CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

761055Orig1s040

Trade Name:	Dupixent
Generic or Proper Name:	dupilumab
Sponsor:	Regeneron Pharmaceuticals, Inc.
Approval Date:	May 20, 2022
Indication:	For the treatment of adult and pediatric patients ages 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis.

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APPROVAL LETTER

BLA 761055/S-040

SUPPLEMENT APPROVAL

Regeneron Pharmaceuticals, Inc.
Attention: Sarah Benvin, MBS, RAC
Associate Director, Regulatory Affairs
777 Old Saw Mill River Road
Tarrytown, NY 10591

Dear Ms. Benvin:

Please refer to your supplemental biologics license application (sBLA), dated and received February 3, 2022, and your amendments, submitted under section 351(a) of the Public Health Service Act for Dupixent (dupilumab) injection.

This Prior Approval supplemental biologics license application provides for the treatment of adult and pediatric patients ages 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis.

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, 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.

Because none of these criteria apply to your application, you are exempt from this requirement

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

Since Dupixent (dupilumab) was approved on March 28, 2017, we have become aware of reports of arthralgia in clinical trials conducted in patients with eosinophilic esophagitis. We consider this information to be "new safety information" as defined in section 505-1(b)(3) of the FDCA.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the signal of a serious risk of arthralgia in patients with eosinophilic esophagitis.

[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.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of arthralgia in patients with eosinophilic esophagitis.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

4276-1 Complete Part C of the ongoing clinical trial, R668-EE-1774, "A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis," to evaluate the safety of long-term use of Dupixent (dupilumab) in adult and pediatric patients ages 12 years and older with eosinophilic esophagitis over 52 weeks of therapy.

The timetable you submitted on May 9, 2022 states that you will conduct this study according to the following schedule:

Trial Completion:	09/2022
Final Report Submission:	03/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 136142, with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **"Required Postmarketing Protocol Under 505(o)", "Required Postmarketing Final Report Under 505(o)", "Required Postmarketing Correspondence Under 505(o)"**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4276-2 A one-year, randomized, double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis.

The timetable you submitted on May 9, 2022, states that you will conduct this study according to the following schedule:

Trial Completion:	04/2023
Final Report Submission:	10/2023

4276-3 A long-term extension study to evaluate the long-term safety of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis, who participated in postmarketing commitment study 4276-2. This study may be conducted as part of postmarketing commitment study 4276-2.

The timetable you submitted on May 9, 2022, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	08/2022
Trial Completion:	08/2025
Final Report Submission:	02/2026

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 136142 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report

submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **"Postmarketing Commitment Protocol," "Postmarketing Commitment Final Report," or "Postmarketing Commitment Correspondence."**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

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.[5] Information and Instructions for completing the form can be found at 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 Mary Chung, Regulatory Project Manager, at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Jessica J. Lee, M.D., M.M.Sc.
Director
Division of Gastroenterology
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

ENCLOSURES:

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

[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

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

DUPIXENT® (dupilumab) injection, for subcutaneous use
Initial U.S. Approval: 2017

RECENT MAJOR CHANGES

Indications and Usage, Asthma (1.2)	10/2021
Indications and Usage, EoE (1.4)	05/2022
Dosage and Administration (2.1; 2.2; 2.4; 2.8)	12/2021
Dosage and Administration, EoE (2.6; 2.7)	05/2022
Warnings and Precautions (5.1; 5.2; 5.7; 5.8; 5.9)	12/2021
Warnings and Precautions (5.2)	05/2022

INDICATIONS AND USAGE

DUPIXENT is an interleukin-4 receptor alpha antagonist indicated:

Atopic Dermatitis

- for the treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. (1.1)

Asthma

- as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2)
  Limitations of Use Not for the relief of acute bronchospasm or status asthmaticus. (1.2)

Chronic Rhinosinusitis with Nasal Polyposis

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

Eosinophilic Esophagitis

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

DOSAGE AND ADMINISTRATION

Atopic Dermatitis

Dosage in Adults

- Recommended dosage is an initial dose of 600 mg (two 300 mg injections), followed by 300 mg given every other week (Q2W). (2.3)

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

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

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

Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older

Initial Loading Dose	Subsequent Dose
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
or	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyposis	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age

Body Weight	Initial Dose and Subsequent Doses
15 to less than 30 kg	100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

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

Chronic Rhinosinusitis with Nasal Polyposis

- Recommended dosage for adult patients is 300 mg given every other week (Q2W). (2.5)

Eosinophilic Esophagitis

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Hypersensitivity: Hypersensitivity reactions including anaphylaxis, serum sickness, angioedema, urticaria, rash, erythema nodosum, and erythema multiforme have occurred. Discontinue DUPIXENT in the event of a hypersensitivity reaction. (5.1)
- Conjunctivitis and Keratitis: Advise patients to report new onset or worsening eye symptoms to their healthcare provider. Consider ophthalmological examination, as appropriate. (5.2)
- Eosinophilic Conditions: Be alert to vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids. (5.3)
- Reduction of Corticosteroid Dosage: Do not discontinue systemic, topical, or inhaled corticosteroids abruptly upon initiation of DUPIXENT. Decrease steroids gradually, if appropriate. (5.5)
- Arthralgia: Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT. (5.7)
- Parasitic (Helminth) Infections: Treat pre-existing helminth infections before initiating DUPIXENT. If patients become infected while receiving DUPIXENT and do not respond to anti-helminth treatment, discontinue DUPIXENT until the infection resolves. (5.8)
- Vaccinations: Avoid use of live vaccines. (5.9)

ADVERSE REACTIONS

Most common adverse reactions are:

- Atopic Dermatitis (incidence ≥1%): injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye. (6.1)
- Asthma (incidence ≥1%): injection site reactions, oropharyngeal pain, and eosinophilia. (6.1)
- Chronic Rhinosinusitis with Nasal Polyposis (incidence ≥1%): injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis. (6.1)
- Eosinophilic Esophagitis (incidence ≥2%): injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. (6.1)

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

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

Revised: 05/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Atopic Dermatitis

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

1.2 Asthma

DUPIXENT is indicated as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma *[see Clinical Studies (14)]*.

Limitations 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).

1.4 Eosinophilic Esophagitis

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

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

DUPIXENT is administered by subcutaneous injection.

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

Use of Pre-filled Pen or Pre-filled Syringe

The DUPIXENT pre-filled pen is for use in adult and pediatric patients aged 12 years and older.

The DUPIXENT pre-filled syringe is for use in adult and pediatric patients aged 6 years and older.

A caregiver or patient 12 years of age and older may inject DUPIXENT using the pre-filled syringe or pre-filled pen. In pediatric patients 12 to 17 years of age, administer DUPIXENT under the supervision of an adult.

In pediatric patients 6 to 11 years of age, administer DUPIXENT pre-filled syringe by a caregiver.

Administration Instructions

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

For atopic dermatitis and asthma patients taking an initial 400 mg dose, administer each of the two DUPIXENT 200 mg injections at different injection sites.

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

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

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

2.2 Vaccination Prior to Treatment

Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with DUPIXENT *[see Warnings and Precautions (5.9)]*.

2.3 Recommended Dosage for Atopic Dermatitis

Dosage in Adults

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

Dosage in Pediatric Patients 6 to 17 Years of Age

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

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

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

Concomitant Topical Therapies

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

2.4 Recommended Dosage for Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older

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

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

Initial Loading Dose	Subsequent Dose
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
or	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyposis	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age

The recommended dosage of DUPIXENT for pediatric patients 6 to 11 years of age is specified in Table 3.

Table 3: Dosage of DUPIXENT in Pediatric Patients 6 to 11 Years of Age with Asthma

Body Weight	Initial[a] and Subsequent Doses
15 to less than 30 kg	100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

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

For pediatric patients 6 to 11 years of age with asthma and co-morbid moderate-to-severe atopic dermatitis, follow the recommended dosage as per Table 1 which includes an initial loading dose *[see Dosage and Administration (2.3)]*.

2.5 Recommended Dosage for Chronic Rhinosinusitis with Nasal Polyposis

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

2.6 Recommended Dosage for Eosinophilic Esophagitis

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

2.7 Missed Doses

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

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

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

2.8 Preparation for Use

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

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

3 DOSAGE FORMS AND STRENGTHS

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

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

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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

5.2 Conjunctivitis and Keratitis

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

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

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)]*.

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

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

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

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

5.3 Eosinophilic Conditions

Patients being treated for asthma may present with serious 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. Healthcare providers should be alert to vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy presenting in their patients with eosinophilia. Cases of eosinophilic pneumonia were reported in adult subjects who participated in the asthma development program and cases of vasculitis consistent with eosinophilic granulomatosis with polyangiitis have been reported with DUPIXENT in adult subjects who participated in the asthma development program as well as in adult subjects with co-morbid asthma in the CRSwNP development program. A causal association between DUPIXENT and these conditions has not been established.

5.4 Acute Asthma Symptoms or Deteriorating Disease

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

5.5 Risk Associated with Abrupt Reduction of Corticosteroid Dosage

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

5.6 Patients with Co-morbid Asthma

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

5.7 Arthralgia

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

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

5.8 Parasitic (Helminth) Infections

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

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. Adverse reactions of helminth infections (5 cases of enterobiasis and 1 case of ascariasis) were reported in pediatric patients 6 to 11 years old who participated in the pediatric asthma development program *[see Adverse Reactions (6.1)]*.

5.9 Vaccinations

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

6 ADVERSE REACTIONS

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

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

6.1 Clinical Trials Experience

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

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled, multicenter trials (SOLO 1, SOLO 2, and CHRONOS) and one dose-ranging trial (AD-1021) evaluated the safety of DUPIXENT in subjects with moderate-to-severe atopic dermatitis. The safety population had a mean age of 38 years; 41% of subjects were female, 67% were White, 24% were Asian, and 6% were Black; in terms of co-morbid conditions, 48% of the subjects had asthma, 49% had allergic rhinitis, 37% had food allergy, and 27% had allergic conjunctivitis. In these 4 trials, 1472 subjects were treated with subcutaneous injections of DUPIXENT, with or without concomitant topical corticosteroids (TCS).

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

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

AD-1225 is a multicenter, open-label extension (OLE) study which assessed the long-term safety of repeat doses of DUPIXENT (through 148 weeks of treatment) in adults with moderate-to-severe AD who had previously participated in controlled studies of DUPIXENT or had been screened for SOLO 1 or SOLO 2. The safety data in AD-1225 reflect exposure to DUPIXENT in 2677 subjects, including 2254 exposed for at least 52 weeks, 1192 exposed for at least 100 weeks, and 357 exposed for at least 148 weeks. In AD-1225, 99.7% of subjects were exposed to DUPIXENT 300 mg weekly dosing (QW).

Weeks 0 to 16 (SOLO 1, SOLO 2, CHRONOS, and AD-1021)

In DUPIXENT monotherapy trials (SOLO 1, SOLO 2, and AD-1021) through Week 16, the proportion of subjects who discontinued treatment because of adverse events was 1.9% in both the DUPIXENT 300 mg Q2W and placebo groups. Table 4 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 4: 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 SOLO 1, SOLO 2, and AD-1021.
[b] Analysis of CHRONOS where subjects were on background TCS therapy.
[c] DUPIXENT 600 mg at Week 0, followed by 300 mg every two weeks.
[d] Conjunctivitis cluster includes conjunctivitis, allergic conjunctivitis, bacterial conjunctivitis, viral conjunctivitis, giant papillary conjunctivitis, eye irritation, and eye inflammation.
[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 (CHRONOS)

In the DUPIXENT with concomitant TCS trial (CHRONOS) through Week 52, the proportion of subjects who discontinued treatment because of adverse events was 1.8% 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.

Safety through 148 Weeks (AD-1225)

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

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

The safety of DUPIXENT was assessed in a trial of 250 pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1526). The safety profile of DUPIXENT in these subjects through Week 16 was similar to the safety profile seen in adults with atopic dermatitis.

The long-term safety of DUPIXENT was assessed in an open-label extension study in pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis (AD-1434). The safety profile of DUPIXENT in subjects followed through Week 52 was similar to the safety profile

observed at Week 16 in AD-1526. The long-term safety profile of DUPIXENT observed in pediatric subjects 12 to 17 years of age was consistent with that seen in adults with atopic dermatitis.

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

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

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

Asthma

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

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

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

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

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

Adverse Reaction	DRI12544 and QUEST		
	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.

Pediatric Subjects 6 to 11 Years of Age with Asthma

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

Chronic Rhinosinusitis with Nasal Polyposis

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

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

Table 6 summarizes the adverse reactions that occurred at a rate of at least 1% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in SINUS-24 and SINUS-52.

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

Adverse Reaction	SINUS-24 and SINUS-52	
	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.

Eosinophilic Esophagitis

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

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

Table 7 summarizes the adverse reactions that occurred at a rate of at least 2% in subjects treated with DUPIXENT and at a higher rate than in their respective comparator group in Parts A and B.

Table 7: Adverse Reactions Occurring in ≥2% of Patients with EoE Treated with DUPIXENT in a Placebo Controlled Trial (Parts A and B; 24-Week Safety Pool)

Adverse Reaction	Parts A and B	
	DUPIXENT 300 mg QW N=122 n (%)	Placebo N=117 n (%)
Injection site reactions[a]	46 (38%)	39 (33%)
Upper respiratory tract infections[b]	22 (18%)	12 (10%)
Arthralgia	3 (2%)	1 (1%)
Herpes viral infections[c]	3 (2%)	1 (1%)

[a] Injection site reactions are composed of several terms including, but not limited to, injection site swelling, pain, and bruising.
[b] Upper respiratory tract infections are composed of several terms including, but not limited to, COVID-19, sinusitis, and upper respiratory tract infection.
[c] Herpes viral infections are composed of oral herpes and herpes simplex.

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

Specific Adverse Reactions

Conjunctivitis and Keratitis

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

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

Among subjects with asthma, the frequency of conjunctivitis and keratitis was similar between DUPIXENT and placebo.

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.

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

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

Eczema Herpeticum and Herpes Zoster

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

Herpes zoster was reported in <1% of the 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). During the long-term OLE trial with data through 148 weeks (AD-1225), 1.9% of DUPIXENT-treated subjects reported herpes zoster (0.99 per 100 subject-years of follow up). Among asthma subjects the frequency of herpes zoster was similar

between DUPIXENT and placebo. Among subjects with CRSwNP or EoE 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 anaphylaxis, serum sickness or serum sickness-like reactions, generalized urticaria, rash, erythema nodosum, and erythema multiforme *[see Contraindications (4), Warnings and Precautions (5.1), and Adverse Reactions (6.2)]*.

Eosinophils

DUPIXENT-treated subjects with atopic dermatitis, asthma, and CRSwNP had a greater initial increase from baseline in blood eosinophil count compared to subjects treated with placebo. An increase from baseline in blood eosinophil count was not observed in subjects with EoE treated with DUPIXENT as compared to placebo. In subjects with atopic dermatitis (SOLO 1, SOLO 2, and AD-1021), the mean and median increases in blood eosinophils from baseline to Week 4 were 100 and 0 cells/mcL, respectively. In adult and pediatric subjects 12 years of age and older with asthma (DRI12544 and QUEST), the mean and median increases in blood eosinophils from baseline to Week 4 were 130 and 10 cells/mcL, respectively. In subjects 6 to 11 years of age with asthma (VOYAGE), the mean and median increases in blood eosinophils from baseline to Week 12 were 124 and 0 cells/mcL, respectively. In subjects with CRSwNP (SINUS-24 and SINUS-52), the mean and median increases in blood eosinophils from baseline to Week 16 were 150 and 50 cells/mcL, respectively.

Across atopic dermatitis, asthma, and CRSwNP 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 <3% of DUPIXENT-treated subjects and <0.5% in placebo-treated subjects (SOLO 1, SOLO 2, and AD-1021; DRI12544, QUEST, and VOYAGE; SINUS-24 and SINUS-52). Blood eosinophil counts declined to near baseline levels during study treatment *[see Warnings and Precautions (5.3)]*.

Cardiovascular

In the 1-year placebo-controlled trial in adult and pediatric subjects 12 years of age and older with asthma (QUEST), cardiovascular thromboembolic events (cardiovascular 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 (CHRONOS), 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 (SINUS-24), 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 (SINUS-52), there were no cases

of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

In the 24-week placebo-controlled trial in subjects with EoE (Parts A and B), there were no cases of cardiovascular thromboembolic events (cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) reported in any treatment arm.

6.2 Immunogenicity

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

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

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

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

Approximately 1% of subjects with EoE who received DUPIXENT 300 mg QW for 24 weeks developed antibodies to dupilumab.

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

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

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

6.3 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of DUPIXENT. Because these reactions are reported voluntarily from a population of uncertain size, it is not

always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: angioedema *[see Warnings and Precautions (5.1)]*

Skin and subcutaneous tissue disorders: Facial skin reactions, including erythema, rash, scaling, edema, papules, pruritus, burning, and pain

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

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

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

Risk Summary

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

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

Use of DUPIXENT in this age group is supported by AD-1526 which included 251 pediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis and AD-1652 which included 367 pediatric subjects 6 to 11 years of age with severe atopic dermatitis. The safety and effectiveness were generally consistent between pediatric and adult patients *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*.

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

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

Asthma

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

Pediatric Subjects 12 to 17 Years of Age:

A total of 107 pediatric subjects 12 to 17 years of age with moderate-to-severe asthma were enrolled in QUEST and received either 200 mg (N=21) or 300 mg (N=18) DUPIXENT (or

matching placebo either 200 mg [N=34] or 300 mg [N=34]) Q2W. Asthma exacerbations and lung function were assessed in both pediatric subjects 12 to 17 years of age and adults. For both the 200 mg and 300 mg Q2W doses, improvements in 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. Dupilumab exposure was higher in pediatric subjects 12 to 17 years of age than that in adults at the respective dose level which was mainly accounted for by difference in body weight *[see Clinical Pharmacology (12.3)]*.

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

Pediatric Subjects 6 to 11 Years of Age:

A total of 408 pediatric subjects 6 to 11 years of age with moderate-to-severe asthma were enrolled in VOYAGE, which evaluated doses of 100 mg Q2W or 200 mg Q2W. Improvement in asthma exacerbations and lung function were demonstrated *[see Clinical Studies (14.2)]*. The effectiveness of DUPIXENT 300 mg Q4W in subjects 6 to 11 years of age with body weight 15 to <30 kg was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W *[see Clinical Pharmacology (12.3)]*. Subjects who completed the treatment period of the VOYAGE study could participate in the open-label extension study (LTS14424). Eighteen subjects (≥15 to <30 kg) out of 365 subjects were exposed to 300 mg Q4W in this study, and the safety profile in these eighteen subjects was consistent with that seen in VOYAGE. Additional safety for DUPIXENT 300 mg Q4W is based upon available safety information from the pediatric atopic dermatitis indication *[see Adverse Reactions (6.1) and Clinical Pharmacology (12.3)]*.

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

CRSwNP

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

EoE

The safety and effectiveness of DUPIXENT for the treatment of EoE have been established in pediatric patients 12 years of age and older, weighing at least 40 kg. Use of DUPIXENT in this population is supported by an adequate and well-controlled study in adults (Parts A and B) which included 72 pediatric patients 12 to 17 years of age, weighing at least 40 kg, and additional pharmacokinetic data. The safety and effectiveness in adults and pediatric patients were similar *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.4)]*.

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

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. Clinical studies of DUPIXENT in atopic dermatitis did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects *[see Clinical Pharmacology (12.3)]*.

Of the 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.

Clinical studies of DUPIXENT in EoE did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

10 OVERDOSAGE

There is no specific treatment for DUPIXENT overdose. In the event of overdosage, contact Poison Control (1-800-222-1222) for the latest recommendations and monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

11 DESCRIPTION

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

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

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

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

Each 200 mg pre-filled syringe or pre-filled pen 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.

Each 100 mg pre-filled syringe delivers 100 mg dupilumab in 0.67 mL which also contains L-arginine hydrochloride (3.5 mg), L-histidine (2.1 mg), polysorbate 80 (1.3 mg), sodium acetate (0.7 mg), sucrose (34 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 driven by IL-4 and IL-13 is an important component in the pathogenesis of asthma, atopic dermatitis, CRSwNP, and EoE. 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. The mechanism of dupilumab action has not been definitively established.

12.2 Pharmacodynamics

Consistent with inhibition of IL-4 and IL-13 signaling, dupilumab treatment decreased certain biomarkers of inflammation. In asthma subjects, fractional exhaled nitric oxide (FeNO) and circulating concentrations of eotaxin-3, total IgE, allergen specific IgE, TARC, and periostin were decreased relative to placebo. Reductions in these biomarkers were comparable for the 300 mg Q2W and 200 mg Q2W regimens. These markers were near maximal suppression after 2 weeks of treatment, except for IgE which declined more slowly. These effects were sustained throughout treatment. The median percent reduction from baseline in total IgE concentrations with dupilumab treatments was 52% at Week 24 (DRI12544) and 70% at Week 52 (QUEST). For FeNO, the mean percent reduction from baseline at Week 2 was 35% and 24% in DRI12544 and QUEST, respectively, and in the overall safety population, the mean FeNO level decreased to 20 ppb.

Antibody Response to Non-Live Vaccines During DUPIXENT Treatment

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

12.3 Pharmacokinetics

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

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 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 195±71.7 mcg/mL for 300 mg administered weekly, and from 29.2±18.7 to 36.5±22.2 mg/L for 200 mg administered Q2W.

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

Distribution

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

Elimination

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

Dose Linearity

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

Weight

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

Age

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

Immunogenicity

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

Specific Populations

Geriatric Patients

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

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

Asthma

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

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

Eosinophilic Esophagitis

In a clinical study (Parts A and B), dupilumab pharmacokinetics were investigated in 35 pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE, receiving 300 mg QW. The mean ± SD steady-state trough concentration of dupilumab was 227 ± 95.3 mcg/mL.

Drug Interaction Studies

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

Cytochrome P450 Substrates

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

14 CLINICAL STUDIES

14.1 Atopic Dermatitis

Adults with Atopic Dermatitis

Three randomized, double-blind, placebo-controlled trials (SOLO 1 (NCT02277743), SOLO 2 (NCT02277769), and CHRONOS (NCT01859988)) enrolled a total of 2119 adult subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score ≥3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score ≥16 on a scale of 0 to 72, and a minimum body surface area involvement of ≥10%. At baseline, 59% of subjects were male, 67% were White, 52% of subjects had a baseline IGA score of 3 (moderate AD), and 48% of subjects had a baseline IGA of 4 (severe AD). The baseline mean EASI score was 33 and the baseline weekly averaged Peak Pruritus Numeric Rating Scale (NRS) was 7 on a scale of 0-10.

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

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

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

Clinical Response at Week 16 (SOLO 1, SOLO 2, and CHRONOS)

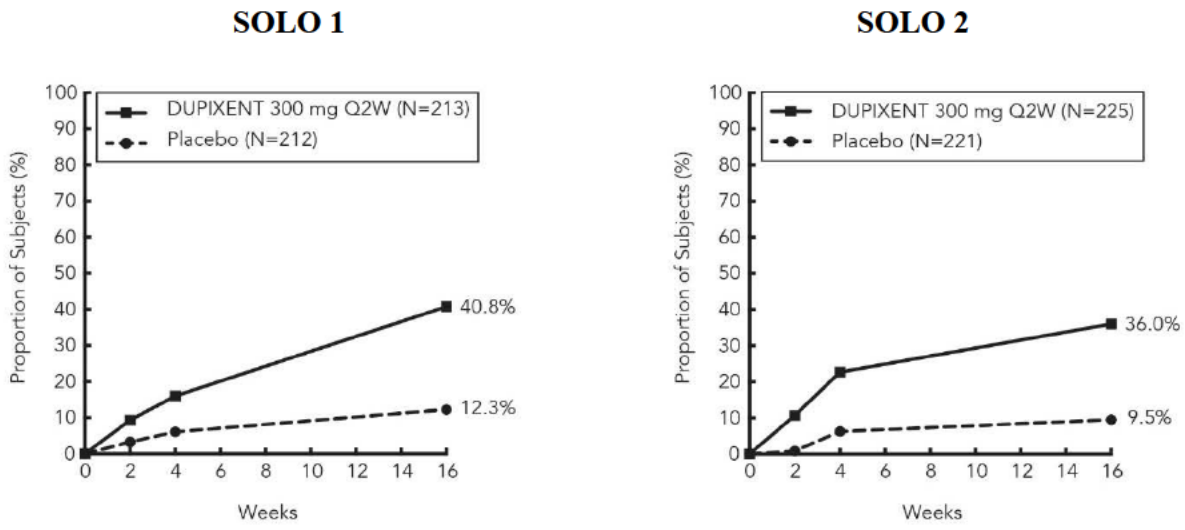
The results of the DUPIXENT monotherapy trials (SOLO 1 and SOLO 2) and the DUPIXENT with concomitant TCS trial (CHRONOS) are presented in Table 7.

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

	SOLO 1		SOLO 2		CHRONOS	
	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 Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD with ≥4-point Improvement on the Peak Pruritus NRS in SOLO 1[a] and SOLO 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 CHRONOS, of the 421 subjects, 353 had been on study for 52 weeks at the time of data analysis. Of these 353 subjects, responders at Week 52 represent a mixture of subjects who maintained their efficacy from Week 16 (e.g., 53% of 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 (CHRONOS) are presented in Table 8.

Table 8: Efficacy Results (IGA 0 or 1) of DUPIXENT with Concomitant TCS at Week 16 and 52 in Adult Subjects 18 Years of Age and Older with Moderate-to-Severe AD

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

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

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

Subjects in SOLO 1 and SOLO 2 who had an IGA 0 or 1 with a reduction of ≥2 points were re-randomized into SOLO CONTINUE (NCT02395133). SOLO CONTINUE 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.

Pediatric Subjects 12 to 17 Years of Age with Atopic Dermatitis

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

Subjects in the 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 AD-1526, 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 AD-1526 are presented in Table 9.

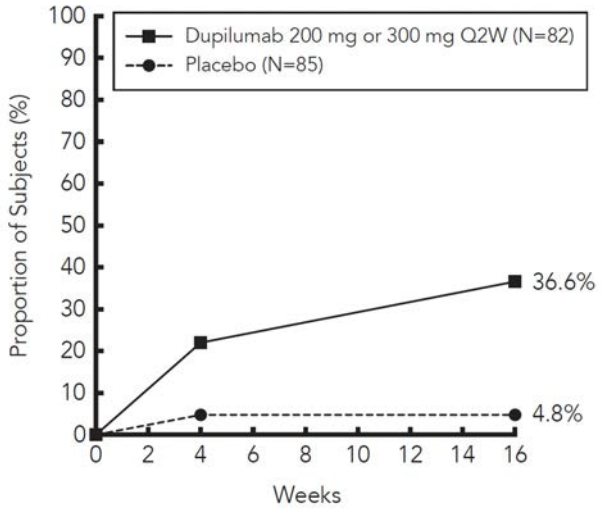
Table 9: Efficacy Results of DUPIXENT in AD-1526 at Week 16 (FAS)[a] in Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD

	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 Pediatric Subjects 12 to 17 Years of Age with Moderate-to-Severe AD with ≥4-point Improvement on the Peak Pruritus NRS in AD-1526[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.

Pediatric Subjects 6 to 11 Years of Age with Atopic Dermatitis

The efficacy and safety of DUPIXENT use concomitantly with TCS in pediatric subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial (AD-1652; NCT03345914) in 367 subjects 6 to 11 years of age, with AD defined by an IGA score of 4 (scale of 0 to 4), an EASI score ≥21 (scale of 0 to 72), and a minimum BSA involvement of ≥15%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Enrollment was stratified by baseline weight (<30 kg; ≥30 kg).

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

In AD-1652, the mean age was 8.5 years, the median weight was 29.8 kg, 50% of subjects were female, 69% were White, 17% were Black, and 8% were Asian. At baseline, the mean BSA involvement was 58%, and 17% had received prior systemic non-steroidal immunosuppressants. Also, at baseline the mean EASI score was 37.9, and the weekly average of daily worst itch score was 7.8 on a scale of 0-10. Overall, 92% of subjects had at least one co-morbid allergic condition; 64% had food allergies, 63% had other allergies, 60% had allergic rhinitis, and 47% had asthma.

The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) at Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-

90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (≥4-point improvement).

Table 10 presents the results by baseline weight strata for the approved dose regimens.

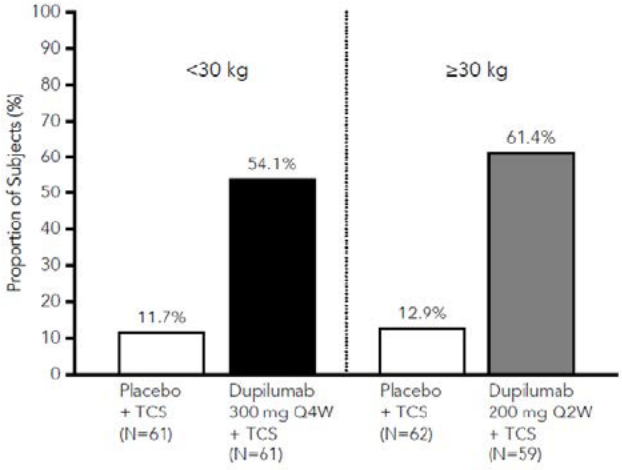
Table 10: Efficacy Results of DUPIXENT with Concomitant TCS in AD-1652 at Week 16 (FAS)[a] in Pediatric Subjects 6 to 11 Years of Age with AD

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

[a] Full Analysis Set (FAS) includes all subjects randomized.
[b] Responder was defined as a subject with an IGA 0 or 1 ("clear" or "almost clear").
[c] Subjects who received rescue treatment or with missing data were considered as non-responders.
[d] At Day 1, subjects received 600 mg of DUPIXENT.
[e] At Day 1, subjects received 200 mg (baseline weight <30 kg) or 400 mg (baseline weight ≥30 kg) of DUPIXENT.

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

Figure 3: Proportion of Pediatric Subjects 6 to 11 Years of Age with AD with ≥4-point Improvement on the Peak Pruritus NRS at Week 16 in AD-1652[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 for patients aged 12 years and older included three randomized, double-blind, placebo-controlled, parallel-group, multicenter trials (DRI12544 (NCT01854047), QUEST (NCT02414854), and VENTURE (NCT02528214)) of 24 to 52 weeks

in treatment duration which enrolled a total of 2888 subjects. Subjects enrolled in DRI12544 and QUEST 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 VENTURE 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 QUEST and VENTURE, 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 VENTURE in which OCS dose was tapered as described below.

DRI12544

DRI12544 was a 24-week dose-ranging study which included 776 adult 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.

QUEST

QUEST was a 52-week study which included 1902 adult and pediatric subjects (12 years of age and older). DUPIXENT compared with placebo was evaluated in 107 pediatric subjects 12 to 17 years of age 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 subjects with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores.

VENTURE

VENTURE was a 24-week oral corticosteroid-reduction study in 210 adult and pediatric subjects 15 years of age and older with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing

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

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

Table 11: Demographics and Baseline Characteristics of Asthma Trials

Parameter	DRI12544 (N=776)	QUEST (N=1902)	VENTURE (N=210)
Mean age (years) (SD)	49 (13)	48 (15)	51 (13)
% Female	63	63	61
% White	78	83	94
Duration of Asthma (years), mean (± SD)	22 (15)	21 (15)	20 (14)
Never smoked (%)	77	81	81
Mean exacerbations in previous year (± SD)	2.2 (2.1)	2.1 (2.2)	2.1 (2.2)
High dose ICS use (%)	50	52	89
Pre-dose FEV_1 (L) at baseline (± SD)	1.84 (0.54)	1.78 (0.60)	1.58 (0.57)
Mean percent predicted FEV_1 at baseline (%) (± SD)	61 (11)	58 (14)	52 (15)
% Reversibility (± SD)	27 (15)	26 (22)	19 (23)
Atopic Medical History % Overall (AD %, NP %, AR %)	73 (8, 11, 62)	78 (10, 13, 69)	72 (8, 21, 56)
Mean FeNO ppb (± SD)	39 (35)	35 (33)	38 (31)
Mean total IgE IU/mL (± SD)	435 (754)	432 (747)	431 (776)
Mean baseline blood Eosinophil count (± SD) cells/mcL	350 (430)	360 (370)	350 (310)

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

Exacerbations

DRI12544 and QUEST evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of ≥300 cells/mcL in DRI12544 and the overall population in QUEST), 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 QUEST, 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 DRI12544 and QUEST are shown in Table 12.

Response rates by baseline blood eosinophils and baseline FeNO for QUEST are shown for the overall population in Figure 4 and Figure 5, respectively. Elevation of FeNO can be a marker of the eosinophilic asthma phenotype when supported by clinical data. Pre-specified subgroup analyses of DRI12544 and QUEST demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels (≥150 cells/mcL) or FeNO (≥25 ppb). In QUEST, 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 and FeNO <25 ppb, similar severe exacerbation rates were observed between DUPIXENT and placebo.

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

Table 12: Rate of Severe Exacerbations in DRI12544 and QUEST

Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, DRI12544)		
		N	Rate (95% CI)	Rate Ratio (95% CI)
DRI12544	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)	
QUEST	DUPIXENT 200 mg Q2W	264	0.37 (0.29, 0.48)	0.34 (0.24, 0.48)
	Placebo	148	1.08 (0.85, 1.38)	
	DUPIXENT 300 mg Q2W	277	0.40 (0.32, 0.51)	0.33 (0.23, 0.45)
	Placebo	142	1.24 (0.97, 1.57)	

Figure 4: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline Blood Eosinophil Count (cells/mcL) in Subjects with Moderate-to-Severe Asthma (QUEST)

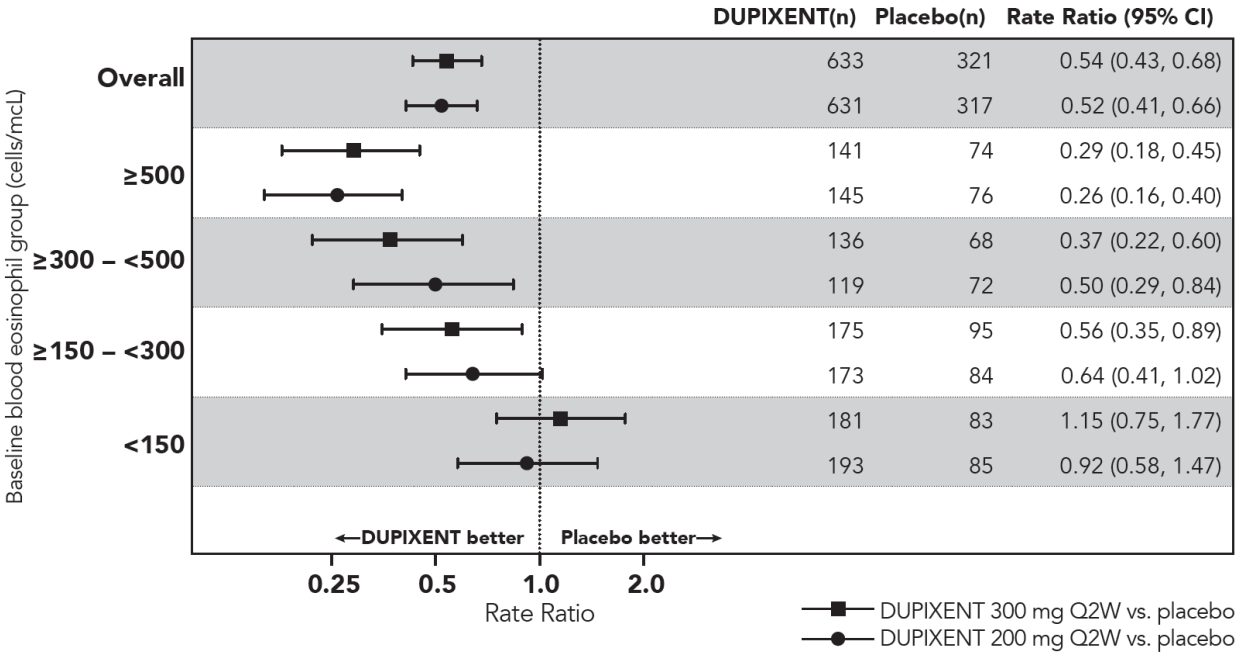
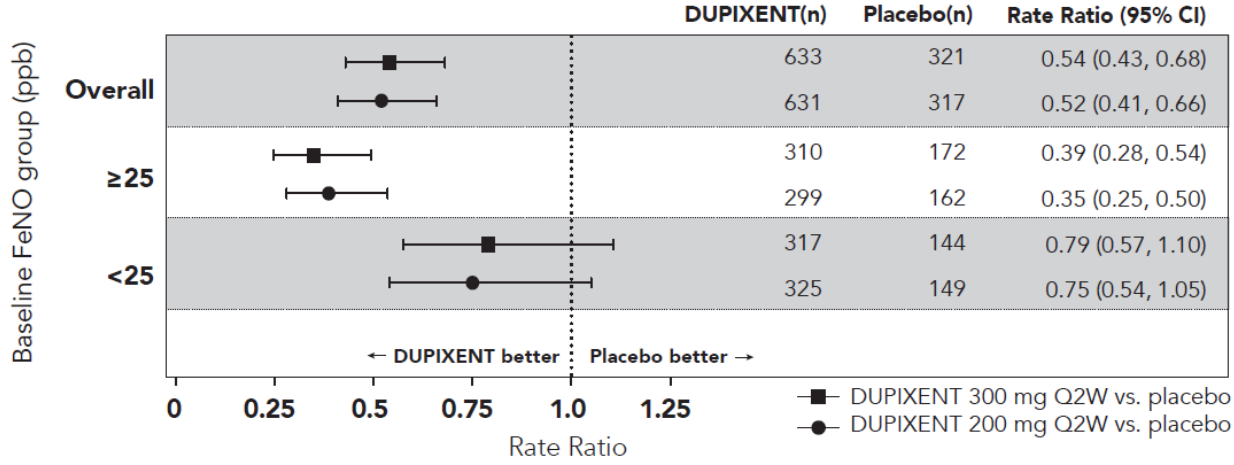
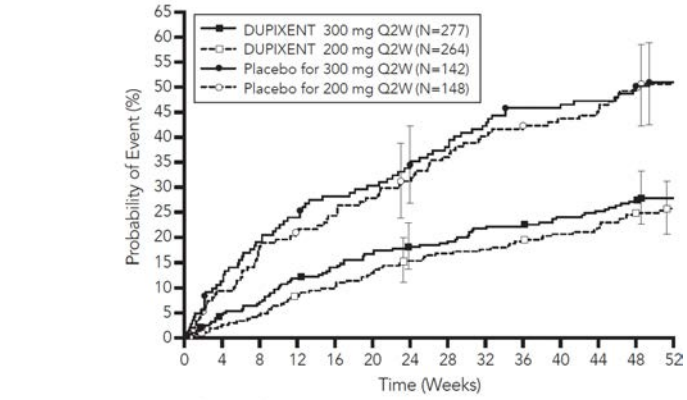


Figure 5: Relative Risk in Annualized Event Rate of Severe Exacerbations across Baseline FeNO Group (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)



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

Figure 6: Kaplan Meier Incidence Curve for Time to First Severe Exacerbation in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥300 cells/mcL (QUEST)[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 subjects had completed Week 52

Lung Function

Significant increases in pre-bronchodilator FEV_1 were observed at Week 12 for DRI12544 and QUEST in the primary analysis populations (subjects with baseline blood eosinophil count of ≥300 cells/mcL in DRI12544 and the overall population in QUEST). In the overall population in QUEST, the 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 DRI12544 and QUEST are shown in Table 13.

Improvements in FEV_1 by baseline blood eosinophils and baseline FeNO for QUEST are shown in Figure 7 and 8, respectively. Subgroup analysis of DRI12544 and QUEST demonstrated greater improvement in subjects with higher baseline blood eosinophils (≥150 cells/mcL) or FeNO (≥25 ppb). In subjects with baseline blood eosinophil count <150 cells/mcL and FeNO <25 ppb, similar differences in FEV_1 were observed between DUPIXENT and placebo.

Mean changes in FEV_1 over time in QUEST are shown in Figure 9.

Table 13: Mean Change from Baseline and Difference vs Placebo in Pre-Bronchodilator FEV_1 at Week 12 in Subjects with Moderate-to-Severe Asthma (DRI12544 and QUEST)

Trial	Treatment	Baseline Blood EOS ≥300 cells/mcL (primary analysis population, DRI12544)		
		N	LS Mean Change from baseline L (%)	LS Mean Difference vs. placebo (95% CI)
DRI12544	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)	
QUEST	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 7: 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 Subjects with Moderate-to-Severe Asthma (QUEST)

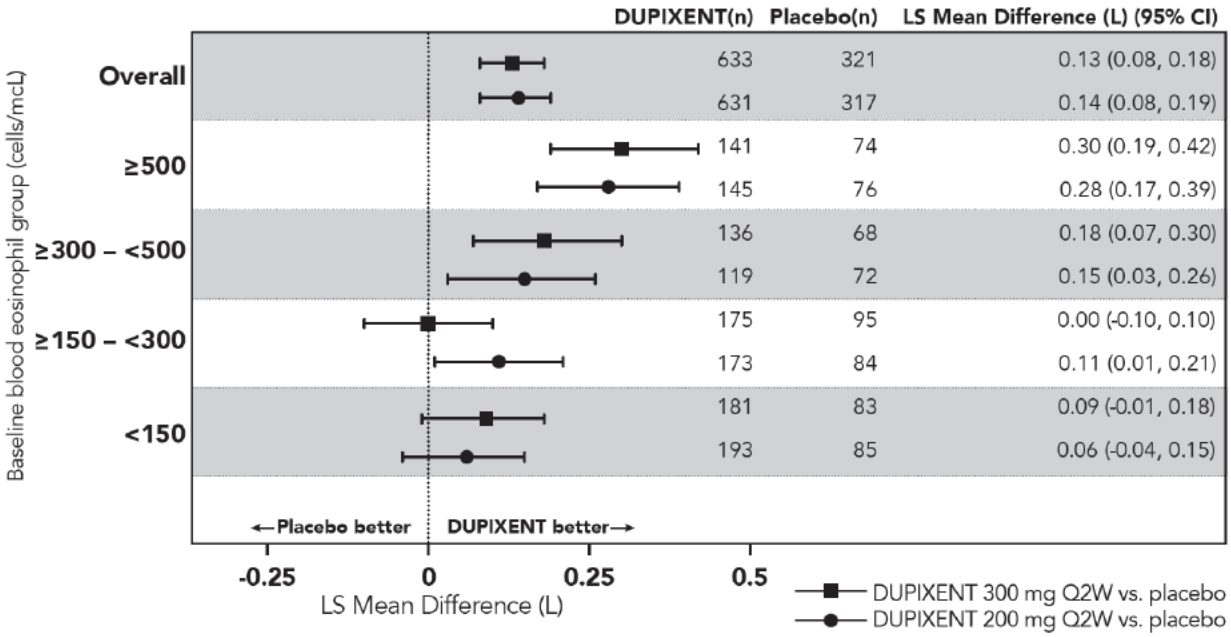


Figure 8: LS Mean Difference in Change from Baseline vs Placebo to Week 12 in Pre-bronchodilator FEV_1 across Baseline FeNO (ppb) in Subjects with Moderate-to-Severe Asthma (QUEST)

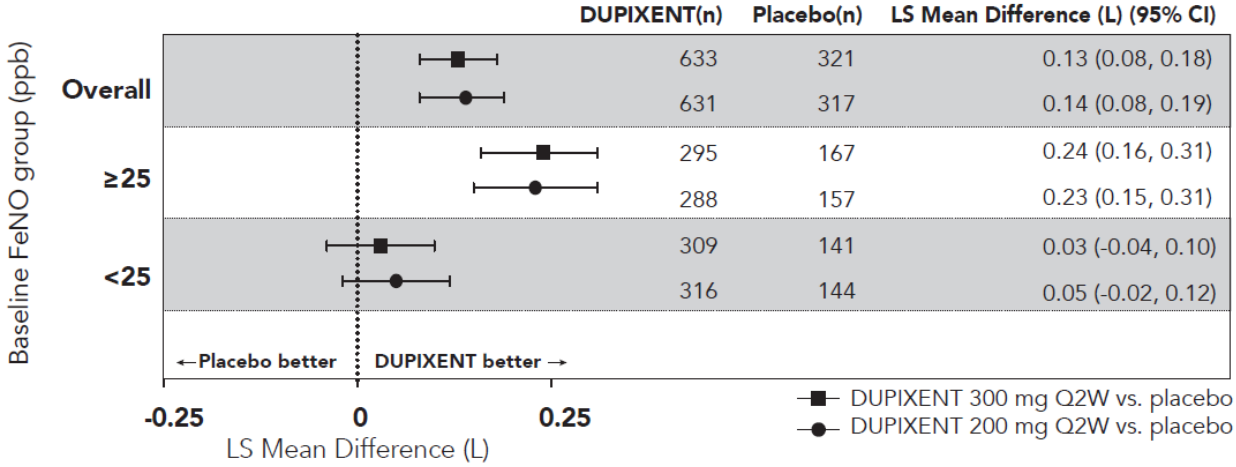
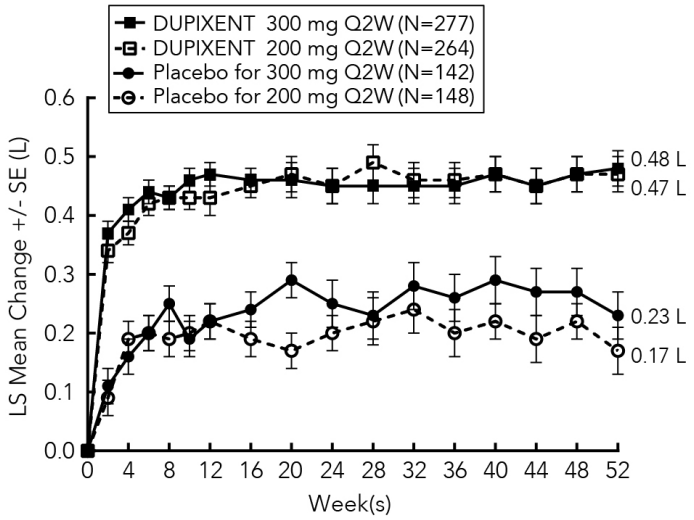


Figure 9: Mean Change from Baseline in Pre-Bronchodilator FEV_1 (L) Over Time in Subjects with Moderate-to-Severe Asthma with Baseline Blood Eosinophils ≥300 cells/mcL (QUEST)



Additional Secondary Endpoints

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

- The ACQ-5 responder rate for 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 (VENTURE)

VENTURE 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 VENTURE and showed improvements similar to those in QUEST.

Pediatric Subjects 6 to 11 Years of Age with Asthma

The efficacy and safety of DUPIXENT in pediatric subjects was evaluated in a 52-week multicenter, randomized, double-blind, placebo-controlled study (VOYAGE; NCT02948959) in 408 subjects 6 to 11 years of age, with moderate-to-severe asthma on a medium or high-dose ICS and a second controller medication or high-dose ICS alone. Subjects were required to have a history of 1 or more asthma exacerbation(s) that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects were randomized to DUPIXENT (N=273) or matching placebo (N=135) every other week based on body weight <30 kg (100 mg Q2W) or ≥30 kg (200 mg Q2W). The effectiveness of DUPIXENT 300 mg Q4W was extrapolated from efficacy of 100 mg Q2W in VOYAGE with support from population pharmacokinetic analyses showing higher drug exposure levels with 300 mg Q4W *[see Pediatric Use (8.4) and Pharmacokinetics (12.3)]*.

The primary endpoint was the annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled period. Severe asthma exacerbations were defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or

emergency room visit due to asthma that required systemic corticosteroids. The key secondary endpoint was the change from baseline in pre-bronchodilator FEV_1 percent predicted at Week 12. Additional secondary endpoints included mean change from baseline and responder rates in the ACQ-7-IA (Asthma Control Questionnaire-7-Interviewer Administered) and PAQLQ(S)-IA (Pediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered) scores.

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

Table 14: Demographics and Baseline Characteristics for VOYAGE

Parameter	VOYAGE (N=408)
Mean age (years) (SD)	9 (2)
% Female	36
% White	88
Mean body weight (kg)	36
Mean exacerbations in previous year (± SD)	2.4 (2.2)
High dose ICS dose (%)	44
Pre-dose FEV_1 (L) at baseline (± SD)	1.48 (0.41)
Mean percent predicted FEV_1 (%) (±SD)	78 (15)
Mean % Reversibility (± SD)	20 (21)
Atopic Medical History % Overall (AD %, AR %)	92 (36, 82)
Mean FeNO ppb (± SD)	28 (24)
% subjects with FeNO ppb ≥20	50
Median total IgE IU/mL (±SD)	792 (1093)
Mean baseline Eosinophil count (± SD) cells/mcL	502 (395)

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

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

Significant improvements in percent predicted pre-bronchodilator FEV_1 were observed at Week 12. Significant improvements in percent predicted FEV_1 were observed as early as Week 2 and were maintained through Week 52 in VOYAGE (Figure 10).

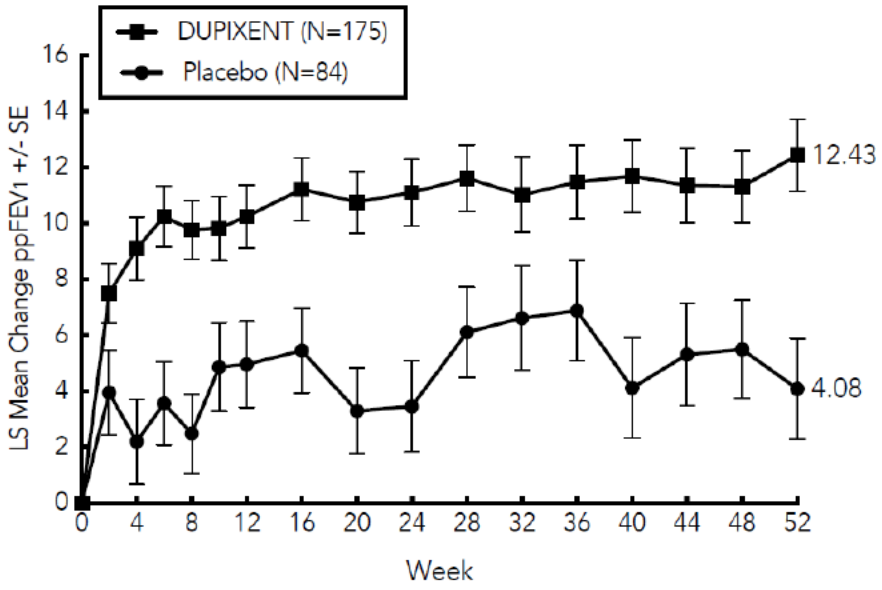
The efficacy results for VOYAGE are presented in Table 15.

Table 15: Efficacy Results of DUPIXENT in VOYAGE

Treatment	EOS ≥300 cells/mcL[a]		
Annualized Severe Exacerbations Rate over 52 Weeks			
	N	**Rate (95% CI)**	**Rate Ratio (95% CI)**
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	175	0.24 (0.16, 0.35)	0.35 (0.22, 0.56)
Placebo	84	0.67 (0.47, 0.95)	
Mean Change from Baseline in Percent Predicted FEV_1 at Week 12			
	N	**LS mean Δ from Baseline**	**LS mean difference vs. Placebo (95% CI)**
DUPIXENT 100 mg Q2W (<30 kg)/ 200 mg Q2W (≥30 kg)	168	10.15	5.32 (1.76, 8.88)
Placebo	80	4.83	

[a] This reflects the prespecified primary analysis population for VOYAGE in the United States.

Figure 10: Mean Change from Baseline in Percent Predicted Pre-bronchodilator FEV_1 (L) Over Time in Pediatric Subjects 6 to 11 Years of Age in VOYAGE (Baseline Blood Eosinophils ≥300 cells/mcL)



Improvements were also observed for ACQ-7-IA and PAQLQ(S)-IA at Week 24 and were sustained at Week 52. Greater responder rates were observed for ACQ-7-IA and PAQLQ(S)-IA compared to placebo at Week 24. The responder rate was defined as an improvement in score of 0.5 or more (scale range 0-6 for ACQ-7-IA and 1-7 for PAQLQ(S)-IA). In the subgroup of subjects with baseline blood eosinophil count ≥300 cells/mcL, DUPIXENT led to a higher proportion of subjects with a response in ACQ-7-IA (80.6% versus 64.3% for placebo) with an

OR of 2.79 (95% CI: 1.43, 5.44), and in PAQLQ(S)-IA (72.8% versus 63.0% for placebo) with an OR of 1.84 (95% CI: 0.92, 3.65) at Week 24.

14.3 Chronic Rhinosinusitis with Nasal Polyposis

The chronic rhinosinusitis with nasal polyposis (CRSwNP) development program included two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454)) in 724 adult subjects 18 years of age and older on background intranasal corticosteroids (INCS). These studies included subjects with CRSwNP despite prior sino-nasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Subjects with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In SINUS-24, a total of 276 subjects were randomized to receive either 300 mg DUPIXENT (N=143) or placebo (N=133) every other week for 24 weeks. In SINUS-52, 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 subject every morning on a 0-3 scale (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). SNOT-22 includes 22 items assessing symptoms and symptom impact associated with CRSwNP with each item scored from 0 (no problem) to 5 (problem as bad as it can be) with a global score ranging from 0 to 110. SNOT-22

had a 2 week recall period. In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sino-nasal surgery (up to Week 52) were evaluated.

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

Table 16: Demographics and Baseline Characteristics of CRSwNP Trials

Parameter	SINUS-24 (N=276)	SINUS-52 (N=448)
Mean age (years) (SD)	50 (13)	52 (12)
% Male	57	62
Mean CRSwNP duration (years) (SD)	11 (9)	11 (10)
Subjects with ≥1 prior surgery (%)	72	58
Subjects 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 (SINUS-24 and SINUS-52)

The results for primary endpoints in CRSwNP studies are presented in Table 17.

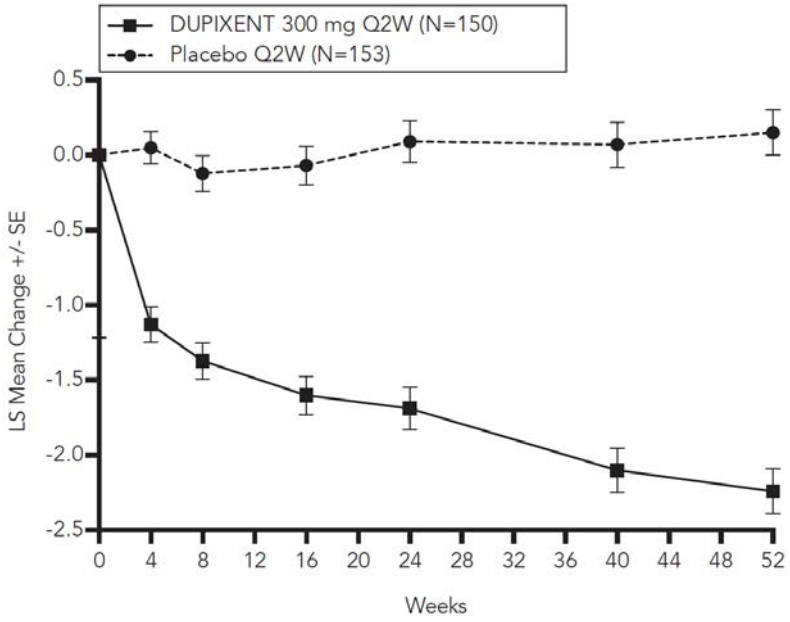
Table 17: Results of the Primary Endpoints in CRSwNP Trials

	SINUS-24					SINUS-52				
	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

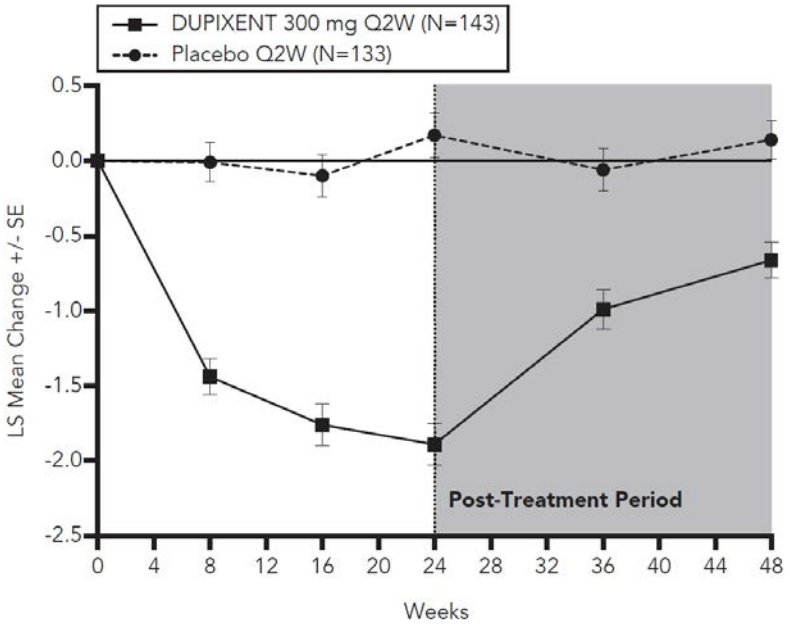
Statistically significant efficacy was observed in SINUS-52 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52 (see Figure 11).

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



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

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



At Week 52, the LS mean difference for nasal congestion in the 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 SINUS-24 and -0.37 (95% CI: -0.46, -0.27) in SINUS-52.

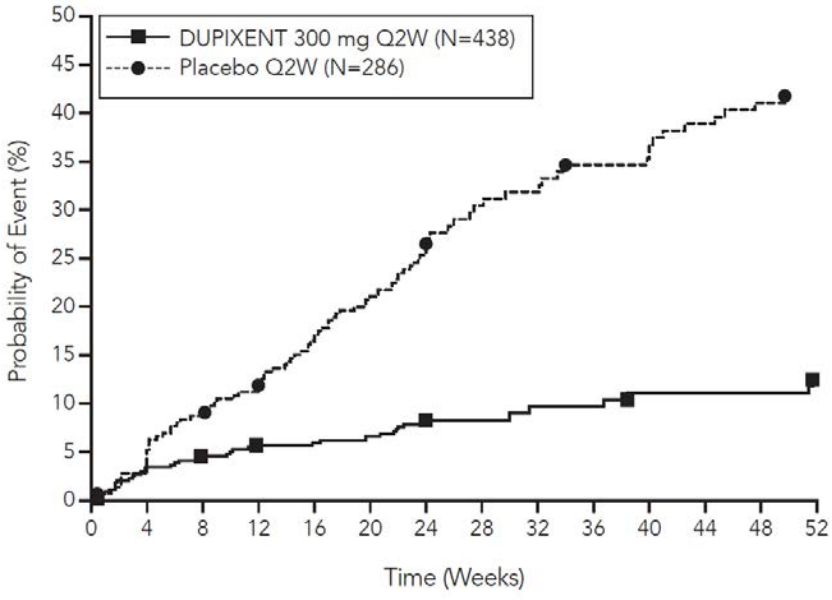
A significant decrease in the LMK sinus CT scan score was observed. The LS mean difference for LMK sinus CT scan score at Week 24 in the DUPIXENT group versus placebo was -7.44 (95% CI: -8.35, -6.53) in SINUS-24 and -5.13 (95% CI: -5.80, -4.46) in SINUS-52. At Week 52, in SINUS-52 the LS mean difference for LMK sinus CT scan score in the 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 SINUS-24 and -0.98 (95% CI: -1.15, -0.81) in SINUS-52. At Week 52, the LS mean difference for loss of smell in the 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 SINUS-24 and -17.36 (95% CI: -20.87, -13.85) in SINUS-52. At Week 52, the LS mean difference in the DUPIXENT group versus placebo was -20.96 (95% CI -25.03, -16.89).

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

Figure 13: Kaplan Meier Curve for Time to First Systemic Corticosteroid Use and/or Sino-Nasal Surgery During Treatment Period in Subjects 18 Years of Age and Older with CRSwNP (SINUS-24 and SINUS-52 Pooled - ITT Population)



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 subjects with prior surgery and without prior surgery.

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

14.4 Eosinophilic Esophagitis

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

Demographics and baseline characteristics were similar in Parts A and B. A total of 81 subjects (61 adults and 20 pediatric subjects) were enrolled in Part A and 159 subjects (107 adults and 52 pediatric subjects) were enrolled in Part B. The mean age in years was 32 years (range 13 to 62 years) in Part A and 28 years (range 12 to 66 years) in Part B. The majority of subjects were

male (60% in Part A and 68% in Part B) and White (96% in Part A and 90% in Part B). The mean baseline DSQ score (SD) was 33.6 (12.4) in Part A and 37.2 (10.7) in Part B.

The coprimary efficacy endpoints in Parts A and B were the (1) proportion of subjects achieving histological remission defined as peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24; and (2) the absolute change in the subject-reported DSQ score from baseline to Week 24.

Efficacy results for Parts A and B are presented in Table 18.

Table 18: Efficacy Results of DUPIXENT at Week 24 in Subjects 12 Years of Age and Older with EoE (Parts A and B)

	Part A			Part B		
	DUPIXENT 300 mg QW[b] N = 42	Placebo[b] N = 39	Difference vs. Placebo (95% CI)[b]	DUPIXENT 300 mg QW[b] N = 80	Placebo[b] N = 79	Difference vs. Placebo (95% CI)[b]
Co-primary Endpoints						
Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf), n (%)	25 (59.5)	2 (5.1)	57.0 (40.9, 73.1)	47 (58.8)	5 (6.3)	53.5 (41.2, 65.8)
Absolute change from baseline in DSQ score (0-84[a]), LS mean (SE)	-21.9 (2.5)	-9.6 (2.8)	-12.3 (-19.1, -5.5)	-23.8 (1.9)	-13.9 (1.9)	-9.9 (-14.8, -5.0)

[a] Total biweekly DSQ scores range from 0 to 84; higher scores indicate greater frequency and severity of dysphagia
[b] For histological remission, the difference in percentages is estimated using the Cochran Mantel Haenszel method, adjusting for randomization stratification factors. For absolute change in DSQ score, the LS mean changes, standard errors, and differences are estimated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as covariates.

In Parts A and B, a greater proportion of subjects randomized to DUPIXENT achieved histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) compared to placebo. Treatment with DUPIXENT also resulted in a significant improvement in LS mean change in DSQ score compared to placebo at Week 24. The results of the anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B is representative of a clinically meaningful within-subject improvement.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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

The pre-filled syringe with needle shield is designed to deliver:

- 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5914-00)
- 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00)
- 100 mg of DUPIXENT in 0.67 mL solution (NDC 0024-5911-00)

The pre-filled pen is designed to deliver:

- 300 mg of DUPIXENT in 2 mL solution (NDC 0024-5915-00)
- 200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5919-00)

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

Pack Size	300 mg/2 mL Pre-filled Syringe with Needle Shield	200 mg/1.14 mL Pre-filled Syringe with Needle Shield	100 mg/0.67 mL Pre-filled Syringe with Needle Shield
Pack of 2 syringes	NDC 0024-5914-01	NDC 0024-5918-01	NDC 0024-5911-02

Pack Size	300 mg/2 mL Pre-filled Pen	200 mg/1.14 mL Pre-filled Pen
Pack of 2 pens	NDC 0024-5915-02	NDC 0024-5919-02

Storage and Handling

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

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

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

Do not expose DUPIXENT to heat or direct sunlight.

Do NOT freeze. Do NOT shake.

17 PATIENT COUNSELING INFORMATION

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

Pregnancy Registry

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

Administration Instructions

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

Patients with Co-morbid Asthma

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

Arthralgia

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

Parasitic (Helminth) Infections

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

Vaccinations

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

Manufactured by:

Regeneron Pharmaceuticals, Inc.

Tarrytown, NY 10591

U.S. License No. 1760

Marketed by:

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

Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)

DUPIXENT® is a registered trademark of Sanofi Biotechnology

REGENERON SANOFI GENZYME

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

What is DUPIXENT?

DUPIXENT is a prescription medicine used:

- to treat adults and children 6 years of age and older with moderate-to-severe atopic dermatitis (eczema) that is not well controlled with prescription therapies used on the skin (topical), or who cannot use topical therapies. DUPIXENT can be used with or without topical corticosteroids.
- with other asthma medicines for the maintenance treatment of moderate-to-severe asthma in adults and children 6 years of age and older whose asthma is not controlled with their current asthma medicines. DUPIXENT helps prevent severe asthma attacks (exacerbations) and can improve your breathing. DUPIXENT may also help reduce the amount of oral corticosteroids you need while preventing severe asthma attacks and improving your breathing.
  DUPIXENT is not used to treat sudden breathing problems.
- with other medicines for the maintenance treatment of chronic rhinosinusitis with nasal polyposis (CRSwNP) in adults whose disease is not controlled.
- to treat adults and children 12 years of age and older, who weigh at least 88 pounds (40 kg), with eosinophilic esophagitis (EoE).

- DUPIXENT works by blocking two proteins that contribute to a type of inflammation that plays a major role in atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis.
- It is not known if DUPIXENT is safe and effective in children with atopic dermatitis or asthma under 6 years of age.
- It is not known if DUPIXENT is safe and effective in children with chronic rhinosinusitis with nasal polyposis under 18 years of age.
- It is not known if DUPIXENT is safe and effective in children with eosinophilic esophagitis under 12 years of age and who weigh at least 88 pounds (40 kg).

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

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

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

  Pregnancy Exposure Registry. There is a pregnancy exposure registry for women who use DUPIXENT during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Your healthcare provider can enroll you in this registry. You may also enroll yourself or get more information about the registry by calling 1-877-311-8972 or going to https://mothertobaby.org/ongoing-study/dupixent/.
- are breastfeeding or plan to breastfeed. It is not known whether DUPIXENT passes into your breast milk.

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

Especially tell your healthcare provider if you:

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

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

How should I use DUPIXENT?

- **See the detailed “Instructions for Use” that comes with DUPIXENT for information on how to prepare and inject DUPIXENT and how to properly store and throw away (dispose of) used DUPIXENT pre-filled syringes and pre-filled pens.**
- Use DUPIXENT exactly as prescribed by your healthcare provider.
- Your healthcare provider will tell you how much DUPIXENT to inject and how often to inject it.
- DUPIXENT comes as a single-dose pre-filled syringe with needle shield or as a pre-filled pen.
  - The DUPIXENT pre-filled pen is only for use in adults and children 12 years of age and older.
  - The DUPIXENT pre-filled syringe is for use in adults and children 6 years of age and older.
- DUPIXENT is given as an injection under the skin (subcutaneous injection).
- If your healthcare provider decides that you or a caregiver can give the injections of DUPIXENT, you or your caregiver should receive training on the right way to prepare and inject DUPIXENT. **Do not** try to inject DUPIXENT until you have been shown the right way by your healthcare provider. In children 12 years of age and older, it is recommended that DUPIXENT be given by or under the supervision of an adult. In children younger than 12 years of age, DUPIXENT should be given by a caregiver.
- **If your dose schedule is every week and you miss a dose of DUPIXENT:** Give the DUPIXENT injection as soon as possible and start a new every week dose schedule from the time you remember to take your DUPIXENT injection.

- **If your dose schedule is every other week and you miss a dose of DUPIXENT:** Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, wait until the next scheduled dose to give your DUPIXENT injection.
- **If your dose schedule is every 4 weeks and you miss a dose of DUPIXENT:** Give the DUPIXENT injection within 7 days from the missed dose, then continue with your original schedule. If the missed dose is not given within 7 days, start a new every 4 week dose schedule from the time you remember to take your DUPIXENT injection.
- If you inject too much DUPIXENT (overdose), get medical help or contact a Poison Center expert right away at 1-800-222-1222.
- Your healthcare provider may prescribe other medicines to use with DUPIXENT. Use the other prescribed medicines exactly as your healthcare provider tells you to.

What are the possible side effects of DUPIXENT?

DUPIXENT can cause serious side effects, including:

- **Allergic reactions. DUPIXENT can cause allergic reactions that can sometimes be severe.** Stop using DUPIXENT and tell your healthcare provider or get emergency help right away if you get any of the following signs or symptoms:
  - o breathing problems or wheezing
  - o fast pulse
  - o fever
  - o general ill feeling
  - o swollen lymph nodes
  - o swelling of the face, lips, mouth, tongue, or throat
  - o hives
  - o itching
  - o nausea or vomiting
  - o fainting, dizziness, feeling lightheaded
  - o joint pain
  - o skin rash
  - o cramps in your stomach-area
- **Eye problems.** Tell your healthcare provider if you have any new or worsening eye problems, including eye pain or changes in vision, such as blurred vision. Your healthcare provider may send you to an ophthalmologist for an eye exam if needed.
- **Inflammation of your blood vessels.** Rarely, this can happen in people with asthma who receive DUPIXENT. This may happen in people who also take a steroid medicine by mouth that is being stopped or the dose is being lowered. It is not known whether this is caused by DUPIXENT. Tell your healthcare provider right away if you have:
  - o rash
  - o worsening shortness of breath
  - o persistent fever
  - o chest pain
  - o a feeling of pins and needles or numbness of your arms or legs
- **Joint aches and pain.** Joint aches and pain can happen in people who use DUPIXENT. Some people have had trouble walking or moving due to their joint symptoms, and in some cases needed to be hospitalized. Tell your healthcare provider about any new or worsening joint symptoms. Your healthcare provider may stop DUPIXENT if you develop joint symptoms.

The most common side effects of DUPIXENT include:

- injection site reactions
- upper respiratory tract infections
- eye and eyelid inflammation, including redness, swelling, and itching, sometimes with blurred vision
- pain in the throat (oropharyngeal pain)
- cold sores in your mouth or on your lips
- high count of a certain white blood cell (eosinophilia)
- trouble sleeping (insomnia)
- toothache
- gastritis
- joint pain (arthralgia)
- parasitic (helminth) infections

The following additional side effects have been reported with DUPIXENT:

- facial rash or redness

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

General information about the safe and effective use of DUPIXENT.

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

What are the ingredients in DUPIXENT?

Active ingredient: dupilumab

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

REGENERON SANOFI GENZYME

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

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

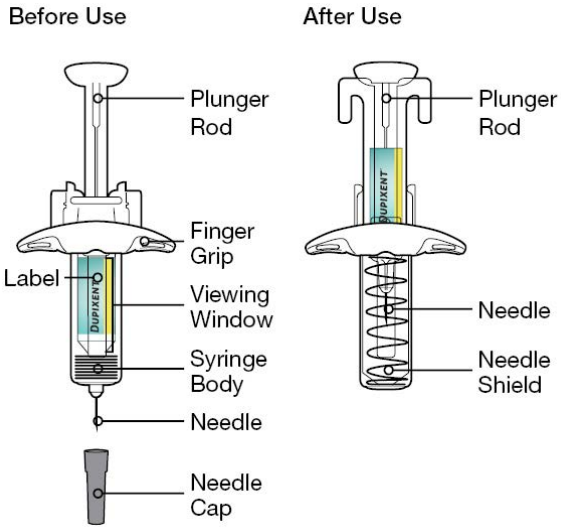
This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: May 2022

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. In children younger than 12 years of age, DUPIXENT should be given by a caregiver. 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.	• 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

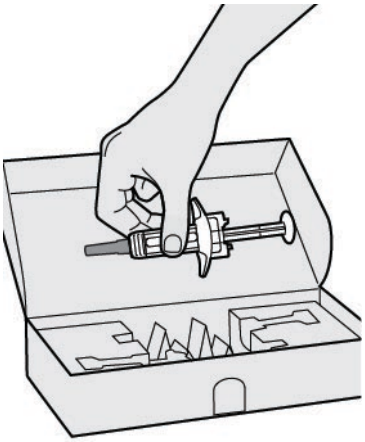
• **Do not** touch the Plunger Rod until you are ready to inject. • **Do not** inject through clothes. • **Do not** get rid of any air bubble in the DUPIXENT Syringe.	Syringe right away after use. See “Step 13: Dispose” below. • **Do not re-use a DUPIXENT Single-Dose Pre-filled Syringe**.
How should I store DUPIXENT? • **Keep DUPIXENT Syringes and all medicines out of the reach of children.** • Store DUPIXENT Syringes in the refrigerator between 36°F to 46°F (2°C to 8°C). • Store DUPIXENT Syringes in the original carton to protect them from light. • DUPIXENT Syringes can be stored at room temperature up to 77°F (25°C) up to 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days. • **Do not** shake the DUPIXENT Syringe. • **Do not** heat the DUPIXENT Syringe. • **Do not** freeze the DUPIXENT Syringe. • **Do not** put the DUPIXENT Syringe into direct sunlight.	

Step 1: Remove

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

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

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

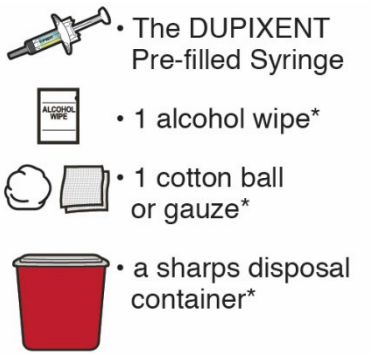


Step 2: Prepare

Ensure you have the following:

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

**Items not included in the carton*

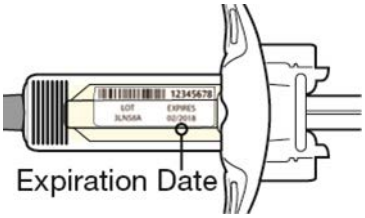


Step 3: Check

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

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

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



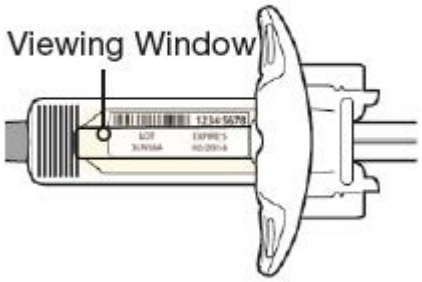
Step 4: Inspect

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

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

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

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



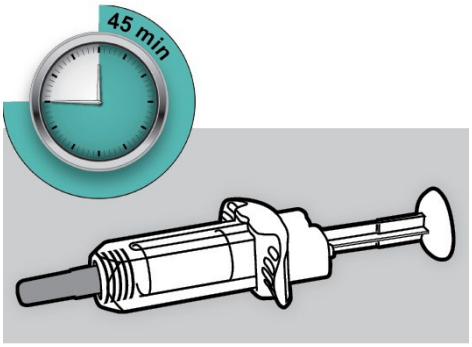
Step 5: Wait 45 minutes

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

Do not heat the DUPIXENT Syringe.

Do not put the DUPIXENT Syringe into direct sunlight.

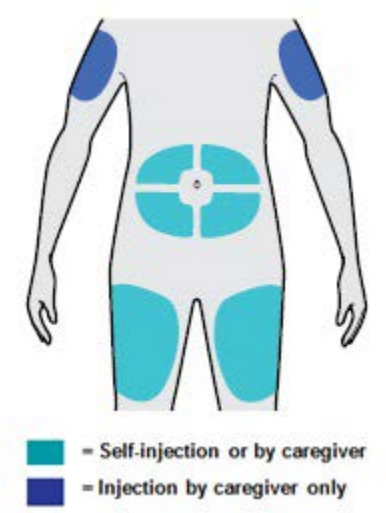
Do not keep DUPIXENT Syringes at room temperature for more than 14 days. Throw away (dispose of) any DUPIXENT Syringes that have been left at room temperature for longer than 14 days.



Step 6: Choose your injection site

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

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



Step 7: Clean

Wash your hands.

Clean the injection site with an alcohol wipe.

Let your skin dry before injecting.

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

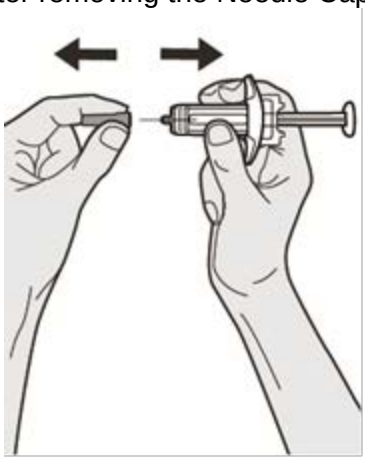
Step 8: Remove Needle Cap

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

Do not put the Needle Cap back on.

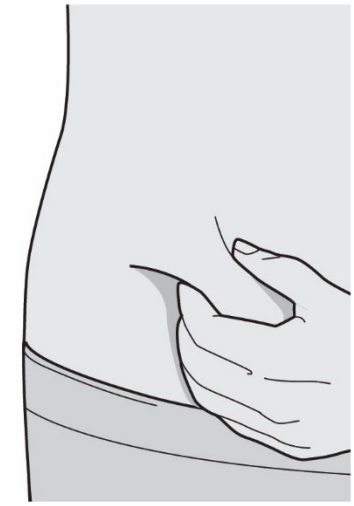
Do not touch the Needle.

Inject your medicine right away after removing the Needle Cap.



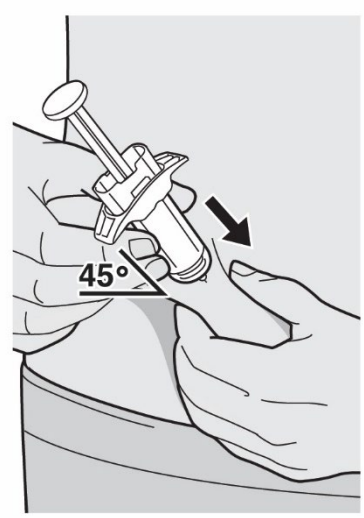
Step 9: Pinch

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



Step 10: Insert

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



Step 11: Push

Relax the pinch.

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

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

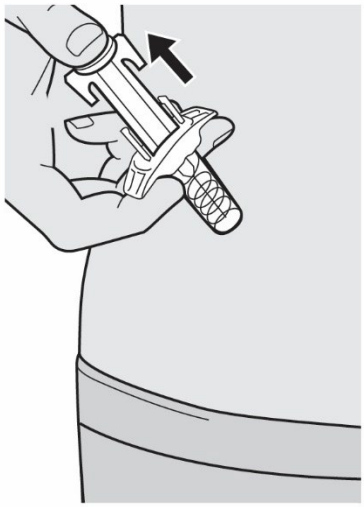
Step 12: Release and Remove

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

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

Do not put the Needle Cap back on.

Do not rub your skin after the injection.



Step 13: Dispose

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

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

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

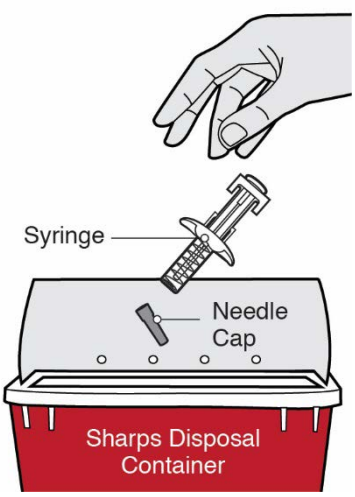
- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container

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

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

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

Do not put the Needle Cap back on.



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

REGENERON SANOFI GENZYME

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

Marketed by: sanofi-aventis U.S. LLC (Bridgewater, NJ 08807) and Regeneron Pharmaceuticals, Inc. (Tarrytown, NY 10591)
DUPIXENT® is a registered trademark of Sanofi Biotechnology

Revised: May 2020

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

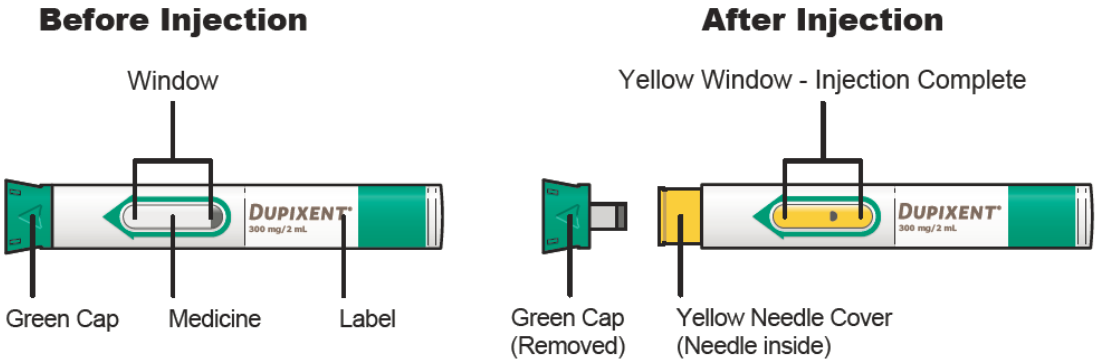
This "Instructions for Use" contains information on how to inject DUPIXENT.

Read this Instructions for Use before using the DUPIXENT Pre-filled Pen. **Do not inject yourself or someone else until you have been shown how to inject DUPIXENT.** Your healthcare provider can show you or your caregiver how to prepare and inject a dose of DUPIXENT before you try to do it yourself for the first time. Keep this Instructions for Use. Call your healthcare provider if you have any questions.

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

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

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



Important Information

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

Storing DUPIXENT

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

A. Get ready to inject

A1. Gather supplies

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

• the DUPIXENT Pre-filled Pen

• 1 alcohol wipe*

• 1 cotton ball or gauze*

• a sharps disposal container* (See Step D)

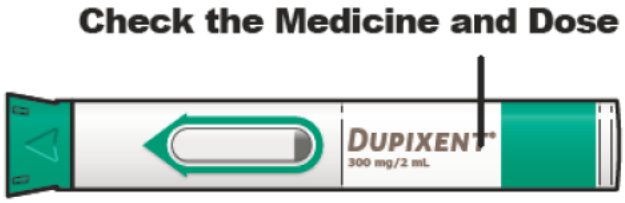
** Items not included in the carton.*

A2. Check the Pen

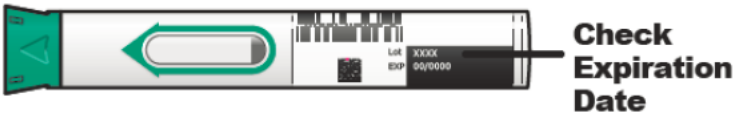
- **Do not** use the DUPIXENT Pre-filled Pen if it has been damaged.
- **Do not** use the DUPIXENT Pre-filled Pen if the Green Cap is missing or not securely attached.
- **Do not** use the DUPIXENT Pre-filled Pen if the Window is yellow before use.

A3. Look at the Label

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



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



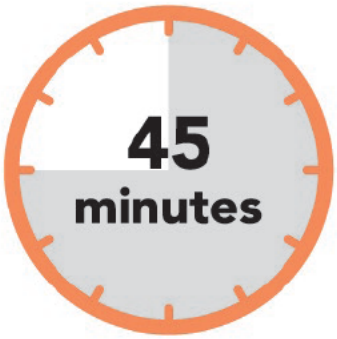
A4. Check the Medicine

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

A5. Wait 45 minutes

- Lay the DUPIXENT Pre-filled Pen on a flat surface and let it warm up at room temperature less than 77°F (25°C) for at least 45 minutes.

- ⚠ **Do not heat the DUPIXENT Pre-filled Pen in a microwave, hot water or direct sunlight.**



B. Choose and prepare your injection site

B1. Wash your hands well with soap and water

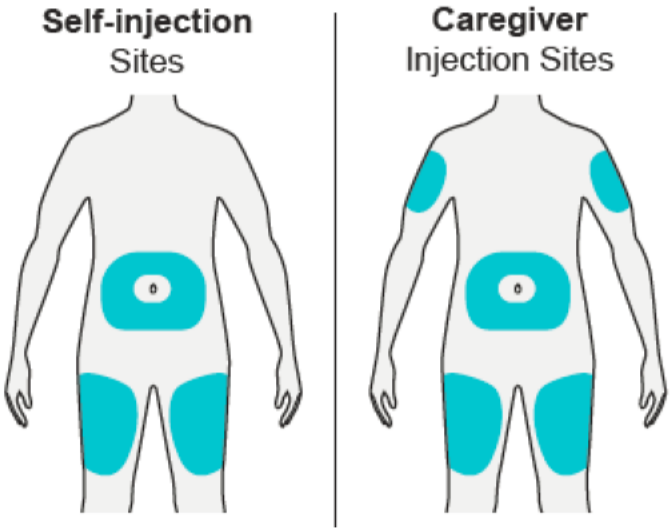
B2. Choose an injection site

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

- Choose a different site for each injection.

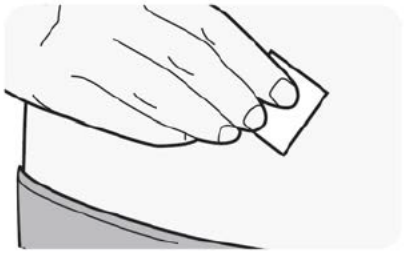
- ⚠ **Do not inject into skin that is tender, damaged, has bruises or scars, or into areas with visible veins.**

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



B3. Prepare the injection site

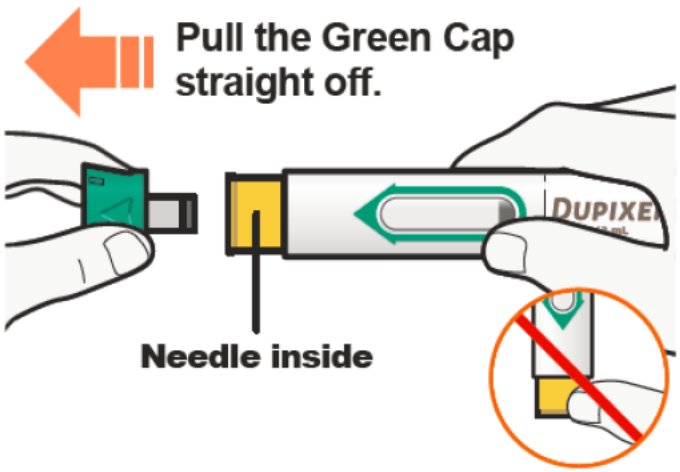
- Clean the injection site with an alcohol wipe.
- Let your skin dry before injecting.
- ⚠ **Do not touch the injection site again or blow on it before the injection.**



C. Give the injection

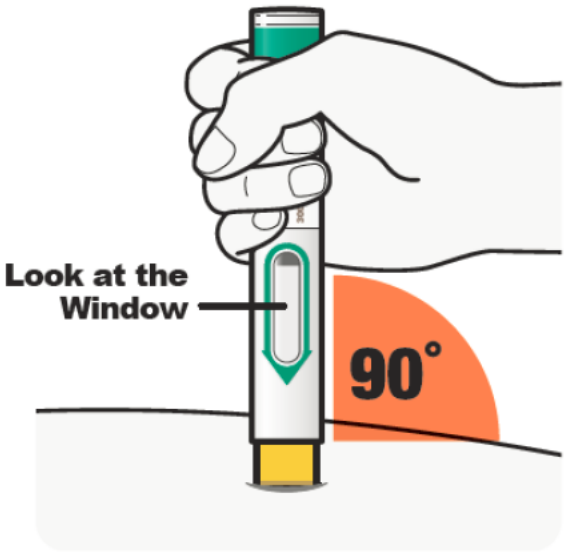
C1. Remove Green Cap

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



C2. Place

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



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

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

C4. Remove

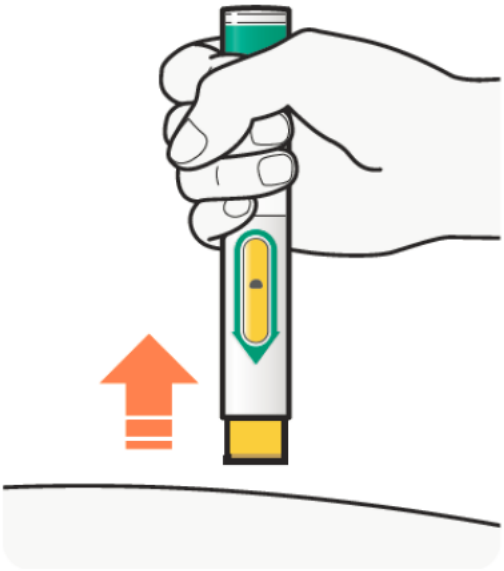
- After you have completed your injection pull straight up to remove DUPIXENT Pre-filled Pen from the skin. The Yellow Needle Cover will cover the needle.

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

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

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

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



D. Dispose of used DUPIXENT Pre-filled Pen

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

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

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

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

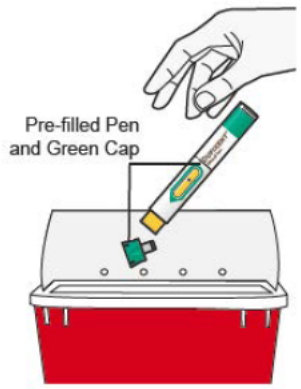
- made of a heavy-duty plastic,
- can be closed with a tightfitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

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

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

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

⚠ **Do not** recycle your used sharps disposal container.



Do not put the Green Cap back on.

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

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

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)

Issued: June 2020

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/

JESSICA J LEE
05/20/2022 01:24:50 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s040

MULTI-DISCIPLINE REVIEW

BLA Multi-Disciplinary Review and Evaluation

Application Type	Supplemental BLA
Application Number(s)	761055/ S-040
Priority or Standard	Priority
Submit Date(s)	Rolling Review August 13, 2021 - February 3, 2022
Received Date(s)	February 3, 2022
PDUFA Goal Date	August 3, 2022
Division/Office	Division of Gastroenterology (DG) / Office of Immunology and Inflammation (OII)
Review Completion Date	May 20, 2022
Established/Proper Name	Dupilumab
(Proposed) Trade Name	Dupixent
Pharmacologic Class	Interleukin-4 receptor alpha antagonist
Applicant	Regeneron
Dosage form	Injection: 300 mg/2 mL solution in a single-dose pre-filled pen Injection: 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield
Applicant proposed Dosing Regimen	300 mg every week subcutaneous
Applicant Proposed Indication(s)/Population(s)	Treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Eosinophilic esophagitis (235599003)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	Eosinophilic esophagitis (235599003)
Recommended Dosing Regimen	300 mg every week subcutaneous

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Reviewers of Multi-Disciplinary Review and Evaluation

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Nonclinical Reviewer (NAI anticipated)	
Nonclinical Team Leader (NAI anticipated)	
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Office of Clinical Pharmacology Team Leader(s)	Insook Kim
Clinical Reviewer	Anna Reed, Matthew Kowalik, Erica Lyons
Clinical Team Leader	Matthew Kowalik, Erica Lyons
Statistical Reviewer	Josh Sampson
Statistical Team Leader	Paul Imbriano
Cross-Disciplinary Team Leader	Matthew Kowalik
Associate Director for Therapeutic Review	Erica Lyons
Division Director (designated signatory authority)	Jessica Lee

Additional Reviewers of Application

DCOA	Christopher St. Clair (primary), David Reasner (secondary, Division Director)
PFSS	Xin Yuan (primary), Lili Garrard (secondary)
OBP	Gunther Boekhoudt
DPMH	Ethan Hausman (primary), Shetarra Walker (secondary)
DMPP	Kelly Jackson (primary), Marcia Britt Williams (secondary), Nyedra Booker (secondary)
Analytics and Informatics Staff **Associate Director for Analytics and Informatics**	Ping Li Matilde Kam
OSI	NAI – no inspection was necessary
OSE/DMEPA	Sherly Abraham (primary), Idalia Rychlik (secondary)
OPDP	Meeta Patel

DCOA=Division of Clinical Outcome Assessments
DMEPA=Division of Medication Error Prevention and Analysis
DMPP= Division of Medical Policy Programs
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
OSI=Office of Scientific Investigations
PFSS=Patient Focused Statistical Support

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology

OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Dupilumab is a human monoclonal IgG4 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 (trade name Dupixent) was first approved by the FDA on March 28, 2017 for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD). Currently, Dupixent is approved for the following indications:

- Treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable
- Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma
- Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)

The labeled dosage by indication is listed in Table 1.

Table 1: Dupixent Dosage by Indication

Indication	Dose (Subcutaneous)
Atopic dermatitis in adults	600 mg followed by 300 mg every 2 weeks
Atopic dermatitis in pediatric patients (6 to 17 years of age)	600 mg followed by 300 mg every 4 weeks (15 to < 30 kg) 400 mg followed by 200 mg every 2 weeks (30 to < 60 kg) 600 mg followed by 300 mg every 2 weeks (≥60 kg)
Asthma in adults and adolescents (12 years and older)	400 mg followed by 200 mg every 2 weeks or 600 mg followed by 300 mg every 2 weeks
Asthma in adults and adolescents (12 years and older) with oral corticosteroid-dependent asthma or co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid CRSwNP	600 mg followed by 300 mg every 2 weeks
Asthma in pediatric patients (6 to 11 years of age)	100 mg every 2 weeks or 300 mg every 4 weeks (15 to < 30kg) 200 mg every 2 weeks (≥30 kg)
Chronic rhinosinusitis with nasal polyps in adults	300 mg every other week

Source: Reviewer generated table, dupilumab USPI updated 12/2021.

There are two approved presentations for Dupixent, a pre-filled syringe with needle shield and a pre-filled pen. The application proposes a new 300 mg weekly (QW) dosage, which is to be administered using the approved presentations.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The multidisciplinary review team recommends approval of this sBLA to expand the indications of dupilumab to include "the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis."

To support this submission, the Applicant conducted a three-part clinical trial, Study R668-EE-1774 (Study 1774). Parts A and B of Study 1774 were conducted as independent parts with distinct populations. Each part had a 24-week treatment period and was randomized, double-blinded, and placebo-controlled. With the exception of the additional 300 mg Q2W dosing regimen (Part A evaluated one active treatment group of 300 mg QW vs placebo), Part B was identical in design, procedures, and conduct to Part A. Part C is an ongoing 28-week extended active treatment period for subjects who completed either Part A or Part B.

Both Parts A and B evaluated coprimary endpoints of:

1. Histologic response (defined as the proportion of subjects achieving a peak esophageal intraepithelial eosinophil count of ≤6 eosinophils per high-power field across all available esophageal levels at Week 24) and
2. Reduction in dysphagia symptoms (defined using the absolute change[1] in the 14-day Dysphagia Symptom Questionnaire [DSQ][2] score from baseline to Week 24).

The review team recommends approval of the 300 mg QW dosage based on the demonstration of substantial evidence of effectiveness through the evaluation of the coprimary endpoints from Part A and Part B of Study 1774. The review team is not recommending approval of the alternative dosage assessed in Part B (i.e., 300 mg Q2W), because analyses of the symptomatic coprimary endpoint did not demonstrate improvement over placebo in subjects that received dupilumab at this dosage.

Subgroup analyses of efficacy assessments in the adolescent subpopulation (i.e., pediatric subjects aged 12 – 17 years, inclusive) also demonstrated improvement on both histologic and symptomatic coprimary endpoints. Although the proportion of adolescent subjects relative to the total number of subjects in Study 1774 was acceptable and consistent with the expected population distribution of adolescents vs adults with EoE in the US (i.e., n=20/81, 25% for Part A, n=79/240, 33% for Part B) (Dellon et al. 2014), the small sample size limited the ability to draw definitive conclusions from independent analyses of the subgroup. Given the similarity of the disease presentation, progression, and expected response to treatment between adults and adolescents, the determination of efficacy in the adolescent subgroup is supported by the results of efficacy analyses from the overall study population. Review of subgroup analyses of

[1] The use of "absolute change" in this review refers to the exact numerical difference between baseline and Week 24 DSQ scores.
[2] The DSQ is a patient-reported outcome (PRO) measure designed to capture the frequency and severity of dysphagia in patients with EoE. For additional details regarding FDA's review and assessment of the DSQ, see Section 15.6.1.

the mean absolute change in 14-day DSQ total scores over time in adolescent and adult subjects provided additional support for the FDA determination that symptomatic efficacy was demonstrated for the entire population studied in Trial 1774 (i.e., adult and pediatric patients aged 12 years and older).

Although the ability to draw definitive conclusions was limited by the open-label study design and limited number of subjects evaluated, descriptive efficacy results from analyses of subjects that received dupilumab 300 mg QW in Part A and continued on dupilumab 300 mg QW in Part C for an additional 28 weeks (total of 52 weeks of active treatment) were supportive of sustained treatment effects on histologic and symptomatic endpoints. For subjects that received placebo in Part A and dupilumab 300 mg QW in Part C (total active treatment period of 28 weeks), the proportion of subjects that achieved histologic response and the magnitude of absolute change from the Part A baseline DSQ score at the end of 28 weeks of treatment were similar to the values observed on the analyses of coprimary endpoints for subjects that received dupilumab 300 mg QW for 24 weeks in Part A and Part B.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Eosinophilic esophagitis (EoE) is a serious, chronic immune/antigen-mediated disease characterized clinically by signs and symptoms related to esophageal dysfunction and histologically by eosinophil-predominant inflammation (Liacouras et al. 2011). Left untreated, EoE leads to esophageal stricture, dysphagia, and risk of food impaction (Warners et al. 2018). In patients with EoE, clinical features and histologic activity can vary independently. Patients can have a reduction or resolution in signs and symptoms despite ongoing histologic activity. Conversely, patients can have histologic remission (defined as a change in peak eosinophils per high-power field [HPF] from a count greater than or equal to 15 to less than or equal to 6) with persistent clinical symptoms (Dellon et al. 2013). As such, candidate therapeutics should demonstrate long-term benefit on both histologic response and symptoms and/or signs to support a determination of effectiveness for this chronic condition.

There are currently no FDA approved therapies for the treatment of patients with EoE. Clinical practice guidelines include recommendations for off-label therapies such as topical corticosteroids and proton pump inhibitors; however, the safety and efficacy of these products for the treatment of EoE have not been established (Dellon et al. 2020). Systemic corticosteroids have been used for severe or refractory cases, but toxicity prohibits their long-term use. Food elimination diets, including restriction to elemental formulas, have been shown in the literature to decrease both clinical symptoms and eosinophilic inflammation (Groetch et al. 2017). The success of dietary restriction in patients with EoE, however, is limited by challenges with long-term adherence and compliance. There is a need for the development of novel therapies for the treatment of EoE.

Dupilumab was originally approved in March 2017 for treatment of adult patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. The AD indication has since been expanded to include patients down to 6 years of age. Dupilumab is also approved for add-on maintenance treatment in adults with inadequately controlled CRSwNP and as add-on maintenance treatment in patients with moderate-to-severe asthma aged 6 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

To support the demonstration of safety and effectiveness of dupilumab for the treatment of adult and pediatric patients aged 12 years and older with EoE, the Applicant conducted a three-part clinical trial, Study R668-EE-1774 (Study 1774). Parts A and B of Study 1774 were conducted as independent parts with distinct populations. To be eligible for enrollment in Part C, subjects must have completed either Part A or Part B of Study 1774. Part A was a randomized, double-blind, placebo-controlled study assessing the safety and efficacy of dupilumab 300 mg QW compared to placebo in adolescents and adults with EoE and dysphagia over a 24-week treatment period. With the exception of the additional 300 mg Q2W dosing regimen, Part B was identical in design, procedures, and conduct to Part A.

Both Parts A and B evaluated coprimary endpoints of (1) histologic response (defined as a peak eosinophil count of ≤6 per high-power field across all available esophageal levels) at Week 24 and (2) reduction in dysphagia symptoms (defined using the absolute change from baseline in the Dysphagia Symptom Questionnaire [DSQ] score from baseline to Week 24). Results of the coprimary endpoint efficacy analyses from Parts A and B are listed below.

- For Part A, the proportion of subjects achieving histologic response at Week 24 was 59.5% for those treated with dupilumab 300 mg QW and 5.1% for those who received placebo; treatment difference of 57.0 (95% CI 40.9, 73.1) p<0.0001.
- For Part B, the proportion of subjects achieving histologic response at Week 24 was 58.8% for those treated with dupilumab 300 mg QW, 60.5% for those treated with dupilumab 300 mg Q2W, and 6.3% for those who received placebo; treatment difference of 53.5 (95% CI 41.2, 65.8) p<0.0001 for the dupilumab 300 mg QW group vs placebo, and treatment difference of 56.0 (95% CI 43.4, 68.5) p<0.0001 for the dupilumab 300 mg Q2W group vs placebo.
- For Part A, the absolute change from baseline in 14-day DSQ total score (DSQ total score)[3] at Week 24 by LS mean change was -21.9 for those treated with dupilumab 300 mg QW and -9.6 for those who received placebo; treatment difference of -12.3 (95% CI -19.1, -5.5) p=0.0004.
- For Part B, the absolute change from baseline in DSQ total score at Week 24 by LS mean change was -23.8 for those treated with dupilumab 300 mg QW, -14.4 for those treated with dupilumab 300 mg Q2W, and -13.9 for those who received placebo; treatment difference of -9.9 (95% CI -14.8, -5.0) p<0.0001 for the dupilumab 300 mg QW group vs placebo, and treatment difference of -0.5 (95% CI -5.4, 4.4) p=0.84 for the dupilumab 300 mg Q2W group vs placebo.

For subjects treated with dupilumab 300 mg QW, improvement over placebo was demonstrated on evaluation of both histologic and symptomatic coprimary endpoints in both Parts A and B. Although analyses for subjects treated with dupilumab 300 mg Q2W in Part B demonstrated improvement on the histologic coprimary endpoint compared to placebo, analyses of the symptomatic coprimary endpoint for this group did not demonstrate improvement over placebo. For this reason, the dosage of 300 mg QW alone is recommended for approval.

To support the clinical relevance of the symptomatic coprimary endpoint results, anchor-based analyses were conducted separately in Parts A and B by the Applicant to inform the determination of a range of change thresholds for the absolute change in the DSQ total score that was representative of clinically meaningful improvements to subjects. FDA did not agree with the Applicant's proposed meaningful change threshold of a 13-point improvement from baseline in the DSQ total score. The Applicant appeared to derive this threshold using Part B data

[3] The 14-day DSQ total score was calculated as the sum of daily scores over 14 days divided by the number of days reported with non-missing data, with a possible range from 0 to 84 (See Section 8.1.2 Statistical Analysis Plan). Unless otherwise specified, DSQ total score refers to the 14-day DSQ total score.

based on the lower bound of the 95% confidence interval (-12.03, -4.84) of change in DSQ total score for subjects who experienced "No Change" on the Patient Global Impression of Severity (PGIS) anchor score. Note that the Applicant's proposed threshold did not appear to take into consideration a higher threshold range derived from Part A data (i.e., a range between 14-point and 23-point improvement from baseline, based on the Applicant's analyses). Based on FDA's anchor-based analyses, that leveraged data from both Parts A and B, the meaningful within-subject change range should be between 20-point and 24-point improvement from baseline in the DSQ total score. FDA derived this range of change scores based on median values of change in DSQ total score for subjects who experienced a 1-category improvement on the PGIS and "Moderately Better" on the Patient Global Impression of Change (PGIC) anchor assessments, while taking into account the baseline PGIS anchor score. Of note, the methods used by FDA to determine the meaningful within-subject change range in the DSQ total score from baseline were consistent with prior FDA recommendations provided at the time of the Breakthrough Therapy Designation (BTD) request. Despite the higher meaningful change range identified by FDA, a greater proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to subjects that received placebo in the FDA-determined range (i.e., 38.1% to 47.6% of subjects treated with dupilumab 300 mg QW vs 15.4% to 25.6% of subjects who received placebo in Part A, and 53.8% to 58.8% of subjects treated with dupilumab 300 mg QW vs 21.8% to 32.1% of subjects who received placebo in Part B).

Given that the interpretability of the anchor-based analyses may be limited by the difference in assessment periods between the 14-day DSQ total score and the PGIS anchor with 7-day recall period, supplementary anchor-based analyses were conducted separately in Parts A and B by the Applicant (upon FDA request) and by FDA to determine a range of meaningful change thresholds for the absolute change from baseline in the 7-day DSQ total score. Consistent with the interpretation of the absolute change from baseline in the 14-day DSQ total score, FDA's analyses indicated that a greater proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to subjects that received placebo in the FDA-determined meaningful change range (i.e., between 10-point and 13-point improvement from baseline) in the 7-day DSQ total score (i.e., 33.3% to 47.6% of subjects treated with dupilumab 300 mg QW vs 20.5% to 30.8% of subjects who received placebo in Part A, and 53.8% to 70.0% of subjects treated with dupilumab 300 mg QW vs 25.6% to 33.3% of subjects who received placebo in Part B). Note that the Applicant did not propose a meaningful within-subject change range from baseline in the 7-day DSQ total score for either Part A or Part B.

Descriptive analyses of open-label data from Part C (i.e., the ongoing 28-week extension study) for subjects that completed Part A (Part A/C) were supportive of sustained treatment effects on histologic and symptomatic endpoints for subjects that received dupilumab 300 mg QW for a total treatment duration of 52 weeks. In addition, results of descriptive efficacy analyses for subjects that received placebo in Part A and dupilumab 300 mg QW in Part C (total treatment duration of 28 weeks) were similar to those observed after 24 weeks of treatment with dupilumab 300 mg QW in Part A and Part B. Blinded data from approximately 74 additional subjects treated with dupilumab 300 mg QW for 52 weeks is anticipated from subjects initially enrolled in Part B that have completed part C (Part B/C, projected to completion July 2022).

Although results from the analyses of the symptomatic coprimary endpoint for the adolescent subpopulation (i.e., pediatric subjects aged 12 – 17 years, inclusive) were less robust than that observed for the overall study population, the ability to precisely characterize the treatment effects within the subpopulation is limited by the small number of adolescent subjects that received either dupilumab 300 mg QW or placebo in Study 1774 (n=20 for Part A, n=52 for Part B). Given the similarity of the disease presentation, progression, and expected response to treatment between adults and adolescents, the determination of efficacy in the adolescent subgroup is supported by the results of efficacy analyses from the overall study population. Review of subgroup analyses of the mean absolute change in DSQ total scores over time in adolescent and adult subjects provided additional support for the demonstration of efficacy in adolescent subjects treated with dupilumab in Study 1774.

The safety of dupilumab for the treatment of adolescent and adult patients with EoE was established by Study 1774 and supported by the phase 2 study, R668-EE-1324 (Study 1324). The rate and type of adverse reactions reported in Studies 1774 and 1324 were similar to those observed with the currently approved indications (i.e., AD, CRSwNP, and asthma). However, upper respiratory tract infections were identified as an adverse reaction in subjects with EoE, which has not been previously described in other indications. Of note, the dose found to be efficacious for the treatment of subjects with EoE (i.e., 300 mg QW) is higher than that currently approved for any indication. The most common adverse reactions (incidence ≥2%, and greater than placebo) in Parts A and B of Study 1774 were injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. No new safety concerns were identified on review of the data from the 28-week study period of Part C for subjects who completed Part A (Part A/C).

The benefit-risk profile of dupilumab 300 mg QW in subjects with EoE appears favorable based on the robust and clinically meaningful results of the coprimary endpoint analyses from Parts A and B; the supportive efficacy data from Part A/C; the reassuring and consistent safety profile observed in subjects that completed Part A, Part B, and Part A/C of Study 1774 and subjects that completed Study 1324; review of the available supportive safety data from the use of dupilumab in the previously approved indications; and review of available supportive safety data from the investigational development of dupilumab for other indications that assessed the dosage of 300 mg QW.

However, given the limited number of subjects with EoE that received the to-be-marketed dosage (i.e., 300 mg QW) for 52 weeks at the time of sBLA submission (n=40), there remain uncertainties with the ability of the available data to detect and characterize adverse events that may occur or worsen with longer-term exposure to dupilumab 300 mg QW in subjects with EoE. There are also uncertainties regarding the potential for subjects to experience risks during chronic treatment due to loss of efficacy. The review team determined that the issuance of a post-marketing requirement (PMR) to ensure the completion and timely reporting of safety and efficacy data from all subjects enrolled in Part C is necessary to further characterize the safety and potential loss of efficacy of dupilumab with chronic use. Part C is currently ongoing with an estimated completion for subjects that completed Part B in July 2022 and is anticipated to provide blinded data from approximately 74

additional subjects with EoE treated with dupilumab 300 mg QW for 52 weeks. As EoE is a serious condition with unmet medical need with no approved therapy, and in consideration of the favorable benefit-risk profile determined during the review of this sBLA, the review team determined that although additional long-term data from Part B/C are needed, the availability of these data should not delay approval of dupilumab for the treatment of patients with EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Eosinophilic esophagitis (EoE) is a chronic immune/antigen-mediated esophageal disease clinically characterized by signs and symptoms related to esophageal dysfunction and histologically characterized by eosinophil predominant inflammation (Liacouras et al. 2011). • Left untreated, EoE leads to dysphagia, esophageal stricture, and risk of food impaction (Warners et al. 2018). In infants and children, it can lead to food refusal, vomiting, and failure to thrive. • In patients with EoE, clinical features and histologic activity can vary independently. Patients can have a reduction or resolution in signs and symptoms despite ongoing histologic activity. Conversely, patients can have histologic remission (defined as a change in peak eosinophils per high-power field (HPF) from a count greater than or equal to 15 to less than or equal to 6) with persistent clinical symptoms (Dellon et al. 2013).	• EoE is a serious condition and can profoundly impact patients' health and well-being. • As EoE is a chronic condition, data to demonstrate long-term efficacy and safety are needed to support the treatment of this chronic condition. • Because the clinical features and histologic activity of EoE can vary independently, the treatment goals of EoE include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient, and healing or control of the esophageal inflammation and its complications. • For a therapy to demonstrate benefit for the treatment of subjects with EoE, efficacy should be demonstrated on both histologic response and through clinically meaningful improvement on symptoms and/or signs.
Current Treatment Options	• The current clinical standard of care for EoE includes dietary modification, off-label use of proton pump inhibitors, and off-label use of topical corticosteroids intended for local action on the esophageal mucosa (Hirano et al. 2020). • Although available published literature suggests initial histologic response with topical corticosteroids, histologic features and clinical symptoms can vary independently in patients with EoE. Further, there are inadequate data to demonstrate that improvement in histologic response predicts improvement in meaningful clinical outcomes (e.g., stricture formation) (Hirano and Aceves 2014). Additionally, studies	• As there are no FDA-approved pharmacological treatments for EoE, and the safety and effectiveness of off-label therapies have not been established, there is a need for novel therapies to treat EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	have described loss of histologic response during long-term treatment (Dellon et al. 2021) and (Straumann et al. 2011). • Systemically acting corticosteroids, such as prednisone, are also used but are typically reserved for more severe or recalcitrant disease. Because of the potential for significant toxicity, long-term use of systemic corticosteroids is generally not recommended. • Food elimination diets, including restriction to elemental formulas, have been shown to decrease both clinical symptoms and eosinophilic inflammation (Groetch et al. 2017); however, their success is limited by challenges with long-term adherence and compliance. • There are no FDA-approved pharmacological treatments for EoE. • Endoscopic dilation may provide relief of dysphagia in patients with esophageal strictures.	
Benefit	• In an adequate and well-controlled trial, Study R668-EE-1774 (Study 1774), dupilumab 300 mg QW demonstrated a statistically significant and clinically meaningful treatment effect on both histologic features and clinical symptoms in subjects with EoE and dysphagia. • Study 1774 consisted of three Parts A-C. Parts A and B of Study 1774 were conducted as independent parts with distinct populations. Participants must have completed either Part A or Part B to be eligible for enrollment in Part C. • To support the demonstration of substantial evidence of effectiveness, both Parts A and B evaluated coprimary endpoints of: 1. histologic response (defined as a peak eosinophil count of ≤6 per high-power field across all available esophageal levels) at Week 24, and 2. reduction in dysphagia symptoms (defined using the absolute change from baseline in the Dysphagia Symptom Questionnaire [DSQ] score from baseline to Week 24). o For Part A, the proportion of subjects achieving histologic response at Week 24 was 59.5% for those treated with dupilumab 300 mg QW and 5.1% for those who received	• Substantial evidence of effectiveness was demonstrated in Parts A and B of the adequate and well-controlled Study 1774 through the evaluation of histologic and symptomatic coprimary endpoints. • FDA anchor-based analyses using both 7-day and 14-day DSQ total scores confirmed that the results of the analyses of the symptomatic coprimary endpoint from Part A and Part B are representative of clinically meaningful improvements for subjects that received dupilumab 300 mg QW compared to those that received placebo. • Subgroup analyses of efficacy assessments in the adolescent subpopulation (i.e., pediatric subjects aged 12 – 17 years, inclusive) also demonstrated improvement on both histologic and symptomatic coprimary endpoints. Although the proportion of adolescent subjects relative to the total number of subjects in Study 1774 was acceptable and consistent with the expected population distribution of adolescents vs adults with EoE (Dellon et al. 2014), the small sample size limited the ability to draw

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo; treatment difference of 57.0 (95% CI 40.9, 71.3) p<0.0001. o For Part B, the proportion of subjects achieving histologic response at Week 24 was 58.8% for those treated with dupilumab 300 mg QW, 60.5% for those treated with dupilumab 300 mg Q2W, and 6.3% for those who received placebo; treatment difference of 53.5 (95% CI 41.2, 65.8) p<0.0001 for the dupilumab 300 mg QW group vs placebo, and treatment difference of 56.0 (95% CI 43.4, 68.5) p<0.0001 for the dupilumab 300 mg Q2W group vs placebo. o For Part A, the absolute change from baseline in DSQ total score at Week 24 by LS mean change was -21.9 for those treated with dupilumab 300 mg QW and -9.6 for those who received placebo; treatment difference of -12.3 (95% CI -19.1, -5.5) p=0.0004. o For Part B, the absolute change from baseline in DSQ total score at Week 24 by LS mean change was -23.8 for those treated with dupilumab 300 mg QW, -14.4 for those treated with dupilumab 300 mg Q2W, and -13.9 for those who received placebo; treatment difference of -9.9 (95% CI -14.8, -5.0) p<0.0001 for the dupilumab 300 mg QW group vs placebo, and treatment difference of -0.5 (95% CI -5.4, 4.4) p=0.84 for the dupilumab 300 mg Q2W group vs placebo. • For subjects treated with dupilumab 300 mg QW, improvement over placebo was demonstrated on evaluation of both histologic and symptomatic coprimary endpoints in both Part A and B. Although analyses for subjects treated with dupilumab 300 mg Q2W in Part B demonstrated improvement on the histologic coprimary endpoint compared to placebo, analyses of the symptomatic coprimary endpoint for this group did not demonstrate improvement over	definitive conclusions from independent analyses of the subgroup. • Given the similarity of the disease presentation, progression, and expected response to treatment between adults and adolescents, the determination of efficacy in the adolescent subgroup is supported by the results of efficacy analyses from the overall study population. • Review of subgroup analyses of the mean absolute change in 14-day DSQ total scores over time in adolescent and adult subjects further supported the demonstration of efficacy in adolescent subjects in Study 1774. • Although there are several limitations to the interpretability of the efficacy results from Part A/C, they were supportive of continued benefit for subjects that received dupilumab 300 mg QW for 52 weeks. • Additional blinded 52-week efficacy data from approximately 74 subjects that received dupilumab 300 mg QW from Part B/C is forthcoming and will be beneficial to further characterize the safety and potential loss of efficacy of dupilumab with chronic use. • Although additional long-term data from Part B/C are anticipated in the near future, as EoE is a serious condition with an unmet medical need with no approved therapy, the availability of these data should not delay approval of dupilumab for the treatment of patients with EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	placebo. For this reason, only the dosage of 300 mg QW is recommended for approval. • The Applicant proposed a meaningful change threshold of a 13-point improvement from baseline in the DSQ total score to support the clinical meaningfulness of the symptomatic coprimary endpoint results from Part A and Part B. This threshold appeared to be derived using Part B data based on the lower bound of the 95% confidence interval (-12.03, -4.84) of change in DSQ score for subjects who experienced "No Change" on the PGIS anchor score. Note that the Applicant's proposed threshold did not appear to take into consideration a higher threshold range derived from Part A data (i.e., a range between 14-point and 23-point improvement based on the Applicant's analyses). • FDA's anchor-based analyses, which leveraged data from both Parts A and B, determined that the meaningful within-subject change range should be between 20-point and 24-point improvement from baseline in the DSQ total score. FDA derived this range of change scores based on median values of change in DSQ score for subjects who experienced a 1-category improvement on the PGIS and "Moderately Better" on the PGIC anchor assessments, while taking into account the baseline PGIS anchor score. • Despite this higher meaningful change range, a higher proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to those treated with placebo in the FDA-determined range (i.e., 38.1% to 47.6% of subjects treated with dupilumab 300 mg QW vs. 15.4% to 25.6% of placebo subjects in Part A, and 53.8% to 58.8% of subjects treated with dupilumab 300 mg QW vs. 21.8% to 32.1% of placebo subjects in Part B). • Given that the interpretability of the anchor-based analyses may be limited by the difference in assessment periods between the 14-day DSQ total score and the PGIS anchor with 7-day recall period, supplementary anchor-based analyses were conducted separately in Parts A and B by the Applicant (upon FDA request) and by FDA to	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	determine a range of meaningful change thresholds for the absolute change from baseline in the 7-day DSQ total score. FDA's analyses indicated that a higher proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to those treated with placebo in the FDA-determined meaningful change range (i.e., between 10-point and 13-point improvement from baseline) in the 7-day DSQ total score (i.e., 33.3% to 47.6% of subjects treated with dupilumab 300 mg QW vs. 20.5% to 30.8% of subjects who received placebo in Part A, and 53.8% to 70.0% of subjects treated with dupilumab 300 mg QW vs. 25.6% to 33.3% of subjects who received placebo in Part B). The Applicant did not propose a meaningful within-subject change range from baseline in the 7-day DSQ total score for either Part A or Part B. • The proportion of adolescent subjects relative to the total number of subjects in Study 1774 was acceptable and consistent with the expected population distribution of adolescents vs. adults with EoE. • Although subgroup analyses of the absolute change from baseline in DSQ total score for the adolescent population (i.e., subjects 12 – 17 years of age inclusive) from Study 1774 revealed less robust results than observed for the overall population, the ability to precisely characterize the treatment effects within the subpopulation was limited by the small number of adolescent subjects. o For adolescents in Part A, the absolute change from baseline in DSQ total score at Week 24 by LS mean change was -23.84 for those treated with dupilumab 300 mg QW and -15.93 for those who received placebo, treatment difference of -7.9 (95% CI -21.8, 6.0). o For adolescents in Part B, the absolute change from baseline in DSQ total score at Week 24 by LS mean change was -19.54 for those treated with dupilumab 300 mg QW and -16.42 those who received placebo, treatment difference of -3.1 (95% CI -12.8, 6.5).	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Although limited by their descriptive nature and open-label study design, the following results of assessments from Part C (i.e., the ongoing 28-week extension study) for subjects that completed Part A (Part A/C) were observed. o The proportion of subjects with histologic response at Part C baseline was 68.4% for those that received dupilumab in Part A and 6.1% for those that received placebo in Part A. At the end-of-treatment for Part C, the proportion of subjects with histologic response was 55.9% for those that received dupilumab in Part A and Part C (dupilumab/dupilumab) and 60.0% for those that received placebo in Part A and dupilumab in Part C (placebo/dupilumab). o The absolute change from baseline in DSQ total score from study baseline (i.e., Part A baseline) at Part C baseline by LS mean change was -21.1 for subjects that received dupilumab in Part A and -10.2 for those that received placebo in Part A. At the end-of-treatment for Part C, the absolute change from baseline in DSQ total score from study baseline (i.e., Part A baseline) by LS mean change was -23.4 for those that received dupilumab in Part A and Part C (dupilumab/dupilumab) and -21.7 for those that received placebo in Part A and dupilumab in Part C (placebo/dupilumab). • Blinded efficacy data from approximately 74 additional subjects treated with dupilumab 300 mg QW for 52 weeks are anticipated from Part B/C with an estimated study completion date of July 2022.	
Risk and Risk Management	• Dupilumab was first approved in March 2017 for treatment of adult patients with moderate-to-severe atopic dermatitis (AD). Currently dupilumab is approved for atopic dermatitis in patients 6 years of age and older, asthma in patients 6 years of age and older, and adults with chronic rhinosinusitis with nasal polyps.	• The observed risk profile for dupilumab for the treatment of adolescents and adult subjects with EoE was largely reflective of that described in the FDA-approved product labelling for other conditions for which dupilumab is currently approved. Upper respiratory tract infections were identified as an adverse reaction in subjects with EoE, which has not been previously described in other

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The dose found to be efficacious for the treatment of subjects with EoE (i.e., 300 mg QW) is higher than that currently approved for other indications. • The safety of dupilumab for the treatment of adolescent and adult subjects with EoE was evaluated in Study 1774. The rate and type of adverse reactions in Study 1774 were similar to those observed with the currently approved indications (i.e., atopic dermatitis, CRSwNP, and asthma). • The most common adverse reactions (incidence ≥2%, and greater than placebo) in Parts A and B of Study 1774 were injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. • In addition to the data from Parts A and B (pivotal to the determination of efficacy), data from Part A/C of Study 1774 were evaluated to support the determination of safety. No new safety findings were observed on review of the data from the treatment period of Part C. • Data from Study 1324 was also reviewed as part of the evaluation of safety and revealed similar results to Study 1774. • In addition to adverse reactions previously identified in dupilumab labeling (i.e., injection site reactions, arthralgia, and herpes viral infections), upper respiratory tract infections were reported in a greater proportion of subjects who received dupilumab 300 mg QW than placebo (20% vs 10%). This adverse reaction has not been previously reported in dupilumab labeling; however, upper respiratory tract infections were noted to have occurred during studies that assessed the 300 mg QW dosing regimen for other indications. Additionally, arthralgia was reported by a greater proportion of subjects who received dupilumab 300 mg QW than placebo (3% vs 1%). Subjects with EoE may be at increased risk of arthralgia, due to an increased risk of connective tissue disorders (Abonia et al. 2013). • 40 subjects from Parts A/C were treated with the to-be-marked dose of 300 mg QW for 52 weeks.	indications. However, the majority of these events were mild to moderate and did not lead to study discontinuation. • The safety profile observed in subjects with EoE (i.e., Part A, Part B, and Part A/C of Study 1774 and Study 1324) was consistent across study populations. • The review team determined that the issuance of a post-marketing requirement (PMR) to evaluate the long-term safety (over 52 weeks of therapy) of dupilumab in adult and pediatric subjects ages 12 years and older with eosinophilic esophagitis (EoE) with respect to arthralgia. • As EoE is a serious condition with unmet medical need with no approved therapy, and in consideration of the favorable benefit-risk profile determined during the review of this sBLA, the review team determined that although additional long-term data from Part B/C is needed, the availability of these data should not delay approval of dupilumab for the treatment of patients with EoE.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Part C is currently ongoing (anticipated completion for subjects that completed Part B - July 2022) and is anticipated to provide blinded data from approximately 74 additional subjects with EoE treated with dupilumab 300 mg QW for 52 weeks. • The small number of subjects with long-term data raised uncertainties in the ability of the available data to detect and characterize adverse events that may occur or worsen with longer-term exposure to dupilumab 300 mg QW in subjects with EoE. There are also uncertainties regarding the potential for subjects to experience risks during chronic treatment due to loss of efficacy.	

1.4. Patient Experience Data

The Applicant included the DSQ, a patient-reported outcome (PRO) instrument, as a coprimary endpoint in Part A and Part B of their three-part adequate and well-controlled trial (Study 1774) to assess subjects' symptom of dysphagia.

Table 2: Patient Experience Data Relevant to this Application

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	DSQ (Sections 1.2, 1.3, 1.4, 6.2, 7.1, 8.1, 14, 15.5, 15.6)
		☐	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

Eosinophilic esophagitis (EoE) is a chronic immune/antigen-mediated esophageal disease clinically characterized by signs and symptoms related to esophageal dysfunction and histologically characterized by eosinophil-predominant inflammation (Liacouras et al. 2011). Left untreated, EoE leads to esophageal stricture, dysphagia, and risk of food impaction (Warners et al. 2018). EoE has an estimated incidence of 5–10 cases per 100,000 persons per year and prevalence of approximately 50–100 cases per 100,000 persons (Dellon and Hirano 2018).

Clinical signs and symptoms of EoE vary with age of the patient. Adults and adolescents most commonly present with dysphagia and food impaction, school-aged children are more likely to present with vomiting or abdominal pain, and infants and toddlers present with feeding difficulties (Straumann and Katzka 2018).

In patients with EoE, clinical features and histologic activity can vary independently. Patients can have a reduction or resolution in signs and symptoms despite ongoing histologic activity; conversely, patients can have histologic remission (defined as a change in peak eosinophils per high-power field (HPF) from a count greater than or equal to 15 to less than or equal to 6) with persistent clinical symptoms (Dellon et al. 2013).

For these reasons, the treatment goals of EoE include resolution or reduction of the signs and symptoms of active disease to provide relief to the patient, and healing or control of the esophageal inflammation and its complications.

2.2. Analysis of Current Treatment Options

There are no FDA approved therapies for the treatment of EoE. Although clinical practice guidelines for the management of EoE recommend off-label use of topical steroids and proton pump inhibitors, the safety and effectiveness of these therapies have not been established for the treatment of patients with EoE (Hirano et al. 2020). Systemic corticosteroids have been used for severe or refractory cases, but toxicity prohibits their long-term use. Food elimination diets, including restriction to elemental formulas, have been shown in the literature to decrease both clinical symptoms and eosinophilic inflammation (Groetch et al. 2017). The success of dietary restriction in patients with EoE, however, is limited by challenges with long-term adherence and compliance. There is a need for the development of novel therapies for the treatment of EoE. Of note, many of the studies cited to support current treatment guidelines focus on the improvement of histologic features of EoE and are predominantly retrospective and/or observational studies. In addition to pharmacologic and dietary therapies, endoscopic dilation may be performed in patients with dysphagia resulting from the presence of esophageal stricture to provide symptomatic relief.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant (Regeneron Pharmaceuticals) submitted efficacy supplement S-040 to biologics license application (BLA) 761055 seeking U.S. Food and Drug Administration (FDA) approval to expand the established indications for Dupixent (dupilumab) to include the treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis.

Dupixent is currently approved and marketed in the US for the following indications:

1. Treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids.
2. Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to severe-asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma
3. Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis

Dupilumab was developed for the treatment of adolescent and adult patients with EoE under IND 136142 and was granted Orphan Drug Designation for the treatment of EoE on September 5, 2017.

Prior to opening IND 136142, the Applicant conducted Trial R668-EE-1324 (Study 1324) under IND 107969 (the existing IND for the atopic dermatitis indication, managed by the Division of Dermatology and Dentistry).

A Type B Pre-IND (PIND) meeting for IND 136142 was held with Regeneron on May 8, 2018 (meeting minutes finalized on May 15, 2018) to discuss the Applicant's EoE development program, including their proposed phase 3 trial (R668-EE-1774). On June 25, 2018, the Applicant submitted a new IND incorporating the majority of FDA advice that was conveyed at the PIND meeting.[4] IND 136142 was activated on July 25, 2018.

A Type C teleconference was held between FDA and the Applicant on September 2, 2020 to discuss whether the clinical data obtained in Part A of their ongoing phase 3 trial (R668-EE-1774) was sufficiently robust and convincing to support the filing of an efficacy supplement (sBLA) for dupilumab for the treatment of adult and pediatric patients aged 12 years and older

[4] Despite FDA advice that secondary endpoints related to changes in the EoE endoscopic reference score, EoE histologic scoring system, and EndoFLIP could not support inclusion in the product label since clinically meaningful changes in these scores have not been established, the Applicant maintained these secondary endpoints for Study 1774.

with EoE. During the teleconference, FDA stated that Part A data alone would not be sufficient to support the filing of an sBLA for the EoE indication. However, FDA communicated that they would be open to opportunities for continued collaboration and the potential for reassessment of their recommendation to complete all parts of the ongoing phase 3 trial (i.e., Parts A, B, and C) prior to sBLA submission as additional trial results became available.

On September 9, 2020, Breakthrough Therapy Designation (BTD) was granted for dupilumab for the treatment of patients 12 years and older with EoE based on review of the data from Part A of Study 1774.

On May 14, 2021, an additional teleconference was held between FDA and the Applicant to discuss whether the results from Part A of the ongoing phase 3 trial (R668-EE-1774), supported by long-term data from subjects in Part A who also completed Part C (i.e., the 28-week open-label extended active treatment period for subjects who completed either Part A or Part B), would be sufficient to support the filing of an sBLA. During the teleconference FDA communicated that the currently available data on a limited number of adult and adolescent subjects were not sufficient to meet the substantial evidence of effectiveness standard to support the sBLA submission and that additional data from Part B were needed to inform the disease-specific benefit-risk assessment and characterize disease-drug interactions in subjects with EoE. The Applicant agreed to include data from Part B in the future sBLA submission.

BLA 761055 S-040 in support of dupilumab for the treatment of adult and pediatric subjects aged 12 years and older with EoE was granted a rolling review on July 19, 2021. Submission of the sBLA containing Parts A, A/C, and B was completed on February 3, 2022. The Applicant acknowledged that additional regimen-blinded safety and efficacy data from subjects with EoE from Part B/C were not included in the submission and are anticipated after study completion in July 2022.

With this sBLA submission, the Applicant requested Priority Review. Priority review was granted due to the seriousness of the condition and the lack of currently available treatments (May 2014).

The Applicant is currently conducting an ongoing phase 3 trial (R668-EE-1877) under IND 136142 to evaluate dupilumab as a treatment for pediatric subjects with EoE 1 to 11 years of age.

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

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were requested on the basis of efficacy or safety concerns as no sites of concern were identified that were driving the efficacy or safety results.

4.2. Product Quality

The proposed drug product is intended to be administered using the approved presentations (i.e., 300 mg prefilled syringe assembled with a safety system [PFS-S] and 300 mg single-use prefilled pen [PFP]). Both the approved PFS-S and PFP contain the same bulk-PFS (except for the final assembled product) and the same drug product formulation (300 mg dupilumab, 20mM histidine, 25mM arginine, 12.5mM acetic acid, 5% sucrose, and 0.2% polysorbate 80). No new product quality data were submitted for review to support the proposed indication.

4.3. Clinical Microbiology

No new microbiology data were submitted for review to support the proposed indication.

4.4. Devices and Companion Diagnostic Issues

There is no companion diagnostic test for review in support of this sBLA. The proposed presentations have been approved in prior submissions to the BLA.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were conducted to support the approval of dupilumab 300 mg QW for the treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis.

6. Clinical Pharmacology

6.1. Executive Summary

Dupilumab is a human monoclonal IgG4 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. Currently, dupilumab is approved for the treatment of AD,

asthma, and CRSwNP. In this BLA efficacy supplement, the Applicant seeks approval of dupilumab for the treatment of adult and pediatric patients aged 12 years and older with EoE. The proposed dosing regimen is 300 mg QW given subcutaneously (SC).

The safety and effectiveness of dupilumab for the treatment of adult and pediatric subjects 12 years of age and older with EoE were assessed in Study 1324 and Study 1774 in adult and adolescent subjects with EoE. The clinical pharmacology review evaluated pharmacokinetic (PK) data, immunogenicity, population pharmacokinetic (PopPK) and exposure-response (E-R) data obtained from Study 1324 and Study 1774.

The PK in subjects with EoE is consistent with those in subjects from other approved indications. Overall, the incidence of treatment-emergent ADA was low and reported in approximately 1% of subjects with EoE who received the 300 mg QW regimen. The proposed SC dosage of 300 mg QW for adult and pediatric patients aged 12 years and older with EoE is acceptable based on the statistically significant improvement over placebo on the coprimary efficacy endpoints (i.e., peak esophageal intraepithelial eosinophil count and reduction in dysphagia symptoms measured by DSQ total score) in Study 1774 and acceptable safety profile. No dosage adjustment based on body weight or age is needed for adult and pediatric patients aged 12 years and older with EoE, weighing at least 40 kg.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this sBLA submission and found it acceptable for approval from a clinical pharmacology standpoint.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Dupilumab is a human monoclonal IgG4 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. Clinical pharmacokinetics of dupilumab have been previously characterized in the original BLA 761055 and supplement BLAs in healthy subjects and subjects with AD, asthma, or CRSwNP. Sparse PK samples were collected in subjects with EoE for population PK analysis, and the PK in subjects with EoE was compared with that in other patient populations. Relevant PK information, as described in Section 12.3 of the current dupilumab product labeling for AD, asthma, or CRSwNP indications, is summarized below.

Absorption

Steady-state concentrations were achieved by Week 16 following the administration of 600 mg starting dose followed by subsequent doses of 300 mg either weekly or Q2W or following the administration of 300 mg Q2W without a loading dose. Across clinical trials, the mean ± SD trough concentrations at steady-state ranged from 60.3±35.1 mcg/mL to 80.2±35.3 mcg/mL for 300 mg administered Q2W and from 173±75.9 mcg/mL to 193±77.0 mcg/mL for 300 mg

administered weekly. The bioavailability of dupilumab following a SC dose is similar between subjects with underlying AD, asthma, and CRSwNP, ranging between 61% and 64%.

Distribution

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

Elimination

After the last steady-state dose of 300 mg Q2W and 300 mg QW dupilumab, the median times to non-detectable concentration (<78 ng/mL) are 10-12 and 13 weeks, respectively.

Dose Linearity

Dupilumab exhibited nonlinear target-mediated pharmacokinetics with exposures increasing in a greater than dose-proportional manner. Following a single dose of dupilumab from 75 mg to 600 mg, the systemic exposure increased by 30-fold when the dose was increased 8-fold.

Intrinsic Factors

Dupilumab trough concentrations were lower in subjects with higher body weight over the range of 32 to 185.6 kg in subjects with AD, asthma, or CRSwNP. Based on population pharmacokinetic analysis, age did not affect dupilumab clearance.

Immunogenicity

Approximately 5% of subjects with AD, asthma, or CRSwNP who received dupilumab 300 mg Q2W for 52 weeks developed antibodies to dupilumab. Development of antibodies to dupilumab was associated with lower serum dupilumab concentrations in subjects with AD, asthma, or CRSwNP.

Clinical Pharmacokinetics in Subjects with EoE

In the current submission, the Applicant evaluated PK of dupilumab in adult and adolescent subjects (≥40 kg) with EoE in Study 1324 and Study 1774.

Overall, mean trough dupilumab concentrations at steady-state in subjects with EoE ranged 189 to 195 mg/L following 300 mg QW dosing (Study 1774 Parts A and B) and was 72.1 mg/L following 300 mg Q2W dosing (Study 1774 Part B), and are similar to that in subjects with asthma, atopic dermatitis, and nasal polyposis receiving dupilumab 300 mg QW or 300 mg Q2W, respectively. Based on PopPK analysis, the predicted dupilumab PK and bioavailability are also comparable across the studied populations including EoE. After accounting for body weight, no new covariates were identified that might impact dupilumab PK in subjects with EoE. Dupilumab concentrations are comparable between adults and adolescents of similar body weight.

The incidence of treatment-emergent ADA to dupilumab was low with approximately 0.7% and 2.6%, respectively, in EoE subjects who received 300 mg QW or Q2W for up to 24 weeks in the pooled Studies 1324 and 1774 (Parts A and B). Given the low incidence of treatment-emergent ADA, the effect of immunogenicity on efficacy, safety, or PK of dupilumab is unknown.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing of dupilumab is 300 mg QW in adult and adolescent subjects with EoE.

Although both 300 mg QW and 300 mg Q2W were studied in Study 1774, only the 300 mg QW dosage is recommended for approval, because results of analyses for both coprimary endpoints (i.e., proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24 and absolute change in DSQ total score from baseline to Week 24) demonstrated significant improvements in subjects treated with 300 mg QW compared to those that received placebo. Analyses of the symptomatic coprimary endpoint for subjects that received dupilumab 300 mg Q2W did not demonstrate improvement compared to those that received placebo. Additionally, a greater proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to subjects that received placebo based on the FDA-determined meaningful change threshold range. See Section 8 Statistical and Clinical Evaluation of this multi-discipline review for details on the efficacy results.

Additionally, the exposure-response analyses for the coprimary efficacy endpoints in Study 1774 were consistent with the dose-response relationships, suggesting greater improvement of dysphagia symptoms (absolute change in DSQ total score at Week 24) associated with the 300 mg QW regimen compared to 300 mg Q2W.

Therapeutic Individualization

No dosage adjustment based on intrinsic or extrinsic factors is needed for adult and adolescent subjects with EoE. See details in Section 6.3.2.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

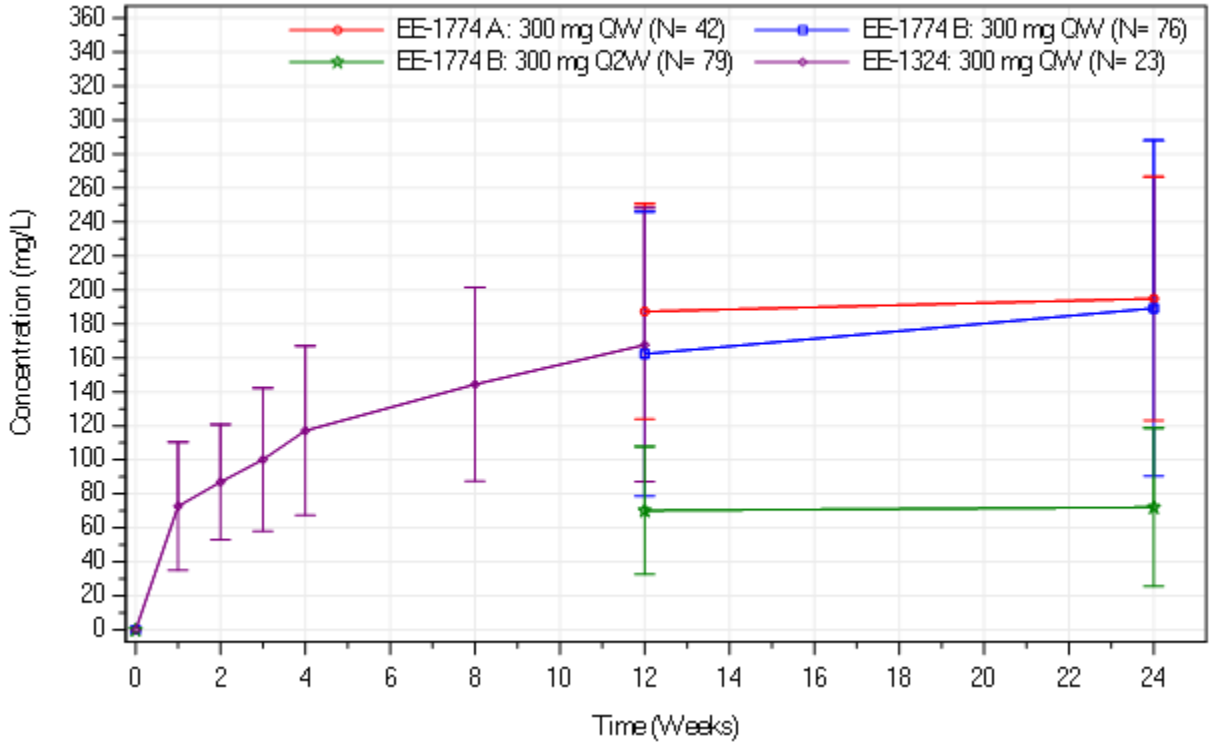
Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin 13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling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

information for dupilumab was reviewed by Dr. Jie Wang during the original application (DARRTS date 12/19/2016) for the treatment of moderate to severe atopic dermatitis. Supplement BLA S07 was reviewed by Dr. Dipak Pisal (DARRTS date 10/19/2018) for the treatment of moderate to severe asthma.

In the current submission, PK of dupilumab in subjects with EoE were characterized by population PK analysis using sparse PK samples collected in Study 1324 and Study 1774.

Comparison of dupilumab trough concentrations at Week 12 following dupilumab 300 mg QW dosing across Studies 1324 and 1774, as well as between Part A and Part B (300 mg QW and 300 mg Q2W) of Study 1774, are presented in Figure 1 and Table 3 below.

Figure 1: Mean (SD) Serum Dupilumab Trough Concentrations by Treatment Group and Week in Subjects Aged 12 Years and Older With Eosinophilic Esophagitis (Parts A and B of Study 1774 and Study 1324)



Source: Applicant's BLA 761055 S-040 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 2.

Table 3: Mean (SD) Serum Dupilumab Concentrations (mg/L) in Adult and Adolescent Subjects With Eosinophilic Esophagitis

		300 mg QW		300 mg Q2W	
Study	**Week**	**n**	**Mean (SD)**	**n**	**Mean (SD)**
R668-EE-1324	12	23	168 (80.6)	NA	NA
R668-EE-1774 Part A	24	35	195 (71.7)	NA	NA
R668-EE-1774 Part B	24	63	189 (98.8)	68	72.1 (46.6)

Source: Adapted from Applicant's BLA 761055 S-040 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 3.
Abbreviations: SD = standard deviation.

Overall, mean trough dupilumab concentrations at steady-state are similar between subjects with EoE and subjects with AD or asthma receiving dupilumab 300 mg QW. Based on PopPK analysis, the predicted dupilumab PK and bioavailability are also comparable across the studied populations including EoE. After accounting for body weight, no new covariates were identified that might impact dupilumab PK in subjects with EoE aged 12 years and older.

6.3.2. Clinical Pharmacology Questions

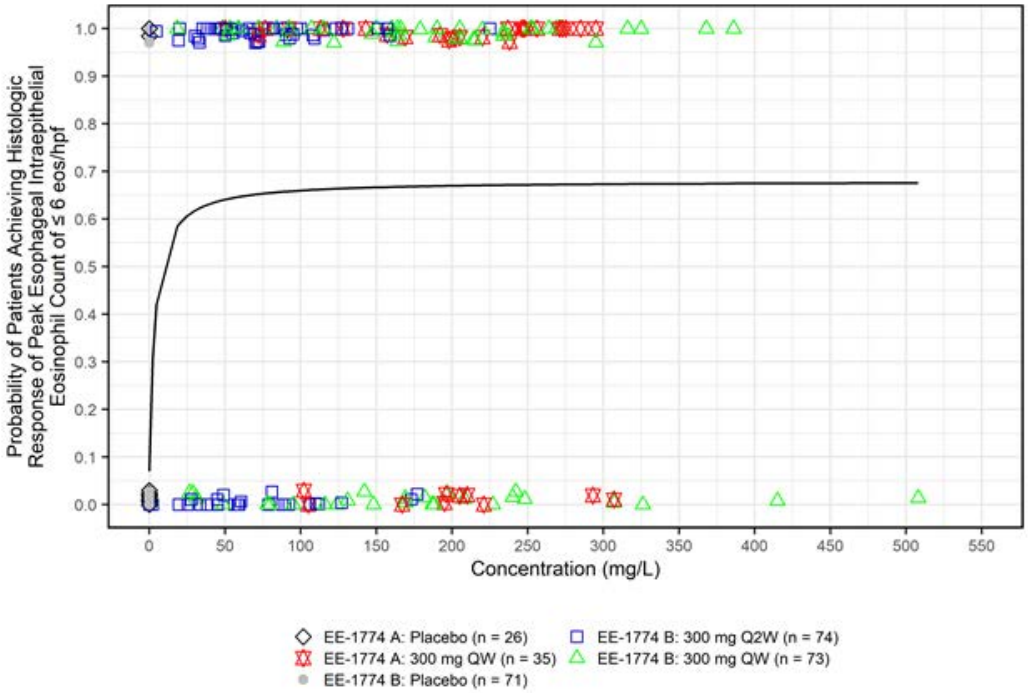
Does the Clinical Pharmacology Program Provide Supportive Evidence of Effectiveness?

Yes. Descriptive exposure-response (E-R) analyses for efficacy were conducted using observed trough concentrations (Ctrough) of dupilumab in Part A and Part B of Study 1774. The analysis included pooled data from subjects receiving placebo or 300 mg SC QW during Part A or Part B of Study 1774 and subjects receiving 300 mg SC Q2W in Part B.

The E-R relationships for esophageal intraepithelial eosinophil count at Week 24 are shown in Figure 2 (proportion of subjects achieving peak esophageal intraepithelial eosinophil counts of ≤6 eos/hpf). The E-R analysis indicated that the maximal response in esophageal intraepithelial eosinophil count was achieved at dupilumab exposure associated with the proposed dose regimen of 300 mg QW, which is consistent with the dose-response relationship.

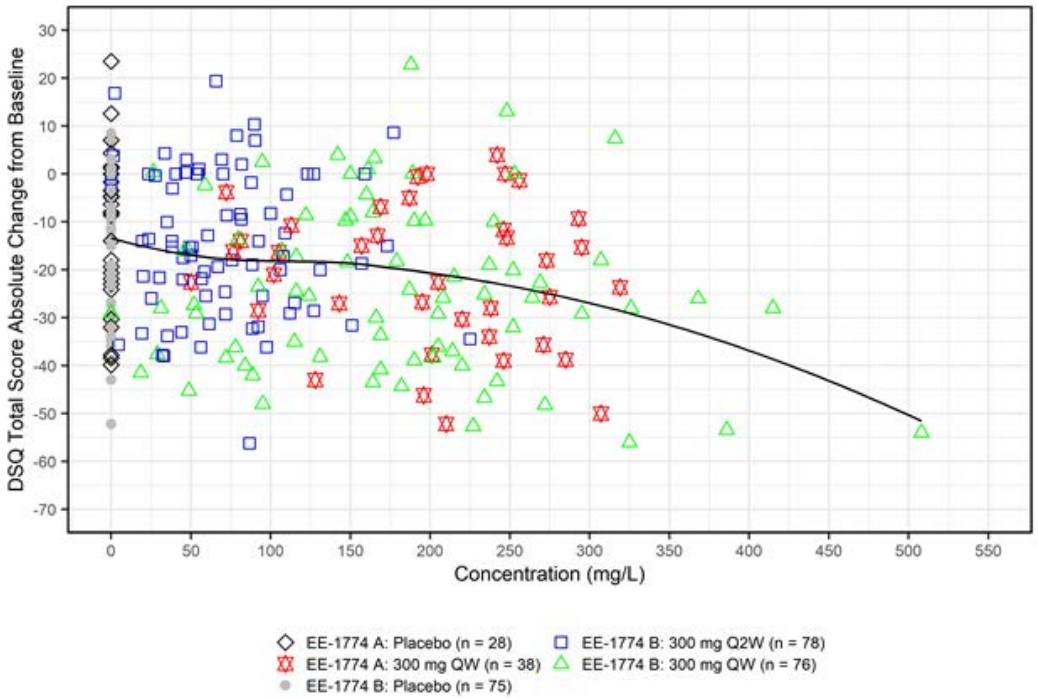
For DSQ total score, the E-R relationship shows a shallow trend towards greater change from baseline at higher dupilumab exposure associated with 300 mg QW compared to that with the 300 mg Q2W regimen (Figure 3). This was also consistent with the dose-response findings in DSQ total score.

Figure 2: Logistic Regression of Probability of Subjects Achieving Histologic Response of Peak Esophageal Intraepithelial Eosinophil Count of ≤6 eos/hpf vs Trough Concentration of Dupilumab at Week 24 in Adult and Adolescent Subjects With Eosinophilic Esophagitis (Parts A and B, Study 1774)



Source: Adapted from Applicant's BLA 761055 S-040 submission Summary of Clinical Pharmacology, Figure 11.

Figure 3: Scatter Plot of Absolute Change from Baseline in DSQ Total Score vs Trough Concentration of Dupilumab at Week 24 by Treatment Group in Adult and Adolescent Subjects With Eosinophilic Esophagitis (Parts A and B, Study 1774)



Source: Adapted from Applicant's BLA 761055 S-040 submission, Summary of Clinical Pharmacology, Figure 14.

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

Yes, the proposed dosing regimen of dupilumab 300 mg QW is appropriate for adolescent and adult patients weighing ≥ 40 kg with EoE based on the following:

- Statistical analyses for both coprimary endpoints (i.e., proportion of subjects achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24 and absolute change in DSQ total score from baseline to Week 24) demonstrated significant improvements in subjects treated with 300 mg QW compared to those that received placebo.
- Exposure-response findings for the coprimary efficacy endpoints in Parts A and B of Study 1774 were consistent with the dose-response relationships, suggesting better improvement of dysphagia symptoms (absolute change in DSQ total score) at Week 24 associated with the 300 mg QW regimen compared to 300 mg Q2W.
- The exposure of dupilumab in adolescents ≥40 kg is expected to be comparable to those in adults following the proposed dosing regimen. Given the similarity of the disease presentation, progression, and expected response to treatment between adults and adolescents, the efficacy in the adolescent subjects is supported by the results of efficacy analyses from the overall study population.
- No evident E-R relationship for AESIs at Week 24 was observed based on Part B data of Study 1774. See Section 15.3.2 for details.

- Based on the overall similar PK across disease populations, the available safety data from the use of dupilumab in the previously approved indications assessed the dosage of 300 mg QW provide supportive safety data. See Section 8 Statistical and Clinical Evaluation.

In conclusion, the benefit-risk profile of dupilumab 300 mg QW in subjects with EoE is favorable based on the observed efficacy and safety data from Parts A and B of Study 1774, and safety data from subjects who completed Study 1324.

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

No. An alternative dosing regimen or management strategy is not necessary for subpopulations based on intrinsic factors for adult and adolescent patients with EoE weighing ≥40 kg.

Age

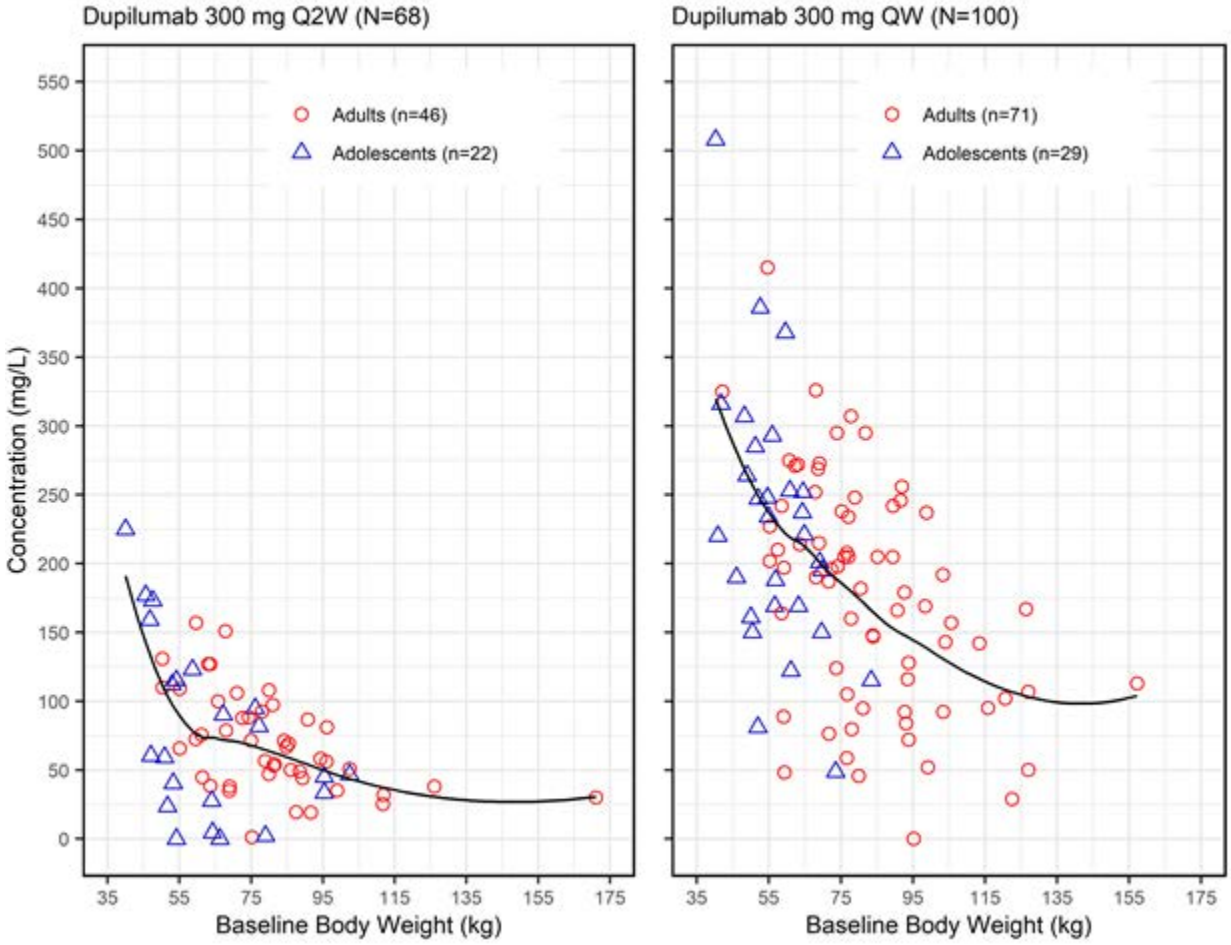
The proposed dosage of 300 mg QW is appropriate for both adolescents and adults with EoE. Adolescent subjects 12 to 17 years of age with EoE, weighing ≥40 kg, were evaluated in Parts A and B of Study 1774. Among them, 35 adolescents received 300 mg QW in Parts A and B, and 25 adolescents received 300 mg Q2W in Part B. Although mean trough concentrations of dupilumab were higher in adolescents compared to adults treated with dupilumab 300 mg QW (Table 4), dupilumab concentrations were similar between these two age groups of similar body weight (Table 5). As presented in Figure 4, individual PK data suggest that adolescents and adults with similar body weight exhibited overlapping exposures.

Table 4: Mean (SD) Serum Dupilumab Concentrations (mg/L) by Time and Age Group in Adults and Adolescents With Eosinophilic Esophagitis Receiving Dupilumab (Parts A and B, Study 1774)

	Study 1774 Parts A and B				Study 1774 Part B			
	Adults 300 mg QW		Adolescents 300 mg QW		Adults 300 mg Q2W		Adolescents 300 mg Q2W	
Week	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
0	79	NA	35	NA	52	NA	25	NA
12	69	156 (68.0)	30	207 (87.2)	47	67.5 (33.0)	20	76.5 (47.3)
24	71	177 (83.3)	29	227 (95.3)	46	69.8 (35.9)	22	77.0 (64.3)

Source: Applicant's BLA 761055 S-040 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 4; Clinical Pharmacology Report R668-EE-1774-CP-03V1, Table 11.
Abbreviations: SD = standard deviation.

Figure 4: Scatter Plot of Dupilumab Concentrations at Week 24 by Baseline Body Weight and Age Group in Adults and Adolescents With Eosinophilic Esophagitis (Study 1774)



Source: Applicant's BLA 761055 S-040 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Figure 6.

Additional cross-study comparisons indicate that mean dupilumab trough concentrations at steady state are similar between adolescents with EoE (Study 1774, mean range of 176 to 243 mg/L) and adults with EoE weighing <70 kg (Study 1324 and Study 1774, mean range of 164 to 254 mg/L) following 300 mg QW dosage.

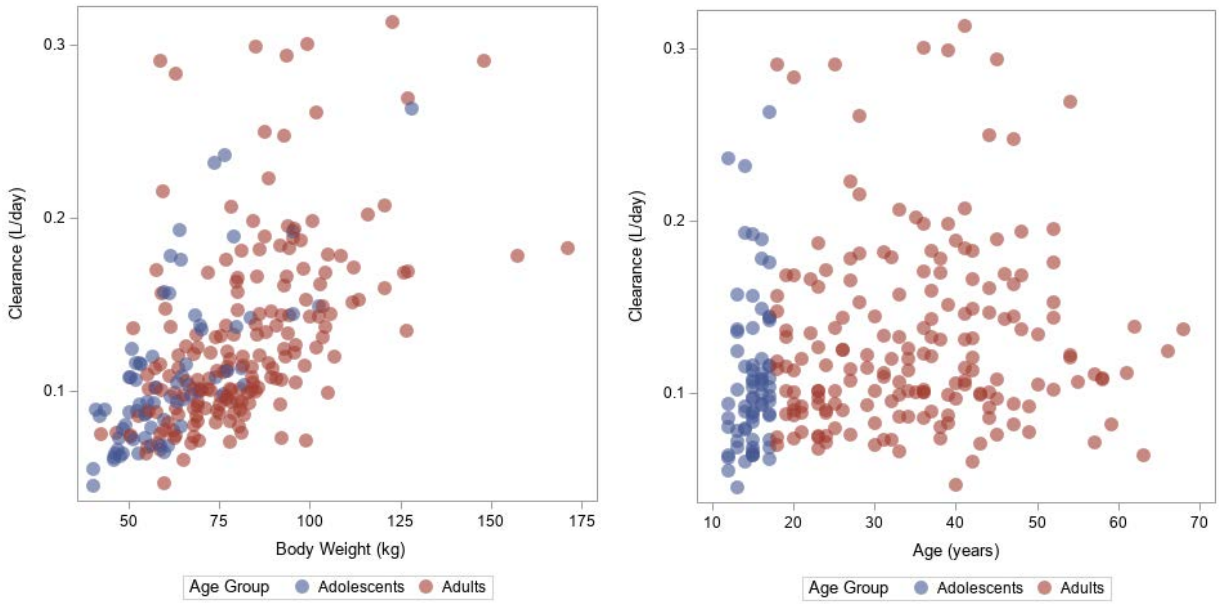
Table 5: Summary of Mean (SD) of Serum Dupilumab Concentrations by Study for Adult and Adolescent Subjects <70 kg With Eosinophilic Esophagitis Receiving Dupilumab 300 mg QW or 300 mg Q2W

	300 mg QW		300 mg Q2W	
Study	**n**	**Mean (SD)**	**n**	**Mean (SD)**
Adults				
R668-EE-1324	7	227 (104)	NA	NA
R668-EE-1774 Part A	5	254 (28.2)	NA	NA
R668-EE-1774 Part A/C	11	164 (78.1)	NA	NA
R668-EE-1774 Part B	15	227 (91.6)	16	91.3 (40.9)
Adolescents				
R668-EE-1774 Part A	9	228 (68.5)	NA	NA
R668-EE-1774 Part A/C	16	176 (87.6)	NA	NA
R668-EE-1774 Part B	18	243 (99.4)	16	86.9 (71.0)

Source: Applicant's BLA 761055 S-040 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 5.
Abbreviations: SD = standard deviation.

In addition, based on population PK analysis, age (12 – 68 years) does not show a significant impact on dupilumab PK after the effect of body weight has been accounted for (Figure 5).

Figure 5: Estimated Dupilumab Clearance by Body Weight and Age in Adolescent and Adult Subjects With EoE From Studies 1324 and 1774 (N=251)



Source: Reviewer's analysis, based on the submitted population PK dataset "nmeoe.xpt".

Body Weight

Dose adjustment based on body weight is not needed for patients weighing ≥40 kg.
The effect of body weight on dupilumab PK is not considered clinically significant based on the subgroup analysis of coprimary endpoints (Table 6), observed flat E-R for AESI, and overall low incidences of TEAEs. In addition, no major difference in safety profile was observed between body weight subgroups of ≥60 kg and <60 kg (see details in Section 8.2 Review of Safety).

Table 6: Subgroup Analysis of Coprimary Endpoints by Baseline Body Weight (Pooled Data From Parts A and B of Study 1774)

		Subjects With Peak Esophageal Intraepithelial Eosinophil Count of <=6 eos/hpf at Week 24		Absolute Change From Baseline in DSQ Total Score at Week 24	
Baseline Body Weight	Treatment	n(%)	Difference (95% CI)	LS Mean Change (SE)	LS Mean Difference (95% CI)
< 60 kg	Dupilumab 300 mg QW (N=30)	14 (46.7)	42.5 (18.51, 66.50)	-26.74 (3.49)	-8.74 (-18.77, 1.30)
	Placebo (N=21)	1 (4.8)		-18.00 (4.38)	
>=60 kg	Dupilumab 300 mg QW (N=92)	58 (63.0)	58.0 (46.66, 9.26)	-21.17 (1.83)	-10.36 (-14.57, -6.15)
	Placebo (N=97)	6 (6.2)		-10.81 (1.86)	

Source: Adapted from Applicant's BLA 761055 S-040 submission, ISS-ISE-Pool 1-Tables, Table 6.1.1.1/7 and Table 6.1.2.1/7.

Of note, dupilumab 300 mg QW has not been studied in subjects with EoE with a body weight <40 kg. Overall, a further dose adjustment based on body weight in patients ≥40 kg is not needed based on subgroup analysis for efficacy, safety, and exposure-response analyses.

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

No. Food-drug interactions are not applicable as dupilumab is administered by SC injection. Dupilumab has no clinically meaningful effect on exposures of substrates for major CYP enzymes as described in Section 12.3 of dupilumab product labeling.

What is the Incidence of the Formation of ADA and the Impact of Immunogenicity on Dupilumab Exposure?

Overall, the incidence of treatment-emergent ADA to dupilumab 300 mg QW or Q2W was low. The incidence of treatment-emergent ADA to dupilumab was approximately 0.7% (1 out of 141 subjects) and 2.6% (2 out of 77 subjects), respectively, in EoE subjects who received 300 mg QW or Q2W for up to 24 weeks in the pooled data from the treatment period of Study 1324 and Study 1774 (Parts A and B). As presented in Table 7, no subjects in Part A of Study 1774 exhibited a treatment-emergent or treatment-boosted ADA response to dupilumab 300 mg QW. In Part B of Study 1774, the incidence of treatment-emergent ADA was approximately 1.3% (N=1/76) and 2.6% (N=2/77) for the 300 mg QW and Q2W regimens, respectively.

Of the three subjects who developed treatment-emergent ADA, two subjects exhibited a low titer and one subject who received dupilumab 300 mg Q2W had a transient ADA response with moderate titer and was also positive for neutralizing antibody (Table 8). The serum dupilumab concentrations of these three subjects with a positive ADA response were within the range of serum dupilumab concentrations in ADA negative subjects with EoE. One subject (300 mg QW) with a low titer reported an adverse event of injection site hypersensitivity that is described in

detail in the adverse events of special interest portion of Section 8.2.4.4. Given the limited number of ADAs observed in the study, the effect of immunogenicity on efficacy, safety, or PK of dupilumab is unknown.

Table 7: Summary of ADA Status and ADA Category by Treatment Group in Adult and Adolescent Subjects With Eosinophilic Esophagitis (Parts A and B, Study 1774)

ADA Status and Category	Placebo n (%)	300 mg QW n (%)	300 mg Q2W n (%)
Part A			
ADA Analysis Set	39 (100%)	42 (100%)	NA
Negative	38 (97.4%)	42 (100%)	NA
Pre-existing Immunoreactivity	1 (2.6%)	0	NA
Treatment-Boosted Response	0	0	NA
Treatment-Emergent Response	0	0	NA
Part B			
ADA Analysis Set	77 (100%)	76 (100%)	77(100%)
Negative	77 (100%)	72 (94.7%)	75 (97.4%)
Pre-existing Immunoreactivity	0	3 (3.9%)	0
Treatment-Boosted Response	0	0	0
Treatment-Emergent Response	0	1 (1.3%)	2 (2.6%)

Source: Adapted from Applicant's BLA 761055 S-040 submission, R668-EE-1774 Part A Appendix 16.1.15 Table 6, R668-EE-1774 Part B Appendix 16.1.15 Table 7.

Table 8: Summary of Treatment Boosted and Treatment Emergent ADA Category and Maximum Titer Category by Treatment Group in Adult and Adolescent Subjects With Eosinophilic Esophagitis (Part B, Study 1774)

ADA Category/Maximum Titer Category	Placebo n (%)	Dupilumab 300 mg Q2W n (%)	Dupilumab 300 mg QW n (%)
ADA Analysis Set	77 (100%)	77 (100%)	76 (100%)
TE			
Persistent	0	0	0
Transient	0	2 (2.6%)	1 (1.3%)
Indeterminate	0	0	0
TE & TB			
Low (<1,000)	0	1(1.3%)	1 (1.3%)
Moderate (1,000 to 10,000)	0	1 (1.3%)	0
High (>10,000)	0	0	0

Source: Applicant's BLA 761055 S-040 submission, Module 2.7.2 Summary of Clinical Pharmacology Studies, Table 8.
Abbreviations: TE = Treatment-emergent, TB = Treatment-boosted.

Comparatively, the treatment-emergent ADA rates in subjects with EoE were lower than previously reported treatment-emergent ADA rates observed during development for other indications (i.e., 5.1%, 9.3%, and 3.5% in the 300 mg Q2W, 200 mg Q2W, and combined placebo

groups, respectively). See clinical pharmacology review by Dr. Dipak Pisal (DARRTS date 10/19/2018) for BLA 760155 S07.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 9: Listing of Clinical Trials Relevant to BLA 761055 S-40

Trial Identity/ NCT no.	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
R668-EE-1774 / NCT# 03633617	Phase 3, R, MC, 3-Part efficacy and safety study Part A was a R, DB, PC, MC study Part B was a R, DB, PC, MC study Part A/C was an OL, MC, extended active treatment period for subjects who completed Part A Part B/C is a R, DB, MC, extended active treatment period for subjects who completed Part B	Part A Dupilumab 300 mg QW SC N=42 Placebo N=39 Part B Dupilumab 300 mg QW SC N = 80 Dupilumab 300 mg Q2W SC N = 81 Placebo N = 79 Part A/C Dupilumab 300 mg QW SC N = 77 Part B/C - *ongoing* Dupilumab 300 mg QW SC Dupilumab 300 mg Q2W SC	Coprimary Endpoints Histologic response, defined as a peak eosinophil count of ≤6 per high-power field across all available esophageal levels at Week 24 AND Reduction in dysphagia symptoms, defined using the absolute change from baseline in the DSQ total score from baseline to Week 24	Part A and B 24 weeks Part C 28 weeks following Part A or Part B An additional 12-week post-treatment follow-up after completing Part C or, if ineligible for Part C, following Part A or B	Part A N=81 Part B: N=240 Part A/C N=77 Part B/C *Ongoing*	Adult and pediatric subjects 12 years of age and older with EoE and dysphagia	Part A Centers 26 Countries 2 Part B Centers 64 Countries 10 Part A/C Centers 26 Countries 2

Trial Identity/ NCT no.	Trial Design	Regimen/Schedule/Route	Study Endpoints	Treatment Duration/Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
Studies to Support Safety							
R668-EE-1324 / NCT# 02379052	Phase 2, R, DB, PC, MC study	Dupilumab 300 mg QW SC N = 23 Placebo N=24	Primary Endpoint Change from baseline in the Straumann dysphagia index at Week 10	12 weeks Post-treatment follow-up: 16 weeks	N=47	Adult subjects with active EoE	Centers 14 Countries 1

Abbreviations: R = randomized, MC = multicenter, DB = double-blind, PC = placebo-controlled, OL = open-label.

7.2. Review Strategy

As stated above, to support the demonstration of safety and effectiveness for dupilumab for the treatment of adult and pediatric patients 12 years of age and older with EoE, the Applicant conducted a three-part clinical trial, Study R668-EE-1774 (Study 1774).

FDA's evaluation of the demonstration of substantial evidence of effectiveness focused on the coprimary endpoints evaluated for both Parts A and B of (1) histologic response (defined as the proportion of subjects achieving a peak esophageal intraepithelial eosinophil count of ≤6 eosinophils per high-power field across all available esophageal levels at Week 24) and (2) reduction in dysphagia symptoms (defined using the absolute change in the Dysphagia Symptom Questionnaire [DSQ] score from baseline to Week 24). Anchor-based analyses were conducted to evaluate the clinical meaningfulness of the symptomatic coprimary endpoint analysis results. Although conducted as part of a single trial, Parts A and B contained distinct subject populations and were analyzed separately.

In addition to the data from Part A and B, the evaluation of safety included a review of safety assessments from subjects from Part A who completed Part C (i.e., the 28-week extended active treatment period) and from subjects who completed R668-EE-1324 (Study 1324). To further support the safety of the 300 mg QW regimen, the Applicant submitted a summary of the available safety information for the 300 mg QW dose in other indications (i.e., asthma and atopic dermatitis).

The efficacy review was performed by the statistical reviewer with input from the clinical reviewer. The safety review was performed by the clinical reviewer with input from the statistical reviewer.

8. Statistical and Clinical Evaluation

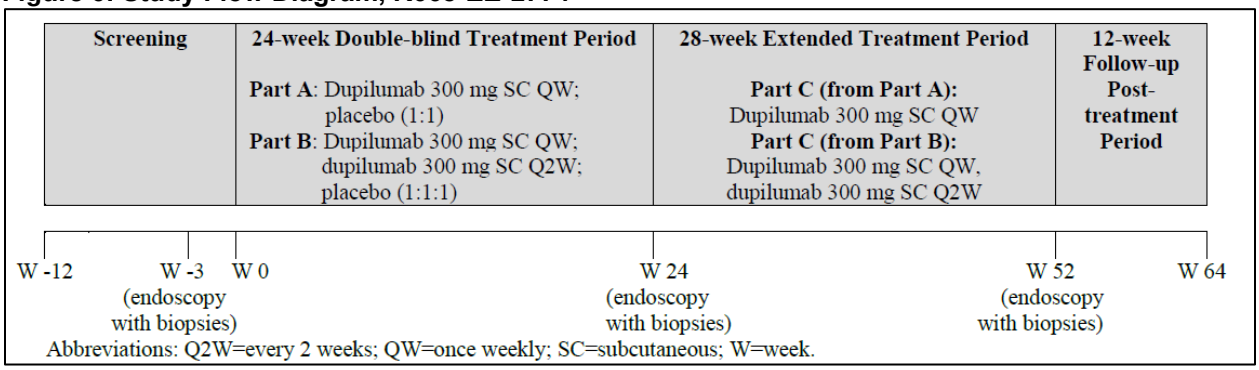
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial R688-EE-1774 Design and Conduct

Trial R668-EE-1774 (Study 1774) was a phase 3 study investigating the efficacy and safety of dupilumab in adults (≥18 years of age) and adolescents (≥12 to <18 years of age) with EoE and dysphagia. The study consisted of three parts. Part A and Part B were phase 3, multi-center, randomized, double-blind, placebo-controlled, 24-week treatment periods, each carried out with a distinct population of subjects (i.e., subjects who participated in Part A were not eligible to participate in Part B). Part C is a phase 3, active treatment extension including subjects who completed Part A or Part B. Data from Parts A and B of Study 1774 were submitted in this sBLA to support the demonstration of effectiveness for dupilumab for the treatment of subjects with EoE and will be the focus of this review. At the time of submission of the sBLA, data from Part C

was only available for subjects who completed Part A and is still being collected for subjects who completed Part B. The overall trial design for Study 1774 is shown in Figure 6.

Figure 6: Study Flow Diagram, R668-EE-1774



Source: Applicant's BLA 761055 S-040 submission, Module 2.7.3 Summary of Clinical Efficacy, Figure 2.

Protocol Amendments

Five protocol amendments were submitted to IND 136142 for Trial R688-EE-1774 as shown in Table 10 below.

Table 10: Summary of Protocol Amendments R688-EE-1774

Amendment Number and Submission Date	Purpose of Amendment
1- Oct 2018	Modifications to the exclusion criteria to exclude subjects with known systemic hypersensitivity to dupilumab or excipients of the drug product, renal impairment defined by eGFR, and severe nephrotic syndrome and clarifications for acceptable contraceptive methods and criteria for resumption of study drug after temporary discontinuation due to a severe laboratory abnormality. These changes were consistent with FDA recommendations.
2- May 2019	Protocol changes including added placebo SC injections to the Q2W dosing group in Part C, EndoFLIP substudy, and revisions to eligibility criteria
3- March 2020	• Add transcriptome sequencing for analyzing RNA expression of eosinophilic esophagitis and type 2 inflammation to the study secondary objectives and endpoints and the quality-of-life questionnaire to collect general health status of EoE subjects. • EoE Endoscopic Reference Score (EoE-EREFS) procedure was revised for centralized reading and scoring • Revised AESI based on FDA recommendations
4- April 2020	To protect patient safety and data integrity during the COVID pandemic by allowing certain study procedures to occur at delayed time points.
5- Nov 2020	• Adjust the sample size for Part B based on the results of Part A, and to add an additional database lock after all patients in Part A complete study Week 52 of Part C • Added primary estimand for primary and secondary endpoints, and clarified sensitivity analysis for coprimary endpoints

Source: Reviewer generated table.

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.

Eligibility Criteria

Selected eligibility criteria for Study 1774 are listed below.

Inclusion Criteria

- A documented diagnosis of EoE including histologic evidence of eosinophilic inflammation on endoscopic biopsy prior to screening, as demonstrated by intraepithelial eosinophilic infiltration (peak cell count ≥15 eosinophils/high power field [eos/hpf]) from at least one esophageal region and performed after at least 8 weeks of treatment with a high dose proton pump inhibitor (PPI) regimen. If the subject discontinued PPI therapy, the biopsy must have been performed within 2 weeks of the date of discontinuation. If a prior (historical) endoscopic biopsy meeting these criteria is not available (or no prior biopsy is available), subjects who meet other clinical and laboratory eligibility criteria will undergo treatment with a high dose PPI regimen for at least 8 weeks during the screening period before their baseline endoscopy/biopsies.
- Baseline endoscopic biopsies with a demonstration on central reading of intraepithelial eosinophilic infiltration (peak cell count ≥15 eos/hpf) in at least 2 of the 3 biopsied esophageal regions (proximal, mid, or distal)
- History (by subject report) of an average of at least 2 episodes of dysphagia (with intake of solids) per week in the 4 weeks prior to screening
- At least 4 episodes of dysphagia in the 2 weeks prior to baseline, documented via eDiary, at least 2 of which require liquids, coughing or gagging, vomiting, or medical attention to obtain relief
- Completed at least 11 of 14 days of the DSQ eDiary data entry in the 2 weeks prior to the baseline visit (visit 3)
- Baseline DSQ score ≥10

Exclusion Criteria

- Body weight ≤40 kg
- Prior participation in a dupilumab clinical trial, or past or current treatment with dupilumab
- Initiation or change of a food-elimination diet regimen or re-introduction of a previously eliminated food group in the 6 weeks prior to screening. Subjects on a food-elimination diet must remain on the same diet throughout the study.
- Other causes of esophageal eosinophilia or the following conditions: hypereosinophilic syndrome and eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome)

Note: Subjects with eosinophilic gastroenteritis are eligible, provided they meet other eligibility criteria.

- Active *Helicobacter pylori* infection
- History of achalasia, Crohn's disease, ulcerative colitis, celiac disease, and prior esophageal surgery
- Any esophageal stricture unable to be passed with a standard, diagnostic, 9 to10 mm upper endoscope or any critical esophageal stricture that requires dilation at screening
- History of bleeding disorders or esophageal varices that, in the opinion of the investigator, would put the subject at undue risk for significant complications from an endoscopy procedure
- Treatment with swallowed topical corticosteroids within 8 weeks prior to baseline

8.1.2. Statistical Analysis Plan

The analysis methods used in Part A and Part B of Study 1774 were generally similar and will be described together.

Populations

The Full Analysis Set (FAS) included all subjects randomized to treatment. The efficacy analyses used the FAS and were based on the treatment allocated by the Interactive Web Response System (IWRS) at randomization. The Safety Analysis Set (SAF) included all randomized subjects who received any study drug during Part A or Part B and is based on the treatment received.

Efficacy Variables

The first coprimary endpoint is the proportion of subjects achieving a histologic response, defined as a peak esophageal intraepithelial eosinophil count of ≤ 6 eos/hpf, at Week 24. A total of 9 mucosal pinch biopsies were collected from 3 esophageal regions: 3 proximal, 3 mid, and 3 distal. The quantity of eosinophils in the most inflamed high-power field (HPF) for each of the 3 esophageal regions (proximal, mid, and distal) was determined by a blinded pathologist at a central pathology reading center. The peak esophageal intraepithelial eosinophil count is the maximum of these quantities.

The second coprimary endpoint is the absolute change in DSQ total score from baseline to Week 24. The DSQ is a PRO that measures the frequency and intensity of dysphagia (Section 15.6.1). The DSQ total score is calculated over a 14-day period as follows:

$$\frac{(sum\ of\ Points\ from\ Items\ 2\ and\ 3\ from\ daily\ DSQ\ eDiary)}{number\ of\ eDiary\ days\ reported\ with\ non-missing\ data} \times 14\ days$$

Source: Applicant's *PRO Dossier for the DSQ* Page 15 of 57, dated December 17, 2021.

First, the daily DSQ total score is calculated as the sum of points from Item 2 and Item 3, with a possible range from 0 to 6. Then, the DSQ total score is calculated as the sum of daily scores over 14 days divided by the number of days reported with non-missing data, with a possible range from 0 to 84. Higher scores indicate more frequent or more severe dysphagia symptom.

Although not considered by the review team to be pivotal to the demonstration of effectiveness, or likely to be informative for patients or prescribers to justify inclusion in the prescribing information, the Applicant identified eight multiplicity controlled secondary endpoints. Two of the secondary endpoints were changes in prespecified transcriptome signatures; the other six include percent change in DSQ total score, percent change in peak esophageal intraepithelial eosinophil count, absolute change in eosinophilic esophagitis histologic scoring system (EoEHSS) mean grade score, absolute change in EoEHSS mean stage score, absolute change in EoE endoscopic reference score (EREFS) total score, and peak esophageal intraepithelial eosinophil count ≤15 eos/hpf at Week 24, where change reflects change from baseline to Week 24. The EoEHSS is a method for evaluating the grade and stage of multiple pathologic features in esophageal biopsies (Collins et al. 2017). The EoE-EREFS is a scoring system for inflammatory and remodeling features of disease that are visible through endoscopy (Hirano et al. 2013).

Calculation of the DSQ Total Score and Sensitivity Analyses

The SAP pre-specified that the calculation of the DSQ total score required at least 8 days of diary entries in the 14-day period; otherwise, the score would be missing. As a prespecified sensitivity analysis, the calculation of the DSQ total score required at least 4 days of diary entries in each week. The SAP also pre-specified that the days when a subject did not eat solid food (i.e., answered “No” to Item 1) would be considered missing for the calculation of the DSQ total score despite diary completion being considered compliant for that day. As a prespecified sensitivity analysis, the daily score was assigned a value of 6 if subjects did not eat solid food due to EoE (i.e., answered “Because of your problems with swallowing solid food” to Item 1a).

Analyses of Efficacy Variables

For the coprimary endpoint of the proportion of subjects achieving histologic response, the estimated difference in proportions between arms and the corresponding 95% confidence interval were computed using the Cochran-Mantel-Haenszel (CMH) approach adjusting for randomization stratification factors (age [group ≥18 vs ≥12 to <18 years of age] and use of PPI at randomization [yes vs no]).

For the coprimary endpoint of absolute change in DSQ total score from baseline to Week 24, the estimated difference in mean change between arms and the corresponding 95% confidence interval were computed using an analysis of covariance (ANCOVA) model with treatment group, randomization stratification factors, and baseline measurement as the covariates.

The analyses of the secondary endpoints were similar to the analyses of the coprimary endpoints, with the appropriate analysis chosen according to whether the outcome was binary or continuous.

Data Imputation and Missing Data Handling

Study 1774 was conducted during the coronavirus disease 2019 (COVID-19) pandemic. For the primary analysis of the proportion of participants achieving a histologic response, the approach for handling missing data depended on whether missing data were related to COVID-19. Missing data due to reasons not related to COVID-19 were handled using non-responder imputation. Of note, subjects receiving a rescue therapy had their values set to missing and were therefore treated as non-responders. Missing data due to COVID-19 were handled using multiple imputation (MI). The MI procedure created 10 multiply imputed datasets using a linear regression approach to impute missing Week 24 peak eosinophil counts. Treatment group, randomization stratification factors, and baseline eosinophil count were included in the imputation model as covariates. The binary endpoint of peak esophageal intraepithelial eosinophil count ≤6 was then derived from the imputed Week 24 peak eosinophil counts. The CMH analysis for the stratified risk difference was performed on each imputed dataset and the results were combined across imputed datasets according to Rubin's formula. The SAP and Clinical Study Report (CSR) for Part A used a modified version of MI that performed the CMH analysis on a single dataset that calculated histologic response based on the average imputed value for each individual with missing data. Finally, in addition to the use of a rescue therapy, two other intercurrent events resulted in the observed Week 24 outcome being set to missing. For Part A, the outcomes for six subjects were set to missing because the Week 24 biopsy was performed after the first dose of the Part C study was administered. For Part B, the outcomes for eleven subjects were also set to missing because COVID-19 restrictions postponed the Week 24 in-clinic visit and there was a treatment interruption during this extended dosing period (i.e., missed 2 or more consecutive doses or 5 or more doses in total during this period). Two additional subjects also had missing outcomes due to reasons related to COVID-19 interruptions.

For the primary analysis of absolute change in DSQ total score, missing data were imputed by MI. Data collected after the use of rescue treatment was set to missing. The MI procedure created 50 multiply imputed datasets using two steps. The first step used the Markov Chain Monte Carlo method to fill in intermittent missing values and the second step filled in the resulting monotone missing data using a regression approach that includes treatment group, randomization stratification factors, and all prior DSQ measurements as covariates. An ANCOVA model was then fit to each completed dataset and results were combined across imputed datasets according to Rubin's formula. Note, for other continuous efficacy variables, missing data due to COVID-19 were imputed by MI, whereas missing data due to reasons not related to COVID-19 were imputed by worst observation carried forward (WOCF).

To assess the robustness of the primary analysis evaluating the change in DSQ total score to the assumption that data are missing at random, a delta-adjusting pattern-mixture approach

(Ratitch et al. 2013) for tipping point analysis was conducted. A sequence of analyses was performed by adding a sequence of negative values in the placebo group and adding a sequence of positive values in the active treatment group for data imputation. A "tipping point" was identified when the result was no longer statistically significant (i.e., p-value >0.05).

Multiplicity Adjustment

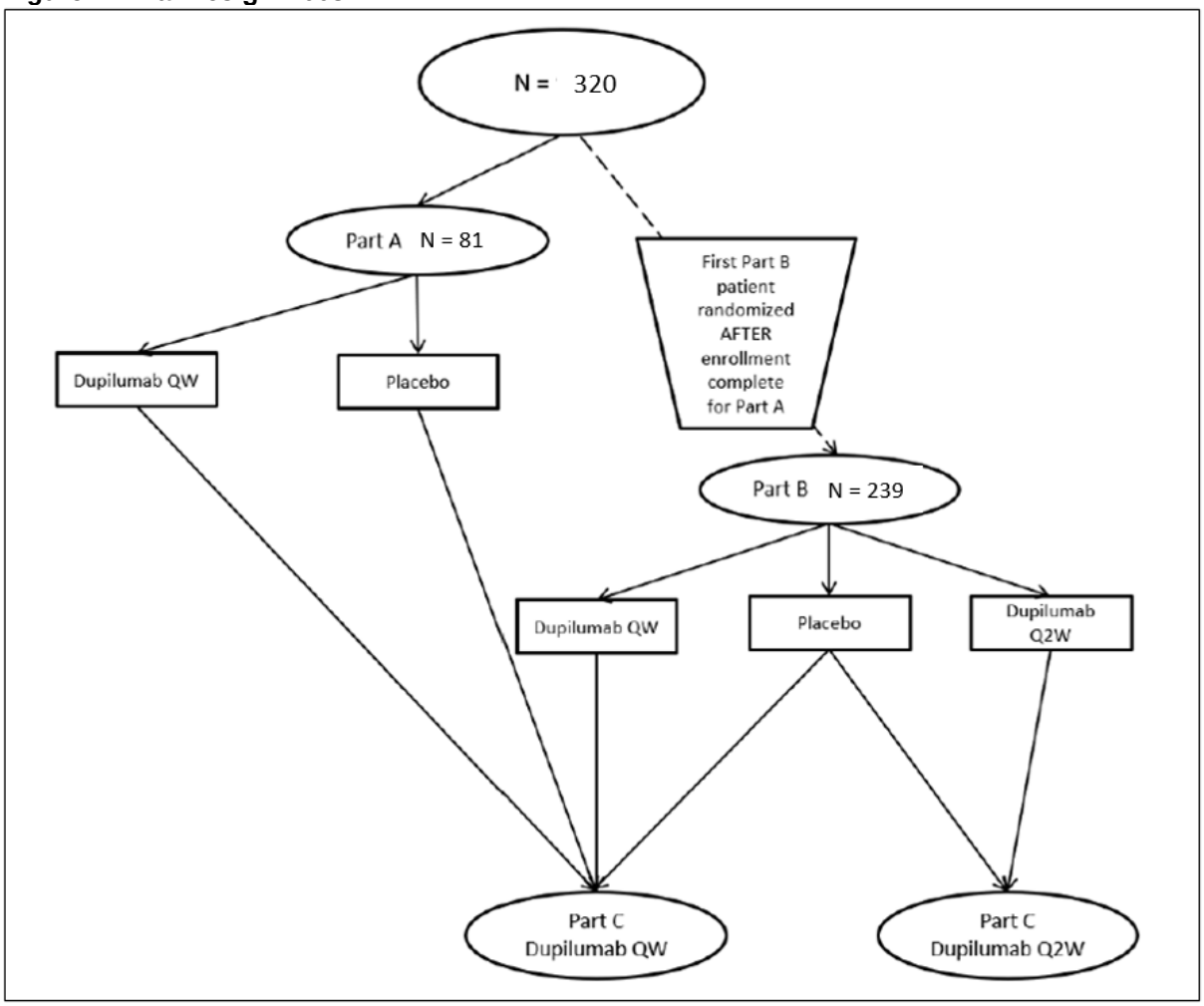
Hypothesis testing was performed independently for Part A and Part B, and the overall type I error rate for each part was controlled at a 2-sided significance level of 0.05. Hypotheses were sequentially tested according to the prespecified hierarchal ordering described in Section 15.4.1. For Part B, the two coprimary and first secondary (percent change from baseline DSQ total score) efficacy endpoints for the 300 mg QW regimen were tested first, followed by the two coprimary and first secondary efficacy endpoints for the 300 mg Q2W regimen. If statistical significance was achieved for all of those endpoints, then testing could proceed to the other secondary endpoints following the specified hierarchal procedure.

8.1.3. Trial Design R688-EE-1774, Parts A and B

The study design for Part A, Part B, and Part C in Study 1774 are shown in Figure 7. Part A was a randomized, double-blind, placebo-controlled 24-week treatment period in which subjects were randomized in a 1:1 ratio to receive subcutaneously (SC) administered dupilumab 300 mg every week or placebo. Upon completion of Part A, eligible subjects could immediately enroll in Part C (Part A/C). Subjects from Part A who did not enter Part C entered a 12-week post-treatment follow-up period.

Part B was a randomized, double-blind, placebo-controlled 24-week treatment period. The study design, procedures, and conduct of Part B were identical to Part A, except Part B had 3 treatment arms versus 2 treatment arms in Part A. Subjects were randomized in a 1:1:1 ratio to receive dupilumab 300 mg QW, dupilumab 300 mg Q2W, or placebo for a 24-week treatment period. At the end of the Part B treatment period, eligible subjects could immediately enroll in Part C (Part B/C portion). Subjects from Part B who did not enter Part C entered a 12-week post-treatment follow-up period.

Figure 7: Trial Design R668-EE-1774



Source: Adapted from Applicant's BLA 761055 S-040 submission Module 5.3.5.1, Protocol R668-EE-1774 Amendment 5, Figure 2.

8.1.4. Results of Analyses

8.1.4.1. Baseline Demographics and Clinical Characteristics

Baseline Demographics

Demographic characteristics for Part A and Part B of Study 1774 are presented in Table 11. Characteristics were generally consistent between Part A, Part B, and those observed in the overall US EoE patient population (Veerappan et al. 2009). The proportions of subjects in the <18 years of age and ≥18 years of age subgroups were balanced across all treatment groups in both Parts A and B and were reflective of the expected population distribution of adolescents vs adults with EoE (Dellon et al. 2014).

For Part A, the majority of subjects were male (60%), and most subjects were White (96%) and not Hispanic or Latino (95%). The mean age was 32 years with a range from 13 to 62 years of

age, and the majority of subjects were adults (75%). The placebo group had a higher proportion of female subjects than the dupilumab 300 mg QW group (46% vs 33%), more subjects in the 18 to less than 40 years of age group (56% vs 31%), and fewer subjects in the 40 to less than 65 years of age group (21% vs 43%).

For Part B, the majority of subjects were male (64%), and most subjects were White (90%) and not Hispanic or Latino (94%). The mean age was 28 years with a range from 12 to 68 years of age and the majority of subjects were adults (67%). The placebo group had a higher proportion of male subjects than either of the dupilumab 300 mg Q2W or dupilumab 300 mg QW groups (73% vs 56%, and 63%, respectively) and fewer subjects in the <60 kg weight group (15% vs 27%, and 26%, respectively).

Overall, the minor differences in baseline demographic characteristics in Part A and Part B did not impact the results of the analyses. Results of subgroup analyses were generally similar to those from the primary analysis of the entire population (See Section 8.1.4.8 Subgroup Analysis).

Table 11: Baseline Demographic Characteristics (Parts A and B, Study 1774, FAS)

	Part A		Part B		
	Placebo N=39	300 mg QW N=42	Placebo N=79[1]	300 mg Q2W N=81	300 mg QW N=80
Age (Years)					
Mean (SD)	29 (13)	34 (16)	28 (13)	28 (13)	29 (14)
Median	28	36	28	23	26
Min : Max	13 : 62	13 : 61	12 : 57	12 : 68	12: 66
Age, n (%)					
12 – < 18 years	9 (23)	11 (26)	26 (33)	27 (33)	26 (33)
18 – < 40 years	22 (56)	13 (31)	38 (48)	35 (43)	38 (48)
40 – < 65 years	8 (21)	18 (43)	15 (19)	18 (22)	15 (19)
≥ 65 years	-	-	-	1 (1)	1 (1)
Ethnicity, n (%)					
Not Hispanic or Latino	38 (97)	38 (90)	74 (94)	77 (95)	75 (94)
Hispanic or Latino	1 (3)	4 (10)	5 (6)	3 (4)	5 (6)
Unknown	-	-	-	1 (1)	-
Race, n (%)					
White	37 (95)	41 (98)	72 (91)	74 (91)	71 (89)
Black or African American	1 (3)	1 (2)	3 (4)	3 (4)	2 (3)
Asian	-	-	1 (1)	1 (1)	3 (4)
Other	1 (3)	-	2 (3)	2 (2)	3 (4)
Not reported	-	-	1 (1)	1 (1)	1 (1)
Sex, n (%)					
Male	21 (54)	28 (67)	58 (73)	45 (56)	50 (63)
Female	18 (46)	14 (33)	21 (27)	36 (44)	30 (38)
Weight (kg)					
Mean (SD)	75 (15)	81 (25)	80 (21)	74 (21)	75 (20)
Median	74	76	77	71	75
Min : Max	43 : 102	41 : 157	44 : 166	40 : 171	40 : 128
Weight Group, n (%)					
<60 kg	9 (23)	9 (21)	12 (15)	22 (27)	21 (26)
≥60 kg	30 (77)	33 (79)	67 (85)	59 (73)	59 (74)

Source: Adapted Applicant's BLA 761055 S-040 submission Module 2.7.3, Summary of Clinical Efficacy, Table 19.

1. One subject randomized to placebo was discontinued from the study prior to receiving investigational product due to a protocol violation. This subject was included in the FAS but not the SAF.

Other Baseline Characteristics (i.e., Disease Characteristics, Prior Therapies, and Co-Morbid Atopic Conditions)

Other baseline characteristics including disease characteristics, prior therapies, and co-morbid atopic diseases for Part A and Part B of Study 1774 are presented in Table 12. Baseline peak eosinophil counts, baseline DSQ total scores, and the proportion of subjects with a history of esophageal dilation were generally consistent between Part A and Part B. The proportion of subjects with a history of prior swallowed topical steroid use, treated with a proton pump inhibitor (PPI) at randomization, and on a food elimination diet at screening were also generally consistent between Part A and Part B.

In Part A and Part B, baseline disease characteristics, prior therapies, and co-morbid atopic conditions were generally balanced between treatment arms. Of note, in Part B, the placebo treatment group had a higher proportion of subjects with a history of esophageal dilation compared to dupilumab 300 mg Q2W and dupilumab 300 mg QW treatment groups (42% vs 32% and 33%, respectively). This small imbalance was not ultimately a concern for the review team as treatment effects were generally similar in subjects with and without a history of esophageal dilation; refer to Section 8.1.4.8 Subgroup Analyses.

Table 12: Baseline Disease Characteristics, Prior Therapies, and Co-morbid Atopic/Allergic Conditions, Study 1774, FAS

	Part A		Part B		
	Placebo N=39	300 mg QW N=42	Placebo N=79[1]	300 mg Q2W N=81	300 mg QW N=80
Duration of Eosinophilic Esophagitis (years)					
Mean (SD)	5 (5)	5 (4)	5 (4)	6 (5)	6 (5)
Median	3	4	3	4	5
Min : Max	0.3 : 20.3	0.1 : 13.7	0.1 : 17.7	0.3 : 23.1	0.1 : 22.1
Baseline Peak Eosinophils Count of Three Regions (/HPF)					
Mean (SD)	97 (55)	83 (41)	84 (41)	88 (50)	89 (47)
Median	85	77	81	81	85
Min : Max	23 : 228	16 : 192	18 : 207	17 : 228	15 : 258
Baseline DSQ Total Score[2] (0-84)					
Mean (SD)	35 (12)	32 (13)	36 (11)	36 (12)	38 (11)
Median	36	34	37	36	41
Min : Max	14 : 63	11 : 52	13 : 56	8 : 70	14 : 57
History of esophageal dilation, n (%)					
Yes	17 (44)	18 (43)	33 (42)	26 (32)	26 (33)
No	22 (56)	24 (57)	46 (58)	55 (68)	54 (68)
History of prior swallowed topical steroid use for EoE, n (%)					
Yes	31 (80)	29 (69)	56 (71)	65 (80)	55 (69)
No	8 (21)	13 (31)	23 (29)	16 (20)	25 (31)
Treated with PPI at randomization, n (%)					
No PPI Use	12 (31)	14 (33)	20 (25)	24 (30)	22 (28)
PPI Use	27 (69)	28 (67)	59 (75)	57 (70)	58 (73)
Food Elimination at Screening, n (%)					
Yes	16 (41)	17 (40)	29 (37)	29 (36)	31 (39)
No	23 (59)	25 (60)	50 (63)	52 (64)	49 (61)

	Part A		Part B		
	Placebo N=39	**300 mg QW N=42**	**Placebo N=79[1]**	**300 mg Q2W N=81**	**300 mg QW N=80**
History of Food Allergy, n (%)					
Yes	18 (46)	19 (45)	41 (52)	42 (52)	46 (58)
No	21 (54)	23 (55)	38 (48)	39 (48)	34 (43)
History of Atopic Dermatitis, n (%)					
Yes	9 (23)	7 (17)	22 (28)	21 (26)	19 (24)
No	30 (77)	35 (83)	57 (72)	60 (74)	61 (76)
History of Asthma, n (%)					
Yes	15 (38)	14 (33)	29 (37)	41 (51)	37 (46)
No	24 (62)	28 (67)	50 (63)	40 (49)	43 (54)
History of Allergic Rhinitis, n (%)					
Yes	23 (59)	26 (62)	52 (66)	52 (64)	49 (61)
No	16 (41)	16 (38)	27 (34)	29 (36)	31 (39)

Source: Adapted from Applicant's BLA 761055 S-040 submission Module 2.7.3 Summary of Clinical Efficacy, Table 20.

1. One subject randomized to placebo was discontinued from the study prior to receiving investigational product due to a protocol violation. This subject was included in the FAS but not the SAF.
2. Calculated from the 14-day period prior to first dose in Part A or B.

8.1.4.2. Treatment Compliance, Concomitant and Rescue Treatment Use

Treatment Compliance

The SAP defined treatment compliance as 100 x N1/N2 where N1 is the number of study drug injections and N2 is the planned number of study drug injections. For Part A, the mean compliance was 99.8%, the interquartile range was 100%-100%, and no subjects had compliance < 80%. For Part B, the mean compliance was 99.1%, the interquartile range was 100% - 100%, and only 3 participants had a compliance < 80%. Compliance was similar across treatment arms.

Rescue Treatment Use

During Part A of Study 1774, no subjects in the dupilumab 300 mg QW group and 4 subjects (10%) in the placebo group received rescue medication. Additionally, 1 subject (3%) in the placebo group received a rescue procedure of esophageal dilation.

In Part B, 1 subject (1%) in the dupilumab 300 mg QW group and 1 subject (1%) in the placebo group received rescue medication. In addition, 1 subject (1%) in the dupilumab 300 mg Q2W group and 1 subject (1%) in the placebo group received the rescue procedure of esophageal dilation. Finally, 1 subject (1%) in the dupilumab 300 mg QW group received a rescue procedure of pylorus dilation. Although the dilation procedure was extraesophageal, this procedure was performed as a rescue therapy for clinical symptoms, and therefore the subject was treated as having received a rescue therapy in all statistical analyses.

During the Part A/C treatment period, 3 subjects (8%) in the placebo/dupilumab 300 mg QW arm received rescue medication; however, these subjects initiated rescue medication during Part A and continued use during Part A/C. Additionally, 1 subject (3%) in the dupilumab 300 mg QW/dupilumab 300 mg QW group underwent an esophageal dilation during the scheduled Week 52 endoscopy.

Although the use of rescue treatment was more common in subjects that received placebo than dupilumab in Part A, an imbalance across treatment groups was not observed in Part B. The small number of subjects that required rescue treatment during Study 1774 limit the ability to conduct meaningful comparisons of rescue treatment use across groups.

8.1.4.3. Subject Disposition

Subject disposition for Parts A and B is shown in Table 13. Overall, few subjects had a premature discontinuation from study treatment or from participation in Part A or B. Study 1774 was performed during the COVID-19 pandemic. During Part A, 1 (3%) and 3 (7%) subjects in the placebo and 300 mg QW treatment arm, respectively, did not have their Week 24 visit performed prior to the database lock due to COVID. Of note, in the primary analysis of the histologic endpoint at Week 24, the missing data for these subjects was imputed using MI.

Additionally, 1 subject (3%) in the placebo arm wanted to withdraw from the study because of a planned pregnancy but could not schedule the early termination visit due to COVID.

Table 13: Subject Disposition (Study 1774, FAS)

	Part A		Part B		
	Placebo N=39	**300 mg QW N=42**	**Placebo N=79[1]**	**300 mg Q2W N=81**	**300 mg QW N=80**
Subjects who completed Week 24[2], n(%)	36 (92)	37 (88)	74 (94)	79 (98)	75 (94)
Ongoing at the time of database lock, n(%)	2 (5)	3 (7)			
COVID-19	1 (3)	3 (7)			
Unconfirmed early termination visit	1 (3)				
Subjects who Discontinued treatment, n(%)	1 (3)	2 (5)	5 (6)	2 (2)	5 (6)
Reason for treatment discontinuation					
Due to COVID-19			2 (3)		
Not Due to COVID-19	1 (3)	2 (5)	3 (4)	2 (2)	5 (6)
Protocol Deviation					
Adverse Event		1 (2)	2 (3)	1 (1)	1 (1)
Pregnancy	1 (3)				
Lack of Efficacy					
Physician Decision					1 (1)
Withdrawal by Subject[3]		1 (2)	1 (1)		2 (3)
Lost to Follow-up					1 (1)
Death					
Other					

Source: Adapted from Applicant's BLA 761055 S-040 submission Module 2.7.3, Summary of Clinical Efficacy, Table 17.

1. One subject randomized to placebo was discontinued from the study prior to receiving investigational product due to a protocol violation. This subject was included in the FAS but not the SAF.
2. A subject is considered to complete Week 24 if their Week 24 visit had occurred and was documented.
3. Subjects listed as "withdrawal by subject" had a withdrawal of consent.

8.1.4.4. Protocol Violations/Deviations

In Part A of Study 1774, 101 protocol deviations in 47 subjects were classified as important. These 101 deviations were related to procedures not being performed (53), treatment compliance (21), receipt of an excluded concomitant treatment (11), failure to satisfy entry criteria (6), procedure performed outside of study window (5), randomization error (4), and visit not being performed (1). Important protocol violations were evenly distributed across treatment arms, with 53 violations occurring in 21 subjects (50%) from the dupilumab 300 mg QW arm and 48 violations occurring in 26 subjects (67%) from the placebo arm.

In Part B of Study 1774, 430 protocol deviations in 153 subjects were classified as important. These 430 deviations were related to procedures not being performed (198), treatment compliance (96), receipt of an excluded concomitant treatment (44), failure to satisfy entry

criteria (21), procedure performed outside of study window (3), receipt of wrong treatment or incorrect dose (27), randomization error (11), visit performed out of window (27), and visit not being performed (3). Important protocol violations were evenly distributed across arms, with 148 violations occurring in 49 subjects (61%) from the dupilumab 300 mg QW arm, 138 violations occurring in 54 subjects (67%) from the dupilumab 300 mg Q2W arm and 144 violations occurring in 50 subjects (63%) from the placebo arm.

Although classified as important, these protocol violations were not considered likely to significantly impact the results of the analyses or the overall conclusions from the study. Of note, the largest grouping of important protocol violations was related to procedures not being performed. Within this grouping, 30 of the 53 important protocol violations in Part A and 101 of the 198 protocol violations in Part B were instances when a subject missed > 6 DSQ assessments in a 14-day window after the baseline visit. There were also 10 instances of completing fewer than 11 DSQ assessments at the baseline visit that were categorized as a failure to satisfy entry criteria.[5] Other frequently reported missed procedures were pregnancy tests, baseline PGIS assessments, and EOE-EREFS assessments. The second largest grouping of protocol violations was related to treatment compliance, with the most frequent violation being a missed administration of the drug. However, the overall rate of compliance was high as discussed in Section 8.1.4.2.

8.1.4.5. Analyses of Coprimary Endpoints

As EoE is a clinicopathologic disorder in which clinical symptoms and histologic activity can vary independently, demonstration of efficacy on both histologic and symptomatic coprimary endpoints is needed to support a determination of benefit. Parts A and B of Study 1774 evaluated identical coprimary endpoints of:

1. Histologic response (defined as a peak eosinophil count of ≤6 per high-power field across all available esophageal levels) at Week 24 and
2. Reduction in dysphagia symptoms (defined using the absolute change from baseline in the DSQ total score from baseline to Week 24).

This review will focus on the results from Part A and Part B of Study 1774. Results from Part A/C are described in Section 15.5.7 of the Appendix.

Histologic Response

As shown in Table 14, in Part A of Study 1774, the dupilumab 300 mg QW treatment group had a statistically significantly higher proportion of histologic responders (59.5%) in comparison with those treated with placebo (5.1%), p-value <0.0001. Multiple imputation was used to handle missing data due to COVID-19, while non-responder imputation was used to handling missing data for all other reasons. The results for the treatment difference, 95% confidence

[5] Three of these instances are not included in the 101 and 430 counts of important protocol violations, as they were only identified at the time of data analysis and were not identified by investigators.

interval, and p-value reported in Table 14 were based on statistical inference using Rubin's rules to combine results across multiply imputed datasets.[6]

Table 14: Subjects With Peak Esophageal Intraepithelial Count ≤ 6 eos/hpf at Week 24 (Part A, Study 1774)

Study/Treatment	Subjects With Peak eos/hpf Count ≤ 6 n (%)[1]	Difference (95% CI)[2]	p-value[2]
Dupilumab 300 mg QW (N = 42)	25 (59.5)	57.0 (40.9, 73.1)	<0.0001
Placebo (N = 39)	2 (5.1)		

Source: Reviewer analysis using Applicant submitted data PKESO.xpt; based on Clinical Study Report for R668-EE-1774 Part A (Table 20, p 66).

1. For the number and percentage of subjects with Peak eos/hpf ≤ 6, the average peak count across the multiply imputed datasets was used for subjects with missing data.
2. The reported difference, 95% CI, and p-value were calculated using the CMH approach, adjusting for randomization stratification factors. Rubin's rules were used to combine results across multiply imputed datasets.

Abbreviations: CI = Confidence Interval, CMH = Cochran-Mantel-Haenszel, eos/hpf = eosinophils/high-power field, QW = every week.

Similar results for histologic response were observed in Part B of Study 1774. As shown in Table 15, both the dupilumab 300 mg QW and the dupilumab 300 mg Q2W treatment groups had statistically significantly higher proportions of histologic responders (58.8% and 60.5%, respectively) in comparison with those treated with placebo (6.3%), p-values <0.0001. The Applicant's reported results for Part B used Rubin's rules for statistical inference on multiply imputed data and match the results reported in Table 15.

Table 15: Subjects With Peak Esophageal Intraepithelial Count ≤ 6 eos/hpf at Week 24 (Part B, Study 1774)

Study/Treatment	Subjects with Peak eos/hpf Count ≤ 6 n (%)[1]	Difference (95% CI)[2]	p-value[2]
Dupilumab 300 mg QW (N=80)	47 (58.8)	53.5 (41.2, 65.8)	<0.0001
Dupilumab 300 mg Q2W (N=81)	49 (60.5)	56.0 (43.4, 68.5)	<0.0001
Placebo (N=79)	5 (6.3)		

Source: Clinical Study Report for R668-EE-1774 Part B (Table 21, p 83); verified by reviewer using Applicant submitted data PKESO.xpt.

1. For the number and percentage of subjects with Peak eos/hpf ≤ 6, the average peak count across the multiply imputed datasets was used for subjects with missing data.
2. The reported difference, 95% CI, and p-value were calculated using the CMH approach, adjusting for randomization stratification factors.

Abbreviations: CI = Confidence Interval, CMH = Cochran-Mantel-Haenszel, eos/hpf = eosinophils/high-power field, QW = every week, Q2W = every other week.

In Part A, 24.7% (20/81) of subjects had missing values at Week 24. However, 4 subjects had missing data due to COVID-19 related reasons and 6 subjects had missing data due to their

[6] The results reported in Table 20 (p 66) of the Applicant's CSR for R668-EE-1774 Part A did not use Rubin's rules to combine results from multiply imputed datasets and instead took the average value across all multiply imputed datasets as the imputed value for subjects with missing data. The method used by the Applicant in the CSR does not appropriately account for uncertainty in the imputed values and is not statistically justified.

measurement coming after enrollment into Part C. Both reasons were considered unrelated to treatment. In Part B, only 10.4% (25/240) of subjects had missing values at Week 24, with 13 subjects having missing data due to COVID-19 related reasons. Given the large effect size, the statistically significant result was robust to all sensitivity analyses. Using an imputation method where all subjects with missing data in the dupilumab arms would be imputed as non-responders and all subjects with missing data in the placebo arms would be imputed as responders, the dupilumab arms would still have had a statistically significantly higher proportion of histologic responders as compared to the placebo arms. Therefore, missing data did not impact the coprimary endpoint results for histologic response. Missing data for the histologic coprimary endpoint analyses is discussed further in Section 15.5.3 and summarized in Table 53 below.

Improvement in Dysphagia Symptoms

In Part A, the estimated mean absolute changes in the DSQ total score from baseline in the dupilumab 300 mg QW and placebo arms were -21.9 and -9.6 points, respectively (Table 16). The estimated difference (dupilumab minus placebo) was -12.3 points (95% CI: -19.1, -5.5), and this difference was statistically significant (p = 0.0004), demonstrating a greater improvement in DSQ total scores for the dupilumab 300 mg QW arm.

Table 16: Absolute Change From Baseline in DSQ Total Score at Week 24 (Part A, Study 1774)

Study/Treatment	Mean Baseline	LS Mean Change[1]	LS Mean Difference vs Placebo (95% CI)[1]	p-value[1]
Dupilumab 300 mg QW (N=42)	32.3	-21.9	-12.3 (-19.1, -5.5)	0.0004
Placebo (N=39)	35.1	-9.6		

Source: Clinical Study Report for R668-EE-1774 Part A (Table 21, p 72); verified by reviewer using Applicant submitted data DSQSC.xpt.

1. The reported mean, difference, 95% CI, and p-value were calculated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as the covariates.

Abbreviations: ANCOVA=analysis of covariance, CI = Confidence Interval, DSQ = Dysphagia Symptom Questionnaire, LS = Least Squares, QW = once weekly.

In Part B, the estimated mean absolute changes in the DSQ total score from baseline in the dupilumab 300 mg QW and placebo arms were -23.8 and -13.9 points, respectively (Table 17). The estimated difference (dupilumab minus placebo) was -9.9 points (95% CI: -14.8, -5.0), and this difference was statistically significant (p = <0.0001), again demonstrating a greater improvement in DSQ total scores in the dupilumab 300 mg QW arm.

However, the estimated mean absolute change in the DSQ total score from baseline in the dupilumab 300 mg Q2W of -14.4 points was similar to that observed in the placebo arm. The resulting difference, as compared to the placebo arm, was -0.5 points (95% CI: -5.4, 4.4), and this difference was not found to be statistically significant (p = 0.84). Therefore, the dupilumab 300 mg Q2W regimen did not demonstrate improvement over placebo on the assessment of the symptomatic coprimary endpoint.

Table 17: Absolute Change From Baseline in DSQ Total Score at Week 24 (Part B, Study 1774)

Study/Treatment	Mean Baseline	LS Mean Change[1]	LS Mean Difference vs Placebo (95% CI)[1]	p-value[1]
Dupilumab 300 mg QW (N=80)	38.4	-23.8	-9.9 (-14.8, -5.0)	<0.0001
Dupilumab 300 mg Q2W (N=81)	35.6	-14.4	-0.5 (-5.4, 4.4)	0.84
Placebo (N=79)	36.1	-13.9		

Source: Clinical Study Report for R668-EE-1774 Part B (Table 23, p 93); verified by reviewer using Applicant submitted data DSQSC.xpt.

1. The reported mean, difference, 95% CI, and p-value were calculated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as the covariates.

Abbreviations: ANCOVA=analysis of covariance, CI = Confidence Interval, DSQ = Dysphagia Symptom Questionnaire, LS = Least Squares, QW = once weekly, Q2W = every other week.

In Study 1774, 18.5% (15/81) of the subjects in Part A and 22.9% (55/240) of the subjects in Part B had missing values for the DSQ total score at Week 24. However, sensitivity analyses (Section 15.5.4) indicate that the primary analysis for the difference in the absolute change in the DSQ total score between the dupilumab 300 mg QW arm and the placebo arm was robust to assumptions about the missing data. Missing data for the symptomatic coprimary endpoint analyses is discussed further in Section 15.5.3 and summarized in Table 54.

The differences in the absolute change in DSQ total scores, between the dupilumab 300 mg QW treatment group and the placebo group, were similar in subgroups defined by sex and race, as compared to the difference observed in the entire study population as discussed in Section 8.1.4.8. However, the absolute change in DSQ total scores in the adolescent subpopulation was slightly lower and will be further discussed in Section 8.1.4.7.

The absolute change in DSQ total score from baseline over time is described in Section 15.5.6, with the observed difference between the dupilumab 300 mg QW and placebo arms occurring early after randomization and being sustained for the duration of the treatment period. The distribution of the change in DSQ total score from baseline to Week 24 is discussed in Section 8.1.5. Also discussed in Section 8.1.5, the results of anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B is representative of a clinically meaningful within-subject improvement.

8.1.4.6. Analyses of Secondary Endpoints

The review team does not consider the secondary endpoints to be pivotal to the demonstration of effectiveness or likely to be informative for patients or prescribers to justify inclusion in the prescribing information. Thresholds for clinically meaningful changes in the EoEHHS or EoE-EREFS scores have not been established to enable results of these assessments to be interpretable or informative for patients or prescribers. Additionally, in Part B, both dupilumab arms showed similar efficacy for the endoscopic and histologic secondary endpoints, despite the dupilumab 300 mg Q2W failing to demonstrate efficacy for the symptomatic coprimary endpoint. Moreover, because of the prespecified approach for controlling the Type I error rate, the Applicant is unable to demonstrate superiority for seven of the secondary endpoints based on the multiple testing procedure for Part B. The endpoints for Part A and Part B were analyzed according to prespecified testing hierarchies to control the Type 1 error rate (Section 15.4.1).

In Part A, the study successfully demonstrated that dupilumab 300 mg QW provided a statistically significant improvement ($p \leq 0.0002$), as compared to placebo, for all secondary endpoints. In Part B, however, all secondary endpoints except for percent change in DSQ total score for the dupilumab 300 mg QW group were ordered below the coprimary endpoints in the dupilumab 300 mg Q2W group. Because the symptomatic coprimary endpoint of absolute change in DSQ total score from baseline to Week 24 did not reach nominal statistical significance for the Q2W group, the Applicant cannot claim success on those secondary endpoints in Part B despite the nominally significant p-values.

The results for the six secondary endpoints unrelated to transcriptome signatures are presented in Table 18 for the dupilumab 300 mg QW and placebo groups. The dupilumab 300 mg Q2W dose showed similar improvements over placebo for the endoscopic and histologic secondary endpoints but did not show an improvement for the percent change in the DSQ total score ($p = 0.52$).

Table 18: Secondary Efficacy Endpoints (Parts A and B, Study 1774)

	Part A			Part B		
	Dupilumab 300 mg QW N=42	Placebo N=39	Difference vs Placebo (95% CI)	Dupilumab 300 mg QW N=80	Placebo N=79	Difference vs Placebo (95% CI)
Percent change in DSQ Total Score, LS mean (SE)[1]	-69.2 (7.4)	-31.7 (8.1)	-37.5 (-57.2, -17.8)	-64.3 (5.1)	-41.4 (5.3)	-22.9 (-36.3, -9.5)
Percent change in peak count, LS mean (SE)[1]	-71.2 (6.9)	-3.0 (7.6)	-68.3 (-86.9, -49.6)	-80.2 (8.3)	8.4 (10.1)	-88.6 (-112.2, -65.1)
Absolute change in EoEHSS mean grade score (0-3[2]), LS mean (SE)[1]	-0.76 (0.06)	-0.00 (0.06)	-0.76 (-0.91, -0.61)	-0.83 (0.04)	-0.15 (0.05)	-0.68 (-0.79, -0.57)
Absolute change in EoEHSS mean stage score (0-3[2]), LS mean (SE)[1]	-0.75 (0.06)	-0.01 (0.06)	-0.74 (-0.88, -0.60)	-0.80 (0.04)	-0.13 (0.04)	-0.67 (-0.78, -0.57)
Absolute change in EoE-EREFS (0-18[3]), LS mean (SE)[1]	-3.2 (0.4)	-0.3 (0.4)	-2.9 (-3.9, -1.8)	-4.5 (0.4)	-0.6 (0.4)	-3.8 (-4.8, -2.9)
Proportion of subjects achieving peak count of <15 eos/hpf, n (%)[4]	27 (64.3)	3 (7.7)	59.4 (43.3, 75.5)	66 (82.5)	6 (7.6)	74.9 (64.3, 85.5)

Source: Clinical Study Report for R668-EE-1774 Part A (Table 17, p 62-63), Clinical Study Report R668-EE-1774 Part B (Table 19, p 78); verified by reviewer using Applicant submitted data DSQSC.xpt, HGSC.xpt, HSSC.xpt, PKESO.xpt.

1. For continuous variables, the results are based on an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as the covariates.
2. EoEHSS scores range from 0 to 3; higher scores indicate greater severity and extent of histological abnormalities
3. EoE-EREFS overall scores range from 0 to 18; higher scores indicate worse endoscopic inflammatory and remodeling findings
4. For the number and percentage of subjects with Peak eos/hpf < 15, the average peak count across the multiply imputed datasets was used for subjects with missing data. The difference and confidence interval were calculated using the CMH approach, adjusting for randomization stratification factors.

Abbreviations: ANCOVA=analysis of covariance, CI = Confidence Interval, CMH = Cochran-Mantel-Haenszel, DSQ = Dysphagia Symptom Questionnaire, eos/hpf = eosinophils/high-power field, LS = Least Squares, QW = once weekly, Q2W = every other week.

8.1.4.7. Analyses of the Coprimary Endpoints in Adolescent Subjects

Although the proportion of adolescent subjects relative to the total number of subjects in Study 1774 was acceptable and consistent with the expected population distribution of adolescents vs adults with EoE (Dellon et al. 2014), the small sample size limited the ability to draw definitive conclusions from independent analyses of the subgroup. Given that disease presentation, progression, and anticipated response to treatment is expected to be similar between adults and adolescents, the determination of efficacy in the adolescent subgroup is supported by the results of efficacy analyses from the overall study population. However, when the analysis for the coprimary endpoint of absolute change in DSQ score was performed separately in the adolescent and adult populations (Table 19), the estimated treatment effect was lower in the adolescent population. Using the combined populations from Part A and Part B, the differences (dupilumab 300 mg QW minus placebo) of the change in mean DSQ score in the adolescent and adult populations were -3.9 (95% CI = -11.9, 4.2) and -13.5 (95% CI = -17.9, -9.1), respectively.

Table 19: Absolute Change From Baseline in DSQ Total Score at Week 24 by Age Group (Study 1774)

Study/Treatment	LS Mean Change[1]	LS Mean Difference vs Placebo (95% CI)[1]
Part A		
12-<18 years old		
Dupilumab 300 mg QW (N = 11)	-23.9	-7.9 (-21.8, 6.0)
Placebo (N = 9)	-15.9	
≥18 years old		
Dupilumab 300 mg QW (N = 31)	-19.2	-13.7 (-21.6, -5.7)
Placebo (N = 30)	-5.6	
Part B		
12-<18 years old		
Dupilumab 300 mg QW (N = 26)	-19.5	-3.1 (-12.8, 6.5)
Dupilumab 300 mg Q2W (N = 27)	-12.1	4.3 (-5.1, 13.7)
Placebo (N = 26)	-16.4	
≥18 years old		
Dupilumab 300 mg QW (N = 54)	-26.7	-13.3 (-19.0, -7.7)
Dupilumab 300 mg Q2W (N = 54)	-16.4	-3.1 (-8.8, 2.7)
Placebo (N = 53)	-13.4	
Part A and B		
12-<18 years old		
Dupilumab 300 mg QW (N = 37)	-21.1	-3.9 (-11.9, 4.2)
Placebo (N = 35)	-17.2	
≥18 years old		
Dupilumab 300 mg QW (N = 85)	-23.6	-13.5 (-17.9, -9.1)
Placebo (N = 83)	-10.1	

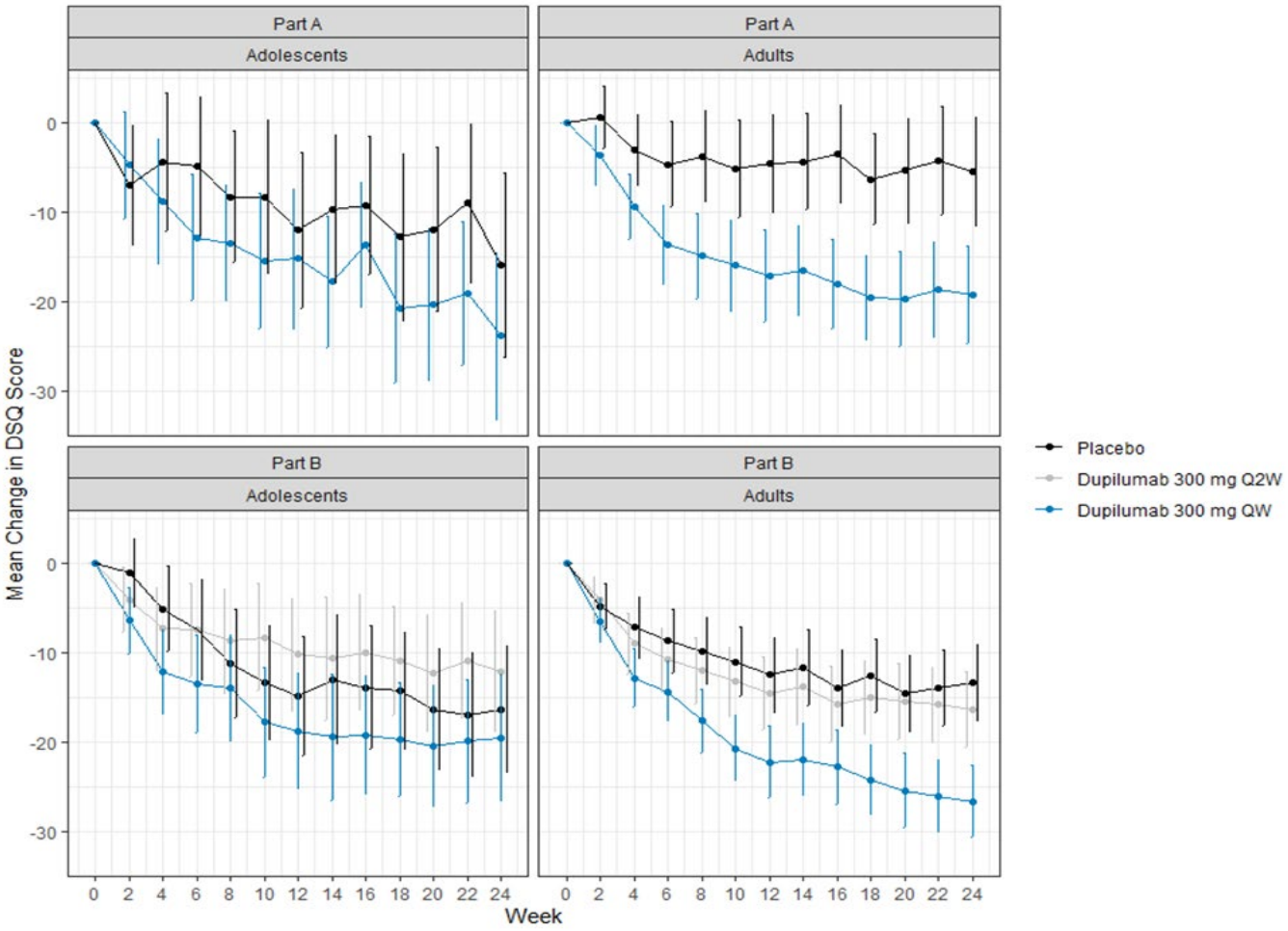
Source: ISS/ISE for R668-EE-1774 (Table 6.1.2.1/1, p309-310); verified by reviewer using Applicant submitted data DSQSC.xpt.

1. The reported mean, difference, and 95% CI were calculated using an ANCOVA model with treatment group, randomization stratification factors, baseline measurement, and, when applicable, study part as the covariates.

Abbreviations: ANCOVA=analysis of covariance, CI = Confidence Interval, DSQ = Dysphagia Symptom Questionnaire, LS = Least Squares, QW = once weekly, Q2W = every other week.

Although the absolute change in DSQ score was lower in the adolescent population, the precision of the estimated change in DSQ score in the adolescent population is limited by the comparatively small sample size for the adolescent population that received either dupilumab 300 mg QW or placebo in Study 1774 (n=20 for Part A, n=52 for Part B). Furthermore, in the combined population, the absolute change in the DSQ score in the dupilumab 300 mg QW arm is similar in the adolescent and adult populations (-21.1 vs -23.6). The less robust results for the adolescent subpopulation are therefore attributable to the larger decrease in the mean DSQ score observed for the adolescents in the placebo group. Given that disease progression in untreated individuals is expected to be similar in adolescents and adults, there is an *a priori* expectation that the response to effective treatment (e.g., decrease in DSQ scores) should be similar in the adult and adolescent subpopulations. To further evaluate the observed symptomatic response, the review team examined the mean change in 14-day DSQ total score over time by treatment arm and age group (Figure 8). As shown below, consistent and progressive improvement over placebo was observed for both adolescent and adult subjects that received dupilumab 300 mg QW throughout the treatment period.

Figure 8: LS Mean[1] Change and 95% Confidence Interval[2] in 14-Day DSQ Total Score From Baseline Over Time in Adolescents and Adults (Study 1774)



Source: Reviewer analysis using Applicant submitted data DSQSC.xpt.

1. The reported means were calculated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as covariates.
2. Vertical bars indicate 95% Confidence Intervals.

Abbreviations: ANCOVA=analysis of covariance, DSQ = Dysphagia Symptom Questionnaire, LS = Least Squares, QW = once weekly, Q2W = every other week.

The analysis for the coprimary endpoint of peak esophageal intraepithelial count was also repeated separately in the adolescent and adult subpopulations (Table 20). Using the combined populations from Part A and Part B, the differences of histological response rates were relatively similar in the adolescent and adult populations, with respective values of 47.9% (95% CI = 30.0, 65.8) and 57.6% (95% CI = 45.8, 69.4).

Table 20: Subjects With Peak Esophageal Intraepithelial Count ≤ 6 eos/hpf at Week 24, Subgroup Analysis by Age Group (Study 1774)

Study/Treatment	Peak Count <6 eos/hpf, N (%)[1]	Rate Difference (95% CI)[2]
Part A		
12-<18 years old		
Dupilumab 300 mg QW (N = 11)	4 (36.4)	36.5 (8.1, 65.0)
Placebo (N = 9)	0 (0.0)	
≥ 18 years old		
Dupilumab 300 mg QW (N = 31)	21 (67.7)	63.9 (45.4, 82.4)
Placebo (N = 30)	2 (6.7)	
Part B		
12-<18 years old		
Dupilumab 300 mg QW (N = 26)	15 (57.7)	52.2 (30.1, 74.4)
Dupilumab 300 mg Q2W (N = 27)	13 (48.1)	42.1 (18.9, 65.4)
Placebo (N = 26)	2 (7.7)	
≥ 18 years old		
Dupilumab 300 mg QW (N = 54)	32 (59.3)	54.1 (39.1, 69.1)
Dupilumab 300 mg Q2W (N = 54)	36 (66.7)	62.8 (48.2, 77.5)
Placebo (N = 53)	3 (5.7)	
Part A and B		
12-<18 years old		
Dupilumab 300 mg QW (N = 37)	19 (51.4)	47.9 (30.0, 65.8)
Placebo (N = 35)	2 (5.7)	
≥ 18 years old		
Dupilumab 300 mg QW (N = 85)	53 (62.4)	57.6 (45.8, 69.4)
Placebo (N = 83)	5 (6.0)	

Source: ISS/ISE for R668-EE-1774 (Table 6.1.1.1/1, p281-282); verified by reviewer using Applicant submitted data PKESO.xpt.

1. For the number and percentage of subjects with Peak eos/hpf ≤ 6, the average peak count across the multiply imputed datasets was used for subjects with missing data.
2. The reported difference and 95% CI were calculated using the CMH approach, adjusting for randomization stratification factors and, when applicable, study part.

Abbreviations: CI = Confidence Interval, CMH = Cochran-Mantel-Haenszel, eos/hpf = eosinophils/high-power field, QW = every week, Q2W = every other week.

After considering the available evidence, the review team determined that the smaller estimated treatment difference in the adolescent subpopulation for the symptomatic coprimary endpoint of absolute change in DSQ total score between dupilumab 300 mg QW and placebo groups is likely related to the small sample size assessed and greater placebo response rate, as compared to adult subjects, than an actual difference in response to dupilumab in adolescent subjects. It is unclear if the greater placebo response rate observed in adolescent subjects is due to intrinsic differences in reporting or chance findings in this small subgroup. The established similarity in disease presentation and progression between adolescent patients and adults with EoE and the similar decrease in absolute change in DSQ total score throughout the study period supported the demonstration of efficacy on the symptomatic coprimary endpoint for the entire population studied in Trial 1774 (i.e., adults and adolescent subjects ≥12 years of age).

8.1.4.8. Subgroup Analyses

The primary analysis for the coprimary endpoint of peak esophageal intraepithelial eosinophil count ≤6 was also repeated in subgroups defined by sex (male, female), race (White, Non-White), and history of esophageal dilation (yes, no) (Table 21). Subgroup results by ethnicity were not examined due to the small number of enrolled subjects who identified as Hispanic or Latino (refer to Section 8.1.4.1). Subgroup results by age (adult versus adolescent) are described in Section 8.1.4.7). History of esophageal dilation was assessed as a subgroup analysis to examine potential confounding caused by an imbalance in the percentage of subjects with a history of esophageal dilation. The dupilumab 300 mg QW arm had a lower percentage of subjects with a history of esophageal dilation as compared to the placebo arm (32.5% vs 41.8%). Although dilation is not anticipated to have an effect on the histologic activity or pathogenesis of EoE, dilation may exacerbate the variability between histologic findings and clinical symptoms (Safroneeva et al. 2022). Whether dilation affects response to therapy remains a knowledge gap. Due to the smaller sample sizes, subgroup analyses are reported for the pooled cohort containing subjects from both Part A and Part B. Results from subgroup analyses were generally similar to those from the primary analysis in the entire population. The observed treatment effect was slightly higher in the non-White group, but the sample size (N = 19) of the non-White group in Study 1774 limited the ability to form definitive conclusions about the relative efficacy in the non-White population.

Table 21: Subjects With Peak Esophageal Intraepithelial Count ≤ 6 eos/hpf at Week 24 by Subgroup[1] (Study 1774)

Group	Placebo Rate[2], N (%)	Dupilumab 300 mg QW Rate[2], N (%)	Rate Difference[3] (95% CI)
Sex			
Male			
300 mg QW (N = 78) vs Placebo (N = 79)	3 (3.8)	41 (52.6)	50.5 (38.1, 62.8)
Female			
300 mg QW (N = 44) vs Placebo (N = 39)	4 (10.3)	31 (70.5)	62.1 (45.9, 78.3)
Race			
White			
300 mg QW (N = 112) vs Placebo (N = 109)	6 (5.5)	63 (56.3)	53.0 (42.7, 63.3)
Other (Non-White)			
300 mg QW (N = 10) vs Placebo (N = 9)	1 (11.1)	9 (90.0)	75.2 (33.9, 116.5)
History of Esophageal Dilation			
Yes			
300 mg QW (N = 44) vs Placebo (N = 50)	2 (4.0)	27 (61.4)	56.8 (41.3, 72.4)
No			
300 mg QW (N = 78) vs Placebo (N = 68)	5 (7.4)	45 (57.7)	52.2 (39.2, 65.3)

Source: Summary of Clinical Efficacy for R668-EE-1774 (Figure 18, p131); verified by reviewer using Applicant submitted data PKESO.xpt.

1. Analysis includes subjects from Part A and Part B.
2. For the number and percentage of subjects with Peak eos/hpf ≤ 6, the average peak count across the multiply imputed datasets was used for subjects with missing data.
3. The reported difference and 95% CI were calculated using the CMH approach, adjusting for randomization stratification factors and study part.

Abbreviations: CI = Confidence Interval, CMH = Cochran-Mantel-Haenszel, eos/hpf = eosinophils/high-power field, QW = every week.

The primary analysis for the coprimary endpoint of absolute change from baseline in DSQ total score was also repeated in subgroups defined by sex (male, female), race (White, Non-White), and history of esophageal dilation (Table 22). Results from subgroup analyses were again generally similar to those from the primary analysis in the entire population. The observed treatment effect was slightly higher in the non-White group, but the sample size (N = 19) of the non-White group in Study 1774 limited the ability to form definitive conclusions about the relative efficacy in the non-White population.

Table 22: Absolute Change From Baseline in DSQ Total Score at Week 24 by Subgroup[1] (Study 1774)

Group	Placebo[2], LS Mean (SE)	Dupilumab 300 mg QW[2], LS Mean (SE)	LS Mean Difference[2] (95% CI)
Sex			
Male			
300 mg QW (N = 78) vs Placebo (N = 79)	-11.7 (1.9)	-21.5 (1.8)	-9.8 (-14.6, -5.1)
Female			
300 mg QW (N = 44) vs Placebo (N = 39)	-12.7 (3.2)	-25.1 (2.9)	-12.4 (-19.4, -5.5)
Race			
White			
300 mg QW (N = 112) vs Placebo (N = 109)	-12.3 (1.6)	-22.2 (1.6)	-9.9 (-13.9, -5.9)
Other (Non-White)			
300 mg QW (N = 10) vs Placebo (N = 9)	-5.3 (9.5)	-21.8 (9.3)	-16.5 (-39.3, 6.3)
History of Esophageal Dilation			
Yes			
300 mg QW (N = 44) vs Placebo (N = 50)	-11.4 (3.9)	-23.5 (4.1)	-12.1 (-18.1, -6.1)
No			
300 mg QW (N = 78) vs Placebo (N = 68)	-12.7 (2.2)	-22.1 (1.9)	-9.4 (-14.7, -4.2)

Source: Summary of Clinical Efficacy for R668-EE-1774 Part B (Figure 19, p 134); verified by reviewer using Applicant submitted data DSQSC.xpt.

1. Analysis includes subjects from Part A and Part B.
2. The reported mean, difference, 95% CI, and p-value were calculated using an ANCOVA model with treatment group, randomization stratification factors, baseline measurement, and study part as the covariates.

Abbreviations: ANCOVA=analysis of covariance, CI = Confidence Interval, DSQ = Dysphagia Symptom Questionnaire, LS = Least Squares, QW = once weekly.

8.1.4.9. Data Quality and Integrity

The data was of sufficient quality to permit a substantive review of efficacy.

8.1.5. Interpretation of Absolute Change from Baseline in 14-Day DSQ Total Score

This section details how clinically meaningful within-subject change (improvement) from baseline in 14-day DSQ total score at the end of treatment (Week 24) was determined using data from Study 1774 to support the determination of clinical meaningfulness for the symptomatic coprimary endpoint results for Parts A and B. Note that one placebo subject in Part B FAS dataset did not have a baseline 14-day DSQ total score due to having less than 8 diary entries during the 14-day baseline assessment period. This subject was not included in the

meaningful change analysis and the reported sample size for Part B FAS placebo arm is 78 in this section.

8.1.5.1. Anchor Assessments in Study 1774

Patient Global Impression of Severity (PGIS)

The PGIS is a single-item PRO assessment of "severity of your difficulty swallowing food over the past week" using a 4-category verbal rating scale, as described in Table 23 below. The PGIS was administered during treatment visits at baseline, Week 12, and Week 24 for both Parts A and B.

Table 23: Patient Global Impression of Severity (PGIS) Item and Scoring

Question	Response Option	Score
Please choose the response below that best describes the severity of your difficulty swallowing food over the past week.	None	1
	Mild	2
	Moderate	3
	Severe	4

Source: Applicant's PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data, Table 3 (page 15 of 47), dated December 17, 2021.

The recall period used in the PGIS (i.e., "the past week") did not match the assessment period used to calculate the DSQ total score (i.e., 14 days). This mismatch presents a challenge to interpreting anchor-based analyses using the PGIS as an anchor scale for the DSQ total score, as the PGIS reflects only 7 of the 14 days included in the DSQ total score calculation at baseline, Week 12, and Week 24. To facilitate interpretation of anchor-based analyses using the PGIS, supplementary analyses were conducted using matching 7-day periods for both the PGIS and the DSQ, as described in Section 8.1.5.6 of this review.

Patient Global Impression of Change (PGIC)

The PGIC is a single-item PRO assessment of "overall change in your difficulty swallowing food now compared to just before you started taking the study injection" using a 7-category verbal rating scale, as shown in Table 24. The PGIC was administered during site visits at Weeks 12, 20, and 24.

Table 24: Patient Global Impression of Change (PGIC) Item and Scoring

Question	Response Option	Score
Please choose the response below that best describes the overall change in your difficulty swallowing food now compared to just before you started taking the study injection.	Very Much Better	0
	Moderately Better	1
	A Little Better	2
	No Change	3
	A Little Worse	4
	Moderately Worse	5
	Very Much Worse	6

Source: Applicant's PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data, Table 4 (page 15 of 47), dated December 17, 2021.

8.1.5.2. Anchor-Based Analyses

To support the clinical relevance of the symptomatic coprimary endpoint results, anchor-based methods supplemented with empirical cumulative distribution function (eCDF) curves were used to establish the thresholds, or a range of thresholds, that constitute a clinically meaningful within-subject change from baseline in 14-day DSQ total score. The anchor-based analyses were conducted separately using pooled data (across arms) in Parts A and B and by both the Applicant and FDA. Of note, while FDA's evaluation leveraged data from both Parts A and B, given the small sample size in Part A (n=81), results based on Part B data are especially important to help inform and confirm a range of meaningful within-subject improvement thresholds.

8.1.5.3. Baseline 14-Day DSQ Total Score

In order to understand the amount of improvement in 14-day DSQ total score that is considered meaningful to subjects, the review team first examined the distribution of baseline 14-day DSQ total scores by treatment arm (Table 25). The 14-day DSQ total scores can range from 0 to 84 (see Section 15.6.1 The Dysphagia Symptom Questionnaire). In Part A of Study 1774, scores ranged from 10.8-52.2 in the dupilumab 300 mg QW group and 14.0-63.0 in the placebo group. In Part B of Study 1774, scores ranged from 14.0-57.3 in the dupilumab 300 mg QW group, 8.4-70.0 in the dupilumab 300 mg Q2W group, and 12.9-56.0 in the placebo group. Overall, baseline DSQ total scores were generally consistent between Part A and Part B.

Table 25: **Distribution of Baseline 14-Day DSQ Total Score by Treatment Arm (Parts A and B, Study 1774)**

							Percentile				
Part	**Treatment**	**N**	**Mean**	**SD**	**Min**	**Max**	**10th**	**25th**	**50th**	**75th**	**90th**
Part A	Dupilumab 300 mg QW	42	32.3	12.7	10.8	52.2	15.0	20.0	34.3	42.0	48.4
	Placebo	39	35.1	12.1	14.0	63.0	18.0	23.7	35.5	44.3	50.0
Part B	Dupilumab 300 mg QW	80	38.4	10.7	14.0	57.3	22.0	30.2	40.9	45.6	51.8
	Dupilumab 300 mg Q2W	81	35.6	12.2	8.4	70.0	18.7	27.0	36.2	42.0	50.6
	Placebo	78	36.1	10.6	12.9	56.0	21.0	29.2	37.0	43.0	49.0

Source: PFSS reviewer generated table. Analysis was conducted by reviewer using Applicant submitted data adqsdsq.xpt.
Abbreviations: Max = maximum, Min = minimum, N = number of subjects in study group, SD = standard deviation.

8.1.5.4. Target Anchor Change Category

Patient Global Impression of Severity (PGIS)

Currently, there is no standard clinical definition for disease severity for EoE. Therefore, the PGIS was used in Study 1774 as a way to classify EoE disease severity based on dysphagia symptoms. The Applicant did not pre-specify a target change category on the PGIS and used a 1-category improvement on the PGIS to support anchor-based meaningful change analyses.

Ideally, a target anchor change category should be pre-specified by the Applicant and agreed upon by FDA during the IND phase. However, based on discussions among the Statistical, Clinical, and DCOA review teams, a 1-category improvement on the 4-category PGIS scale was determined to be acceptable to support further anchor-based meaningful change analyses. A 1-category improvement on the PGIS anchor scale could occur in the following ways:

- Change from “severe dysphagia” to “moderate dysphagia”
- Change from “moderate dysphagia” to “mild dysphagia”
- Change from “mild dysphagia” to “no dysphagia”

What subjects consider to be clinically meaningful improvement may be impacted by their baseline dysphagia symptom severity. Subjects’ baseline symptom severity should be considered when determining clinically meaningful within-subject improvement thresholds. Table 26 shows the distribution of change patterns in global dysphagia symptom severity between baseline and Week 24 for Parts A and B, using data pooled across arms.

Table 26: Category Change (n (%)) in PGIS From Baseline to Week 24 by Baseline PGIS (Parts A and B, Study 1774)

Part	Baseline PGIS	Improved 3 Categories	Improved 2 Categories	Improved 1 Category	No Change	Worsened 1 Category
Part A	None (N=1)	0	0	0	1 (100.0%)	0
	Mild (N=30)	0	0	11 (36.7%)	18 (60.0%)	1 (3.3%)
	Moderate (N=26)	0	11 (42.3%)	8 (30.8%)	5 (19.2%)	2 (7.7%)
	Severe (N=4)	2 (50.0%)	1 (25.0%)	1 (25.0%)	0	0
Part B	None (N=1)	0	0	0	1 (100.0%)	0
	Mild (N=89)	0	0	37 (41.6%)	44 (49.4%)	8 (9.0%)
	Moderate (N=97)	0	21 (21.6%)	52 (53.6%)	20 (20.6%)	4 (4.1%)
	Severe (N=17)	3 (17.7%)	6 (35.3%)	5 (29.4%)	3 (17.7%)	0

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adsl.xpt and adqspgi.xpt.

Change in global dysphagia symptom severity tends to vary among subjects with different baseline symptom severity. The majority of subjects reported mild to moderate symptoms at baseline. One subject each in Part A and Part B started with “no symptom” at baseline and remained “no symptom” (i.e., no change) at Week 24. For subjects who started with mild dysphagia symptoms, most reported no change (60.0% in Part A and 49.4% in Part B) followed by a 1-category improvement (36.7% in Part A and 41.6% in Part B) in their global dysphagia symptom at Week 24. For subjects who started with moderate dysphagia symptoms at baseline, most reported a 2-category improvement (42.3%) followed by 1-category improvement (30.8%) in Part A at Week 24; and most reported a 1-category improvement (53.6%) followed by a 2-category improvement (21.6%) in Part B at Week 24. For subjects who started with severe dysphagia symptoms at baseline, 50% of subjects (i.e., two out of four subjects) reported a 3-category improvement in Part A at Week 24; and in Part B 17.7% of subjects reported a 3-category improvement, 35.3% of subjects reported a 2-category improvement, and 29.4% of subjected reported a 1-category improvement at Week 24.

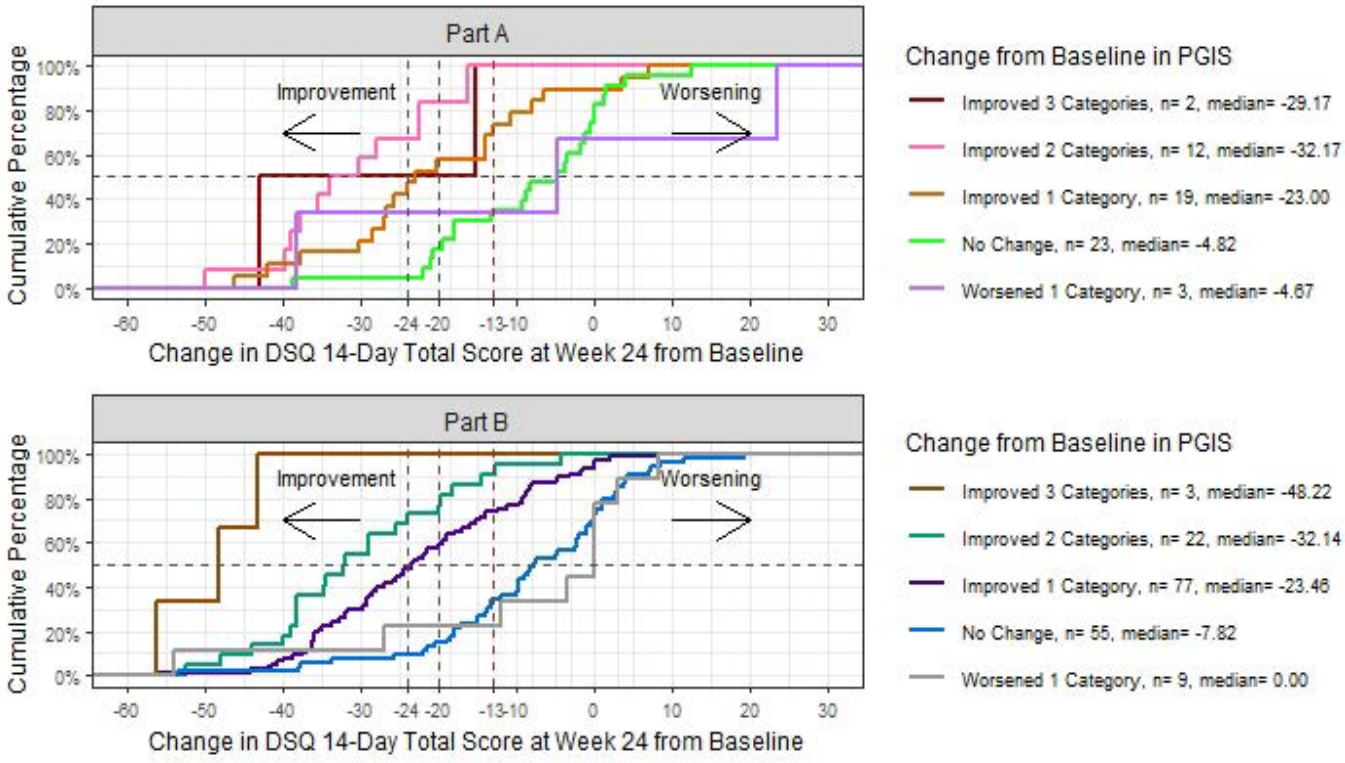
Patient Global Impression of Change (PGIC)

During FDA's review of the Applicant's BTD request, FDA did not agree with using the response category of "A Little Better" on the PGIC to define a clinically meaningful change in the anchor. FDA considers "Moderately Better" on the PGIC as a more appropriate target anchor category. The Applicant continued to use "A Little Better" on the PGIC to support anchor-based meaningful change analyses. FDA position remains unchanged that "Moderately Better" on the PGIC should be used as the target anchor category. FDA's anchor-based analyses using "Moderately Better" on the PGIC and a 1-category improvement on the PGIS produced consistent results in both Parts A and B. Refer to Section 8.1.5.5 for more details on the anchor-based analyses conducted by FDA.

8.1.5.5. Clinically Meaningful Change in 14-Day DSQ Total Score Results

Figure 9 below shows the eCDF plots of absolute change from baseline in 14-day DSQ total score at Week 24 by PGIS category of change from baseline for Parts A and B. In summary, the eCDF plots show clear and consistent separation between the "1-category improvement" and "no change" curves. According to Appendix E of the Applicant's PRO dossier, "a minimum 13-point reduction in the DSQ biweekly total score could be considered a clinically meaningful within-patient change, ie, 13 points is excluded from the 95% CI [confidence interval] boundaries for patients who experience a 0-point change on the PGIS." The Applicant's conclusion appeared to be based on Part B alone, given that the 95% CI of change in DSQ score for subjects who experienced no change on the PGIS is (-12.03, -4.84) for Part B and (-13.37, -3.47) for Part A. In addition, the Applicant's proposed threshold did not appear to take into consideration a higher threshold range (i.e., a range between 14- and 23-point improvement from baseline in the 14-day DSQ total score) derived from Part A data, according to the Applicant's Part A summary report of psychometric analysis results for the DSQ (submitted under SDN 1589). Furthermore, the Applicant's threshold (-13) resulted in classifying >20% of subjects who reported no change on the 7-day global severity item as experiencing meaningful change.

Figure 9: eCDF, Change From Baseline in 14-Day DSQ Total Score to Week 24 by PGIS Category of Change From Baseline (Parts A and B, Study 1774)



Source: PFSS reviewer generated figure. Analysis was verified by reviewer using Applicant submitted data adqsdsq.xpt.

FDA does not agree with the Applicant that a 13-point change from baseline in the 14-day DSQ score would be considered a clinically meaningful within-subject improvement for subjects in Study 1774. FDA's anchor-based analyses that leveraged data from both Parts A and B suggested that the meaningful within-subject improvement threshold range should be between 20-point and 24-point. FDA derived this range of change scores based on median values of change in DSQ score for subjects who experienced a 1-category improvement on the PGIS and "Moderately Better" on the PGIC anchor assessments, while taking into account the baseline PGIS score (see Table 27 and Table 28). Overall, consistent results were obtained using different anchor scales (i.e., PGIS and PGIC) based on all subjects in Part A and Part B. Note that to allow for comparative analyses with the data generated from the change in PGIS anchor categories (i.e., anchor-based methods), the eCDF curves were created using raw change scores consistent with the current recommendation in the FDA guidance for industry: *Eosinophilic Esophagitis: Developing Drugs for Treatment* (September 2020).

Table 27: Change From Baseline in 14-Day DSQ Total Score by Baseline PGIS for Subjects Who Achieved a 1-Category Improvement on PGIS (Parts A and B, Study 1774)

Part	PGIS at Baseline	N	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
Part A	Mild	10	-32.4	-25.7	-21.6	-14.0	-11.9
	Moderate	8	-46.2	-36.2	-27.6	-7.2	3.5
	Severe	1	7.0	7.0	7.0	7.0	7.0
Part B	Mild	30	-39.2	-32.0	-23.9	-16.0	-13.2
	Moderate	44	-37.0	-34.7	-24.1	-8.8	-1.8
	Severe	3	-9.3	-9.3	0	2.0	2.0

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adqsdsq.xpt and adqspgi.xpt.

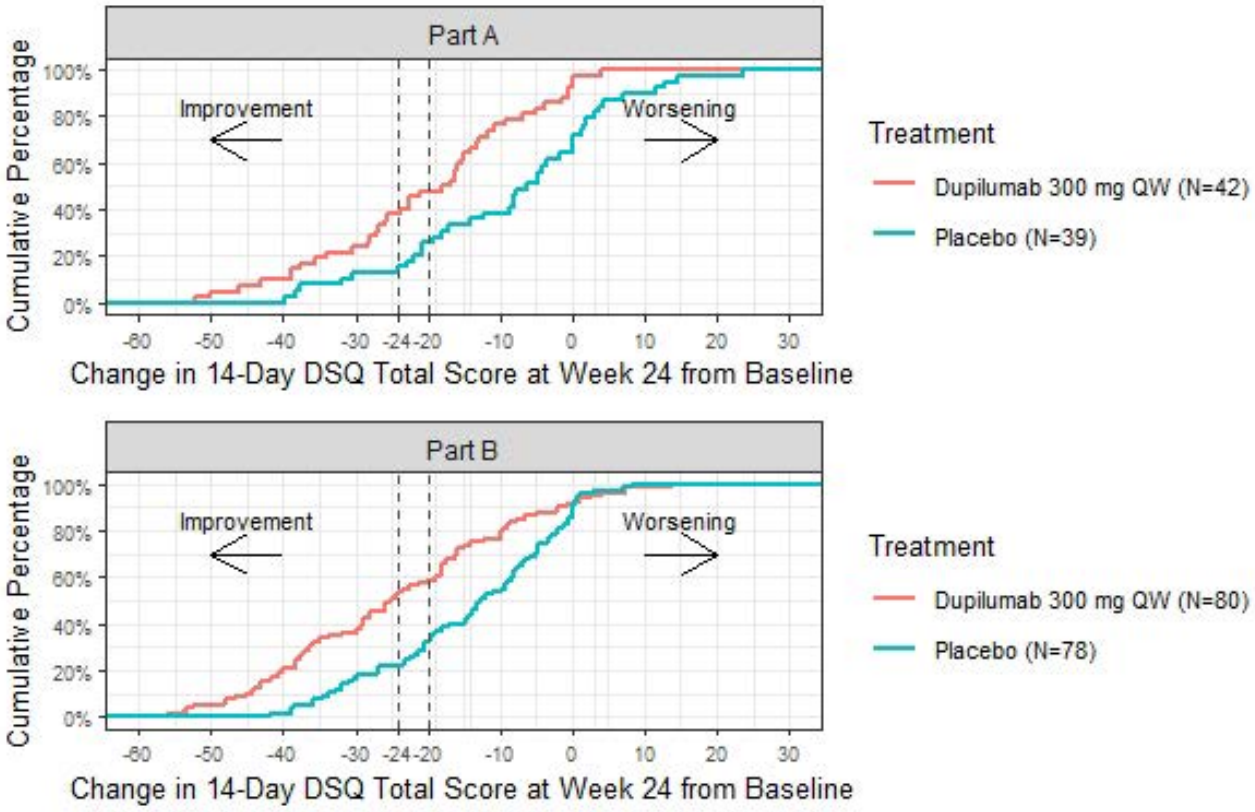
Table 28: Change From Baseline in 14-Day DSQ Total Score at Week 24 by PGIC (Parts A and B, Study 1774)

Part	PGIC	N	10th Percentile	25th Percentile	50th Percentile	75th Percentile	90th Percentile
Part A	Worsening (a little, moderately, very much)	4	-38.4	-17.1	5.7	15.3	23.5
	No change	14	-23.0	-18.0	-2.6	1.5	7.0
	A little better	12	-26.7	-21.3	-10.1	-3.5	0.0
	Moderately better	15	-42.0	-34.0	-24.1	-8.0	0.0
	Very much better	20	-46.5	-38.9	-24.1	-15.7	-13.1
Part B	Worsening (a little, moderately, very much)	5	-26.9	-9.7	-8.2	0.1	8.3
	No change	26	-12.1	-8.3	0.0	2.8	7.0
	A little better	39	-36.2	-22.0	-9.3	-0.4	4.3
	Moderately better	44	-38.8	-32.5	-23.1	-12.3	-5.1
	Very much better	63	-44.3	-37.6	-28.0	-19.4	-14.0

Source: PFSS reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adqsdsq.xpt and adqspgi.xpt.

Furthermore, the eCDF plots of within-subject changes in 14-day DSQ total score from baseline by treatment arm for Parts A and B (Figure 10) show a clear and consistent separation between treatment arms based on visual inspection in the FDA-proposed meaningful change range of 20-point and 24-point improvement. Even with the higher meaningful change range identified by FDA, a greater proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to subjects that received placebo in the FDA-determined range.

Figure 10: eCDF, Change From Baseline in 14-Day DSQ Total Score at Week 24 by Treatment Arm (Parts A and B, Study 1774)



Source: PFSS reviewer generated figure. Analysis was verified by reviewer using Applicant submitted data adqsdsq.xpt.

To supplement the eCDF plots of within-subject changes in 14-day DSQ total score by treatment arm (Figure 10), the proportion of subjects reporting a meaningful improvement along with the difference in response rates and corresponding 95% confidence intervals (CIs) by treatment arm at Week 24 were examined by the FDA at various thresholds within the FDA-determined meaningful threshold range. As shown in Table 29, at the thresholds of 20-point and 24-point within the FDA-determined meaningful threshold range, the differences in response rates by treatment arm (dupilumab 300 mg QW – placebo) are 21.3% and 22.1% in Part A, and 26.6% and 31.8% in Part B.

Table 29: Proportion of Subjects Who Achieved Meaningful Improvement at Week 24 From Baseline in 14-Day DSQ Total Score at Various Thresholds (Parts A and B, Study 1774)

Part	Threshold	Dupilumab 300 mg QW (n)	Placebo (n)	Difference From Treatment (95% CI)[1]
Part A	≥ 24 points	38.1% (16)	15.4% (6)	22.1% (2.6%, 39.4%)
	≥ 22 points	45.2% (19)	17.9% (7)	26.7% (6.2%, 44.2%)
	≥ 20 points	47.6% (20)	25.6% (10)	21.3% (0.3%, 39.9%)
Part B	≥ 24 points	53.8% (43)	21.8% (17)	31.8% (16.7%, 44.8%)
	≥ 22 points	56.3% (45)	26.9% (21)	29.1% (13.8%, 42.6%)
	≥ 20 points	58.8% (47)	32.1% (25)	26.6% (11.1%, 40.4%)

Source: PFSS reviewer generated table. Analysis was conducted by reviewer using Applicant submitted data adqsdsq.xpt.

1. Cochran-Mantel-Haenszel (CMH) test stratified by age group (>=12 to <18 vs >=18) and use of PPI at randomization (Yes vs No). Subjects who had missing change in 14-day DSQ total score were classified as not achieving clinically meaningful improvement.

In summary, FDA concludes that the results of the anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B in subjects treated with dupilumab 300 mg QW, as assessed by the symptomatic coprimary endpoint of absolute change from baseline in 14-day DSQ total score, is representative of a clinically meaningful within-subject improvement.

8.1.5.6. Additional Supplementary Analyses

Given that the interpretability of the anchor-based analyses may be limited by the difference in assessment periods between the 14-day DSQ total score and the PGIS anchor with 7-day recall period, supplementary anchor-based analyses were conducted separately in Parts A and B by the Applicant (upon FDA request) and by FDA to determine a range of meaningful change thresholds for the absolute change from baseline in the 7-day DSQ total score. The 7-day DSQ total score was calculated as follows, with a possible score range of 0 to 42.

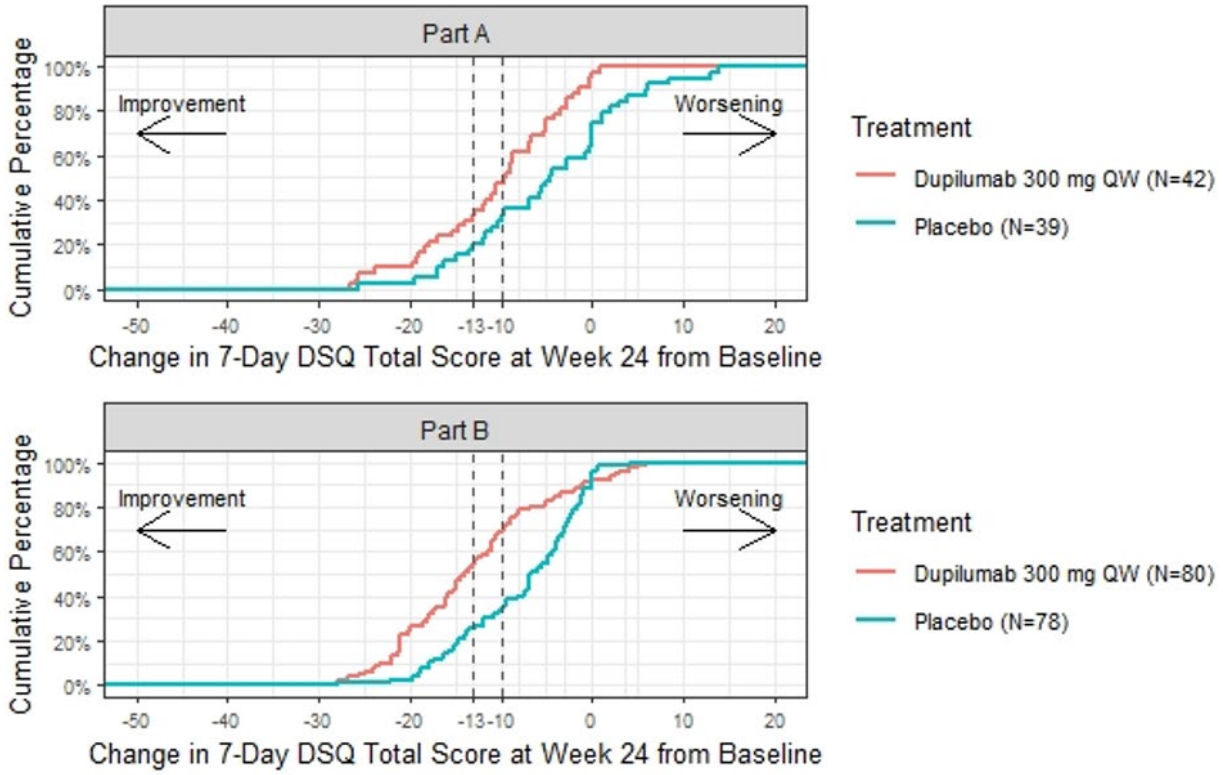
$$\frac{(sum\ of\ Points\ from\ Items\ 2\ and\ 3\ from\ daily\ DSQ\ eDiary)}{number\ of\ eDiary\ days\ reported\ with\ non-missing\ data} \times 7\ days$$

Source: Applicant's *Response to FDA Request for Information* Page 5 of 18, dated March 22, 2021.

Using the same approach to determine the meaningful within-subject change range in the 14-day DSQ total score, FDA determined a clinically meaningful within-subject change range of 10-point to 13-point improvement in the 7-day DSQ total score. Consistent results were obtained using different anchor scales (i.e., PGIS, PGIC) based on all subjects in Part A and Part B. The eCDF plots of within-subject changes in 7-day DSQ total score from baseline by treatment arm (Figure 11) show clear and consistent separation between treatment arms in the FDA-determined meaningful change range. Consistent with the interpretation of the change from baseline in the 14-day DSQ total score, a greater proportion of subjects treated with dupilumab 300 mg QW experienced meaningful change compared to subjects that received placebo in the FDA-determined meaningful change range in the 7-day DSQ total score (i.e., 33.3% to 47.6% of subjects treated with dupilumab 300 mg QW vs 20.5% to 30.8% of subjects who received placebo in Part A, and 53.8% to 70.0% of subjects treated with dupilumab 300 mg QW vs 25.6%

to 33.3% of subjects who received placebo in Part B). Note that the Applicant did not propose a meaningful within-subject change range from baseline in the 7-day DSQ total score for either Part A or Part B.

Figure 11: eCDF, Change From Baseline in 7-Day DSQ Total Score at Week 24 by Treatment Arm (Parts A and B, Study 1774)



Source: PFSS reviewer generated figure. Analysis was verified by reviewer using Applicant submitted data adqsdsq.xpt.

8.1.6. Integrated Assessment of Effectiveness

Substantial evidence of effectiveness for dupilumab 300 mg QW as a treatment for adult and pediatric subjects 12 years of age and older, weighing at least 40kg, with EoE was established in Study 1774. Although conducted as part of a single trial, Parts A and B of Study 1774 contained distinct subject populations and were analyzed separately. The assessment of histologic and symptomatic coprimary endpoints at Week 24 for both Parts A and B revealed significant treatment differences between subjects treated with dupilumab 300 mg QW and those who received placebo. Anchor-based analyses, conducted to enable the interpretability of benefit for the symptomatic coprimary endpoint results, confirmed that the improvement in absolute change in DSQ total score from baseline in subjects treated with dupilumab 300 mg QW was representative of clinically meaningful improvement.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review of this application focused on the data from Part A and Part B of Study 1774. Data from Part C for subjects who completed Part A (Part A/C) of Study 1774 and subjects enrolled in Study 1324 were reviewed and considered supportive of the assessment of safety. A summary of the clinical trials that contributed data to inform the clinical safety evaluation for dupilumab is located in Table 9. Additionally, the Applicant submitted a summary of the available safety information for the 300 mg QW dose in other indications (i.e., asthma and atopic dermatitis). This information was also reviewed as supportive safety information.

Analyses of Part A and Part B of Study 1774 represent adverse events that occurred through Week 24. Additional safety data were provided after the completion of Part A of Study 1774 in the open-label continued treatment period (i.e., Part C for subjects that completed Part A [Part A/C]); however, the interpretability of those data is limited by the lack of a concurrent comparator arm. Additionally, data were provided from Study 1324, a phase 2 study that assessed dupilumab 300 mg QW vs placebo for 12 weeks in adult subjects with EoE. The shorter treatment period and the large proportion of subjects did not complete the study (25%) limit meaningful comparisons and the interpretability of combined analyses with the data from Study 1774. The Applicant submitted data from other indications (i.e., atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis [CRSwNP]) for the dupilumab 300 mg QW dose. Although it is common for patients with an atopic condition to have other atopic conditions, the differences in these populations limit the interpretability of the data most relevant for EoE. Additionally, the dupilumab 300 mg QW dose has not been approved for any condition.

Clinical trial data were analyzed using JMP and JMP Clinical software. All safety assessments and conclusions are those of the clinical review team unless otherwise specified. The review team did not identify any major data quality or integrity issues that precluded performing a thorough safety review.

Pooling of Safety Data Across Clinical Trials

The primary safety analyses were performed on the pooled safety data from Part A and Part B of Study 1774. Of note, data for dupilumab 300 mg Q2W are only from Part B, as this dose was not studied in Part A. The pooling of the data from Part A and Part B was appropriate as the study design, demographics, baseline disease characteristics, and prior and concomitant therapy were similar between Part A and Part B. This provided an assessment of adverse events in a larger safety database, as compared to evaluating each study individually.

To ensure a thorough evaluation of all available safety information, the data from the phase 2 study (Study 1324) and Part A/C of Study 1774 were also reviewed independently. However, no new safety signals were identified from the review of Study 1324 and Part A/C results, and the

data on AEs, laboratory findings, and vital signs were consistent with those observed during the evaluation of the Part A and Part B of Study 1774.

8.2.2. Review of the Safety Database

Overall Exposure

The overall safety database (i.e., Study 1774 and 1324) consisted of a total of 367 subjects and included 73 adolescent subjects as described in Table 30. The total number of unique subjects that received the recommended dupilumab dosage regimen was 182 (122 from Part A and Part B of Study 1774, 37 from Part A/C of Study 1774, and 23 from Study 1324). The maximum duration of Study 1774 was 52 weeks (Part A/C); 40 subjects completed 52 weeks of treatment (blinded dupilumab 300 mg QW during Part A and open-label dupilumab 300 mg QW during Part C) including 10 adolescent subjects.

Table 30: Overview of the Overall Safety Database

	Placebo	300 mg Q2W	300 mg QW	Placebo/ 300 mg QW	300 mg QW/ 300 mg QW
Part A and B, Study 1774, N	117	81	122	-	-
Part A/C[1], Study 1774, N	-	-	-	37	40
Study 1324, N	24	-	23	-	-

Source: Adapted from Applicant's BLA 761055S-040 submission Module 2.7.4, Summary of Clinical Safety, Table 15.
Subjects entered Part A/C following completion of Part A.

The safety analyses focused primarily on Study 1774 that included 122 subjects who received the recommended dupilumab dosage regimen (300 mg QW), of which, 91 received at least 24 weeks of 300 mg QW. Additional safety data were reviewed for 60 subjects (23 from Study 1324 and 37 from Part A/C) who received dupilumab 300 mg QW of which 13 received at least 12 weeks (Study 1324) and 32 received at least 24 weeks (Part A/C of Study 1774). Additional exposure information for Study 1774 is provided in Table 31.

Table 31: Summary of Study Drug Dose Administration and Treatment Duration (Parts A and B, Study 1774)

Exposure Characteristic	Placebo	300 mg Q2W	300 mg QW
Treatment duration (Days)			
N	117	81	122
Mean (SD)	173 (32)	172 (13)	171 (25)
Median (min, max)	168 (35, 309)	168 (126, 230)	168 (56, 242)
Subjects treated by duration, n			
≥1 dose	117	81	122
≥ 84 days (12 weeks)	115	81	120
≥ 168 days (24 weeks)	93	62	91

Source: Adapted from Applicant's BLA 761055S-040 submission Module 5.3.5.3, Integrated Analysis Pool 1, 2a and 2b, Table 5.1.1/1a.

In addition to the safety information provided by the Applicant, Part B/C of Study 1774 (i.e., Part C for subjects that completed Part B) was ongoing at the time of this submission. The

Applicant reported that 227 subjects (74 subjects from placebo, 79 subjects from dupilumab 300 mg Q2W, and 74 subjects from dupilumab 300 mg QW) entered Part B/C. The 74 subjects from the 300 mg QW arm will continue on 300 mg QW for an additional 28 weeks (i.e., a total of 52 weeks). Similarly, the 79 subjects from the 300 mg Q2W arm will continue on 300 mg Q2W for an additional 28 weeks. Subjects who received placebo during Part B and entered Part B/C (74 subjects) will be randomized (1:1) to either 300 mg QW or 300 mg Q2W. Therefore, additional 52-week safety data from approximately 74 subjects who received dupilumab 300 mg QW is expected from Part B/C. Refer to Section 13 regarding the PMR issued under Section 505(o)(3) of FDAAA.

Adequacy of the Safety Database

The safety database is adequate for the assessment of safety of dupilumab for the common AEs and safety events with short latency. However, the exposure of subjects with EoE to the to-be-marketed dose does not meet the recommendations for exposure for drugs intended to treat chronic conditions set forth in the FDA guidance for industry: *The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions (ICH) E1* (March 1995) (i.e., the duration of exposure for most subjects in Study 1774 was 24 weeks, 40 of the 122 subjects in the FAS received dupilumab 300 mg QW for 52 weeks). To support the safety of the proposed dose for chronic administration, the Applicant provided long-term safety information from other indications that received dupilumab 300 mg QW during their respective development programs. Review of these data revealed a safety profile that was similar to the findings in subjects with EoE treated with dupilumab 300 mg QW. Finally, the Applicant's ongoing Part B/C is anticipated to be completed in July 2022 and is expected to provide long-term safety data in an additional 74 subjects with EoE exposed to dupilumab 300 mg QW for a duration of 52 weeks. At the time of this review, there are no approved therapies for the treatment of EoE. Given the seriousness of the condition, the unmet medical need, the available long-term safety data across multiple indications, and no emergence of concerning new safety signals in subjects with EoE treated with dupilumab; the available safety data appears adequate to inform the benefit/risk assessment of dupilumab for the treatment of EoE. To confirm the findings of the safety review in a larger population of subjects with EoE and to further characterize the long-term safety of dupilumab in subjects with EoE with respect to arthralgia, a PMR will be issued to ensure that Part B/C is completed as anticipated and that a full report of safety data from Part B/C is submitted for review.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No issues regarding data integrity or submission quality were identified.

Categorization of Adverse Events

Adverse events (AEs) were graded as mild, moderate, or severe as per the Investigator's judgement.

- **Mild**: Does not interfere in a significant manner with the patient's normal functioning level. It may be an annoyance. Prescription drugs are not ordinarily needed for relief of symptoms, but may be given to the patient.
- **Moderate**: Produces some impairment of functioning but is not hazardous to health. It is uncomfortable or an embarrassment. Treatment for symptom may be needed.
- **Severe**: Produces significant impairment of functioning or incapacitation and is a definite hazard to the subject's health. Treatment for symptom may be given and/or patient hospitalized.

Injection site reaction (ISR) adverse events were graded according to the following scale (semi-colon indicates "or" within description of grade).

- **Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity
- **Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity
- **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis

Serious adverse reactions (SAEs) were appropriately defined consistent with 21 CFR 32.32(a) and reported as required.

All AEs, including SAEs that occurred within 30 days of the last dose of treatment with the investigational drug, whether elicited and/or spontaneously reported, were included. Any SAE that was ongoing when the subject completed the trial or discontinued from the trial was followed by the investigator until the event had resolved, stabilized, or returned to baseline status.

The causal relationship between the investigational drug and the AE was characterized by the Investigator as related or not related, according to definitions outlined in the study protocol.

Routine Clinical Tests

The Applicant assessed clinical laboratory testing as detailed in Section 15.7.2. Hematology, chemistry, urinalysis, and pregnancy testing samples were analyzed by a central laboratory. The criteria for determining whether an abnormal laboratory test finding should be reported as an AE included the following:

- The test result is associated with accompanying symptoms
- The test result requires additional diagnostic testing or medical/surgical intervention
- The test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

8.2.4. Safety Results

8.2.4.1. Deaths

No deaths were reported in Study 1774 or Study 1324.

8.2.4.2. Serious Adverse Events

Serious adverse events (SAEs) for pooled data from Part A and Part B of Study 1774 are shown in Table 32. Overall, the SAE rates were low; however, a higher proportion of subjects who received dupilumab 300 mg QW reported at least one SAE (7/122, 6%) compared to those who received placebo (2/117, 2%) or dupilumab 300 mg Q2W (1/81, 1%).

Table 32: Serious Adverse Events During 24-Week Treatment Period (Pooled Data From Parts A and B, Study 1774)

Serious Adverse Event (PT)[1]	Placebo N=117 n (%)	300 mg Q2W N=81 n (%)	300 mg QW N=122 n (%)
Subjects with SAE	2 (2)	1 (1)	7 (6)
Gastrointestinal disorders			
Abdominal pain	-	-	1 (1)
Infections and infestations			
Campylobacter colitis	-	-	1 (1)
Investigations			
Blood creatinine phosphokinase increased	-	-	1 (1)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)			
Breast Cancer	-	-	1 (1)
Psychiatric disorders			
Depression suicidal	-	-	1 (1)
Suicidal ideation	1 (1)	1 (1)	
Mental status change	1 (1)	-	
Reproductive system and breast disorders			
Uterine polyp	-	-	1 (1)
Respiratory, thoracic, and mediastinal disorders			
Pneumonia aspiration			1 (1)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.
1. Coded as MedDRA 24.0 preferred term.

As shown in Table 32, there were no SAEs reported by more than a single subject for pooled data from Parts A and B of Study 1774 for any treatment arm. There were no SAEs that reflect adverse events of special interest (AESIs). The SAEs of abdominal pain, campylobacter colitis, blood creatinine phosphokinase increased, suicidal ideation, mental status change, uterine polyp, and pneumonia aspiration were resolved during the study and did not lead to treatment discontinuation. The SAE of depression suicidal was in an adolescent with a history of depression whose symptoms were reported to be resolving at the last study assessment (Part B of Study 1774). The SAE of breast cancer was ongoing and led to discontinuation from the study; this SAE is described in more detail in Section 8.2.4.2.

Given that a single subject reported each SAE, no discernable pattern was identified based on

the reported SAEs. The reported SAEs have not been previously identified as adverse reactions of dupilumab in other approved indications, nor has an overall increased risk of malignancy.

In Part A/C of Study 1774, 1 (3%) of the 37 subjects in the placebo/dupilumab 300 mg QW arm reported one SAE. The SAE (PT: systemic inflammatory response syndrome) led to discontinuation from the study and is described in more detail in Section 8.2.4.3. No SAEs were reported in the dupilumab 300 mg QW/dupilumab 300 mg QW arm.

In Study 1324, a single subject each, in the dupilumab 300 mg QW arm, reported an SAE of abortion spontaneous, food allergy, and blood creatine phosphokinase increase. All three SAEs were reported during the 16-week post-treatment follow-up period after the 12-week treatment period. The SAEs occurred 10, 13, and 90 days after the last dose of study drug, respectively. Additionally, the following information provided by the Applicant supports that the SAEs were not related to dupilumab: 1) the subject that reported a spontaneous abortion had a medical history of cervical carcinoma and cervicectomy, 2) the subject that reported a food allergy following consumption of a drink with multiple ingredients was later identified to have multiple food allergies by an allergist, and 3) the subject that had an elevation in blood creatine phosphokinase was asymptomatic and reported strenuous exercise prior to the measurement.

8.2.4.3. Study Discontinuations Due to Adverse Events

Adverse events that led to study discontinuation for pooled data from Parts A and B of Study 1774 are shown in Table 33. Overall, study discontinuation due to AEs was rare. The number of subjects with AEs that led to study discontinuation were similar between the treatment arms.

Table 33: Adverse Events Leading to Study Discontinuation During 24-Week Treatment Period (Pooled Data from Parts A and B, Study 1774)

Adverse Event Leading to Discontinuation (PT)[1]	Placebo N=117 n (%)	300 mg Q2W N=81 n (%)	300 mg QW N=122 n (%)
Number of AEs leading to discontinuation	2	3	4
Subjects with AE leading to discontinuation	2 (2)	2 (2)	3 (2)
Musculoskeletal and connective tissue disorders			
Arthralgia	-	-	1 (1)
Hypermobility syndrome	-	-	1 (1)
Myalgia	-	-	1 (1)
Rhabdomyolysis	-	1 (1)	-
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)			
Breast cancer	-	-	1 (1)
Congenital, familial, and genetic disorders			
Congenital coronary artery malformation	-	1 (1)	-

Adverse Event Leading to Discontinuation (PT)[1]	Placebo N=117 n (%)	300 mg Q2W N=81 n (%)	300 mg QW N=122 n (%)
Respiratory, thoracic, and mediastinal disorders			
Dyspnoea	-	1 (1)	-
Infections and infestations			
Oral herpes[2]	1 (1)	-	-
Investigations			
Hepatic enzyme increased	1 (1)	-	-

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.
Shown in descending order based on dupilumab 300 mg QW.
1. Coded as MedDRA 24.0 preferred term .
2. Reported term of "cold sores, worsening."

As shown in Table 33, there were no AEs that led to study discontinuation reported by more than a single subject for pooled data from Part A and Part B of Study 1774 for any treatment arm.[7] The AEs that led to discontinuation are discussed in more detail below:

- One subject, a 39-year-old female with a past medical history of hypermobility syndrome, in the 300 mg QW arm reported worsening foot pain associated with their hypermobility syndrome and myalgia on study day 31. No corrective treatment was reported, and the subject was discontinued from the study due to physician decision on study day 61. Myalgia and foot pain have not been previously reported as adverse reactions of dupilumab. Although arthralgia has been reported, the worsening of pre-existing foot pain and symptoms of myalgia are likely related to the subject's underlying hypermobility syndrome.
- One subject in the 300 mg QW arm reported an SAE of breast cancer that led to discontinuation from the study. The subject was a 39-year-old female with no relevant medical history or concomitant therapies. On study day 55, the subject noticed a left breast mass. The mass was believed to be cystic and study treatment was continued. On study day 85, the subject had a mammogram and was diagnosed with breast cancer. The subject was withdrawn from the study on the same day. Pathology results on study day 103 showed invasive ductal carcinoma with histologic grade 2 of 3 with lymphovascular invasion. The subject was diagnosed with ductal carcinoma in situ with intermediate grade and solid pattern. No cases of breast cancer or an increased risk of malignancy have been reported in dupilumab labeling. Additionally, the role of IL-13 and IL-4 signaling in the development or progression of malignancy has not been fully described (Braddock et al. 2018).
- One subject in the 300 mg QW arm, a 17-year-old male with a history of generalized foot pain, reported an AE of arthralgia on study day 106. The affected joint(s) was not defined. The subject received 400 mg ibuprofen until the event resolved. The final dose of study drug was administered on study day 112, and the subject was discontinued

[7] In Part A/C of Study 1774, another subject discontinued from the study due to arthralgia. With the addition of this subject, 2 (1%) of the 159 subjects in the overall safety database reported an AE of arthralgia that led to study discontinuation.

from the study on study day 122. Arthralgia is an adverse reaction described in the dupilumab labeling. The mechanism by which dupilumab may cause arthralgia is unclear; however, IL-4 and IL-13 signaling may have a protective role at the enthesis (Bridgewood et al. 2021). Additionally, EoE is associated with several inherited connective tissue disorders (Abonia et al. 2013), which may increase the risk of arthralgia (or other connective tissue) adverse reactions in subjects with EoE who receive dupilumab treatment.

- One subject in the 300 mg Q2W arm, a 15-year-old male with a medical history of Klinefelter Syndrome and asthma, reported increasing dyspnea and was discovered to have congenital coronary artery malformation on study day 170. The study drug was withdrawn, and the subject was discontinued from the study on study day 259. Congenital cardiac disease is associated with Klinefelter Syndrome and is likely the cause of this AE that led to discontinuation.
- One subject in the 300 mg Q2W arm, a 30-year-old male with no relevant medical history, reported an AE of rhabdomyolysis. At screening, the subject had an elevated creatine phosphokinase (CPK) of 855 IU/L (normal range: 24-207 IU/L) and at baseline the CPK remained elevated at 286 IU/L. On study day 115, the subject reported rhabdomyolysis, a CPK value on study day 129 was 4795 IU/L and a muscle biopsy was performed on study day 135 (results not provided). On study day 162, the subject's CPK level was 245 IU/L, and the subject was discontinued from the study. The last dose of study drug was on study day 120. The Investigator considered the AE of rhabdomyolysis as related to study drug. Rhabdomyolysis has not been reported as an adverse reaction in dupilumab labeling. As noted above, one subject in the 300 mg QW arm of Part B and one subject in the 300 mg QW arm of Study 1324 reported SAEs of increased blood creatine phosphokinase (and were not reported at rhabdomyolysis); however, both subjects were reported to have exercised excessively prior to the CPK measurements. Given the subject had an elevated CPK prior to receiving dupilumab, it appears unlikely that the AE of rhabdomyolysis was related to dupilumab.

In Part A/C of Study 1774, 2 (5%) of the 37 subjects in the placebo/dupilumab 300 mg QW treatment arm reported an AE that led to discontinuation. In this treatment arm of Study 1774, one subject in the placebo/dupilumab 300 mg QW arm reported an SAE of systemic inflammatory response syndrome that led to study discontinuation. The subject was a 24-year-old female with relevant medical history of asthma, food allergy, hives, and environmental allergies (e.g., mold, dust mites, plants). On study day 237 (69 days after starting dupilumab), the subject was awakened from sleep by severe shortness of breath and diaphoresis. Of note, the same day the subject had administered the investigational product (within 12 hours of the SAE). The subject administered albuterol at home without relief and proceeded to the emergency room (ER). On evaluation at the ER, the subject had stable vital signs and an elevated white blood cell count (30,000 cells/m^3). They were then admitted to the hospital for observation and started on intravenous antibiotics. The subject was subsequently discharged from the hospital the following day having reported no further symptoms and a decrease in WBC to 16,000 cells/m^3 was noted. The SAE was considered resolved on study day 257. The

subject was discontinued from the study due to the SAE. The Investigator considered the SAE as related to study drug.

Additionally, one subject in the placebo/dupilumab 300 mg QW arm of Part A/C of Study 1774 reported an AE of arthralgia that led to discontinuation. The subject was a 36-year-old male with no relevant medical history reported bilateral elbow pain (preferred term "arthralgia") of moderate severity on study day 219. The subject received ibuprofen 200 mg on study day 268 for the arthralgia. The AE of arthralgia was ongoing at the time of study discontinuation, which occurred on study day 315. As mentioned previously, arthralgia has been identified as an adverse reaction of dupilumab. This is the second subject with EoE that was discontinued from Study 1774 due to arthralgia. No study discontinuations due to arthralgia have been described in the dupilumab label for subjects treated for other indications; however, the label describes that some subjects recovered following discontinuation of dupilumab. Although the number of subjects with arthralgia was small, additional data to further characterize this risk in subjects with EoE are needed and are expected to be provided upon completion of Part B/C as described above.

There were no AEs that led to discontinuation in the dupilumab 300 mg QW/dupilumab 300 mg QW treatment arm in Part A/C of Study 1774.

In Study 1324, 1 (4%) of the 23 subjects in the dupilumab 300 mg QW treatment arm reported an AE of a nail disorder that led to study discontinuation. The subject was a 27-year-old female with no relevant medical history. On study day 37, they reported left index fingernail indentation of moderate severity and was discontinued from the study. Of note, nail disorders have not previously been reported in dupilumab labeling. There were no AEs that led to discontinuation in the placebo treatment arm in Study 1324.

8.2.4.4. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for pooled data from Part A and Part B of Study 1774 are shown in Table 34. The following AEs were specified as AESIs by the Applicant:

- Anaphylactic reactions
- Systemic hypersensitivity reactions
- Helminthic infections
- Severe Conjunctivitis/Blepharitis
- Keratitis
- Clinically symptomatic eosinophilia
- Severe injection site reactions
- Herpes simplex infection
- Arthralgia

There were more AESIs reported in the 300 mg QW treatment arm compared to placebo or 300 mg Q2W treatment arms for pooled data from Part A and Part B of Study 1774. The most common AESIs were herpes simplex infection and arthralgia. The reported events of herpes

simplex infections did not involve the esophagus. There were no AESIs of anaphylactic reactions, helminthic infections, severe conjunctivitis/blepharitis, keratitis, clinically symptomatic eosinophilia, or severe injection site reactions.

Table 34: Adverse Events of Special Interest During 24-Week Treatment Period (Pooled Data From Parts A and B, Study 1774)

Adverse Event of Special Interest (PT)[1]	Placebo N=117 n (%)	300 mg Q2W N=81 n (%)	300 mg QW N=122 n (%)
Subjects with at least one AESI[2]	3 (3)	1 (1)	7 (6)
General disorders and administration site conditions			
Injection site hypersensitivity	-	-	1 (1)
Infections and infestations			
Herpes simplex	-	-	2 (2)
Oral herpes	1 (1)	1 (1)	1 (1)
Immune system disorders			
Hypersensitivity	1 (1)	-	-
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (1)	-	3 (3)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.
Shown in descending order based on dupilumab 300 mg QW.
1. Coded as MedDRA 24.0 preferred term.
2. A subject is counted once if the subject reported one or more events.

In the pooled data from Part A and Part B of Study 1774, 3 (3%) of the 122 subjects in the 300mg QW arm reported an AESI of arthralgia.[8] One event of arthralgia led to study discontinuation; refer to Section 8.2.4.3 above for additional details. The other two subjects reported three AESIs of arthralgia in the 300mg QW arm. One subject reported "right hip pain" and "left shoulder pain," and the other subject reported "arthralgias." Both subjects' AESI were reported as mild to moderate in severity, they continued on treatment, and were resolved. Arthralgia has been previously identified as an adverse reaction in the dupilumab label and subjects with EoE may be at greater risk of arthralgia due to an increased risk of connective tissue disorders (Abonia et al. 2013).

In the 300 mg QW arm, 3 (3%) of the 122 subjects reported an AESI related to herpes simplex infection. One of the three subjects reported two AESIs of oral herpes (verbatim for both events: "cold sore"), which occurred on study days 3 and 73 and were resolved on days 7 and 76, respectively. No treatment for the events were reported. Two of the three subjects reported an AESI of herpes simplex infection: one subject with a history of herpes simplex developed an "exacerbation of HSV1" on study day 45 and received acyclovir; another subject reported a lesion with mild redness on their interior lower lip on study day 129, which was diagnosed as herpes simplex on study day 135. Both subjects' AESI of herpes simplex infection

[8] Two additional subjects with EoE who received 300 mg QW reported an AESI of arthralgia (one in Part A/C and one in Study 1324). In the overall safety database, 5/182 (3%) subjects reported an AESI of arthralgia.

resolved and they continued on treatment. Oral herpes and herpes simplex infections are known adverse reactions of dupilumab. In subjects with atopic dermatitis, oral herpes, and other herpes infections (i.e., herpes simplex, genital herpes, herpes simplex otitis externa, and herpes virus infection but excluding eczema herpeticum) were reported in a greater proportion of subjects who received dupilumab than placebo. Eczema herpeticum and herpes zoster were reported in a similar frequency in subjects with atopic dermatitis or asthma and was not reported in subjects with CRSwNP.

In the 300 mg QW arm, 1 (1%) of the 122 subjects reported an AESI of injection site hypersensitivity. On the same day as the second administration of study drug (study day 8), the subject reported an injection site reaction consisting of erythema and edema at the injection site (upper left quadrant). Three days after the study drug administration (study day 11) the subject reported an itchy, erythematous area at the injection site, which was reported as a "delayed hypersensitivity reaction." The following day (study day 12), a second erythematous satellite lesion was noted on physical exam. The subject received cephalexin, fexofenadine, and paracetamol following referral to urgent care. On study day 13, the subject experienced low-grade fever, chills, malaise, and fatigue. On study day 16, the symptoms were resolved. The event was considered related to the study drug and reported as injection site hypersensitivity. Of note, the subject had a positive ADA result on study day 84 (a low, transient titer with no neutralizing antibody); however, no additional clinical manifestations suggestive of hypersensitivity were reported for this subject and they completed the study.

In the 300 mg Q2W arm, 1 (1%) of the 81 subjects reported an AESI of oral herpes. The subject reported an intermittent outbreak of oral herpes (verbatim: "labial herpes simplex, intermittent outbreak") on study day 2. The subject received valaciclovir and the AESI was considered resolved on study day 25.

In Part A/C of Study 1774, 2 (5%) of the 37 subjects in the placebo/dupilumab 300 mg QW arm and 1 (3%) of the 40 subjects in the dupilumab 300 mg QW/dupilumab 300 mg QW arm reported at least one AESI. The one subject in the placebo/dupilumab 300 mg QW arm reported an AESI of arthralgia. This AESI led to study discontinuation and is described in more detail Section 8.2.4.3. Another subject in the placebo/dupilumab 300 mg QW arm reported an AESI of vernal keratoconjunctivitis of moderate severity. The AESI started on study day 297, was treated with topical olopatadine and prednisone acetate, and resolved on study day 339. The AE of vernal keratoconjunctivitis was categorized as a systemic hypersensitivity reaction and keratitis AESI. Both hypersensitivity and keratitis are adverse reactions that have been previously identified in the dupilumab label.

In the dupilumab 300 mg QW/dupilumab 300 mg QW arm, 1 (3%) of the 40 subjects with a history of multiple food allergies (milk, eggs, and tree nuts) reported an AESI of anaphylactic reaction and anaphylactic shock (6 days after Week 37 dose and 7 days after Week 44 dose, respectively) – cross-contamination of food and an energy drink were considered the suspected causes, respectively.

In Study 1324, there were no reported AESI; however, fewer AEs were designated as AESI by the Applicant (i.e., anaphylactic reactions, severe ISRs, and severe infections) as compared to Study 1774. Of note, 1 (4%) of the 23 subjects in the 300 mg QW arm reported an AE of arthralgia, which was considered an AESI in Study 1774. The AE occurred in a 27-year-old female with no relevant past medical history. The AE was described as "joint pain" of moderate severity, which occurred on study day 37. The dose of dupilumab was not changed, and the subject completed the study. As described previously, arthralgia is a known adverse reaction of dupilumab that may be exacerbated by disease-drug interactions in patients with EoE.

8.2.4.5. Treatment Emergent Adverse Events and Adverse Reactions

An overview of treatment emergent adverse events (TEAEs) for pooled data from Part A and Part B of Study 1774 are shown in Table 35. Overall, the proportion of subjects with at least one TEAE was higher in the dupilumab 300 mg QW arm (103/122, 82%) compared to placebo (87/117, 74%). The majority of the TEAEs were mild or moderate in severity. The proportion of subjects with a severe TEAE was higher in the dupilumab 300 mg QW arm (8/122, 7%) compared to the placebo (2/117, 2%) and dupilumab 300 mg Q2W (1/81, 1%) arms.

All of the severe TEAEs were reported in a single subject each and included the following in the 300 mg QW arm: abdominal pain, breast cancer, COVID-19, depression suicidal, large intestine infection, pneumonia aspiration, syncope, and uterine polyp. The severe TEAE of depression suicidal was an SAE and is discussed in detail in Section 8.2.4.2. The severe TEAE of breast cancer led to study discontinuation; refer to the Section 8.2.4.3 for additional details. The remaining severe TEAEs did not lead to study discontinuation. There were no clear patterns or trends observed among the reported severe TEAEs.

Table 35: Overview of Treatment-Emergent Adverse Events During 24-Week Treatment Period (Pooled Data From Parts A and B, Study 1774)

	Placebo N=117 n (%)	300 mg Q2W N=81, n (%)	300 mg QW N=122, n (%)
Any TEAE, n (%)	87 (74)	63 (78)	103 (82)
Any SAE, n (%)	2 (2)	1 (1)	7 (6)
Any SAE leading to discontinuation, n (%)	-	-	1 (1)
Any TEAE leading to discontinuation, n (%)	2 (2)	2 (2)	3 (2)
Maximum intensity for any TEAE, n (%)			
Mild	60 (51)	42 (52)	68 (56)
Moderate	25 (21)	20 (25)	27 (22)
Severe	2 (2)	1 (1)	8 (7)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

The common TEAEs with a preferred term (PT) occurring in ≥2% of subjects in the dupilumab 300 mg QW treatment arm and greater than placebo are shown in Table 36. The most common

TEAEs were injection site reactions.[9] The proportion of subjects who reported at least one injection site reaction was greater in the dupilumab treatment arms as compared to placebo (38% 300 mg QW, 54% 300 mg Q2W, and 33% placebo). The most common injection site reaction that occurred in a greater proportion of subjects in the 300 mg QW arm compared to placebo were injection site swelling (12% vs 3%) and injection site pain (9% vs 6%).

Upper respiratory tract infections[10] were the next most common TEAE. A greater proportion of subjects in the 300 mg QW arm reported upper respiratory tract infections as compared to placebo or 300 mg Q2W (20% 300 mg QW, 16% 300 mg Q2W, and 10% placebo). The most common upper respiratory tract infections that occurred in a greater proportion of subjects in the 300 mg QW arm compared to placebo were upper respiratory tract infection (6% vs 2%), sinusitis (4% vs 2%), and COVID-19 (3% vs 1%). COVID-19 infection is discussed in more detail in Section 8.2.5.2.

Clinically significant adverse reactions previously identified in other indications and reflected in the Warnings and Precautions of the Dupixent label were reported as AESI (e.g., hypersensitivity, conjunctivitis and keratitis, arthralgia, parasitic infections); refer to Section 8.2.4.4.

The following adverse reactions, identified in other indications and reflected in the Adverse Reactions of the Dupixent label, were reported in the 300 mg QW arm in at least 2% of subjects and greater than placebo: injection site reactions, herpes viral infections, and arthralgia. These TEAEs were also reported as AESIs, refer to Section 8.2.4.4 for further analysis.

[9] Injection site reactions includes several preferred terms. Refer to Section 15.7.1 of the Appendix for FDA's Preferred Term Grouping Strategy.
[10] Injection site reactions includes several preferred terms. Refer to Section 15.7.1 of the Appendix for FDA's Preferred Term Grouping Strategy.

Table 36: Treatment-Emergent Adverse Events Occurring at ≥2% in Dupilumab 300 mg QW Treatment Arm and Greater than Placebo During 24-Week Treatment Period (Pooled Data From Parts A and B, Study 1774)

Treatment-Emergent Adverse Events (PT)[1]	Placebo N=117 n (%)	300 mg Q2W N=81 n (%)	300 mg QW N=122 n (%)
Injection site reactions[2]	39 (33)	44 (54)	46 (38)
Upper respiratory tract infections[3]	12 (10)	13 (16)	22 (18)
Pyrexia	2 (2)	3 (4)	7 (6)
Gastroenteritis[4]	2 (2)	3 (4)	4 (3)
Hypertension	1 (1)	1 (1)	5 (4)
Cough	2 (2)	3 (4)	3 (3)
Syncope	-	2 (3)	3 (2)
Anxiety	1 (1)	2 (3)	3 (3)
Herpes viral infections[5]	1 (1)	1 (1)	3 (2)
Arthralgia	1 (1)	-	3 (2)
Rhinorrhea	-	-	3 (2)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.
Subjects are counted once in each row, regardless of the number of events they may have reported.
Gray shading indicates TEAE considered likely to represent an adverse drug reaction by the clinical reviewer.

1. Coded as MedDRA 24.0 preferred term.
2. Injection site reactions include several preferred terms. Refer to Section 15.7.1 of the Appendix for FDA's Preferred Term Grouping Strategy.
3. Upper respiratory tract infections include several preferred terms. Refer to Section 15.7.1 of the Appendix for FDA's Preferred Term Grouping Strategy.
4. Gastroenteritis includes the PTs gastroenteritis and gastroenteritis viral.
5. Herpes viral infections includes the PTs herpes simplex and oral herpes.

The following PTs were reported in at least 2% of subjects in the 300 mg QW group and greater than placebo; however, these PTs are not recommended to be included in labeling for the following reasons:

- Pyrexia, cough, and rhinorrhea were reported in the setting of other PTs that better capture the event (e.g., pyrexia in the setting of pharyngitis, cough in the setting of an upper respiratory tract infection).
- Gastroenteritis (i.e., PTs of gastroenteritis and viral gastroenteritis) was uncommon and has not been previously reported as an AR for dupilumab. None of the gastroenteritis TEAEs were SAEs, led to study discontinuation, or led to an interruption in therapy. The small imbalance between treatment arms is likely stochastic and not related to dupilumab.
- Hypertension was reported in 5 subjects in the 300 mg QW group compared to 1 subject in placebo; however, only one TEAE, which was reported by a subject with a history of hypertension, was potentially clinically significant (i.e., a systolic blood pressure of ≥160 mmHg and increase of ≥20 mmHg from baseline). Given that the other TEAEs of hypertension were not clinically significant, the single event of potentially clinically significant hypertension does not warrant inclusion in the labeling.
- Syncope was reported in a greater proportion of subjects in the 300 mg QW group compared to placebo. Most of the subjects (2/3, 67%) that reported syncope in the 300 mg QW group were adolescents, and the most common verbatim term was "vasovagal syncope." One adult subject reported syncope on the day of their clinic visit, shortly after the injection of study drug. Vital signs at the time of the visit were normal. None of

the subjects who reported syncope reported hypersensitivity or allergic reactions during the trial. None of the TEAEs of syncope were SAEs, led to discontinuation, or led to an interruption in therapy. Syncope has not been previously identified as an AR for dupilumab in other indications and an association between syncope and dupilumab administration is not supported by a mechanistic rationale. The imbalance between treatment arms for this TEAE is likely stochastic and not related to dupilumab.

- TEAEs of anxiety were overall uncommon during the trial. The majority of subjects that reported TEAEs of anxiety had a past medical history of anxiety. Additionally, anxiety disorder (Reed et al. 2020) and anxiety related to the symptoms of EoE (Taft et al. 2021) are more common in subjects with EoE. Therefore, the small imbalance between treatment arms is likely stochastic and not related to dupilumab.

In Part A/C of Study 1774 and Study 1324, the overall trend of TEAEs and TEAE severity was similar to the pooled data from Part A and Part B of Study 1774. There were no TEAEs that were unique to Part A/C of Study 1774 or Study 1324 that were not represented by the safety data from Part A and Part B.

8.2.4.6. Laboratory Findings, Vital Signs, and Electrocardiograms

Laboratory Findings

Routine clinical laboratory testing was performed during Screening, at Baseline, and at Weeks 12 and 24 in Parts A and B of Study 1774. During Part A/C, laboratory testing was performed at Weeks 36 and 52. During Study 1324, laboratory testing was performed during Screening, at Baseline, and at Weeks 2, 4, 8, and 12. The laboratory parameters assessed by the Applicant are described Section 15.7.2.

Hematology

In the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324, there were no clinically meaningful trends in changes from baseline in hematology parameters in any treatment group.

Chemistry

In the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324, there were no clinically meaningful trends in changes from baseline in chemistry parameters observed in any treatment group. The majority of subjects that had a potentially clinically significant value reported the event as a TEAE and are described above. The remainder of cases were reviewed and found to not be associated with the development of clinical symptoms.

In addition, in the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324, there were no Hy's Law cases in any treatment group and no discernable trends suggestive of elevated transaminase levels in any treatment arm.

Urinalysis

In the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324, there were no clinically meaningful trends in changes from baseline in urinalysis parameters in any treatment group.

Vital Signs

Overall, there were no trends in the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324 in changes from baseline in vital sign parameters or body weight in any treatment group. Of note, five subjects reported a TEAE of hypertension in the dupilumab 300 mg QW compared to one subject each in the placebo and dupilumab 300 mg Q2W arms. However, only one subject, who had a history of hypertension, had a potentially clinically relevant increase in systolic blood pressure (i.e., ≥160 mmHg and increase of ≥20 mmHg from baseline) in the dupilumab 300 mg Q2W arm, refer to Section 8.2.4.5 for additional details.

Electrocardiograms

No trends were observed in the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324 in clinically meaningful shifts from baseline in electrocardiogram (ECG) parameters in any treatment group.

8.2.4.7. Immunogenicity

The incidence of treatment-emergent ADA-positive responses was low in all treatment groups in the pooled data from Part A and Part B of Study 1774, Part A/C of Study 1774, and Study 1324. The Applicant's planned analysis to assess for potential associations between immunogenicity and safety was not performed due to the low incidence of treatment emergent ADA-positive subjects.

In the pooled data from Part A and Part B of Study 1774, 2 (3%) of the 77 subjects and 1 (1%) of the 118 subjects were ADA-positive in the 300 mg Q2W and 300 mg QW treatment arms, respectively. All ADA positive responses were transient. Of the two subjects in the 300 mg Q2W arm, one subject had a low titer (<1,000) and one subject had a moderate titer (1,000 to ≤10,000). Additionally, one subject in the 300 mg Q2W arm was positive for neutralizing antibody. The two subjects in the dupilumab 300 mg Q2W arm that were ADA-positive did not report any adverse events that could have been related to immunogenicity.

The one subject in the 300 mg QW arm had a low titer and was negative for neutralizing antibody. This subject reported an AESI of injection site hypersensitivity, reported by the Investigator as "delayed hypersensitivity reaction." Although the AESI was reported on study day 11 and the positive ADA result was reported on study day 84, ADA testing was not performed at the time of the injection site hypersensitivity; therefore, it is unknown whether the subject had a positive ADA at the time. However, no additional clinical manifestations

suggestive of hypersensitivity were reported for this subject and they completed the study. This AESI is described in detail in Section 8.2.4.4.

8.2.5. Analysis of Submission-Specific Safety Issues

The following safety issues were identified for this submission.

8.2.5.1. Arthralgia

Arthralgia was identified as an AESI for Study 1774 based on the adverse drug reaction noted in other indications for which dupilumab is approved. The Dupixent label includes a Warnings and Precautions statement regarding arthralgia and advises patients to report new or worsening joint symptoms to their healthcare provider.

> *1.7 Arthralgia*
>
> *Arthralgia has been reported with the use of DUPIXENT with some patients reporting gait disturbances or decreased mobility associated with joint symptoms; some cases resulted in hospitalization [see Adverse Reactions (6.1)]. In postmarketing reports, onset of arthralgia was variable, ranging from days to months after the first dose of DUPIXENT. Some patients' symptoms resolved while continuing treatment with DUPIXENT and other patients recovered or were recovering following discontinuation of DUPIXENT. Advise patients to report new onset or worsening joint symptoms to their healthcare provider. If symptoms persist or worsen, consider rheumatological evaluation and/or discontinuation of DUPIXENT.*[11]

In Section 6.1, Clinical Trial Experience, of the current Dupixent prescribing information, arthralgia was reported in 13 (3%) of the 440 and 5 (2%) of the 282 subjects with CRSwNP who received Dupixent 300 mg Q2W and placebo, respectively. Arthralgia was not reported in the clinical trial experience for atopic dermatitis or asthma; however, case reports of arthralgia have been described in the literature in patients with these conditions (Willsmore et al. 2019; de Wijs et al. 2020), (Willsmore et al. 2019).

Subjects with EoE may be at an increased risk of more frequent or more severe arthralgia, as literature suggests that there is an increased risk of connective tissue disorders in patients with EoE (Abonia et al. 2013). In the overall safety database, 5 (3%) of the 182 subjects who received dupilumab 300 mg QW (including subjects from Part A, Part B, placebo/dupilumab arm of Part A/C of Study 1774, and Study 1324) reported a TEAE of arthralgia, as compared to 1 (1%) of the 141 subjects who received placebo. Although AEs leading to discontinuation were uncommon, two subjects discontinued due to an AE of arthralgia (one subject from Part A and one subject from Part A/C). Arthralgia was the only AE that led to discontinuation that was reported by more than one subject in the overall safety database.

[11] See [Dupixent USPI, Revised: 12/2021] at https://www.accessdata.fda.gov/scripts/cder/daf/.

As disease-specific risks for the development and severity of occurrence for arthralgia may be present in patients with EoE and this AE impacted the successful completion of Study 1774 in individual affected subjects with EoE, the review team recommends that arthralgia be included in the table of adverse reactions in Section 6.1 of the Dupixent label for the EoE indication. The descriptive information in Section 5.7 of the Dupixent label regarding arthralgia is sufficient. Additionally, a postmarketing requirement will be issued under FDAAA to further characterize the long-term safety of dupilumab in subjects with EoE with respect to arthralgia, refer to Section 13.

8.2.5.2. COVID-19

Study 1774 was performed during the COVID-19 pandemic. As noted above, TEAEs of COVID-19 were reported in a greater proportion of subjects in the dupilumab treatment arms (4/122, 3% in 300 mg QW and 5/81, 6% in 300 mg Q2W) compared to placebo (1/117, 1%). Most of the cases of COVID-19 were mild (8/10, 80%) or moderate (1/10, 10%). One subject (1/10, 10%) in the 300 mg QW arm reported severe COVID-19. None of the COVID-19 TEAEs, including the one that was reported as severe, were serious TEAEs or required hospitalization or supplemental oxygen. All TEAEs occurred during Part B of Study 1774, which was performed between March 16, 2020 and April 8, 2021. The subject that reported severe COVID-19 was a 12-year-old female with no pertinent past medical history. The COVID-19 TEAE started on study day 1, the same day that the subject was assessed at the study site for their first injection. Of note, the subject's vital signs at the study site were normal. The subject received oral Vitamin D, ibuprofen/pseudoephedrine, paracetamol, zinc, and fexofenadine. The TEAE resolved on study day 19. The subject was continued on 300 mg QW during the TEAE and completed the study.

To further investigate the imbalance in COVID-19 TEAEs in the dupilumab treatment arms as compared to placebo in Study 1774, the Applicant reported pooled safety data from 7 double-blind, placebo-controlled dupilumab studies completed during the COVID-19 pandemic. In the pooled safety data, AEs of COVID-19 were higher in dupilumab arms (20/802, 2.5%) compared to placebo (8/529, 1.5%). Since the COVID-19 cases were generally mild, did not result in hospitalization, supplemental oxygen, or discontinuation from the study, COVID-19 cases were incorporated in the TEAE safety analysis by grouping these TEAEs with upper respiratory tract infection TEAEs. This is consistent with the symptoms of mild to moderate COVID-19 infection, which may result in upper respiratory tract signs and symptoms, similar to other coronavirus infections.

8.2.5.3. Safety in Subjects Who Received Dupilumab 300 mg QW For Other Indications

The exposure of subjects with EoE to the to-be-marketed dosage does not meet the recommendations for exposure for drugs intended to treat chronic conditions set forth in the ICH E1, because the duration of exposure for most subjects in Study 1774 was 24 weeks. There were 40 subjects that received dupilumab 300 mg QW for 52 weeks during Part A/C of Study 1774. Safety information from Part A/C was reviewed in each of the respective sections of the Review of Safety and no new safety signals were identified; however, the interpretability of the data from Part A/C is limited due to the open-label design.

To further support the safety of the 300 mg QW dosage, the Applicant provided summary safety information for other indications (atopic dermatitis, asthma, and CRSwNP) that assessed dupilumab 300 mg QW compared to placebo during their respective development programs. Although the ability of these data to characterize the safety of dupilumab in patients with EoE is limited, since it consists of subjects with an alternative indication, review of the collective data did not reveal any new safety concerns and is considered to be supportive of the safety evaluation of dupilumab 300 mg QW in subjects with EoE.

Overall, the proportion of subjects that reported SAEs, TEAEs leading to discontinuation, AESIs, and any TEAEs were similar between EoE and atopic dermatitis, asthma, and CRSwNP. The AEs that were categorized as SAEs, TEAEs leading to discontinuation, and AESIs were also similar between subjects with EoE and atopic dermatitis, asthma, and CRSwNP.

The adverse reactions identified in Dupixent labeling (e.g., hypersensitivity, conjunctivitis, keratitis, arthralgia, parasitic infections, herpes simplex, injection site reactions) occurred with a similar frequency in subjects with atopic dermatitis, asthma, or CRSwNP who received dupilumab 300 mg QW compared to subjects with EoE who received dupilumab 300 mg QW. Additionally, similar to subjects with EoE, there was a trend of increased upper respiratory tract infections (e.g., PTs: nasopharyngitis, upper respiratory tract infection, viral upper respiratory tract infection) in subjects with atopic dermatitis, asthma, or CRSwNP who received dupilumab 300 mg QW compared to placebo.

In addition to the data submitted by the Applicant for this submission, the safety database used to support the determination of safety and effectiveness for the atopic dermatitis indication was reviewed. The analyses of AEs in atopic dermatitis consisted of a pool of studies with 16-week duration that assessed dupilumab monotherapy versus placebo (“16-week-monotherapy pool”) and a single long-term treatment study of 52-week duration that assessed dupilumab and topical corticosteroids versus placebo and topical corticosteroids (“Study 1224”). The safety review identified a potential dose-dependent increase in upper respiratory tract infections in the 16-week-monotherapy pool, which is consistent with what was observed in subjects with EoE. However, this trend was not observed in Study 1224 (a 52-week study). A dose-dependent increase in injection site reactions was observed for both the 16-week-monotherapy pool and Study 1224. Ultimately, the 300 mg Q2W dose was approved because no clinically meaningful benefit of QW over Q2W was demonstrated in subjects with atopic dermatitis.

In asthma and CRSwNP, dupilumab 300 mg QW was not assessed in their phase 3 studies.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

No COA analyses were submitted as part of this application to inform safety/tolerability.

8.2.7. Safety Analyses by Demographic Subgroups

Safety analyses were performed for the following demographic subgroups:

- Age (12 to less than 18 years of age and at least 18 years of age)
- Sex (male and female)
- Race (White, Non-White)

8.2.7.1. Safety Analyses by Age, Sex, and Race

Adolescent Subjects (12 to Less Than 18 Years of Age)

An overview of TEAEs in adolescent subjects for pooled data from Part A and Part B of Study 1774 are shown in Table 66 in Section 15.7.3.1 of the Appendix. Overall, the number of adolescent subjects with at least one TEAE, TEAEs leading to discontinuation, and TEAE severity were generally similar to adults. However, there was a higher proportion of adolescent subjects who reported an SAE as compared to adults, and most SAEs were reported in subjects that received 300 mg QW (similar to adults).

One subject each in the 300 mg QW arm reported an SAE of blood creatine phosphokinase increased, campylobacter colitis, depression suicidal, pneumonia aspiration, and suicidal ideation. These SAEs are described in detail in Section 8.2.4.2. The SAE of aspiration pneumonia occurred in an adolescent subject with a pertinent medical history of Silver-Russell syndrome. The subject reported a choking/dysphagia event that led to coughing and vomiting to release the food. Two days later the subject developed fever and dyspnea and was treated with antibiotics (oral azithromycin and intramuscular ceftriaxone); however, the subject's symptoms did not improve, and he was hospitalized, where he received IV antibiotics. The subject recovered and the event was resolved after 13 days. The subject continued on treatment and completed the study. Given the aspiration event occurred in the setting of a choking episode, it is not likely related to dupilumab.

One subject in the 300 mg QW arm and one subject in the 300 mg Q2W arm each discontinued due to a TEAE; these TEAEs were described previously in Section 8.2.4.3. The majority of AEs were mild or moderate in intensity in adolescents, similar to adults. Similar to the overall population, there is no discernable pattern of SAEs, TEAEs leading to discontinuation, and severe TEAEs in adolescents.

The common TEAEs with a PT occurring in ≥5% of adolescent subjects in the dupilumab 300 mg QW treatment arm and greater than placebo are shown in Table 67 in Section 15.7.3.1 of the Appendix. Overall, TEAEs in adolescent subjects were similar to adults. The most common TEAEs were injection site reactions and upper respiratory tract infections. In adolescent subjects, pyrexia, COVID-19, fatigue, gastroenteritis, and syncope were more common in the 300 mg QW arm compared to placebo, similar to adults.

In Part A/C of Study 1774, the number of subjects with at least one TEAE, TEAEs leading to discontinuation, SAEs, and severity of TEAEs was generally similar between adolescent subjects and adults. Of note, one adolescent subject in the placebo/dupilumab 300 mg QW arm reported an AE of arthralgia, which was considered an AESI and led to discontinuation. This AE is described in more detail in Section 8.2.4.3.

There were no adolescent subjects enrolled in Study 1324.

Adult Subjects (at Least 18 Years of Age)

Overall, the number of adult subjects with at least one TEAE, SAEs, TEAEs leading to discontinuation, and TEAE severity were generally similar to the overall population as shown in Table 68 in Section 15.7.3.2 of the Appendix. There were no notable differences between adults and the overall population with respect to the reported TEAEs.

Sex (Male and Female)

Overall, there were no notable differences between the treatment groups within the subgroups of male and female subjects (Section 15.7.3.3 and 15.7.3.4 of the Appendix). There were more male subjects enrolled in Study 1774 and 1324; however, this is consistent with the distribution observed in the overall EoE patient population (Dellon et al. 2014).

Race (White and Non-White [Black or African American, Asian, Other])

Although no discernable differences were observed, the interpretability of subgroup analyses by race was limited due to the small number of non-White subjects.

8.2.8. Specific Safety Studies/Clinical Trials

A 90-day safety update report (SUR) was received on April 28, 2022. The SUR included safety information up to the data cutoff date of December 10, 2021 from Part B/C of Study 1774, which is ongoing at the time of this review. Part B/C is a blinded, 28-week extended active treatment period for subjects who completed Part B. Subjects who received dupilumab during Part B were continued on the same dupilumab dosage during Part B/C. Subjects who received placebo during Part B were randomized (1:1) to either dupilumab 300 mg QW or 300 mg Q2W. Of the 228 subjects who completed the week 24 visit of Part B, 227 subjects entered Part B/C. The disposition of subjects in part B/C at the time of the data cutoff date is described in Table 37.

Table 37: Subject Disposition (Part B/C, Study 1774, Data Cutoff Date, December 21, 2021)

	Placebo/ Dupilumab 300 mg Q2W (N=37)	Placebo/ Dupilumab 300 mg QW (N=37)	Dupilumab 300 mg Q2W/ Dupilumab 300 mg Q2W (N=79)	Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=74)
Subjects who completed Week 52[1], n (%)				
Yes	26 (70)	28 (76)	56 (71)	52 (70)
Ongoing	8 (22)	8 (22)	19 (24)	14 (19)
No	3 (8)	1 (3)	4 (5)	8 (11)
Due to COVID-19	-	-	-	-
Not due to COVID-19	3 (8)	1 (3)	4 (5)	8 (11)
Protocol deviation	-	-	2 (3)	1 (1)
Adverse event	1 (3)	-	-	-
Lack of efficacy	1 (3)	-	-	-
Physician decision	1 (3)	-	1 (1)	1 (1)
Withdrawal by subject	-	1 (3)	-	5 (7)
Lost to follow-up				
Death	-	-	1 (1)	1 (1)
Other	-	-	-	-

Source: Adapted from Applicant's BLA 761055S-040 submission Module 5.3.5.3, 120-Day Safety Update Report, Table 2.
1. A subject is considered to complete Week 52 if their Week 52 visit had occurred and was documented.

No deaths were reported in the SUR. Five subjects reported SAEs, three in the dupilumab 300 mg QW/dupilumab 300 mg QW treatment arm and two in the placebo/dupilumab 300 mg treatment QW arm. In the dupilumab 300 mg QW/dupilumab 300 mg QW treatment arm, one subject reported SAEs of diarrhea and rectal tenesmus, one subject reported an SAE of enterocolitis infectious, and one subject reported an SAE of chest pain. In the placebo/dupilumab 300 mg QW treatment arm, one subject reported an SAE of cyclic vomiting syndrome, and one subject reported an SAE of cellulitis. The SAEs reported in the SUR have not been previously reported in Part A, Part B, or Part A/C of Study 1774 or Study 1324. Additionally, the reported SAEs have not been previously identified as adverse reactions of dupilumab in other approved indications. Given that a single subject reported each SAE, no discernable pattern was identified based on the reported SAEs.

In the SUR, three subjects reported AEs that led to study discontinuation including one subject in the placebo/dupilumab 300 mg QW treatment arm and two subjects in the placebo/dupilumab 300 mg Q2W treatment arm. The AEs that led to study discontinuation are described in more detail below:

- One subject in the placebo/dupilumab 300 mg QW treatment arm, a 39-year-old female with no relevant medical history, reported an SAE of cellulitis (verbatim term, "worsening cellulitis") on study day 222. The subject reported cellulitis following intramuscular injection of ondansetron in the right thigh to treat nausea. Following the injection, the injection site developed redness and the subject reported a fever. The subject presented to the emergency room where she received IV antibiotics (cefepime and vancomycin). The subject was admitted to the hospital and developed leukocytosis with spreading of the area of involvement of the cellulitis. The subject received broader

spectrum antibiotics (linezolid and meropenem) and the vancomycin was discontinued. The subject was subsequently discharged from the hospital on oral antibiotics (levofloxacin) on study day 235 after improvement in the cellulitis and leukocytosis. On study day 241, the subject was found to have persistent soft tissue infection and abscess. On the same day, the subject was admitted to the hospital for incision and drainage of the abscess. The subject was discharged from the hospital on study day 248 and the SAE of cellulitis was considered resolved with sequalae (scar at the site of the incision and drainage and numbness at the site) on study day 301. The suspected cause was ondansetron IM injection, which occurred two days before the cellulitis and was on the same side (right thigh). Of note, the dupilumab injection prior to the onset of right thigh cellulitis was into the subject's upper left thigh. Given the injection of dupilumab occurred in a different location, it is unlikely that this SAE that led to study discontinuation was due to dupilumab.

- One subject in the placebo/dupilumab 300 mg Q2W treatment arm, a 28-year-old male with no relevant medical history, reported an AE of alanine aminotransferase (ALT) increased, aspartate (AST) aminotransferase increased, and blood creatine phosphokinase (CPK) increased that led to study discontinuation. At screening, baseline, and study day 177 (during Part B), the subject had elevated CPK (279 to 385 IU/mL; normal range: 24-207 IU/L). During other study visit, the subjects CPK returned to the normal range. On study day 274, the subject reported elevated ALT and AST (70 IU/L and 68 IU/L, respectively; normal range: 10-40 and 10-43 IU/L). At the same time, the subjects CPK was elevated at 933 IU/L, but the total bilirubin remained normal. On the same day, the subject was discontinued from the study due to these AEs. The AEs of AST and ALT elevated were considered resolved on study day 289 and CPK elevated was considered resolved on study day 306.
- One subject in the placebo/dupilumab 300 mg Q2W treatment arm, a 38-year-old male with no relevant medical history, reported an AE of joint noise (verbatim term: "joint crepitation") that led to study discontinuation. On study day 204 the subject reported an AE of joint injury that occurred during hiking. On study day 321, the subject reported an AE of joint noise, which was described as a painless "loud popping joint," and the subject requested to discontinue the drug on the same day.

Overall, the reported TEAEs were generally similar in Part B/C as Part A and Part B of Study 1774. As a result, no new safety concerns were identified. Of note, as described in Section 8.2.5, arthralgia was an adverse reaction that may be a disease-specific risk for subjects with EoE. In the SUR for Part B/C, two subjects reported AEs of arthralgia (one subject in the placebo/dupilumab 300 mg QW treatment arm and one subject in the dupilumab 300 mg QW/dupilumab 300 mg QW).

8.2.9. Additional Safety Explorations

No additional safety explorations were performed.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Dupilumab is not currently approved in subjects 12 years of age and older with EoE in any country.

Expectations on Safety in the Postmarket Setting

Additional safety data in subjects with EoE is expected, as the Applicant's Part C for subjects that completed Part B of Study 1774 (Part B/C) is ongoing. Part B/C is expected to provide long-term safety information (i.e., 52 weeks duration) for approximately 153 additional subjects including 74 subjects in the dupilumab 300 mg QW/dupilumab 300 mg QW arm and 79 subjects in the dupilumab 300 mg Q2W/dupilumab 300 mg Q2W arm. The 74 subjects that received placebo during Part B will be randomized 1:1 to receive dupilumab 300 mg QW or dupilumab 300 mg Q2W for 28 weeks.

8.2.11. Integrated Assessment of Safety

The available safety data were supportive of an acceptable safety profile as part of the benefit-risk assessment for treatment with dupilumab 300 mg QW in subjects with EoE. Overall, SAEs and AEs that led to discontinuation were uncommon and the majority of subjects completed the study. In general, the safety profile of dupilumab 300 mg QW was similar to the 300 mg Q2W dosage in subjects with EoE. There were no discernable trends among demographic subgroups, including adolescent subjects at least 12 years of age to less than 18. Most of the TEAEs that occurred in a greater proportion of subjects in the 300 mg QW arm compared to placebo have previously been identified in dupilumab labeling (e.g., injection site reactions, herpes viral infections, arthralgia). However, upper respiratory tract infections have not been previously described as an adverse reaction in Dupixent labeling.[12] In the pooled data from Part A and Part B of Study 1774, upper respiratory tract infections (URIs) were more common in subjects who received dupilumab 300 mg QW than placebo. This adverse reaction was further supported by data from Study 1324 as well as data from other indications that assessed the 300 mg QW dosage. Of note, TEAEs of COVID-19 were reported in a greater proportion of subjects who received dupilumab compared to placebo. Since the COVID-19 TEAEs were generally mild, did not lead to study discontinuation, did not require hospitalization or supplemental oxygen, and coronaviruses are a common cause of URIs, these TEAEs were incorporated in the evaluation of safety as URIs. Notably, the majority of URIs (including COVID-19) did not result in study discontinuation and were mild or moderate in severity. Additionally, there was no discernable trend of serious infections in subjects who received dupilumab (in EoE or other indications). Therefore, inclusion of a description of the occurrence of these AEs in subjects with EoE in Section 6 is sufficient to inform prescribers of this adverse reaction.

[12] Upper respiratory tract infections include several preferred terms. Refer to Section 15.7.1 of the Appendix for FDA's Preferred Term Grouping Strategy.

As noted in Section 8.2.5.1, arthralgia is an adverse reaction that has been previously identified in dupilumab labeling. Arthralgia was also highlighted as an adverse reaction of concern by FDA during the dupilumab development program, as subjects with EoE may be at increased risk of more frequent or more severe arthralgia. In the pooled data from Part A and Part B of Study 1774, a greater proportion of subjects who received 300 mg QW reported arthralgia compared to placebo. This trend was supported by data from Part A/C of Study 1774 and Study 1324.

Additionally, arthralgia was the only AE that led to discontinuation that was reported by more than one subject. Arthralgia should be included in the dupilumab labeling in Section 6 to inform prescribers of the risk for this adverse reaction in patients with EoE. Arthralgia is currently described in the Warnings and Precautions sections to inform prescribers of the clinical significance of arthralgia adverse reactions, and this description is adequate based on the available data; however, additional data are needed to further characterize the risk of arthralgia in patients with EoE. As such, a PMR under Section 505(o)(3) of FDAAA will be issued for the Applicant to complete the ongoing Part B/C of Study 1774 to evaluate the long-term safety of dupilumab subjects with EoE with respect to arthralgia.

EoE is a serious condition that can profoundly impact patient's health and well-being. There is an unmet medical need, as there are no approved therapies to treat this chronic condition. Although additional safety information is expected from Part B/C, the safety analyses submitted by the Applicant support the benefit-risk assessment in favor of approval. In general, the safety profile of dupilumab 300 mg QW was similar to the 300 mg Q2W dosage in subjects with EoE, and the 300 mg Q2W dosage is approved for use in other indications. Other than URI, no new EoE-specific adverse reactions were identified as a result of treatment with dupilumab, including esophageal infection, that patients with EoE may be susceptible to due to disruption of the normal esophageal mucosa.[13] The safety data, in combination with the efficacy data reviewed above, support a favorable risk-benefit assessment to support approval of the 300 mg QW dose for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis.

8.3. Statistical Issues

There were no major statistical issues identified that affected the safety or efficacy analyses.

8.4. Conclusions and Recommendations

The review team recommends approval of the 300 mg QW dosage of dupilumab for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with EoE. The 300 mg QW dosage was superior to placebo in the assessment of histologic and symptomatic coprimary endpoints at Week 24 for both Parts A and B of Study 1774. Anchor-

[13] No cases of herpes esophagitis were reported. One subject in the 300 mg QW arm of Study 1774 reported an AE of esophageal candidiasis; however, the AE was reported on study day 1 (the same day dupilumab was started). Of note, the subject had received topical corticosteroids prior to enrolling in the study.

based analyses supported that the treatment differences observed for the symptomatic coprimary endpoint for each part were representative of clinically meaningful change in favor of 300 mg QW dupilumab treatment. Although conducted as part of a single trial, Parts A and B contained distinct subject populations and were analyzed separately. The 300 mg Q2W dosage was not superior to placebo in the assessment of the symptomatic coprimary endpoint at Week 24 for Part B of Study 1774; therefore, this dosage is not recommended for approval.

The 300 mg QW dosage of dupilumab was well-tolerated, and serious AEs and AEs that led to discontinuation were uncommon. Upper respiratory tract infections were identified as a new adverse reaction in subjects with EoE treated with dupilumab 300 mg QW; however, the observed URIs were generally mild and did not lead to treatment interruption or discontinuation. Arthralgia, which has been identified as an adverse reaction to dupilumab in other indications, was also observed in subjects with EoE and noted to lead to treatment discontinuation in subjects with EoE. The proposed labeling adequately informs prescribers and patients about this risk based on available data; however, additional characterization of this adverse reaction in subjects with EoE will be performed as part of a PMR under FDAAA.

Although a limited number of subjects with EoE were exposed to the to-be-marketed dosage (i.e., 300 mg QW) for 52 weeks at the time of sBLA submission (n=40), additional long-term data are expected to be available upon completion of Part B/C of Study 1774, and adequate reporting of these data will be assured through the issuance of the PMR as discussed below. In consideration of the favorable benefit-risk profile determined during the review of this sBLA and the unmet need for treatment for this serious and chronic condition, the availability of additional long-term data from Part B/C should not delay approval of dupilumab for the treatment of adult and pediatric patients aged 12 years and older, weighing at least 40 kg, with EoE.

9. Advisory Committee Meeting and Other External Consultations

There were no safety or efficacy concerns identified during the review of this sBLA that required an Advisory Committee Meeting or other external consultations.

10. Pediatrics

Although this development program received Orphan Drug Designation for the treatment of eosinophilic esophagitis (EoE) on September 5, 2017, and is therefore exempt from Pediatric Research Equity Act (PREA) requirements, the application included an assessment and a request for indication for pediatric patients aged 12 years and older.

Additionally, the Applicant is currently conducting an ongoing phase 3 trial (R668-EE-1877) under IND 136142 to evaluate dupilumab as a treatment for pediatric patients with EoE 1 to less than 12 years of age.

Although the requirements for pediatric study under PREA do not apply, EoE also occurs in younger pediatric patients and can lead to significant morbidity. The Division recognizes the unmet medical need for therapies to treat EoE in younger pediatric patients, as there are no approved therapies for this condition. The Applicant agreed to conduct the following post-marketing commitments (PMCs), which will be issued at the time of approval of the application to complete the ongoing study in younger pediatric patients:

4276-2

A one-year, randomized, double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis.

4276-3

A long-term extension study to evaluate the long-term safety of (Dupixent) dupilumab in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis, who participated in postmarketing commitment study 4276-2. This study may be conducted as part of postmarketing commitment study 4276-2.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

A summary of labeling changes is described in Table 38.

Table 38: Summary of Changes to the Prescribing Information

Full Prescribing Information Sections	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI
1 INDICATIONS AND USAGE	The indication statement, the treatment of adult and pediatric patients aged 12 years of age and older with EoE, was updated to include the minimum weight of 40kg that was required for Study 1774.
2 DOSAGE AND ADMINISTRATION	Similar to Section 1, the minimum weight of 40 kg was added to the dosage and administration information in Section 2.6. In Section 2.7, instructions to administer a missed weekly dose as soon as possible and start a new weekly schedule from the date of the last administration was added.
5 WARNINGS AND PRECAUTIONS	There were no new warnings and precautions proposed by the Applicant. The review team agreed that no new warnings and precautions were necessary based on review of the submitted data.
6 ADVERSE REACTIONS	In Section 6.1, adverse reactions that occurred in at least 2% of subjects treated with dupilumab and greater than placebo included injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. Injection site reactions included several related terms, including but not limited to, injection site swelling, pain, and bruising. Similarly, upper respiratory tract infections included several related terms, including but not limited to, COVID-19, sinusitis, and upper respiratory tract infection. Herpes viral infections includes herpes simplex and oral herpes infections. Section 6.1 was also updated to reflect that the data to support safety was from Part A and Part B of Study 1774. (b) (4) The Specific Adverse Reactions in Section 6.1 were updated to reflect incidences noted in Study 1774. In general, the Applicant's proposal was acceptable; (b) (4) he Applicant altered the statement to describe that an increase in blood eosinophil count was not observed in subjects with EoE, which was deemed acceptable. Section 6.2 was updated to reflect the immunogenicity findings in subjects with EoE.
8 USE IN SPECIFIC POPULATIONS	Section 8.4 was updated to reflect that the safety and effectiveness of dupilumab was established in pediatric patients 12 years of age and older, weighing at least 40kg, with EoE, as supported by Parts A and B of Study 1774. It was also described that the safety and effectiveness in adults and pediatric patients were similar. The Applicant's statement that the safety and effectiveness in pediatric patients less than 12 years of age and weighing less than 40 kg has not been established, was acceptable.

Full Prescribing Information Sections	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI
12 CLINICAL PHARMACOLOGY	(b) (4) Section 12.3 was updated to include PK information from subjects with EoE.

Full Prescribing Information Sections	High-Level Summary of the Major Issues With the Applicant's Proposed Draft PI and How Those Major Issues Were Addressed in the Finalized PI
14 CLINICAL STUDIES	The Applicant proposed Section 14.4 describing the results of Study 1774. The Section was edited to be consistent with FDA's evaluation and analyses of the efficacy data from Study 1774. The following edits reflect the changes made to the Section: Since a single study was conducted, the name of the study was removed, and references changed to "Part A" and "Part B." (b) (4) The demographic and baseline characteristics information was edited to provide relevant details (b) (4) (b) (4) (b) (4) The Division revised the description of the symptomatic coprimary endpoint results to incorporate the results of the anchor-based analyses that incorporated the subjects' perspectives that indicated that the observed improvement in dysphagia in Parts A and B is representative of a clinically meaningful within-subject improvement.

12. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

13. Postmarketing Requirements and Commitment

The following PMR under Section 505(o)(3) of FDAAA will be issued at the time of approval of the application.

4276-1

Complete Part C of the ongoing clinical trial, R668-EE-1774, "A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis," to evaluate the long-term use of Dupixent (dupilumab) in adult and pediatric patients ages 12 years and older with eosinophilic esophagitis (EoE) over 52 weeks of therapy.

Trial Completion: 09/2022
Final Report Submission: 03/2023

The following PMCs will be issued at the time of approval of the application.

4276-2

A one-year, randomized, double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis.

Trial Completion: 04/2023
Final Report Submission: 10/2023

4276-3

A long-term extension study to evaluate the long-term safety of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age, with active eosinophilic esophagitis, who participated in postmarketing commitment study 4276-2. This study may be conducted as part of postmarketing commitment study 4276-2.

Final Protocol Submission: 08/2022
Trial Completion: 08/2025
Final Report Submission: 02/2026

14. Division Director (Clinical) Comments

I concur with the recommendation of the review team to approve supplemental BLA 761055/S-040 for Dupixent (dupilumab) to expand the indications to include the treatment of adult and

pediatric patients aged 12 years and older, weighing at least 40 kg, with eosinophilic esophagitis (EoE). Dupixent, a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 by binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes, was granted a breakthrough therapy designation for EoE and will be the first product to be approved for use in this indication. The recommended dosage is 300 mg administered subcutaneously once weekly (QW). Data submitted in the sBLA support the conclusion that the benefits of treatment with Dupixent in the intended population outweigh the identified risks.

I agree with the review team that data submitted in this sBLA are adequate to support a conclusion that the effectiveness of Dupixent has been established in subjects with EoE. To support the indication, the Applicant conducted a three-part adequate and well-controlled clinical trial, Study R668-EE-1774 (Study 1774). Parts A and B of Study 1774 were randomized, double-blind, and placebo-controlled, and were conducted as independent parts with distinct populations; those who completed either Part A or Part B were eligible to enroll in Part C (open-label for those enrolling from Part A, and regimen-blinded for those enrolling from Part B). This sBLA submission included results from all parts except Part C of subjects who completed Part B (Part B/C), which is anticipated to complete in July 2022.

In both Parts A and B, coprimary endpoints of histologic response and reduction in dysphagia symptoms (assessed by Dysphagia Symptom Questionnaire [DSQ], a well-defined and reliable PRO instrument) demonstrated statistically significant treatment differences between subjects treated with dupilumab 300 mg QW and those who received placebo at Week 24. FDA review team's anchor-based analyses confirmed that the treatment differences observed for the symptomatic coprimary endpoint were representative of clinically meaningful change in favor of dupilumab treatment.

Although limited by the open-label study design, descriptive analyses of subjects in Part A that continued to receive 300 mg QW through Part C (Part A/C) for a total of 52 weeks were supportive of sustained treatment effects on both histologic and symptomatic endpoints. Subgroup analyses of efficacy assessments in the adolescent subpopulation also demonstrated improvement on both histologic and symptomatic coprimary endpoints, albeit a smaller effect than adults on the symptomatic coprimary endpoint. Given the similarity of disease presentation, progression, and expected response to treatment between adults and adolescents with EoE, the determination of efficacy in the adolescent subgroup is supported by the results of efficacy analyses from the overall study population. Subgroup analyses of the mean change in 14-day DSQ total scores over time in adolescent and adult subjects further supported the demonstration of efficacy in adolescent subjects treated with dupilumab.

The safety profile of Dupixent in adults and adolescents with EoE was similar to that seen in other indications. The most common adverse reactions observed In Study 1774 were injection site reactions, upper respiratory tract infections, arthralgia, and herpes viral infections. Upper respiratory tract infections were identified as a new adverse reaction in subjects with EoE; however, the URIs were generally mild and did not lead to treatment interruption or discontinuation. Arthralgia, which has been identified as an adverse reaction to dupilumab in

other indications, was also observed in subjects with EoE. The Prescribing Information and Medication Guide adequately inform prescribers and patients about this risk, which is monitorable and treatable. Additional characterization of this adverse reaction in subjects with EoE will be performed as part of a PMR under FDAAA; a REMS will not be required.

Although the benefit-risk profile of dupilumab in subjects with EoE was favorable, the limited number of subjects with EoE that received the to-be-marketed dosage (i.e., 300 mg QW) for 52 weeks at the time of sBLA submission (n=40) led to some uncertainties regarding the ability of the available data to detect and adequately characterize adverse events that may occur or worsen with longer-term exposure to dupilumab. Thus, the following post-marketing requirement (PMR) will be issued to ensure the completion and timely reporting of safety and efficacy data from all subjects enrolled in Part C, which is anticipated to provide blinded data from approximately 74 additional subjects with EoE treated with dupilumab 300 mg QW for 52 weeks:

4276-1

Complete Part C of the ongoing clinical trial, R668-EE-1774, "A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients with Eosinophilic Esophagitis," to evaluate the long-term use of Dupixent (dupilumab) in adult and pediatric patients ages 12 years and older with eosinophilic esophagitis (EoE) over 52 weeks of therapy.

Dupixent has an orphan drug designation for EoE and, therefore, the Applicant is exempt from Pediatric Research Equity Act requirements. However, the Applicant agreed to conduct the following postmarketing commitment studies:

4276-2

A one-year, randomized, double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis.

4276-3

A long-term extension study to evaluate the long-term safety of Dupixent (dupilumab) in pediatric patients 1 to less than 12 years of age with active eosinophilic esophagitis, who participated in postmarketing commitment study 4276-2. This study may be conducted as part of postmarketing commitment study 4276-2.

As EoE is a serious condition with unmet medical need with no approved therapy, and in consideration of the favorable benefit-risk profile determined during the review of this sBLA, the availability of additional long-term data from Part B/C should not delay approval of dupilumab for the treatment of patients with EoE.

15. Appendices

15.1. References

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15.2. Financial Disclosure

The Applicant provided financial disclosures for the following covered clinical studies.

Covered Clinical Studies

- A Phase 3, Randomized, 3-Part Study to Investigate the Efficacy and Safety of Dupilumab in Adult and Adolescent Patients With Eosinophilic Esophagitis (EoE) / R668-EE-1774
- A Randomized, Double-Blind, Parallel, Placebo-Controlled Study of the Efficacy, Safety and Tolerability of Dupilumab in Adult Patients with Active Eosinophilic Esophagitis / R668-EE-1324

Table 39. Study R668-EE-1324

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 114		
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): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 40. Study R668-EE-1774

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 573		
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): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Study: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Population PK analysis

The Applicant conducted population pharmacokinetic (PopPK) analysis to:

- Assess the PK of dupilumab in subjects with EoE using an external validation approach with a PopPK model developed for dupilumab in healthy subjects and subjects with asthma or atopic dermatitis (AD);

- Update the PopPK model developed for dupilumab in healthy subjects and subjects with asthma or AD with the addition of PK data in subjects with EoE;
- Investigate the effects of selected EoE covariates on PK parameters; and
- Generate individual subject PK parameters and exposure predictions across patient populations.

A total of 251 adult and adolescent subjects with EoE in Studies 1324 and 1774 were included in the PopPK analysis. An external validation of the PK data from subjects in Studies 1324 and 1774 was conducted using the previously developed global PopPK model, which was developed using data from 20 clinical studies in healthy subjects (N = 202) and subjects with atopic dermatitis (N = 1913) or asthma (N = 2026). The previous model included dupilumab administered intravenously (IV) (1 to 12 mg/kg, single dose) or SC (75 to 600 mg single or repeated doses QW, Q2W, or Q4W) either alone or with concomitant topical corticosteroids (TCS). The global PopPK model was a 2-compartment model with first-order SC absorption, parallel linear and non-linear (Michaelis-Menten) elimination and weight-dependent elimination and volume of distribution. The external validation analysis demonstrated that dupilumab PK in subjects with EoE is consistent with AD and asthma patient populations. Following the external validation, the PopPK model was re-fit to a pooled dataset which included subjects with EoE.

Summaries of subject characteristics for the combined 22 studies, stratified by patient population are provided in Table 41 and Table 42. Categorical and continuous covariates for subjects with EoE from Studies 1324 and 1774 were further stratified and summarized in Table 43 and Table 44, respectively.

Table 41: Summary of Categorical Covariates in All Studies

Population	Patient Population			Healthy Subjects	Total
	EoE [a]	Asthma	AD		
N (%) Subjects	251	2015	1839	202	4307
Age Group					
Adults (≥ 18 years)	183 (72.9%)	1946 (96.6%)	1839 (100.0%)	202 (100.0%)	4170 (96.8%)
Adolescents (≥ 12 to < 18 years)	68 (27.1%)	69 (3.4%)	0 (0.0%)	0 (0.0%)	137 (3.2%)
ADA Status [b]					
Negative [c]	241 (96.0%)	1730 (85.9%)	1602 (87.1%)	135 (66.8%)	3708 (86.1%)
Positive (Low Titer)	8 (3.2%)	244 (12.1%)	221 (12.0%)	56 (27.7%)	529 (12.3%)
Positive (Moderate Titer)	2 (0.8%)	24 (1.2%)	15 (0.8%)	10 (5.0%)	51 (1.2%)
Positive (High Titer)	0 (0.0%)	17 (0.8%)	1 (0.1%)	1 (0.5%)	19 (0.4%)

AD = Atopic dermatitis; EoE = Eosinophilic esophagitis; N = Number; ADA = Anti-drug antibody
Notes: Negative ADA status means that the subject did not exhibit ADA, pre-existing ADA levels were not treatment-boosted, or did not fall into the categories of low, moderate or high titer, defined as "low" > 0 to < 1000, "moderate" ≥ 1000 to < 10000, and "high" ≥10000.
[a] Studies R668-EE-1324 and R668-EE-1774
Source: Population Pharmacokinetic Report R668-PK-21229-SR-01V1, Table 4.

Table 42: Summary of Continuous Covariates in All Studies

Population	Patient Population			Healthy Subjects	Total
	EoE [a]	Asthma	AD		
Number of Subjects	251	2015	1839	202	4307
Age (years)					
Mean (SD)	29.8 (13.4)	48.0 (14.7)	37.9 (13.6)	34.6 (11.45)	42.0 (15.2)
Median (Min, Max)	28 (12, 68)	50 (12, 83)	36 (18, 88)	32 (18, 63)	42 (12, 88)
Missing	0	0	0	0	0
Weight (kg)					
Mean (SD)	76.4 (21.3)	80.0 (19.6)	76.5 (18.4)	76.0 (9.9)	78.1 (18.9)
Median (Min, Max)	75.0 (40.0, 171.1)	78.0 (32.0, 185.6)	74.0 (39.8, 175.4)	77.3 (52.1, 94.6)	76.0 (32.0, 185.6)
Missing	0	0	0	0	0

AD = Atopic dermatitis; EoE = Eosinophilic esophagitis; SD = Standard deviation; Min = Minimum; Max = Maximum
[a] Studies R668-EE-1324 and R668-EE-1774
Source: Population Pharmacokinetic Report R668-PK-21229-SR-01V1, Table 5.

Table 43: Summary of Categorical Covariates at Baseline for Subjects with EoE, Stratified by Study

Population	R668-EE-1324	R668-EE-1774	EoE Total
N (%) Subjects	23	228	251
Gender			
Males	13 (56.5%)	138 (60.5%)	151 (60.2%)
Females	10 (43.5%)	90 (39.5%)	100 (39.8%)
Age Group			
Adults (≥ 18 years)	23 (100%)	160 (70.2%)	183 (72.9%)
Adolescents (≥ 12 to < 18 years)	0 (0%)	68 (29.8%)	68 (27.1%)
ADA Status [a]			
Negative [b]	21 (91.3%)	220 (96.5%)	241 (96.0%)
Positive (Low Titer)	2 (8.7%)	6 (2.6%)	8 (3.2%)
Positive (Moderate Titer)	0 (0%)	2 (0.9%)	2 (0.8%)
Positive (High Titer)	0 (0%)	0 (0%)	0 (0%)

EoE = Eosinophilic esophagitis; N = Number; ADA = Anti-drug antibody;
Notes: Negative ADA status (No treatment emergent ADA) means that the subject did not exhibit ADA, pre-existing ADA levels were not treatment-boosted, or did not fall into the categories of low, moderate or high, defined as "low" > 0 to < 1000, "moderate" ≥ 1000 to < 10000, and "high" ≥10000.
Source: Population Pharmacokinetic Report R668-PK-21229-SR-01V1, Table 6.

Table 44: Summary of Continuous Covariates at Baseline for Subjects With EoE by Study

Population	R668-EE-1324	R668-EE-1774	EoE Total
Number of Subjects	23	228	251
Age (years)			
Mean (SD)	33.1 (8.7)	29.5 (13.8)	29.8 (13.4)
Median (Min, Max)	33 (19, 48)	27 (12, 68)	28 (12, 68)
Missing	0	0	0
Weight (kg)			
Mean (SD)	84.7 (23.9)	75.6 (20.9)	76.4 (21.3)
Median (Min, Max)	80.4 (46.3, 148.0)	74.1 (40.0, 171.1)	75.0 (40.0, 171.1)
Missing	0	0	0
Baseline DSQ Total Score [a]			
Mean (SD)	NA	35.6 (11.9)	35.6 (11.9)
Median (Min, Max)	NA	37.9 (8.4, 70.0)	37.9 (8.4, 70.0)
Missing	23	0	23
Baseline Peak Eosinophil Count			
Mean (SD)	102.1 (53.5)	87.6 (47.8)	88.9 (48.4)
Median (Min, Max)	86.0 (22.0, 233.0)	79.0 (15.0, 258.0)	80.0 (15.0, 258.0)
Missing	0	0	0
Baseline EREFS Total Score			
Mean (SD)	NA	6.8 (3.1)	6.8 (3.1)
Median (Min, Max)	NA	7.0 (0.0, 16.0)	7.0 (0.0, 16.0)
Missing	23 [b]	0	23
Baseline Eosinophilic Esophagitis Histology Scoring System Grade Mean Score			
Mean (SD)	1.4 (0.4)	1.3 (0.4)	1.3 (0.4)
Median (Min, Max)	1.3 (0.7, 2.4)	1.2 (0.5, 2.3)	1.3 (0.5, 2.4)
Missing	0	0	0
Baseline Eosinophilic Esophagitis Histology Scoring System Stage Mean Score			
Mean (SD)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)
Median (Min, Max)	1.3 (0.9, 2.1)	1.3 (0.4, 2.2)	1.3 (0.4, 2.2)
Missing	0	0	0
Baseline Alkaline Phosphatase (IU/L)			
Mean (SD)	61.0 (15.3)	104.5 (76.5)	100.5 (74.1)
Median (Min, Max)	61.0 (36.0, 94.0)	76.0 (31.0, 454.0)	75.0 (31.0, 454.0)
Missing	0	0	0
Baseline Alanine Aminotransferase (IU/L)			
Mean (SD)	21.7 (8.8)	21.6 (14.1)	21.6 (13.7)
Median (Min, Max)	23.0 (10.0, 40.0)	18.0 (7.0, 97.0)	18.0 (7.0, 97.0)
Missing	0	0	0
Baseline Aspartate Aminotransferase (IU/L)			
Mean (SD)	20.3 (6.1)	22.2 (10.2)	22.0 (9.9)
Median (Min, Max)	18.0 (11.0, 35.0)	20.0 (9.0, 103.0)	20.0 (9.0, 103.0)
Missing	0	0	0

EoE = Eosinophilic esophagitis; SD = Standard deviation; Min = Minimum; Max = Maximum; DSQ = Dysphagia Symptom Questionnaire; EREFS = Endoscopic Reference Score; NA = Not applicable

[a] Study R668-EE-1324 did not collect DSQ information, so the values were recorded as "missing" and the summary statistic for the total column is the same as that reported for Study R668-EE-1774.

[b] Study R668-EE-1324 used a different EREFS instrument than Study R668-EE-1774, with different scoring scales; therefore, the scores were not comparable and Study R668-EE-1324 was recorded as missing and not included in the summary measures (total).

Source: Population Pharmacokinetic Report R668-PK-21229-SR-01V1, Table 7.

The parameter estimates for the updated PopPK model with the pooled dataset (22 studies) were compared to the parameter estimates from the previous global PopPK model (20 studies).

As shown in Table 45, the structural parameter estimates for the updated final model were within 20% of the previous global model with the confidence intervals mostly overlapped. The goodness-of-fit plots for the updated final PopPK model are presented in Figure 12.

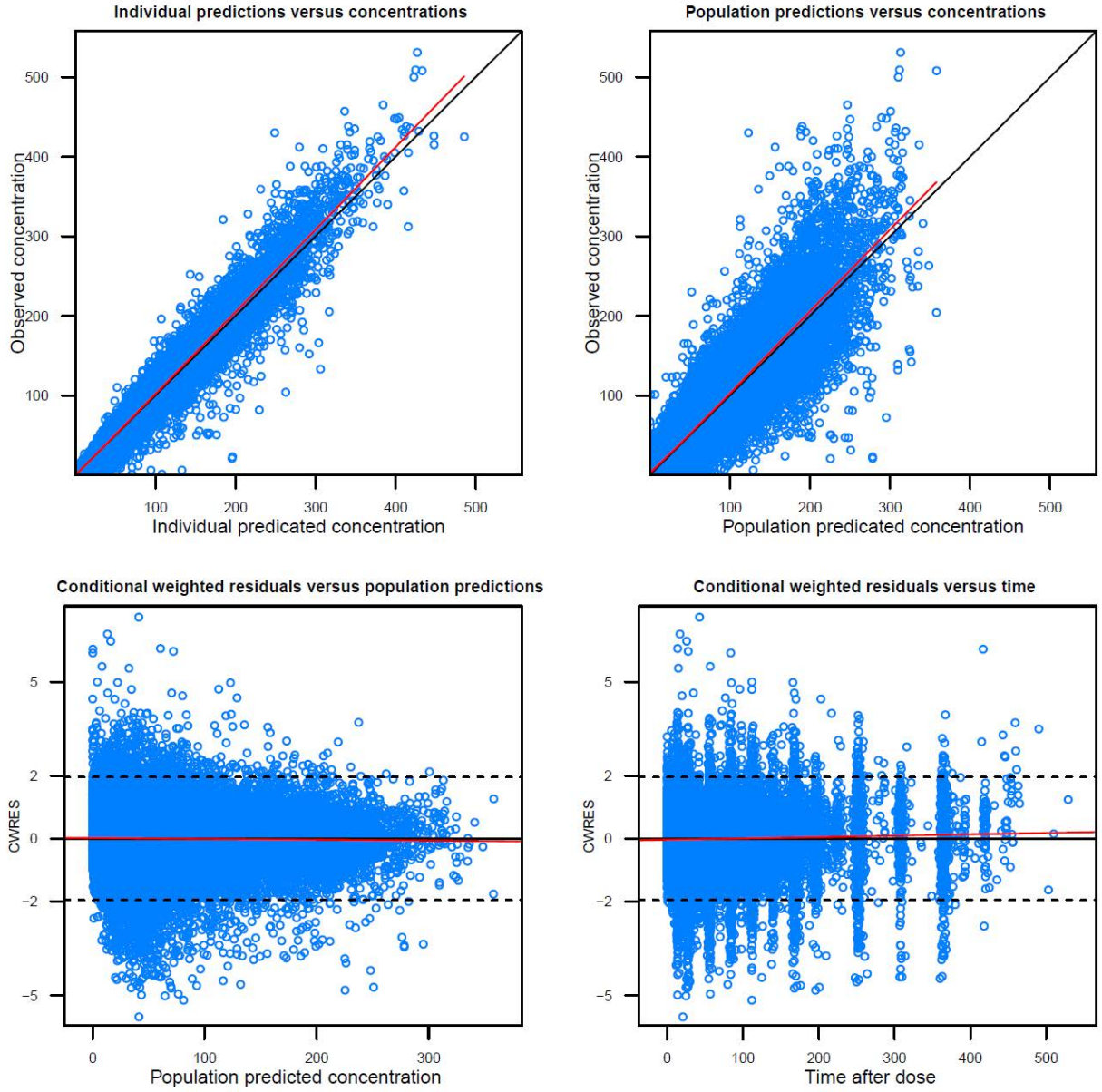
Table 45: Final PopPK Model Comparison

Parameters	Global Model Estimates [a] 20 Studies (Bootstrap 95%CI) [b]	Updated Final Model Estimates 22 Studies (95% CI)	Percent Difference
Fixed Effects			
K_{EL} (day^{-1})	0.041 (0.037, 0.044)	0.040 (0.038, 0.041)	-2.4%
Vc (L)	2.79 (2.63, 2.97)	2.93 (2.84, 3.02)	5.0%
K_{CP} (day^{-1})	0.089 (0.06, 0.11)	0.080 (0.073, 0.086)	-10.1%
K_{PC} (day^{-1})	0.15 (0.13, 0.17)	0.15 (0.14, 0.15)	0.0%
V_{MAX} (mg/L/day)	1.48 (1.24, 1.61)	1.39 (1.33, 1.46)	-6.1%
Km (mg/L)	2.52 (1.84, 3.01)	2.41 (2.01, 2.82)	-4.4%
KA (day^{-1})	0.25 (0.22, 0.29)	0.26 (0.25, 0.27)	4.0%
F1	0.628 (0.536, 0.680)	0.628 FIX	--
CL (L/day)	0.114	0.117	--
V3 (L)	1.66	1.56	--
WT on Vc (ref: 76 kg)	0.72 (0.67, 0.75)	0.73 (0.70, 0.76)	1.4%
WT on V_{MAX} (ref: 76 kg)	0.33 (0.22, 0.44)	0.32 (0.25, 0.40)	-3.0%
WT on K_{EL} (ref: 76 kg)	0.12 (0.05, 0.20)	0.14 (0.08, 0.20)	16.7%
IIV (CV%) [Shrinkage%]			
K_{EL}	21.7 [41%]	22.9 [40%]	
Vc	8.09 [63%]	17.5 [23%]	
V_{MAX}	29.1 [43%]	33 [41%]	
KA	44.0 [58%]	45.8 [60%]	
F1	41.9 [31%]	0 FIX	
Residual Error			
Proportional **(%)**	0.17	0.17	
Additive (mg/L)	2.06	2.0	

K_{EL} = Linear elimination rate constant; Vc = Volume of the central compartment; K_{CP} = Inter-compartment distribution rate constant from central to peripheral; K_{PC} = Inter-compartment distribution rate constant from peripheral to central; V_{MAX} = Maximum target mediated rate of elimination; Km = Concentration of half-maximal nonlinear clearance (Michaelis constant); KA = Absorption rate constant; F1 = Bioavailability; CL = clearance (derived value); V3 = Vp = Volume of the peripheral compartment (derived value); WT = Body weight; IIV = Inter individual variability; CV% = Percent coefficient of variation; OFV = Objective function value; ref = Reference value for body weight

Source: Population Pharmacokinetic Report R668-PK-21229-SR-01V1, Table 9.

Figure 12: Goodness-of-fit Plots for the Updated Final Model



Source: Reviewer's analysis, based on the submitted population PK dataset "nmeoe.xpt".

The final model (including all 22 studies) predicted steady-state exposures that were comparable across multiple indications, including EoE, AD, and asthma, suggesting no differences in dupilumab PK across the studied populations. Covariate analysis identified no new covariates that might impact dupilumab PK in subjects with EoE, in addition to the existing effects of body weight on linear CL and Vc in the updated global PopPK model. No further covariates were explored in this analysis.

Reviewer's Comments: *The Applicant's population PK analyses is acceptable for describing dupilumab PK in adolescent and adult subjects with EoE (N=251). Body weight (40 to 171 kg)*

was identified as a significant covariate on dupilumab PK: higher systemic exposure as the body weight gets lower. However, its impact on efficacy and safety at the proposed dosing regimen of 300 mg QW is not considered clinically relevant based on the observed flat E-R for AESI (Section 15.3.2), and overall low incidences of TEAEs by body weight. The overall efficacy was established in subjects weighing ≥ 40 kg, and the subgroup analysis of coprimary efficacy endpoints showed numerically similar response rates by body weight (Table 6). After the effect of body weight is accounted for, dupilumab PK does not differ by age in the range of 12 to 68 years (Figure 5).

15.3.2. Exposure-Response Analyses

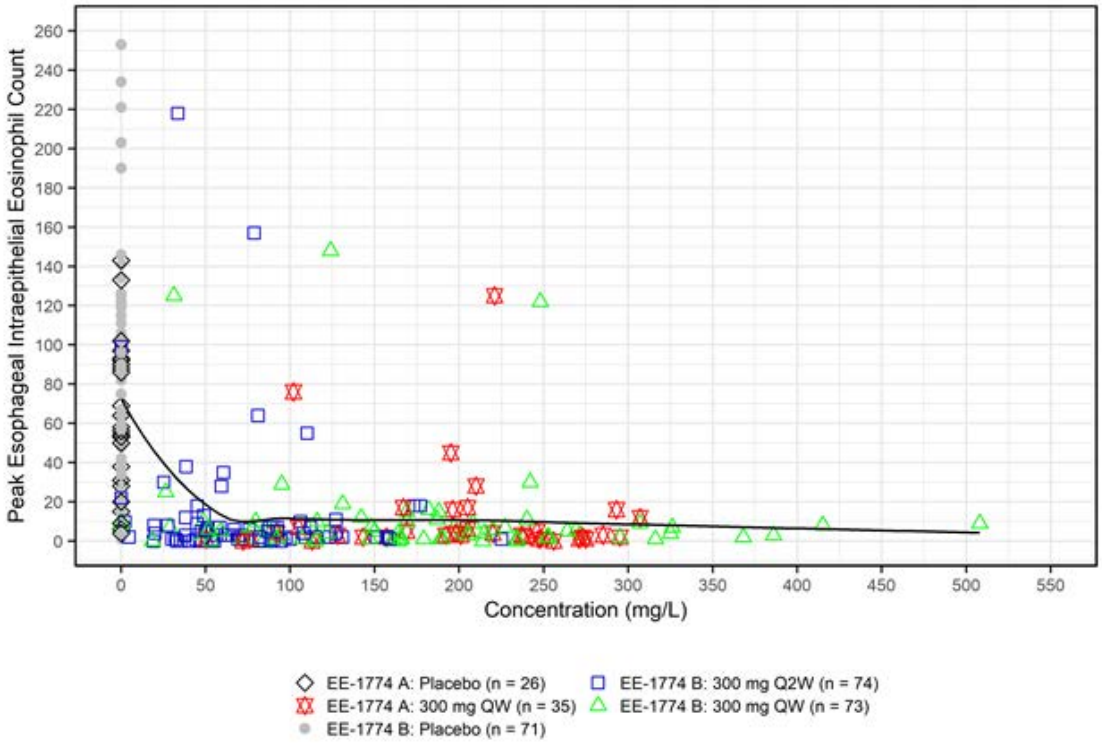
The Applicant conducted descriptive exposure-response (E-R) analyses using observed trough concentrations (Ctrough) of dupilumab in Part A and Part B of Study 1774. The E-R analysis for efficacy included pooled data from subjects receiving placebo or 300 mg SC QW during Part A or Part B of Study 1774 and subjects receiving 300 mg SC Q2W during Part B. The key efficacy endpoints were evaluated, with a focus on the coprimary clinical efficacy endpoints of the proportion of subjects achieving peak esophageal intraepithelial eosinophil counts ≤6 eos/hpf and the absolute and percent change from baseline in DSQ total score at Week 24. The E-R analysis for safety was conducted for AESI only in Part B of Study 1774, as it provided a representative number of events for a meaningful E-R analysis. Part A data were not included in the E-R safety analysis due to varying definitions of AESI between Part A and Part B.

The E-R relationships for esophageal intraepithelial eosinophil count at Week 24 are shown in Figure 2 and Figure 13. The E-R findings were consistent with the dose-response relationship, indicating that the maximal response in esophageal intraepithelial eosinophil count was achieved at dupilumab exposure levels associated with the higher dosage of 300 mg QW.

For DSQ total score, the E-R relationship (see Figure 3) showed a shallow trend towards greater change from baseline at higher dupilumab exposure associated with 300 mg QW compared to that with 300 mg Q2W regimen. This was also consistent with the dose-response findings in DSQ total score.

The E-R analysis for AESI based on Part B only did not identify a relationship between dupilumab Ctrough and AESI at Week 24. However, this analysis might be limited due to overall low number of AESIs included.

Figure 13: Plot of Peak Esophageal Intraepithelial Eosinophil Count vs Trough Concentration of Dupilumab at Week 24 in Adult and Adolescent Subjects With Eosinophilic Esophagitis (Study 1774 Part A and Part B)



Source: Adapted from Applicant's BLA 761055 S-040 submission. Summary of Clinical Pharmacology, Figure 12.

15.3.3. Bioanalytical Method Report

The bioanalytical methods used for the EoE program to determine dupilumab concentrations in human serum samples are the same as those previously submitted and reviewed in the original marketing application for AD, and bioanalytical methods to assess the immunogenicity are the same as those previously submitted and reviewed in the marketing application for asthma (Table 46). Please refer to the clinical pharmacology review by Dr. Jie Wang during the original application (DARRTS date 12/19/2016) for the treatment of moderate to severe atopic dermatitis and supplement BLA S07 reviewed by Dr. Dipak Pisal (DARRTS date 10/19/2018) for the treatment of moderate to severe asthma.

Table 46: Summary of Validation Reports Used in Clinical Studies for Eosinophilic Esophagitis

Validation (Method) Study Report	Analyte	Matrix (MRD)	LLOQ Sensitivity (ng/mL)	Drug Tolerance	Accuracy (%AR)	Within-run Precision (CV%)	Between-run Precision (CV%)	Clinical Studies
REGN668-AV-13074-VA-01V1 (a)	functional dupilumab	human serum (1:50)	78	NA	96 - 105	≤9	≤9	R668-EE-1324 R668-EE-1774 (Part A, Part B and Part C)
REGN668-AV-13089-VA-01V3 (b)	anti-dupilumab antibodies	human serum (1:30)	6.9	205 µg/mL	NA	NA	NA	R668-EE-1324 R668-EE-1774 (Part A, Part B and Part C)
REGN668-AV-13112-VA-01V2 (b)	dupilumab neutralizing antibodies	human serum (1:10)	125	298 ng/mL	NA	NA	NA	R668-EE-1324 R668-EE-1774 (Part A, Part B and Part C)

Source: Applicant's BLA 761055 S-040 submission Module 2.7.1 Summary of Biopharmaceutic Studies, Table 1.
Note: (a) Report provided in the original marketing application for atopic dermatitis.
(b) Report provided in the marketing application for asthma.
Abbreviations: %AR = %Analytical Recovery, CV = Coefficient variation, LLOQ = Lower limit of quantitation, MRD = Minimum required dilution, NA = Not applicable.

Bioanalytical in-study analysis reports for Study 1324 and Study 1774 (Parts A, B, and C) in adult and adolescent subjects with EoE are provided in this submission and overall are acceptable. Bioanalytical in-study analysis reports for dupilumab serum concentrations are described briefly below.

For bioanalytical in-study analysis report for Study 1324, quality control (QC) samples at 3 different concentrations (4.5, 20, and 75 ng/mL) were prepared. The %analytical recovery (%AR) ranged from 99% to 111% for the non-zero standards and QCs. The %coefficient of variation (CV%) for the non-zero standards and QCs ranged from 2% to 5%.

For bioanalytical in-study analysis reports for Study 1774, quality control (QC) samples at 3 different concentrations (4.5, 20, and 75 ng/mL) were prepared for Parts A, B, and C. In Part A, the %AR ranged from 94% to 104% for the non-zero standards and QCs, and CV% for the non-zero standards and QCs ranged from 1% to 8%. In Part B, the %AR ranged from 91% to 102% for the non-zero standards and QCs, and CV% for the non-zero standards and QCs ranged from 2% to 11%. In Part C, the %AR ranged from 91% to 103% for the non-zero standards and QCs, and CV% for the non-zero standards and QCs ranged from 2% to 10%.

15.4. Supplemental Statistical Methods

15.4.1. Adjustment for Multiple Comparisons

Part A and Part B each had their own 2-sided significance level of 0.05. For each Part, the hypotheses were tested sequentially to control the overall Type-1 error rate. The prespecified hierarchical orders are defined in Table 47 and Table 48.

Table 47: Hierarchical Testing Order for Part A

	Endpoints	Dupilumab 300 mg QW
Coprimary	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24	1
	Absolute change in DSQ score from baseline to Week 24	
Secondary	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to Week 24	2
	Absolute change in EoEHSS mean grade score from baseline to Week 24	3
	Absolute change in EoEHSS mean stage score from baseline to Week 24	4
	Absolute change in EoE EREFS total score from baseline to Week 24	5
	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at Week 24	6
	Percent change in DSQ from baseline to Week 24	7
	NES for the relative change from baseline to Week 24 in the EoE diagnostic panel (EDP) transcriptome signature	8
	NES of the relative change from baseline to Week 24 in the type 2 inflammation transcriptome signature	9

Source: Clinical Study Report for R668-EE-1774 Part A (p48-49).
Abbreviations: DSQ = Dysphagia Symptom Questionnaire, NES = Normalized Enrichment Score.

Table 48: Hierarchical Testing Order for Part B

	Endpoints	Dupilumab 300 mg QW	Dupilumab 300 mg QW
Coprimary	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤6 eos/hpf at Week 24	1	3
	Absolute change in DSQ score from baseline to Week 24		
Secondary	Percent change in DSQ from baseline to Week 24	2	4
	Percent change in peak esophageal intraepithelial eosinophil count (eos/hpf) from baseline to Week 24	5	8
	Absolute change in EoEHSS mean grade score from baseline to Week 24	6	9
	Absolute change in EoEHSS mean stage score from baseline to Week 24	7	10
	Absolute change in EoE EREFS total score from baseline to Week 24	11	12
	Proportion of patients achieving peak esophageal intraepithelial eosinophil count of <15 eos/hpf at Week 24	13	14
	NES for the relative change from baseline to week 24 in the EoE diagnostic panel (EDP) transcriptome signature	15	17
	NES of the relative change from baseline to Week 24 in the type 2 inflammation transcriptome signature	16	18

Source: Clinical Study Report for R668-EE-1774 Part B (p53).
Abbreviations: DSQ = Dysphagia Symptom Questionnaire, NES = Normalized Enrichment Score.

15.5. Supplemental Efficacy Analyses

15.5.1. Missing Data: DSQ Scoring Algorithm

As described in Section 8.1.2, the Applicant's SAP specifies that the calculation of the 14-day DSQ total score requires at least 8 days of diary entries (including days when subjects responded "No" to Item 1 -- "Since you woke up this morning, did you eat solid food?") in the 14-day period. If a subject answers "No" to Item 1 on a particular day, the daily DSQ score is considered missing for score calculation, but diary completion is considered compliant for that day. According to the Applicant's calculation, the requirement of having "at least 8 days of diary entries" does not take into consideration whether any of the daily score is missing. This differs from FDA's calculation that requires at least 8 days of diary entries with non-missing data, which is implied by the DSQ scoring formula (See Section 8.1.2 for the DSQ scoring formula).

To demonstrate the difference in the missing data rules used by the Applicant and by FDA, an example using data from one subject (ID: (b) (6)) at Week 24 in Part A is presented in Table 49. This subject did not eat solid food on Days 163 and 165. FDA considers

these two daily scores missing, resulting in 6 non-missing daily diaries and not meeting FDA's scoring requirement of at least 8 days of diary entries with non-missing data. Therefore, the 14-day DSQ total score is missing for this subject. However, according to the Applicant's calculation, Days 163 and 165 are considered compliant for diary completion, resulting in 8 diary entries despite missing daily scores for Days 163 and 165, and a 14-day DSQ total score of 30.3 is calculated for this subject.

Table 49: Example DSQ Total Score Calculation For Subject (ID: (b) (6) at Week 24 in Part A

Date	Answer to Item 1	Reason not Eating Solid Food	DSQ Daily Score	Num of Non-missing Daily Diaries		14-Day DSQ Total Score	
				Applicant	FDA	Applicant	FDA
157	Yes		4	8	6	30.3	Missing
159	Yes		3				
161	Yes		3				
162	Yes		3				
163	**No**	Due to EoE	**Missing**				
165	**No**	Not related to EoE	**Missing**				
166	Yes		0				
167	Yes		0				

Source: Patient-Focused Statistical Support (PFSS) reviewer generated table. Analysis was verified by reviewer using Applicant submitted data adqsdsq.xpt.

Table 50 shows the number of subjects impacted by the Applicant's missing data rule. As shown, the Applicant's missing data rule affected very few subjects, and minimum impact is expected on the efficacy analysis results after comparing the baseline and Week 24 14-day DSQ total score summary statistics calculated using the Applicant's and FDA's methods. In addition, given that the Applicant's missing data rule was pre-specified in the SAP, FDA considers the Applicant's DSQ scoring algorithm acceptable for this sBLA. For any future use of the DSQ, FDA's DSQ scoring algorithm should be used.

Table 50: Number of Subjects Impacted by the Applicant's Missing Data Rule (Parts A and B)

Score	Part A		Part B	
	Baseline (N=81)	Week 24 (N=77)	Baseline (N=240)	Week 24 (N=228)
14-Day DSQ Total Score	0	1	0	2
7-Day DSQ Total Score[1]	0	1	1	0

Source: PFSS reviewer generated table. Analysis was conducted by reviewer using Applicant submitted data adqsdsq.xpt.
1. Refer to Section 8.1.5.6 for discussion on the 7-day DSQ total score.

Table 51 shows the number of missing daily diaries over the 14-day period at baseline and Week 24 by treatment arm for Parts A and B. Overall, there are similar proportions of subjects with more than 6 days of missing daily diaries by treatment arm in Parts A and B.

Table 51: Number of Missing Daily Diaries Over 14-Day Period at Baseline/Week 24 (Parts A and B)

			Number of Missing Daily Diaries[1]		
Part	**Time**	**Treatment Arm**	**0**	**1-6**	**7-14**
Part A	Baseline	Dupilumab 300 mg QW (N=42)	13 (31.0%)	29 (69.0%)	0
		Placebo (N=39)	9 (23.1%)	30 (76.9%)	0
	Week 24	Dupilumab 300 mg QW (N=41)	9 (22.0%)	29 (70.7%)	3 (7.3%)
		Placebo (N=36)	9 (25.0%)	24 (66.7%)	3 (8.3%)
Part B[2]	Baseline	Dupilumab 300 mg QW (N=80)	33 (41.3%)	47 (58.8%)	0
		Dupilumab 300 mg Q2W (N=81)	25 (30.9%)	56 (69.1%)	0
		Placebo (N=78)	25 (32.1%)	53 (67.9%)	0
	Week 24	Dupilumab 300 mg QW (N=76)	22 (28.9%	43 (56.6%)	11 (14.5%)
		Dupilumab 300 mg Q2W (N=79)	14 (17.7%)	49 (62.0%)	16 (20.3%)
		Placebo (N=72)	17 (23.6%)	45 (62.5%)	10 (13.9%)

Source: PFSS reviewer generated table. Analysis was conducted by reviewer using Applicant submitted data adqsdsq.xpt.

1. Subjects who dropped out were excluded from the numbers.
2. One placebo subject in Part B FAS dataset did not have a baseline 14-day DSQ total score due to having less than 8 diary entries during the 14-day baseline assessment period. This subject was not included in the analysis.

15.5.2. Missing Data: Solid Food Avoidance Assessed by DSQ Item 1

During the IND phase, FDA communicated concerns to the Applicant that it would be risky to have missing data in the DSQ daily score due to avoiding solid food because of EoE severity. It is important to appropriately score and document subjects fitting this scenario, as it would affect the interpretation of the DSQ endpoint scores. Therefore, FDA examined the number of subjects by number of days avoiding solid food by treatment arm over the 14-day period at baseline and Week 24, for Parts A and B (Table 52). Overall, few subjects avoided solid food on at least 1 day at baseline or Week 24 in Part A and Part B. Among all cases of solid food avoidance, a higher proportion of placebo subjects avoided solid food due to EoE compared to dupilumab 300 mg QW subjects at Week 24 in both Parts A and B.

Table 52: Number of Subjects by Number of Days Avoiding Solid Food Over 14-Day Period (Parts A and B)

			Number of Days Avoiding Solid Food[1]						
Part	**Time**	**Treatment Arm**	**1**	**2**	**3**	**4**	**5-14**	**Total (%)**	**% Due to EoE [2]**
Part A	Baseline	Dupilumab 300 mg QW (42)	0	0	0	0	0	0	--
		Placebo (39)	4	0	0	0	0	4 (10.3%)	25.0%
	Week 24	Dupilumab 300 mg QW (41)	1	0	0	0	0	1 (2.4%)	0%
		Placebo (36)	2	2	0	0	0	4 (11.1%)	33.3%
Part B[3]	Baseline	Dupilumab 300 mg QW (80)	3	1	0	1	0	5 (6.3%)	88.9%
		Dupilumab 300 mg Q2W (81)	8	0	1	1	0	10 (12.3%)	73.3%
		Placebo (78)	1	1	0	0	0	2 (2.6%)	66.7%
	Week 24	Dupilumab 300 mg QW (76)	0	0	0	0	0	0	--
		Dupilumab 300 mg Q2W (79)	4	0	1	0	0	5 (6.3%)	42.9%
		Placebo (72)	3	0	0	0	0	3 (4.2%)	33.3%

Source: PFSS reviewer generated table. Analysis was conducted by reviewer using Applicant submitted data adqsdsq.xpt.

1. Subjects answered "No" to Item 1 (i.e., "Since you woke up this morning, did you eat solid food?").
2. Subjects responded, "Because of your problems with swallowing solid food." to Item 1A (i.e., "Please select the reason for not eating solid food since you woke up this morning.").
3. One placebo subject in Part B FAS dataset did not have a baseline 14-day DSQ total score due to having less than 8 diary entries during the 14-day baseline assessment period. This subject was not included in the analysis.

To evaluate the impact of missing data due to solid food avoidance, the Applicant conducted a pre-specified sensitivity analysis by imputing a DSQ daily score of 6 for subjects who did not eat solid food due to problems with swallowing solid food. Results of this sensitivity analysis are consistent with the primary efficacy analysis results (see Section 15.5.4 for more details).

15.5.3. Missing Data For Primary Analyses

For the coprimary endpoint of peak esophageal intraepithelial eosinophil count ≤6, 20 (24.7%) of the 81 subjects in Part A and 25 (10.4%) of the 240 subjects in Part B had missing values for the Week 24 outcome (Table 53). For the coprimary endpoint of change in DSQ score, 15 (18.2%) of the 81 subjects in Part A and 55 (22.9%) of the 240 subjects in Part B had missing values for the Week 24 outcome (Table 54). In Part A, the missing rates were slightly higher for both endpoints in the placebo arm as compared to the dupilumab 300 mg QW arm, as all 5 subjects receiving rescue therapy were in the placebo arm, whereas in Part B, the missing rates for both outcomes were similar across the three arms.

Table 53: Number of Imputed Values for Coprimary Endpoint of Peak Esophageal Intraepithelial Eosinophil Count ≤6

	Part A		Part B		
	Placebo (N=39)	Dupilumab 300 mg QW (N=42)	Placebo (N=79)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)
Imputed, N	13	7	10	6	9
Rescue medication[1]	5	0	2	1	2
Measurement after Part C enrollment[1]	4	2	0	0	0
COVID-19 related Reason[2]	1	3	6	4	3
Other Reason[1]	3	2	2	1	4

Source: Reviewer generated table using Applicant submitted data ADSL.xpt, ADXEESO.xpt, and PKESO2R.xpt.
1. Imputed by non-responder imputation for the primary analysis.
2. Imputed by multiple imputation for the primary analysis.

Table 54: Number of Imputed Values for Coprimary Endpoint of Change in DSQ Score

	Part A		Part B		
	Placebo (N=39)	Dupilumab 300 mg QW (N=42)	Placebo (N=79)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)
Imputed, N	11	4	19	19	17
Rescue medication	5	0	2	1	2
< 8 daily DSQ entries	6	4	17[1]	18	15

Source: Reviewer generated table using Applicant submitted data ADSL.xpt, ADQSDSQ.xpt, and DSQSC.xpt.
1. This number includes two subjects who discontinued the study early, but still entered daily e-diaries after discontinuation.
Abbreviations: DSQ = Dysphagia Symptom Questionnaire.

15.5.4. Missing Data: Alternative Approaches for Handling Missing DSQ Data

The study considered two alternative approaches for handling the missing data used to calculate the DSQ total score. The first approach required that a subject completed four diary entries per week to qualify as non-missing. The second approach assigned a value of 6 to days when a subject did not eat solid food due to EoE. The primary statistical analyses were repeated using both alternative approaches and resulted in similar conclusions.

Table 55: Summary of Sensitivity Analyses for Absolute Change From Baseline in DSQ Total Score at Week 24

		Part A		Part B		
Analysis	Statistics[1]	Placebo (N=39)	Dupilumab 300 mg QW (N=41)	Placebo (N=79)	Dupilumab 300 mg Q2W (N=81)	Dupilumab 300 mg QW (N=80)
Primary	LS Mean Change (SE)	-9.6	-21.9	-13.9	-14.4	-23.8
	LS Mean Difference (95% CI)		-12.3 (-19.1, -5.5)		-0.5 (-5.4, 4.4)	-9.9 (-14.8, -5.0)
	P-value		0.0004		0.8393	<0.0001
Require 4 daily entries per period	LS Mean Change (SE)	-9.6	-21.1	-13.9	-14.4	-24.5
	LS Mean Difference (95% CI)		-11.5 (-18.2, -4.8)		-0.5 (-5.6, 4.6)	-10.6 (-15.6, -5.5)
	P-value		0.0008		0.85	<0.0001
DSQ Daily Score = 6 if did not eat solid food due to EoE	LS Mean Change (SE)	-9.4	-22.0	-13.8	-14.5	-23.9
	LS Mean Difference (95% CI)		-12.6 (-19.4, -5.8)		-0.7 (-5.7,4.2)	-10.1 (-15.1, -5.1)
	P-value		0.0003		0.77	<0.0001

Source: Clinical Study Report for R668-EE-1774 Part A (Table 22, p 75-76), Clinical Study Report for R668-EE-1774 Part B (Table 24, p 95-96); verified by reviewer using Applicant submitted data ADQSDSQ.xpt, DSQ3SC.xpt.

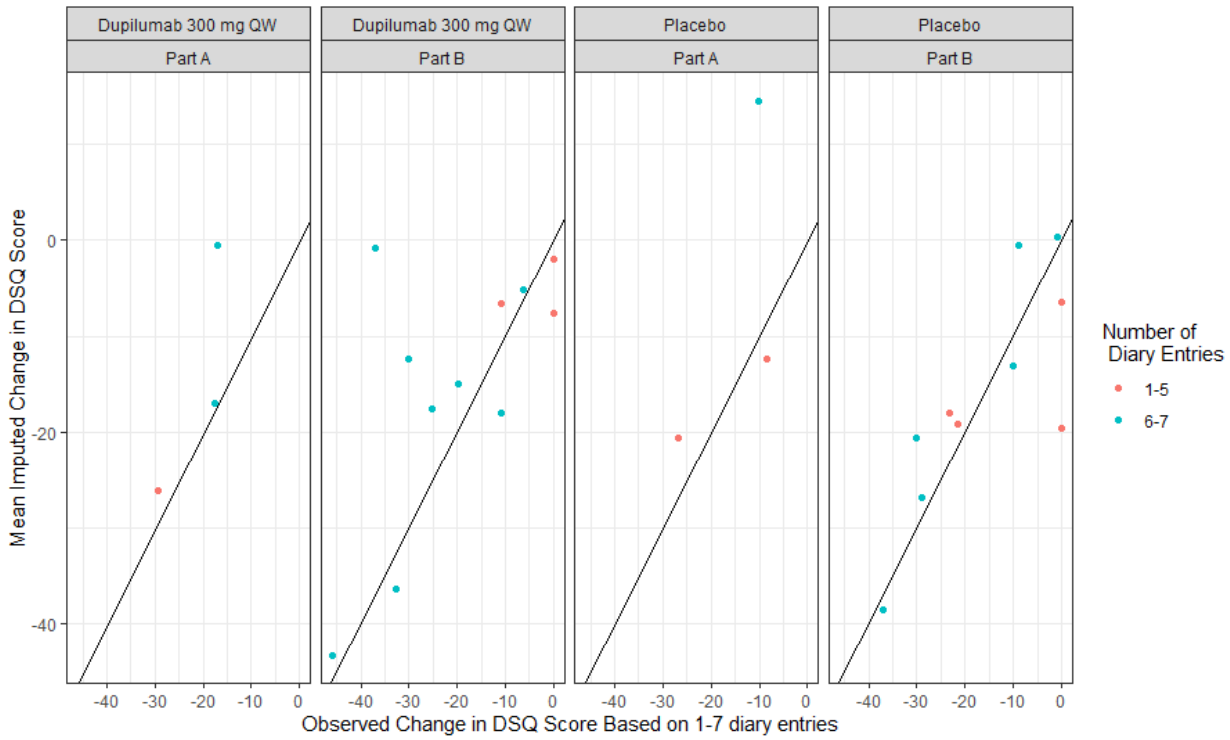
1. The reported means, differences, 95% CIs, and p-values were calculated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as the covariates.

Abbreviations: ANCOVA=analysis of covariance, CI = Confidence Interval, DSQ = Dysphagia Symptom Questionnaire, LS = Least Squares, QW = once weekly.

15.5.5. Missing Data: Sensitivity and Supplementary Analyses

The review team examined the impact of using imputed values in the primary analysis of the change in DSQ score. For Part A, the dupilumab 300 QW arm had minimal missing data. The placebo arm had a higher proportion of subjects with missing data, but 5 of the subjects in this group required rescue therapy and were therefore likely to be showing less improvement in their DSQ score. Of note, an analysis based on only the observed measurements, which would likely unfairly advantage the placebo arm due to rescue therapy usage, would still have resulted in a statistically significant LS mean difference of -10.57 (95% CI = -17.75, -3.39). For Part B, the rates of missing data and distribution of imputed values were similar across the three treatment arms, suggesting that the methods for handling missing data were unlikely to have biased the results in favor of dupilumab. Finally, 6 of the 15 subjects with imputed values in part A and 21 of the 36 subjects with imputed values in the dupilumab 300 mg QW and placebo arms of part B did not receive rescue medication and had between 1 and 7 daily diary entries during the Week 24 14-day period. Among these 27 subjects, the mean of the observed daily measurements was similar to the mean of the 50 imputed values in each subject (Figure 14) indicating that multiple imputation likely did not bias results in favor of dupilumab.

Figure 14: Comparison of Observed and Imputed[1] Values for Change in DSQ Score from Baseline to Week 24



Source: Reviewer analysis using Applicant submitted data ADQSDSQ.xpt, ADSL.xpt, DSQSC.xpt.
1. The mean of the imputed values for each subject.
Abbreviations: DSQ = Dysphagia Symptom Questionnaire.

To assess the robustness of analysis results under a MNAR assumption, a delta-adjusting pattern-mixture approach (Ratitch et al. 2013) for tipping point analysis was conducted for the coprimary endpoint of change in DSQ score (Table 56,Table 57). In Part A, the results were no longer statistically significant when the mean shifts in two arms (placebo/dupilumab 300 mg QW) were 0/-20, +15/-15, or +20/-10 (Table 56). In Part B, the results were no longer statistically significant when the mean shifts in the two arms were +10/-15, +15/-10, or +20/0 (Table 57). The mean shift (denoted as delta in the tables) indicates the difference in the mean of the imputed DSQ scores in the tipping point scenario compared to the mean of the imputed DSQ scores under missing at random for subjects with missing data. The large shifts in means required to lose statistical significance were considered implausible given the distribution of rescue medication usage by arm and the similarity of observed DSQ scores and imputed DSQ scores under the missing at random assumption for subjects who had less than 8 days of daily diary entries. It was noted that the MCMC step used in MI did not include covariates and, for the tipping point analysis, the regression step in MI did not include the randomization stratification variables as covariates. Therefore, as part of the review, an additional tipping point analysis was conducted using full conditional specification (FCS) for MI with covariates for treatment and randomization stratification variables. These results were similar to those reported in Table 56 and Table 57 and further confirm the conclusion that efficacy is robust to assumptions about missing data.

Table 56: Tipping Point Sensitivity Analysis for Part A: LS Mean Difference (p-value) Between Dupilumab 300mg QW and Placebo in Absolute Change From Baseline in DSQ Total Score at Week 24

	Delta for Dupilumab QW: 0	Delta for Dupilumab QW: 5	Delta for Dupilumab QW: 10	Delta for Dupilumab QW: 15	Delta for Dupilumab QW: 20
Delta for Placebo: 0	-11.29[1](0.0011)	-10.90 (0.0019)	-10.45 (0.0034)	-9.98 (0.0060)	-9.51 (0.0106)
Delta for Placebo: -5	-10.05 (0.0032)	-9.66 (0.0052)	-9.21 (0.0088)	-8.74 (0.0149)	-8.27 (0.0245)
Delta for Placebo: -10	-8.87 (0.0088)	-8.47 (0.0136)	-8.03 (0.0215)	-7.56 (0.0340)	**-7.09 (0.0523)**
Delta for Placebo: -15	-7.73 (0.0223)	-7.33 (0.0326)	-6.88 (0.0486)	**-6.42 (0.0718)**	**-5.95 (0.1034)**
Delta for Placebo: -20	**-6.64 (0.0508)**	**-6.24 (0.0702)**	**-5.79 (0.0984)**	**-5.33 (0.1367)**	**-4.86 (0.1852)**

Source: Submitted as a response to an information request (Sequence #1039, SDN 1791, 4/21/2022), verified by reviewer using Applicant submitted data adqsdsq.xpt.

1. For the primary analysis, the estimated difference in the absolute change from baseline is -12.3. The discrepancy (i.e., -11.29 vs -12.3) results from minor differences in the multiple imputation procedure used for the primary and tipping point analyses.
2. Values in bold represent analyses with a p-value >0.05.

Table 57: Tipping Point Sensitivity Analysis for Part B: LS Mean Difference (p-value) Between Dupilumab 300mg QW and Placebo in Absolute Change From Baseline in DSQ Total Score at Week 24

	Delta for Dupilumab QW: 0	Delta for Dupilumab QW: 5	Delta for Dupilumab QW: 10	Delta for Dupilumab QW: 15	Delta for Dupilumab QW: 20
Delta for Placebo: 0	-9.61 (<0.0001)	-8.60 (0.0007)	-7.57 (0.0040)	-6.53 (0.0169)	**-5.48 (0.0547)**
Delta for Placebo: -5	-8.63 (0.0004)	-7.62 (0.0025)	-6.58 (0.0115)	-5.54 (0.0410)	**-4.50 (0.1124)**
Delta for Placebo: -10	-7.79 (0.0013)	-6.78 (0.0066)	-5.75 (0.0263)	**-4.70 (0.0805)**	**-3.66 (0.1931)**
Delta for Placebo: -15	-7.09 (0.0033)	-6.08 (0.0144)	**-5.05 (0.0502)**	**-4.00 (0.1355)**	**-2.96 (0.2909)**
Delta for Placebo: -20	-6.49 (0.0070)	-5.48 (0.0273)	**-4.45 (0.0841)**	**-3.41 (0.2039)**	**-2.36 (0.3990)**

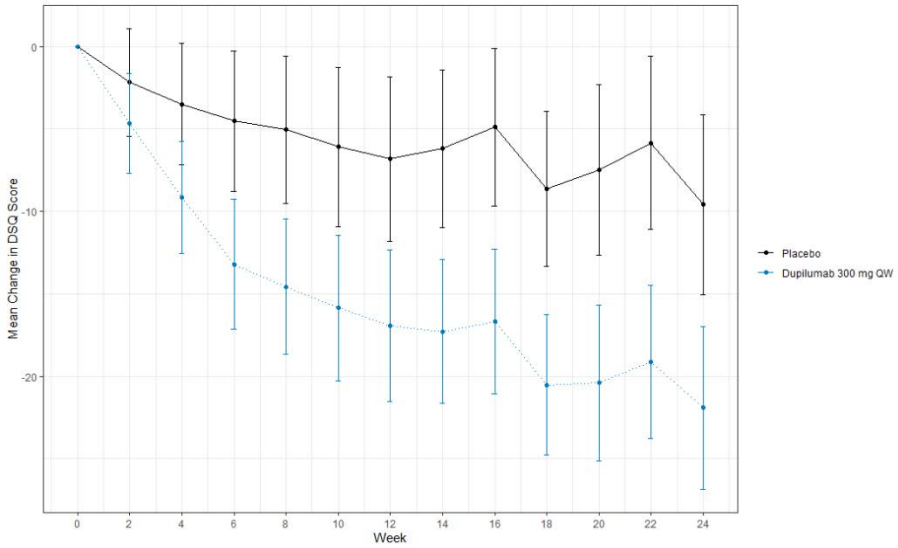
Source: Clinical Study Report for R668-EE-1774 Part B (Table 6.1.2.1/8B, post-text tables p 281), verified by reviewer using Applicant submitted data adqsdsq.xpt.

1. Values in bold represent analyses with a p-value >0.05.

15.5.6. Change in DSQ Total Score By Week

The primary analysis for the coprimary endpoint of change from baseline in DSQ total score was performed biweekly during the study. Nominally significant differences in the DSQ total score between the dupilumab 300 mg QW and placebo groups were observed by Week 4 and sustained for the remainder of the 24-week treatment period in both Part A (Figure 15) and Part B of the study (Figure 16).

Figure 15: LS Mean (95% CI) in Absolute Change in DSQ Total Score From Baseline by Week[1] (Part A)

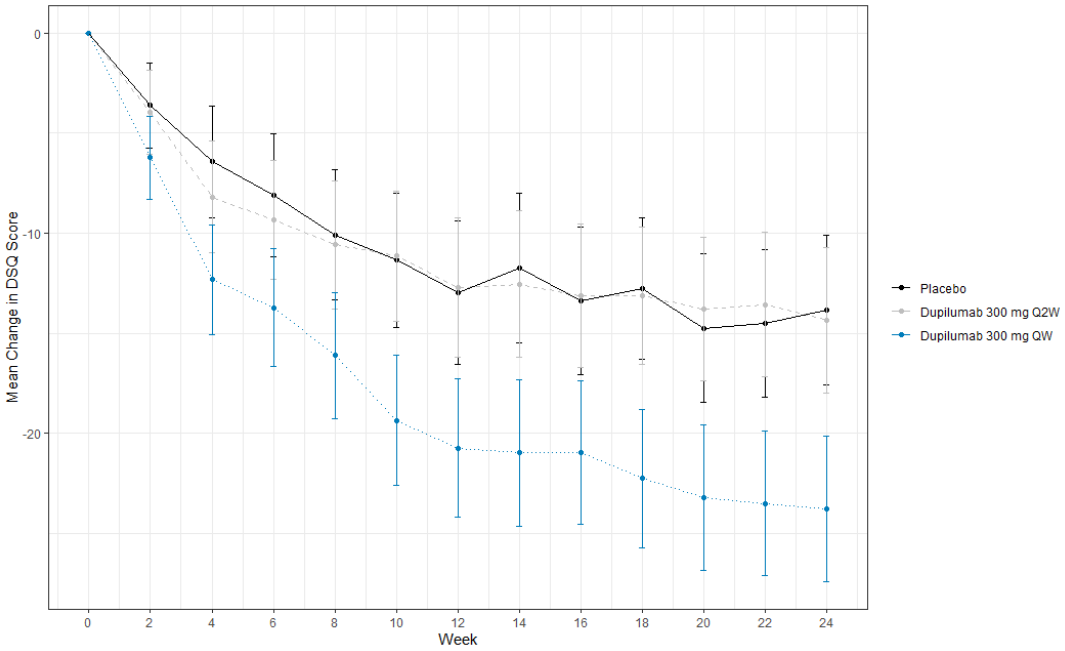


Source: Reviewer analysis using Applicant submitted data DSQSC.xpt; based on Summary of Clinical Efficacy for R668-EE-1774 (Figure 4, p 91).

1. The reported mean and confidence interval were calculated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as the covariates.

Abbreviations: CI = confidence interval, DSQ = Dysphagia Symptom Questionnaire, LS = least squares, QW = once weekly.

Figure 16: LS Mean (95% CI) in Absolute Change in DSQ Total Score From Baseline by Week[1] (Part B)



Source: Reviewer analysis using Applicant submitted data DSQSC.xpt; based on Summary of Clinical Efficacy for R668-EE-1774 (Figure 5, p 91).

1. The reported mean and confidence interval were calculated using an ANCOVA model with treatment group, randomization stratification factors, and baseline measurement as the covariates.

Abbreviations: CI = confidence interval, DSQ= Dysphagia Symptom Questionnaire, LS = least squares, QW = once weekly, Q2W = every other week.

15.5.7. Descriptive Efficacy Assessments - Part A/C

Subjects that completed Part A or Part B were offered the opportunity to enroll in Part C (i.e., the ongoing 28-week extension treatment period of Study 1774 for subjects that completed either Part A [Part A/C] or Part B [Part B/C]). Data from Part A/C is available, while Part B/C is ongoing. All subjects in Part A/C received open-label treatment with dupilumab 300 mg QW. The efficacy assessments from Part C were descriptive in nature and limited by the open-label study design. However, the results obtained from these assessments are suggestive of sustained treatment effects on histologic and symptomatic endpoints for subjects that received dupilumab 300 mg QW in Part A and continued on dupilumab 300 mg QW in Part C. Moreover, among subjects who transitioned from placebo to dupilumab 300 mg QW for Part C, the decrease in the mean DSQ score during Part C and the proportion of subjects with a peak esophageal intraepithelial eosinophil count ≤6 at the end of Part C were consistent with the treatment effects observed in Part A for subjects initially randomized to dupilumab 300 mg QW (Table 58).

Table 58: Descriptive Efficacy Assessments After Open-Label Treatment Part A/C

Part A/Part C Treatment	Subjects With Peak eos/hpf Count ≤ 6 n (%), Part C Baseline	Subjects With Peak eos/hpf Count ≤ 6 n (%), Part C EOT	Mean (SD) Change From Part A Baseline DSQ Total Score, Part C Baseline	Mean (SD) Change From Part A Baseline DSQ Total Score, Part C EOT
Dupilumab 300 mg QW/ Dupilumab 300 mg QW (N=38 Baseline, N=34 EOT)	26 (68.4%)	19 (55.9%)	-21.12 (14.6)	-23.4 (16.1)
Placebo/Dupilumab 300 mg QW (N=33, N=30 EOT)	2 (6.1%)	18 (60.0 %)	-10.2 (16.2)	-21.7 (17.1)

Source: Clinical Study Report for R668-EE-1774 Part A/C (Table 18, p 60); verified by reviewer using Applicant submitted data ADQSDSQ.xpt, ADXEESO.xpt.
Abbreviations: DSQ = Dysphagia Symptom Questionnaire, eos/hpf = eosinophils/high-power field, EOT = End of Treatment.

15.6. Efficacy: Additional Information and Assessment

15.6.1. The Dysphagia Symptom Questionnaire

The DSQ is a PRO instrument for assessing symptoms of dysphagia. The version of the DSQ used in Study 1774 is the modified DSQ version 4, which is modified from the DSQ version 4 published in the literature (Hudgens et al. 2017). This COA review concludes that the modified DSQ version 4 is a well-defined and reliable PRO instrument for measuring dysphagia in adult and adolescent subjects with EoE, based on evidence to support content validity from concept elicitation and cognitive interviews in qualitative research participants with EoE and evidence to support measurement properties from exploratory psychometric analyses of Study 1774 data. Additionally, interpretability of DSQ data from Study 1774 is supported by evidence of clinically meaningful within-subject changes in DSQ scores, as described in Section 8.1.5 above.

The modified DSQ version 4 used in Study 1774 consists of four items assessing avoidance of solid food, presence of dysphagia symptoms, severity of dysphagia symptoms, and painful swallowing, plus one novel item assessing the reason for avoiding solid food, if applicable. The modified DSQ version 4 is described in Table 59 below.

Table 59: Dysphagia Symptom Questionnaire Items and Scoring

Item	Response Option	Action	Score
1. Since you woke up this morning, did you eat solid food?	No Yes	Proceed to Item 1A Proceed to Item 2	No score assigned
1A. Please select the reason for not eating solid food since you woke up this morning:	Because of your problems with swallowing solid food	eDiary stops	No score assigned (sensitivity analysis: score of 6)
	Because of a reason NOT related to your problems with swallowing solid food		No score assigned
2. Since you woke up this morning, has food gone down slowly or been stuck in your throat?	No Yes	eDiary stops Proceed to Item 3	0 2
3. For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?	No, it got better or cleared up on its own	Proceed to Item 4	0
	Yes, I had to drink liquid to get relief		1
	Yes, I had to cough and/or gag to get relief		2
	Yes, I had to vomit to get relief		3
	Yes, I had to seek medical attention to get relief		4
4. What was the worst pain you had while swallowing food over the past 24 hours?	None, I had no pain Mild Moderate Severe Very severe	eDiary stops	Exploratory item

Source: Reviewer's table adapted from Applicant's *PRO Dossier for the DSQ*, Table 2 (page 15 of 57), dated December 17, 2021.

Content Validity

Content validity of the DSQ in adults and adolescents with EoE is adequately supported by evidence from hybrid concept elicitation/cognitive interviews of DSQ version 1 in 20 participants (10 adults and 10 adolescents), cognitive interviews of DSQ version 2 in 20 participants (10 adults and 10 adolescents), field testing of DSQ version 3 in 37 participants (19 adults and 18 adolescents), and cognitive interviews of the modified DSQ version 4 conducted by the Applicant in 24 participants (18 adults and 6 adolescents). The cognitive interviews conducted by the Applicant confirm that the modified DSQ version 4 measures concepts that are relevant and meaningful to the target population, that the instrument is understandable and usable as intended, and that no important content is omitted from the instrument.

The Applicant also conducted usability testing of their DSQ eDiary in 17 participants (14 participants with EoE plus 3 elderly healthy participants) prior to use in Study 1774, which found that the eDiary was usable as intended. Of note, 3 participants with EoE commented that they might prefer to complete the DSQ after midnight, so a flexible eDiary window was implemented for subjects who may need to report data after midnight.

The DSQ was linguistically translated and culturally adapted into 17 languages for Study 1774, in accordance with best practices published by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) (Wild et al. 2005).

Test-Retest Reliability

Test-retest reliability was analyzed using mean DSQ total scores from subjects who were stable on the PGIS or PGIC at Week 20 and Week 24. As shown in Table 60 below, intraclass correlation coefficients (ICCs) were > 0.90 for both PGIS and PGIC analyses from both Parts A and B, and changes in mean scores during the test-retest period were not statistically significant.

Table 60: Summary of Test-retest Reliability of the Dysphagia Symptom Questionnaire

Test-Retest Subsample	n		ICC (95% CI)[1]		Mean Score Difference Week 20 vs Week 24 (95% CI), p-value	
	Part A	Part B	Part A	Part B	Part A	Part B
Patients with no change on PGIS	31	78	0.96 (0.93 to 0.98)	0.92 (0.89 to 0.95)	-0.22 (-2.04 to 1.6) 0.81	0.65 (-0.87 to -2.16), 0.40
Patients with no change on PGIC	28	85	0.93 (0.86 to 0.97)	0.97 (0.95 to 0.98)	0.99 (-1.19to 3.17) 0.36	0.10 (-0.99 to -1.19), 0.85

Source: Applicant's PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data, Table 12 (page 27 of 47), dated December 17, 2021.

1. ICC computed using McGraw and Wong two-way mixed-effect ANOVA model.

Abbreviations: CI = confidence interval, ICC = intraclass correlation coefficient, PGIC = Patient Global Impression of Change, PGIS = Patient Global Impression of Severity.

Convergent Validity

Pearson correlation coefficients were calculated to evaluate the associations between DSQ total score and scores on other measures at baseline and Week 24 for both Parts A and B. As shown in Table 61 below, moderate to high correlations (i.e., 0.3 to 0.7) were seen between the DSQ total score and PGIS at baseline and Week 24 in both Parts A and B.

Table 61: Summary of Convergent Validity Analysis for the DSQ Total Score at Baseline and Week 24

	Pearson Correlation Coefficient With DSQ Biweekly Total Score (n)			
	Baseline		Week 24	
Measure	Part A	Part B	Part A	Part B
PGIS	0.38 (73)	0.47 (228)	0.70 (64)	0.69 (175)

Source: Applicant's PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data, Table 13 (page 28 of 47), dated December 17, 2021.
Abbreviations: DSQ = Dysphagia Symptom Questionnaire, PGIS = Patient Global Impression of Severity.

Known-Groups Validity

Known-groups validity was analyzed using mean DSQ total scores by known groups based on the PGIS at baseline and Week 24 for both Parts A and B. As shown in Table 62, higher mean DSQ scores corresponded to greater severity on the PGIS at both time points for both Parts A and B.

Table 62: Summary of Known-Groups Analysis for the Dysphagia Symptom Questionnaire Biweekly Total Score at Baseline and Week 24

	Mean (SD) DSQ Biweekly Total Score,[1] (n)			
Known-Group	Baseline		Week 24	
Measure	Part A	Part B	Part A	Part B
PGIS				
None	27.20 (-), 2	19.09 (-), 1	2.32 (5.53), 27	3.82 (6.88), 57
Mild	29.30 (10.38), 35	31.48 (10.71), 100	22.01 (15.16), 28	18.03 (15.79), 85
Moderate	37.67 (11.69), 32	39.68 (9.81), 107	38.67 (-), 7	38.39 (14.17), 28
Severe	43.25 (-), 4	48.02 (7.64), 20	40.66 (-), 2	47.38 (-), 5
ANOVA p value	0.0091	< 0.0001	< 0.0001	< 0.0001

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 14 (pages 29-30 of 47), dated December 17, 2021.
1. SD not reported for groups with sample size of n < 10.
Abbreviations: ANOVA = analysis of variance, DSQ = Dysphagia Symptom Questionnaire; PGIS = Patient Global Impression of Severity, SD = standard deviation.
Note: DSQ biweekly total scores range from 0 to 84, where higher scores indicate more severe dysphagia.

Ability to Detect Change

Ability to detect change was analyzed using mean DSQ total scores by categories of improvement, no change, or worsening on the PGIS and PGIC, and by categories of histologic responder or non-responder, for both Parts A and B. As shown in Table 63 below, notable improvements in mean DSQ scores were seen in subjects who reported improvement on the PGIS and PGIC compared to subjects who reported no change or worsening. Although monotonic relationships were not observed between "No change" and "Worsened" subgroups on the PGIS and PGIC in Part B, this is considered acceptable given the small sample sizes of subjects who reported worsening on the PGIS and PGIC.

Table 63: Summary of Ability to Detect Change of the Dysphagia Symptom Questionnaire Biweekly Total Score From Baseline to Week 24

Responsiveness Measure	Subgroup	DSQ Biweekly Total Change Score Mean (SD),[1] n		Within-Group SES		Between-Group SES	
		Part A	Part B	Part A	Part B	Part A	Part B
PGIS change from baseline to Week 24	Improved	-24.78 (13.76), 33	-24.93 (13.83), 102	-1.80	-1.80	NC	NC
	No change	-8.42 (11.45), 23	-8.43 (13.29), 55	-0.74	-0.63	NC	NC
	Worsened	-6.52 (-), 3	-9.47 (-), 9	-0.21	-0.48	NC	NC
	ANOVA p value	0.0002	< 0.0001	NC	NC	NC	NC
	Improved vs no change	NC	NC	NC	NC	-1.27	-1.21
	Improved vs worsened	NC	NC	NC	NC	-1.19	-1.08
	No change vs worsened	NC	NC	NC	NC	-0.13	0.07
PGIC at Week 24	Better	-21.91 (14.49), 47	-22.24 (15.12), 146	-1.51	-1.47	NC	NC
	No change	-6.10 (12.66), 14	-3.02 (11.06), 26	-0.48	-0.27	NC	NC
	Worse	-0.90 (-), 4	-7.28 (-), 5	-0.03	-0.55	NC	NC
	ANOVA p value	0.0005	< 0.0001	NC	NC	NC	NC
	Better vs no change	NC	NC	NC	NC	-1.12	-1.32
	Better vs worse	NC	NC	NC	NC	-1.36	-0.99
	No change vs worse	NC	NC	NC	NC	-0.32	0.38

Source: Applicant's PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data, Table 15 (pages 31-32 of 47), dated December 17, 2021.

1. SD not reported for groups with sample size of n < 10.

Abbreviations: ANOVA = analysis of variance, DSQ = Dysphagia Symptom Questionnaire, NC = analysis Not Conducted, PGIC = Patient Global Impression of Change, PGIS = Patient Global Impression of Severity, SD = standard deviation, SES = standardized effect size.

Note: DSQ biweekly total scores range from 0 to 84, where higher scores indicate more severe dysphagia.

Conclusions

Qualitative research conducted by the instrument developers and the Applicant established that the DSQ instrument measures relevant and meaningful concepts to the target population, is understandable and usable as intended, and does not omit important content. As administered in Study 1774, the DSQ demonstrated robust test-retest reliability and the 14-day

DSQ total score demonstrated expected relationships with other variables and measures that established both convergent and divergent validity. When the PGIS and PGIC items were used to establish groups with known symptom severity and varying levels of reported change, analysis of the 14-day DSQ total score supported the Applicant's conclusion of known groups validity and sensitivity to change.

This COA review concludes that the modified DSQ version 4 is a well-defined and reliable PRO instrument for measuring dysphagia in adults and adolescents with EoE, based on evidence to support content validity from concept elicitation and cognitive interviews in participants with EoE and evidence to support measurement properties from exploratory psychometric analyses of Study 1774 data. Additionally, interpretability of DSQ data from Study 1774 is supported by evidence of clinically meaningful within-subject changes in DSQ scores, as described in Section 8.1.5 above. Therefore, the Applicant has provided sufficient evidence to establish that that modified DSQ version 4, and its corresponding efficacy endpoint, can be relied on to support regulatory decision-making.

15.7. Safety: Additional Information

15.7.1. Preferred Term Grouping Strategy

Table 64: Reviewer's Preferred Term (PT) Grouping Strategy for Assessment for Adverse Drug Reactions

Grouped Term	PTs Included in Each Grouping[1]
Gastroenteritis	Gastroenteritis, gastroenteritis viral
Herpes viral infections	Herpes simplex, oral herpes
Injection site reactions	Injection site bruising, discolouration, erythema, extravasation, haematoma, hypersensitivity, induration, inflammation, mass, nodule oedema, pain, pruritus, rash, reaction, swelling, and urticaria
Upper respiratory tract infections	Acute sinusitis, COVID-19, nasopharyngitis, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection

Source: Reviewer generated table.
1. Coded as MedDRA 24.0 preferred term.

15.7.2. Laboratory Tests

Table 65: Laboratory Tests

Blood Chemistry

Sodium	Total protein, serum	Total and indirect bilirubin
Potassium	Creatinine	Total cholesterol
Chloride	Blood urea nitrogen (BUN)	Low-density lipoprotein (LDL)
Carbon dioxide	AST	High-density lipoprotein (HDL)
Calcium	ALT	Triglycerides
Glucose	Alkaline phosphatase	Uric acid
Albumin	Lactate dehydrogenase (LDH)	Creatine phosphokinase (CPK)[1]
	Estimated glomerular filtration rate (eGFR)	

[1] CPK isoenzymes will be measured when CPK >5 × ULN

Hematology

Hemoglobin	Differential:
Hematocrit	Neutrophils
Red blood cells (RBCs)	Lymphocytes
White blood cells (WBCs)	Monocytes
Red cell indices	Basophils
Platelet count	Eosinophils

Urinalysis

Microscopic analysis will only be done in the event of abnormal dipstick results.

Color	Glucose	RBC
Clarity	Blood	Hyaline and other casts
pH	Bilirubin	Bacteria
Specific gravity	Leukocyte esterase	Epithelial cells
Ketones	Nitrite	Crystals
Protein	WBC	Yeast

Source: Adapted from Applicant's BLA 761055 S-040 submission Module 5.3.5.1, Protocol R668-EE-1774 Amendment 5, Section 8.2.3.5.

- The following tests were performed at screening: HIV, HBsAg, HBsAb, HBcAb, Hepatitis C Ab, TB, and alcohol and drug screen test.
- Pregnancy testing was performed for all women of childbearing potential. Serum or urine pregnancy testing was performed at Screening; Baseline; and Weeks 4, 8, 12, 16, 20, and 24 of the active treatment period.

15.7.3. Supplementary Subgroup Analyses

15.7.3.1. Adolescent Subjects (12 to Less Than 18 Years of Age)

Table 66: Overview of Treatment-Emergent Adverse Events During 24-Week Treatment Period (Subjects 12 to Less Than 18 Years of Age, Pooled Data From Parts A and B, Study 1774)

	Placebo N=35 n (%)	300 mg Q2W N=27 n (%)	300 mg QW N=37 n (%)
Any TEAE, n (%)	28 (80.0)	23 (85.2)	35 (94.6)
Any SAE, n (%)	-	1 (3.7)	4 (11.4)
Any SAE leading to discontinuation, n (%)	-	-	-
Any TEAE leading to discontinuation, n (%)	-	1 (3.7)	1 (2.7)
Maximum intensity for any TEAE, n (%)			
Mild	19 (54.3)	16 (59.3)	21 (56.8)
Moderate	9 (25.7)	7 (25.9)	10 (27.0)
Severe	-	-	4 (10.8)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

Table 67: Treatment-Emergent Adverse Events Occurring at ≥5% in Dupilumab 300 mg QW Treatment Arm and Greater Than Placebo During 24-Week Treatment Period (Subjects 12 to Less Than 18 Years of Age, Pooled Data from Parts A and B, Study 1774)

Treatment-Emergent Adverse Events (PT)[1]	Placebo N=35 n (%)	300 mg Q2W N=27 n (%)	300 mg QW N=37 n (%)
Injection site reactions[2]	17 (49)	16 (59)	17 (46)
Upper respiratory tract infections[3]	4 (11)	3 (11)	8 (22)
Pyrexia	-	2 (7)	2 (5)
Fatigue	1 (3)	1 (4)	3 (8)
Gastroenteritis[5]	1 (3)	1 (4)	3 (8)
Syncope	-	-	2 (5)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.
Subjects are counted once in each row, regardless of the number of events they may have reported.
Shown in descending order based on dupilumab 300 mg QW.

1. Coded as MedDRA 24.0 preferred term.
2. Injection site reactions include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
3. Upper respiratory tract infections include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
4. Sinusitis includes the PTs acute sinusitis and sinusitis.
5. Gastroenteritis includes the PTs gastroenteritis and gastroenteritis viral.

15.7.3.2. Adult Subjects (18 Years of Age and Older)

Table 68: Overview of Treatment-Emergent Adverse Events During 24-Week Treatment Period (Subjects at Least 18 Years of Age, Pooled Data From Parts A and B, Study 1774)

	Placebo N=82 n (%)	300 mg Q2W N=54, n (%)	300 mg QW N=85 n (%)
Any TEAE, n (%)	59 (72)	40 (74)	68 (80)
Any SAE, n (%)	2 (2)	-	3 (4)
Any SAE leading to discontinuation, n (%)	-	-	1 (1)
Any TEAE leading to discontinuation, n (%)	2 (2)	1 (2)	2 (2)
Maximum intensity for any TEAE, n (%)			
Mild	41 (50)	26 (48)	47 (55)
Moderate	16 (20)	13 (24)	17 (20)
Severe	2 (2)	1 (2)	4 (5)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

Table 69: Treatment-Emergent Adverse Events Occurring at ≥5% in Dupilumab 300 mg QW Treatment Arm and Greater Than Placebo During 24-Week Treatment Period (Subjects at Least 18 Years of Age, Pooled Data From Parts A and B, Study 1774)

Treatment-Emergent Adverse Events (PT)[1]	Placebo N=82 n (%)	300 mg Q2W N=54 n (%)	300 mg QW N=85 n (%)
Injection site reactions[2]	22 (27)	28 (52)	29 (34)
Upper respiratory tract infections[3]	8 (10)	10 (19)	16 (20)
Hypertension	1 (1)	1 (2)	4 (5)
Pyrexia	2 (2)	1 (2)	5 (6)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

1. Coded as MedDRA 24.0 preferred term.
2. Injection site reactions include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
3. Upper respiratory tract infections include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.

15.7.3.3. Male Subjects

Table 70: Overview of Treatment-Emergent Adverse Events During 24-Week Treatment Period (Male Subjects, Pooled Data From Parts A and B, Study 1774)

	Placebo N=78 n (%)	300 mg Q2W N=45 n (%)	300 mg QW N=78 n (%)
Any TEAE, n (%)	56 (72)	31 (69)	66 (85)
Any SAE, n (%)	1 (1)	1 (2)	2 (3)
Any SAE leading to discontinuation, n (%)	-	-	-
Any TEAE leading to discontinuation, n (%)	1 (1)	2 (4)	1 (1)
Maximum intensity for any TEAE, n (%)			
Mild	39 (50)	21 (47)	43 (55)
Moderate	16 (21)	10 (22)	20 (26)
Severe	1 (1)	-	2 (3)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

Table 71: Treatment-Emergent Adverse Events Occurring at ≥5% in Dupilumab 300 mg QW Treatment Arm and Greater Than Placebo During 24-Week Treatment Period (Male Subjects, Pooled Data From Parts A and B, Study 1774)

Treatment-Emergent Adverse Events (PT)[1]	Placebo N=78 n (%)	300 mg Q2W N=45 n (%)	300 mg QW N=78 n (%)
Injection site reactions[2]	24 (31)	19 (42)	28 (36)
Upper respiratory tract infections[3]	10 (13)	7 (16)	17 (22)
Gastroenteritis[4]	1 (1)	2 (4)	4 (5)
Pyrexia	1 (1)	2 (4)	4 (5)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

1. Coded as MedDRA 24.0 preferred term.
2. Injection site reactions include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
3. Upper respiratory tract infections include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
4. Gastroenteritis includes the PTs gastroenteritis and gastroenteritis viral.

15.7.3.4. Female Subjects

Table 72: Overview of Treatment-Emergent Adverse Events During 24-Week Treatment Period (Female Subjects, Pooled Data From Parts A and B, Study 1774)

	Placebo N=39 n (%)	300 mg Q2W N=36 n (%)	300 mg QW N=44 n (%)
Any TEAE, n (%)	31 (79)	32 (89)	37 (84)
Any SAE, n (%)	1 (3)	-	5 (11)
Any SAE leading to discontinuation, n (%)	-	-	1 (2)
Any TEAE leading to discontinuation, n (%)	1 (3)	-	2 (5)
Maximum intensity for any TEAE, n (%)			
Mild	21 (54)	21 (58)	25 (64)
Moderate	9 (23)	10 (28)	7 (16)
Severe	1 (3)	1 (3)	6 (14)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

Table 73: Treatment-Emergent Adverse Events Occurring at ≥5% in Dupilumab 300 mg QW Treatment Arm and Greater Than Placebo During 24-Week Treatment Period (Female Subjects, Pooled Data From Parts A and B, Study 1774)

Treatment-Emergent Adverse Events (PT)[1]	Placebo N=39 n (%)	300 mg Q2W N=36 n (%)	300 mg QW N=44 n (%)
Injection site reactions[2]	15 (38)	25 (69)	18 (41)
Upper respiratory tract infections[3]	2 (5)	6 (17)	7 (16)
Pyrexia	1 (3)	1 (3)	3 (7)
Hypertension	-	1 (3)	3 (7)
Herpes viral infections[4]	1 (3)	-	2 (5)

Source: Reviewer analysis using Applicant submitted data, ADAE.xpt.

1. Coded as MedDRA 24.0 preferred term.
2. Injection site reactions include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
3. Upper respiratory tract infections include several preferred terms. Refer to Table 64 for FDA's Preferred Term Grouping Strategy.
4. Herpes viral infections includes the PTs herpes simplex and oral herpes.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Shen (Steven) Li	OCP/DIIP	Section: 6, 15.3	**Select one:** _X__ Authored ___ Approved
	Signature: Shen Li -S Digitally signed by Shen Li -S Date: 2022.05.18 13:51:42 -04'00'			
Clinical Pharmacology secondary reviewer	Ping Ji	OCP/DIIP	Section: 6, 15.3	**Select one:** _X__ Authored _X__ Approved
	Signature: Ping Ji -S Digitally signed by Ping Ji -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Ping Ji -S, 0.9.2342.19200300.100.1.1=2000364393 Date: 2022.05.18 21:56:49 -04'00'			
Clinical Pharmacology Team Leader	Insook Kim	OCP/DIIP	Section: 6, 15.3	**Select one:** ___ Authored _X__ Approved
	Signature: Insook Kim -S Digitally signed by Insook Kim -S Date: 2022.05.18 16:48:29 -04'00'			
Pharmacometrics Team Leader	Lian Ma	OCP/DPM	Section: 6, 15.3	**Select one:** ___ Authored _X__ Approved
	Signature: Lian Ma -S Digitally signed by Lian Ma -S Date: 2022.05.18 20:46:32 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Patient-Focused Statistical Support (PFSS) Reviewer	Xin Yuan	OB/DBIII	Sections: 1.3, 8.1.2, 8.1.5, 15.5.1, 15.5.2	**Select one:** _X__ Authored ___ Approved
	Signature: Xin Yuan -S Digitally signed by Xin Yuan -S Date: 2022.05.18 11:32:45 -04'00'			
Patient-Focused Statistical Support Team Leader	Lili Garrard	OB/DBIII	Sections: 1.3, 8.1.2, 8.1.5, 15.5.1, 15.5.2	**Select one:** ___ Authored _X__ Approved
	Signature: Lili Garrard -S Digitally signed by Lili Garrard -S Date: 2022.05.18 11:51:46 -04'00'			
Statistical Reviewer	Joshua Sampson	OB/DBIII	Sections: 8.1.1, 8.1.2, 8.1.3, 8.1.4, 8.3, 15.4, 15.5.3, 15.5.4, 15.5.5, 15.5.6, 15.5.7, 15.6	**Select one:** _X_ Authored ___ Approved
	Signature: Joshua N. Sampson -S Digitally signed by Joshua N. Sampson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014378933, cn=Joshua N. Sampson -S Date: 2022.05.18 12:07:03 -04'00'			
Statistical Team Leader	Paul Imbriano	OB/DBIII	Sections: 7, 8.1.1, 8.1.2, 8.1.3, 8.1.4, 8.1.6, 8.3, 8.4, 15.4, 15.5.3, 15.5.4, 15.5.5, 15.5.6, 15.5.7, 15.6	**Select one:** ___ Authored _X__ Approved
	Signature: Paul M. Imbriano -S Digitally signed by Paul M. Imbriano -S Date: 2022.05.18 11:16:30 -04'00'			
Division Director (OB)	Laura Lee Johnson	OB/DBIII	Sections: 1.3, 7, 8.1, 8.3, 8.4, 15.4, 15.5, 15.6	**Select one:** ___ Authored _X__ Approved
	Signature: Laura L. Johnson -S Digitally signed by Laura L. Johnson -S Date: 2022.05.18 11:55:35 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Anna Reed	OII/DG	Sections: 2, 3, 7, 8.1.1	**Select one:** _X_ Authored ___ Approved
	Signature: Anna W. Reed -S Digitally signed by Anna W. Reed -S Date: 2022.05.18 14:33:16 -04'00'			
Clinical Team Leader/ Cross-Disciplinary Team Leader	Matthew Kowalik	OII/DG	Sections: 1, 2, 3, 4, 7, 8.2, 10, 11, 13, 15	**Select one:** _X__ Authored _X__ Approved: all sections
	Signature: Matthew R. Kowalik -S Digitally signed by Matthew R. Kowalik -S Date: 2022.05.18 13:38:14 -04'00'			
Associate Director for Therapeutic Review (Clinical)	Erica Lyons	OII/DG	Sections: 1, 2, 3, 7, 8.1.1, 8.1.3, 8.1.4.6, 8.1.4.7, 8.1.6, 8.4, 9, 10, 15.2	**Select one:** _X__ Authored _X__ Approved: all sections
	Signature: Erica M. Lyons -S Digitally signed by Erica M. Lyons -S Date: 2022.05.18 14:36:56 -04'00'			
Division Director (Clinical)	Jessica Lee	OII/DG	Sections: 14	**Select one:** _X_ Authored: section 14 _X_ Approved: all sections

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

/s/

MATTHEW R KOWALIK
05/20/2022 01:20:49 PM

JESSICA J LEE
05/20/2022 01:22:55 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s040

PRODUCT QUALITY REVIEW(S)

Memorandum of Assessment:

Submission Tracking Number (STN):	761055 (1685/EDR1030)
Subject:	PAS Supplement 40: Efficacy treatment of eosinophilic esophagitis in patients aged 12 years and older
Date Received:	February 3, 2022
Assessment/Revision Date:	March 31, 2022
Primary Assessor:	Gunther H. Boekhoudt, Ph.D., Product Quality Assessor CDER/OPQ/OBP/DBRR IV
Secondary Assessor:	Jennifer Swisher, Ph.D., Review Chief, CDER/OPQ/OBP/DBRR IV
Tertiary Assessor:	Jennifer Swisher, Ph.D., Review Chief, CDER/OPQ/OBP/DBRR IV
RBPM:	Rabiya Haider, CDER/OPQ/OPRO
Consults:	N/A
Applicant:	Regeneron Pharmaceuticals, Inc.
Product:	Dupixent (dupilumab)
Indication:	• 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. • as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitation of Use - Not for the relief of acute bronchospasm or status asthmaticus. • as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).
Filing Action Date:	April 4 10, 2022
Action Due Date:	August 3, 2022

1. Summary Basis of Recommendation:

a. Recommendation:

Approvability of this supplement is deferred to OND.

b. Justification:

In this supplement, Regeneron is providing the final clinical study reports to support the new dupilumab indication for the treatment of Eosinophilic Esophagitis (EoE). The clinical study reports provided are:

- R668-EE-1324 (Phase 2 study)
- R668-EE-1774, Part A (Phase 3 study)
- R668-EE-1774 Part C results for Part A patients (Phase 3 study, extended active treatment period)
- R668-EE-1774, Part B (Phase 3 study).

2. Suggested Language for Action Letter:
Action letter language is deferred to OND.

3. Assessment:
This supplement contains no new CMC information. This supplement contains the final results for the above mentioned clinical studies.

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).

Primary Product Quality Assessor Comment:
The categorical exclusion request from the requirement to submit an environmental assessment is acceptable.

4. Assessment conclusions:
This supplement contains no new CMC information and does qualify for categorical exclusion. I recommend approval of this supplement.

5. Future Inspection Items:
None.

6. Status of PMC/PMR:
N/A

Gunther Boekhoudt

Digitally signed by Gunther Boekhoudt
Date: 4/06/2022 01:02:38PM
GUID: 508da6d7000262c4c5e3578cc0a15fbf

Jennifer Swisher

Digitally signed by Jennifer Swisher
Date: 4/06/2022 01:51:09PM
GUID: 508da6d7000262dc015dcdc5f6541612

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761055Orig1s040

OTHER REVIEW(S)

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2021357
IND/NDA/BLA#:	BLA 761055/S-040
Sponsor:	Regeneron Pharmaceuticals, Inc.
Established Name/Trade Name:	Dupilumab (DUPIXENT®)
Indication:	Treatment of adult and adolescent patients 12 years or older with eosinophilic esophagitis (EoE) ☒Rare Disease/Orphan Designation ☒Pediatrics
Meeting Type:	BLA review
Review Division:	Division of Gastroenterology (DG)
Clinical Reviewer	Anna Reed, MD
Clinical Team Leader (TL)	Matthew Kowalik, MD; Erica Lyons, MD, FAAP
Regulatory Project Manager:	Mary Chung, PharmD
COA Reviewer:	Christopher St. Clair, PharmD
COA Director:	David Reasner, PhD
Date Consult Request Received:	September 3, 2021
Date COA Briefing Package/Submission Received:	February 3, 2022
Instruments reviewed:	Dysphagia Symptom Questionnaire (DSQ) ☒ Patient-reported outcome (PRO) ☐ Observer-reported outcome (ObsRO) ☐ Clinician-reported outcome (ClinRO) ☐ Performance outcome (PerfO) ☐ Digital health technology tool (exclude ePRO/eObsRO) ☐ Others (e.g., passive monitoring)

1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to BLA 761055/S-040 for dupilumab (DUPIXENT®). This efficacy supplement seeks approval of dupilumab for treatment of adult and adolescent patients age 12 years or older with eosinophilic esophagitis (EoE).

The Division of Gastroenterology (DG) seeks COA review of the Dysphagia Symptom Questionnaire (DSQ), a patient-reported outcome (PRO) instrument that supported a co-primary symptom endpoint in the phase 3 clinical trial intended to support demonstration of efficacy.

Summary of Study Design

Evidence of efficacy is proposed to come from the results of Study R668-EE-1774 ("Study 1774"), a phase 3 randomized, double-blind, placebo-controlled (R, DB, PC) study in adults and adolescents age ≥ 12 years with EoE. Study 1774 consists of 3 parts:

- Part A (completed): 24-week R, DB, PC study in 80 subjects randomized 1:1 to dupilumab once weekly or placebo once weekly

- Part B (completed): 24-week R, DB, PC study in 210 subjects randomized 1:1:1 to dupilumab once weekly, placebo once weekly, or dupilumab every 2 weeks (with placebo every alternating week to maintain the blind)

- Part C: 28-week extended active treatment for subjects completing Part A or Part B

    - Part A/C (completed): subjects who received treatment (dupilumab once weekly) or placebo in Part A were all assigned to receive dupilumab once weekly for 28 weeks

    - Part B/C (ongoing): subjects who received treatment (dupilumab once weekly or dupilumab every 2 weeks) continue their treatment assignment for 28 weeks, while subjects who received placebo are re-randomized to receive either dupilumab once weekly or dupilumab every 2 weeks for 28 weeks

Summary of Endpoints
Co-primary endpoints are as follows:

- Co-primary (histologic): proportion of patients achieving a histologic response of esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 visit

- Co-primary (symptomatic): absolute change from baseline in the Dysphagia Symptom Questionnaire (DSQ) total score at week 24

Documents Reviewed
This BLA submission included a PRO dossier with evidence to support content validity, measurement properties, and meaningful within-patient change thresholds for the DSQ.[1] This COA review also makes reference to the multi-disciplinary review (the "Unireview") for this BLA supplement.

Conclusions
The modified DSQ version 4 is a well-defined and reliable PRO instrument for measuring dysphagia in adult and adolescent patients with EoE, based on evidence of content validity from concept elicitation and cognitive interviews in patients and evidence of measurement properties using data from Study 1774.

[1] BLA 761055 eCDT submission dated 2022-02-03 (eCDT Sequence Number: 1030; eCDT Supporting Document Number: 1685). Section 5.3.5.4: Patient Reported Outcome Dossier for the Dysphagia Symptom Questionnaire. Available from: \\CDSESUB1\evsprod\bla761055\1030\m5\53-clin-stud-rep\535-rep-effic-safety-stud\eosinophilic-esophagitis\5354-other-stud-rep\prodossier\

2. SUGGESTED COMMENTS TO APPLICANT

- Not applicable. No COA-related comments for the Applicant were identified during this BLA review.

3 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

- Refer to Unireview Section 3 (Regulatory Background).

- DCOA was involved in this program under IND 136142. Relevant regulatory history includes granting of breakthrough therapy designation (BTD) on September 9, 2020. The review team considered the DSQ to be an appropriate measure to support the co-primary symptom endpoint, but the Sponsor was asked to provide justification for the threshold for clinically meaningful within-patient change.

4 CLINICAL OUTCOME ASSESSMENT REVIEW

4.1 Clinical Trial Design

- Refer to Unireview Section 8.1 (Review of Relevant Individual Trials Used to Support Efficacy).

- Study 1774 used a co-primary endpoint approach as recommended by FDA guidance.[2] Co-primary endpoints are as follows:

    - Co-primary (histologic): proportion of patients achieving a histologic response of esophageal intraepithelial eosinophil count of ≤6 eos/hpf at week 24 visit

    - Co-primary (symptomatic): absolute change from baseline in the Dysphagia Symptom Questionnaire (DSQ) total score at week 24

4.2 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant's proposed labeling describes the results of the co-primary endpoints. The review team agreed that labeling should also include a statement regarding the results of anchor-based analyses, to convey that DSQ results were both statistically significant and clinically meaningful. Therefore, Section 14.4 (Clinical Studies, Eosinophilic Esophagitis) was revised to reflect the following:

> *In Parts A and B, a greater proportion of subjects randomized to DUPIXENT achieved histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf) compared to placebo. Treatment with DUPIXENT also resulted in a significant*

[2] FDA Guidance for Industry: Eosinophilic Esophagitis: Developing Drugs for Treatment. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/eosinophilic-esophagitis-developing-drugs-treatment-guidance-industry

improvement in LS mean change in DSQ score compared to placebo. The results of the anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B is representative of a clinically meaningful within-subject improvement.

4.3 Clinical Outcome Assessment(s)

4.3.1 Executive Summary

4.3.2 The Dysphagia Symptom Questionnaire (DSQ)

The DSQ is a PRO instrument for assessing symptoms of dysphagia. The version of the DSQ used in Study 1774 is the modified DSQ version 4, which is modified from the DSQ version 4 published in the literature.[3] This COA review concludes that the modified DSQ version 4 is a well-defined and reliable PRO instrument for measuring dysphagia in adult and adolescent subjects with EoE, based on evidence to support content validity from concept elicitation and cognitive interviews in qualitative research participants with EoE and evidence to support measurement properties from exploratory psychometric analyses of Study 1774 data. Additionally, interpretability of DSQ data from Study 1774 is supported by evidence of clinically meaningful within-subject changes in DSQ scores.

The modified DSQ version 4 used in Study 1774 consists of four items assessing avoidance of solid food, presence of dysphagia symptoms, severity of dysphagia symptoms, and painful swallowing, plus one novel item assessing the reason for avoiding solid food, if applicable. The modified DSQ version 4 is described in Table 46 below.

Table 1. Dysphagia Symptom Questionnaire Items and Scoring

Item	Response Option	Action	Score
1. Since you woke up this morning, did you eat solid food?	No	Proceed to Item 1A	No score assigned
	Yes	Proceed to Item 2	
1A. Please select the reason for not eating solid food since you woke up this morning:	Because of your problems with swallowing solid food	eDiary stops	No score assigned (sensitivity analysis: score of 6)
	Because of a reason NOT related to your problems with swallowing solid food		No score assigned
2. Since you woke up this morning, has food gone	No	eDiary stops	0
	Yes	Proceed to Item 3	2

[3] Hudgens, S., C. Evans, E. Phillips, and M. Hill. 2017. 'Psychometric validation of the Dysphagia Symptom Questionnaire in patients with eosinophilic esophagitis treated with budesonide oral suspension', *J Patient Rep Outcomes*, 1: 3.

down slowly or been stuck in your throat?			
3. For the most difficult time you had swallowing food today (during the past 24 hours), did you have to do anything to make the food go down or to get relief?	No, it got better or cleared up on its own	Proceed to Item 4	0
	Yes, I had to drink liquid to get relief		1
	Yes, I had to cough and/or gag to get relief		2
	Yes, I had to vomit to get relief		3
	Yes, I had to seek medical attention to get relief		4
4. What was the worst pain you had while swallowing food over the past 24 hours?	None, I had no pain	eDiary stops	Exploratory item
	Mild		
	Moderate		
	Severe		
	Very severe		

Source: Reviewer's table adapted from Applicant's *PRO Dossier for the DSQ*, Table 2 (page 15 of 57), dated December 17, 2021

4.3.3 Scoring Method

The DSQ scoring method used to support the co-primary endpoint (the "total score") is defined as the sum of scores of Items 2 and 3, prorated for a 14-day period. The DSQ total score calculation is described as follows:

$$DSQ\ Biweekly\ Total\ Score = \frac{(sum\ of\ points\ from\ Questions\ 2\ and\ 3\ from\ daily\ DSQ\ eDiary)}{number\ of\ eDiary\ days\ reported\ with\ non\text{-}missing\ data} \times 14\ days$$

Source: Applicant's *PRO Dossier for the DSQ* page 15 of 57, dated December 17, 2021

The range of possible daily scores for Item 2 + Item 3 is 0 to 6; therefore, the range of possible DSQ total scores over a 14-day period is 0 to 84. Subjects must have at least 8 days of non-missing data for a total score to be calculated. If a subject responds "No" to Item 1 (eating solid food), then the DSQ score for that day is considered missing, but diary completion is counted for that day.

To evaluate the impact of missing data due to solid food avoidance, the Applicant also conducted a pre-specified sensitivity analysis by imputing a DSQ daily score of 6 (i.e., the maximum daily score) for subjects who did not eat solid food due to problems with swallowing solid food. Overall, few subjects avoided solid food on at least 1 day at baseline or Week 24 in Part A and Part B, and results of this sensitivity analysis were consistent with the primary efficacy analysis results.

4.3.4 Content Validity

Content validity of the DSQ in adults and adolescents with EoE is adequately supported by evidence from hybrid concept elicitation/cognitive interviews of DSQ version 1 in 20 participants (10 adults and 10 adolescents), cognitive interviews of DSQ version 2 in 20 participants (10 adults and 10 adolescents), field testing of DSQ version 3 in 37 participants (19 adults and 18 adolescents), and cognitive interviews of the modified DSQ version 4 conducted by the Applicant in 24 participants (18 adults and 6 adolescents). The cognitive interviews conducted by the Applicant confirm that the modified DSQ version 4 measures concepts that are relevant and meaningful to the target population, that the instrument is understandable and usable as intended, and that no important content is omitted from the instrument.

The Applicant also conducted usability testing of their DSQ eDiary in 17 participants (14 participants with EoE plus 3 elderly healthy participants) prior to use in Study 1774, which found that the eDiary was usable as intended. Of note, 3 participants with EoE commented that they might prefer to complete the DSQ after midnight, so a flexible eDiary window was implemented for subjects who may need to report data after midnight.

The DSQ was linguistically translated and culturally adapted into 17 languages for Study 1774, in accordance with best practices published by the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).[4]

4.3.5 Other Measurement Properties

Measurement properties of the DSQ are adequately supported by analyses of test-retest reliability, known-groups validity, and ability to detect change using data from Parts A and B of Study 1774.

Test-Retest Reliability

Test-retest reliability was analyzed using mean DSQ total scores from subjects who were stable on the PGIS or PGIC at week 20 and week 24. As shown in Table 2 below, intraclass correlation coefficients (ICCs) were > 0.90 for both PGIS and PGIC analyses from both Parts A and B, and changes in mean scores during the test-retest period were not statistically significant.

Table 2. Summary of Test-retest Reliability of the Dysphagia Symptom Questionnaire

Test-Retest Subsample	n		ICC (95% CI)		Mean Score Difference Week 20 vs. Week 24 (95% CI), p value	
	Part A	Part B	Part A	Part B	Part A	Part B

[4] Wild, D., A. Grove, M. Martin, S. Eremenco, S. McElroy, A. Verjee-Lorenz, and P. Erikson. 2005. 'Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation', Value Health, 8: 94-104.

Patients with no change on PGIS	31	78	0.96 (0.928 to 0.983)	0.92 (0.885 to 0.951)	-0.22 (-2.037 to 1.603), 0.8095	0.65 (-0.868 to -2.161), 0.3978
Patients with no change on PGIC	28	85	0.93 (0.858 to 0.967)	0.97 (0.947 to 0.977)	0.99 (-1.192 to 3.172), 0.3603	0.10 (-0.989 to -1.192), 0.8536

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 12 (page 27 of 47), dated December 17, 2021
CI, confidence interval; ICC, intraclass correlation coefficient; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity.

Convergent Validity

Pearson correlation coefficients were calculated to evaluate the associations between DSQ total score and scores on other measures at baseline and week 24 for both Parts A and B. As shown in Table 3 below, moderate to high correlations (i.e., 0.3 to 0.7) were seen between the DSQ total score and PGIS at baseline and week 24 in both Parts A and B.

Table 3: Summary of Convergent Validity Analysis for the DSQ Total Score at Baseline and Week 24

Measure	Pearson Correlation Coefficient with DSQ Biweekly Total Score (n)			
	Baseline		Week 24	
	Part A	Part B	Part A	Part B
PGIS	0.38 (73)	0.47 (228)	0.70 (64)	0.69 (175)

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 13 (page 28 of 47), dated December 17, 2021
DSQ: Dysphagia Symptom Questionnaire; PGIS: Patient Global Impression of Severity

Known-Groups Validity

Known-groups validity was analyzed using mean DSQ total scores by known groups based on the PGIS at baseline and week 24 for both Parts A and B. As shown in Table 4 below, higher mean DSQ scores corresponded to greater severity on the PGIS at both time points for both Parts A and B. Results of analyses using the EoE-SQ and histology were considered exploratory for the purposes of this review, as content validity of the EoE-SQ has not been established and symptoms of EoE are known to vary independently from histology.

Table 4. Summary of Known-Groups Analysis for the Dysphagia Symptom Questionnaire Biweekly Total Score at Baseline and Week 24

Known-Group Measure	Mean (SD) DSQ Biweekly Total Score, n			
	Baseline		Week 24	
	Part A	Part B	Part A	Part B
PGIS				
None	27.20 (13.011), 2	19.09 (-), 1	2.32 (5.532), 27	3.82 (6.885), 57
Mild	29.30 (10.378), 35	31.48 (10.714),	22.01 (15.163), 28	18.03 (15.793), 85

Moderate	37.67 (11.687), 32	39.68 (9.805), 107	38.67 (17.389), 7	38.39 (14.167), 28
Severe	43.25 (17.746), 4	48.02 (7.635), 20	40.66 (39.688), 2	47.38 (7.383), 5
ANOVA p value	0.0091	< 0.0001	< 0.0001	< 0.0001
EoE-SQ Frequency "Chest Pain"				
Present	33.65 (12.875), 57	38.32 (11.106),	26.21 (21.955), 22	27.78 (17.627), 66
Absent	33.76 (9.515), 16	32.06 (10.818), 58	9.97 (12.743), 41	11.39 (15.317),
T-test p value	0.9756	0.0002	0.0004	< 0.0001
EoE-SQ Frequency "Stomach Pain"				
Present	38.48 (11.441), 38	40.16 (10.720),	28.74 (20.673), 20	29.71 (18.962), 60
Absent	28.46 (10.802), 35	32.48 (10.680),	9.54 (13.131), 43	11.23 (13.845),
T-test p value	0.0003	< 0.0001	< 0.0001	< 0.0001
EoE-SQ Frequency "Heartburn"				
Present	34.32 (12.658), 54	38.02 (11.373),	19.79 (21.414), 29	23.62 (19.202), 87
Absent	31.83 (10.701), 19	32.92 (10.446), 58	12.10 (14.172), 34	11.59 (14.586), 87
T-test p value	0.4465	0.0029	0.0933	< 0.0001
EoE-SQ Frequency "Regurgitation"				
Present	37.54 (10.346), 51	38.04 (11.018),	24.57 (20.741), 27	23.32 (18.823), 99
Absent	24.72 (11.473), 22	30.74 (10.996), 41	8.94 (12.467), 36	10.06 (13.792), 75
T-test p value	< 0.0001	0.0002	0.0004	< 0.0001
EoE-SQ Frequency "Throw Up"				
Present	39.67 (12.023), 23	41.38 (12.833), 65	46.82 (23.006), 5	34.13 (18.866), 25
Absent	30.92 (11.297), 50	34.87 (10.153),	12.95 (15.101), 58	14.83 (16.396),
T-test p value	0.0036	< 0.0001	< 0.0001	< 0.0001
Peak Esophageal Intraepithelial Eosinophil Count				
≤ 6 eos/hpf	[a]	[a]	12.26 (15.384), 27	15.62 (18.587), 81
> 6 to < 15 eos/hpf	[a]	[a]	14.00 (24.249), 3	13.00 (15.930), 31
≥ 15 eos/hpf	[a]	[a]	21.11 (18.339), 29	21.85 (17.732), 70
ANOVA p value	[a]	[a]	0.1634	0.0316

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 14 (pages 29-30 of 47), dated December 17, 2021

[a] As specified in the PAP, analysis not conducted because the study inclusion criteria required patients to have eos/hpf ≥15 at baseline, thereby limiting the dynamic range of scores.

ANOVA, analysis of variance; DSQ, Dysphagia Symptom Questionnaire; EoE-SQ, Eosinophilic Esophagitis Symptom Questionnaire; eos/hpf, eosinophils per high-power field; PAP, Psychometric Analysis Plan; PGIS, Patient Global Impression of Severity; SD, standard deviation.

Note: DSQ biweekly total scores range from 0 to 84, where higher scores indicate more severe dysphagia; negative change scores denote improvement.

Ability to Detect Change

Ability to detect change was analyzed using mean DSQ total scores by categories of improvement, no change, or worsening on the PGIS and PGIC, and by categories of histologic responder or non-responder, for both Parts A and B. As shown in Table 5 below, notable improvements in mean DSQ scores were seen in subjects who reported improvement on the PGIS and PGIC compared to subjects who reported no change or worsening. Although monotonic relationships were not observed between "No change" and "Worsened" subgroups on

the PGIS and PGIC in Part B, this is considered acceptable given the small sample sizes of subjects who reported worsening on the PGIS and PGIC. Results of analyses using histology are considered exploratory for the purposes of this review, as symptoms of EoE are known to vary independently from histology.

Table 5. Summary of Ability to Detect Change of the Dysphagia Symptom Questionnaire Biweekly Total Score From Baseline to Week 24

Responsiveness Measure	Subgroup	DSQ Biweekly Total Change Score Mean (SD), n		Within-Group SES		Between-Group SES	
		Part A	Part B	Part A	Part B	Part A	Part B
PGIS change baseline to week 24	Improved	-24.78 (13.757), 33	-24.93 (13.829), 102	-1.80	-1.80	[a]	[a]
	No change	-8.42 (11.448), 23	-8.43 (13.285), 55	-0.74	-0.63	[a]	[a]
	Worsened	-6.52 (30.990), 3	-9.47 (19.587), 9	-0.21	-0.48	[a]	[a]
	ANOVA p value	0.0002	< 0.0001	[a]	[a]	[a]	[a]
	Improved vs. no change	[a]	[a]	[a]	[a]	-1.27	-1.21
	Improved vs. worsened	[a]	[a]	[a]	[a]	-1.19	-1.08
	No change vs. worsened	[a]	[a]	[a]	[a]	-0.13	0.07
PGIC at week 24	Better	-21.91 (14.488), 47	-22.24 (15.120), 146	-1.51	-1.47	[a]	[a]
	No change	-6.10 (12.655), 14	-3.02 (11.062), 26	-0.48	-0.27	[a]	[a]
	Worse	-0.90 (26.401), 4	-7.28 (13.122), 5	-0.03	-0.55	[a]	[a]
	ANOVA p value	0.0005	< 0.0001	[a]	[a]	[a]	[a]
	Better vs. no change	[a]	[a]	[a]	[a]	-1.12	-1.32
	Better vs. worse	[a]	[a]	[a]	[a]	-1.36	-0.99

	No change vs. worse	[a]	[a]	[a]	[a]	-0.32	0.38
Peak esophageal intraepithelial eosinophil count at week 24	Responder (≤ 6 eos/hpf)	-20.48 (13.473), 27	-21.59 (16.718), 81	-1.52	-1.29	[a]	[a]
	Non-responder (> 6 eos/hpf)	-15.35 (19.193), 32	-17.41 (14.932), 101	-0.80	-1.17	[a]	[a]
	T-test p value	0.2484	0.0773	[a]	[a]	[a]	[a]
	Responder vs. non-responder	[a]	[a]	[a]	[a]	-0.30	-0.27

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 15 (pages 31-32 of 47), dated December 17, 2021
[a] Analysis not conducted.
ANOVA, analysis of variance; DSQ, Dysphagia Symptom Questionnaire; PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity; SD, standard deviation; SES, standardized effect size.
Note: DSQ biweekly total scores range from 0 to 84, where higher scores indicate more severe dysphagia; negative change scores denote improvement.

4.3.6 Interpretation of Meaningful Within-Patient Score Changes

Two anchor scales were included in Study 1774: a Patient Global Impression of Severity (PGIS) and a Patient Global Impression of Change (PGIC). Both anchor scales are useful to facilitate interpretation of clinically meaningful within-patient changes in DSQ scores.

Patient Global Impression of Severity (PGIS)

The PGIS is a single-item PRO assessment of "severity of your difficulty swallowing food over the past week" using a 4-point verbal rating scale, as described in Table 6 below. The PGIS was administered during treatment visits at baseline, week 12, and week 24 for both Parts A and B.

Table 6. Patient Global Impression of Severity Items and Scoring

Question	Response Option	Score
Please choose the response below that best describes the severity of your difficulty swallowing food over the past week.	None	1
	Mild	2
	Moderate	3
	Severe	4

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 3 (page 15 of 47), dated December 17, 2021

The recall period used in the PGIS (i.e., "the past week") did not match the assessment period used to calculate the DSQ total score (i.e., 14 days). This presents a challenge to interpreting anchor-based analyses using the PGIS as an anchor scale for the DSQ total score, as the PGIS reflects only 7 of the 14 days included in the DSQ total score calculation at baseline, week 12, and week 24. To facilitate interpretation of anchor-based analyses using the PGIS, sensitivity analyses were conducted using matching 7-day periods for both the PGIS and the DSQ, as described in Section 8.1.5 of the Unireview.

Reviewer's comment: Future studies should use a Patient Global Impression of Severity (PGIS) scale with a recall period that matches the assessment period of the DSQ (e.g. "past 14 days").

Patient Global Impression of Change (PGIC)
The PGIC is a single-item PRO assessment of "overall change in your difficulty swallowing food now compared to just before you started taking the study injection" using a 7-point verbal rating scale, as shown in Table 7 below. The PGIC was administered during site visits at weeks 12, 20, and 24.

Table 7. Patient Global Impression of Change Items and Scoring

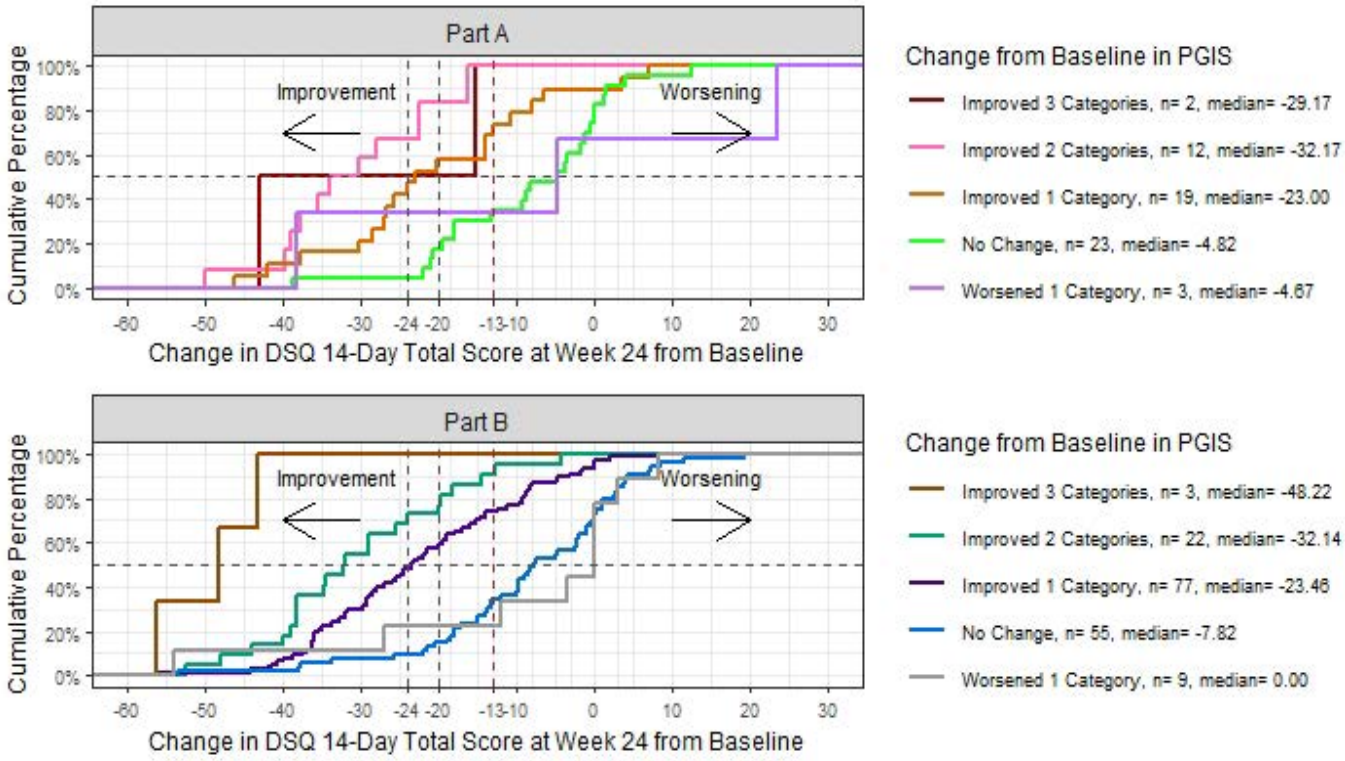
Question	Response Option	Score
Please choose the response below that best describes the overall change in your difficulty swallowing food now compared to just before you started taking the study injection.	Very Much Better	0
	Moderately Better	1
	A Little Better	2
	No Change	3
	A Little Worse	4
	Moderately Worse	5
	Very Much Worse	6

Source: Applicant's *PRO Dossier for the DSQ, Appendix E: Dysphagia Symptom Questionnaire Psychometric Analysis Report – Part A and Part B Data*, Table 4 (page 15 of 47), dated December 17, 2021

4.3.7 Anchor-Based Analyses

Refer to Section 8.1.5 of the Unireview for anchor-based analyses conducted by the Patient-Focused Statistical Support (PFSS) team. Figure 1 below shows the eCDF plots of absolute change from baseline in 14-day DSQ total score at Week 24 by PGIS category of change from baseline for Parts A and B. In summary, the Applicant proposed that a 13-point change from baseline in the 14-day DSQ score would be considered a clinically meaningful within-subject improvement for subjects in Study 1774, but PFSS's anchor-based analyses that leveraged data from both Parts A and B suggested that the meaningful within-subject improvement threshold range should be between 20-24 points.

Figure 1: eCDF, Change from Baseline in 14-Day DSQ Total Score to Week 24 by PGIS Category of Change From Baseline (Parts A and B, Study 1774)



Source: PFSS reviewer generated figure

PFSS's rationale for a meaningful change threshold of 20-24 points included that the Applicant's proposed threshold (13-point change) appeared to be based on Part B data alone and did not appear to take into consideration a higher threshold range (i.e., a range between 14- and 23-point improvement from baseline in the 14-day DSQ total score) derived from Part A data, and the Applicant's proposed threshold resulted in classifying > 20% of subjects who reported "no change" on the 7-day PGIS as experiencing meaningful change.

PFSS derived this range of change scores based on median values of change in DSQ score for subjects who experienced a 1-category improvement on the PGIS and "Moderately Better" on the PGIC anchor assessments, while taking into account the baseline PGIS score. Overall, consistent results were obtained using different anchor scales (i.e., PGIS, PGIC) based on all subjects in Part A and Part B. The eCDF curves were created using raw change scores consistent with the current recommendation in the FDA guidance for industry *Eosinophilic Esophagitis: Developing Drugs for Treatment*.[2]

6. APPENDICES

Appendix A: Dysphagia Symptom Questionnaire Screenshots

Source: Applicant's *PRO Dossier for the DSQ, Appendix D: Dysphagia Symptom Questionnaire Psychometric Analysis Plan – Part B* (pages 38-39 of 62), dated December 17, 2021

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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:	April 28, 2022
To:	Mary Chung, RPM Regulatory Project Manager **Division of Gastroenterology (DG)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Nyedra Booker, PharmD, MPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	DUPIXENT (dupilumab)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761055
Supplement Number:	S-040
Applicant:	Regeneron Pharmaceuticals, Inc.

1 INTRODUCTION

On February 3, 2022, Regeneron Pharmaceuticals, Inc. submitted for the Agency's review a Prior Approval Supplement (PAS) Efficacy to their Biologics License Application (BLA) 761055 DUPIXENT (dupilumab) injection, for subcutaneous use. This efficacy supplement proposes the addition of the indication of treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis (EoE).

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 Gastroenterology Products (DG) on February 25, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for DUPIXENT (dupilumab) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft DUPIXENT (dupilumab) PPI and IFU received on February 3, 2022, and received by DMPP and OPDP on April 22, 2022.
- Draft DUPIXENT (dupilumab) Prescribing Information (PI) received on February 3, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 22, 2022.

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%. A reading ease score of 60% corresponds to an 8th grade reading level.

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

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU 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. The IFU is acceptable as submitted.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
04/28/2022 06:13:02 PM

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

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

Memorandum

Date: April 26, 2022

To: Mary Chung, Regulatory Project Manager, (DG)

Joette Meyers, Associate Director for Labeling, (DG)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

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

BLA: 761055/Supplement 40

In response to DG's consult request dated February 25, 2022, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), and Instructions for Use (IFU) for the BLA submission for Dupixent. This supplement (S040) is an efficacy supplement that includes the indication for EoE.

OPDP's comment on the proposed labeling in Section 14 is based on the draft labeling received by electronic mail from DG on April 22, 2022, and are provided below.

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

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Version: April 22, 2022

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Shetarra Walker, MD, MSCR, Clinical Team Leader, DPMH
John J. Alexander, MD, MPH, Deputy Director, DPMH

BLA #: 761,055; supplement 40

Applicant: Regeneron Pharmaceuticals, Inc.

Drug: Dupixent (dupilumab)

Indications: Approved: Patients ≥ 6 years, with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. May be used with or without topical corticosteroids.

Approved: Add-on maintenance treatment of patients ≥ 6 years with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. Limitations of Use: Not for the relief of acute bronchospasm or status asthmaticus.

Approved: Add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP).

Proposed: Treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis (EoE).

Dosage Form: Injection (solution) for subcutaneous (SC) use

Proposed Regimen: 300 mg given every week (QW)

Request: The Division of Gastroenterology (DG) requests DPMH-Pediatric assistance in review of this supplemental BLA intended to add on the proposed indication.

Background

Drug: On March 28, 2017, FDA approved Dupixent (hereafter, dupilumab) 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. Dupilumab may be used with or without topical corticosteroids. Studies for patients under 6 months of age were waived due to impracticability, and studies in patients 6 months to < 18 years were deferred. Two required pediatric studies for patients 6 to less than 18 years have been completed and are reflected in labeling (i.e., PMR 3183-1 and PMR 3183-2). Two required pediatric studies are pending:

- PMR 3183-3: An open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe atopic dermatitis. Requested study report submission date: March 2023. Status: Ongoing.
- PMR 3183-4: Conduct a safety, pharmacokinetic (PK), and efficacy study in subjects 6 months to less than 6 years with severe atopic dermatitis. Requested study report submission date: November 2021. Status: Study report submitted and under review.

On October 19, 2018, FDA approved dupilumab for 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. Studies for patients under 2 years of age were waived due to impracticability, and studies in patients 2 to less than12 years were deferred. One required pediatric study (PMR 3508-1) for patients 6 to less than 12 years was completed and is reflected in labeling. An additional required pediatric study is pending completion:

- PMR 3508-2: Conduct a safety and efficacy study with dupilumab in children 2 years to < 6 years of age with moderate to severe asthma with a continued safety evaluation out to a minimum of 52 weeks (Study EFC14771). Requested study report submission date: June 2027. Status: Ongoing.

On June 26, 2019, FDA approved dupilumab for add-on maintenance treatment in adults with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). Pediatric study requirements were waived due to impracticability, because inadequately controlled CRSwNP is rare in children.

No pediatric written request (PWR) has been issued.

On September 5, 2017, dupilumab received orphan drug designation for treatment of EoE.

On February 3, 2022, the Applicant submitted the current efficacy supplement intended to add an indication for treatment of patients with EOE, ages 12 years and older. The Applicant intends to support the indication by establishment of effectiveness and safety in a single, three-part, clinical study. The study is a 24-week, randomized, double-blind, placebo-controlled, efficacy and safety study with a 28-week follow-up period. Efficacy

was based on histological remission and improved dysphagia symptoms as co-primary endpoints. Use of these co-primary endpoints is consistent with current FDA guidance.[1]

Disease: EoE is a chronic allergic/immune disorder characterized by esophageal inflammation with elevated eosinophilic granulocytes (Eos). For diagnosis, patients must be both symptomatic and have esophageal biopsy specimens with greater than 15 Eos per high power field (hpf) on light microscopic examination (commonly defined as 400 to 500x magnification);[2,3] however, some sources recommend a diagnostic cut-off of 20 Eos per hpf to help distinguish from esophageal neutrophilic infiltrates in patients with gastroesophageal reflux disorder (GERD).[4] The FDA guidance on the drug development plan for EoE uses the 15 Eos per hpf definition, which is reasonable.[5]

Potential etiologies/contributing factors include food allergies, acid reflux, and other ill-defined allergic/immunologic disturbances. Untreated patients may develop heartburn, dysphagia, and achalasia. EoE is currently thought to be distinct from other allergic enteropathies (e.g., eosinophilic gastritis, or celiac disease).

If offending food allergens are identified, a selective elimination diet may be attempted; however, lack of response is common. Clinicians commonly prescribe proton-pump inhibitors (PPI) and oral steroids in off-label fashion. Curiously, chronic use of PPIs for other reasons such as GERD has been associated with eosinophilic mucosal infiltration of the esophagus, which may not resolve upon discontinuation of PPIs. Whether some patients with PPI-associated EoE represent nascent cases of non-PPI associated EoE or whether PPIs are a causative factor for EoE in some patients is a matter of academic debate. Disease recrudescence is thought to be common in patients who initially respond to PPI or corticosteroids.

There are no approved drug or biologic treatments for patients with EoE. Therefore, a drug or biologic that demonstrates effectiveness and an acceptable safety profile would benefit a population with an unmet medical need.

Labeling Review

Text which DPMH recommends deleting is noted by ~~strike-out~~, and any text which DPMH recommends adding is noted in **bold red**.

There is no prior or proposed boxed warning. Labeling recommendations will focus on the pediatric portions only of sections 1 (Indications and Usage), 2 (Dosage and Administration; pediatric sections only), 5 (Warnings and Precautions), and 8.4 (Pediatric Use). Review of other sections [e.g., 12 (Clinical Pharmacology) and 14 (Clinical

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[1] FDA Guidance for Industry: Eosinophilic Esophagitis: Developing drugs for treatment. September 2020. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/eosinophilic-esophagitis-developing-drugs-treatment-guidance-industry. Website accessed, March 9, 2022.
[2] Dellon ES. Eosinophilic esophagitis: Diagnostic test and criteria. Curr Opin Gastroenterol. 2012 July; 28(4): 382–388.
[3] Kim D, Pantanowitz L, Schuffler P, et al. (Re) Defining the high-power field for digital pathology. J Pathol Inform 2020; 11:33.
[4] Rodrigo S, Abboud G, Oh D, et al. High intraepithelial eosinophil counts in esophageal squamous epithelium are not specific for eosinophilic esophagitis in adults. Am J Gastroenterol. 2008 Feb;103(2):435-42
[5] FDA Guidance for Industry: Eosinophilic Esophagitis: Developing drugs for treatment. September 2020. Ibid.

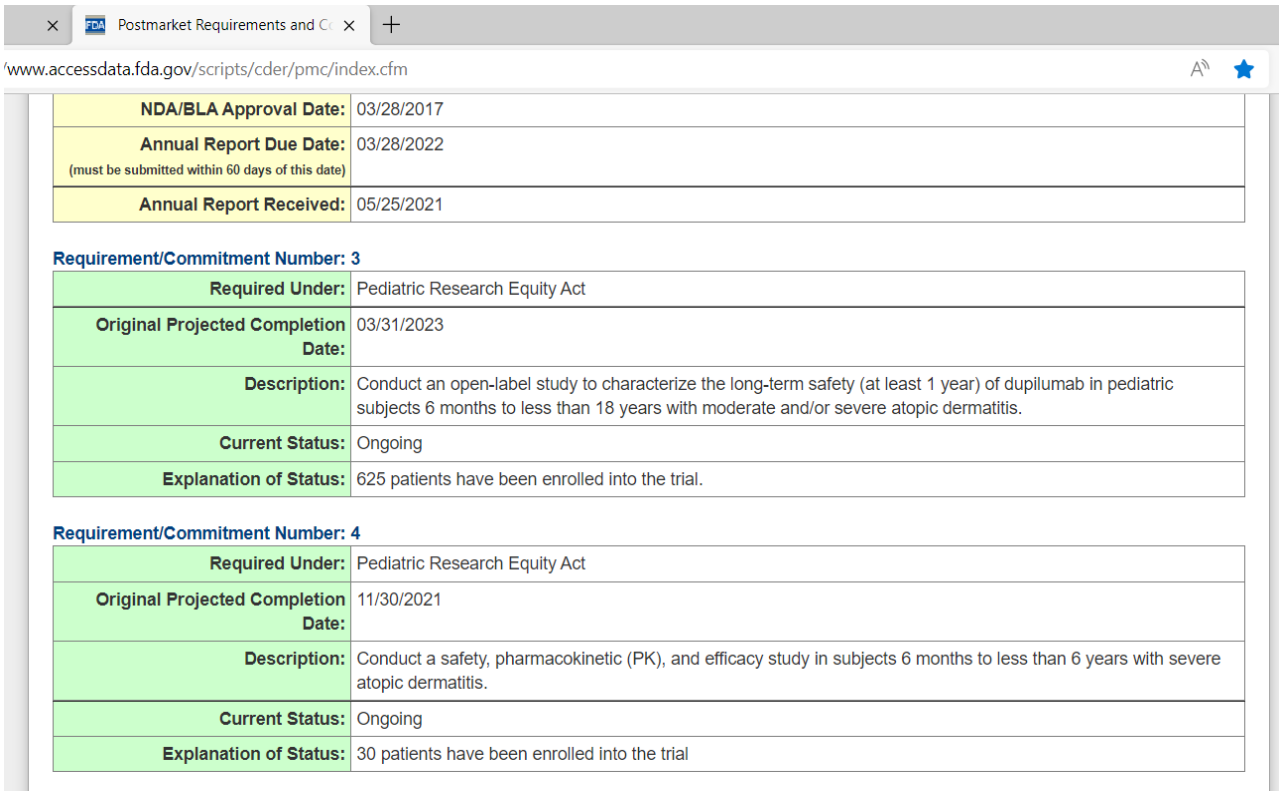
Studies)] is deferred to other disciplines as required (e.g., DG and Clinical Pharmacology).

The comments below were provided to DG on April 20, 2022. The reader is directed to final approved labeling, which may include revised language not addressed in this review.

(b) (4)

[redacted]

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page



NDA/BLA Approval Date:	03/28/2017
Annual Report Due Date: (must be submitted within 60 days of this date)	03/28/2022
Annual Report Received:	05/25/2021

Requirement/Commitment Number: 3

Required Under:	Pediatric Research Equity Act
Original Projected Completion Date:	03/31/2023
Description:	Conduct an open-label study to characterize the long-term safety (at least 1 year) of dupilumab in pediatric subjects 6 months to less than 18 years with moderate and/or severe atopic dermatitis.
Current Status:	Ongoing
Explanation of Status:	625 patients have been enrolled into the trial.

Requirement/Commitment Number: 4

Required Under:	Pediatric Research Equity Act
Original Projected Completion Date:	11/30/2021
Description:	Conduct a safety, pharmacokinetic (PK), and efficacy study in subjects 6 months to less than 6 years with severe atopic dermatitis.
Current Status:	Ongoing
Explanation of Status:	30 patients have been enrolled into the trial

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/s/

ETHAN D HAUSMAN
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JOHN J ALEXANDER
04/22/2022 04:58:25 PM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 12, 2022
Requesting Office or Division:	Division of Gastroenterology (DG)
Application Type and Number:	BLA 761055/S-040
Product Name and Strength:	Dupixent (dupilumab) injection, 300 mg/ 2mL (150 mg/mL), 200 mg/ 1.14 mL (175 mg/mL), and 100 mg/0.67 mL (149 mg/mL)
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Regeneron Pharmaceuticals Inc.
FDA Received Date:	February 3, 2022
OSE RCM #:	2022-462
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

Regeneron Pharmaceuticals Inc. submitted a supplement for Dupixent (dupilumab) injection to provide for a new indication for the treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis (EoE). Subsequently, the Division of Gastroenterology (DG) requested that we review the proposed Dupixent prescribing information (PI) and patient package insert (PPI) 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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

We note that DMEPA 1 human factors (HF) team is currently evaluating the use-related risk analysis (URRA) and Sponsor's justification and conclusion as to why no human factor studies are needed for the proposed new indication of treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis (EoE).

Though we find the Patient Information acceptable from medication error perspective, proposed prescribing information (PI) may be improved to promote the safe use of this product. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Regeneron Pharmaceuticals Inc.

4 RECOMMEDATIONS FOR DIVISION OF GASTROENTEROLOGY (DG)

Table 2. Identified Issues and Recommendations for Division of Gastroenterology (DG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Note that DMEPA 1 is evaluating the HF related submission (use-related risk analysis (URRA) and Sponsor's justification and conclusion as to why no human factor studies are needed) under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.		
Full Prescribing Information – Section 2 Dosage and Administration			
(b) (4)			

5 RECOMMENDATIONS FOR REGENERON PHARMACEUTICALS INC.

Note that human factor comments may be forthcoming when we have completed our evaluation of your human factors related submission (use-related risk analysis (URRA) and Sponsor's justification and conclusion as to why no human factor studies are needed).

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Dupixent that Regeneron Pharmaceuticals Inc. submitted on February 3, 2022.

Table 3. Relevant Product Information for Dupixent	
Initial Approval Date	March 28, 2017
Proper Name	dupilumab
Indication	DUPIXENT is an interleukin-4 receptor alpha antagonist indicated: Atopic Dermatitis • for the treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. DUPIXENT can be used with or without topical corticosteroids. Asthma • as an add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. (1.2) *Limitations of Use:* Not for the relief of acute bronchospasm or status asthmaticus. Chronic Rhinosinusitis with Nasal Polyposis • as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP). Eosinophilic Esophagitis • for the treatment of adult and pediatric patients aged 12 years and older with eosinophilic esophagitis (EoE).
Route of Administration	subcutaneous
Dosage Form	injection
Strength	300 mg/ 2mL (150 mg/mL), 200 mg/ 1.14 mL (175 mg/mL), and 100 mg/0.67 mL
Dose and Frequency	Atopic Dermatitis Dosage in Adults

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

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

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

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

Asthma

Dosage in Adult and Pediatric Patients 12 Years and Older

Initial Loading Dose	Subsequent Dose
400 mg (two 200 mg injections)	200 mg every 2 weeks (Q2W)
or	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)
Dosage for patients with oral corticosteroid-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid chronic rhinosinusitis with nasal polyposis	
600 mg (two 300 mg injections)	300 mg every 2 weeks (Q2W)

Dosage in Pediatric Patients 6 to 11 Years of Age

Body Weight	Initial Dose and Subsequent Doses
15 to less than 30 kg	100 mg every other week (Q2W) or 300 mg every four weeks (Q4W)
≥30 kg	200 mg every other week (Q2W)

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

Chronic Rhinosinusitis with Nasal Polyposis

<table>
<tr><td></td><td>
Recommended dosage for adult patients is 300 mg given every other week (Q2W).
Eosinophilic Esophagitis
Recommended dosage for adult and pediatric patients 12 years of age and older is 300 mg given every week (QW).
</td></tr>
<tr><td>How Supplied</td><td>
DUPIXENT (dupilumab) Injection is a clear to slightly opalescent, colorless to pale yellow solution, supplied in single-dose pre-filled syringes with needle shield or pre-filled pens.
The pre-filled syringe with needle shield is designed to deliver:

300 mg of DUPIXENT in 2 mL solution (NDC 0024-5914-00)
200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5918-00)
100 mg of DUPIXENT in 0.67 mL solution (NDC 0024-5911-00)

The pre-filled pen is designed to deliver:

300 mg of DUPIXENT in 2 mL solution (NDC 0024-5915-00)
200 mg of DUPIXENT in 1.14 mL solution (NDC 0024-5919-00)

DUPIXENT is available in cartons containing 2 pre-filled syringes with needle shield or 2 pre-filled pens.
<table>
<tr><th>Pack Size</th><th>300 mg/2 mL Pre-filled Syringe with Needle Shield</th><th>200 mg/1.14 mL Pre-filled Syringe with Needle Shield</th><th>100 mg/0.67 mL Pre-filled Syringe with Needle Shield</th></tr>
<tr><td>Pack of 2 syringes</td><td>NDC 0024-5914-01</td><td>NDC 0024-5918-01</td><td>NDC 0024-5911-02</td></tr>
</table>
<table>
<tr><th>Pack Size</th><th>300 mg/2 mL Pre-filled Pen</th><th>200 mg/1.14 mL Pre-filled Pen</th></tr>
<tr><td>Pack of 2 pens</td><td>NDC 0024-5915-02</td><td>NDC 0024-5919-02</td></tr>
</table>
</td></tr>
<tr><td>Storage</td><td>
Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.
If necessary, DUPIXENT may be kept at room temperature up to 25°C (77°F) for a maximum of 14 days. Do not store above 25°C
</td></tr>
</table>

	(77°F). After removal from the refrigerator, DUPIXENT must be used within 14 days or discarded. Do not expose DUPIXENT to heat or direct sunlight. Do NOT freeze. Do NOT shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On April 6, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, 'dupixent'. Our search identified eleven previous reviews[a,bc,d,e,f,g,h,i,jk], and we considered our previous recommendations to see if they are applicable for this current review.

[a] Patel, M. Label and Labeling Review for Dupixent (dupilumab) (BLA 761055/S-40). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2022 MAR 15. RCM No.: 2022-100

[b] Howard, C. Use-Related Risk Analysis Review for Dupixent (dupilumab) (IND 107969). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 SEP 21. RCM No.: 2021-1252.

[c] Owen, L. Label and Labeling Review for Dupixent (dupilumab) (BLA 761055/S-031). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 26. RCM No.: 2021-266.

[d] Shah, M.. Comparative Analyses and Use-Related Risk Analysis Review for Dupixent (IND 105379). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 02. RCM No.: 2020-1779.

[e] Patel, M. Label and Labeling Review Memorandum for Dupixent (dupilumab) (BLA 761055/S-12). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019-FEB 14 RCM No.: 2018-1924-1.

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

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

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

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

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

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

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,[l] along with postmarket medication error data, we reviewed the following Dupixent labels and labeling submitted by Regeneron Pharmaceuticals Inc.

- Patient Information received on February 3, 2022, available from \\CDSESUB1\evsprod\bla761055\1030\m1\us\114-labeling\draft\labeling\proposed-ppi-eoe.docx
  \\CDSESUB1\evsprod\bla761055\1030\m1\us\114-labeling\draft\annotated\annotated-ppi-eoe.docx

- Prescribing Information (Image not shown) received on February 3, 2022, available from \\CDSESUB1\evsprod\bla761055\1030\m1\us\114-labeling\draft\labeling\proposed-uspi-eoe.docx
  \\CDSESUB1\evsprod\bla761055\1030\m1\us\114-labeling\draft\annotated\annotated-uspi-eoe.docx

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

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/s/

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