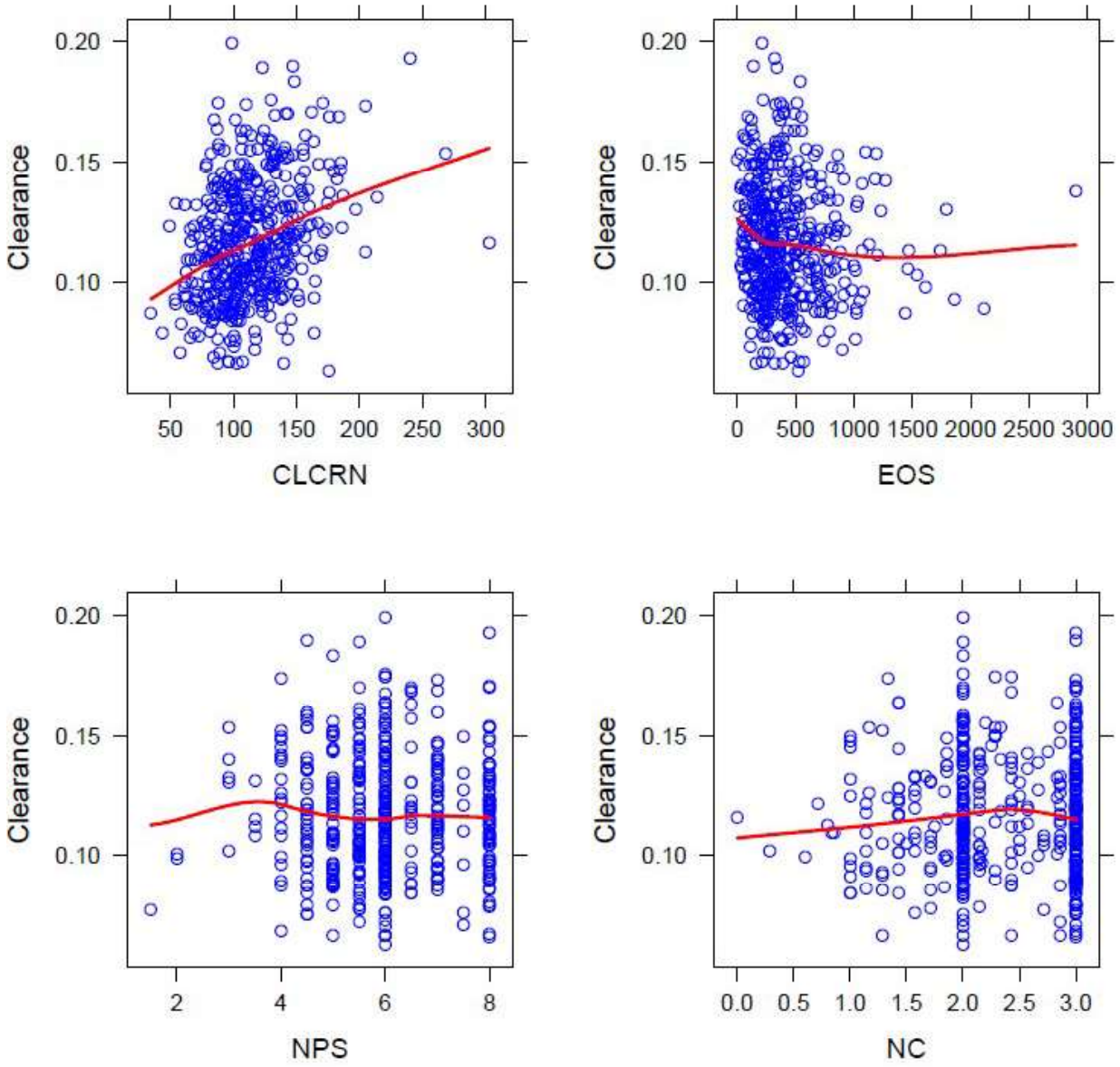
ALB = albumin; AGEY = age in years; BLWT =baseline of body weight ; BILI = bilirubin

Figure 32. Covariate Effects on PK Parameters: Laboratory Values



AST = aspartate aminotransferase; ALT = alanine aminotransferase; ALP = alkaline phosphatase; CLCR = creatinine clearance.

Figure 33. Covariate Effects on PK Parameters: Creatinine Clearance, Eosinophil Counts, and Disease Characteristics



CLCR = creatinine clearance; EOS = eosinophil count; NPS = Nasal Polyps Score; NC = nasal congestion.

15.2.1.2.2. Results

The parameter estimates for the final covariate model in the population PK analysis are listed in Table 59 to Table 61. The goodness-of-fit plots for the final covariate model for all data are shown in Figure 34. The Visual Predictive Check plot for the final covariate model with all data is shown in Figure 35.

Table 59. Parameter Estimates for the Final Model: Theta

Theta	Description	Estimate	FIX	SE	RSE	95%CI
1	K_{EL} 1/day	0.0367	-	0.0006	1.7%	0.035-0.038
2	V_C L	3.08	-	0.0496	1.6%	2.983-3.177
3	K_{CP} 1/day	0.0893	FIX	0	0%	0.089-0.089
4	K_{PC} 1/day	0.15	FIX	0	0%	0.15-0.15
5	V_{MAX} mg/L/day	1.16	-	0.0535	4.6%	1.055-1.265
6	K_M mg/L	2.52	FIX	0	0%	2.52-2.52
7	K_A 1/day	0.254	FIX	0	0%	0.254-0.254
8	F1	0.628	FIX	0	0%	0.628-0.628
9	WT_V_C	0.717	FIX	0	0%	0.717-0.717
10	WT_V_{MAX}	0.326	FIX	0	0%	0.326-0.326
11	WT_K_{EL}	0.121	FIX	0	0%	0.121-0.121

K_{EL} = elimination rate constant; V_C = central volume of distribution; K_{CP} = transfer rate constant, central to peripheral; K_{PC} = transfer rate constant, peripheral to central; V_{MAX} = maximum velocity; K_M = Michaelis-Menten constant; K_A = association constant; F1 = bioavailability; SE = standard error; CI = confidence interval; RSE = relative standard error.

Table 60. Parameter Estimates for the Final Model: Omega

Omega	Description	Estimate	SE	RSE	Etabar	P-value	Shrinkage
1,1	IIV_1_K_{EL} %CV	0.0301	0.0059	19.5%	-0.009 (0.005)	0.0376	43.9%
2,2	IIV_2_V_C %CV	0.0065	.	.	-0.004 (0.001)	0.0023	69%
5,5	IIV_5_V_{MAX} %CV	0.0846	.	.	0.017 (0.005)	0.0022	59.4%
7,7	IIV_7_K_A %CV	0.194	.	.	-0.013 (0.005)	0.0135	74.6%
8,8	IIV_8_F1 %CV	0.175	.	.	-0.002 (0.012)	0.8571	40.6%

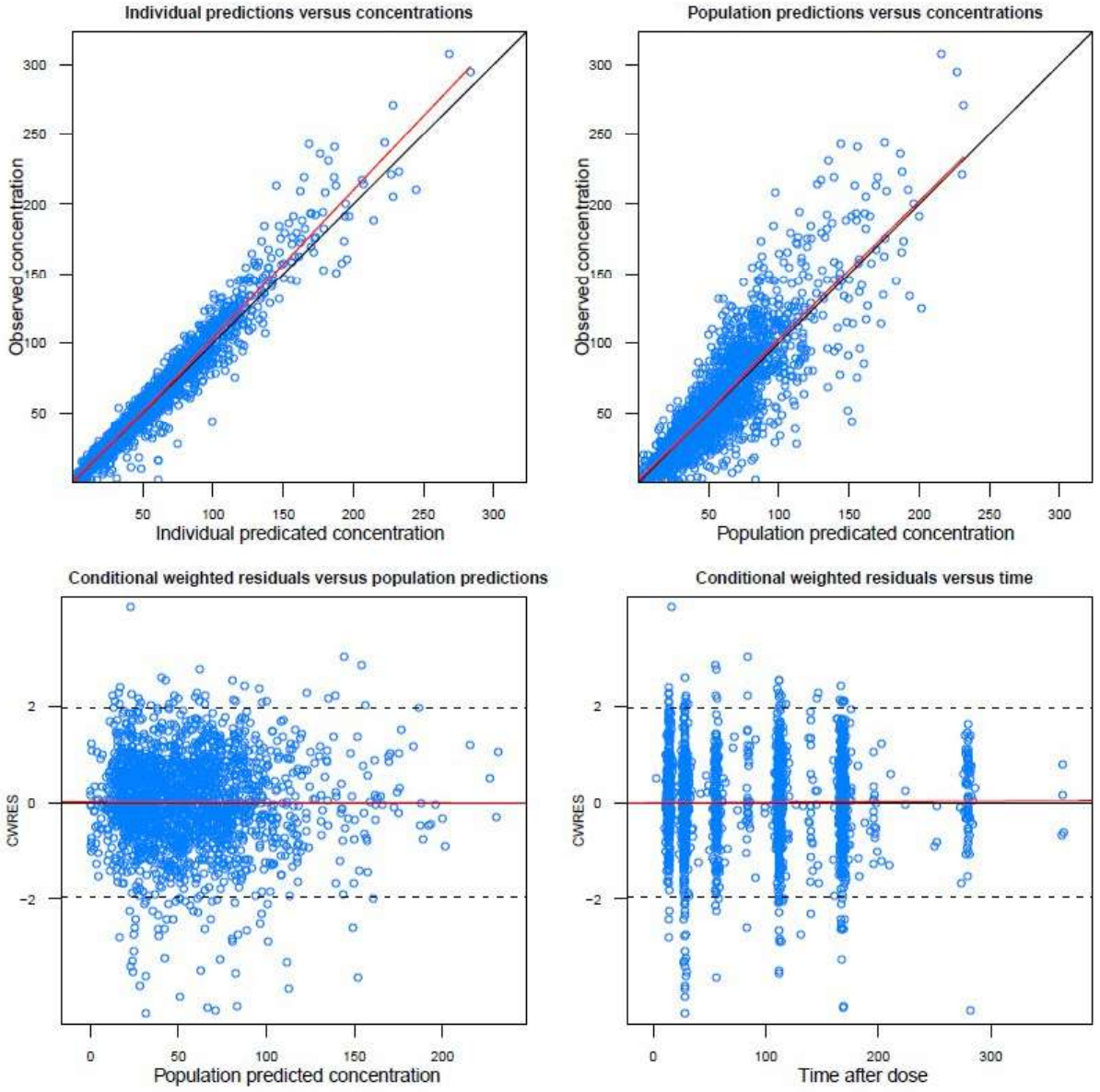
IIV = inter-individual variability;- K_{EL} = elimination rate constant; V_C = central volume of distribution; V_{MAX} = maximum velocity; K_A = association constant; SE = standard error; RSE = relative standard error.

Table 61. Parameter Estimates for the Final Model: Sigma

Sigma	Description	Estimate	SE	RSE	Shrinkage
1,1	PROP	0.0241	0.0008	(3.1%)	14.6%
2,2	ADD	11.6	1.01	(8.7%)	14.6%

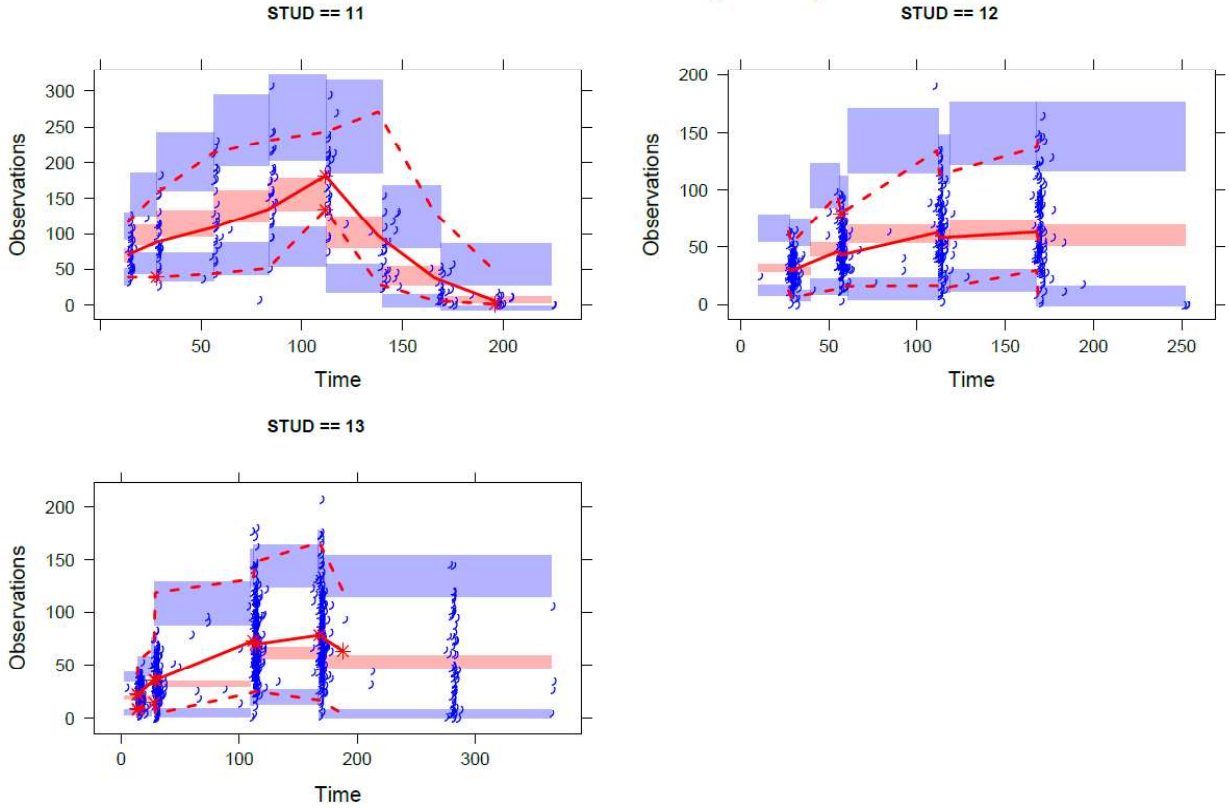
SE = standard error; RSE = relative standard error.

Figure 34. Goodness-of-Fit Plots for Final Covariate Model



The black line in the observed vs. IPRED plots represents the line of unity (y=x). The black line in the IWRES vs. PRED/TIME/Dose plots represents the horizontal line (y=0). The red line represents a smooth regression line.

Figure 35. Visual Predictive Check Plots for Final Covariate Model



Note: Legend: blue dots: observations; solid and read dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.

Reviewer's comments: *The applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the updated population PK model is adequate in characterizing the PK profile of dupilumab in subjects with NP. The applicant's analyses were verified by the reviewer, with no significant discordance identified.*

More specifically, the developed model was used to support the current submission as outlined in Table 62.

Table 62. Specific Comments on Applicant's Final Population PK Model

	Utility of the final model		Reviewer's Comments
Support labeling statements about intrinsic and extrinsic factors	Intrinsic factor	No updated statement on CRSwNP.	
	Extrinsic factor	No updated statement on CRSwNP.	
Derive exposure metrics for Exposure-response analyses	C_{min}, C_{max} (30.5+/-9.39 mcg/ml), AUC, C_{ss} (80.2+/-35.3 300 mg w/o loading dose); median time to non-detectable concentration after the last steady state dose of 300 mg 12 weeks		The applicant's final model is generally acceptable for generating exposure metrics for exposure-response analyses.

15.2.1.3. Exposure-Response Analysis

15.2.1.3.1. Dupilumab Exposure

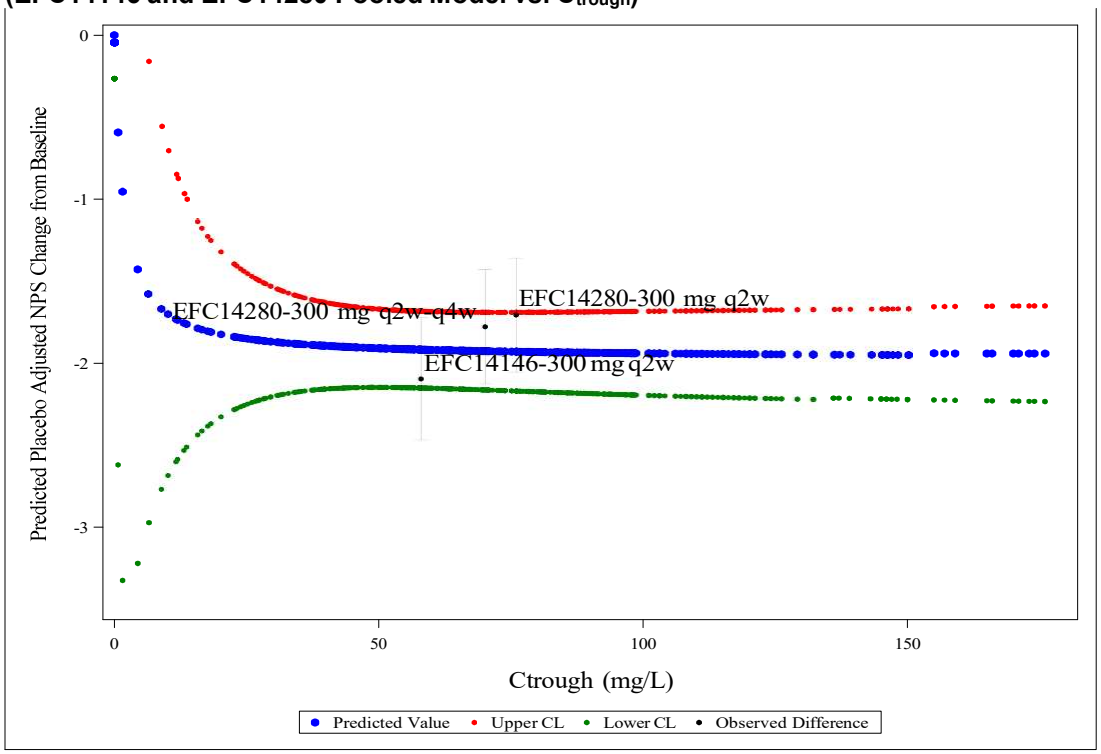
The observed lowest concentration (C_{trough}) was used for both quartile descriptive analysis and exposure response modeling of the four efficacy endpoints at Week 24. At Week 52, Study EFC14280 had the PK data cutoff as August 6, 2018. About 70% of Week 52 observed C_{trough} data were available. Missing observed C_{trough} at Week 52 data were predicted using the relevant post hoc population PK estimate (EFC14146 and EFC14280). The ER relationship assessment at Week 24 is limited by the range of exposure associated with the single dose regimen studied (300 mg q2w) and caution should be exercised in interpreting the data. The incidence of safety events was too low to make conclusions based on ER analysis for safety.

15.2.1.3.2. Nasal Polyps Score

Exposure-Response Modeling at Week 24

An E_{max} (maximal effect) model was selected as the base model. Additional covariates were selected via a forward variable selection. The half maximal effective concentration (EC_{50}) was stably estimated but with a large confidence interval that reflected the high variability of responses at the low concentration range. Higher baseline age or higher UPSIT score was associated with significantly decreased placebo-adjusted treatment effect at Week 24 (significantly increased mean change score) given a fixed C_{trough}, while higher baseline periostin was associated with significantly increased placebo-adjusted treatment effect at Week 24. The pharmacokinetic/pharmacodynamic (PK/PD) model prediction is shown in Figure 36.

Figure 36. PK/PD Model Predicted Nasal Polyps Score Change from Baseline at Week 12 (EFC14146 and EFC14280 Pooled Model vs. C_{trough})

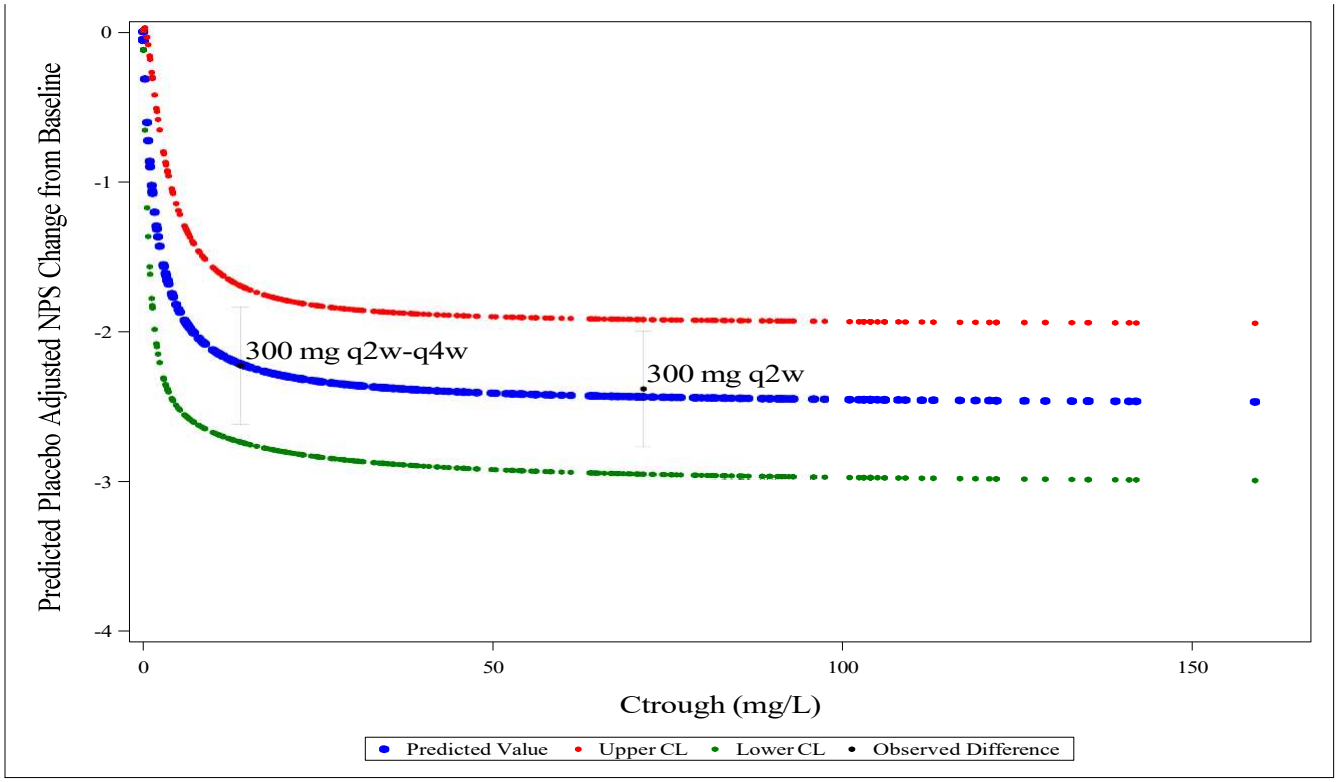


Predicted based on the final PK/PD model and at EFC14146 and EFC14280 Median E_{max}, which is median value of estimated E_{max} parameters by baseline covariates in EFC14146 and EFC14280.

Exposure response modeling at Week 52

An E_{max} model was selected as the base model. Additional covariates were selected via a forward variable selection. The PK/PD model prediction of NPS indicated that the treatment effect approached, but did not reach, the E_{max} at the exposure of 300 mg q2w-q4w and reached a plateau at the exposure of 300 mg q2w. These results are in line with a numerically greater improvement in NPS observed for 300 mg q2w compared to 300 mg q2w-q4w at Week 52. The PK/PD model prediction is shown in Figure 37.

Figure 37. PK/PD Final Model Predicted Nasal Polyps Score Change from Baseline vs. C_{trough} at Week 52 in EFC14280



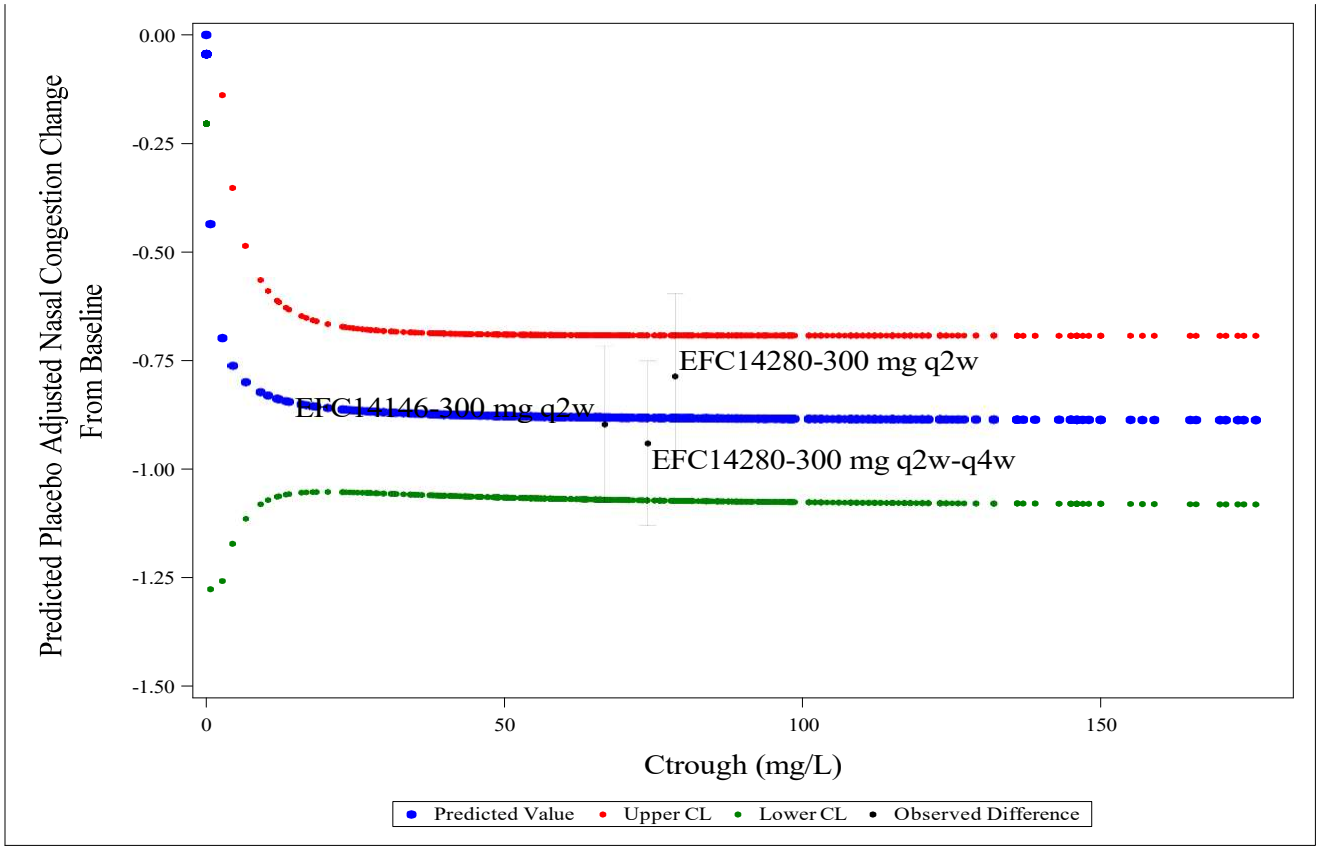
Predicted based on the final PK/PD model and at EFC14280 Median E_{max}, which is median value of estimated E_{max} parameters by baseline covariates in EFC14280.

15.2.1.3.3. Nasal Congestion

Exposure-Response Modeling at Week 24

An E_{max} model is selected as the base model. Additional covariates were selected via a forward variable selection. The EC_{50} was stably estimated but with a large confidence interval, which reflected the data variability. Higher baseline EOS or a prior history of asthma were each associated with significantly increased placebo-adjusted treatment effect at Week 24 (significantly decreased mean change score) given a fixed C_{trough} at Week 24. The PK/PD model prediction is shown in Figure 38.

Figure 38. PK/PD Model Predicted Nasal Congestion Change from Baseline at Week 24 in EFC14146 and EFC14280

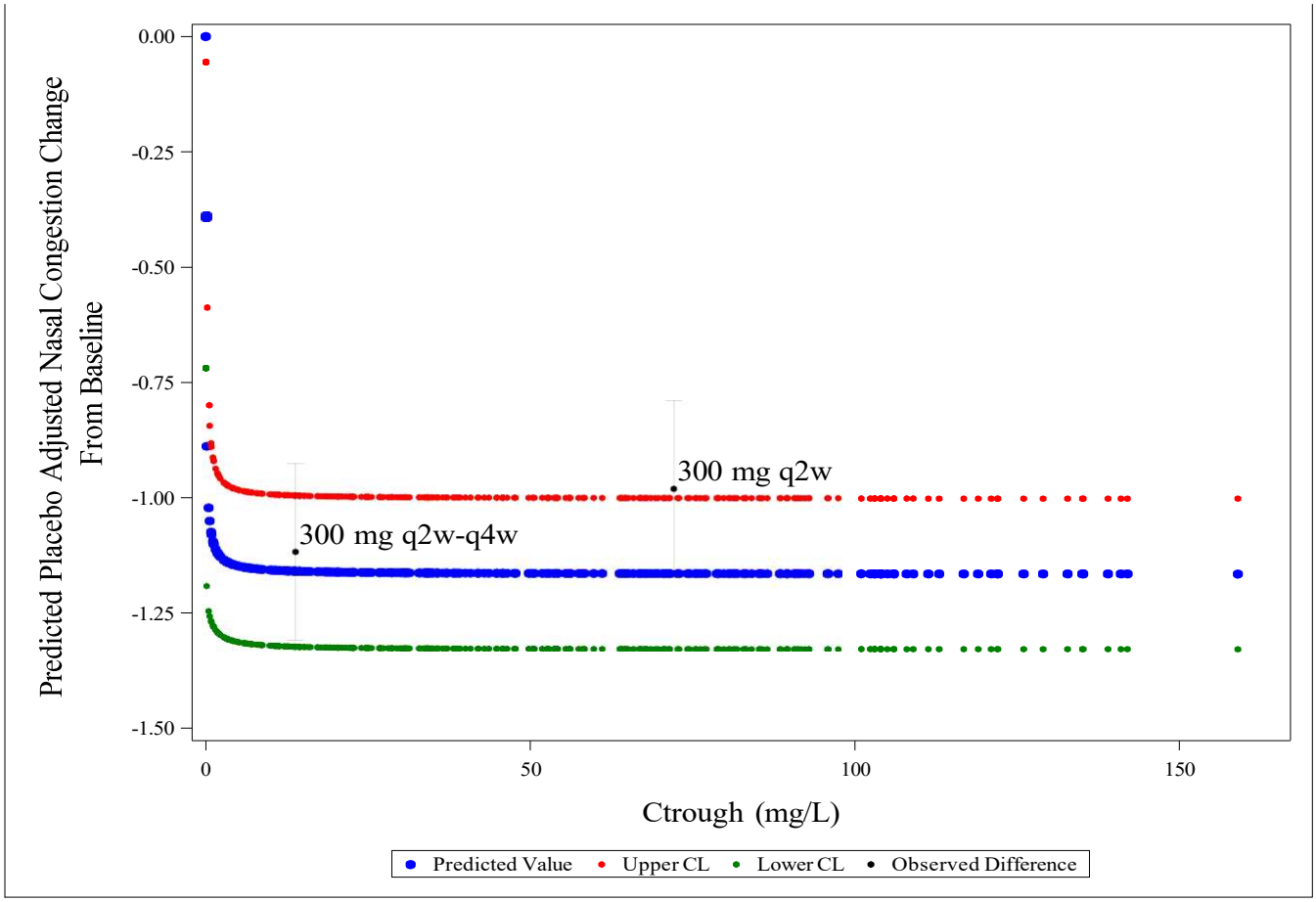


Predicted based on the final PK/PD model and at EFC14146 and EFC14280 Median E_{max}, which is median value of estimated E_{max} parameters by baseline covariates in EFC14146 and EFC14280.

Exposure-Response Modeling at Week 52

The PK/PD model prediction of NC indicated that the treatment effect reached a plateau at the exposure of 300 mg q2w-q4w and 300 mg q2w. A numerically greater improvement in NC observed for 300 mg q2w-q4w compared to 300 mg q2w at Week 52. The PK/PD model prediction is shown in Figure 39.

Figure 39. PK/PD Model Predicted Nasal Congestion Change from Baseline vs. C_{trough} at Week 52 in EFC14280



Predicted based on the final PK/PD model at EFC14280. Median E_{max}, which is median value of estimated E_{max} parameters by baseline covariates in EFC14280.

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/s/

SALLY M SEYMOUR
06/25/2019 07:52:21 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation and Research
Silver Spring, MD 20993

DATE: May 31, 2019
FROM: Rekha Jhamnani
THROUGH: Miya Okada Paterniti
TO: File for BLA 761055, Supplement 14
Re: Clinical Review for BA 761055, S-014

The clinical review for the Division of Pulmonary, Allergy and Rheumatology review is complete and has been added to the multidisciplinary review and evaluation document. My review is based on the information currently in the administrative record. If I must review information that is subsequently added to the administrative record, I will update my part of the multidisciplinary review and evaluation document accordingly.

Regeneron Pharmaceuticals, Inc. submitted a supplemental BLA for Dupixent (dupilumab) prefilled syringe. They are seeking a new indication:

1. Add-on maintenance treatment in adult patients with Inadequately controlled nasal polyps

The clinical reviewer recommends approval as the risk-benefit profile supports the approval of Dupixent prefilled syringe for the above indications, however the final indication is still under discussion. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

REKHA D JHAMNANI
05/30/2019 09:45:59 AM

MEMORANDUM	DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION CENTER FOR DRUG EVALUATION AND RESEARCH
DATE:	6/2/2019
TO:	File for BLA 761055/S-014
THROUGH:	Bhawana Saluja, Ph.D.
FROM:	Dipak S. Pisal, M.S. Ph.D.
SUBJECT:	Clinical Pharmacology Primary Review
APPLICATION/DRUG:	BLA 761055/S-014 DUPIXENT (Dupilumab)

Regeneron submitted a supplemental biologics license application (sBLA) for dupilumab to BLA 761055 for the treatment of patients with inadequately controlled (b) (4) chronic rhinosinusitis with nasal polyposis.

The clinical pharmacology data included pharmacokinetic (PK), pharmacodynamic (PD), and exposure-response (E-R) data for dupilumab from one phase 2a proof-of-concept study (ACT12340) and two pivotal phase 3 studies (EFC14146 and EFC14280) for treatment periods ranging from 16 weeks to 52 weeks.

The Office of Clinical Pharmacology (OCP) recommends approval of this supplement.

A multi-disciplinary unireview has been used for this supplement, and the clinical pharmacology review will be submitted as part of this unireview.

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/s/

DIPAK PISAL
06/04/2019 04:26:08 PM

BHAWANA SALUJA
06/04/2019 04:29:43 PM

MEMORANDUM

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

DATE: May 31, 2019

TO: File for BLA 761055, S-0014

THROUGH: Carol Galvis, PhD, Acting Pharmacology/Toxicology Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

FROM: Yu-Mee Kim, PhD, Pharmacology/Toxicology Reviewer, DPARP

SUBJECT: Nonclinical Primary Review

APPLICATION/DRUG: BLA 761055 DUPIXENT® (dupilumab), S-0014

Regeneron Pharmaceuticals, Inc. submitted a supplemental BLA for DUPIXENT® (dupilumab) to the BLA 761055 for add-on maintenance treatment in adult patients with inadequately controlled nasal polyps.

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.

The original BLA DUPIXENT® (dupilumab) was approved on March 28, 2017 for the treatment of adult patients with moderate-to-severe atopic dermatitis in the Division of Dermatology and Dental Products.

This sBLA relies on the nonclinical data presented for the initial BLA approval of dupilumab. Please see the nonclinical primary review under BLA 761055 dated December 05, 2016, and the Multi-disciplinary Review and Evaluation for additional details. No new nonclinical studies were submitted for this sBLA.

Recommendation
There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of this application.

Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

YU-MEE KIM
05/31/2019 05:26:04 PM

CAROL M GALVIS
06/03/2019 08:17:07 AM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2019106
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	sBLA 761055
Applicant:	Regeneron Pharmaceuticals, Inc.
Established Name/Trade Name:	DUPIXENT
Indication:	(b) (4)
Meeting Type/Deliverable:	Advice Letter/Advice to Division
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Product (DPARP)
Clinical Reviewer	Rekha Jhamnani
Clinical Team Leader (TL)	
Review Division Project Manager:	Elaine Sit
COA Reviewer:	Hongling Zhou
COA TL:	Wen-Hung Chen
COA Associate Director:	Elektra Papadopoulos
Date Consult Request Received:	3/26/2019
Date COA Review Completed:	4/22/2019

Please check all that apply: ☐Rare Disease/Orphan Designation
☐Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to sBLA 761055 for DUPIXENT. The applicant is in phase 3 of their drug development program, with two completed phase 3 clinical trials. The proposed indication is for the treatment (b) (4) .

The applicant proposes the Patient-Reported Outcome Sino-Nasal Outcome Test (SNOT-22) in their randomized, double-blind, placebo-controlled phase 3 clinical trials in adult patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids.

Table 1. COA Included in Study EFC14280 and Study EFC14146

COA Name (COA Type)	Concept(s)	Endpoint Position[1]	Copy of COA
Sino-Nasal Outcome Test (SNOT-22; PRO)	Symptoms and symptom impact	Secondary	Appendix A

PRO= Patient-reported outcome

This submission is a supplemental BLA. The Division seeks COA Staff input on whether the SNOT-22 is a valid patient reported outcome for the target population as the analysis of these elements could support additional indications of chronic (b) (4).

[1] Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

The review concludes that SNOT-22 is acceptable as an outcome measure to assess symptoms and symptom impacts for patients with [redacted] (b) (4) chronic sinusitis with nasal polyps (see Table 2). The instrument has face validity based on discussion with Clinical. Its content validity has been supported by literature describing the development of its original version, [redacted] (b) (4) where the patients and clinicians were interviewed, and literature were reviewed[2]. The psychometric properties are also supported by publications in the literature[3,4]. As such, the total score of SNOT-22 is appropriate for use to support patient-reported symptoms and impacts improvement.

However, we do not agree with the proposed responder definition defined as improvement in SNOT-22 score change from baseline [redacted] (b) (4). The threshold of [redacted] (b) (4) labeled as the minimal clinically important difference (MCID) in [redacted] (b) (4) was the difference of the SNOT-22 average scores between two subgroups (i.e., 'a little better' and 'no change') that was not derived using FDA recommended methods and did not represent meaningful within-patient change. Future studies to determine the within-patient meaningful change score for SNOT-22 is recommended. However, this does not preclude the use of SNOT-22 to assess the symptoms and symptom impacts and to support its inclusion in the labeling.

Please refer to Section B for detailed comments.

B. SUGGESTED COMMENTS TO APPLICANT

No COA-related questions were submitted by the applicant. In completion of our COA Review, we have the following comments:

1. The SNOT-22 instrument appears to have face validity and its content validity has been supported by literature where the patients and clinicians were interviewed. The psychometric properties are also supported by publications in the literature. As such, the total score of SNOT-22 is appropriate for use as a PRO endpoint to assess symptoms and symptom impacts associated with rhinosinusitis.
2. We do not agree with the proposed responder definition where responder is defined as improvement in SNOT-22 score change from baseline [redacted] (b) (4). The threshold of [redacted] (b) (4) labeled as the minimal clinically important difference (MCID) [redacted] (b) (4) was the difference of the SNOT-22 average scores between the 'a little better' and 'no change' groups. This is the cross-sectional difference between two subgroups of the patients that does not represent within-patient meaningful change. From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores, from the patient perspective, rather than the average scores

[redacted] (b) (4)

between-group difference. The threshold for meaningful within-patient change should be derived from anchor-based methods supplemented with both anchor-based empirical cumulative distribution function (eCDF) and probability density function (PDF; many times estimated using kernel density estimation) curves.

C. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Previous COA Reviews:

- [redacted] (b) (4)

Background:

Chronic [redacted] (b) (4) sinusitis with nasal polyposis (CRSwNP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the osteomeatal complex (OC) and the spheno-ethmoid recess and characterized by mucosal inflammation of the nasal cavity and paranasal sinuses with symptoms lasting more than 12 weeks. Clinically, CRSwNP is defined by long-term symptoms of nasal obstruction and congestion, reduction in or loss of sense of smell, and anterior and posterior rhinorrhea. These symptoms can impact greatly upon a patient's quality of life (QoL). The presence or absence of polyps is confirmed by performing endoscopy. With an estimated prevalence of 2% to 4% (in Europe and the United States [US]), CRSwNP has a high burden of symptoms and a high relapse rate after treatment.

The therapeutic armamentarium of clinically proven medical interventions for CRSwNP is limited. First-line treatment is topical corticosteroids. Intranasal corticosteroid sprays (INCS) improve the symptoms of nasal obstruction, secretion, and sneezing to some extent. However, their effect in reducing polyp size and on improving the sense of smell, a cardinal symptom of nasal polyposis (NP) is limited.

Dupilumab is a systemic targeted immunomodulatory agent, inhibiting the Th2 pathway. It is a fully human mAB directed against the interleukin-4 receptor alpha (IL-4Rα) subunit, a component of IL-4 receptors Type I and Type II, which mediate signaling by IL-4 (both receptors) and by IL-13 (Type II receptor). Dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 activation of their respective receptors. Dupilumab is in clinical development for the treatment of CRSwNP worldwide. However, in the US, based on FDA feed-back, this clinical development program will support the indication of nasal polyposis.

Other materials reviewed:

- EFC14280 16.1.1 Protocol, titled "A randomized, double-blind, 52-week, placebo-controlled efficacy and safety study of dupilumab, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids" (SDN 436, Dec 23, 2018)
- EFC14146 16.1.1 Protocol, titled "A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in

patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids (SDN 436, Dec 23, 2018)

- EFC14280-1-15 Clinical Study Report (SDN 436, Dec 23, 2018)
- EFC14146-1-15 Clinical Study Report (SDN 436, Dec 23, 2018)
- Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)

2 FIT-FOR-PURPOSE SUMMARY

Table 2. Fit-for-purpose assessment (based on available evidence)

COA Name(s)	Attribute sufficiently established[5]	Supported by:	Location of Supporting Materials
SNOT-22	☒ Yes ☐ Potentially - insufficient evidence available; additional information is needed ☐ No	☒ Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) ☒ Evidence of content validity ☒ Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) ☒ COA well-defined and concept is able to be accurately communicated ☐ COA is sensitive to detect change ☐ COA is culturally adapted and adequately translated, if appropriate	Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)

3 CONTEXT OF USE

3.1 Clinical Trial Population

The target population for Studies EFC14280 and EFC14146 are adult patients with bilateral sino-nasal polyposis.

A complete list of the inclusion and exclusion criteria is summarized in Sections 7.1 and 7.2 of the Protocol EFC14280 and Protocol EFC14146.

3.2 Clinical Trial Design

Table 3 describes the clinical trial design of Studies EFC14280 and EFC14146.

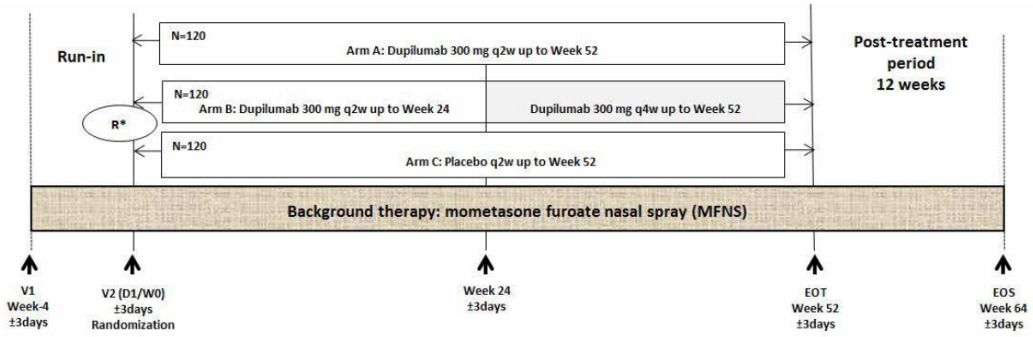
Table 3. Clinical Trial Design for Studies EFC14280 and EFC14146

[5] See Sections 5 and 6 of this COA review for more detailed information.

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	☐ Single arm ☐ Open label ☒ Double-blind ☒ Randomized ☒ Placebo-/Vehicle-controlled ☐ Active comparator-controlled ☐ Cross-over ☒ Multinational ☐ Non-inferiority	52 weeks (EFC14280); 24 weeks (EFC14146)	Yes

Refer to the Clinical Study Protocol EFC14280 and Protocol EFC14146 for more details on the clinical trial design.

Reviewer's comment(s): The schema for Study EFC14280:

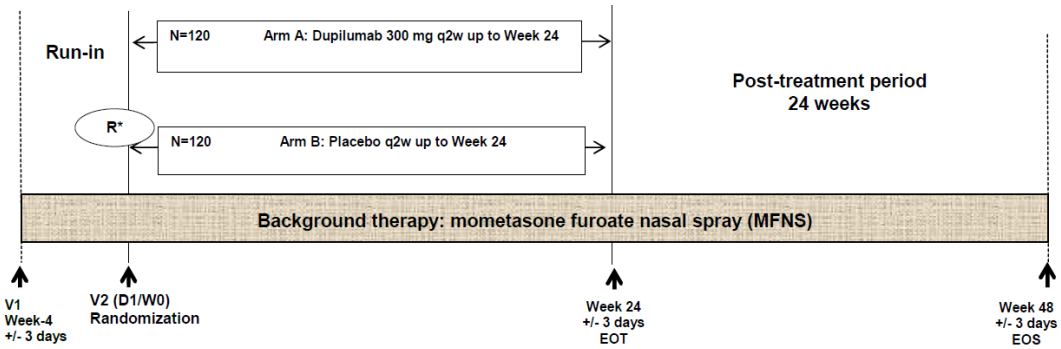


R*= Randomization; EOT: end of treatment; EOS: end of study; V: Visit; D: Day; q2w: every 2 weeks; q4w: every 4 weeks;

IMP: Regardless of the treatment group, all randomized patients will receive q2w subcutaneous administrations of dupilumab or placebo. For Arm B, after week 24 dupilumab administration will be alterned by placebo matched injection every other week up to week 50 (last IMP administration). Every other week investigational product administrations must be separated by at least 11 days. At V2 the Investigator or delegate will perform the injection. After V2, every other week administration of IMP will be performed at the investigational site up to at least Week 8 (V6). Patients will be monitored at the study site for at least 30 minutes or minimum time required by your local regulator after injections. From Week 10, every other week home administration of IMP (patient, caregiver, or health care professional) is possible if the patient (or the caregiver) has been trained. If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site.

Non-investigational medicinal product: mometasone furoate nasal spray (MFNS) will be self-administered by the patient twice daily or once daily (if they cannot tolerate twice daily). At each visit the Investigator must ensure that the patient has the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.

The schema for Study EFC14146:



BID twice daily; D day; EOS end of study; EOT end of treatment; IMP investigational medicinal product; q2w every 2 weeks; MFNS mometasone furoate nasal spray; R* randomization; QD once daily; SC subcutaneous; V visit; W week

IMP: Regardless of the treatment group, all randomized patients will receive q2w SC administrations of dupilumab or placebo. Every other week IMP administrations must be separated by at least 11 days. At V2 the Investigator or delegate will perform the injection. After V2, every other week administration of IMP will be performed at the investigational site up to at least Week 8 (Visit 6). Patients will be monitored at the study site for at least 30 minutes or the minimum time required by your local regulator after injections. From Week 10, every other week home administration of IMP (patient, caregiver, or health care professional) is possible if the patient (or the caregiver) has been trained. If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or healthcare professionals to administer IMP for the doses not scheduled to be given at the study site.

Non-investigational medicinal product: MFNS will be self-administered by the patient BID or QD (if they cannot tolerate BID). At each visit the Investigator must ensure that the patient has the necessary doses up to the next visit, knowing that one MFNS device (1 bottle) contains sufficient doses for: either 2 weeks of BID treatment/regimen or 4 weeks of QD treatment/regimen.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study EFC14280.

Table 4. Endpoint Position, Definition, and Assessment Schedule for Study 14280 and Study 14146

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Co-Primary	Nasal Congestion/ obstruction severity (NC; PRO)	Nasal Congestion/obstruction severity (NC)	Change from baseline in the nasal congestion/obstruction at Week 24	☒ Daily ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Co-Primary	nasal polyposis score (NPS; nasal endoscopy)	Nasal polyposis	NP is graded based on polyp size (0, 1, 2,3,4) from no polyps to large polyps causing complete obstruction of the inferior nasal cavity)	☐ Daily ☐ Weekly ☒ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	Total symptom score (TSS, PRO)	Symptom	Change from baseline in TSS (total symptom score) at Week 24: composite severity score consisting of the patient daily AM assessed nasal congestion/obstruction, decreased/loss of sense of smell, anterior/posterior rhinorrhea.	☒ Daily ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	University of Pennsylvania Smell Identification Test (UPSIT, ClinRO)	smell	Change from baseline in UPSIT (University of Pennsylvania Smell Identification Test) smell test at Week 24.	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: Week 0, 2, 8,16,24, 48(EFC14146); week 0, 2, 4,16,24, 52, 64 (EFC14280) ☒ Assessment at cross-over or early discontinuation
Secondary ☒ Multiplicity adjusted	Decreased/loss of sense of smell (PRO)	Smell	Change from baseline in the severity of decreased/loss of smell daily at Week 24.	☒ Daily ☐ Weekly ☐ Monthly ☐ Other: ☐ Assessment at cross-over or early discontinuation

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary ☒ Multiplicity adjusted	Sino-nasal outcome test (SNOT-22; PRO)	Symptoms and social/emotional impact	Change from baseline in SNOT-22 at Week 24.	☐ Daily ☐ Weekly ☐ Monthly ☒ Other: Every 8 weeks (EFC14146); week 0, 4, 8, 16, 24, 40, 52 (EFC14280) ☐ Assessment at cross-over or early discontinuation

ClinRO= Clinician-reported outcome; **PRO=** Patient-reported outcome

3.4 Labeling or promotional claim(s) based on the COA

The applicant has proposed specific targeted COA-related labeling claims that include the analysis results that compared SNOT-22 between the test drug and placebo groups.

The targeted labeling claims are:

> "In both studies, key secondary end-points at Week 24 included change from baseline in: LMK sinus CT scan score, total symptoms score (TSS), University of Pennsylvania smell identification test (UPSIT), daily loss of smell, and **22-item sino-nasal outcome test (SNOT-22**)."

Table 9: 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 Smell test (UPSIT) score[a] (SD), range 0-40	14.6 (8.5)	13.6 (8)
Mean Sense of smell loss 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)	201 (282)	212 (257)
Atopic (type 2 inflammatory disease) Medical History % Overall	75%	82%
Asthma (%)	58	60
Mean FEV1 (L) (SD)	2.69 (0.96)	2.57 (0.83)
Mean FEV1 percent predicted (%) (SD)	85 (20)	83 (18)
Mean ACQ-6 score[a] (SD)	1.6 (1.1)	1.6 (1.1)
NSAID-ERD (%)	30	27

[a]Higher scores indicate greater disease severity except UPSIT, where higher scores indicate lower disease severity
SD = standard deviation; AM = morning; NPS = nasal polyps score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item sino-nasal outcome test; FEV_1 = Forced expiratory volume in 1 second; ACQ-6 = Asthma Control Questionnaire-6; NSAID-ERD = asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease

Table 10: Results of the Primary and Secondary Endpoints in CRSwNP Trials

	CSNP Trial 1					CSNP Trial 2				
	Placebo (n=133)		DUPIXENT 300mg Q2W (n=143)		LS mean difference vs. Placebo (95%CI)	Placebo (n=153)		DUPIXENT 300mg 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)
Key Secondary 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	
LMK sinus CT scan score	19.55	-0.74	18.55	-8.18	-7.44 (-8.35, -6.53)	17.65	-0.09	18.12	-5.21	-5.13 (-5.80, -4.46)
Total symptom score	7.28	-1.17	6.82	-3.77	-2.61 (-3.04, -2.17)	7.08	-1.00	7.30	-3.45	-2.44 (-2.87, -2.02)
UPSIT	14.44	0.70	14.68	11.26	10.56 (8.79, 12.34)	13.78	-0.81	13.53	9.71	10.52 (8.98, 12.07)
Loss of smell	2.73	-0.29	2.70	-1.41	-1.12 (-1.31, -0.93)	2.72	-0.23	2.77	-1.21	-0.98 (-1.15, -0.81)
SNOT-22	50.87	-9.31	48.0	-30.43	-21.12 (-25.17, -17.06)	53.48	-10.40	51.02	-27.77	-17.36 (-20.87, -13.85)
Key Secondary Endpoints at Week 52										
						Placebo (n=153)		DUPIXENT 300mg Q2W (n=150)		LS mean difference vs. Placebo (95%CI)
						Baseline mean	LS mean change	Baseline mean	LS mean change	
NPS (nasal polyps score) (range 0 to 8)						5.96	0.15	6.07	-2.24	-2.40 (-2.77, -2.02)
NC (nasal congestion/obstruction) score (range 0 to 3)						2.38	-0.37	2.48	-1.35	-0.98 (-1.17, -0.79)
LMK sinus CT scan score (range 0 to 24)						17.65	0.11	18.42	-6.83	-6.94 (-7.87, -6.01)
Total symptom score (range 0 to 9)						7.08	-0.94	7.31	-3.79	-2.85 (-3.35,-2.35)
UPSIT score (range 0 to 40)						13.78	-0.77	13.46	9.53	10.30 (8.50, 12.10)
Loss of Smell score (range 0 to 3)						2.72	-0.19	2.81	-1.29	-1.10 (-1.31, -0.89)
SNOT-22 (22-item sino-nasal outcome test) score (range 0 to 110)						53.48	-8.88	50.16	-29.84	-20.96 (-25.03, -16.89)

A reduction in score indicates improvement except UPSIT, where an increase indicates improvement.
NPS = nasal polyps score; NC = nasal congestion/obstruction; TSS = total symptom score; UPSIT = University of Pennsylvania smell identification test; SNOT-22 = 22-item sino-nasal outcome test

4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the COAs are summarized in Table 5.

Table 5. Concepts of Interest for COAs Included in Studies EFC14280 and EFC14146

COA name	Concept(s)
SNOT-22	Symptoms and symptom impacts

The conceptual framework(s) for SNOT-22 is not included in the submission. The result of the factor analysis conducted for [redacted] (b) (4) suggested the items assess a mixture of concepts including disease-specific signs, symptoms, sleep, functional and emotional impacts.

TABLE II

Maximum Likelihood Factor Analysis: Factor Loading Shown By Item

	Factor					
	1	2	3	4	5	6
Nasal symptoms						
Stuffy/blocked Nose	0.41					
Runny Nose	0.41					
Sneezing			0.52			
Itchy nose						
Decreased sense of smell	0.71					
Decreased sense of taste	0.62					
Postnasal discharge	0.54					
Thick nasal discharge/debris	0.71					
Eye symptoms						
Itchy eyes			0.88			
Watery eyes			0.73			
Sore eyes						
Swollen eyes	0.48					
Sleep						
Difficulty getting to sleep					0.69	
Wake up during the night					0.84	
Lack of a good night's sleep					0.89	
Wake up tired					0.75	
Ear symptoms						
Fullness				0.47		
Ringing				0.40		
Dizziness				0.42		
Pain				0.66		
Decreased hearing	0.48					
General symptoms						
Fatigue/worn out		0.64				
Dry mouth						
Reduced productivity		0.69				
Poor concentration		0.64				
Headache		0.58				
Wheezing						
Facial pain/pressure		0.46				
Cough		0.48				
Short of breath		0.45				
Daytime Sleepiness						
Practical problems						
Inconvenience of having to carry tissues		0.50				
Need to rub nose/eyes		0.60	0.43			
Need to blow nose repeatedly	0.41	0.59				
Bad breath		0.56				
Emotional consequences						
Frustrated						0.79
Impatient or restless						0.56
Feeling depressed or sad						0.62
Irritable						0.74
Embarrassed by your symptoms						0.66

5 CLINICAL OUTCOME ASSESSMENT(S)

SNOT-22

This is a 22-item patient-report outcome (PRO) tool intended to assess physical problems, functional limitations, and emotional consequences of rhinosinusitis and its treatment. The items of the SNOT-22 are scored 0 ('no problem') to 5 ('problem as bad as it can be') and are summed to form a total score ranging 0 to 110, with higher scores indicating worse condition.

6 SCORING ALGORITHM

SNOT-22

The items of the SNOT-22 are scored 0 ('no problem') to 5 ('problem as bad as it can be') and are summed to form a total score ranging 0 to 110, with higher scores indicating worse condition.

Reviewer's comment(s):

In patients where some SNOT-22 items were incomplete, a total score for the SNOT-22 was imputed from the mean of completed items, providing more than 50% of items had been completed. Although this is a common practice. We recommend, for future submissions, a justification of the scoring algorithm and the missing data rules are provided.

7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- ☒ Copy of instrument
- ☒ Literature review and/or publications
- ☐ Documentation of expert input
- ☐ Qualitative study protocols and interview guides for focus group or patient interviews
- ☐ Chronology of events for item generation, modification, and finalization (item tracking matrix)
- ☐ Synopsis of qualitative findings
- ☐ Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- ☐ Quantitative summary report with evidence to support item retention and scoring
- ☐ Transcripts (if available)

Table 6 documents the adequacy of the content of the COAs.

Table 6. Review of Content Validity for SNOT-22

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	☒ Yes ☐ No	☒ Literature ☒ Clinical input e.g. discussion with clinical reviewer	Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)
Content validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ The item concepts are relevant/important to target patient population and appropriate to the study design and objectives ☒ The instrument is comprehensive with respect to the concept (i.e., does not omit important content) ☒ Target sample for qualitative research is appropriate. ☒ Studied sample for qualitative research adequately represents the target patient population ☒ Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives ☒ Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) ☒ COA is culturally adapted and adequately translated ☐ Descriptive statistics (if available) support content relevance ☐ Other (see Reviewer's comments)	Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)

Reviewer's comment(s):

A SNOT-22 PRO evidence dossier was submitted with this supplemental NDA submission. The evidence of content validity is supported by literature. The applicant did not conduct any qualitative study to collect data to support its content validity. Based on the review of the literature, it appears that patients and clinicians were interviewed during the development of the original (b) (4). It also appears that SNOT-22 has included the most relevant and important symptoms and impacts from the patient's perspectives. It is noted that not all items

included in SNOT-22 are the most important concepts, however, this does not preclude the use of SNOT-22 as a secondary endpoint. However, examining the results of the individual items, especially the nasal symptoms is recommended to ensure that the change in the Total score is not dominate by other items.

8 OTHER MEASUREMENT PROPERTIES

To date, the following information has been submitted (check all that apply):

- ☒ Literature review and/or publications
- ☐ Quantitative analysis synopsis
- ☐ Full quantitative analysis plan
- ☐ Quantitative summary report with evidence to support reliability, construct validity, ability to detect change and scoring

Table 7 documents the adequacy of the other measurement properties of the COAs.

Table 7. Review of Other Measurement Properties for SNOT-22

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Internal consistency reliability estimates in acceptable range (e.g., Cronbach's $\alpha > 0.70$) ☒ Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC $\geq$0.70) ☐ Inter-rater reliability estimates in acceptable range ☐ Other (see Reviewer's comments)	Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)
Construct validity	☒ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☐ No	☒ Relationship to other assessments with similar concepts is as expected ☐ Relationship to other assessments with dissimilar concepts is as expected ☒ COA differentiates between clinically distinct groups (i.e., known groups validity) ☐ COA scores are related to a known gold standard assessment of the same concept ☐ Other (see Reviewer's comments)	Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)
Ability to detect change	☒ Yes ☐ Potentially – insufficient evidence available;	☒ COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept	Patient-Reported Outcome Dossier for the SNOT-22

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
	additional information is needed ☐ No	☐ Other (see Reviewer's comments)	(SDN 436, Dec 23, 2018)

Reviewer's comment(s):

A SNOT-22 PRO evidence dossier was submitted with this supplemental NDA submission. The evidence of other measurement properties is supported by literature. The applicant did not conduct any psychometric analysis to evaluate the measurement properties of SNOT-22. As there are multiple publications reporting good measurement properties, measurement properties of SNOT-22 is deemed acceptable.

9 INTERPRETATION OF SCORES

The evidence to support the score interpretation of SNOT-22 is included in the PRO Dossier referencing the results reported in (b) (4) We do not agree with the proposed responder definition where responder is defined as improvement in SNOT-22 score change from baseline (b) (4). The threshold of (b) (4) labeled as the minimal clinically important difference (MCID) in (b) (4) was the difference of the SNOT-22 average scores between the 'a little better' and 'no change' groups. From a regulatory standpoint, we are more interested in what constitutes a clinically meaningful within-patient change in scores, from the patient perspective, rather than the average scores between-group difference.

Table 8 documents the adequacy of the score interpretability of the COA.

Table 8. Review of Score Interpretability for SNOT-22

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	☐ Yes ☐ Potentially – insufficient evidence available; additional information is needed ☒ No	☐ Appropriate global anchor scales were included for anchor-based analyses ☐ Threshold(s) for within-patient meaningful change identified (anchor-based methods) ☐ Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) ☐ Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) ☒ Other (see Reviewer's comments)	Patient-Reported Outcome Dossier for the SNOT-22 (SDN 436, Dec 23, 2018)

Reviewer's comment(s):

Future studies to determine the within-patient meaningful change score for SNOT-22 is recommended. The within-patient meaningful change score should be determined using anchor-based method and supported by eCDF and PDF.

D. APPENDICES

Appendix A: Sino-Nasal Outcome Test (SNOT-22)

SINO-NASAL OUTCOME TEST (SNOT-22)

(b) (4)

[redacted]

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/

HONGLING ZHOU
05/30/2019 05:07:43 PM

WEN-HUNG CHEN
05/30/2019 06:07:45 PM
Signed with the concurrence of the Associate Director, Dr. Elektra Papadopoulos.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s014

PRODUCT QUALITY REVIEW(S)

Memorandum of Review:

Submission Tracking Number (STN):	761055/436 (EDR0400)
Subject:	PAS Supplement 14: Efficacy supplement for the treatment of adult patients with (b) (4) chronic rhinosinusitis with nasal polyposis (CRSwNP)
Stamp Date:	December 26, 2018
Review/Revision Date:	April 6, 2019/May 31, 2019
Primary Reviewer:	Gunther Boekhoudt, Ph.D., Product Quality Reviewer CDER/OPQ/OBP/DBRR IV
Secondary Reviewer:	Haoheng Yan, MD, Ph.D., Product Quality Team Leader CDER/OPQ/OBP/DBRR IV
RBPM:	Melinda Bauerlien
Consults:	N/A
Applicant:	Regeneron Pharmaceuticals Inc.
Product:	Dupixent (dupilumab)
Indication:	• 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. • 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. •
Filing Action Date:	January 24, 2019
Action Due Date:	June 26, 2019

Quality review comments are in italic. Tables and figures were copied from the submission in order to provide sufficient detail. Text that was directly copied or paraphrased from the submission is indicated by quotation marks.

Summary and Recommendation:

In this efficacy supplement, Regeneron is adding an indication for the treatment of adult patients with (b) (4) chronic rhinosinusitis with nasal polyposis (CRSwNP). The supplement does not include any changes related to CMC information in the BLA. The validation reports of the immunogenicity assays were provided and reviewed during original BLA application and during the efficacy supplement # 7 for asthma population. The submission is subject to categorical exclusion for Environmental Assessment (EA) per 21 CFR 25.31(a). I recommend approval of this supplement.

Suggested Language for Action Letter:

Action letter language is deferred to OND.

Environmental Assessment or Claim of Categorical Exclusion
Regeneron requested categorical exclusion from the requirements of environmental assessment pursuant to the provisions provided under 21 CFR 25.31(a).

Immunogenicity Assay
The validation reports and cut point determination for the immunogenicity assays used in the adolescent AD and asthma clinical studies were previously reviewed. The cut points used for asthma population were used for the CRSwNP population. On March 29, 2019, an IR was sent requesting justification for using the asthma population cut points. The IR read:

"Immunogenicity of dupilumab was analyzed for the CRSwNP patients using the cut points determined from asthma population. Provide a justification that the cut points (for both anti-drug antibody assay and neutralizing antibody assay) determined using the asthma population are appropriate for determining the immunogenicity of dupilumab in the CRSwNP patients."

On April 4, 2019, Regeneron submitted their responses. In summary, The ADA analysis of the CRSwNP pivotal Phase 3 studies (EFC14146 and EFC14280) was conducted using the asthma population specific cut points for both the ADA and the neutralizing antibody (NAb) assays. The justification of this approach is that a proportion of patients with background signal in baseline samples in the CRSwNP study population was similar to that observed in the asthma population, and approximately 59% of CRSwNP patients in these studies had co-morbid asthma. A total of approximately 718 CRSwNP patients were analyzed in the ADA assay from both CRSwNP Phase 3 studies (EFC14146 & EFC14280). Applying the asthma population specific cut point factor, 34 out of 718 baseline serum samples were positive in the ADA screening assay for an observed false positive rate of (b)(4)%. This rate is similar to the targeted false positive rate of (b)(4)% for the ADA assay which provided assurance that no ADA positives were not missed. This was also the case regarding the Nab assay cut point, where three out of 281 placebo treated CRSwNP patients from both phase 3 studies were positive in the NAb assay. This resulting in an observed false positive rate of approximately (b)(4)% which was similar to the targeted false positive rate of (b)(4)% for the asthma NAb assay. *Using the cut points determined from asthma population in the CRSwNP population to calculate the Immunogenicity of dupilumab is acceptable.*

Gunther Boekhoudt

Digitally signed by Gunther Boekhoudt
Date: 5/31/2019 02:57:30PM
GUID: 508da6d7000262c4c5e3578cc0a15fbf

Haoheng Yan

Digitally signed by Haoheng Yan
Date: 5/31/2019 04:51:09PM
GUID: 54e4d29c0006b60003d1272740430bcc

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s014

OTHER REVIEW(S)

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 22, 2019
To:	Sally Seymour, MD Acting Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon W. Williams, MSN, BSN, RN Senior Patient Labeling Reviewer, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Kyle Snyder, 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-014
Applicant:	Regeneron Pharmaceuticals, Inc.

1 INTRODUCTION

On December 26, 2018, Regeneron Pharmaceuticals, Inc. submitted for the Agency's review a 351(a) Supplemental Biologics Licensing Application (sBLA) for DUPIXENT (dupilumab) injection, for subcutaneous use. Regeneron Pharmaceuticals, Inc. proposes to add the use of dupilumab as add-on maintenance treatment in adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyposis.

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 Pulmonary, Allergy, and Rheumatology Products (DPARP) on February 6, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for DUPIXENT (dupilumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft DUPIXENT (dupilumab) PPI received on February 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 13, 2019.
- Draft DUPIXENT (dupilumab) Prescribing Information (PI) received on February 6, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 13, 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 we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is 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 is 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 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.

Please let us know if you have any questions.

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

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

Memorandum

Date: May 22, 2019

To: Elaine Sit
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Kyle Snyder
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: BLA 761055/S-014
OPDP comments on draft PI and PPI for DUPIXENT® (dupilumab) injection, for subcutaneous use

---

Reference is made to DPARP's consult request dated February 6, 2019, requesting review of the proposed Package Insert (PI) and Patient Package Insert (PPI) for DUPIXENT® (dupilumab) injection, for subcutaneous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on May 13, 2019, and are provided below.

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

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions or concerns, please contact Kyle Snyder at 240-402-8792 or kyle.snyder@fda.hhs.gov.

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CLINICAL INSPECTION SUMMARY

Date	April 11, 2019
From	Min Lu, M.D., M.P.H., Medical Officer Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Rekha Jhamnani, M.D., Medical Officer Miya Paterniti, M.D., Clinical Team Leader Elaine Sit, Pharm. D. Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
BLA	761055/S014
Applicant	Regeneron Pharmaceuticals, Inc.
Drug	Dupixent (dupilumab)
NME	No
Therapeutic Classification	Interleukin-4 receptor alpha antagonist
Proposed Indication	Add-on maintenance treatment in adult patients with severe chronic rhinosinusitis with nasal polyposis (CRSwNP).
Consultation Request Date	January 18, 2019
Summary Goal Date	May 8, 2019
Action Goal Date	June 26, 2019
PDUFA Date	June 26, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Bachert and Gross) were selected for inspections for Protocols EFC14280 and EFC14146 for this application. The study data derived from these two clinical sites, based on the inspections, are considered reliable and the studies in support of this application appear to have been conducted adequately.

The preliminary classification for the inspections for two sites is No Action Indicated (NAI). Preliminary classification is based on communications with the ORA investigators. Inspection classification becomes final when the Establishment Inspection Report (EIR) is received from the field, has been reviewed, and a letter is issued to the inspected entity.

2. BACKGROUND

DUPIXENT (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. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE. The current approved indication of dupilumab is for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) and adolescent and adult patients with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

In this application, the sponsor proposes dupilumab as add-on maintenance treatment in adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyposis (CRSwNP).

The sponsor's clinical development program for dupilumab in support of the proposed indication included two Phase 3 clinical studies (Studies EFC14146 and EFC14280) and a Phase 2 study (ACT12340). CDER DPARP requests two clinical sites for inspections for the two Phase 3 clinical trials.

Protocol EFC14146

Protocol Title: A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids – EFC14146

This was a Phase 3, multi-national, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate dupilumab administered subcutaneously (SC) for 24 weeks in patients with bilateral nasal polyposis (NP).

The primary objective of the study was to evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of mometasone furoate nasal spray (MFNS) in reducing nasal congestion (NC)/obstruction severity and endoscopic nasal polyps score (NPS) in patients with bilateral nasal polyposis (NP).

The coprimary efficacy endpoints were the change from baseline in NPS and NC at Week 24.

The study enrolled 276 subjects from the 67 clinical sites in 13 countries including (Bulgaria, Czech Republic, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom, and the United States). The study enrolled the first subject on December 5, 2016 and the last patient completed the study on July 5, 2018.

Protocol EFC14280

Protocol Title: A randomized, double-blind, 52-week, placebo-controlled efficacy and safety study of dupilumab, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids – EFC14280

This was a Phase 3, multi-national, multicenter, randomized, double-blind, placebo-controlled, parallel group study to evaluate dupilumab administered subcutaneously (SC) for 52 weeks in patients with bilateral NP.

The primary objective of the study was to evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of MFNS in reducing nasal congestion (NC)/obstruction severity and endoscopic nasal polyps score (NPS) in patients with bilateral nasal polyposis (NP).

The coprimary efficacy endpoints were the change from baseline in NPS and NC at Week 24.

The study enrolled 448 subjects from the 117 clinical sites in 14 countries including Argentina, Australia, Belgium, Canada, Chile, Israel, Mexico, Portugal, Russia, Spain, Sweden, Turkey, Japan, and United States. The study enrolled the first subject on November 28, 2016 and the last subject completed the last treatment on August 29, 2018.

Rationale for Site Selection

The clinical sites were chosen based on risk ranking in the site selection tool, numbers of enrolled subjects, high treatment response, financial disclosure, and prior inspectional history.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Enrolled Subjects	Inspection Date	Classification
Claus Bachert, M.D. Corneel Heymanslaan 10 Gent, NA 9000 Belgium	Site #560001 Protocol EFC14280 18 Subjects	April 1-5, 2019	NAI*
Gary Gross, M.D. 5499 Glen Lakes Dr., Suite 200 Dallas, TX 75231	Site #8400001 Protocol EFC14146 6 Subjects	March 5-11, 2019	NAI

Key to Compliance Classifications
NAI (No Action Indicated) = No deviation from regulations.
VAI (Voluntary Action Indicated) = Deviation(s) from regulations.
OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.
* Pending = Preliminary classification is based on communication with the field investigator. EIR is pending at present time. Final classification occurs after EIR is reviewed and when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1. Claus Bachert, M.D. (Site #560001, Gent, Belgium)

The site screened 24 subjects and enrolled 18 subjects in Study Protocol EFC14280. Among the 18 enrolled subjects, 16 subjects completed the study and two subjects (Subjects (b) (6) and (b) (6)) discontinued the study due to adverse events. Subject (b) (6) (dupilumab 300 mg q2w group) experienced folliculitis and discontinued study treatment. Subject (b) (6) (dupilumab 300 mg q2w up to Week 24 and 300 q4w from Week 24 to Week 52 group) died of bicycle accident during the follow-up period. An audit of all enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, Ethics Committee approvals (EC), site signature and responsibility logs, electronic case forms (eCRF), study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint of nasal congestion (NC) data was verifiable in all enrolled subjects at the study site. The subjects' Visits 2 and 8 nasal endoscopy videos were reviewed in ten of 18 enrolled subjects and the correct videos were sent to BMS (sponsor's vendor) for scoring for the NPS primary efficacy endpoint assessment. No under-reporting of adverse events was noted. Protocol deviations noted at the site generally matched with the data listings provided in the BLA submission. Minor protocol deviations noted at site not in data listings included out of window visits and missing ECGs in two subjects at the end of treatment visits. Records were considered adequate at site except one concomitant medication in source documents was not in the eCRF (Subject (b) (6) [placebo group] received one Medrol IM injection for shoulder pain during treatment period).

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were identified. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Gary Gross, M.D. (Site #8400001, Dallas, TX)

The site screened 10 subjects and enrolled six subjects in Study Protocol EFC14146. An audit of all enrolled subjects' records was conducted. All six subjects completed the study.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and correspondence with the IRB, monitors, and sponsor were also inspected. Source documents for enrolled subjects whose records were

reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoints were verifiable at the study site. No transcription errors were noted from source data captured within the EDC system against data listings. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were identified. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Central Doc. Rm.
Review Division /Clinical Team Leader/ Miya Paterniti
Review Division/Medical Officer/ Rekha Jhamnani
Review Division /Project Manager/ Elaine Sit
OSI/DCCE/ Division Director/ Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/GCP Reviewer/Min Lu
OSI/ GCP Program Analyst/Yolanda Patague

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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:	April 11, 2019
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761055/S-014
Product Name and Strength:	Dupixent (dupilumab) Injection 200 mg/1.14 mL (175 mg/mL) 300 mg/2 mL (150 mg/mL) Prefilled Syringe
Product Type:	Combination Product (Drug-Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals, Inc.
FDA Received Date:	December 26, 2018, March 15, 2019
OSE RCM #:	2019-302
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

Regeneron Pharmaceuticals, Inc. submitted a supplement for Dupixent (dupilumab) Prefilled Syringe to propose an additional indication as an add-on maintenance treatment in adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyposis (CRSwNP). Subsequently, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the proposed Dupixent prescribing information and patient information for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 CONCLUSION

Our evaluation of the proposed Dupixent prescribing information and patient information did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Dupixent that Regeneron Pharmaceuticals, Inc. submitted on December 26, 2018.

Table 2. Relevant Product Information for Dupixent	
Initial Approval Date	March 28, 2017
Active Ingredient	Dupilumab
Indication	Current: • 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. 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 Additional Proposed: • as an add-on maintenance treatment in adult patients with inadequately controlled severe chronic rhinosinusitis with nasal polyposis (CRSwNP). (b) (4)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	200 mg/1.14 mL and 300 mg/2 mL

Dose and Frequency	**Atopic Dermatitis** • The recommended dose is an initial dose of 600 mg (two 300 mg injections in different injection sites), followed by 300 mg given every other week. (2.1) **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 (b) (4) (b) (4) 300 mg given every other week. (2.3)
How Supplied	In cartons containing 2 single-dose pre-filled syringes with needle shield
Storage	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.
Container Closure	A 2.25 mL clear glass syringe barrel equipped with a 27 Gauge (G) ½" (inch) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 4, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Dupixent. Our search identified eight previous reviews[a,bcdefgh], and we confirmed that our previous recommendations were implemented.

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[a] Patel, M. Label and Labeling Memo for Dupixent (BLA 761055/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 14. RCM No.: 2018-1924-1.

[b] Patel, M. Labeling Review for Dupixent (BLA 761055/S-012). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 FEB 12. RCM No.: 2018-1924.

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

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

[e]Mena-Grillasca, C. Label and Labeling Review for Dupixent (BLA 761055/S-005). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 OCT 06 RCM No.: 2017-1806

[f]Mena-Grillascsa, C. Human Factors, Label, Labeling, and Packaging Review for Dupilumab (IND 107969). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 MAR 10. RCM No.: 2016-1727 and 2016-2020

[g] Mena- Grillascsa, C. Human Factors Protocol Memo for Dupilumab (IND 107969). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 FEB 01. RCM No.: 2016-89

[h] Mena- Grillascsa, C. Human Factors Protocol Review for Dupilumab (IND 107969). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 NOV 04. RCM No.: 2015-2076

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

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

- Patient Information (Image not shown) received on December 26, 2018 and March 15, 2019
- Prescribing Information (Image not shown) received on December 26, 2018 and March 15, 2019

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

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