NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	Supplemental Biologics Licensing Application
Application Number(s)	761055
Priority or Standard	Standard
Submit Date(s)	December 20, 2017
Received Date(s)	December 20, 2017
PDUFA Goal Date	October 20, 2018
Division/Office	DPARP/ODEII
Review Completion Date	October 19, 2018
Established Name	Dupilumab
(Proposed) Trade Name	DUPIXENT
Pharmacologic Class	Interleukin-4 receptor alpha antagonist
Applicant	Regeneron Pharmaceuticals, Inc.
Formulation(s)	Subcutaneous solution for injection
Dosing Regimen	200 mg every 2 weeks with a 400 mg loading dose or 300 mg every 2 weeks with a 600 mg loading dose
Applicant Proposed Indication(s)/Population(s)	Add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, (b) (4)
Recommendation on Regulatory Action	Approval

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Glossary

ACQ	Juniper Asthma Control Questionnaire
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire
BD	bronchodilator
BLA	Biologic License Application
BMI	body mass index
CI	confidence interval
CLCRN	creatinine clearance normalized to body surface area
CSR	clinical study report
CV	cardiovascular
DB	double-blind
EGPA	eosinophilic granulomatosis with polyangiitis
EOS	eosinophil
ER	exposure response
FDA	Food and Drug Administration
FeNO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
FEV1-12wk	FEV1 at week 12

G/L	billion cells per liter
GCP	good clinical practice
GINA	Global Initiative for Asthma
HEos	high eosinophil
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IND	Investigational New Drug
ITT	intention to treat
LABA	long-acting beta agonist
LS	least squares
MACE	major adverse cardiovascular event
MAR	missing at random
MMRM	mixed-effect model with repeated measures
NDA	new drug application
OCS	oral corticosteroids
PD	pharmacodynamic
PK	pharmacokinetic
	(b) (4)
PMM-MI	pattern mixture model-multiple imputation
PPK	population pharmacokinetics
PT	preferred term
PY	patient-years
q2w	once every 2 weeks
q4w	once every 4 weeks
SAE	serious adverse event
sBLA	supplemental biologics license application
SC	subcutaneous
SD	standard deviation
SOC	system organ class
TARC	thymus and activation-regulated chemokine
VPC	visual predictive check
WT	body weight

1. Executive Summary

1.1. Product Introduction

Dupilumab is an interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab is the first-in-class anti-IL4Ra monoclonal antibody proposed for an asthma indication. Dupilumab is proposed as add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, (b) (4) . The Applicant also proposes dupilumab for maintenance therapy to improve lung function, and as maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients. The application supports the indication of add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, with an eosinophilic phenotype. The proposed indications of improving lung function and reducing oral steroid are considered to be encompassed within the broader indication of the maintenance treatment of asthma.

Dupilumab 300 mg q2w with a 600 mg loading dose was approved in March 2017 for 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.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action from a clinical perspective is approval of dupilumab 200 mg subcutaneous (SC) every 2 weeks (q2w) with a loading dose of 400 mg and 300 mg SC with a loading dose of 600 mg q2w for use as add-on maintenance treatment in patients 12 years of age and older with moderate-to-severe asthma and an eosinophilic phenotype. The 300 mg SC q2w dose, with a 600 mg loading dose, is recommended as the starting dose for patients requiring concomitant oral corticosteroids or with comorbid moderate-to-severe atopic dermatitis for which dupilumab is indicated.

To support this application, the Applicant has completed a 6-month dose-ranging trial and a 1-year efficacy and safety trial. Both studies demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations and lung function in patients with moderate-to-severe asthma with an eosinophilic phenotype for both the 200 mg SC q2w with a loading dose of 400 mg and the 300 mg SC q2w with a loading dose of 600 mg. While both studies enrolled subjects regardless of baseline blood eosinophil level, efficacy was not consistently demonstrated in subjects without an eosinophilic phenotype. In addition, a third pivotal trial demonstrated that 300 mg SC q2w (with a loading dose of 600 mg) enabled control of underlying asthma with decreased oral corticosteroids (OCS). Efficacy was similar between doses and there were no major dose-related safety concerns.

The adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. This review recommends approval in this age group, as there are no age-related

differences in the pharmacokinetic (PK) and pharmacodynamic (PD) parameters, and no safety concerns for dupilumab in adolescent patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Dupilumab is an interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab was approved in March 2017 for 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 is a first-in-class monoclonal antibody proposed for an asthma indication. Dupilumab is proposed for the add-on maintenance treatment of moderate-to-severe asthma in patients ≥12 years of age. The submission supports modifying the proposed indication to patients with an eosinophilic phenotype and to patients with oral corticosteroid dependent asthma.

The efficacy and safety of dupilumab was evaluated in three well-controlled and adequately designed trials including a 6-month dose-ranging trial, a 1-year efficacy and safety trial, and one oral corticosteroid reduction trial. The 6-month dose-ranging trial and the 1-year efficacy and safety trial demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations and lung function for patients with moderate-to-severe asthma with an eosinophilic phenotype for both the 200 mg SC q2w with a loading dose of 400 mg and the 300 mg SC q2w with a loading dose of 600 mg. While both studies enrolled subjects regardless of baseline blood eosinophil level, efficacy was not consistently demonstrated in subjects without an eosinophilic phenotype. In addition, a third pivotal trial demonstrated that 300 mg SC q2w (with a loading dose of 600 mg) enabled control of underlying asthma with decreased OCS, irrespective of baseline eosinophilia. The adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. This review recommends approval in this age group, as there are no age-related differences in the PK and PD, and no safety concerns for the use of dupilumab in adolescent patients.

The program included an assessment of safety concerns related to immunomodulatory therapy and biologics including infections, malignancy, hypersensitivity events, and immunogenicity. Injection-site reactions were the most common adverse event and were dose-related. Hypersensitivity events were also dose-related. Major adverse cardiovascular events (MACE) were reported at a slightly higher frequency in the 300 mg q2w dose group compared to placebo, but not in the 200 mg q2w dose group. One anaphylaxis case was reported for dupilumab. Multiple cases of eosinophilic granulomatosis with polyangiitis and one case of eosinophilic pneumonia were reported. The ocular safety issues seen in the atopic dermatitis program were not identified in the asthma studies. No safety concerns that offset the efficacy benefits provided by dupilumab were identified for the overall or adolescent populations.

This review recommends approval of dupilumab in patients 12 years of age and older with moderate-to-severe asthma and an eosinophilic phenotype for both proposed doses as efficacy was similar between doses and there were no major dose-related safety

concerns. No safety concerns that would preclude approval were identified in the overall population or the adolescent population. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness and coughing caused by underlying airway inflammation and airway hyper-responsiveness. Episodic increases in symptoms are referred to as asthma exacerbations. The disease is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction leading to chronic symptoms despite current standard of care treatment. While many exacerbations may be managed as outpatient with the use of oral corticosteroids, severe exacerbations may require hospitalization and may even lead to death.	Asthma is a common condition. While most patients can be treated with existing therapies, a small percentage of the asthma population continues to experience significant morbidity and the potential for mortality from this condition.
Current Treatment Options	• Omalizumab is an anti-IgE for treatment of allergic asthma. There are three anti-IL5s approved for the treatment of patients with severe asthma and an eosinophilic phenotype. Dupilumab is first-in-class anti-IL4Ra for the treatment of asthma.	While there is an anti-IgE approved for moderate-to-severe asthma, it is limited to allergic asthma (defined by perennial aeroallergen sensitivity) and by weight and serum IgE restrictions. There are also three approved therapies for asthma with an eosinophilic phenotype; however, these are limited to severe asthma and have distinct safety profiles due the different mechanism of action. (continued below)

Current Treatment Options (continued)		Additional treatment options are preferable for those who are ineligible for existing treatments, or unable to tolerate them.
Benefit	• In two, well-controlled and well-designed studies, dupilumab demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations and lung function in patients with moderate-to-severe asthma with an eosinophilic phenotype. Dosages were: (1) 200 mg SC q2w, with a loading dose of 400 mg; and (2) 300 mg SC q2w with a loading dose of 600 mg. While both studies enrolled subjects regardless of baseline blood eosinophil level, efficacy was not consistently demonstrated in subjects without an eosinophilic phenotype. • In addition, a third pivotal trial demonstrated a lower requirement for OCS to control a patient's underlying asthma with 300 mg SC q2w, and a loading dose of 600 mg. • The adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. This review recommends approval in this age group, as there are no age-related differences in the PK and PD, and no safety concerns for the use of dupilumab in adolescent patients.	Dupilumab is a clinically relevant, beneficial treatment for patients ≥12 years of age with moderate-to-severe asthma with an eosinophilic phenotype.

Risk	• Injection-site reactions were the most common adverse event and were dose-related. • Hypersensitivity events were also dose-related. • MACE were reported at a slightly higher frequency in the 300 mg q2w dose group compared to placebo, but not in the 200 mg q2w dose group. • One anaphylaxis case was reported for dupilumab. • Multiple cases of eosinophilic granulomatosis with polyangiitis and one case of eosinophilic pneumonia were reported. • The ocular safety issues seen in the atopic dermatitis program were not identified in the asthma studies. • The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.	The program does not demonstrate any safety findings that offset the efficacy findings.
Risk Management	• No risk evaluation and mitigation strategies are proposed.	The safety findings that were seen in the program can be managed through labeling and routine pharmacovigilance.

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Cross-Disciplinary Team Leader
Miya Okada Paterniti

2. Therapeutic Context

2.1. Analysis of Condition

Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness, and coughing caused by underlying airway inflammation and airway hyper-responsiveness. It is typically associated with variable and reversible airflow obstruction, but progressive airway remodeling may lead to persistent asthma associated with partially or fully irreversible airway obstruction.

IL-4 is a central mediator of T lymphocyte cell differentiation; it induces the production of Type 2 associated cytokines and chemokines (IL-5, IL-9, IL-13, thymus and activation-regulated chemokine (TARC/CCL17) and eotaxins-3), isotype class switching of B cells to produce serum IgE, and the recruitment of eosinophils and other inflammatory cells (including tissue eosinophils).[1] Although IL-13 displays some redundancies in these pro-inflammatory processes, it has additional roles in mediating goblet cell hyperplasia, mucus production, smooth muscle contractility, and airway hyperresponsiveness.[2] Together, IL-4 and IL-13 play critical roles in the induction and effector phases of asthma.

The diagnosis and management of this common condition are outlined in the NAEPP[3] and Global Initiative for Asthma (GINA)[4] guidelines, which include a treatment approach of escalating daily maintenance therapy in accordance with a patient's symptoms. While the majority of patients are successfully managed with this step-wise treatment approach, a subset of patients remains uncontrolled despite maximal medical management.

2.2. Analysis of Current Treatment Options

Dupilumab is the first anti-IL4Ra proposed for the treatment of asthma. Three anti-IL5 biologics are approved for the add-on maintenance treatment of patients with severe asthma and an eosinophilic phenotype. Omalizumab is an anti-IgE that is also approved for treatment of asthma; however, the indication is limited to allergic asthma defined by a positive skin test or in vitro reactivity to a perennial aeroallergen. Corresponding to the uncertainty in the clinical community on how best to clinically define an eosinophilic phenotype, previous programs have enriched for this subgroup in different ways. Mepolizumab evaluated patients with a recent peripheral blood eosinophil count of ≥150 cells/µl or 12-month historical value of ≥300 cells/µl; reslizumab used a cutoff of 400 cells/µl just prior to enrollment. Benralizumab enriched for patients with counts ≥300 cells/µl just prior to enrollment but also included patients with values <300 cells/µl in its pivotal phase 3 trials. Dupilumab is not an anti-IL5 and was not expected to specifically treat

[1] Brandt EB, U Sivaprasad, 2011, Th2 Cytokines and Atopic Dermatitis, J Clin Cell Immunol, 2(3):110.
[2] Corren J, 2013, Role of interleukin-13 in asthma, Curr Allergy Asthma Rep, 13(5):415-420.
[3] National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute (NHLBI), 2007, National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma, NIH publication no. 07-4051.
[4] Global Initiative for Asthma (GINA), 2013, Global Strategy for Asthma Management and Prevention, accessed April 28,2015: http://www.ginasthma.org/.

asthma with an eosinophilic phenotype due to the different mechanism of action, therefore, the sponsor did not enrich for patients with eosinophil counts ≥300 cells/µl, but stratified the randomization based on eosinophil group. Studies of dupilumab also enrolled patients with moderate-to-severe asthma, which differs from the anti-IL-5 clinical programs that enrolled patients with severe asthma.

Table 1: Summary of Treatments Relevant to Proposed Indication

Product Name	Indication	Dose	Efficacy Information and population studied
Omalizumab *Approved 2003*	Moderate-to-severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms are inadequately controlled with inhaled corticosteroids	75 mg to 375 mg SC every 2 to 4 weeks, depending on weight and serum IgE	The study designs and patient population were not comparable to the other approved products.
Mepolizumab *Approved 2015*	Add-on maintenance treatment in patients ≥12 years of age with severe asthma with an eosinophilic phenotype	100 mg SC every 4 weeks	*Exacerbations* One phase 2b exacerbation trial demonstrated a reduction in exacerbations. The population was enriched with patients meeting criteria believed to identify an eosinophilic phenotype. These criteria included peripheral blood eosinophil counts, airway eosinophil counts and loss of control with OCS dose reduction and FeNO. One pivotal exacerbation trial demonstrated a reduction in exacerbations in severe asthma patients on background standard of care with peripheral blood eosinophil count ≥150 cells/µl[1] or historical count ≥300 cells/µl[2] with a history of two exacerbations in the prior 12 months. *Oral Corticosteroid Reduction* One trial demonstrated an ability to reduce oral corticosteroids dosage in severe asthma patients with peripheral blood eosinophil count ≥150 cells/µl[1] or historical count ≥300 cells/µl. *Lung Function* No consistent improvement in lung function was seen in this development program. *Adolescents* 28 adolescents were evaluated in the program with a trend toward exacerbation reduction in mepolizumab treated patients.

Reslizumab *Approved 2016*	Add-on maintenance therapy in patients ≥18 years old with severe asthma with an eosinophilic phenotype	3 mg/kg IV every 4 weeks	*Exacerbations* Two pivotal trials demonstrated a reduction in exacerbations and improvements in lung function in severe asthma patients with a peripheral blood eosinophil count ≥400 cells/μl[3] and a history of at least one asthma exacerbation in the prior 12 months. *Lung function* The two exacerbation trials and a third lung function trial in severe asthma patients with a peripheral blood eosinophil count ≥400 cells/μl demonstrated an improvement in lung function. *All eosinophil counts* One trial evaluated lung function in asthma patients unselected for blood eosinophil levels. A lung function benefit was demonstrated in the overall population. No association between a treatment effect and blood eosinophil levels was seen. *Adolescents* 39 adolescents were evaluated in the program with point estimates favoring placebo in two exacerbation studies. Reslizumab is approved for use in patients 18 years of age and older given an unfavorable risk benefit assessment in the adolescent population.

Benralizumab *Approved 2017*	Add-on maintenance treatment in patients ≥12 years of age with severe asthma with an eosinophilic phenotype	30 mg SC every 4 weeks x 3 doses, then every 8 weeks	*Exacerbations* Two pivotal trials demonstrated a reduction in exacerbations in severe asthma patients with a peripheral blood eosinophil count ≥300 cells/μl[3] (primary analysis population) and a history of at least 2 asthma exacerbations in the prior 12 months. OCS use was allowed. Reductions in exacerbation rates were observed irrespective of baseline eosinophil counts; however, patients with a baseline eosinophil count of ≥300 cells/uL showed a numerically greater response than those with <300 cells/uL. The exacerbation benefit was not statistically significant in those with < 300 cells/uL. *Lung function* One dose-ranging and two exacerbation trials demonstrated an improvement in lung function in the high eosinophil population. *Oral Corticosteroid Reduction* One trial demonstrated an ability to reduce oral corticosteroids dosage in severe asthma patients with peripheral blood eosinophil count ≥150 cells/μl[1]

[1] within 6 weeks of dosing
[2] within 12 calendar months of enrollment
[3] within 3 to 4 weeks of dosing
FeNO = fractional exhaled nitric oxide; IV = intravenous; OCS = oral corticosteroids; SC = subcutaneous

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The key regulatory history is summarized in Table 2.

Table 2. Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
PIND	July 8, 2009	Study full spectrum of disease
IND filed	Sept 10, 2009	FIH study
Type C	Oct 11, 2011	Eosinophilic asthma is not well defined Conduct POC and dose-ranging studies in adults prior to enrolling adolescents

Table 2. Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
Type C	Dec 7, 2012	POC withdrawal design results artificially elicits exacerbation Exacerbation definition includes self-limited decrease in PF w/out symptom change
EOP2	Feb 3, 2015	DRI12544 may be used as a pivotal study Include 200 mg q2w dose EFC13579
Agreed iPSP	Oct 28, 2015	Deferral <12 years Agreed Amended iPSP March 15 2017
Type C	Feb 2, 2016	Discuss loading dose rationale
Type C	Apr 9, 2016	(b) (4) manufacturing process – (b) (4) – include ~100 patients with (b) (4) (withou (b) (4)) for sensitivity analysis
Pre-sBLA	May 8, 2017	Include 24-week safety pool, exposure-adjusted rates for 52-week pool Interim efficacy analysis problematic. Applicant proposes it as final Submit OCS sparing study with sBLA

EOP2 = end of phase 2; FIH = first in human; IND = investigational new drug; iPSP = initial pediatric study plan; PIND = pre-investigational new drug; (b) (4) 2; POC = Proof-of-concept; sBLA = supplemental biologics license application; q2w = every other week

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

4.1. Office of Scientific Investigations

An Office of Scientific Investigations consult was requested due to the large clinical development program. Four sites (Edmond, Okla.; Rolling Hills Estates, Calif. (two sites); Poland) were recommended for inspection due to higher enrollment, risk ranking, United States enrollment, and serious adverse effect (SAE) rate for studies EFC13579 and EFC13691. No issues were identified.

4.2. Product Quality

With this supplement, the Applicant introduced a new presentation of dupilumab (200 mg/1.14 mL in a single-dose pre-filled syringe with a needle shield). The manufacturing of the new 200 mg/1.14 mL presentation is similar to the approved processes except for a slightly different (b) (4) and the smaller drug product container closure system. The data provided in the supplement support the conclusion that the proposed control strategy for the new 200 mg/1.14 mL presentation combined with in process, release, and stability testing ensure process consistency and drug substance, formulated drug substance, and drug product with appropriate quality attributes. The Office of Biotechnology Products recommends approval.

4.2.1. (b) (4) Contaminant Sensitivity Analysis

(b) (4) which may affect lung inflammation in asthma or have local pro-inflammatory effects at the injection site. The Applicant discovered the (b) (4) contaminant due to issues with stability. During the conduct of Study EFC13579, dupilumab underwent a manufacturing change to remove (b) (4) to improve stability. The to-be-marketed product is (b) (4) -free.

The asthma proof-of-concept study (ACT11457) was conducted without (b) (4), and the dose-ranging study (DRI1254) was conducted with (b) (4). There were no concerning safety differences. Per our recommendation, the Applicant conducted an efficacy sensitivity analysis for the 1-year study (EFC13579) for patients who received only (b) (4) -free dupilumab compared to those who received only dupilumab with (b) (4). Analysis on the 374 patients who were treated with the (b) (4) -free dupilumab showed that there was no noticeable difference in the efficacy estimates compared to the ITT analysis (Table 65).

As this is a previously approved product, there were no chemistry, manufacturing, and controls issues. See Dr. Gunther Boekhoudt's review for further details.

4.3. Clinical Microbiology

The Division of Microbiology Assessment recommends approval based on review of the product quality microbiology and sterility assurance. For further details, see the review by Dr. Lakshmi Narasimhan.

4.4. Devices and Companion Diagnostic Issues

There is no companion diagnostic test for review in support of this sBLA.

The Center for Devices and Radiological Health reviewed the device constituent of the combination product and recommends approval. The dupilumab pre-filled syringe is supplied as a ready-to-use, sterile, single dose, prefilled and disposable glass syringe assembled with a plunger rod and inserted within a safety system preassembled with a finger flange.

See the Center for Devices and Radiological Health review by Dr. Rong Guo for additional details.

5. Nonclinical Pharmacology/Toxicology

5.1. Referenced NDAs, BLAs, Drug Master Files

This supplemental biologics license application (sBLA) relies on the nonclinical data presented for the initial BLA approval of dupilumab. Please refer to the nonclinical primary review under BLA 761055 dated December 5, 2016, for details. No new nonclinical toxicology studies were submitted for this sBLA.

5.2. Pharmacology

5.2.1. Brief Description of the Animal Model and its Development

Dupilumab does not bind mouse IL-4Rα, and mouse IL-4 does not bind to human IL-4Rα. Therefore, a double humanized mouse strain was generated in which both the murine IL-4 and the ectodomain of murine IL-4Rα were replaced with their corresponding human sequences (*Il4ra*$^{hu/hu}$ *Il4*$^{hu/hu}$). In a 4-week House Dust Mite (HDM) allergen-induced lung inflammation model using *Il4ra*$^{hu/hu}$ *Il4*$^{hu/hu}$ mice, subcutaneous administration of 10 or 25 mg/kg dupilumab twice per week prevented goblet cell metaplasia, inflammatory lung infiltrates (eosinophils, CD23^{+} B cells, and ST2^{+} CD4^{+} T cells), and expression of eotaxin 1, *IL4, IL5,* and *IL6*. In addition, dupilumab treatment prevented HDM-induced impairment of lung function as measured by $FEV_{0.1}$.

5.3. Toxicology

5.3.1. Carcinogenicity

The Applicant provided an amended carcinogenicity risk assessment for dupilumab in this sBLA. The Applicant stated that an updated carcinogenicity literature search was performed, and no new publications were identified that would change the conclusions of the original document. The original carcinogenicity risk assessment for dupilumab was submitted to the Division of Dermatology and Dental Products on April 4, 2014 and reviewed under IND 107969.

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Primary Reviewer	Team Leader
Yu-Mee Kim	Carol Galvis

6. Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking the approval of DUPIXENT (dupilumab) as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, (b) (4)

Dupilumab is provided as a single-dose pre-filled syringe with needle shield:

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

The clinical pharmacology information of this sBLA consists of PK, PD, and exposure response (ER) data for dupilumab in patients with asthma (12 years and older) obtained from phase 2 and phase 3 efficacy/safety studies (Study ACT11457, Study DRI12544, Study EFC13579, Study EFC13691, and Study LTS12551). Results from the population pharmacokinetic (PPK) analysis using data pooled from phase 1 to phase 3 studies in healthy subjects (Study POH0530) and patients with asthma were included. Exposure-response or PK/PD analyses for efficacy endpoints in asthma patients (Studies POH531and POH0563) were also included and discussed. Dupilumab concentrations were measured in the target asthma population in two phase 2 (ACT11457, DRI12544) and three phase 3 studies (EFC13579, EFC13691 and LTS12551).

The proposed dose regimen is 200 mg q2w following an initial dose of 400 mg for the add-on treatment for patients with uncontrolled moderate-to-severe asthma. For those with severe steroid-dependent asthma, the recommended dose is 300 mg q2w following an initial dose of 600 mg. Both doses have demonstrated clinical efficacy and tolerable safety profile in asthma patients in the phase 3 trials (see sections 1.3, 7.3, and 7.4).

There was no clear dose/exposure response observed, as efficacy appears to reach a plateau with exposures achieved in the 200 mg q2w dose group. Clinical efficacy of the proposed 200 mg q2w and 300 mg q2w dosing regimens are demonstrated in studies DRI12544 and EFC13579. The incidence of safety events was too low to support meaningful exposure response (ER) analysis for safety. Population PK and ER analyses demonstrated that steady state is achieved earlier with the loading dose.

The proposed dosing regimen is acceptable (see section 6.2.2). No dose adjustment is recommended for any intrinsic factors. The incidence of treatment-emergent anti-drug antibodies was low (6 to 9% for the dupilumab group) in patients with asthma (see section 6.3.2).

Recommendations

From a Clinical Pharmacology standpoint, this sBLA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

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

Dupilumab PK is comparable between healthy subjects, asthma, and AD patient populations.

In patients with asthma, dupilumab is well-absorbed, with an estimated SC bioavailability at 61%; distributes primarily within the vascular compartment (4.37 L); and exhibits non-linear target mediated elimination.

The median time to steady state is 6 weeks for 200 mg q2w with 400 mg loading dose, and 8 weeks for 300 mg q2w with 600 mg loading dose based on PPK analysis. At steady state, observed mean trough concentration increased from 36.5 mg/L to 67.8 mg/L (1.86 fold) for a 1.5-fold increase in SC dose from 200 to 300 mg q2w.

There was no clear dose/exposure response observed, as efficacy appears to reach a plateau with exposures achieved in the 200 mg q2w dose group. Clinical efficacy of the proposed 200 mg q2w and 300 mg q2w dosing regimens are demonstrated in studies DRI12544 and EFC13579. The incidence of safety events was too low to support meaningful ER analysis for safety. Population PK and ER analyses demonstrated that steady state is achieved earlier with the loading dose.

Body weight is the primary factor responsible for dupilumab PK variability. Other intrinsic factors including age, gender, race/ethnicity, renal function (normal to moderately decreased), lab parameters (albumin, ALP, AST and ALT), Type 2 inflammation, and disease markers do not have a meaningful effect on dupilumab pharmacokinetics. The magnitude of body weight effect on exposure is not likely to yield a clinically meaningful effect on efficacy, given the lack of exposure-response relationship. No dose adjustment is recommended with respect to the PK covariates.

The incidence of treatment emergent ADA was 5.1%, 9.3%, and 3.5% in the 300 mg q2w, 200 mg q2w, and combined placebo groups, respectively. The incidence of persistent ADA was 2.1%, 4.2% and 1.1% in the 300 mg q2w, 200 mg q2w, and combined placebo groups, respectively.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of dupilumab for adults and adolescents (12 years of age and older) is:

- An initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week. The dose may be increased to 300 mg every other week based on physician assessment.
- An initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week for patients with oral corticosteroids-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated.

Clinical efficacy of the proposed 200 mg q2w and 300 mg q2w dosing regimens are demonstrated in studies DRI12544 and EFC13579 (section 7.2 and 7.3). There was no clear dose/exposure response observed as efficacy appears to plateau after 200 mg dose. Clinical efficacy of the proposed 200 mg q2w and 300 mg q2w dosing regimens are demonstrated in studies DRI12544 and EFC13579. Population PK and ER analyses demonstrated that steady state is achieved earlier with the loading dose. (Refer to the pharmacometric (PM) review for details)

The incidence of safety events was too low to support meaningful ER analysis for safety. The overall safety profiles were comparable for the two dosing regimens. Age was not a significant covariate on dupilumab exposure after adjusting for the effect by body weight. The magnitude of body weight effect on exposure is not likely to yield a clinically meaningful effect on efficacy, given the lack of exposure-response relationship. No dose adjustment is recommended with respect to the PK covariates including body weight. Therefore, both 200 mg q2w and 300 mg q2w appear acceptable for the proposed indication in adult and adolescent.

Therapeutic Individualization

Patient intrinsic factors including body weight, age, gender, race, renal function, and hepatic function were not found to have a clinically important effect on dupilumab pharmacokinetics in asthma patients. Dose adjustment is not necessary for these factors.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

PK Characteristics of Dupilumab in Asthma Patients Following SC Administration

Dupilumab PK has been assessed in healthy subjects and in patients with atopic dermatitis. For details, see clinical pharmacology review by Dr. Jie Wang in DARRTs (Reference ID 4030358).

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

Dupilumab PK is comparable between healthy subjects, asthma, and AD patient populations. In patients with asthma, dupilumab is well absorbed with an estimated SC bioavailability at 61% (64% in the AD population), distributes primarily within the vascular compartment (4.37 L) and exhibits non-linear target-mediated elimination. After the last dose at the steady-state, the median times for the serum concentration to decrease below the lower limit of quantitation are 9 or 11 weeks for 200 mg q2w or 300 mg q2w dupilumab.

The median time to steady state is 6 weeks for 200 mg q2w with 400 mg loading dose and 8 weeks for 300 mg q2w with 600 mg loading dose based on PPK analysis. At steady-state, the observed mean trough concentration increased from 36.5 mg/L to 67.8 mg/L (1.86 fold) for a 1.5-fold increase in SC dose from 200 to 300 mg q2w.

Intrinsic Factors Affecting PK

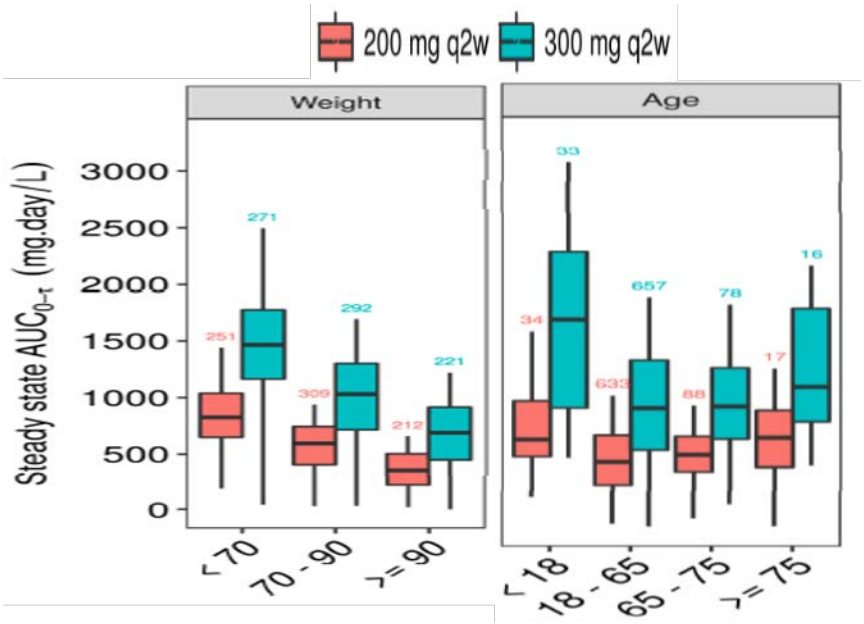
A combination of descriptive analyses and PPK analyses was used to assess the effect of intrinsic factors on the PK of dupilumab in asthma. (Refer to PM review for details).

Body weight was the primary factor responsible for dupilumab PK variability. Other intrinsic factors including age, gender, race/ethnicity, renal function (normal to moderately decreased), lab parameters (albumin, ALP, AST and ALT), Type 2 inflammation, and disease markers do not have a meaningful effect on dupilumab pharmacokinetics.

The magnitude of body weight effect on exposure is not likely to yield a clinically meaningful effect on efficacy given the lack of exposure-response relationship.

Age was not found to be a significant covariate after adjusting for body weight. Dupilumab exposure was higher in adolescent patients than that in adults at the respective dose level which was mainly accounted for by difference in body weight (Figure 1). Therefore, the proposed dose is reasonable for both adolescent and adults.

Figure 1: Dupilumab Steady State Exposure ($AUC_{T,ss}$) by Covariate Category in Patients With Asthma from Studies DRI12544 and EFC13579



Note: Lower and upper end of whisker indicated 5th and 95th percentile of $AUC_{T,ss}$; lower and upper boundary of the box and the median line represent the 25%, 75% and 50% percentiles of $AUC_{T,ss}$. Numbers inside plot panel indicate the counts of patients. Weight (kg), Age (years).
Source: Figure 7, summary of clinical pharmacology, page 45

No dose adjustment is recommended with respect to the PK covariates in the asthma adult and adolescent population.

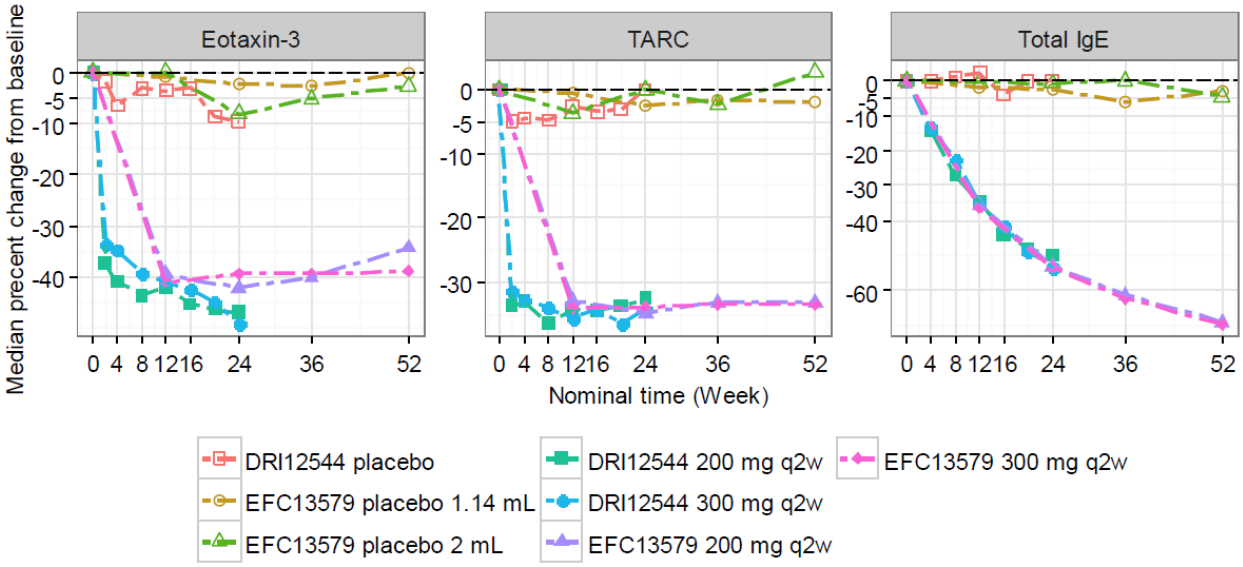
PD Characteristics of Dupilumab in Asthma Patients Following SC Administration

Dupilumab binds specifically to the IL-4Rα subunit and inhibits IL-4 and IL-13 mediated signaling. The blocking of the IL-4Rα receptor subunit with dupilumab inhibits IL-4 and IL-13 (Type 2) cytokine-induced responses, including the release of proinflammatory cytokines, chemokines, and IgE through this pathway. Biomarkers of Type 2 inflammation, including eosinophil, IgE, TARC/CCL17, periostin, eotaxin-3, and airway inflammation biomarker FeNO, were assessed across the studies. Dupilumab treatment has been shown to consistently induce rapid and substantial reduction in FeNO, TARC, periostin, eotaxin-3 as well as total and antigen specific IgE.

Biomarker responses (the median percent change from baseline) over time for 200 mg q2w and 300 mg q2w dupilumab treatments or matching placebos for 24 or 52 weeks in the pivotal studies (EFC13579 and DRI12544) are illustrated in Figure 2: Median Percent Change in Type 2 Inflammation Biomarkers Over Time Following 24 or 52 Weeks of SC Treatments of Dupilumab or Placebo in Patients With Asthma (Studies DRI12544 and EFC13579)

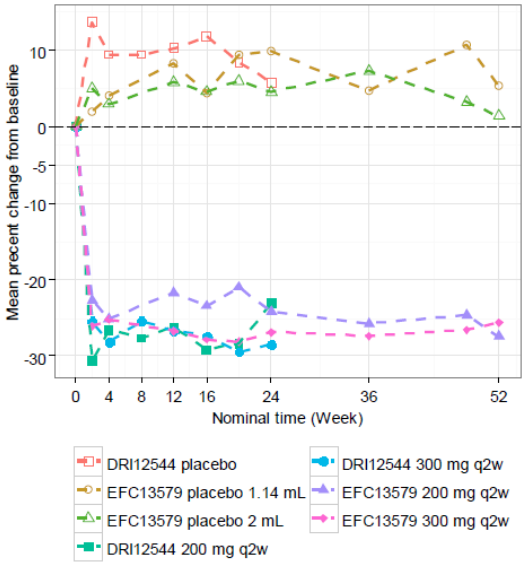
These profiles of PD responses for TARC, exotoxin-3 and total IgE were consistent across the two studies.

Figure 2: Median Percent Change in Type 2 Inflammation Biomarkers Over Time Following 24 or 52 Weeks of SC Treatments of Dupilumab or Placebo in Patients With Asthma (Studies DRI12544 and EFC13579)



Note: N was as follows for each biomarker: EFC13579 placebo 1.14 mL =315; EFC13579 200 mg q2w =629; EFC13579 placebo 2 mL =321; EFC13579 300 mg q2w =632; DRI12544 placebo =158; DRI12544 200 mg q2w =148; DRI12544 300 mg q2w =156
(Source: Summary of Clinical Pharmacology, Figure 12, page 55).

Figure 3: Median Percent Change in FeNO Over Time Following 24 or 52 Weeks of SC Treatments of Dupilumab or Placebo in Patients With Asthma (Studies DRI12544 and EFC13579)

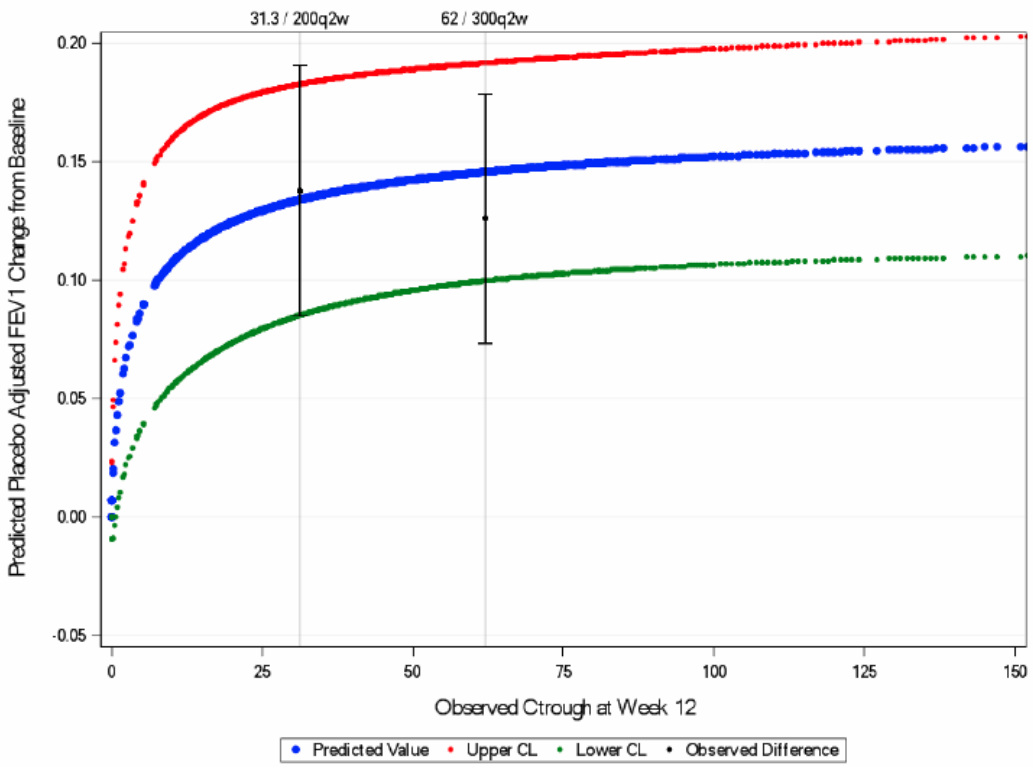


Source: Summary of Clinical Pharmacology, Figure 11, page 54.
FeNO = fractional exhaled nitric oxide

Exposure-Response Relationship for Efficacy

The FEV1 response increased with increasing dupilumab concentrations(C_{trough}) and appeared to approach a plateau at the exposures achieved with the 200 mg and 300 mg q2w dose groups, which is consistent with the clinical observation (Figure 4).

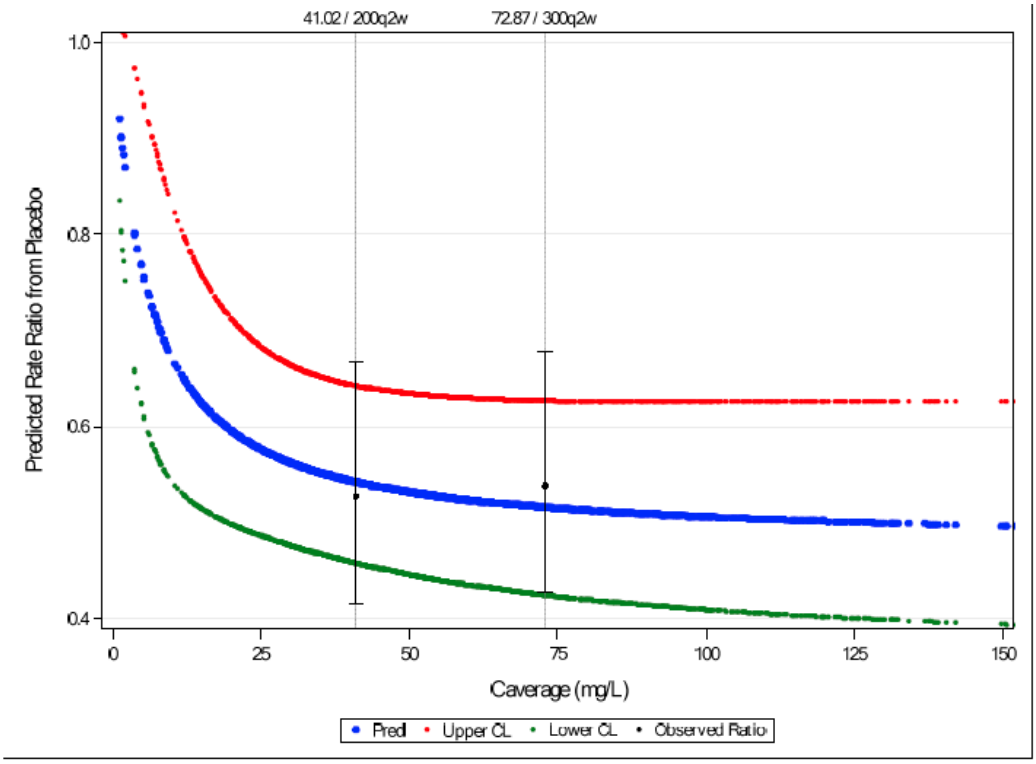
Figure 4: Empirical PK/PD Model-Predicted FEV1 Change From Baseline at Week 12 for Patients in Study EFC13579 (Source: Summary of Clinical Pharmacology, Figure 17, page 63)



Placebo adjusted FEV_1 change from baseline with 95% CI. The vertical lines represented the median values of the observed trough concentration for each dose regimen. Point estimates with error bar represent the LS mean (95% CI) for the observed effects

Similarly; the annualized exacerbation event rate appears to approach a plateau at the exposures achieved with the 200 mg and 300 mg q2w dose groups, which is consistent with the clinical observation (Figure 5).

Figure 5: PK/PD Model Predicted Severe Exacerbation Event Ratio from Placebo (Relative Risk) for Patients in Study EFC13579



Model predicted relative risk of severe exacerbation with 95% CI. The vertical lines represented the median values of the $C_{average}$ (average exposure estimated by the Pop PK model derived AUC during the event observation period /by observation days) for each dose regimen. Point estimates with error bar represent the relative risk (95% CI)calculated from the observed data.

Source: Summary of Clinical Pharmacology, Figure 18, page 65)

6.3.2. Clinical Pharmacology Questions

What is the Composition of To-Be-Marketed Formulation of Dupilumab?

Dupilumab solution for injection is a clear to slightly opalescent, colorless to pale yellow, aqueous buffered, sterile solution at pH 5.9. The drug product is supplied as a single-use prefilled syringe assembled with a safety system, a plunger rod, and a finger flange to deliver minimum 1.14 mL of (b) (4) mg/mL dupilumab for subcutaneous injection. The entire content is intended to be injected, providing a 200 mg dose of dupilumab. The 300 mg/2 mL solution in a single-dose pre-filled syringe with needle shield is already approved for AD indication.

What Was the Impact of Immunogenicity on Dupilumab Exposure?

The incidence of treatment emergent ADA was 5.1%, 9.3%, and 3.5% in the 300 mg q2w, 200 mg q2w, and combined placebo groups, respectively. The incidence of persistent ADA was 2.1%, 4.2% and 1.1% in the 300 mg q2w, 200 mg q2w, and combined placebo groups, respectively.

Treatment-emergent ADA positive patients appeared to have lower mean exposure compared with that of ADA negative patients (Figure 6

Figure 6: Impact of Immunogenicity on Pharmacokinetic Exposures of Dupilumab (Studies DRI12544 and EFC13579)

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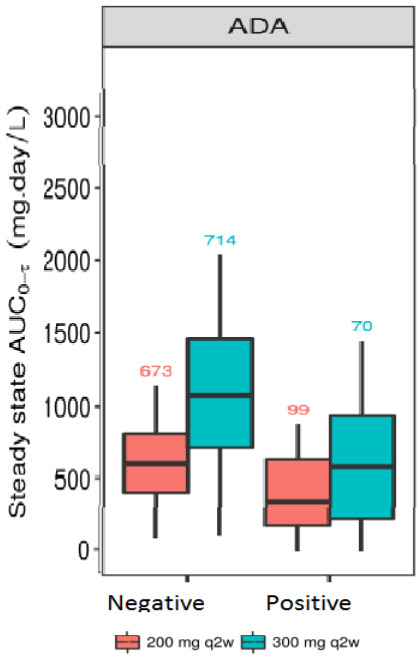
Figure 6: Impact of Immunogenicity on Pharmacokinetic Exposures of Dupilumab (Studies DRI12544 and EFC13579)



Note: ADA status: negative ADA represents negative ADA at all the time; positive ADA represents positive ADA at any time.
(Source: Summary of clinical pharmacology, Figure 7, page 45)

ADA was identified as a statistically significant covariate, but the magnitude of ADA effect on dupilumab exposure is small (i.e., less than 20% increase in overall clearance). In PM reviewer's analyses, high tier ADA response (>480) was identified as statistically significant covariate and increase overall clearance by up to 57%. These findings are consistent with observation of substantially lower dupilumab concentration in the presence of high tier ADA response. (Refer PM review for details).

There was no clear evidence of lack or loss of efficacy in patients developing low to moderate ADA titers (including neutralizing antibody), and ADA was not a significant covariate for efficacy endpoints in the PK PD analysis.

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

The proposed dosing regimen is acceptable. There was no clear dose/exposure response observed as efficacy appears to plateau after 200 mg dose. Clinical efficacy of the proposed 200 mg q2w and 300 mg q2w dosing regimens are demonstrated in studies DRI12544 and EFC13579. The incidence of safety events was too low to support meaningful ER analysis for safety. Population PK and ER analyses demonstrated that steady state is achieved earlier with the loading dose. (Refer PM review for details)

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

No. The covariates age, gender, race, indicators of liver function (i.e., alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase), and renal function, were not identified as significant covariates for dupilumab clearance.

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

Body Weight Was Identified as a Covariate Affecting Dupilumab Clearance and Volume Parameters.

A trend of exposure increase with decreasing body weight was observed in the asthma studies. (Figure 1). A summary of post hoc estimates of individual steady-state exposure for patients in the pivotal studies EFC13579 and DRI12544 is presented by body weight category in Table 3. A consistent effect of body weight on dupilumab exposure was also observed in the severe OCS-dependent asthma patients from the pivotal study EFC13691.

Table 3: Mean (SD)[CV%] of Functional Dupilumab Steady State Exposure by Body Weight Category in Patients With Asthma

	200 mg q2w				300 mg q2w			
Body weight (kg)	N	$AUC_{\tau,ss}$[a] (mg•day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)	N	$AUC_{\tau,ss}$[a] (mg•day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)
<70 kg	251	830 (355) [42.8%]	66.3 (26.4) [39.8%]	52.8 (24.6) [46.5%]	271	1460 (616) [42.2%]	115 (46.4) [40.3%]	94.2 (43.2) [45.9%]
70 to < 90 kg	309	569 (248) [43.6%]	46.4 (18.7) [40.2%]	34.8 (17.3) [49.6%]	292	999 (448) [44.8%]	80.0 (33.5) [41.8%]	62.6 (30.7) [49.0%]
≥90 kg	212	360 (187) [51.9%]	30.5 (14.0) [45.9%]	21.4 (13.2) [61.8%]	221	682 (357) [52.3%]	55.7 (26.9) [48.2%]	42.3 (24.7) [58.4%]

a $AUC_{\tau,ss} = AUC_{[Week\ 22 - Week\ 24]}$ for 200 mg and 300 mg q2w Two patients from EFC13579 with missing information for ADA are excluded for summary.

Note: 200 mg q2w with a loading dose of 400 mg and 300 mg q2w with a loading dose of 600 mg

Source: Summary of Clinical Pharmacology, Table 8, page 46
AUC = area under the curve; $C_{max,ss}$, $C_{min,ss}$ = maximum and minimum steady-state plasma drug concentration, respectively; CV% = coefficient of variance; q2w = once every 2 weeks

The magnitude of body weight effect on exposure is not likely to yield a clinically meaningful effect on efficacy given the lack of exposure-response relationship. No dose adjustment is recommended with respect to the PK covariates.

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

The concomitant use of common asthma medications (ICS) has no effect on dupilumab PK.

Dupilumab has no clinically meaningful effect on the activities of major drug-metabolizing CYPs. Please refer to the clinical pharmacology review by Dr. Anand Balakrishnan, in DARRTs dated Reference ID 4233885.

Are the bioanalytical methods properly validated to measure PK and PD in plasma samples?

Plasma concentrations of dupilumab in the asthma studies were determined with a validated bioanalytical ELISA assay, which was reviewed as part of the original BLA submission for atopic dermatitis. Please refer to the clinical pharmacology review by Dr. Jie Wang in DARRTs dated Reference ID 4030358).

See signature page	See signature page
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Clinical Pharmacology Reviewer Dipak Pisal	Pharmacometric Reviewer Nan Zheng
See signature page	See signature page
X	X
Division of Clinical Pharmacology Team Leader, Anshu Marathe	Division of Pharmacometrics Team Leader Jingyu Yu

7. Clinical Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.2. Table of Clinical Studies

Table 4: Listing of Clinical Trials Relevant to This NDA

Trial Date	Trial Design/ Duration	Regimen/ schedule/ route	N[x]	Population	Primary Endpoints	No. of Centers/ Countries
DRI12544 Jun 2013 - Apr 2015	R, DB, PC 24 weeks	200 mg q2w[v] 300 mg q2w[†] 200 mg q4w[v] 300 mg q4w[†] Placebo	150 157 154 157 158	Moderate-to-severe asthmatics ≥18 years of age uncontrolled on med-high dose ICS/LABA + 2nd controller w/hx of one exacerbation	Change from baseline in FEV1 to 12 Weeks	174 sites - Argentina, Australia, Chile, France, Italy, Japan, Mexico, Poland, Russia, South Africa, South Korea, Spain, Turkey, Ukraine, and USA
EFC13579 Apr 2015 – Jul 2017	R, DB, PC 52 weeks	200 mg q2w[v] 300 mg q2w[†] Placebo	631 633 638	Moderate-to-severe asthmatics ≥12 years of age uncontrolled on med-high dose ICS/LABA + 2nd or 3rd controller w/hx of one exacerbation	Annualized rate of severe exacerbation during the 52 weeks Absolute change in FEV1 at Week 12	331 sites - Argentina, Australia, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Italy, Japan, Mexico, Poland, Russia, South Africa, South Korea, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and USA
EFC13691 Oct 2015 – Sept 2017	R, DB, PC 24 weeks	300 mg q2w[†] Placebo	103 107	Severe asthmatics ≥12 years of age on OCS + high dose ICS + 2nd controller	%reduction from baseline of investigator-prescribed OCS dose at Week 24, while maintaining asthma control	68 sites - Argentina, Belgium, Brazil, Canada, Chile, Colombia, Hungary, Israel, Italy, Mexico, Netherlands, Poland, Romania, Russia, Spain, Ukraine, and USA

Table 4: Listing of Clinical Trials Relevant to This NDA

Trial Date	Trial Design/ Duration	Regimen/ schedule/ route	N[ж]	Population	Primary Endpoints	No. of Centers/ Countries
LTS12551 Aug 2014 – Jul 2017 (data cut off)	OL 1 to 2 years**	300 mg q2w	1981∞	Subjects from Studies DRI12544, EFC13579, EFC13691	Safety	330 sites- Argentina, Australia, Belgium, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Israel, Italy, Japan, Mexico, The Netherlands, Poland, Romania, Russia, South Africa, South Korea, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States

γ with 400 mg loading dose; † with 600 mg loading dose; ж: Randomized population; **The total study duration was of 111 weeks for patients enrolled prior to Amendment 04 and of 60 weeks for patients enrolled after, ∞ Study EFC13691 n=137, Study DRI12544 n=531, Study EFC13579 n =1312
R = randomized, DB = double-blind, PC = placebo-controlled, ICS = inhaled corticosteroids, LABA = long-acting beta agonist, OCS = oral corticosteroids, OL = open-label; hx = history
Source: DRI12544 CSR Table 12, pg. 77 and Synopsis; EFC13579 CSR Table 11, pg. 81 and Synopsis; EFC13691 CSR Table 11, pg. 65 and Synopsis; LTS12551 CSR Table 9, pg. 72 and Table 11, pg. 76 and Synopsis

7.3. Review Strategy

The clinical review consisted of one primary clinical reviewer. The sBLA submission contained three, randomized, placebo-controlled, double-blind studies that were evaluated for efficacy and safety. These included a 6-month dose-ranging study, a 1-year efficacy and safety study, and a 6-month OCS-sparing study. Section 7.5 includes the protocol, efficacy, and safety review for each study. An integrated review of efficacy for the three studies is included in Section 7.6. An open-label, long-term extension study was also conducted and is reviewed briefly in Section 7.7.6.1.

The 6-month dose-ranging study and the 1-year efficacy and safety studies were pooled for safety for the first 6-months and discussed in Section 7.7. The OCS-sparing was not pooled for safety given the different study populations.

The clinical studies included different dosing regimens of 200 mg and 300 mg. The 200 mg doses included a 400 mg loading dose and the 300 mg doses included a 600 mg loading dose for all studies, although the loading dose is not specifically mentioned at all points in the review.

Data Sources

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

7.4. Financial Disclosure

- The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA. Details of the financial disclosure are outlined below:

- Covered Clinical Studies (Name and/or Number): DRI12544, EFC13579, EFC13691

Table 5. Financial Disclosure		
Total number of investigators identified: 2417		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
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)): (n/a) 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: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Applicant of covered study: 1		
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)

- The Applicant submitted FDA Form 3454 (v.10/09) certifying investigators and their spouses/dependents were in compliance with 21 Code of Federal Regulations (CFR) Part 54.

- The two principal investigators and two sub-investigators disclosed their financial interests/arrangements and implemented appropriate actions to protect the studies from potential bias.

7.5. Review of Relevant Individual Trials Used to Support Efficacy

7.5.1. Study DRI12544

7.5.1.1. Administrative Information

- **Study title**: A randomized, double-blind, placebo-controlled, dose-ranging study to evaluate dupilumab in patients with moderate-to-severe uncontrolled asthma
- **Study dates:** June 10, 2013, to April 8, 2015
- **Study sites:** Argentina, Australia, Chile, France, Italy, Japan, Mexico, Poland, Russia, South Africa, South Korea, Spain, Turkey, Ukraine, and United States
- **Study report date:** February 24, 2016, with addendum on September 15, 2017

7.5.1.2. Objectives

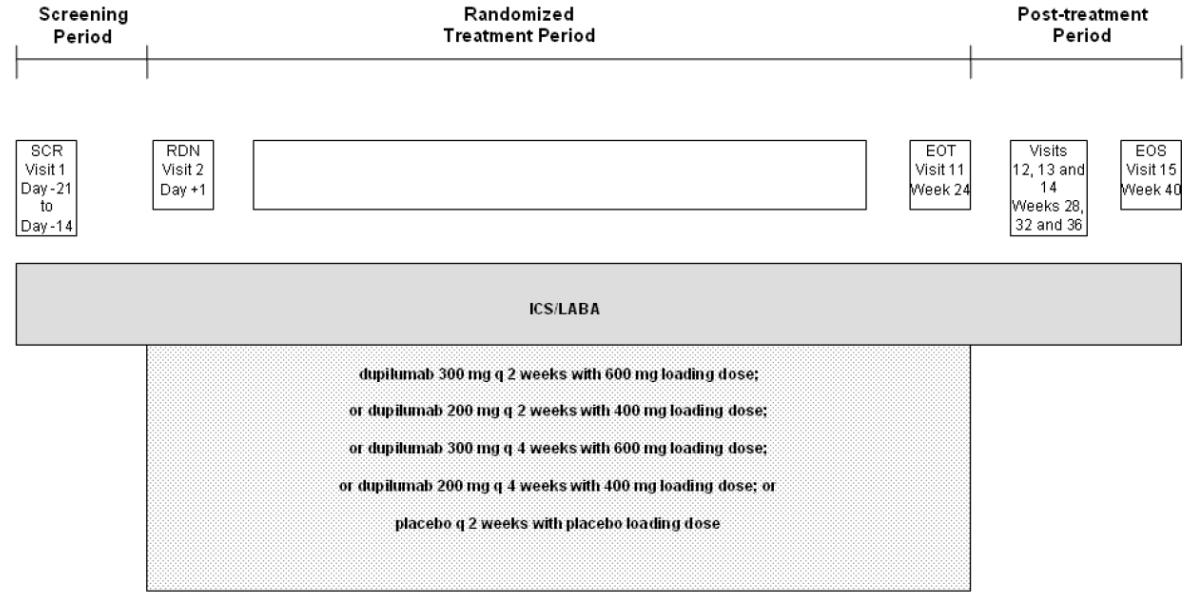
The primary objective of the study was to evaluate the efficacy of different doses and regimens of dupilumab in patients with moderate-to-severe uncontrolled asthma.

7.5.1.3. Study Design and Conduct

Study DRI12544 was a randomized, double-blind, placebo-controlled, dose-ranging, parallel-group study comparing 200 mg every 4 weeks (q4w), 300 mg q4w, 200 mg q2w, and 300 mg q2w of dupilumab administered subcutaneously (SC) to placebo as add-on therapy to medium-to-high dose ICS/LABA therapy for 24 weeks in patients with moderate-to-severe uncontrolled asthma. Each dose also included a 2x loading dose (e.g. 400 mg for 200-mg dose and 600 mg for 300-mg dose. Randomization was stratified by blood eosinophil count at screening (≥0.3 G/L, 0.2 to 0.29 G/L, and <0.2 G/L) and country.

The study schematic is shown in Figure 7.

Figure 7: Study DRI12544 Study Schematic



SCR = Screening; RDN = Randomization; EOT = End of treatment; ICS/LABA = inhaled corticosteroids / long-acting beta agonist combination product; EOS = End of study; SC = subcutaneous

Source: Study DRI12544 CSR, Figure 1, page 24

7.5.1.3.1. Procedures

The study consisted of three phases: screening/randomization, treatment, and follow-up. A 2-3 week screening period was used to establish level of asthma control. The post-treatment follow-up period was 16 weeks.

A schedule of assessments is provided in Table 6.

Table 6: Schedule of Assessments

	SCR [a]	Randomized Treatment Period																								Post-treatment Period			
		RDN																							EOT [b]				EOS
Week	-3 to -2	0		2		4		6		8		10		12				16				20				24	28	32	36	40
Day		D1																											
VISIT[c]	1	2		3		4		5		6		7		8				9				10				11	12	13	14	15
Informed consent	X																													
Patient demography	X																													
Medical & surgical history	X																													
Entry criteria	X	X																												
Verify ACQ-5 score >1.5	X	X																												
Verify ICS/LABA compliance		X																												
Reversibility [d]	X																													
Chest X-Ray (if none within previous 12 months)	X																													
Prior & concomitant medications[e]	X	X		X		X		X		X		X		X				X				X				X	X	X	X	X
Physical examination	X													X												X				X
ACQ-5[f]	X	X		X		X				X				X				X				X				X	X	X	X	X
Spirometry[g]	X	X		X		X				X				X				X				X				X	X	X	X	X
Randomization		X																												
Call IVRS	X	X		X		X				X				X				X				X				X				X
Investigational product administration[h]		X		X		X		X		X		X		X		X		X		X		X		X						
Dispense home dosing diary														X				X				X								
Review home dosing diary																		X				X				X				
Dispense or download electronic diary/PEF meter	X	X		X		X		X		X		X		X				X				X				X	X	X	X	X
Reliever medication prn[j]	|----------																													----------|
Exhaled NO [k]	X			X		X				X				X				X				X				X	X	X	X	X
SNOT-22		X												X												X				X
Adverse event observation period	|----------																													----------|
Vital signs[l]	X	X		X		X		X		X		X		X				X				X				X	X	X	X	X
ECG	X			X		X								X												X				X
Pregnancy test[m]	X	X				X				X				X				X				X				X				X
Clinical lab testing[n]	X	X				X				X				X				X				X				X				X
Urinalysis	X													X												X				X
Serum IgG, IgM, IgA	X													X												X				X
PK sampling[o]		X		X		X				X				X				X				X				X	X	X	X	X
Anti-drug antibodies[o]		X		X		X				X				X				X				X				X				X
Biomarker set A: TARC, eotaxin-3, ECP[o]	X	X		X		X				X				X				X				X				X	X	X	X	X
Periostin[o]		X												X												X				X
Serum total IgE[o]	X	X				X				X				X				X				X				X		X		X

Biomarker set B : Allergen-specific IgE panels, S. aureus enterotoxin A & B IgE[o]		X																						X				X
DNA sampling[o,p]		X																										
RNA sampling[o,p]	X	X		X																								
Archival serum sampling[q]		X										X												X				
AQLQ		X										X												X				
HADS		X										X												X				
EQ-5D-3L		X										X												X				
Resource utilization[r]		X				X				X			X				X				X				X	X	X	X	X
ICS/LABA reminder[s]	X	X		X		X		X		X		X	X				X				X				X	X	X	X	
Medication withhold reminder[t]	X	X		X				X				X	X				X				X				X	X	X	X	

SCR = Screening period; RDN = Randomization; ACQ-5 = Asthma Control Questionnaire, 5-item version; PEF = peak expiratory flow; NO = nitric oxide; SNOT-22 = Sinonasal Outcome Test; AQLQ = Asthma Quality of Life Questionnaire; HADS = Hospital Anxiety and Depression Scale; EQ-5D-3L = EQ-5D-3L quality of life questionnaire

a The screening period was 14-21 days in duration to collect ≥14 days of baseline data on asthma control.

b Patients who discontinued treatment early were assessed as soon as possible using the procedures normally planned for the EOT Visit and the 4 post-treatment period visits.

c Randomization visit (Visit 2) was defined as Day 1. Visit windows for subsequent visits were +/- 3 days.

d Three attempts might be made during the screening period to meet the qualifying criteria for reversibility.

e Prior to screening, patients had to be on a stable dose of moderate to high-dose combination product ICS/LABA (≥ fluticasone propionate 250 µg twice daily or equipotent) for ≥1 month prior to Visit 1.

f ACQ-5 was completed in the patient's electronic diary during clinic visits.

7.5.1.3.2. Patient Population

Key Inclusion Criteria

1. Moderate-to-severe uncontrolled asthma for ≥1 year per GINA 2009 guidelines, and the following criteria:
    a. Medium or high-dose ICS/LABA on a stable dose for ≥1 month (leukotriene antagonists/modifiers at a stable dose for ≥1 month was also allowed)
    b. FEV1 40 to 80% predicted at screening and prior to randomization
    c. Juniper Asthma Control Questionnaire, 5-item version (ACQ-5) ≥1.5 at screening and randomization
    d. Reversibility in FEV1 (12% and 200 mL) at screening
    e. Exacerbation requiring systemic steroids or hospitalization/emergency/urgent care visit

Reviewer comment: Although this study population does not specify uncontrolled or moderate-to-severe, the enrollment criteria are consistent with uncontrolled and moderate-to-severe asthmatics (e.g., requiring medium to high dose ICS with a second controller, ACQ ≥1.5, and FEV1 <80%) per the NHLBI guidelines. Compared to the anti-IL5 asthma programs, which are indicated for severe asthma, this population differs in that subjects had to have one or more exacerbations (compared to 1 to 2 or more), subjects were not enriched for high blood eosinophils, and oral steroids were not allowed.

Key Exclusion Criteria

1. <18 years of age
2. Women of childbearing potential not on effective contraception
3. Pregnant or breast-feeding

4. Other lung diseases
5. Current smoker, cessation within 6 months, or >10-pack per year history
6. Beta-blocker use
7. Omalizumab with 130 days or other biologic therapy within 6 months or five half-lives
8. Initiation of allergy immunotherapy within 3 months (or planned dose change during study)
9. Previous enrollment in another dupilumab study
10. Systemic corticosteroids (>10 mg/day prednisone or equivalent) within 28 days
11. Methylxanthines within 14 days
12. Diagnosed active parasitic infection; suspected or high risk unless active infection ruled-out
13. Immunosuppression, HIV, active immunosuppressive therapy or autoimmune disease
14. Acute or chronic infection requiring treatment
15. Live attenuated vaccine within 12 weeks

7.5.1.3.3. Treatment

Dupilumab was provided in 5-mL glass vials; each vial contained a deliverable volume of 2 mL: 150 mg/mL solution (300-mg dose/2 mL) or 100 mg/mL solution (200-mg dose/2 mL). Sterile placebo was provided in matched glass 5 mL vials that were identical with the dupilumab vials; each vial contained a deliverable volume of 2 mL. The 200 mg doses included a 400 mg loading dose and the 300 mg doses included a 600 mg loading dose for all dosing arms.

Subcutaneous injection sites were alternated between the four quadrants of the abdomen (avoiding the navel and the waist area) or upper thighs so that the same injection site was not used for two consecutive weeks.

The first injection was administered by study site personnel. The second injection was administered by the patient (or caregiver) under supervision by study site personnel, with six supervised injections required prior to self-injection at home. Subjects were monitored for 1 hour after administration at the clinical sites. For doses administered at home, diaries were provided to record information related to the injections.

ICS/LABA use was recorded twice daily in an electronic diary. Rescue short albuterol use was allowed.

7.5.1.3.4. Efficacy Endpoints

Primary:

- Change in FEV1 from baseline to Week 12

Secondary:

- Relative change (%) from baseline at Week 12 in FEV1
- Annualized rate of loss of asthma control events during the treatment period (see definition below)
- Annualized rate of severe exacerbation events during the treatment period (see definition below)
- Time to loss of asthma control events during the treatment period
- Time to severe exacerbation events during the treatment period
- Time to loss of asthma control events during overall study period
- Time to severe exacerbation events during overall study period
- Health care resource utilization
- Change from baseline at Week 12 in:
    - Morning and evening asthma symptom scores
    - ACQ-5 score
    - Asthma Quality of Life Questionnaire (AQLQ) score
    - Morning and evening peak expiratory flow
    - Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
    - Nocturnal awakenings

Biomarkers were also included: eosinophil count and eotaxin-3

7.5.1.3.5. Efficacy Parameters

Severe exacerbation was defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days or
- Hospitalization or emergency room visit, requiring systemic corticosteroids

ACQ-5[5]

This patient-reported outcome measures the adequacy of asthma control and change in asthma control. The questionnaire consists of five items that are self-administered queried over a 1-week recall period. The items are as follows:

1. How often were you woken by your asthma during the night?
2. How bad were your asthma symptoms when you woke up in the morning?

5 Juniper, EF, PM O'Byrne, GH Guyatt, PJ Ferrie, and DR King, 1999, Development and validation of a questionnaire to measure asthma control, Eur Respir J, 14: 902–907.
Juniper, EF, J Bousquet, L Abetz, and ED Bateman, 2006, Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire, Respiratory Medicine, (100): 616–621.
Juniper, EF, K Svensson, AC Mork, and E Stahl, 2005, Measurement properties and interpretation of three shortened versions of the asthma control questionnaire, Respiratory Medicine, (99): 553–558.

3. How limited were your activities because of your asthma?
4. How much shortness of breath did you experience because of your asthma?
5. How much of the time did you wheeze?

Items were scored on a scale from 0 to 6, with 6 being maximum impairment. Total scores range between 0 (totally controlled) and 6 (severely uncontrolled). The minimally important difference is a change in score of 0.5.

AQLQ[6]

This patient-reported outcome is a disease-specific health-related quality of life instrument that assess both the physical and emotional impact of the disease. AQLQ is a 32-item questionnaire with a 2-week recall. The questionnaire includes the following categories: symptoms (11 items), activity limitation (12 items, five of which are individualized), emotional function (five items), and environmental exposure (four items). Items are scored on a scale from 1 to 7, with 7 being not impaired at all and 1 being severely impaired. The minimal clinically important difference is 0.5 for overall quality of life and for each of the individual domains.

Reviewer comment: Whether FEV1 was pre or post-BD was not specified within the protocol; however, spirometry was performed between 6 and 10:30 AM after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for 6 hours and withholding the last dose of ICS/LABA for 12 hours and prior to administration of investigational product, if applicable. Therefore, FEV1 was essentially pre-BD.

7.5.1.3.6. Safety Parameters

Safety parameters included clinical labs (hematology, serum chemistry, urine analysis, serum immunoglobulins, anti-nuclear antibody, hepatitis and HIV screening, and pregnancy testing), vital signs (blood pressure, heart rate, respiratory rate, temperature, and weight), physical examination, and electrocardiogram.

7.5.1.3.7. Statistical Analysis Plan

A pre-specified interim analysis plan was performed when the last patient had completed 12 weeks of treatment to facilitate the setup activities for the future studies. There was not an intention to change the conduct of the study (or stop the study) based on the interim analysis results.

The primary analysis population was the high eosinophil (HEos) intent-to-treat (ITT) population based on the planned treatment group.

6 Juniper, EF, GH Guyatt, A Willan, and LE Griffith, 1994, Determining a minimal important change in a disease-specific quality of life questionnaire, J Clin Epidemiol, 47(1): 81–87

The primary safety analysis was conducted in the HEos safety population (all randomized HEos patients exposed to study medication).

The analysis populations are defined as in Table 7.

Table 7: Study DRI12544 Analysis Populations

Analysis Population	Definition
Intent-to-treat (ITT)	All randomized patients
HEos ITT population	ITT population with blood eosinophils (≥0.3 g/L) at baseline
Safety population	All randomized patients who received at least one dose of the study treatment
HEos safety population	Safety population with blood eosinophils (≥0.3 g/L)

HEos = high eosinophil; ITT = intention to treat

7.5.1.3.8. Compliance with Good Clinical Practice

The study was conducted in accordance with Good Clinical Practice (GCP) as required by the International Council on Harmonisation (ICH) guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

The Applicant certified that all clinical investigations in this sBLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the United States conducted under IND 105379 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in GCP.

One study site (850032; William Storms Allergy Clinic, Colorado Springs, CO) had GCP non-compliance violations (failed to maintain adequate records of the investigation and failed to ensure that the investigation was conducted in accordance with the investigational plan) found during an FDA site inspection. The Applicant terminated the site. Three patients were randomized and completed the study at this site. A sensitivity analysis removing these three patients was consistent with the primary efficacy analysis.

7.5.1.4. Study Results

7.5.1.4.1. Protocol Amendments

One protocol amendment was introduced November 8, 2013, after the study's start. The main change was to increase the enrolled subjects from 600 to 750 due to a lower rate for HEos patients than expected, to have 300 patients with HEos.

7.5.1.4.2. Protocol Deviations

Twelve patients (three in each of the dupilumab dose groups) reported protocol deviations: failure to meet FEV1 40% to 80% predicted at screening and randomization; failure to meet ACQ-5 ≥1.5 at screening and randomization; failure to meet reversibility of 12% and 200 mL in FEV1 at screening; and treatment compliance >80%. Overall the number of patients for each deviation was small (1 to 3) and the distribution was even throughout the treatment groups.

7.5.1.4.3. Efficacy

7.5.1.4.3.1. Disposition

Patient disposition is summarized in Table 8.

Table 8: Study DRI12544 Disposition

	Placebo	Dupilumab 200q4w	Dupilumab 300q4w	Dupilumab 200q2w	Dupilumab 300q2w
Randomized	158 (100%)	154 (100%)	157 (100%)	150 (100%)	157 (100%)
ITT	158 (100%)	154 (100%)	157 (100%)	150 (100%)	157 (100%)
HEos	68 (43%)	62 (40%)	66 (42%)	65 (43%)	64 (41%)
Safety Population	158 (100%)	150 (97%)	157 (100%)	148 (99%)	156 (99%)
HEos	68 (43%)	59 (38%)	66 (42%)	64 (43%)	64 (41%)
Treated	158 (100%)	150 (97%)	157 (100%)	148 (99%)	156 (99%)
Completed 12-weeks	153 (97%)	143 (93%)	146 (93%)	141 (94%)	149 (95%)
Completed study treatment	146 (92%)	135 (88%)	142 (90%)	137 (91%)	149 (95%)
Completed study period	147 (93%)	140 (92%)	142 (90%)	141 (94%)	147 (94%)
Discontinued	11 (7%)	10 (7%)	15 (10%)	7 (5%)	9 (6%)
Patient request	7 (4%)	9 (6%)	10 (6%)	5 (3%)	6 (5%)
Adverse event	2 (1%)	1 (1%)	5 (3%)	1 (1%)	3 (2%)
Poor compliance	1 (1%)	0	0	0	0
Other	1 (1%)	0	0	1 (1%)	0

Source: Reviewer generated table in JMP using ADSL dataset without screen failures, Study CSR DRI12544, Table 8, page 70, Table 12, page 77
HEos = high eosinophil; ITT = intention to treat; q2w = once every 2 weeks; q4w = once every 4 weeks

The disposition for Study DRI12544 was similar between treatment groups. Most subjects completed the study period and study treatment (88% to 95%). Only a few subjects across treatment groups discontinued to adverse events.

7.5.1.4.3.2. Demographics

The demographics are summarized in Table 9.

Table 9: Study DRI12544 Baseline Demographics (Randomized Population)

	Placebo		Dupilumab 200q4w		Dupilumab 300q4w		Dupilumab 200q2w		Dupilumab 300q2w		Total	
N	**158**		**154**		**157**		**150**		**157**		**776**	
Sex	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Female	104	66%	87	57%	100	64%	96	64%	103	66%	490	63%
Male	54	34%	67	44%	57	36%	54	36%	54	34%	286	37%
Race												
White	119	75%	125	81%	120	76%	114	76%	129	82%	607	78%
Asian	25	16%	20	13%	23	15%	25	17%	22	14%	115	15%
Black or African American	9	6%	7	5%	12	8%	9	6%	5	3%	42	5%
Other	5	3%	2	1%	1	0.6%	1	0.7%	1	0.6%	10	1%
American Indian or Alaska Native	0	0	0	0	0	0	1	0.7%	0	0	1	<1%
Native Hawaiian or other Pacific Islander	0	0	0	0	0	0	0	0	0	0	1	<1%
Age in Years												
Mean	49		48		48		51		48		49	
SD	13		13		13		13		12		13	
Min	18		18		18		19		18		18	
Max	87		76		80		83		72		87	
Age in class, n (%)												
<65 years	145	92%	139	90%	142	90%	130	87%	146	93%	702	90%
≥65 years	13	8%	15	10%	15	10%	20	13%	11	7%	74	10%

Source: Reviewer generated table in JMP using ADSL dataset without screen failures, Study CSR DRI12544 Table 13, page 39
Max = maximum; Min = minimum; N = number; SD = standard deviation; q4w = once every 4 weeks; q2w = once every 2 weeks

Baseline demographics were balanced between groups. The majority of subjects were white (78%) females (63%) with a mean age of 49 years, and a BMI of 29.

Baseline disease characteristics are summarized in Table 10.

Table 10: Study DRI12544 Baseline Disease Characteristics (Randomized Population)

	Placebo		Dupilumab 200q4w		Dupilumab 300q4w		Dupilumab 200q2w		Dupilumab 300q2w		Total	
N	158		154		157		150		157		776	
Age at onset of asthma (yrs)												
Mean	27		24		27		27		27		27	
Std Dev	18		19		19		18		17		18	
Min	0		0		0		0		0		0	
Max	67		66		75		65		61		75	
Time since first diagnosis of asthma (yrs)												
Mean	22		24		20		24		20		22	
Std Dev	16		17		14		16		13		15	
Min	1		2		1		1		1		1	
Max	70		73		66		69		64		73	
Atopic hx	N	%	N	%	N	%	N	%	N	%	N	%

Table 10: Study DRI12544 Baseline Disease Characteristics (Randomized Population)												
	Placebo		**Dupilumab 200q4w**		**Dupilumab 300q4w**		**Dupilumab 200q2w**		**Dupilumab 300q2w**		**Total**	
Yes	119	77%	115	76%	125	81%	118	79%	113	73%	590	77%
No	35	23%	36	24%	30	19%	31	21%	41	27%	173	23%
Smoking hx												
Never	124	79%	119	78%	119	76%	118	79%	121	77%	601	78%
Former	34	22%	34	22%	38	24%	32	21%	36	23%	174	23%
FEV1 (L)												
Mean	1.8		1.9		1.9		1.8		1.9		1.8	
Std Dev	0.6		0.5		0.6		0.5		0.5		0.5	
Min	0.9		0.9		0.8		0.8		0.8		0.8	
Max	3.6		3.9		4.2		3.4		3.8		4.2	
Percent pred FEV1 (%)												
Mean	61		60		61		61		61		61	
Std Dev	11		11		10		11		10		11	
Min	40		40		41		40		40		40	
Max	80		81		80		89		80		89	
FEV1 reversibility (%)												
Mean	28		26		26		27		27		27	
Std Dev	14		14		15		18		17		15	
Min	12		12		7		-1		12		-1	
Max	85		84		131		133		132		133	
Num of asthma exacerbations in past yr*												
Mean	2		2		2		2		2		2	
Std Dev	2		3		2		1		2		2	
Min	1		1		1		1		1		1	
Max	20		20		12		12		15		20	
1	79	50%	85	56%	75	48%	87	58%	72	46%	398	51%
2	35	22%	33	22%	43	27%	27	18%	43	27%	181	23%
3	19	12%	18	12%	19	12%	23	15%	18	11%	97	13%
≥4	25	16%	17	11%	20	13%	13	9%	24	15%	99	13%
ACQ-5												
Mean	3		3		3		3		3		3	
Std Dev	1		1		1		1		1		1	
Min	2		1		1		2		0		0	
Max	5		6		5		6		5		6	
AQLQ												
Mean	4		4		4		4		4		4	
Std Dev	1		1		1		1		1		1	
Min	2		1		2		1		1		1	
Max	7		7		6		7		7		7	
Num of puffs of albuterol in 24 hours												
Mean	3		3		3		3		3		3	
Std Dev	3		3		3		3		3		3	
Min	0		0		0		0		0		0	
Max	15		16		23		15		19		23	
ICS/LABA												
High	77	50%	70	47%	83	54%	75	52%	79	52%	384	51%
Medium	78	50%	80	53%	70	46%	69	48%	74	48%	371	49%
Blood eosinophil (Giga/L)												

Table 10: Study DRI12544 Baseline Disease Characteristics (Randomized Population)

	Placebo		Dupilumab 200q4w		Dupilumab 300q4w		Dupilumab 200q2w		Dupilumab 300q2w		Total	
Mean	0.34		0.38		0.33		0.36		0.32		0.35	
Std Dev	0.30		0.76		0.27		0.35		0.25		0.43	
Min	0.03		0.02		0.01		0.04		0.05		0.01	
Max	2.06		8.75		1.88		2.65		1.78		8.75	
≤0.3	93	58.86%	98	63.64%	94	59.87%	86	57.33%	98	62.42%	469	60.44%
>0.3	65	41.14%	56	36.36%	63	40.13%	64	42.67%	59	37.58%	307	39.56%

* Asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma
Yrs=years, hx = history, mnths = months, ACQ = Juniper Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; Max = maximum; Min = minimum; q2w = once every 2 weeks; q4w = once every 4 weeks; SD = standard deviation
Source: Reviewer generated table in JMP using ADSL dataset without screen failures. Smoking and AQLQ modified from Study CSR DRI12544 Table 14, page 83

The baseline characteristics were balanced between groups. The average age at onset of asthma was 27 years, with 22 years since diagnosis (which coincides with the mean study age of 49 years). The majority (77%) of subjects had an atopic history and never smoked (78%). The mean FEV1 was 1.8 L and 61% predicted (within the 40% to 80% as determined by the inclusion criteria), with 27% reversibility. About half of subjects had one exacerbation within the past year, with a mean of two exacerbations per year. Medium- and high-dose ICS/LABA baseline use was split about evenly. About 60% of subjects were considered HEos with a blood eosinophil count of ≥0.3 G/L. The mean blood eosinophil count was 0.35 G/L. Mean ACQ-5 and AQLQ scores were 3 and 4, respectively. This is consistent with the inclusion criteria of ACQ-5 ≥1.5, which indicates not well-controlled asthma. The mean number of puffs of rescue short-acting BD (albuterol) per day was three, which is consistent with moderate-to-severe asthma (based on NHLBI guidelines).

7.5.1.4.3.3. Primary Endpoint

The primary efficacy endpoint was the change in baseline in FEV1 at Week 12 in the HEos (≥0.3 G/L) population. The primary endpoint of change from baseline at Week 12 in FEV1 at Week 12 was significantly improved in all dosing regimens, except for 200 mg q4w (Table 43). The treatment difference for the 200 mg q2w and 300 mg q2w dosing regimens was similar without a clear dose response (FEV1 (L): 0.26 (95% CI: 0.11, 0.40) for 200 mg q2w and 0.21 (95% CI: 0.06, 0.36) for 300 mg q2w). This supported both q2w doses being carried forward into the 1-year efficacy and safety study (EFC13579).

7.5.1.4.3.4. Secondary Endpoints

7.5.1.4.3.5. Exacerbation

The annualized event rate of severe exacerbation over the treatment period for the primary analysis population (HEos, ≥0.3 G/L) was significantly reduced for all dosing arms, except for 300 mg q4w. Dupilumab 300 mg q2w had the lowest rate, with a rate ration of 0.19 compared to placebo (95% confidence interval (CI): 0.07, 0.56).

7.5.1.4.3.6. Eosinophilia subgroup analysis

Analysis in the ITT population for the change from baseline in FEV1 at Week 12 (Table 44) and the annualized rate of exacerbation (Table 47) were also conducted. For the FEV1 endpoint, all dose regimens resulted in a significant improvement. For the exacerbation endpoint, the results were similar to the HEos (≥0.3 G/L) subgroup, with the all dose groups showing a significant reduction except for the 300 mg q4w group.

Subgroup analysis for different eosinophil levels for both the primary endpoint of change from baseline in FEV1at Week 12 and the annualized rate of exacerbation showed that patients in the lower eosinophilic group (<0.15 G/L) for both the 200 mg q2w and 300 mg q2w dose groups that were carried forward into Study EFC13579 did not demonstrate significant improvement compared to the placebo group (Figure 14 – FEV1, Figure 16 - exacerbation). Therefore, the ITT population results were driven by the HEos subgroup.

7.5.1.4.3.7. Change in FEV1 over time

The trends in the change in FEV1 from baseline over time (as shown in Figure 15 in the statistical section) were similar to the primary endpoint findings in that the 200 q4w regimen was lower than the other dosing regimens. The 200 mg q2w and 300 mg q2w doses carried forward into the 1-year study had similar trends over time. All dosing regimens showed a significant improvement in FEV1 from baseline at Week 24.

7.5.1.4.3.8. Percent FEV1 change from baseline

Percent change from baseline in FEV1 was also analyzed and was similar to the primary endpoint, with the largest treatment difference in the 200 q2w treatment arm at 12% (95% CI: 7, 17) at Week 12 in the ITT population.

7.5.1.4.3.9. ACQ-5 and AQLQ

Responder rates for AQLQ and ACQ-5 were included as secondary endpoints. A responder analysis was conducted for change from baseline in AQLQ global score and ACQ-5 at Week 24, with a responder defined as a patient with change from baseline in AQLQ global score or ACQ-5 ≥0.5, which is considered the minimal clinically importance difference. The ACQ-5 responder rates for dupilumab 200 mg and 300 mg q2w in the overall population were 77% and 73% respectively, compared to 61% for the placebo; and the AQLQ(S) responder rates were 64% and 65% respectively, compared to 51% for placebo. In the HEos (>0.3 G/L) population, the responder rates for both ACQ-5 and AQLQ were slightly higher compared to placebo.

7.5.1.4.3.10. Loading dose sensitivity analysis

The Division expressed concerns regarding the use of a loading dose for a chronic disease where a fast onset of action is typically not a priority. One concern was that efficacy endpoints may reflect the effects of the loading dose, making it unclear if observed clinical responses would be

maintained during chronic use. The Division acknowledged that these issues did not apply to atopic dermatitis (where fast onset of action would be clinically meaningful), for which dupilumab was initially developed and which includes a loading dose.

To address these concerns, the Applicant conducted a sensitivity analysis for the annualized rate of severe exacerbation to evaluate the loading dose. The half-life of dupilumab is about 12 weeks, therefore efficacy was evaluated from 0 to 12 weeks (effect of the loading dose) and 12 to 24 weeks. During the first 12 weeks, the loading dose decreased the annualized rate of severe exacerbation significantly in all four treatment groups compared to placebo. During the 12-to-24-week period, the q4w regimens were not statistically different than placebo; however, the doses that were carried forward into Study EFC13579 were similar in the two analysis periods. FEV1 was stable from Weeks 8 to 24. This supports that the efficacy over time is demonstrated and not solely reflective of the loading dose.

7.5.1.4.4. Safety

7.5.1.4.4.1. Deaths

Two subjects died, both in the dupilumab 300 mg q4w group:

1. Patient (b) (6) was a 43-year-old male who died due to acute cardiovascular failure on Day 62. He was found to have died in his sleep, 8 days after the last dupilumab injection. He had received six doses. His underlying medical conditions included hypertension treated with verapamil 80 mg. The autopsy noted atherosclerotic cardiac disease with coronary artery stenosis up to 50%. He also had elevated ethanol levels (blood: 3.2%, urine: 3.1%). Twenty days prior he had a blood pressure of 143/88 mm HG, pulse 90 beats per minute, and a normal electrocardiogram.

2. Patient (b) (6) was a 45-year-old male who died on Day 289 due to metastatic gastric cancer. He completed the 24-week treatment and died 26 days after his last dupilumab injection. His underlying medical conditions included allergic rhinitis, chronic cholecystitis, chronic pancreatitis, urolithiasis, fatty liver disease, and vegetative vascular dystonia (dysautonomia). He was hospitalized on Day 275 with an asthma exacerbation. Pleural effusion was noted. Pleural puncture and drainage suggested an underlying malignancy. His condition progressed to bilateral subtotal organizing pneumonia and severe acute cor pulmonale. No signs or symptoms of underlying malignancy were noted during screening or treatment. Autopsy noted invasive growth in the region of the small gastric curvature. Complications were pulmonary carcinomatosis, tumor metastases to the intrathoracic and mesenteric lymphatic nodes of the greater omentum, right-sided metastases of the pleura and bilateral subtotal organizing pneumonia, acute cor pulmonale, myocardiosclerosis, and nonuniform congestion of the liver, kidneys, and spleen.

Overall, these deaths are unlikely due to dupilumab as both of these events are conditions that likely occurred over a longer period of time than the length of time exposed to dupilumab.

7.5.1.4.4.2. SAE

The SAEs that occurred more frequently on treatment than placebo are summarized in Table 11 below.

Table 11: Study DRI12544 SAEs Greater Than Placebo (Safety Population)

		Placebo q2w	Dupilumab 200q4w	Dupilumab 300q4w	Dupilumab 200q2w	Dupilumab 300q2w
	N=	158	150	157	148	156
SOC	PT	Count (%)				
Any SAE		9 (6)	6 (4)	16 (10)	10 (7)	13 (8)
Blood and lymphatic system disorders	Eosinophilia	0	0	0	0	1 (1)*
Cardiac disorders	Atrioventricular block complete	0	1 (1)	0	0	0
	Cardiac failure acute	0	0	1 (1)	0	0
	Cor pulmonale acute	0	0	1 (1)	0	0
Gastrointestinal disorders	Colitis	0	0	0	1 (1)	0
	Large intestine polyp	1 (1)	0	0	0	0
	Subileus	0	0	0	0	1 (1)**
Hepatobiliary disorders	Cholecystitis	0	0	0	0	1
	Hepatitis cholestatic	0	0	1 (1)	0	0
Immune system disorders	Anaphylactic reaction	0	0	0	0	1 (1)
	Drug hypersensitivity	0	0	1 (1)	0	0
Infections and infestations	Appendicitis	1 (1)	0	0	0	1 (1)**
	Diverticulitis	0	0	1 (1)	0	0
	Epiglottitis	0	0	0	1 (1%)	0
	Erysipelas	0	0	1 (1)	0	0
	Gastroenteritis	0	0	0	0	2 (1)
	Pneumonia	0	0	1 (1)	0	2 (1)
	Sinusitis	0	0	0	1 (1)	0
Injury, poisoning and procedural complications	Bone fissure	0	0	1 (1)	0	0
	Comminuted fracture	1 (1)	0	0	0	0
	Joint dislocation	0	1 (1)*	0	0	0
	Procedural intestinal perforation	0	0	0	0	1 (1)*
	Procedural pain	0	0	0	1 (1)	0
	Soft tissue injury	0	0	1 (1)	0	0
	Upper limb fracture	0	1 (1)*	0	0	0
Investigations	Blood pressure increased	0	0	0	0	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Benign neoplasm of thyroid gland	0	1 (1)	0	0	0
	Bowen's disease	0	0	1 (1)	0	0
	Breast cancer metastatic	0	0	1 (1)	0	0
	Colon cancer	1 (1)	0	0	0	0
	Hypergammaglobulinemia benign monoclonal	0	0	1 (1)	0	0
	Metastatic gastric cancer	0	0	1 (1)	0	0
Nervous system disorders	Syncope	0	0	1 (1)	0	0
	Abortion spontaneous	0	0	1 (1)	2 (1)*	0

Table 11: Study DRI12544 SAEs Greater Than Placebo (Safety Population)

			Placebo q2w	Dupilumab 200q4w	Dupilumab 300q4w	Dupilumab 200q2w	Dupilumab 300q2w
		N=	158	150	157	148	156
SOC	PT		Count (%)				
Pregnancy, puerperium and perinatal conditions	Pregnancy		0	0	0	0	1 (1)
Psychiatric disorders	Suicide attempt		0	0	1 (1)	0	0
Reproductive system and breast disorders	Uterine prolapse		0	0	0	0	1 (1)
Respiratory, thoracic and mediastinal disorders	Organizing pneumonia		0	0	1 (1)	0	0
	Pulmonary embolism		0	0	1 (1)	0	0
Skin and subcutaneous tissue disorders	Dermal cyst		0	1 (1)	0	0	0
	Eczema		0	0	0	0	1 (1)
Vascular disorders	Hypertension		0	0	0	1 (1)**	0

*,** represents same and distinct patients in treatment group
PT = preferred term; q2w = once every 2 weeks; q4w = once every 4 weeks; SAE = serious adverse event; SOC = system organ class
Source: Reviewer generated table in JMP using ADSL and ADAE datasets (TRT01A, TRTEMFL, AESER, PSOCFL)

The number of overall SAEs was generally similar to placebo (placebo: 6% versus dupilumab 4% to10%) without a dose-related increase. Two SAEs occurred in more than one subject (abortion spontaneous and gastroenteritis). Events of specific interest for dupilumab will be discussed further in Section 7.7.5, Analysis of Submission-Specific Safety Issues.

7.5.1.4.4.3. AEs Leading to Discontinuation

AEs leading to discontinuation that occurred more commonly in the dupilumab groups compared to placebo are summarized in Table 12.

Table 12: Study DRI12544 AE Leading to Discontinuation (Safety Population)

AESOC	AEDECOD	Placebo q2w	Dupilumab 200q4w	Dupilumab 300q4w	Dupilumab 200q2w	Dupilumab 300q2w
N		N=158	N=150	N=157	N=148	N=156
		Count (%)				
Any AE		5 (3)	7 (5)	10 (6)	6 (4)	4 (3)
Blood and lymphatic system disorders	Eosinophilia	0	0	0	0	1 (1)
Cardiac disorders	Atrioventricular block complete	0	1 (1)	0	0	0
	Cardiac failure acute	0	0	1 (1)	0	0
Gastrointestinal disorders	Colitis	0	0	0	1 (1)	0

Table 12: Study DRI12544 AE Leading to Discontinuation (Safety Population)

AESOC	AEDECOD	Placebo q2w	Dupilumab 200q4w	Dupilumab 300q4w	Dupilumab 200q2w	Dupilumab 300q2w
N		N=158	N=150	N=157	N=148	N=156
				Count (%)		
General disorders and administration site conditions	Injection site erythema	0	0	1 (1)	0	2 (1)[*, **]
	Injection site inflammation	0	0	0	0	1 (1)[**]
	Injection site edema	0	0	0	0	2 (1)[*, **]
	Injection site pain	0	0	0	0	2 (1)[*, **]
	Injection site pruritus	0	1 (1)	0	1 (1)	1 (1)[*]
	Localized edema	0	0	0	1 (1)	0
	Edema peripheral	0	0	1 (1)	1 (1)	0
Infections and infestations	Epiglottitis	0	0	0	1 (1)	0
Injury, poisoning and procedural complications	Post-traumatic neck syndrome	0	0	1 (1)	0	0
Investigations	Alanine aminotransferase increased	1 (1)	1 (1)	0	2 (1)	0
Musculoskeletal and connective tissue disorders	Arthralgia	0	0	1 (1)	0	0
	Rhabdomyolysis	0	0	1 (1)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer metastatic	0	0	1 (1)	0	0
Nervous system disorders	Headache	0	1 (1)	0	0	1 (1)
	Presyncope	0	0	1 (1)	0	0
	Trigeminal nerve disorder	0	1 (1)[*]	0	0	0
Pregnancy, puerperium and perinatal conditions	Pregnancy	0	1 (1)	1 (1)	0	0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	0	0	1 (1)	0	0
Skin and subcutaneous tissue disorders	Eczema	0	1 (1)[*]	0	0	0
	Rash pruritic	0	1 (1)	0	0	0

*,** represents same and distinct patients in treatment group
AESOC = adverse event system organ class; q2w = once every 2 weeks; q4w = once every 4 weeks
Source: Reviewer generated table in JMP using ADSL and ADAE datasets (TRT01A, TRTEMFL, PSOCFL, AEACN)

The number of adverse events (AEs) leading to discontinuation were low (3% to 6%) and higher in the treatment groups compared to placebo, with the exception of the highest dose group (300 mg q2w). When taken in totality, the most common AEs leading to discontinuation related to injection-site reactions (erythema, inflammation, edema, pain, localized edema, and peripheral edema) were dose-related. Alanine aminotransferase increase also occurred in more than one subject in the 200 mg q2w group, with one occurrence at 200 mg q4w and in placebo.

7.5.1.4.4.4. Common Adverse Events

Adverse events that occurred in at least 2% of subjects and occurred more often in any treatment group as compared to placebo are summarized in Table 13.

Table 13: Study DRI12544 Common Adverse Events ≥2% and Greater Than Placebo in Any Treatment Group (Safety Population)

	Placebo q2w	Dupilumab 200q4w	Dupilumab 300q4w	Dupilumab 200q2w	Dupilumab 300q2w
	N=158	N=150	N=157	N=148	N=156
Adverse Event	Count (%)	Count (%)	Count (%)	Count (%)	Count (%)
Injection site erythema	12 (7.6)	13 (8.7)	12 (7.6)	21 (14.2)	34 (21.8)
Injection site pain	7 (4.4)	5 (3.3)	6 (3.8)	7 (4.7)	14 (9)
Injection site pruritus	5 (3.2)	3 (2)	0	10 (6.8)	12 (7.7)
Bronchitis	16 (10.1)	10 (6.7)	11 (7)	11 (7.4)	19 (12.2)
Influenza	5 (3.2)	10 (6.7)	13 (8.3)	6 (4.1)	9 (5.8)
Nasopharyngitis	15 (9.5)	9 (6)	19 (12.1)	15 (10.1)	16 (10.3)
Respiratory tract infection	6 (3.8)	7 (4.7)	5 (3.2)	3 (2)	3 (1.9)
Rhinitis	5 (3.2)	4 (2.7)	5 (3.2)	5 (3.4)	5 (3.2)
Sinusitis	11 (7)	12 (8)	13 (8.3)	5 (3.4)	6 (3.8)
Back pain	6 (3.8)	7 (4.7)	4 (2.5)	8 (5.4)	12 (7.7)
Cough	5 (3.2)	3 (2)	7 (4.5)	4 (2.7)	11 (7.1)
Rhinitis allergic	5 (3.2)	3 (2)	7 (4.5)	3 (2)	5 (3.2)

Source: Reviewer generated table in JMP Clinical
q2w = once every 2 weeks; q4w = once every 4 weeks

The most common adverse events were related to the injection site (erythema, pain, pruritus) and were dose related. The most common adverse event was injection site erythema, occurring in 22% of subjects treated with the highest dose. Other adverse events that appeared dose related were bronchitis and back pain. Overall these adverse events are expected within this study population.

7.5.2. Study EFC13579

7.5.2.1. Administrative Information

- **Study title**: A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma
- **Study dates:** April 27, 2015 to July 29, 2017
- **Study sites:** Argentina, Australia, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Italy, Japan, Mexico, Poland, Russia, South Africa, South Korea, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States
- **Study report date:** December 4, 2017

7.5.2.2. Objectives

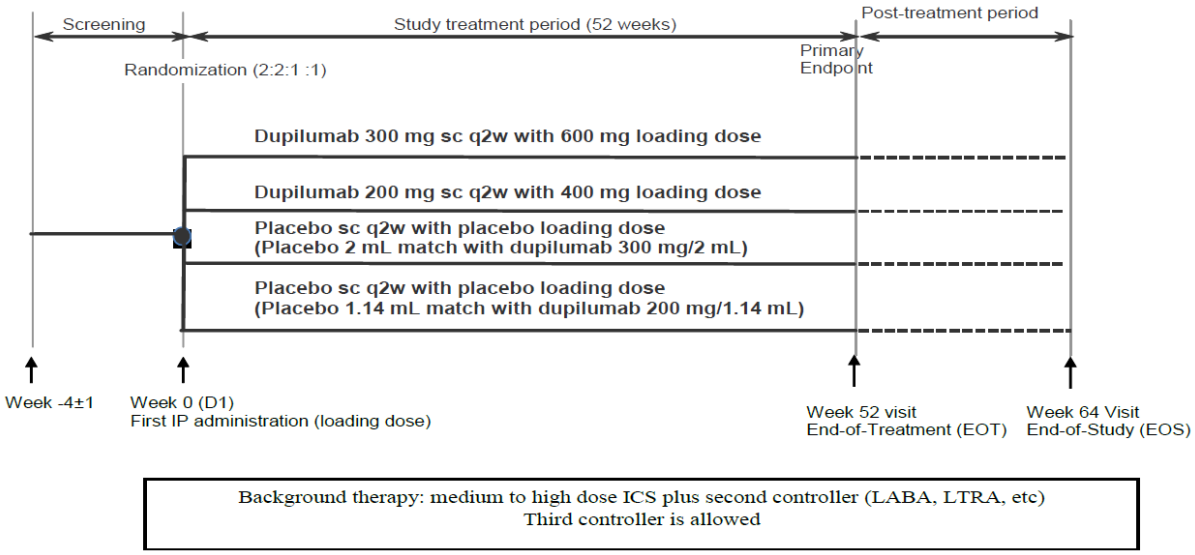
The primary objective of the study was to evaluate the efficacy of dupilumab in patients with persistent asthma.

7.5.2.3. Study Design and Conduct

Study EFC13579 was a randomized, double-blind, placebo-controlled, parallel-group study comparing dupilumab 200 mg q2w, and 300 mg q2w administered SC to placebo as add-on therapy to medium-to-high dose ICS/LABA therapy for 52 weeks in patients with persistent asthma. Each dose also included a 2x loading dose (e.g., 400 mg for the 200-mg dose and 600 mg for the 300-mg dose). There were two placebo groups given the difference in volume for the two dupilumab doses. For the purposes of this review, the placebo groups were combined and treated as the same. Randomization was stratified by age (<18 years and ≥18 years), blood eosinophil count at screening (<0.3 G/L and ≥0.3 G/L), ICS dose level (medium, high), and country.

The study schematic is shown in Figure 8.

Figure 8. Study EFC13579 Study Schematic



ICS = inhaled corticosteroids; LABA = long-acting beta agonist; LTRA = leukotriene receptor antagonists; q2w = once every 2 weeks
Source: Study EFC13579 CSR, Figure 1, page 31

7.5.2.3.1. Procedures

The study consisted of three phases: screening (4 weeks), randomized treatment (52 weeks), and post-treatment follow-up (12 weeks). The screening period was used to establish level of asthma control.

A schedule of assessments is provided in Table 14.

Table 14: Schedule of Assessments

	SCR[a]	Randomized Treatment Period																										Post-treatment Period		
		RND[c]																									EOT[b]			EOS
Week	-4±1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Informed Consent	X																														
Incl/Excl Criteria	X	X																													
Patient Demography	X																														
Medical/Surgical History	X																														
Reversibility[d]	X		X	X		X		X						X						X								X			X
Spirometry[e]	X	X[f]	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
CXR (if none within previous year)[g]	X																														
Prior & concomitant[h]	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
Physical Examination	X													X														X			X
Randomization		X																													
Call IVRS/IWRS	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X			X
Investigational Product Administration[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Dispense or download e-diary/PEF meter	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
Dispense/Review Home Dosing Diary[j]								X		X		X		X		X		X		X		X		X		X		X			
ACQ-7[k]	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
AQLQ(S)		X						X						X						X		X						X			X
Health Care Resource Utilisation		X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Exhaled NO[l]	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
Vital Signs[m]	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
ECG	X		X	X				X		X		X		X		X		X		X								X			X
Pregnancy test[n]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X			X
Clinical lab testing[o]	X	X		X		X		X		X		X		X		X		X		X		X		X		X		X	X	X	X
Hepatitis B viral load[p]		X						X						X						X								X			
AE/SAE recording	X	X	X	X	X	X	X	X		X		X		X		X		X		X		X		X		X		X	X	X	X
Urinalysis	X							X						X						X								X			X
Serum immunoglobulins (IgG, IgM, IgA)	X							X						X						X								X			X
Systemic drug concentration[q]		X	X	X		X		X		X				X						X								X	X	X	X
Anti-drug antibodies[q]		X	X	X				X						X						X								X			X
Biomarker[r]		X	X	X		X		X		X				X						X								X	X	X	X
Archival serum[s]		X						X						X						X								X			
Pharmacogenetics: blood samples for DNA and RNA[t]		X																													
EQ-5D-5L		X						X						X						X								X			X
HADS[u]		X						X						X						X								X			X
SNOT-22[v]		X						X						X						X								X			X

RQLQ(S) +12[w]		x						x						x						x									x
Vaccine IgG	x[x]	y	y	y	y	y	y	y		y		y		y		y		y		y		y		y		y		y	y	y	y

a The Screening Period is 4±1 weeks (21-35 days) in duration to collect baseline data on asthma control and assure eligibility criteria.

b Patients who permanently discontinue treatment early will continue the remaining visits for follow up assessment until end of study.

c Randomization Visit (Visit 2) is defined as Day 1. Visit windows for subsequent visits are +/- 3 days.

d Three attempts may be made during the Screening Period to meet the qualifying criteria for reversibility. During the treatment period, post-bronchodilator FEV1 will be determined at the designated treatment visits.

e Forced expiratory volume (FEV1), PEF, Forced vital capacity (FVC), Forced expiratory flow between 25% to 75% of vital capacity (FEF25%-75%) at all visits; pulmonary function tests should be performed in the morning. Spirometry after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and with the last dose of Long-Acting Muscarinic Antagonist (LAMA) for at least 24 hrs.

f Treatment Period stability limits will be established for FEV1 and PEF. Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2 ((Day1). There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

g Perform chest X-ray if no chest imaging (X-ray, CT, MRI) available within the previous year or if there is local requirement.

h Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1 (patients requiring oral steroids as controller medication or biologics are excluded).

i Every 2 week (q2w) investigational product administrations must be separated by at least 11 days. The randomized Treatment Period visits occur every 2 weeks up to Week 12 and then every 4 weeks, alternating with q2w home administration of IMP (patient, caregiver, or health care professional) without study visit up to the end of treatment period at Week 52. After Week 12, if the patient or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site by way of unscheduled visits. Patients will be monitored at the study site for a minimum of 30 minutes after injections in the first 12 weeks.

j Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, oral steroid requirements, nocturnal awakenings due to asthma symptoms, morning and evening asthma symptom NRS scores and AM and PM PEF. This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days.

k ACQ-7 is completed in the patient's electronic diary during clinic visits. ACQ-7 (Asthma Control Questionnaire 7-question version) score will be used to follow up evaluations in adolescents (12 years to less than 18 years) while ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at visit 1 and visit 2 for all patients and follow up evaluations in adults (≥ 18 years).

l Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

m Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) only. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

n Serum pregnancy test at Visit 1 and urine dipstick pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization.

o Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at Visit 1 includes hepatitis screen covering hepatitis B surface antigen (HBs Ag), Hepatitis B surface antibody(HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C antibodies (HC Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

p This is only applicable for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at the screening visit.

q Systemic drug concentration and ADA samples are to be collected prior to dosing.

r Biomarker includes Eotaxin-3, eosinophil cationic protein (ECP), antigen-specific IgE, total IgE, Thymus and Activation-Regulated Chemokine (TARC),). Blood eosinophil count will be measured as part of hematology test. Exhaled nitric oxide assessment is described separately in the flowchart.

s Archival serum in case needed for retrospective safety follow-up or additional biomarker analysis, and this is optional and a separate written consent form must be signed.

t This is optional and a separate written consent form must be signed.

u HADS includes Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale- Depression subscale.

v For those patients with bilateral nasal polyposis/chronic rhinosinusitis.

w For those patients with comorbid allergic rhinitis.

x Patients will be encouraged to provide vaccination plans for any vaccines which are in line with the patients age and local medical practice (Live attenuated vaccines are excluded) during the study. Subjects planning to receive any vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccination.

y Optional collection of blood for assay of vaccine IgG in serum for each vaccine: the first sample should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

ACQ = Juniper Asthma Control Questionnaire; AE = adverse event; CXR = chest x-ray; ECG = electrocardiogram; HADS = Hospital Anxiety and Depression Scale; IVRS =; IWRS =; NO =; PEF = peak expiratory flow; RQLQ =; SAE = serious adverse event; SNOT = Sino Nasal Outcome Test
Source: EFC13579 Protocol, Figure 1.2, pg. 16

7.5.2.3.2. Patient Population

Key Inclusion Criteria

1. Asthma for ≥1 year per GINA 2014 guidelines, and the following criteria:
    a. Medium or high-dose ICS in combination with a second controller (e.g., LABA or leukotriene receptor antagonist), with or without a third controller, for at least 3 months on a stable dose for ≥1 month.
    b. FEV1 40% to 80% predicted at screening and prior to randomization
    c. ACQ-5 ≥1.5 at screening and randomization
    d. Reversibility in FEV1 (12% and 200 mL) at screening
    e. Exacerbation requiring systemic steroids or hospitalization/emergency/urgent care visit

Reviewer comment: Although this study population does not specify uncontrolled or moderate-to-severe, the enrollment criteria are consistent with uncontrolled and moderate-to-severe asthmatics (e.g., requiring medium to high dose ICS with a second controller, ACQ ≥1.5, and FEV1 <80%) per the NHLBI guidelines. Compared to the anti-IL5 asthma programs, which are indicated for severe asthma, this population differs in that subjects had to have one or more exacerbations (compare to two or more), were not enriched for high blood eosinophil levels, and oral steroids were not allowed.

Key Exclusion Criteria

1. <12 years of age
2. Women of childbearing potential not on effective contraception
3. Pregnant or breast-feeding
4. Other lung diseases
5. Severe asthma exacerbation within 4 weeks
6. Upper or lower respiratory tract infection within 4 weeks
7. Current smoker, cessation within 6 months, or >10-pack year history
8. Beta-blocker use
9. Omalizumab with 130 days or other biologic therapy within 6 months or five half-lives
10. Initiation of allergy immunotherapy within 3 months (or planned dose change during study)
11. Previous enrollment in another dupilumab study
12. Systemic corticosteroids (>10 mg/day prednisone or equivalent) within 28 days
13. Methylxanthines within 14 days
14. Diagnosed active parasitic infection; suspected or high risk unless active infection ruled-out
15. Immunosuppression, HIV, active immunosuppressive therapy, or autoimmune disease
16. Acute or chronic infection requiring treatment
17. Live attenuated vaccine within 12 weeks
18. Malignancy within 5 years
19. Systemic hypersensitivity reaction (other than a localized injection-site reaction) to any biologic drug
20. Underlying hepatobiliary disease and/or ALT >3x upper limit of normal
21. Abnormal lab values: creatine phosphokinase >10 upper limit of normal, platelets <100,000 cells/mm^3, eosinophils >1500 cells/mm^3

Reviewer comment: The major differences between DRI12544 and this study is the enrollment of subjects 12 to 17 years of age. A few other exclusion criteria were added (severe asthma exacerbation within 4 weeks, upper or lower respiratory tract infection within 4 weeks, malignancy within 5 years, and systemic hypersensitivity reaction to any biologic) and will be noted during the review.

7.5.2.3.3. Treatment

The following treatments were administered by SC injection once every 2 weeks.

1. Dupilumab 200 mg q2w (1.14 mL) after a 400 mg loading dose
2. Placebo matched to No. 1 (1.14 mL) q2w after a loading dose (2 x 1.14 mL)
3. Dupilumab 300 mg q2w (2 mL) after a 600 mg loading dose
4. Placebo to No. 3 (2 mL) after a loading dose (2 x 2 mL)

The dosing schedule was the same as in Study DRI12544 in regard to self-administration, monitoring (except that this study monitored for 30 minutes instead of 1 hour), and injection site.

As in Study DRI12544, ICS and other controller use was recorded via an electronic diary.

7.5.2.3.4. Efficacy Endpoints

Primary:

- Annualized rate of severe exacerbation events
- Absolute change from baseline in pre-BD FEV1 at Week 12

Reviewer comment: Exacerbations were a secondary endpoint for Study DRI12544.

Secondary:

- Relative change (%) from baseline at Week 12 in FEV1
- Absolute and percent change from baseline in FEV1 at Week 12 (eosinophils ≥0.3 giga/L)
- Annualized rate of severe exacerbation events (eosinophils ≥0.15 gig/L)
- Absolute and percent change from baseline in FEV1 at Week 12 (eosinophils ≥0.15 giga/L)
- Absolute and percent change from baseline in FEV1 at Weeks 2, 4, 8, 24, 36 and 52
- Time to loss of asthma control events during the treatment period
- Time to severe exacerbation events during the treatment period
- Time to loss of asthma control events during overall study period
- Time to severe exacerbation events during overall study period
- Health care resource utilization
- Change from baseline in other lung function measurements (% predicted FEV1, AM/PM peak expiratory flow, forced vital capacity , forced expiratory flow 25 to 75%, post-BD FEV1) at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control events during the treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit
- Time to first severe exacerbation event

- Time to first loss of asthma control event
- Change from baseline in ACQ-5 score (for adults) and ACQ-7 (for adolescents) at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
    - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
    - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 4, 8, 12, 24, 36, and 52.
- Change from baseline in PROs at Week 12, 24, 36, and 52:
    - AQLQ with Standardized Activities Self-Administered (≥12 years)
    - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
    - Hospital Anxiety and Depression Scale
    - 22-item Sino Nasal Outcome Test in those patients with comorbid bilateral nasal polyposis
    - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ in those patients with comorbid allergic rhinitis

The following biomarkers were also assessed: thymus and activation regulated chemokine, eotaxin-3, total immunoglobulin E, antigen-specific immunoglobulin E, fractional exhaled nitric oxide (FeNO), eosinophil cationic protein), and periostin.

Reviewer comments: Compared to Study DRI12544, the secondary endpoints for this study looked at specific subgroups of eosinophilia (≥0.3 giga/L and ≥0.15 giga/L) and looked at several different timepoints through the 52- week treatment period. The general composition of the endpoints was similar.

7.5.2.3.5. Efficacy Parameters

The definitions for severe exacerbation and loss of asthma control were the same as in Study DRI12544. In this study it was specified that events would be counted separately if they were separated by at least 4 weeks.

7.5.2.3.6. Safety Parameters

Same as Study DRI12544

7.5.2.3.7. Statistical Analysis Plan

The analysis populations are defined as in Table 15.

Table 15: Study EFC13579 Analysis Populations

Analysis Population	Definition
ITT (primary efficacy population)	Randomized population analyzed by treatment group allocated by randomization
Safety	Received at least one dose or part of a dose, analyzed by treatment received. Also included patients who were treated without randomization
Pharmacokinetics	Safety population with at least one non-missing result for dupilumab concentration, analyzed by treatment received
ADA	Safety population with at least one non-missing ADA result

ITT = intention to treat

The primary efficacy population was the ITT population.

Reviewer comment: The primary analysis for Study DRI12544 was in the high eosinophil group. Given the statistically significant results in the ITT population regardless of baseline eosinophilia, study EFC13579 looked at all subjects regardless of their baseline eosinophilia as the primary analysis.

7.5.2.3.8. Compliance with Good Clinical Practice

The study was conducted in accordance with GCP as required by the (ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

The Applicant certified that all clinical investigations in this sBLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the United States conducted under IND 105379 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in GCP.

Based on an internal Sanofi investigation into a discrepancy in the handling and documentation of investigational medicinal product at the site, one site was terminated (Site No. 840049, Dr. John Panuto, Site Management Organization network-Clinical Research Solutions, Middleburg Heights, Ohio). The Institutional Review Board and relevant health authorities were notified as per applicable laws and regulations. Six patients were randomized at this site.

During the study, one of the principal investigators was (b) (6) (Site No. 392179, Dr. Taniguchi, Tosei General Hospital, Japan). An internal Sanofi investigation concluded that there was no evidence of potential misconduct or impact on the study although there were two randomized patients at this site. The principal investigator's responsibilities were transferred to the sub-investigator.

7.5.2.4. Study Results

7.5.2.4.1. Protocol Amendments

Eight amendments were made to the protocol, most occurring after the first patient entered the study. These spanned the 2-year study duration. The placebo arms were initially planned to be analyzed together, but per request from the European Medicines Agency, the placebo arms were unpooled, as reflected in the September 21, 2015, amendment. Also, per European Medicines Agency request, to ensure that the benefit/risk was shown for both moderate and severe patients, this amendment also capped the number of medium-dose ICS subjects to ensure at least 50% were on high-dose ICS. Another amendment (August 9, 2016) added 220 patients to provide additional exposure to the commercial drug product, as well as examining whether the loading dose impacts the duration of sustained efficacy with regard to exacerbations, per our request.

7.5.2.4.2. Protocol Deviations

A total of 96 patients (69 (6%) in the dupilumab groups and 27 (4%) in the placebo groups reported major protocol deviations. The two most common major protocol deviations were not being on a medium- to high-dose ICS (14 (1%) dupilumab and 7 (1%) placebo; most received less ICS dose than required), or FEV1 <80% predicted (15 (1%) dupilumab versus 2 (0.3%) placebo). Overall the distribution was even throughout the treatment groups and was therefore unlikely to affect the conclusions.

7.5.2.4.3. Efficacy

7.5.2.4.3.1. Disposition

Patient disposition is summarized in Table 16.

Table 16: Study EFC13579 Disposition

	Placebo	Dupilumab 200 q2w	Dupilumab 300 q2w
Randomized	638 (100%)	631 (100%)	633 (100%)
ITT	638 (100%)	631 (100%)	633 (100%)
SAFFL	634 (99%)	631 (100%)	632 (100%)
Completed study treatment	478 (74%)	487 (77%)	469 (74%)
Discontinued study treatment	73 (11%)	70 (11%)	85 (13%)
Patient request	51 (8%)	54 (9%)	51 (8%)
Adverse event	29 (5%)	21 (3%)	46 (7%)
Poor compliance	7 (1%)	3 (1%)	1 (<1%)
Other	29 (5%)	42 (7%)	35 (6%)
Discontinued from study prior to Week 52	34 (5.3%)	28 (4.4%)	41 (6.5%)
Patient request	30 (4.7%)	23 (3.6%)	31 (4.9%)
Adverse event	8 (1.3%)	4 (0.6%)	12 (1.9%)
Poor compliance	3 (0.5%)	1 (0.2%)	2 (0.3%)
Other	29 (5%)	23 (3.6%)	27 (4.3%)

HEos = high eosinophil; ITT = intention to treat; q2w = once every 2 weeks
Source: Reviewer generated table in JMP using ADSL dataset without screen failures, Study CSR EFC13579, Table 7, pg. 70 and Table 11, page 81

The number of subjects who completed the study was generally balanced across treatment groups. There were slightly more subjects who discontinued due to adverse events in the high-dose group compared to placebo.

7.5.2.4.3.2. Demographics

Baseline demographics are summarized in Table 17.

Table 17: Study EFC13579 Baseline Demographics (Randomized Population)

	Placebo		Dupilumab 200 mg q2w		Dupilumab 300 mg q2w		Total	
N		**638**		**631**		**633**		**1902**
Sex	N	%	N	%	N	%	N	%
Female	416	65%	387	61%	394	62%	1197	63%
Male	222	35%	244	39%	239	38%	705	37%
Race								
White	538	84%	510	81%	529	84%	1577	83%
Asian	66	10%	78	12%	79	12%	223	12%
Black or African American	26	4%	33	5%	21	3%	80	4%
Other	7	1%	9	1%	4	1%	20	1%
American Indian or Alaska Native	1	<1%	0	0	0	0	1	<1%
Native Hawaiian or other Pacific Islander	0	0	1	<1%	0	0	1	<1%
Age in Years								
Mean		48		48		48		48
SD		15		15		16		15
Median		12		12		12		12
Min-Max		84		81		83		84
Age in class, n (%)								
18 to 64	516	81%	512	81%	516	82%	1544	81%
65 or greater	83	13%	85	13%	83	13%	251	13%
less than 18	39	6%	34	5%	34	5%	107	6%

Max = maximum; Min = minimum; q2w = once every 2 weeks; SD = standard deviation
Source: Reviewer generated table in JMP using ADSL dataset without screen failures, SCE Table 16, page 55

Baseline demographics were balanced between groups. In general, the subjects were mainly white (83%) females (63%), with a mean age of 48 years. Demographics were balanced between treatment groups.

The baseline disease characteristics are summarized in Table 18.

Table 18: Study EFC13579 Baseline Disease Characteristics (Randomized Population)

	Placebo		Dupilumab 200 mg q2w		Dupilumab 300 mg q2w		Total	
N	158		150		157		776	
Age at onset of asthma (yrs)								
Mean	27		27		27		27	
Std Dev	19		19		19		19	
Min	0		0		0		0	
Max	71		77		78		78	
Time since first diagnosis of asthma (yrs)								
Mean	21		21		21		21	
Std Dev	15		16		15		15	
Min	1		1		1		1	
Max	76		72		70		76	
Atopic hx	N	%	N	%	N	%	N	%

Table 18: Study EFC13579 Baseline Disease Characteristics (Randomized Population)

	Placebo		Dupilumab 200 mg q2w		Dupilumab 300 mg q2w		Total	
Yes	533	84%	526	83%	517	82%	1576	83%
No	105	16%	107	17%	114	18%	326	17%
Atopic Dermatitis	N	%	N	%	N	%	N	%
No	555	87%	566	89%	559	89%	1680	88%
Yes	83	13%	67	11%	72	11%	222	12%
Smoking hx								
Never	512	80%	517	82%	505	80%	1534	81%
Former	126	20%	116	18%	126	20%	368	19%
FEV1 (L)								
Mean		1.8		1.8		1.8		1.8
Std Dev		0.6		0.6		0.6		0.6
Min		0.5		0.4		0.4		0.4
Max		3.7		3.8		4.2		4.2
Percent pred FEV1 (%)								
Mean		58		58		59		58
Std Dev		14		14		14		14
Min		13		20		17		13
Max		90		99		89		99
FEV1 reversibility (%)								
Mean		26		27		26		26
Std Dev		18		23		24		22
Min		-24		-37		-15		-37
Max		168		147		269		269
Num of Asthma Exacerbations in past yr*								
Mean		2		2		2		2
Std Dev		2		3		2		2
Min		1		1		1		1
Max		12		50		24		50
1	294	46%	330	52%	340	54%	964	52%
2	184	29%	158	25%	163	26%	505	27%
3	85	13%	65	10%	64	10%	214	11%
≥4	75	12%	80	13%	64	10%	219	12%
ACQ-5								
Mean		3		3		3		3
Std Dev		1		1		1		1
Min		1		1		0		0
Max		6		6		6		6
AQLQ								
Mean		4		4		4		4
Std Dev		1		1		1		1
Min		1		1		2		1
Max		7		7		7		7
Num of puffs of albuterol in 24 hours								
Mean		3		3		3		3
Std Dev		4		4		3		4
Min		0		0		0		0
Max		30		33		30		33

Table 18: Study EFC13579 Baseline Disease Characteristics (Randomized Population)

	Placebo		Dupilumab 200 mg q2w		Dupilumab 300 mg q2w		Total	
ICS/LABA								
High	339	53%	323	51%	317	50%	979	51%
Medium	295	46%	303	48%	310	49%	908	48%
Low	4	1%	7	1%	4	1%	15	1%
Blood Eosinophil (Giga/L)								
Mean		0.38		0.35		0.35		0.36
Std Dev		0.38		0.37		0.35		0.37
Min		0		0		0		0
Max		3.58		4.33		3.61		4.33
<0.3	347	54%	356	56%	366	58%	1069	56%
≥0.3	290	46%	277	44%	264	42%	831	44%

*Asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma
Yrs = years, hx = history, mnths = months; ACQ = Juniper Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; FEV1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; Max = maximum; Min = minimum; q2w = once every 2 weeks; SD = standard deviation
Source: Reviewer generated table in JMP using ADSL dataset without screen failures, SCE Table 17 and 18, pages 61-70

Baseline demographics were generally balanced between treatment groups. The mean age of onset of asthma was 27 years old, with 21 years since diagnosis (which coincides with the mean study age of 48 years). Most subjects were atopic (83%), never smokers (81%), with a mean FEV1 of 1.8 L (58% predicted) with 26% reversibility. Subjects had an average of two asthma exacerbations in the past year, with about half of subjects having one exacerbation, and only 12% have four or more exacerbations. The study was enriched for subjects who had at least one exacerbation with in the past year. The mean ACQ-5 and AQLQ were 3 and 4, respectively. This is consistent with the inclusion criteria of ACQ-5 ≥1.5, which indicates not well controlled asthma. The mean number of puffs of rescue short-acting BD (albuterol) per day was three, which is consistent with moderate-to-severe asthma (based on NHLBI guidelines).

The overall baseline disease characteristics were similar to Study DRI12544 (see demographics Table 9 in 7.5.1.3.2).

7.5.2.4.3.3. Co-primary endpoints

For the co-primary endpoint of annualized event rate of severe exacerbation in the overall population (primary analysis population), both dupilumab treatment arms showed a significantly lower event rate compared to placebo (Table 48). Both doses showed about a 50% reduction compared to placebo during the 1-year study period (200 mg: rate ratio: 0.52, 95% CI: 0.41, 0.66; 300 mg: rate ratio: 0.54, CI: 0.43, 0.68). The co-primary endpoint of change from baseline in FEV1 at Week 12 in the overall population were significantly higher for both dupilumab doses with similar mean treatment differences for both dose groups (200 mg: 0.14 (95% CI: 0.08, 0.19), 300 mg: 0.13 (95% CI: 0.08, 0.18), relative to the respective matching placebo group (Table 52). The primary efficacy analysis was similar for both doses which supported approval both doses for the moderate-to-severe asthma population.

7.5.2.4.3.4. Secondary

7.5.2.4.3.5. Eosinophilia subgroup analysis

Subgroup analysis for different eosinophil levels for both the co-primary endpoints of change from baseline in FEV1at Week 12 and the annualized rate of exacerbation over the 52-week treatment period showed efficacy in higher eosinophil subgroups and a lack of efficacy in the lower eosinophil subgroups.

For subjects with eosinophils ≥0.3 G/L, the annualized event rate of severe exacerbations was lower in both dose groups compared to placebo (200 mg q2w: 0.34, 95% CI: 0.24, 0.48; 300 mg q2w: 0.32, 95% CI: 0.23, 0.45) and was numerically lower than in the overall population (Table 56). For subjects with eosinophils <0.3 G/L the annualized event rate of severe exacerbations was not significantly lower for either dose group (Table 58). The interaction test on four eosinophil subgroups (<0.15 Giga/L, ≥0.15 to <0.3 Giga/L, ≥0.3 to <0.5 Giga/L, ≥0.5 Giga/L) showed significant treatment-by-subgroup interaction p<0.001 and <0.001 for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively (Figure 26).

The analysis by eosinophil subgroup for change in FEV1 from baseline at Week 12, also showed a dependency on higher eosinophils. For subjects with eosinophils ≥0.3 G/L, the treatment difference for the change in FEV1 from baseline compared to placebo was similar and significant for both dose groups (200 mg q2w: 0.21, 95% CI: 0.13, 0.29; 300 mg q2w: 0.24, 95% CI: 0.16, 0.32: Table 56). For subjects with eosinophils >0.3 G/L, only the 200 mg q2w had a significant treatment difference, however the 95% almost crosses 0 (0.08 L, (95% CI: 0.01, 0.15), Table 58). The improvement in FEV1 was not statistically significant in either dose group in the low baseline eosinophil subgroup (<0.15 Giga/L: 200 mg q2w: 0.09, CI: -0.01, 0.18, 300 mg q2w: 0.06, CI: -0.04, 0.15, Figure 27).

Therefore, the ITT population results were driven by the HEos subgroup.

7.5.2.4.3.1. FeNO subgroups

FeNO was included as a prespecified exploratory subgroup analysis based on FeNO subgroups, for both annualized rate of exacerbation (Figure 23) and change in FEV1 at Week 12 (Figure 25). A trend for higher FeNO was demonstrated, however we had several concerns with including FeNO within the prescribing information. Analyses by baseline FeNO level were not among the many planned subgroup analyses and were among twenty different subgroup analyses specified in the SAP. Therefore, the evaluation of treatment effects by FeNO level were selected from among many different subgroup analyses and are exploratory and hypothesis-generating. It is unclear whether such results may represent chance findings or may be subject to bias. This is different than exploratory subgroup analyses by baseline eosinophil level where there was a priori expectation of greater effects in patients with greater levels of eosinophils, there was enrichment by eosinophil level, and there was a planned emphasis on analyses within subgroups based on eosinophil level. Furthermore, even if an interaction between FeNO level and effects

of dupilumab were true, the clinical applicability and whether FeNO is clinically meaningful for asthma is still debated within the scientific literature. FeNO can be affected by smoking, viral respiratory infections, and various foods. How these confounding factors were controlled in your study is not clear, acknowledging that you did not enroll smokers. It is also not clear if FeNO was an independent factor in your study as FeNO is associated with eosinophils, despite the post-hoc analysis between eosinophilic subgroups and FeNO subgroups.

7.5.2.4.3.2. Change in FEV1 over time

The change from baseline in FEV1 over time showed significant differences compared to placebo as early as Week 3. The two dupilumab doses showed similar trends over time (Figure 1).

7.5.2.4.3.3. Time to First Severe Exacerbation

Kaplan-Meier analysis on the time to first severe exacerbation event during the 52-week treatment period in the ITT population showed that the dupilumab treatment groups had delayed exacerbation events compared to the placebo groups (Figure 17).

7.5.2.4.3.4. ACQ-5 and AQLQ

Responder rates for AQLQ and ACQ-5 were included as secondary endpoints. A responder analysis was conducted for change from baseline in AQLQ global score and ACQ-5 at Week 24, with a responder defined as a patient with change from baseline in AQLQ global score or ACQ-5 ≥0.5, which is considered the minimal clinically importance difference. For AQLQ, the responder rate for dupilumab 200 mg q2w was significantly higher than placebo (64% versus 57%, p=0.01). The responder rate for dupilumab 300 mg q2w was similar to placebo (66% versus 65%, p>0.05). For ACQ-5, the responder rate for dupilumab was significantly higher than placebo (76% for dupilumab 200 mg q2w, 73% for dupilumab 300 mg q2w, and 68% and 66% for matching placebo) with an odds ratio of 1.6 (nominal p=0.005) for dupilumab 200 mg q2w and 1.4 (nominal p=0.02) for the dupilumab 300 mg q2w group. The AQLQ and ACQ-5 responder rates were slightly higher in the higher eosinophil group (≥0.3 G/L) compared to the lower eosinophil group (<0.3 G/L).

7.5.2.4.3.5. Demographic and Baseline Characteristics Subgroup Analysis

Estimated effects for the primary endpoint, annualized event rate of severe exacerbation, on various subgroups were largely consistent across the subgroups (Figure 22). Of note, the reduction in the rate of severe exacerbation in the adolescent population (<18 years) was not statistically significant for either dose group (200 mg q2w: rate ratio 0.5, CI: 0.2, 1.2; 300 mg q2w 1.1, CI: 0.5, 2.7). However, the subgroup analyses in the adolescent population are subject to considerable uncertainty due to the small sample size (n=107 (6%)) resulting in very wide confidence intervals. Patients in both dupilumab dose groups showed significant improvement in pre-BD FEV1 endpoint in the adolescent subgroup (Figure 24).

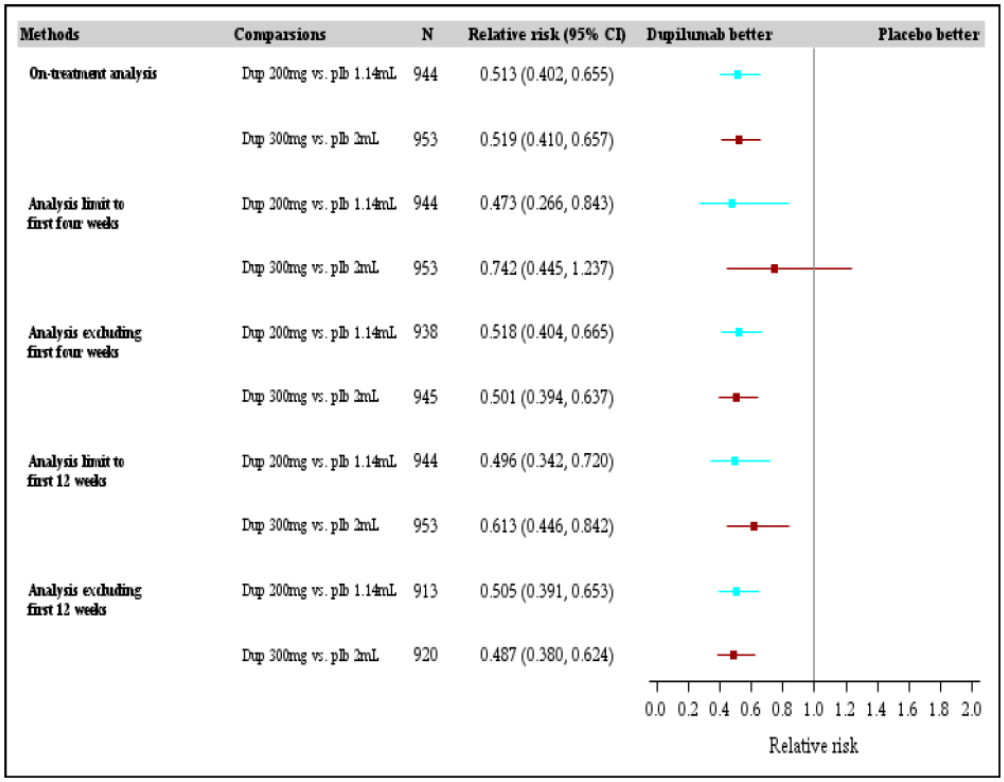
Other baseline characteristic subgroups analyzed for an effect on the annualized rate of severe exacerbation included FeNO, ICS dose level, ACQ-5 score, number of previous exacerbations, and age of onset of asthma (Figure 23). Lower FeNO (<25 ppm) showed a numerically lower effect than the higher FeNO levels (>25 ppm) as did earlier age of onset of asthma (<18 years of age) compared to later age (>18 years). Other baseline characteristics in both dupilumab doses demonstrated largely consistent improvement over the matching placebo. Similar trends were seen for change in baseline FEV1 (Figure 25).

7.5.2.4.3.6. Loading dose sensitivity analysis

The Division expressed concerns regarding the use of a loading dose for a chronic disease where a fast onset of action is typically not a priority. One concern was that efficacy endpoints may reflect the effects of the loading dose, making it unclear if observed clinical responses would be maintained during chronic use. The Division acknowledged that these issues did not apply to atopic dermatitis (where fast onset of action would be clinically meaningful), for which dupilumab was initially developed and which includes a loading dose.

To address these concerns, the Applicant conducted a sensitivity analysis to examine the influence of the loading dose on maintenance of dupilumab' s treatment effect on the annualized rate of severe exacerbation events over 52 weeks. The Applicant noted complete saturation of PD response within 4 weeks, with steady-state by week 12. The sensitivity analysis, therefore, excluded either the first 4 or 12 weeks of treatment, as summarized in Figure 9.

Figure 9. Study EFC13579: Loading Dose Sensitivity Analysis on Annualize Event Rate of Severe Exacerbation (ITT)



CI = confidence interval; Dup = dupilumab; plb = placebo
Source: SCS, Figure 23, page 168

The efficacy analysis that excluded the first 4 or 12 weeks was similar to the overall efficacy analysis, which is consistent with maintenance of efficacy beyond the effects of the loading dose.

7.5.2.4.4. Safety

7.5.2.4.4.1. Deaths

Nine deaths were reported during the study, with one death occurring 6 months after treatment discontinuation. Deaths are summarized in Table 19.

Table 19: Study EFC13579 Deaths (Safety Population)

	Placebo	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
N	**634**	**631**	**632**
Total	**3 (0.4%)**	**1 (0.1%)**	**5 (0.6%)**
PT			
Acute myocardial infarction	0	0	1
Anaplastic thyroid cancer	1	0	0

Table 19: Study EFC13579 Deaths (Safety Population)			
	Placebo	**Dupilumab 200 mg q2w**	**Dupilumab 300 mg q2w**
N	**634**	**631**	**632**
Total	**3 (0.4%)**	**1 (0.1%)**	**5 (0.6%)**
PT			
Cardiac failure congestive	0	0	1
Cardio-respiratory arrest	0	0	1
Suicide	1	0	0
Pulmonary embolism	1	1	0
Respiratory depression		0	1*
Hemorrhagic necrotic pancreatitis			1**

Counted by number of subjects
* One subject died of cardio-respiratory arrest and respiratory depression and was counted as respiratory depression only.
** Death occurred approximately 6 months after treatment discontinuation
PT = preferred term; q2w = once every 2 weeks
Source: Reviewer generated table in JMP using ADSL and ADAE datasets (TRT01A)

The incidence of death was similar between treatment (six, 0.4%) and placebo (three, 0.4%). There were four cardiovascular deaths (acute myocardial infarction, cardiac failure congestive, cardio-respiratory arrest, and pulmonary embolism) in the treatment group compared to one in placebo (pulmonary embolism).

7.5.2.4.4.2. SAEs

The SAEs for Study EFC13579 are summarized in Table 20.

Table 20: EFC13579 SAEs > Two Events in Combined Treatment Groups and > Placebo (Safety Population)				
SOC	**PT**	**Placebo N=634**	**Dupilumab 200 mg q2w N=631**	**Dupilumab 300 mg q2w N=632**
Subjects reporting SAEs		**53 (8.4%)**	**49 (7.8%)**	**55 (8.7%)**
Respiratory, thoracic and mediastinal disorders		16 (2.5%)	16 (2.5%)	12 (1.9%)
	Pulmonary embolism	1 (0.2%)	1 (0.2%)	1 (0.2%)
Infections and infestations		6 (0.9%)	0	5 (0.8%)
	Pneumonia	2 (0.3%)	0	4 (0.6%)
	Bronchitis	0	0	2 (0.3%)
Injury, poisoning and procedural complications		8 (1.3%)	3 (0.5%)	5 (0.8%)
	Fall	0	0	2 (0.3%)

Table 20: EFC13579 SAEs > Two Events in Combined Treatment Groups and > Placebo (Safety Population)

SOC	PT	Placebo N=634	Dupilumab 200 mg q2w N=631	Dupilumab 300 mg q2w N=632
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		6 (0.9%)	7 (1.1%)	5 (0.8%)
	Basal cell carcinoma	0	2 (0.3%)	1 (0.2%)
	Malignant melanoma	0	0	2 (0.3%)
	Adenocarcinoma of colon	0	1 (0.2%)	1 (0.2%)
Cardiac disorders		0	4 (0.6%)	10 (1.6%)
	Acute myocardial infarction	0	0	2 (0.3%)
	Cardio-respiratory arrest	0	0	2 (0.3%)
	Myocardial ischemia	0	1 (0.2%)	1 (0.2%)
Gastrointestinal disorders		2 (0.3%)	3 (0.5%)	6 (0.9%)
Nervous system disorders		4 (0.6%)	3 (0.5%)	2 (0.3%)
	Loss of consciousness	0	1 (0.2%)	1 (0.2%)
General disorders and administration site conditions		1 (0.2%)	1 (0.2%)	3 (0.5%)
	Chest pain	0	1 (0.2%)	1 (0.2%)
Hepatobiliary disorders		1 (0.2%)	2 (0.3%)	4 (0.6%)
	Cholecystitis	0	1 (0.2%)	1 (0.2%)
	Cholecystitis acute	0	0	2 (0.3%)
Vascular disorders		2 (0.3%)	1 (0.2%)	1 (0.2%)
	Hypertension	0	1 (0.2%)	1 (0.2%)
Pregnancy, puerperium and perinatal conditions		2 (0.3%)	0	2 (0.3%)
	Pregnancy	0	0	2 (0.3%)
Immune system disorders		0	2 (0.3%)	1 (0.2%)
	Anaphylactic reaction	0	1 (0.2%)	1 (0.2%)

*Not included in CSR table
PT = preferred term; q2w = once every 2 weeks; SAE = serious adverse event; SOC = system organ class
Source: Reviewer generated table in JMP using ADSL and ADAE datasets (SAFFL, TRT01A, TRTEMFL, AESER, PSOCFL, AEBODSYS, AEDECOD); CSR EFC13579 Table 61, pg. 287

The number of subjects reporting SAEs was similar across treatment groups. The most commonly reported SAE was asthma, with a higher rate in placebo compared to the two dupilumab treatment groups, which is expected. There were four SAEs within the Neoplasm system organ class (SOC) that occurred more commonly than placebo (uterine leiomyoma, basal cell carcinoma, malignant melanoma, adenocarcinoma of the colon), however when looking at

the overall preferred terms (PTs) in the Neoplasm SOC, these were similar between groups (0.9% placebo versus 1.1% dupilumab 200 mg and 0.8% dupilumab 300 mg). The imbalance in the dupilumab 200 mg group was mainly driven by two events of basal cell carcinoma.

There was a dose-dependent imbalance in cardiac events (zero placebo, four (0.6%) dupilumab 200 mg, 10 (1.6%) dupilumab 300 mg), which is further discussed in Review of Safety, Analysis of Submission-Specific Safety Issues.

7.5.2.4.4.3. AEs leading to discontinuation

Table 21: EFC13579 AEs Leading to Discontinuation, >2 Events in Combined Treatment Groups and > Placebo (Safety Population)

SOC	PT	Placebo N=634	Dupilumab 200 mg q2w N=631	Dupilumab 300 mg q2w N=632
Subjects reporting AEs		29 (4.6%)	19 (3.0%)	44 (7.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		5 (0.8%)	3 (0.5%)	3 (0.5%)
	Malignant melanoma	0	0	2 (0.3%)
Blood and lymphatic disorders		2 (0.3%)	2 (0.3%)	2 (0.3%)
	Eosinophilia	1 (0.2%)	1 (0.2%)	2 (0.3%)
Immune system disorders		0	0	3 (0.2%)
	Hypersensitivity	0	0	2 (0.2%)
Pregnancy, puerperium, and perinatal conditions		3 (0.5%)	1 (0.2%)	4 (0.6%)
	Pregnancy	3 (0.5%)	1 (0.2%)	4 (0.6%)
General disorders and administration site conditions		1 (0.2%)	4 (0.6%)	12 (2%)
	Injection site erythema	0	4 (0.6%)	10 (1.6%)
	Injection site pruritus	0	1 (0.2%)	6 (0.9%)
	Injection site edema	0	1 (0.2%)	5 (0.9%)
	Injection site inflammation	0	0	4 (0.6%)
	Injection site pain	0	2 (0.2%)	3 (0.5%)
Investigations		2 (0.3%)	4 (0.6%)	4 (0.6%)
	Blood creatinine phosphokinase increased	1 (0.2%)	3 (0.5%)	0

AE = adverse event; q2w = once every 2 weeks
Source: CSR EFC13579 Table 62, pg. 297

The adverse events leading to discontinuation occurred more frequently in the high-dose dupilumab group compared to placebo and the low-dose dupilumab group. The imbalance was

driven by injection-site reactions. The hypersensitivity and pregnancy imbalance will be discussed further in 7.7.5 Analysis of Submission-Specific Safety Issues.

7.5.2.4.4.4. Common Adverse Events

The Common AEs are summarized in Table 22.

Table 22: EFC13579 Common AEs, ≥3% Events in Either Treatment Groups and > Placebo (Safety Population)

PT	Placebo N=634	Dupilumab 200 mg q2w N=631	Dupilumab 300 mg q2w N=632
Any AE	527 (83%)	508 (81%)	515 (82%)
Injection site erythema	35 (6%)	76 (12%)	98 (16%)
Injection site edema	7 (1%)	23 (4%)	40 (6%)
Injection site pruritus	4 (1%)	21 (3%)	31 (5%)
Back pain	23 (4%)	30 (5%)	25 (4%)
Gastroenteritis	21 (3%)	10 (3%)	24 (4%)
Contusion	12 (2%)	10 (2%)	18 (3%)
Injection site pain	12 (2%)	20 (3%)	18 (3%)
Nasopharyngitis	12 (2%)	14 (2%)	18 (3%)
Oropharyngeal pain	10 (2%)	24 (4%)	18 (3%)
Eosinophilia	2 (<1%)	12 (3%)	17 (3%)
Diarrhea	15 (2%)	21 (3%)	15 (2%)

Source: CSR-EFC13579-16.2.7-EN, Table 16.2.7.1.4, page 166

Overall, the number of AEs across treatment groups was balanced. The most common AEs were injection-site reactions (erythema, edema, and pruritus), which were dose-dependent. Injection-site reactions are discussed further in Section 7.4.5 Analysis of Submission-Specific Safety Issues.

7.5.3. Study EFC13691

7.5.3.1. Administrative Information

- **Study title**: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma
- **Study dates:** October 15, 2015, to September 20, 2017
- **Study sites:** Argentina, Belgium, Brazil, Canada, Chile, Columbia, Hungary, Israel, Italy, Mexico, Netherlands, Poland, Romania, Russia, Spain, Ukraine, and United States
- **Study report date:** December 13, 2017

7.5.3.2. Objectives

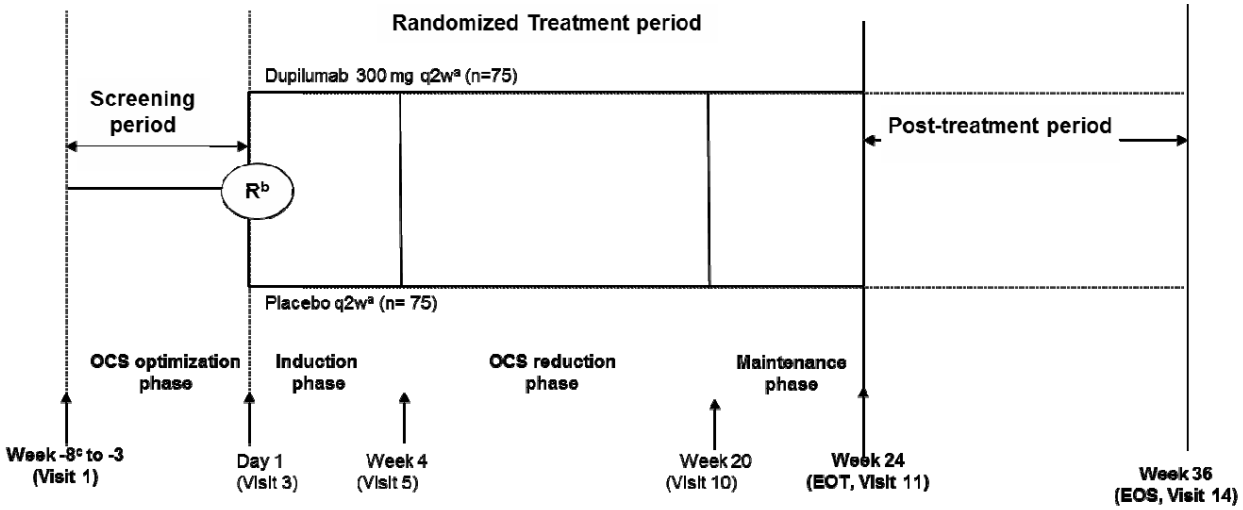
The primary objective of the study was to evaluate the efficacy of dupilumab, compared with placebo, for reducing the use of maintenance oral corticosteroids in patients with severe steroid-dependent asthma.

7.5.3.3. Study Design and Conduct

Study EFC13691 was a 24-week, randomized, double-blind, placebo-controlled study comparing dupilumab 300 mg every 2 weeks (with a 600 mg loading dose) administered SC to placebo as add-on therapy to maintenance OCS and high-dose inhaled corticosteroids with a second controller therapy in patients with severe persistent asthma. For the purposes of this review, the placebo groups were combined and treated as the same. Randomization was stratified by optimized OCS dose (≤10 mg/day and >10 mg/day) and by country.

The study schematic is shown in Figure 10.

Figure 10. Study EFC13691 Study Schematic



EOT = end of treatment; OCS = oral corticosteroids; q2w = once every 2 weeks
Source: Study EFC13691 Protocol, page 16

7.5.3.3.1. Procedures

The study consisted of three phases: screening (3 to 8 weeks), randomized treatment (24 weeks) that started with a 4-week induction phase where the optimized OCS dose was held stable, and post-treatment follow-up (12 weeks). The screening period was used to establish the level of asthma control and optimize the OCS dose.

A schedule of assessments is provided in Table 23.

Table 23: Schedule of Assessments

	Screening Period/ OCS Optimization Phase[a]		Randomized Treatment Period													Post-treatment Period		
			RND[b]	Induction Phase		OCS Reduction Phase								Maintenance Phase				
Week	-8 to -3	-7 to -2	0	2	4	6	8	10[c]	12	14[c]	16	18[c]	20	22[c]	24	28	32	36
Visit	1	2[d]	3	4	5	6	7		8		9		10		11/EOT	12	13	14
Informed consent	x																	
Inclusion/exclusion criteria	x	x	x															
Patient demography	x																	
Medical/surgical history	x																	
Reversibility[e]	x																	
Post-bronchodilator FEV_1			x						x						x			x
Spirometry[f]	x	x	x[g]	x	x	x	x		x		x		x		x	x	x	x
CXR (if none within previous year)[h]	x																	
Prior & concomitant meds[i]	x	x	x	x	x	x	x		x		x		x		x	x	x	x
Physical examination	x														x			
Randomization			x															
Call IVRS	x		x	x	x	x	x		x		x		x		x			x
Investigational product administration[j]			x	x	x	x	x	x	x	x	x	x	x	x				
Dispense or download e-diary/PEF meter[k]	x	x	x	x	x	x	x		x		x		x		x	x	x	x
Dispense/review home dosing diary							x		x		x		x		x			
ACQ[l]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
AQLQ	x		x						x						x			x
FeNO[m]	x	x	x	x	x	x	x		x		x		x		x	x	x	x
Vital signs[n]	x	x	x	x	x	x	x		x		x		x		x	x	x	x
OCS reduction criteria review[o]		x	x		x		x		x		x		x		x			
OCS dose adjustment[p]		x			x		x		x		x		x		x[q]			
ECG	x		x						x						x			x
Pregnancy test[r]	x		x		x		x		x		x		x		x			x
Clinical lab testing[s]	x		x		x		x		x		x		x		x			x
Urinalysis	x		x						x						x			x
Serum IEP (IgG, IgM, IgA)	x		x						x						x			x
PK sampling[t]			x	x	x		x		x		x				x			x
Anti-drug antibodies[u]			x		x		x		x						x			x
Pharmacodynamics/ biomarkers			x		x				x				x		x			
Archival serum[v]			x						x						x			
Pharmacogenetics: blood DNA and RNA (optional)			x															
SNOT-22[w]	x		x						x						x			x
HADS	x		x						x						x			x
EQ-5D-5L	x		x						x						x			x
Health resource utilization	x	x	x	x	x	x	x		x		x		x		x	x	x	x
AE/SAE recording	x	x	x	x	x	x	x		x		x		x		x	x	x	x
Optional assessments (for select study sites in Canada)																		
Sputum collection[x]			x												x			x
Methacholine challenge[y]			x												x			x

ACQ = Juniper Asthma Control Questionnaire; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; CXR = chest x-ray; ECG = electrocardiogram; EOT = end of treatment; EQ-5D-5L = o European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels; FeNO = Fractional exhaled nitric oxide; HADS = Hospital Anxiety and Depression Scale; IEP=; IVRS =; OCS = oral corticosteroids; PEF = peak expiratory flow; PK = pharmacokinetic; SAE = serious adverse event; SNOT = Sino Nasal Outcome Test

Source: EFC13691 Protocol, Figure 1.2, pg. 17

7.5.3.3.2. Patient Population

Key Inclusion Criteria

2. Asthma for ≥1 year per GINA 2014 guidelines and the following criteria:
    a. OCS use (Prednisone 5 to 35 mg/daily) for ≥6 months and stable for ≥4 weeks.
    b. High-dose ICS in combination with a second controller (e.g., LABA or leukotriene receptor antagonist) with or without a third controller for at least 3 months on a stable dose for ≥1 month.
    c. FEV1 80% predicted at screening and prior to randomization
    d. ACQ-5 ≥1.5 at screening and randomization
    e. Reversibility in FEV1 (12% and 200 mL) at screening or positive methacholine test within 12 months

Reviewer comment: This study differs from EFC13579 in that subjects were required to have severe persistent OCS dependent asthma, and the population was not enriched for severe asthma exacerbations. No lower bound limit was set for FEV1 criteria.

Key Exclusion Criteria

Exclusion criteria were similar to Study EFC13579 with the exception of exclusion subjects who required 12 puffs or more of rescue medication on any 1 day in the week prior to Visit 1.

Reviewer comment: The intent of the additional exclusion criteria was to improve OCS optimization.

7.5.3.3.3. Treatment

The following treatments were administered by SC injection once every 2 weeks.

1. Dupilumab 300 mg q2w (2 mL) after a 600 mg loading dose
2. Placebo (2 mL) after a loading dose (2 x 2 mL)

The dosing schedule was the same as in Study EFC13579 in regard to self-administration, monitoring and injection site.

As in studies DRI12544 and EFC13579, ICS and other controller use was recorded via an electronic diary.

7.5.3.3.3.1. Oral Steroids

Screening

The OCS dose was optimized to the lowest effective dose during screening. OCS dose was titrated (based on a pre-specified titration schedule (Table 24)) 1 week after the screening visit if the asthma was controlled (none of the OCS optimization phase interruption criteria were met). OCS dose continued to be decreased until at least one of the OCS optimization phase interruption criteria were met at which point the OCS dose was increased by one step. The decision to titrate was ultimately based on the investigator's clinical judgement.

Table 24: OCS Optimization Titration Schedule During Screening

Time course	OCS dose (mg/day)								
Starting dose (Visit 1)	35	30	25	20	15	12.5	10	7.5	5
Dose reduction (Visit 2)	30	25	20	15	12.5	10	7.5	5	2.5
+1 week	25	20	15	12.5	10	7.5	5	2.5	
+1 week	20	15	12.5	10	7.5	5	2.5		
+1 week	15	12.5	10	7.5	5	2.5			
+1 week	12.5	10	7.5	5	2.5				
+1 week	10	7.5	5	2.5					
+1 week	7.5	5	2.5						

OCS=oral corticosteroid

Source: EFC13691 protocol, Table 1, page 201

Reviewer comment: Basing the OCS titration decision on the investigator's clinical judgement was recommended by the Division so as to follow the practice of medicine.

OCS Optimization Phase Interruption Criteria

The lowest effective dose was defined as the lowest dose a patient could tolerate without experiencing any of the following:

- Increase in ACQ-5 of ≥0.5 from the last ACQ-5 score
- Severe asthma exacerbation
- Clinically significant event (based on investigator judgement) requiring treatment by OCS dose adjustment

Subjects were randomized once the lowest effective OCS dose was stable for 2 weeks. Subjects were considered screen failures if their OCS dose was titrated down to 2.5 mg or lower.

If asthma exacerbations occurred during screening, the screening period could be increased for up to 10 weeks to allow for 2 weeks of stabilization before randomization. Exacerbations were treated with at least double the maintenance OCS dose and then continued OCS treatment one step higher than the pre-exacerbation OCS dose.

Randomized Treatment

OCS titration started after the 4-week induction phase, with decreases occurring every 4 weeks, through Week 20, per Table 25.

Table 25: OCS Titration Schedule During the OCS Reduction Phase

Time course	OCS dose (mg/day)								
Optimized OCS dose	35	30	25	20	15	12.5	10	7.5	5
First dose reduction	25	20	15	10	10	10	5	5	2.5
+4 week	15	10	10	5	5	5	2.5	2.5	0
+4 week	10	5	5	2.5	2.5	2.5	0	0	
+4 week	5	2.5	2.5	0	0	0			
+4 week	2.5	0	0						

OCS=oral corticosteroid

Source: EFC13691 protocol, Table 2, page 202

The OCS dose was not decreased if any of the following were met:

- Change in ACQ-5 score ≥0.5 from the prior month OCS dose assessment
- Clinically significant asthma exacerbation(s)
- FEV1 20% reduction from baseline stability limit
- Mean morning peak expiratory flow <70% of baseline stability limit as assessed in the week prior to the clinical visit
- Rescue medication use requiring four or more puffs/day above the mean baseline value for any two consecutive days in the prior week, or ≥12 puffs on any 1 day in the week prior to the clinical visit
- Clinically significant event, based on investigator judgment that required treatment by OCS dose adjustment.

Severe exacerbations were treated with double the OCS dose for 3 to 7 days and then continued one step higher than the pre-exacerbation OCS dose. OCS titration was stopped if a second exacerbation occurred. The OCS dose stayed stable past Week 20 and into the long-term extension study.

7.5.3.3.4. Efficacy Endpoints

Primary

- Percent reduction of OCS dose at Week 24

Key Secondary

- Proportion of patients achieving an OCS dose reduction of ≥50% at Week 24
- Proportion of patients achieving an OCS dose <5 mg/day at Week 24

Other Notable Efficacy Variables:

- Annualized rate of severe exacerbation
- Time to first severe asthma exacerbation even
- Change from baseline in pre-BD FEV1

7.5.3.3.5. Efficacy Parameters

The definitions for severe exacerbation were the same as in studies DRI12544 and EFC13579 where increased OCS use was considered at least double the current dose.

7.5.3.3.6. Safety Parameters

Same as Study EFC13579

7.5.3.3.7. Statistical Analysis Plan

Same as Study EFC13579

7.5.3.3.8. Compliance with Good Clinical Practice

The study was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection. Compliance with these requirements also constitutes conformity with the ethical principles of the Declaration of Helsinki.

The Applicant certified that all clinical investigations in this sBLA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the United States conducted under IND 105379 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in GCP.

7.5.3.4. Study Results

7.5.3.4.1. Protocol Amendments

A total of seven amendments were made to the protocol, most occurring after the first patient entered the study. These spanned the 2-year study duration. Pertinent modifications included adding instructions to allow the investigator to stop the downward titration of OCS in case of a safety concern. The number of subjects was increased to 180 from 150 to increase the power of detecting a significant difference in the key secondary endpoint of patients achieving a 50% reduction in OCS dose from 74% to 81%. Subgroup analysis by baseline blood eosinophil count was added for the key secondary endpoints.

Reviewer Comment: The subgroup by baseline blood eosinophil count in OCS dependent subjects is not as relevant as in the non-OCS dependent subjects in Studies EFC13579 and DRI12577 as OCS use decreases eosinophils. The OCS dependent subject eosinophil level does not likely reflect the non-OCS eosinophil level.

7.5.3.4.2. Protocol Deviations

Twenty-two patients (21%) in the dupilumab groups and 19 (18%) in the placebo groups reported major protocol deviations. A sensitivity analysis was conducted excluding these patients for the primary efficacy endpoint, and results were consistent with the primary analysis.

The two most common major protocol deviations were (1) not being on a high-dose ICS, and/or (2) being on more than three controllers, which occurred in 17% of subjects on dupilumab and 15% on placebo. Other frequently reported major protocol deviations were not meeting reversibility in FEV1, positive methacholine challenge, or FEV1 <80% predicted. Overall the distribution was similar throughout the treatment groups and was therefore unlikely to affect the conclusions.

7.5.3.4.3. Efficacy

7.5.3.4.3.1. Disposition

Patient disposition is summarized in Table 26.

Table 26: Study EFC13691 Disposition

	Placebo	Dupilumab 300 q2w
Randomized	107 (100%)	103 (100%)
ITT	107 (100%)	103 (100%)
SAFFL	107 (100%)	103 (100%)
Completed study period	107 (100%)	102* (99%)
Completed study treatment	102 (95%)	101 (98%)
Discontinued	5 (5%)	2 (2%)
Adverse event	4 (4%)	1 (1%)
Other	1 (1%)	1 (1%)

*Discontinued study per patient request
ITT = intention to treat; q2w = once every 2 weeks
Source: Study CSR EFC13691, Table 11, pg. 65 and Table 8, page 60

The number of subjects who completed the study was generally balanced across treatment groups. There were slightly more subjects who discontinued due to adverse events in the placebo group compared to dupilumab.

7.5.3.4.3.2. Demographics

The baseline demographics are summarized in Table 27.

Table 27: Study EFC13691 Baseline Demographics (Randomized Population)

	Dupilumab 300 mg q2w		Placebo		Total	
N	103		107		210	
Sex	N	%	N	%	N	%
Female	62	60%	65	61%	127	61%
Male	41	40%	42	39%	83	40%
Race						
White	97	94%	100	94%	197	94%
Asian	4	4%	1	1%	5	2%
Black or African American	1	1%	2	2%	3	1%
Other	1	1%	2	2%	2	1%
American Indian or Alaska Native	0	0	2	2%	2	1%
Native Hawaiian or other Pacific Islander	1	1%	0	0	1	<1%
Age in Years						
Mean	52		51		51	
SD	13		13		13	
Min	15		15		15	
Max	77		77		77	
Age (years) in class, n (%)						
<18	1	1%	2	2%	3	1%
18 to 64	91	88%	88	82%	179	85%
65 or greater	10	10%	16	15%	26	12%
less than 18	1	1%	2	2%	3	1%

max = maximum; min = minimum; q2w = once every 2 weeks; SD = standard deviation
Source: Reviewer generated table in JMP using ADSL dataset without screen failures, Study EFC13691 CSR Table 11, page 65

Generally, the baseline demographics were balanced between treatment groups. Subjects had a mean age of 51 years, the were majority white (94%) and female (61%). Only 1% of subjects were less than 18 years old.

The baseline disease characteristics are summarized in Table 28.

Table 28: Study EFC13691 Baseline Demographics (Randomized Population)

	Placebo		Dupilumab 300 mg q2w		Total	
N	107		103		210	
Age at onset of asthma (yrs)						
Mean	32		31		31	
Std Dev	16		19		18	
Min	0		0		0	
Max	65		65		65	
Time since first diagnosis of asthma (yrs)						
Mean	19		21		20	
Std Dev	13		15		14	
Min	1		2		1	
Max	57		64		64	
Atopic hx	N	%	N	%	N	%
Yes	77	72%	74	72%	151	72%
Atopic Dermatitis	N	%	N	%	N	%
Yes	8	8%	8	8%	16	8%
Smoking hx						
Never	90	84%	79	77%	169	81%
Former	17	16%	24	23%	41	20%
FEV1 (L)						
Mean	1.6		1.5		1.6	
Std Dev	0.6		0.5		0.6	
Min	0.6		0.7		0.6	
Max	3.6		3.1		3.6	
Percent pred FEV1 (%)						
Mean	53		52		52	
Std Dev	15		15		15	
Min	21		18		18	
Max	81		96		96	
FEV1 reversibility (%)						
Mean	18		21		19	
Std Dev	23		24		23	
Min	-16		-24		-24	
Max	181		132		181	

Table 28: Study EFC13691 Baseline Demographics (Randomized Population)						
	Placebo		**Dupilumab 300 mg q2w**		**Total**	
N	107		103		210	
Num of Asthma Exacerbations in past yr*						
Mean	2		2		2	
Std Dev	2		2		2	
Min	0		0		0	
Max	12		12		12	
0	18	17%	21	20%	39	19%
1	31	29%	29	28%	60	29%
2	27	25%	24	23%	51	24%
3	17	16%	12	12%	29	14%
≥4	14	13%	17	17%	31	15%
ACQ-5						
Mean	3		2		3	
Std Dev	1		1		1	
Min	0		0		0	
Max	5		5		5	
AQLQ						
Mean	4		4		4	
Std Dev	1		1		1	
Min	2		1		1	
Max	7		7		7	
Blood Eosinophil (Giga/L)						
Mean	0.33		0.37		0.35	
Std Dev	0.30		0.32		0.31	
Min	0.00		0.00		0.00	
Max	1.52		1.83		1.83	
<0.3	66	62%	55	53%	121	58%
≥0.3	41	38%	48	47%	89	42%
Num of puffs of albuterol in 24 hours						
Mean	5		4		5	
Std Dev	7		4		6	
Min	0		0		0	
Max	42		23		42	
Controller medications						
Three controller medications	56	53%	56	54%	112	54%
ICS/LABA/LAMA	19	18%	24	23%	43	21%
ICS/LABA/Anti-leukotrienes	23	22%	25	24%	48	23%
Optimized oral corticosteroids (mg/day)						

Table 28: Study EFC13691 Baseline Demographics (Randomized Population)

	Placebo		Dupilumab 300 mg q2w		Total	
N	107		103		210	
Mean	12		11		11	
Std Dev	6		6		6	
Min	5		5		3	
Max	35		35		35	
<5	20	19%	20	19%	40	19%
5- 10	53	50%	49	48%	102	49%
10 to 15	15	14%	15	15%	30	14%
15 to 25	18	17%	15	15%	33	16%
>25	1	1%	4	4%	5	2%

ACQ = Juniper Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; FEV1 = forced expiratory volume in 1 second; hx = history; ICS = inhaled corticosteroids; LABA = long-acting beta agonist; LAMA = long-acting muscarinic antagonist; max = maximum; min = minimum; q2w = once every 2 weeks
Source: Reviewer generated table in JMP using ADSL dataset without screen failures, EFC13691 CSR, Table 13, pg. 68: Table 14, page 73; EFC13691: Table 15, page 77; Table 16, pg. 77

The baseline demographics were similar to the DRI12544 and EFC13579 studies except for the smaller amount of FEV1 reversibility (19% for EFC136791 compared to 26% for EFC13579 and 27% for DRI12544), an increase in the number of subjects with no asthma exacerbations in the past year (19% of subjects in EFC136791 did not have an exacerbation within in the past year compared to 0% for the other two studies that were enriched for exacerbations, although the majority of these patients fell into the one exacerbation per year group (29% EFC13691 and ~50% for DRI12544 and EFC13579)) despite the mean exacerbations per year being similar (mean of two per year), and higher mean albuterol puffs in 24 hours (five for EFC13691 compared to three for the other two studies). These differences are consistent with the intended patient population for this oral steroid sparing study in subjects with oral steroid dependent asthma.

7.5.3.4.3.3. Primary Endpoint

The primary endpoint of mean percent reduction in OCS dose at Week 24 was greater in the dupilumab group (least squares (LS) mean 70%) compared to placebo (LS mean 42%) with an absolute difference of 28% (95% CI: 16, 41) (Table 60).

7.5.3.4.3.4. Secondary Endpoint

The proportion of patients with a ≥50% reduction in OCS dose compared to baseline at Week 24 was significantly greater in the dupilumab group (80%) than in the placebo group (50%) (Table 61). The odds of a ≥50% reduction in the OCS dose was 3.9 times (95% CI: 2.1, 7.7) as high with dupilumab as compared to placebo ($p<0.001$).

The proportion of patients achieving a reduction in OCS dose to <5 mg/day at week 24 was significantly greater in the dupilumab group (70%) than in the placebo group (30%) (Table 62). The odds of OCS dose reduction were 4.5 times (95% CI: 2.4, 8.4) as high with dupilumab as compared to placebo ($p<0.001$).

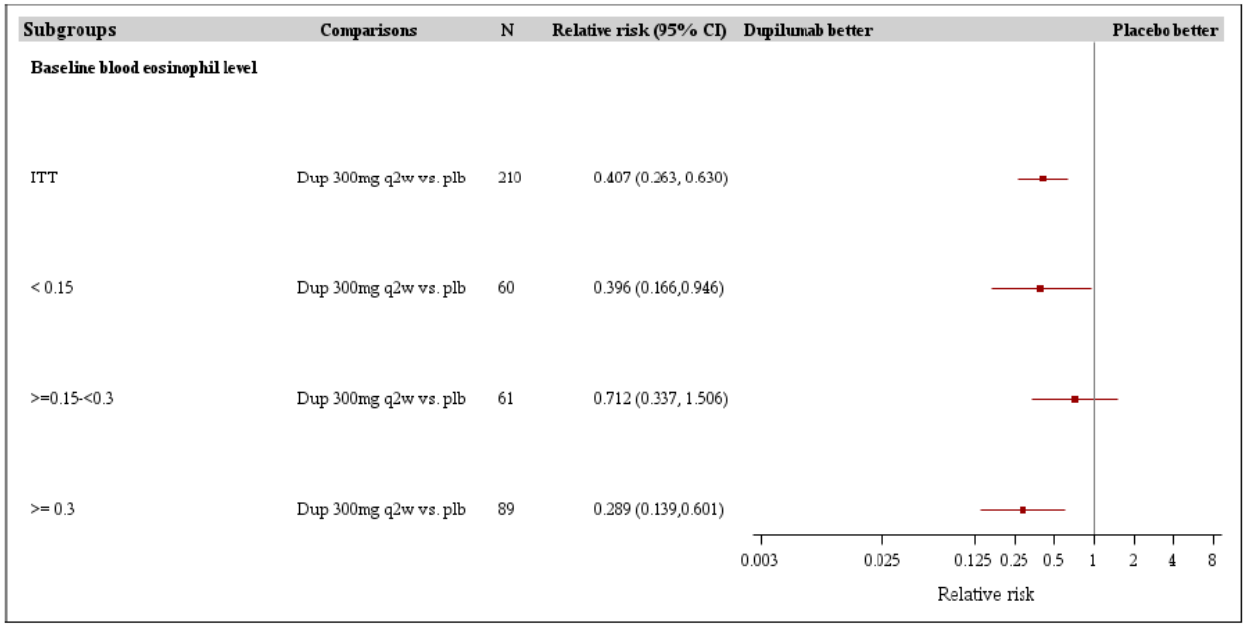
The dupilumab group also had a significant reduction in the annualized event rate of severe exacerbation compared to the placebo group (rate ratio: 0.41, CI: 0.26, 0.63) (Table 63).

In addition, the mean change in pre-BD FEV1 from baseline was significantly higher (Table 64) for the dupilumab group with a mean difference of 0.22 (CI: 0.09, 0.34).

Analysis by eosinophil subgroup for the efficacy endpoints did not demonstrate a clear correlation with eosinophil level as was seen in Studies DRI12544 and EFC13579. The percentage reduction of OCS dose across eosinophil subgroups is displayed below (Figure 29).

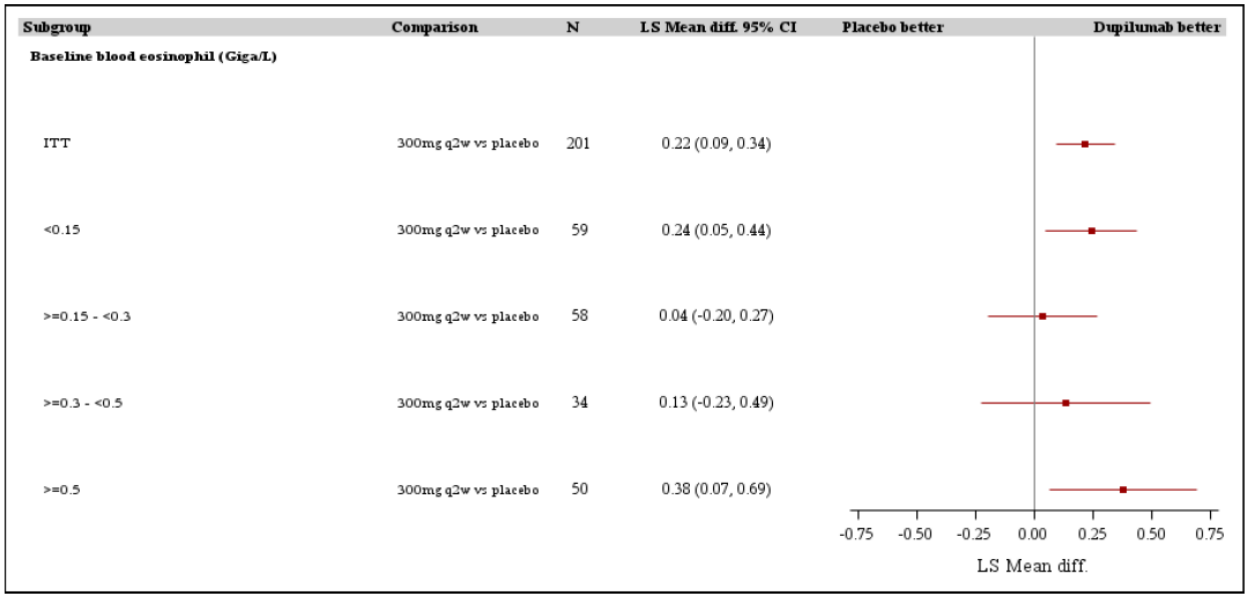
There was also no clear eosinophil dependence on exacerbation benefit (Figure 11) or on FEV1 benefit (Figure 12) in patients with oral steroid dependent asthma.

Figure 11. EFC13691: Relative Risk of Annualized Event Rate of Severe Exacerbation by Eosinophil (Giga/L) subgroups (ITT population)



Source: Sponsor's IR response dated June 18, 2018

Figure 12. EFC13691: Change from Baseline in Pre-BD FEV1 (L) at Week 24 by Eosinophil (Giga/L) subgroups (ITT population)



Source: Sponsor's IR response dated June 18, 2018

7.5.3.4.4. Safety

Percentages were not included in the safety tables for Study EFC13691 as the column totals were similar (except for the common adverse events for completeness).

7.5.3.4.4.1. Deaths

No deaths were reported.

7.5.3.4.4.2. SAEs

The SAEs for Study EFC13691 are summarized in Table 29.

Table 29: Study EFC13691 SAE (Safety Population)			
		Placebo N=107	**Dupilumab 300 mg q2w N=103**
Number of subjects with any SAE		**6 (6%)**	**9 (9%)**
SOC	**PT**	**No. adverse events**	
Blood and lymphatic system disorders	Eosinophilia	0	2
Infections and infestations	Pneumonia	0	1
	Respiratory tract infection	0	1
Injury, poisoning and procedural complications	Acetabulum fracture	0	1
	Foreign body aspiration	0	1
Metabolism and nutrition disorders	Type 2 diabetes mellitus	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Gastrointestinal stromal tumor	1	0
Respiratory, thoracic and mediastinal disorders	Asthma	3	3
	Asthmatic crisis	1	0
	Chylothorax	0	1
	Pneumonia aspiration	0	1
	Pneumothorax	0	2
	Pulmonary mass	0	1

PT = preferred term; SOC = system organ class
Source: Reviewer generated table in JMP using ADSL and ADAE dataset, AESOC and AEDECO, EFC13691 CSR, Table 62, pg. 166

The SAEs only occurred in one subject, with the exception of eosinophilia and pneuomothorax, which occurred in two subjects on dupilumab compared to zero on placebo. Asthma also occurred in more than one subject, but was balanced between the two treatment groups.

7.5.3.4.4.3. AEs leading to discontinuation

AEs leading to discontinuation are summarized in Table 30.

Table 30: Study EFC13691 AEs Leading to Discontinuation (Safety Population)		
	Placebo N=107	**Dupilumab 300 mg q2w N=103**
Number with any AE leading to discontinuation	4 (4%)	1 (1%)
PT	**No. adverse events**	
Adrenal insufficiency	1	0
Arthralgia	0	1
Asthmatic crisis	1	0
Eosinophilia	1	0
Gastrointestinal stromal tumor	1	0

PT = preferred term; q2w = once every 2 weeks
Source: Reviewer generated table in JMP using ADSL and ADAE dataset, AEDECO, EFC13691 CSR, Table 63, pg. 168

The AEs leading to discontinuation did not occur in more than one subject and generally occurred more commonly in placebo, except for arthralgia.

7.5.3.4.4.4. Common Adverse events

Common adverse events are summarized in Table 31.

Table 31: Study EFC13691 Common Adverse Events ≥2% and Greater in Dupilumab Group (Safety Population)

		Placebo N=107	Dupilumab 300 mg q2w N=103
No. with a common adverse event		**69 (65%)**	**64 (62%)**
SOC	**PT**	**No. adverse events**	
Infections and Infestations		45 (42%)	42 (41%)
	Bronchitis	6 (6%)	7 (7%)
	Sinusitis	4 (4%)	7 (7%)
	Lower respiratory tract infection	1 (1%)	4 (4%)
	Pharyngitis	2 (2%)	4 (4%)
	Upper respiratory tract infection	3 (3%)	4 (4%)
	Rhinitis	2 (2%)	3 (3%)
Blood and lymphatic system disorders			
	*Eosinophilia	1 (1%)	7 (7%)
Respiratory, thoracic and mediastinal disorders			
	Asthma	3 (3%)	4 (4%)
	Cough	1 (1%)	4 (4%)
Gastrointestinal disorders			
	Gastroesophageal reflux disease	1 (1%)	4 (4%)
	Nausea	2 (2%)	3 (3%)
Skin and subcutaneous tissue disorders			
	Pruritus	1 (1%)	3 (3%)
	Rash	1 (1%)	3 (3%)
Musculoskeletal and connective tissue disorders			
	Back pain	1 (1%)	5 (5%)
	Arthralgia	2 (2%)	3 (3%)
General disorders and administrative site conditions			
	Injection site pain	1 (1%)	5 (5%)

*Eosinophil count increased not listed as the results were the same as eosinophilia
PT = preferred term; q2w = once every 2 weeks; SOC = system organ class
Source: EFC13691 CSR, Table 61, pg. 163

Common adverse events were similar to studies DRI12544 and EFC13579. The most common adverse events were bronchitis and sinusitis, which occurred in 7% of subjects on dupilumab compared to 4% on placebo. Injection-site reactions were less common in this study (5%) than studies DRI12544 and EFC13579 (16 to 22%) perhaps due to the baseline oral steroid treatment.

7.6. Integrated Review of Efficacy

7.6.1. Disposition

The 6-month dose-ranging study in adults (Study DRI12544) enrolled 776 subjects, with 150 to 158 for each treatment arm (placebo and dupilumab 200 mg q4w, 300 mg q4w, 200 mg q2w, and 300 mg q2w. The 1-year efficacy and safety study in ≥12-year-olds (Study EFC13579) enrolled 1,902 subjects, with 631 to 638 subjects per treatment arm (placebo and dupilumab 200 mg and 300 mg q2w). The oral-steroid sparing study (Study EFC13691) enrolled 210 subjects, with 107 subjects enrolled in placebo and 103 subjects enrolled in the dupilumab 300 mg q2w treatment arm. Study completion rates were lower for Study EFC13579 (74 to 77%) than for Study DRI12544 and Study EFC13691 (88 to 95%) likely due to the longer study (1 year versus 6 months). For studies DRI12544 and EFC1357, the most common reason for study discontinuation was patient request. For Study EFC13691, the most common reason for study discontinuation was adverse event, but this only occurred in a small number of subjects (four (4%) dupilumab 300 mg q2w versus one (1%) placebo).

7.6.2. Demographics

Baseline demographics were balanced between groups for all three studies. The majority of subjects were white (78 to 94%), females (61 to 63%), with a mean age of 48 to 51 years. The next most common racial group was Asian (12 to 15% for studies DR12544 and EFC13579 and 2% for EFC13691). Study EFC13579 enrolled the highest number of subjects <18 years of age (107 (6%)). Study DRI12544 enrolled adults only and Study EFC13691 only enrolled 3 (1%) adolescents.

Baseline characteristics were balanced between groups for all three studies. For studies DRI12544 and EFC13579, the average age at onset of asthma was 27 years. The majority (77 to 83%) of subjects had an atopic history and never smoked (78 to 81%). The mean FEV1 was 1.8 L (58 to 61% predicted, which is within the 40 to 80% as determined by the inclusion criteria), with 26 to 27% reversibility. About half of subjects had one exacerbation within the past year, with a mean of two exacerbations per year for the total population. Medium- and high-dose ICS/LABA baseline use was split about evenly. About 56 to 60% of subjects were considered HEos with a blood eosinophil count of ≥0.3 G/L. The mean blood eosinophil count was 0.35 to 0.36 G/L. Mean ACQ-5 and AQLQ scores were 3 and 4, respectively. This is consistent with the inclusion criteria of ACQ-5 ≥1.5, which indicates not well-controlled asthma. The mean number of puffs of rescue short-acting BD (albuterol) per day was three. The population enrolled was consistent with moderate-to- severe asthma based on based on NHLBI guidelines. The moderate-to-severe asthma population differs from the severe asthma population that was enrolled in the anti-IL-5 studies. Depending on the anti-IL5 study, subjects could be on baseline oral corticosteroids, had to have 2 or more exacerbations, and were enriched for high blood eosinophil levels.

The oral steroid sparing study (EFC13691) had slight differences in the baseline characteristics. The FEV1 was lower (1.6 L with 52% predicted), as was the FEV1 reversibility (19%). Although

the mean number of exacerbations in the past year was the same (two), the study was not enriched for exacerbations, which lead to 39 (19%) of subjects not having any exacerbations within the past year. The number of albuterol puffs was also increased to five per day. Overall, the baseline characteristics of the subjects enrolled in EFC13691 reflected more severe disease which is expected for an oral-steroid dependent asthma population.

7.6.3. Primary Endpoints

The dose-ranging study (DRI12544) showed a significant treatment difference in change from baseline at Week 12 in FEV1 for the primary analysis population of high eosinophils (≥0.3 G/L), for the both the 200 mg (0.26 L (95% CI: 0.11, 0.40) and 300 mg q2w (0.21 L (95% CI: 0.06, 0.36) dosing regimens, without a clear dose effect.

The 1-year efficacy study (EFC13579) demonstrated a significantly lower annualized exacerbation event rate and significantly improved change from baseline in FEV1 at Week 12 for both doses compared to placebo, without a clear dose effect, in the overall population (primary analysis population). Both doses showed about a 50% reduction in the annualized exacerbation event rate compared to placebo during the 1-year study period (200 mg q2w: rate ratio: 0.52, 95% CI: 0.41, 0.66; 300 mg q2w: rate ratio: 0.54, CI: 0.43, 0.68). Change from baseline in FEV1 at Week 12 in the overall population was significantly improved for both dupilumab doses, with similar mean treatment differences for both dose groups (200 mg q2w: 0.14 L (95% CI: 0.08, 0.19), 300 mg q2w: 0.13 L (95% CI: 0.08, 0.18), relative to the respective matching placebo group.

The OCS-sparing study (Study EFC13591) demonstrated a significant reduction in the mean percent OCS dose at Week 24 for dupilumab 300 mg q2w compared to placebo with an absolute difference of 28% (95% CI: 16, 41).

7.6.4. Secondary and Other Endpoints

For the dose-ranging study (DRI12544), the annualized rate of exacerbation over the 6-month treatment period for the HEos group (≥0.3 G/L) also demonstrated a significantly lower event rate compared to placebo for both the 200 mg q2w (rate ratio: 0.29 (95% CI: 0.22, 0.76)) and 300 mg q2w groups (rate ratio: 0.19 (95% CI: 0.07, 0.56).

The OCS sparing study (EFC13691) also showed a significant reduction in the annualized event rate of severe exacerbation in the 300 mg q2w dupilumab group compared to the placebo (rate ratio: 0.41; CI: 0.26, 0.63) and in the mean change in pre-BD FEV1 from baseline (treatment difference of 0.22 (CI: 0.09, 0.34).

For the dose-ranging study (DRI12544), change in FEV1 from baseline in Week 12 and the annualized rate of exacerbation were significantly improved in the overall population. However,

eosinophilic subgroup analysis for subjects with eosinophils <0.15 G/L for the 200 mg and 300 mg q2w dose groups did not demonstrate significant improvement compared to the placebo group for either endpoint. Therefore, the ITT population results were driven by the HEos subgroup.

For the 1-year efficacy study (EFC13579), change in FEV1 from baseline in Week 12 and the annualized rate of exacerbation had slightly larger improvements in the HEos (≥0.3 G/L) population compared to the overall population; however, neither endpoint was significant for the <0.3 G/L eosinophil group.

For the OCS-sparing study (EFC13691), no clear effects based on eosinophil subgroup were seen, likely due to the eosinophil lowering effects of OCS use.

For the adolescent population (12 to <18 years of age), both dose groups showed significant improvement in the change from baseline in FEV1 at Week 12. The rate of severe exacerbation was not statistically significant for either dose group; however, the subgroup analyses in the adolescent population are subject to considerable uncertainty due to the small sample size (n=107 (6%)) resulting in very wide confidence intervals.

The change from baseline in FEV1 over time showed significant differences compared to placebo as early as Week 3. For the two doses carried forward into the 1-year study the trends were similar over time. All dosing regimens showed a significant improvement in FEV1 from baseline at Week 24. Similar results were seen for Study EFC13579.

Time to first severe exacerbation for Study EFC13579 showed that the both the 200 mg q2w and 300 mg q2w dupilumab groups had delayed exacerbation events compared to placebo.

Both the ACQ-5 and AQLQ responder rates favoured dupilumab for both studies DRI12544 and EFC13579, with higher response rates in the HEos (>0.3 G/L) population compared to the lower eosinophil group (<0.3 G/L).

7.6.5. Integrated Assessment of Effectiveness

The efficacy of both dupilumab doses (200 mg q2w and 300 mg q2w) was demonstrated for the add-on maintenance treatment of moderate-to-severe asthma in subjects ≥12 years of age with an eosinophilic phenotype. Efficacy for the 200 mg q2w and 300 mg q2w dosing regimens were similar without a clear dose response which supported approval of both the 200 mg q2w and the 300 mg q2w doses for moderate-to-severe asthma. The 6-month dose-ranging and 1-year efficacy study demonstrated a statistically significant difference in the change from baseline in FEV1 at Week 12 and the annualized rate of severe exacerbation for the high eosinophil population. Efficacy was not demonstrated for either endpoint for the <0.15 G/L eosinophil subgroup in the 6-month study (DRI12544). Efficacy was also not demonstrated for the <0.3 G/L eosinophil subgroup for either endpoint in the 1-year study (EFC13579). The lack of efficacy

within the lower eosinophil populations supports the indication of asthma with an eosinophilic phenotype. No clear effect of eosinophil level was demonstrated in the oral-steroid sparing study (EFC13691) likely due to the eosinophil lowering effects of OCS, therefore the eosinophilic phenotype limitation does not clearly apply to oral corticosteroid dependent asthma. Efficacy is further supported by a consistent change from baseline in FEV1 over time for both the 6-month and 1-year efficacy studies, a delayed time to first exacerbation for the 1-year study, and favorable ACQ-5 and AQLQ responder rates compared to placebo. Furthermore, dupilumab significantly reduced OCS use in the 6-month OCS sparing study.

7.7. Integrated Review of Safety

7.7.1. Safety Review Approach

7.7.2. Review of the Safety Database

The 6-month dose-ranging study (DRI12544), the 1-year study (EFC13579), and the 6-month OCS-sparing study (EFC13691) were evaluated for safety under each individual protocol in Section 7.5. Dose-effect on safety was evaluated both in the dose-ranging study and in the 1-year efficacy study, which included the two highest doses from the dose-ranging study. In addition, safety is supported by findings from the open-label extension Study LTS12551, which is reviewed separately in Section 7.7.6.1. The review tools used to conduct independent reviewer analyses included JMP Clinical, JMP, JReview and the clinical investigator site selection tool. Safety issues identified a priori include injection-site reactions and hypersensitivity reactions based on potential pharmacologic mechanism of action.

The safety for the 6-month dose-ranging study (DRI12544) and the first 6 months of the 1-year study (EFC13579) were pooled as the study populations and treatment arms were similar. The 6-month safety pool is reviewed in this section.

Overall Exposure

The overall exposure for the dupilumab program is summarized in Table 32.

Table 32: Studies DRI12544, EFC13579, and EFC3691: Overall Exposure

	Placebo N=899	Dupilumab 200 mg q2w N=779	Dupilumab 300 mg q2w N=891
DRI12544			
Number	158	148	156
Mean (SD)	162 (26)	162 (27)	162 (29)
Min:Max	14:175	14:176	14:180
EFC13579			
Number	634	631	632
Mean (SD)	341 (70)	340 (74)	333 (84)
Min:Max	14:444	14:395	14:405
EFC13691			
Number	107		103
Mean (SD)	165 (18)		166 (18)
Min:Max	14:181		28:178
Exposure categories, n (%)			
>4 weeks	888 (99%)	768 (99%)	878 (99%)
>8 weeks	883 (98%)	758 (97%)	859 (96%)
>12 weeks	876 (97%)	751 (96%)	853 (96%)
>16 weeks	866 (96%)	744 (96%)	844 (95%)
>24 weeks	674 (75%)	627 (80%)	655 (74%)
>36 weeks	577 (64%)	577 (74%)	562 (63%)
>44 weeks	568 (63%)	567 (73%)	550 (62%)
>52 weeks	177 (20%)	192 (25%)	158 (18%)

q2w = once every 2 weeks
Source: Study DRI12544 CSR, Table 50, page 216; EFC13579 Table 57, page 269; EFC13691, Table 58, page 159

The exposure was balanced across treatment groups for all three studies. A total of 1,117 subjects were treated with dupilumab for at least 44 weeks.

Adequacy of the safety database:

Overall, the safety database is of sufficient size and duration for moderate-to-severe asthma to assess the safety of the proposed doses of dupilumab given the previous safety support for the approved indication of atopic dermatitis.

7.7.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this supplemental BLA. Office of Scientific Investigations audits of sites No. 840112 and No. 840020 for Study EFC13579 and sites No. 616001 and No. 840014 for Study EFC13691 did not reveal any substantial issues related to data integrity.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events and serious adverse events in the protocols. AEs were captured from signing of informed consent through the final follow up visit.

Treatment emergent adverse events were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the final follow-up visit. AEs were coded using the MedDRA dictionary version 17.1.

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

7.7.4. Safety Results

7.7.4.1. Deaths

Seven deaths occurred in the 6-month safety pool, as summarized in Table 33.

Table 33: Study DRI12544 and EFC135679 Deaths (6 Month Safety Pool)

	Placebo	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Group size	**N=792**	**N=779**	**N=788**
Deaths	**3 (0.4%)**	**0**	**4 (0.6%)**
PT	**n**	**n**	**n**
Acute myocardial infarction	0	0	1
Anaplastic thyroid cancer	1	0	0
Cardiac failure congestive	0	0	1
Cardio-respiratory arrest	0	0	1
Suicide	1	0	0
Pulmonary embolism	1	0	0
Respiratory depression		0	1*

*Counted by number of subjects. One subject died of cardio-respiratory arrest and respiratory depression and was counted as respiratory depression only.
PT = preferred term; q2w = once every 2 weeks
Source: Reviewer generated table in JMP using ADSL and ADAE datasets (TRT01A) – verified with Applicant's table ISS appendix 1.9, Table 1.9.2.4, pg. 7982-7963: differed by pulmonary embolism event which occurred on Day 179 and was therefore included in this table.

The number of deaths was low and generally similar between dupilumab and placebo. An imbalance in MACE events was noted for Study EFC13579 and will be included in the prescribing information. Cardiac deaths are reviewed in more detail in Section 7.7.5.1.

7.7.4.2. Serious Adverse Events

Serious adverse events are summarized in Table 34.

Table 34. Study DRI12544 and EFC135679 SAEs Greater Than Placebo (6-Month Safety Pool)

	Placebo N=792	Dupilumab 200 mg q2w N=779	Dupilumab 300 mg q2w N=788
Number with any SAE	35 (4.4%)	28 (3.6%)	35 (4.4%)
SOC PT		**No. adverse events**	
Blood and lymphatic system disorders	1 (0.1%)	0	2 (0.3%)
Eosinophilia	0	0	2 (0.3%)
Cardiac disorders	0	2 (0.3%)	5 (0.6%)
Acute myocardial infarction	0	0	1 (0.1%)
Atrioventricular block second degree	0	0	1 (0.1%)
Cardiac failure congestive	0	0	1 (0.1%)
Cardio-respiratory arrest	0	0	2 (0.3%)
Coronary artery disease	0	1 (0.1%)	0
Tachyarrhythmia	0	1 (0.1%)	0
Congenital, familial and genetic disorders	0	1 (0.1%)	0
Sickle cell anemia	0	1 (0.1%)	0
Gastrointestinal disorders	2 (0.3%)	1 (0.1%)	1 (0.1%)
Colitis	0	1 (0.1%)	0
Pancreatitis acute	0	0	1 (0.1%)
General disorders and administration site conditions	0	0	3 (0.4%)
Chest pain	0	0	1 (0.1%)
Impaired healing	0	0	1 (0.1%)
Injection site erythema	0	0	1 (0.1%)
Injection site inflammation	0	0	1 (0.1%)
Injection site edema	0	0	1 (0.1%)
Hepatobiliary disorders	1 (0.1%)	1 (0.1%)	1 (0.1%)
Cholecystitis	0	1 (0.1%)	0
Cholecystitis acute	0	0	1 (0.1%)
Immune system disorders	0	2 (0.3%)	1 (0.1%)
Anaphylactic reaction	0	1 (0.1%)	1 (0.1%)
Anaphylactic shock	0	1 (0.1%)	0
Infections and infestations	9 (1.1%)	4 (0.5%)	12 (1.5%)
Abscess	0	0	1 (0.1%)
Chronic sinusitis	0	0	1 (0.1%)
Clostridium difficile colitis	0	0	1 (0.1%)
Epiglottitis	0	1 (0.1%)	0 (0.0%)
Gastroenteritis	1 (0.1%)	0	2 (0.3%)
Mastoiditis	0	1 (0.1%)	0
Medical device site infection	0	0 (0.0%)	1 (0.1%)
Otitis media	0	1 (0.1%)	0
Pneumonia	2 (0.3%)	0	4 (0.5%)
Post procedural cellulitis	0	1 (0.1%)	0
Pyelonephritis	0	0	1 (0.1%)
Sinusitis	0	1 (0.1%)	0
Injury, poisoning and procedural complications	5 (0.6%)	2 (0.3%)	3 (0.4%)
Contusion	0	0	1 (0.1%)
Facial bones fracture	0	0	1 (0.1%)
Fall	0	0	1 (0.1%)
Foot fracture	0	1 (0.1%)	0
Multiple injuries	0	1 (0.1%)	0
Procedural intestinal perforation	0	0 (0.0%)	1 (0.1%)

Table 34. Study DRI12544 and EFC135679 SAEs Greater Than Placebo (6-Month Safety Pool)

	Placebo N=792	Dupilumab 200 mg q2w N=779	Dupilumab 300 mg q2w N=788
Number with any SAE	35 (4.4%)	28 (3.6%)	35 (4.4%)
SOC PT	**No. adverse events**		
Investigations	0	1 (0.1%)	1 (0.1%)
Alanine aminotransferase increased	0	1 (0.1%)	0
Blood pressure increased	0	0	1 (0.1%)
Musculoskeletal and connective tissue disorders	0	2 (0.3%)	1 (0.1%)
Costochondritis	0	1 (0.1%)	0
Myalgia	0	1 (0.1%)	0
Pathological fracture	0	0	1 (0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4%)	2 (0.3%)	1 (0.1%)
Basal cell carcinoma	0	0	1 (0.1%)
Rectal adenocarcinoma	0	1 (0.1%)	0
Uterine leiomyoma	0	1 (0.1%)	0
Nervous system disorders	2 (0.3%)	2 (0.3%)	2 (0.3%)
Loss of consciousness	0	1 (0.1%)	1 (0.1%)
Sciatica	0	1 (0.1%)	0
Pregnancy, puerperium and perinatal conditions	0	0	2 (0.3%)
Pregnancy	0	0	2 (0.3%)
Psychiatric disorders	1 (0.1%)	0	2 (0.3%)
Anxiety	0	0	1 (0.1%)
Depression	0	0	1 (0.1%)
Reproductive system and breast disorders	0	1 (0.1%)	0
Ovarian cyst	0	1 (0.1%)	0
Respiratory, thoracic and mediastinal disorders	12 (1.5%)	9 (1.2%)	9 (1.1%)
Dyspnea	0	1 (0.1%)	0
Eosinophilic pneumonia chronic	0	0	1 (0.1%)
Laryngeal edema	0	1 (0.1%)	0
Nasal polyps	0	0	1 (0.1%)
Non-infective bronchitis	0	1 (0.1%)	0
Pleurisy	0	0	1 (0.1%)
Pneumothorax spontaneous	0	0	1 (0.1%)
Respiratory depression	0	0	1 (0.1%)

Eosinophilia = blood eosinophils >3.0 G/L
PT = preferred term; q2w = once every 2 weeks; SAE = serious adverse event; SOC = system organ class
Source: Reviewer generated table in JReview (SAFFL, first 6 months): verified with Applicant table ISS-appendix 1.9, Table 1.9.2.1, pg. 7934-7941

The only SAEs that occurred in more than one subject in the dupilumab treatment arms were cardio-respiratory arrest (2), gastroenteritis (2), pregnancy (2), and pneumonia (4).

The imbalance in cardiac events was driven by Study EFC13579 and was not seen in Study DRI12544. Further details regarding this imbalance are provided in Section 7.7.5.1. Anaphylaxis is also discussed further in Section 7.7.5.2 Anaphylaxis.

7.7.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to discontinuation for the 6-month safety pool are summarized in Table 35.

Table 35: Study DRI12544 and EFC135679 AEs Leading to Discontinuation, n≥2 in Any Group and Greater Than Placebo (6 Month Safety Pool)

	Placebo	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Group size	**N=792**	**N=779**	**N=788**
No. with any AE Leading to D/C	21 (2.7%)	19 (2.4%)	39 (4.9%)
		No. adverse events	
Eosinophilia	1 (0.1%)	0	3 (0.4%)
Injection site erythema	0	4 (0.5%)	12 (1.5%)
Injection site inflammation	0	0	5 (0.6%)
Injection site edema	0	1 (0.1%)	7 (0.9%)
Injection site pain	0	1 (0.1%)	5 (0.6%)
Injection site pruritus	0	2 (0.3%)	7 (0.9%)
Hypersensitivity	0	0	2 (0.3%)
Alanine aminotransferase increased	1 (0.1%)	3 (0.4%)	0
Blood creatinine phosphokinase increased	0	3 (0.4%)	0
Pregnancy	2 (0.3%)	0	3 (0.4%)

AE = adverse event; D/C = discontinuation; ISS =; q2w = once every 2 weeks
Eosinophilia = blood eosinophils >3.0 G/L
Source: Reviewer generated table in JReview (SAFFL, first 6 months): verified with Applicant table ISS-appendix 1.9, Table 1.9.2.1, pg. 7912-7917

The most common adverse event leading to discontinuation was injection-site reactions. Overall injection-site reactions were responsible for 5% (n=36) of treatment discontinuations for the 300 mg q2w dupilumab group and 1% (n=8) of the treatment discontinuations for the 200 mg q2w dupilumab group compared to 0 for placebo.

7.7.4.4. Common AEs

Common adverse events leading for the 6-month safety pool are summarized in Table 36.

Table 36: Study DRI12544 and EFC135679 Common AEs, ≥1% in Any Group and Greater Than Placebo (6-Month Safety Pool)

	Placebo	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Group size	**N=792**	**N=779**	**N=788**
No. with any AE	528 (67%)	522 (67%)	553 (70%)
		No. adverse events	
Injection-site reactions	70 (9%)	181 (23%)	256 (32%)
Headache	43 (5%)	44 (6%)	44 (6%)
Back pain	17 (2%)	27 (4%)	25 (3%)
Nasopharyngitis	9 (1%)	9 (1%)	15 (2%)
Oropharyngeal pain	7 (1%)	13 (2%)	19 (2%)
Eosinophilia	2 (<1%)	17 (2%)	16 (2%)
Myalgia	8 (1%)	8 (1%)	14 (2%)

Injection-site reactions included erythema, edema, pruritus, pain, and inflammation. Erythema was the most common (39 (5%), 93 (12%), and 128 (16%), respectively).
Eosinophilia = blood eosinophils >3.0 G/LAE = adverse event; q2w = once every 2 weeks
Source: Reviewer generated table in JReview (SAFFL, first 6 months): verified with Applicant table ISS-appendix 1.9, Table 1.9.1.4, pg. 7749-7792

Overall, adverse events were similar across treatment groups. A dose-related effect was noted for injection-site reactions. The common adverse events table in the prescribing information differs from this table as this table represents number of events, and the prescribing information reflects number of subjects.

7.7.4.5. Laboratory Findings

Eosinophilia

Eosinophils increased in subjects treated with dupilumab compared to placebo across the asthma clinical studies. Over time eosinophils returned close to baseline. The Applicant hypothesizes that this is due to the reduction of lung eosinophils, which results in an increase in serum eosinophils. This is based on a 4-week mouse house dust-mite study where dupilumab completely prevented lung eosinophil infiltration, which was associated with a trend toward an increase in eosinophils in the blood.

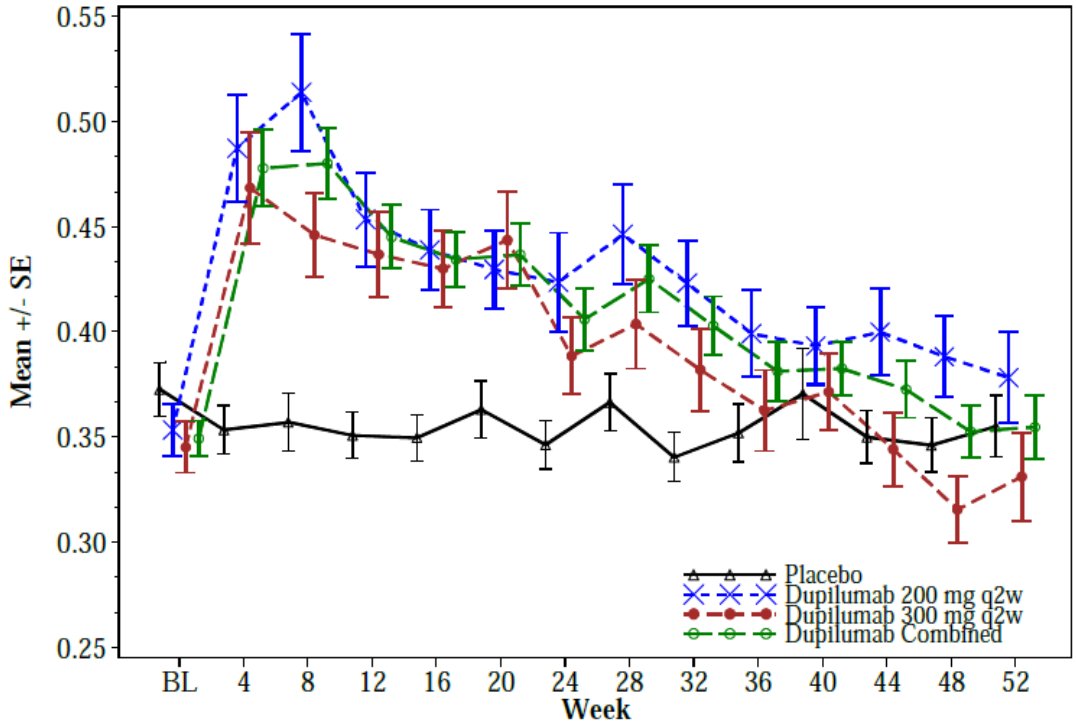
IL-4 and IL-13 are involved in eosinophil recruitment and migration (Gessner 2005, Pope 2001). Eosinophils also release IL-4 and IL-13 and contain the IL-4 receptor (Gessner, Corren, Steinke). The known effects of IL-4 and IL-13 on eosinophils support the Applicant's hypothesis that blocking recruitment and migration of serum eosinophils into tissue could increase the number of serum eosinophils.

Conversely, other biologics approved for asthma include anti-IL5. IL-5 is also involved in eosinophil migration and recruitment. IL-5 also promotes the release of eosinophils from the bone marrow and specifically promotes survival and migration (Pope 2001). Thus, anti-IL-5 would lead to the abatement of bone marrow eosinophil recruitment, and decreased eosinophil survival may explain why antil-IL5 causes a drop in serum eosinophilia.

Results

For studies EFC13579 and DRI12544 (200 and 300 mg q2w only), the mean eosinophil count over time is shown in Figure 13.

Figure 13. Studies EFC13579 + DRI12544 (200 and 300 mg q2w Only) Over Time (Pooled Safety Population): Mean Eosinophil Count (Giga/L) Over Time



# subjects														
Placebo	791	760	752	743	732	716	705	565	563	555	551	544	531	464
Dupilumab 200 mg q2w	778	752	731	725	720	705	698	564	555	561	555	553	542	452
Dupilumab 300 mg q2w	788	766	725	726	727	707	697	557	540	542	539	532	522	450
Dupilumab Combined	1566	1518	1456	1451	1447	1412	1395	1121	1095	1103	1094	1085	1064	902

BL = baseline; q2w = once every 2 weeks; SE =
Source: ISS Appendices Page 3147, Figure 1.5.1.2.12

In the dupilumab treatment groups, the eosinophilia peak occurred around 4 weeks and slowly decreased to close to baseline at the end of the 52-week study. The increase in eosinophil count did not appear to be dose dependent. The mean baseline eosinophilia was 0.25 giga/L, which increased to a mean of 0.48 giga/L by Week 4 (mean change from baseline 0.13 giga/L). By Week 52, the mean eosinophilia was 0.36 giga/L with a mean change from baseline of 0.11 giga/L.

In the long-term extension study (LTS12551), the mean eosinophil counts increased in the first 4 months (after at least a 14-week treatment free period). By Week 72, eosinophil counts returned to baseline.

Subjects were excluded from the clinical studies (with the exception of DRI12544) for eosinophilia greater than 1.5 giga/L. Eosinophilia AEs were reported for elevations above 3.0 giga/L. For studies EFC13579 and DRI12544 (200 and 300 mg q2w only), more subjects on

dupilumab had a blood eosinophilia greater than 5.0 giga/L (1.1%) compared to placebo (0.4%). Eosinophilia AEs were reported in 53 (3.4%) of dupilumab treated subjects compared to 4 (0.5%) on placebo.

In the OCS withdrawal study (EFC13691) the difference in subjects reporting blood eosinophilia greater than 5.0 giga/L was slightly greater (2.9% in dupilumab versus 0.9% in placebo) likely due to the increased dose of OCS in the placebo group compared to dupilumab. This was also seen in the eosinophilia AEs, which occurred in 14 (13.6%) of dupilumab subjects versus 1 (0.9%) on placebo.

The long-term safety study (LTS12551) showed 0.2% of subjects with >5.0 giga/L in eosinophilia at any time, with 28 (1.4%) of subjects reporting eosinophilia AEs. This is consistent with the gradual decline in eosinophils over time.

Several eosinophilia related AEs were reported in all three studies (Table 37). In the 120-day safety update, three additional cases of eosinophilic granulomatosis with polyangiitis were identified. Two cases were from Study EFC13579 (300 mg q2w dupilumab), with one subject who rolled over to the open-label study, and the other was from Study EFC13691 (also rolled into the open-label study).

Table 37: Studies DRI12544, EFC13579, and EFC13691: Eosinophilia Related AEs

Group size	Placebo N=899	Dupilumab 300 mg q4w N=157	Dupilumab 200 mg q2w N=779	Dupilumab 300 mg q2w N=891	Dupilumab Total N=1827
PT			**No. Adverse Events**		
Chronic eosinophilic pneumonia				1 (0.1%)	1 (0.1%)
Pneumonitis				1 (0.1%)	1 (0.1%)
EGPA	1 (0.1%)	1 (0.6%)		3 (0.3%)	4 (0.2%)
Worsening of hypereosinophilia				1 (0.1%)	1 (0.1%)
Myositis				1 (0.1%)	1 (0.1%)
Myalgia and arthralgia (same pt)				1 (0.1%)	1 (0.1%)

EGPA =; eosinophilic granulomatosis with polyangiitis; pt = patient; q2w = once every 2 weeks
Source: Each study CSR and the 120-day safety update

The cases of adverse events from eosinophilia are concerning, specifically the four cases of eosinophilic granulomatosis with polyangiitis (EGPA) for subjects on dupilumab compared to one subject on placebo. The Applicant notes that EGPA can be uncovered with reduced oral steroid therapy. The prescribing information will include the cases of eosinophilic pneumonia and EGPA to inform prescribers of this risk.

7.7.4.6. Vital Signs

Blood pressure, heart rate, respiratory rate, and weight were included as safety parameters. No relevant mean changes from baseline were observed.

7.7.4.7. Electrocardiograms (ECGs)

ECGs were assessed in all three studies. Overall, none of ECG parameters showed a clinically relevant trend towards increase or decrease over time.

7.7.5. Analysis of Submission-Specific Safety Issues

7.7.5.1. Cardiac SAE imbalance in EFC13579

There was a dose-dependent imbalance in cardiac SAEs (zero placebo, four (0.6%) dupilumab 200 mg, 10 (1.6%) dupilumab 300 mg) in Study EFC13579. This imbalance was not seen in any other asthma study. Based on this imbalance, the Applicant performed a blinded external adjudication of potential cardiovascular events by an expert independent panel of cardiologists. The Applicant provided an Adjudication Committee Charter that outlined their algorithm used to identify potential MACE events and a listing of all events referred for adjudication. The Applicant also notes a cardiovascular imbalance was not seen in the atopic dermatitis studies.

The Applicant collected pre-treatment and treatment-emergent SAEs by primary SOC/PTs associated with the cardiac disorders SOC, the vascular disorders SOC, and the central nervous system SOCs, as well as all deaths, regardless of cause or timing for Study EFC13579. This query identified 30 subjects with 37 events sent to the adjudicators for a blinded review, including the 14 SAEs in the cardiac disorders SOC, one pre-treatment event in the cardiac disorders SOC, and 15 cases from the additional search criteria mentioned above. One case of myocardial ischemia in the dupilumab 200 mg treatment group was not able to be adjudicated. The results of the adjudicated subjects are listed in Table 38. The adjudicated events were also evaluated for major adverse cardiovascular events, MACE + hospitalization of unstable angina (with or without urgent revascularization), and cardiovascular death. The results of this analysis are also shown in Table 38.

Table 38: Study EFC13579 Potential Cardiovascular Events or Death by Blinded Independent Adjudication Results, Including MACE Analysis (Safety Population)

Group size	Placebo N=634	Dupilumab 200 mg q2w, N=631	Dupilumab 300 mg q2w, N=632	Dupilumab, N=1263
Adjudication category/PT		**No. events**		
CV death (N)*	**1 (0.2%)**	**0**	**3 (0.5%)**	**3 (0.2%)**
Pulmonary embolism	1 (0.2%)	0	0	0
Cardio-respiratory arrest	0	0	1 (0.2%)	1 (0.2%)
Acute MI	0	0	1 (0.2%)	1 (0.2%)
Cardiac failure congestive	0	0	2[1] (0.3%)	2[1] (0.3%)
Ventricular tachycardia	0	0	1[1] (0.2%)	1[1] (0.2%)
Multiple organ dysfunction syndrome	0	0	1[1] (0.2%)	1[1] (0.2%)
Cardiac failure acute			1 (300 q4)	
Non-fatal MI*	**0**	**1 (0.2%)**	**1 (0.2%)**	**2 (0.2%)**
Acute coronary syndrome	0	1 (0.2%)		1 (0.2%)
Acute MI	0	0	2[2] (0.3%)	2[2] (0.3%)
Non-fatal stroke*	**1 (0.2%)**	0	0	**0**
Ischemic stroke	1 (0.2%)	0	0	0

Table 38: Study EFC13579 Potential Cardiovascular Events or Death by Blinded Independent Adjudication Results, Including MACE Analysis (Safety Population)

Group size	Placebo N=634	Dupilumab 200 mg q2w, N=631	Dupilumab 300 mg q2w, N=632	Dupilumab, N=1263
Adjudication category/PT		**No. events**		
MACE (CV death + non-fatal MI + non-fatal stroke)	**2 (0.3%)**	**1 (0.2%)**	**4 (0.6%)**	**5 (0.4%)**
Unstable angina (with and without urgent revascularization)	0	0	**1 (0.2%)**	**1 (0.2%)**
Angina pectoris	0	0	1 (0.2%)	1 (0.2%)
MACE + hospitalization for unstable angina (with or without revascularization)	**2 (0.3%)**	**1 (0.2%)**	**5 (0.8%)**	**6 (0.5%)**
Non-fatal CV event	**2 (0.3%)**	**2 (0.3%)**	**2 (0.3%)**	**4 (0.3%)**
Syncope	2 (0.3%)	0	1 (0.2%) (1 300 q4)	1 (0.2%)
Coronary artery disease	0	1 (0.2%)	0	1 (0.2%)
Loss of consciousness	0	1 (0.2%)	1 (0.2%)	2 (0.2%)
Metastatic gastric cancer			1 (300 q4)	
Organizing pneumonia			1 (300 q4)	
Cor pulmonale acute			1 (300 q4)	
Non-CV death (N)	**2 (0.3%)**	**1 (0.2%)**	**2 (0.3%)**	**3 (0.2%)**
Suicide	1 (0.2%)	0	0	0
Anaplastic thyroid cancer	1 (0.2%)	0	0	0
Pulmonary embolism	0	1 (0.2%)	0	1 (0.2%)
Cardio-respiratory arrest	0	0	1[3] (0.2%)	1[3] (0.2%)
Respiratory depression	0	0	1[3] (0.2%)	1[3] (0.2%)
Hemorrhagic necrotic pancreatitis	0	0	1[4] (0.2%)	1[4] (0.2%)
Abdominal sepsis	0	0	1[4] (0.2%)	1[4] (0.2%)
Arrhythmia w/out ischemia	0	0	**2 (0.3%)**	**2 (0.3%)**
AV block 2nd degree	0	0	1 (0.2%)	1 (0.2%)
AV block complete			1 (200 q4)	
Atrial fibrillation	0	0	1 (0.2%)	1 (0.2%)
Venous thromboembolism	0	0	**1 (0.2%)**	**1 (0.2%)**
Pulmonary embolism	0	0	1 (0.2%) (1 300 q4)	1 (0.2%)

Table 38: Study EFC13579 Potential Cardiovascular Events or Death by Blinded Independent Adjudication Results, Including MACE Analysis (Safety Population)

Group size	Placebo N=634	Dupilumab 200 mg q2w, N=631	Dupilumab 300 mg q2w, N=632	Dupilumab, N=1263
Adjudication category/PT		**No. events**		
Non-CV event	**1 (0.2%)**	**3 (0.5%)**	**3 (0.5%)**	**6 (0.5%)**
Migraine	1 (0.2%)	0	0	0
Tachyarrhythmia	0	1 (0.2%)	0	1 (0.2%)
Sciatica	0	2[5] (0.3%)	0	2[5] (0.3%)
Headache	0	1 (0.2%)	0	1 (0.2%)
Wolff-Parkinson-White Syndrome	0	0	1 (0.2%)	1 (0.2%)
Myocardial ischemia	0	0	1 (0.2%)	1 (0.2%)
Ischemic cardiomyopathy	0	0	1 (0.2%)	1 (0.2%)

1, 2, 3, 4, 5: applied to same patient x 5
CV = cardiovascular; MACE = major adverse cardiovascular event; MI = myocardial infarction; PT = preferred term
Source: CSR EFC13579 Displays of adverse events 15.3.1, Table 13 page 172

Based on the 37 adjudicated adverse events in 30 subjects, the MACE analysis showed an increase in the high-dose dupilumab (300 mg) treatment group with four (0.6%) subjects compared to two (0.3%). The low-dose dupilumab treatment group showed less MACE than placebo. There were also more cardiovascular deaths in the high-dose dupilumab group (three (0.5%)) compared to placebo (one (0.2%). Overall, although the MACE analysis showed an imbalance favor placebo, the events were low.

Two myocardial ischemia events could be characterized as MACE events. One of these (in the dupilumab 200 mg q2w group) was not able to be adjudicated, and the other was adjudicated as a non-CV event, as it was categorized as non-cardiac chest pain. If these were characterized as MACE events, then the total dupilumab group events increase by two, bringing the total to seven (0.6%, with two (0.3%) in the 200 mg q2w group, and five (0.8%) in the 300 mg q2w group). Regardless, MACE events were more numerous with dupilumab than with placebo (two, 0.3%).

For the DRI12544 study, in the dupilumab treatment groups there were one CV death (cardiac failure acute: 300 mg q4w), three non-fatal CV events (metastatic gastric cancer, organizing pneumonia, and cor pulmonale acute in the 300 mg q4w treatment arm all in the same subject), and 1 arrhythmia without ischemia event (atrioventricular block complete in the dupilumab 200 mg q4w). For the MACE analysis, this would add one event in the 300 mg q4w group.

The Applicant also conducted a MACE analysis by patient-years for Study EFC13579, the combined EFC13579 + DRI12544 safety pool, and a safety pool for all asthma studies (ACT11457 + DRI12544 + EFC13579 + EFC13691), which were all consistent with the by-event results for Study EFC13579. Prior to the 120-day safety update, the long-term extension study (LTS12551) was also included in a MACE analysis and showed one (0.9%) event in a previously placebo treated subject and no cardiovascular deaths.

The 120-day safety update included three additional SAEs reported in subjects who were previously on dupilumab (myocardial ischemia, myocarditis, and acute coronary syndrome). No subjects died. These patients were not included in the adjudicated cases; however, based on the

narratives, both the myocardial ischemia and acute coronary syndrome would be considered MACE.

Total cholesterol was evaluated in Study EFC13579. More subjects in the dupilumab 300 mg q2w treatment group had total cholesterol levels higher than 7.74 mmol/L (or 300 mg/dL) (42/630 (6.7%)) compared to placebo (35/630 (5.6%)). The number of subjects with elevated cholesterol was similar in the dupilumab 200 mg q2w treatment arm compared to placebo. Triglycerides, HDL, and LDL were not evaluated. The increased cholesterol in the dupilumab 300 mg q2w treatment group was low and likely did not have a major impact on the increased cardiovascular events in the dupilumab 300 mg q2w treatment group compared to placebo.

Overall, the concern for the imbalance in SAE is low given that this imbalance was isolated to the EFC13579 study, it was not seen in the other asthma studies or the atopic dermatitis program, and the MACE analysis showed a low number of events. The MACE results will be included in Section 6 of the prescribing information to inform prescribers of this risk.

7.7.5.2. Anaphylaxis

Given the known risk of anaphylaxis for biologics and the higher incidence in the atopic study populations, anaphylaxis was included as an adverse event of special interest. Anaphylaxis was identified based on a narrow SMQ query. The anaphylaxis events are summarized in Table 39.

Table 39: Anaphylaxis Events for Studies DRI12544, EFC13579

Treatment group	**Placebo**	**Dupilumab 200 mg q2w**	**Dupilumab 300 mg q2w**
Group size	**N=792**	**N=779**	**N=788**
Event		**No. events**	
Total	0	2 (0.3%)	2 (0.3%)
Anaphylactic reaction	0	1 (0.1%)*	2 (0.3%)**
Anaphylactic shock	0	1 (0.1%)$	0

*bee sting
** one event occurred 4 months after last dose after eating grapes; other subject with reaction during injection and had previous history of anaphylaxis to lebrikizumab
$ with IV contrast 14 days after last dose
q2w = once-every-2-weeks
Source: SCS Table 32, page 148;

Four episodes of anaphylaxis were reported in the DRI12544 and EFC13579 studies. Two of these occurred in the 300 mg dupilumab group, and two occurred in the 200 mg dupilumab group. No cases were reported in placebo. One of the anaphylaxis episodes in the low-dose group was considered anaphylactic shock. No events were reported in Study EFC13691.

Based on review of the narratives, this reviewer agrees that the four identified cases were anaphylaxis. Three of the four reactions likely had other triggers for the event as follows:

1. Anaphylaxis occurred within minutes of a bee sting with a history of bee sting allergy
2. Anaphylaxis occurred four months after dupilumab discontinuation. The subject attributes it to grapes. She did not report a previous allergy to grapes, but did have other food allergies. She self-administered epinephrine.
3. Anaphylaxis occurred within minutes of receiving iodine contrast for a computed tomography scan.

Given the clear association with other triggers (bee string, food allergen four months after dupilumab dose, intravenous contrast) it is likely that only one of these can be attributed to dupilumab.

7.7.5.3. Hypersensitivity

Given the known risk of hypersensitivity for antibody products and the higher incidence in the atopic study populations, hypersensitivity was included as an adverse event of special interest. Hypersensitivity was identified based a narrow SMQ query. The hypersensitivity events for studies EFC13579 and DRI12544 (300 q2w and 200 q2w only) are summarized in Table 40.

Table 40. Study EFC13579 and DRI12544 Hypersensitivity Events (Safety Population)

Group size	Placebo N=792	Dupilumab 200 mg q2w, N=779	Dupilumab 300 mg q2w, N=788
No. with hypersensitivity events	**20 (2.5%)**	**23 (3.0%)**	**34 (4.3%)**
SOC/PT	**No. hypersensitivity events**		
Eye disorders	**0**	**1 (0.1%)**	**1 (0.1%)**
Eyelid edema	0	0	1 (0.1%)
Conjunctivitis allergic	0	1 (0.1%)	0
Respiratory, thoracic and mediastinal disorders	**2 (0.3%)**	**0**	**0**
Allergic pharyngitis	1 (0.1%)	0	0
Bronchospasm	1 (0.1%)	0	0
Skin and subcutaneous tissue disorders	**12 (1.5%)**	**20 (2.6%)**	**28 (3.6%)**
Urticaria	5 (0.6%)	4 (0.5%)*	10 (1.3%)
Rash	1 (0.1%)	5 (0.6%)	4 (0.5%)
Rash pruritic	3 (0.4%)*	3 (0.4%)*	4 (0.5%)
Erythema nodosum	0	0	3 (0.4%)
Dermatitis	1 (0.1%)	0	2 (0.3%)
Dermatitis allergic	0	2 (0.3%)	1 (0.1%)
Angioedema	0	2 (0.3%)	1 (0.1%)
Dermatitis atopic	0	0	1 (0.1%)
Pruritus allergic	0	0	1 (0.1%)
Rash maculo-papular	0	1 (0.1%)	1 (0.1%)
Drug eruption	1 (0.1%)	0	0
Idiopathic urticaria	1 (0.1%)	1 (0.1%)	0
Rash generalized	0	1 (0.1%)	0
Urticaria chronic	0	1 (0.1%)	0
General disorders and administration site conditions	**1 (0.1%)**	**1 (0.1%)**	**0**
Face edema	1 (0.1%)	1 (0.1%)	0
Investigations	**0**	**0**	**1 (0.1%)**
Skin test positive	0	0	1 (0.1%)

*AEs leading to discontinuation: Rash pruritic (2 placebo and 1 dupilumab 200 mg); Urticaria (1 dupilumab 200 mg)
AE = adverse event; PT = preferred term; q2w = once every 2 weeks; SOC = system organ class
Source: SCS, Table 32, page 148

Hypersensitivity events were higher in the 300 mg dupilumab (34 (4.3%) and 200 mg dupilumab (23 (3.0%)) groups compared to placebo (20 (2.5%)) and were dose-dependent. The most frequent hypersensitivity event was urticaria, with similar incidences in the 200 mg dupilumab group (4 (0.5%)) compared to placebo (5 (0.6%)), and higher incidence in the 300 mg dupilumab group (10 (1.3%)). The majority of hypersensitivity adverse events did not lead to treatment discontinuation, with only four events leading to discontinuation with a similar incidence between dupilumab groups and placebo (rash pruritic (two placebo and one dupilumab 200 mg); urticaria (one dupilumab 200 mg).

For Study EFC13691 hypersensitivity (rash) was reported for two patients (1.9%) in the dupilumab group and one patient (1.0%) in the placebo group

7.7.5.4. Injection-Site Reactions

For studies EFC13579 and DRI12544 (300 q2w and 200 q2w only), injection-site reactions occurred more commonly in dupilumab treated subjects (283 (18%)) than placebo (71 (9.0%)) and was dose related (125 (16%) for 200 mg q2w and 158 (20%) for 300 mg q2w). Study EFC13691 also showed a higher frequency of injection-site reactions for dupilumab (9%) compared to placebo (4%). The most common injection site adverse event was erythema. Injection-site reactions were dose dependent and were most common after the loading dose.

In the long-term safety study (LTS12551), injection-site reactions were reported at a lower incidence (9% for rollover from studies DRI12544 and EFC13579 and 4% for subjects who rolled over from EFC13691, which includes the 120-day safety update). Subjects who were previously treated with placebo had a higher incidence of injection-site reactions than patients previously treated with dupilumab (30% versus 16% for Study DRI12544 and 7% versus 4% for Study EFC12544 before the 120-day safety update). This supports that injection-site reactions were most common with the first (loading) dose.

Injection reactions that were SAEs or serious (and lasted longer than 24 hours) occurred in 13 (0.8%) of subjects Studies DRI12544 and EFC12579 compared to 0 events in placebo. One event was an SAE in the 300 mg dupilumab treatment group in Study EFC13579 as the size of the rash increase to 6.5 cm after 5 days and dupilumab was permanently discontinued. In the 6-month DRI12544 and EF13579 safety pool, Thirty-six (4.6%) subjects discontinued due to injection-site reactions on dupilumab compared to none in placebo.

7.7.5.5. Infections

In the studies EFC13579 and DRI12544 (300 q2w and 200 q2w only), infection and infestation AEs were slightly increased in the combined dupilumab group (32 (2.0%)) or 35 (2.2) per 100 patient-years (PY) compared to placebo (13 (1.6%) or 13 (1.8) per 100 PY) with the increased drive by the 300 mg dupilumab group (24 (3.0%) or 24 (3.3) per 100 PY) and not the 200 mg dupilumab group (8 (1.0%) or 8 (1.1) per 100 PY). SAEs of infection and infestation were similar with 25 (1.6%) in the combined treatment group compared to 12 (1.5%) in the placebo group, however, there was a higher frequency in the 300 mg dupilumab group (19 (2.4%)) compared to the 200 mg dupilumab dose group (6 (0.8%)).

One subject died due to abdominal sepsis, although the triggering event was hemorrhagic necrotic pancreatitis that occurred 6 months after the last dose of dupilumab; however acute pancreatitis and cholecystitis occurred while on dupilumab and was the reason for early discontinuation of dupilumab (after ~ 5 months of therapy). A similar number of subjects discontinued due to an infection or infestations AE across treatment groups.

The most common infection or infestation AE was pneumonia, with the highest incidence in the 300 mg dupilumab group (five (0.6%)) compared to two (0.3%) in placebo and zero in the 200 mg dupilumab treatment arm. Gastroenteritis and bronchitis were the only other two AEs that occurred more than once and were higher in the dupilumab group compared to placebo.

In Study EFC13691 two (1.9%) subjects (pneumonia, pneumothorax, chylothorax for one patient; respiratory tract infection for the other) reported severe or serious infections compared to one (0.9%; pneumonia) for placebo. These events were considered SAEs but did not lead to treatment discontinuation or death.

The long-term open-label safety study had a similar infection rate (32 (1.7%)) compared to the dupilumab arms in the controlled studies through the 120-day safety update cut off.

Parasitic infections were reported in one subject on dupilumab and one on placebo in Study EFC13579 outside of the 6-month safety pool. The subject on 300 mg of dupilumab was a 43-year-old from Brazil who experienced acrodermatitis (human scabies sarcoptes scabiei) and was treated with Ivermectin and temporarily discontinued dupilumab until recovery. The subject on placebo was a 15-year-old from Argentina who reported parasitic gastroenteritis from giardia lamblia. Investigational treatment was not discontinued, and the subject recovered with appropriate therapy.

Opportunistic infection AEs were reported based on the investigator checking the box of infection type “opportunistic.” Opportunistic infections were reported less frequently in the dupilumab treatment group (four (0.3%): herpes zoster, streptococcus pneumonia, viremia, parotitis) compared to placebo (six (0.8%)): five AEs of herpes zoster and one of varicella zoster). None of the cases of herpes zoster were disseminated. Two subjects on placebo with herpes zoster discontinued the investigational product. In Study DRI12544, two additional opportunistic infection of subcutaneous abscess on antecubital left arm in the 200 mg q4w treatment arm and erysipelas of the right leg in the 300 mg q4w treatment group were reported. If we add this to the dupilumab treatment arm (total of six (0.4%), the incidence is still lower than placebo (six 0.8%).

For Study LTS12551,five (0.3%; pneumonia x 2, herpes zoster, mycobacterium avium complex, and salmonellosis) subjects reported opportunistic infections. Four of the five subjects were previously on dupilumab.

7.7.5.6. Hepatic disorders

Hepatic disorders in studies EFC13579 and DRI12544 (300 q2w and 200 q2w only) occurred at a similar incidence in dupilumab treated subject (26 (1.7%) or 28 (1.9) per 100 PY) compared to placebo (14 (1.8%) or 18 (2.5) per 100 PY). The most common AE was alanine aminotransferase increased (18 (1.1%) dupilumab versus 13 (1.6%) placebo). No dose-related increase was noted between the 300 mg q2w and 200 mg q2w treatment groups. No hepatic AEs led to death. One

event in the 200 mg q2w group was an SAE. Less AEs lead to discontinuation in the dupilumab group (three (0.2%)) compared to placebo (three (0.4%)).

In Study EFC13691, hepatic AEs were lower in the dupilumab group (one (1%)) compared to placebo (four (3.7%)).

In Study LTS12551, 15 (0.8%) of subjects reported hepatic AEs, including the 120-day safety update. None were serious or severe.

No cases met Hy's law criteria within the asthma program.

7.7.5.7. Pregnancy

Pregnancies for studies DRI12544 and EFC13579 are summarized in Table 41. Study EFC13691 did not report any pregnancy events.

Table 41: Study EFC13579 and DRI12544 Pregnancy Events (Safety Population)

Group size	Placebo N=792	Dupilumab 200 mg q2w N=779	Dupilumab 300 mg q2w N=788
Total N	4 (0.5%)	6 (0.8%)	6 (0.8%)
SOC/PT		**No. events**	
Abortion spontaneous		2	
Induced Abortion		1	1
Turner's Syndrome			1
Ectopic pregnancy	1		
Ongoing	1	1	1
Healthy live births	2	2	3

Two subjects in the dupilumab 200 mg q2w treatment group were pregnant prior to study enrollment
One subject who had a healthy live birth in the 300 mg q2w treatment group had twins
PT = preferred term; q2w = once every 2 weeks; SOC = system organ class
Source: SCS, page 176

Sixteen subjects reported pregnancies in the asthma clinical studies. Twelve were treated with dupilumab (0.8%) and four (0.5%) were on placebo. Overall, the incidence of harmful outcomes (spontaneous abortion and Turner's syndrome) were higher in dupilumab (three (0.2%)) compared to placebo (zero); however, the number of healthy lives births was similar in dupilumab (five (0.3%)) compared to placebo (two (0.3%)).

An additional two pregnancies were reported in the 200 mg q4w (elective abortion) and 300 mg q4w (spontaneous abortion) treatment groups. Three pregnancies were reported in Study LTS12551. One lead to a healthy live birth and the other two were spontaneous abortions. No additional pregnancies were reported in the 120-day safety update. A pregnancy registry was included in the atopic dermatitis approval.

7.7.5.8. Malignancy

In studies EFC13579 and DRI12544 (300 q2w and 200 q2w only) the incidence of malignancies was lower in the dupilumab group (five (0.6%) in each of the dupilumab groups) compared to placebo (seven (0.9%)). Malignancy melanoma, adenocarcinoma of the colon, basal cell carcinoma, gastrointestinal submucosal tumor occurred in more than one subject and at a higher incidence than placebo. The most common malignancy adverse event was basal cell carcinoma (three (0.2%) dupilumab versus one (0.2%) placebo). The patient-year analysis for the combined safety of Studies DRI12544 and EFC13579 also showed a lower incidence of malignancy AEs in the dupilumab treatment groups (0.7 for each) compared to placebo (1.0). One subject treated on placebo died from anaplastic thyroid cancer.

In Study EFC13691, one (0.9%) subject in the placebo group had gastrointestinal stroma tumor. In Study LTS12551, subjects enrolled in the DRI12544 or the EFC13579 studies had 12 (0.7%) subjects reporting malignancies. The per-100 PY risk was higher in the dupilumab group compared to placebo in the subjects rolled over from Study DRI12544 (8.2 versus 2.2) but was similar for the subjects who rolled over from Study EFC13579 (3.3 versus 1.6). One (0.7%) subject previously on placebo who rolled over from Study EFC13691 had basal cell carcinoma. No additional malignancy AEs were reported in the 120-day safety update.

7.7.6. Specific Safety Studies/Clinical Trials

7.7.6.1. Study LTS12551

Study LTS12551 was a multinational, multicenter, 2-year open-label extension study evaluating dupilumab 300 mg q2w as add-on therapy to ICS/LABA therapy or other acceptable controller therapies as stabilized during the parent study.

Study LTS12551 was initiated on August 5, 2015. At the time of the interim data cut date (January 31, 2016), only patients from study DRI12544 (n=532; 111 previously on placebo and 421 previously on dupilumab) were rolled over into this study, with 95% continuing treatment. Cumulative exposure was 500 patient-years. Demographics were similar to the parent studies. One subject who was previously on dupilumab died of lung cancer 9 months after enrolling in the open-label study.

The 120-day safety update included approximately 0.3% additional exposure since the sBLA cutoff for Study EFC13579. Study DRI12544, and EFC13691 were complete at the time of the initial sBLA submission. A total of 2,249 patients from studies DRI12544 (532 patients), EFC13579 (1,530 patients) and EFC13691 (187 patients) rolled over into and were exposed to dupilumab in the long-term study LTS12551. Of these, 725 patients were previously treated with placebo and 1,524 patients previously treated with dupilumab.

The safety profile of the open-label safety study and the 120-day safety update was generally similar to the parent studies, and no new safety concerns were identified. Reference is made to Study LTS12551 and to the 120-day safety update throughout the safety review, for specific safety analyses.

7.7.7. Additional Safety Explorations

7.7.7.1. Safety by Baseline Characteristics

No effect on safety was demonstrated based on pre-defined intrinsic factors (age, sex (<18 years, 18 to 64 and ≥65 years), race, weight, BMI, blood eosinophil level, ACQ-5, number of previous severe asthma exacerbations)

7.7.7.2. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of symptomatic overdose occurred.

7.7.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Dupilumab was approved on March 28, 2017, for atopic dermatitis. Two post-marketing deaths have occurred as of October 31, 2017. One subject was a 79-year-old male who experienced pneumonia after sustaining an open wound from a fall approximately 2 months after the first dose of dupilumab and 48 hours after the last dupilumab dose for atopic dermatitis. The patient also experienced pneumonia-related complication (not specified). There was one fatal case concerning a patient with history of Asperger's disorder, head injury, and seizures, who presented to the emergency room with complaints of malaise (not feeling well) and palpitations (heart was racing) for an unspecified period, 18 days after commencement of dupilumab. He died in the emergency room. Drug screen was positive for methamphetamine.

Since approval in the United States, more than (b) (4) patients have been treated with dupilumab. The primary safety pool in the atopic dermatitis submission consisted of dupilumab 300 mg q2w and weekly dose groups from three placebo-controlled studies of 16-week treatment duration. In the atopic dermatitis studies (primary safety pool), a greater proportion of patients in dupilumab groups reported AEs related to conjunctivitis (placebo 11 (2%) versus dupilumab 300 mg q2w 49 (9%) and 300 mg weekly (41 (8%)) and herpes infections (excluding eczema herpeticum) (placebo 18 (4%) versus dupilumab 300 mg q2w 34 (6%) and 300 mg weekly 25 (5%)) than placebo. These imbalances were not observed in the asthma studies.

7.7.9. Integrated Assessment of Safety

Safety analysis was based on a 6-month safety pool of the 200 mg and 300 mg q2w doses from the 6-month dose-ranging study (DRI12544) and the first 6-months of the 1-year efficacy and safety study (EFC13579).

For the safety pool, there were seven deaths, with four in the dupilumab 300 mg q2w group (acute myocardial infarction, cardiac failure congestive, cardio-respiratory arrest, and respiratory depression) and three in placebo (anaplastic thyroid cancer, suicide, pulmonary embolism). Two additional deaths occurred in Study DRI12544 in the 300 mg q4w group (acute cardiovascular failure in a 43-year-old male and metastatic gastric cancer in a 45-year-old male) and one

additional death in the dupilumab 200 mg q2w group (pulmonary embolism) occurred past the 6-month safety pool cutoff in Study EFC13579. The number of deaths was low and generally similar between dupilumab and placebo. An imbalance in MACE events (which includes cardiovascular deaths) was noted for Study EFC13579 and will be included in the prescribing information. No deaths were reported for Study EFC13691.

For the safety pool, 63 (4%) patients had an SAE (including fatal events). A similar percentage of subjects reported SAEs in the dupilumab 300 mg q2w group (35 (4.4%) compared to placebo (35 (4.4%)), and fewer subjects reported SAEs in the 200 mg q2w treatment group (28 (3.6%)) compared to placebo.

Pneumonia was the most commonly reported SAE, with a higher incidence in the 300 mg q2w dupilumab group (four (0.5%)) compared placebo (two (0.3%). Injection-site reactions (erythema, inflammation, and edema) were reported in three (0.4%) subjects for the 300 mg q2w dose only. Cardio-respiratory arrest, gastroenteritis, pregnancy were the only other SAEs reported in more than one subject. A pregnancy registry is being conducted based on a post-marketing requirement from the atopic dermatitis approval. An imbalance in MACE events was noted for Study EFC13579 and will be included in the prescribing information. Additional SAEs noted in the full 1-year safety period for Study EFC13579 included malignancy events in more than one subject (basal cell, three (<1%) dupilumab versus zero in placebo; malignant melanoma, two (<1%) dupilumab versus zero placebo, and adenocarcinoma (two (<1%) dupilumab versus zero in placebo). Overall the incidence of malignancies was lower in the dupilumab groups compared to placebo for the combined EFC13579 and DRI12544 safety evaluation, as noted in Section 7.7.5.8.

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

For the 6-month safety pool, 79 subjects had AEs leading to discontinuation of investigational product, with 58 subjects on dupilumab. More subjects receiving the higher dose of dupilumab (300 mg q2w) discontinued due to an adverse event (39 (4.9%)) compared to the lower dupilumab dose (200 mg q2w; 19 (2.4%)) or placebo (21 (2.7%)). The most common AE leading to discontinuation was injection-site reactions (300 mg q2w: 36 (5%); 200 mg q2w (8 (1%)) with a clear dose-response. No injection-site reaction leading to discontinuation was reported in the placebo group. No additional consistent treatment related safety findings are seen from a review of AEs leading to discontinuation data from the larger pooling of placebo-controlled trials or review of the data from the individual trials.

For the 6-month safety pool, the overall common adverse event incidence was similar across treatment groups. The most common adverse event was injection-site reactions, occurring in 256 (32%) of subject on 300 mg q2w of dupilumab and 181 (23%) on 200 mg q2w of dupilumab compared to 70 (9%) on placebo. A dose-related effect for injection-site reactions was noted. Other common AEs of headache, back pain, nasopharyngitis, oropharyngeal pain, eosinophilia, and myalgia were reported at a slightly higher incidence than placebo.

For studies DRI12544 and EFC13579, eosinophils increased immediately after the first dose of dupilumab (which included a loading dose). Eosinophils peaked around 4 weeks after the first dose and slowly decreased to close to baseline at the end of 52 weeks. The increase in eosinophilia did not appear to be dose dependent. The mean baseline eosinophilia was 0.25 giga/L, which increased to a mean of 0.48 gig/L by Week 4 (mean change from baseline 0.13 giga/L). By Week 52, the mean eosinophilia was 0.36 giga/L with a mean change from baseline of 0.11 giga/L. In the long-term extension study (LTS12551) the mean eosinophil counts increased in the first 4 months (after at least a 14-week treatment free period). By week 72, eosinophil counts returned to baseline. Eosinophilia adverse events were noted in all 3 studies, including the open-label extension study and the 120-day safety update. One case of eosinophilic pneumonia and four cases of EGPA were reported for dupilumab compared to one case of EGPA in subjects treated with placebo. The prescribing information will include the cases of eosinophilic pneumonia and EGPA to inform prescribers of this risk.

There was a dose-dependent imbalance in cardiac SAEs isolated to the 1-year study (EFC13579). Major adverse cardiovascular events (MACE; cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes) were reported in 1 (0.2%) of the dupilumab 200 mg q2w group, 4 (0.6%) of the dupilumab 300 mg q2w group, and 2 (0.3%) of the placebo group. The MACE results will be included in Section 6 of the prescribing information to inform prescribers of this risk.

Four anaphylaxis events were reported in studies DRI12544 and EFC13579. Three of events were closely associated with another trigger (bee string, food allergen four months after dupilumab dose, intravenous contrast), therefore it is likely that only one of these can be attributed to dupilumab. Anaphylaxis as a risk of dupilumab was added to Section 5.1. This was a modification from the atopic dermatitis prescribing information as no anaphylaxis events were reported in the atopic dermatitis clinical studies. No anaphylaxis events were reported in Study EFC13691. Hypersensitivity events occurred more frequently for subjects on dupilumab (200 mg q2w: 23 (3.0%); 300 mg q2w: 34 (4.3%)) compared to placebo (20 (2.5%)) and were dose-dependent. The most frequent hypersensitivity event occurring more frequently in the dupilumab arm compared to placebo was urticaria, followed by rash and erythema nodosum. The majority of hypersensitivity adverse events did not lead to treatment discontinuation. Urticaria, rash, and erythema nodosum was added to the prescribing information under Section 5.1.

Injection-site reactions were the dose-dependent and occurred more frequently after the loading dose. Injection site erythema was the most commonly reported injection-site reaction. In Studies DRI12544 and EFC13579, less than 1% of subjects had injection site a serious or severe adverse event. In the 6-month safety pool, less than 5% of subjects discontinued due to injection-site reactions.

The most common infection or infestation AE was pneumonia. Safety concerns noted in the atopic dermatitis clinical studies included conjunctivitis, eczema herpeticum, and herpes zoster. This was not noted in the asthma program. Parasitic infections were reported in one subject on

dupilumab and one on placebo in Study EFC13579 outside of the 6-month safety pool. Both subjects recovered.

Pregnancies were reported in 21 subjects in the asthma clinical studies. Seventeen were treated with dupilumab (0.8%) and four (0.5%) were on placebo. Overall, the incidence of harmful outcomes was higher in dupilumab compared to placebo; however, the number of healthy lives births was similar in dupilumab compared to placebo. A pregnancy registry was included in the atopic dermatitis approval.

No safety differences were noted in the subgroups based on baseline characteristics include age <18 years.

The ocular safety issues (conjunctivitis, blepharitis, keratitis, eye pruritus, and dry eye), eczema herpeticum and herpes zoster that were identified in the atopic dermatitis program were not identified in the asthma studies.

Overall, the safety profile in moderate-to-severe asthma in subjects ≥12 years of age is favorable.

SUMMARY AND CONCLUSIONS

7.8. Conclusions and Recommendations

The recommended regulatory action from a clinical perspective is approval of dupilumab 200 mg SC q2w with a loading dose of 400 mg and 300 mg SC with a loading dose of 600 mg q2w for use as add-on maintenance treatment in patients 12 years of age and older with moderate-to-severe asthma and an eosinophilic phenotype as efficacy was similar between doses and there were no major dose-related safety concerns. The 300 mg SC q2w dose, with a 600 mg loading dose, is recommended as the starting dose for patients requiring concomitant oral corticosteroids or with comorbid moderate-to-severe atopic dermatitis for which dupilumab is indicated.

To support this application, the Applicant has completed a 6-month dose-ranging trial and a 1-year efficacy and safety trial. Both studies demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations and lung function in patients with moderate-to-severe asthma with an eosinophilic phenotype for both the 200 mg SC q2w with a loading dose of 400 mg and the 300 mg SC q2w with a loading dose of 600 mg. While both studies enrolled subjects regardless of baseline blood eosinophil level, efficacy was not consistently demonstrated in subjects without an eosinophilic phenotype. In addition, a third pivotal trial demonstrated that 300 mg SC q2w (with a loading dose of 600 mg) enabled control of underlying asthma with decreased oral corticosteroids irrespective of eosinophilia.

The adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. This review recommends approval in this age group, as there are no age-related

differences in the pharmacokinetic and pharmacodynamic parameters, and no safety concerns for dupilumab in adolescent patients.

The program included an assessment of safety concerns related to immunomodulatory therapy and biologics including infections, malignancy, hypersensitivity events, and immunogenicity. Injection-site reactions were the most common adverse event and were dose-related. Hypersensitivity events were also dose-related. Major adverse cardiovascular events were reported at a slightly higher frequency in the 300 mg q2w dose group compared to placebo, but not in the 200 mg q2w dose group. One anaphylaxis case was reported for dupilumab. Multiple cases of eosinophilic granulomatosis with polyangiitis and one case of eosinophilic pneumonia were reported. The ocular safety issues seen in the atopic dermatitis program were not identified in the asthma studies. No safety concerns that offset the efficacy benefits provided by dupilumab were identified for the overall or adolescent populations. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

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8. Statistical Evaluation

8.1.1. Table of Clinical Studies

Refer to the table of clinical studies in Section 7.2 (Table 4)

8.1.2. Review Strategy

Data Sources

The Applicant submitted the BLA 761055 on December 20, 2017. The application includes protocols, statistical analysis plans (SAP), study reports, and all referenced literature. The data and final study report for the electronic submission were archived under the network path location \\CDSESUB1\evsprod\BLA761043BLA761055\761043761055.enx

Data and Analysis Quality

The data submitted by the Applicant has sufficient quality for review, and I was able to reproduce the primary and major secondary analyses from the analysis data model (ADaM) and legacy datasets. The Applicant provided adequate documentation for the datasets and the analysis methods were explained in the SAP.

8.2. Review of Relevant Individual Trials Used to Support Efficacy

8.2.1. Study DRI12544

8.2.1.1. Trial Design and Endpoints

The study design and endpoints of Study DRI12544 are described in the clinical section (Section 7).

8.2.1.2. Sample Size Calculations

For study DRI12544, the Applicant computed that 300 HEos patients (60 per group) would be needed to provide 94% power to detect a mean difference of 0.24 L in the FEV1 primary endpoint. Assuming a 40% recruitment rate for the HEos category, approximately 750 patients were expected to be randomized to achieve 300 HEos patients. These sample size calculations were made by assuming a common standard deviation of 0.35 L, a 0.24 L mean difference between the highest dupilumab dose and the placebo group in change from baseline in FEV1, and an expected early discontinuation rate of 10%.

8.2.1.3. Statistical Methodologies

The primary efficacy endpoint (change from baseline in FEV1 at Week 12) in the HEos ITT population was analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model included factors (fixed effects) for treatment, pooled countries/regions, visit, treatment-by-visit interaction, and FEV1 baseline value and baseline-by-visit interaction as covariates. An unstructured correlation matrix was used to model the within-patient errors. Parameters were estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Each dose regimen of dupilumab was tested versus placebo. Statistical inferences on treatment comparisons for the primary endpoint, change from baseline in FEV1 at Week 12, were derived from the mixed-effect model.

For analyzing the secondary endpoint, number of severe exacerbations, a negative binomial regression model was used with the total number of confirmed events occurring during the observation period as response variable, and treatment group, pooled countries/regions and number of asthma events prior to the study (number of asthma exacerbation during 1 year prior to visit one) as covariates. Log-transformed duration was used as the offset variable.

8.2.1.4. Handling Missing Data and Sensitivity Analysis

In the primary analyses, data collected after treatment discontinuation was set as missing, and no imputation was performed for the MMRM model.

To assess sensitivity of the primary analysis on the missing data assumption, the MMRM analysis was conducted with the FEV1 measurements collected during the follow up period if the patient discontinued the study treatment before the end of treatment period.

Based on FDA's feedback on handling of missing data for study EFC13579, the Applicant conducted similar sensitivity analysis methods to assess impact of missing data on change from baseline in FEV1 and severe exacerbation during the 24-week treatment period. In particular, the sensitivity analyses were conducted in the overall ITT population and consisting of 1) a MMRM analysis including on-treatment FEV1 values up to Week 12 and including all FEV1 measurements regardless of the use of systemic corticosteroids 2) excluding all FEV1 measurements collected on and after first day of systemic corticosteroid use, 3) analysis using all on-study data regardless if the patient was on treatment or not, 4) pattern-mixture model multiple imputation, 5) control based pattern mixture model, and 6) tipping point analyses. The sensitivity analysis methodologies were similar to Study EFC13579 and more details are given in section 8.2.2.4.

8.2.1.5. Multiple Comparisons and Multiplicity

Study DRI12544 was originally designed as a dose-ranging study, and there was no strong type I error rate control for multiple endpoints, multiple doses and multiple populations planned in the SAP.

8.2.2. Study EFC13579

8.2.2.1. Trial Design and Endpoints

The study design and endpoints of Study EFC13579 are described in the clinical section (Section 7.5.2).

8.2.2.2. Sample Size Calculations

The Applicant computed the sample size based on comparisons between dupilumab 300 mg q2w versus placebo with regard to the two primary endpoints and with an assumption that the number of severe asthma exacerbations follows a negative binomial distribution with a dispersion parameter of 2. Assuming that the placebo annualized rate of exacerbations is 0.6, with a randomization ratio of 2:2:1:1, the Applicant estimated that 1,638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group) would provide 99% power to detect a 55% relative risk reduction (i.e., annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe asthma exacerbations at the two-tailed significance level of α=0.05, and would provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at week 12, in the overall population. The Applicant stopped recruitment of patients on a medium dose of ICS when approximately 819 had been randomized into the study, to ensure at least 50% patients were on a high dose of ICS.

Later, by amending the protocol, the Applicant proposed to add approximately 220 patients to provide additional exposure to dupilumab manufactured with the intended commercial process. FDA reviewed the protocol amendment on July 18, 2016 and stated that the proposed sample size was reasonable. At the time of the data cutoff date, 235 patients with ongoing treatment had completed at least 47 weeks of the 52-week treatment period.

8.2.2.3. Statistical Methodologies

The primary endpoint, annualized rate of severe exacerbation events, was analyzed using a negative binomial regression model. The model included the total number of events occurring during the observation period (response variable) with the covariates of treatment group, age, region (pooled country), baseline eosinophil stratum (<0.3 Giga/L or ≥0.3 Giga/L), baseline ICS dose level, and number of severe asthma exacerbations within one year prior to the study. The log-transformed duration of observation was used as the offset variable. In the primary analysis, off-treatment measurements of patients who prematurely discontinued treatment were included for the analysis, with all severe exacerbation events that happened up to visit 18 (Week 52) included in the analysis, whether the patient was on treatment or not, and the observation duration was defined as from randomization to visit 18. In addition, the pairwise comparisons of the annualized event rates between each dose of dupilumab and placebo were derived by testing each dupilumab group versus the matching placebo group separately.

The second primary endpoint, absolute change from baseline in FEV1 at week 12, was analyzed using an MMRM approach. The model included change from baseline in pre-BD FEV1 values up to week 12 as response variables, and treatment, age, sex, baseline height, region, visit, baseline eosinophil stratum, baseline ICS dose level, treatment-by-visit interaction, baseline pre-BD FEV1 value, and baseline-by-visit interaction as covariates. Statistical inferences for treatment comparisons of change from baseline in pre-BD FEV1 at week 12 were derived from the mixed-effect model. Differences in the LS mean change from baseline with the corresponding 95% CI and p-value with Kenward-Roger adjustment are used for comparison of each dupilumab group with the matching placebo group.

8.2.2.4. Handling Missing Data and Sensitivity Analysis

The primary analysis of the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period assessed the efficacy of dupilumab in an intention-to-treat setting. In this primary approach, off-treatment measurements of patients who prematurely discontinue treatment were included for the analysis. Patients who permanently discontinued the study medication were encouraged to return to the clinic for all remaining study visits. If a patient stayed in study until the end of 52-week treatment period, all severe exacerbation events that happened up to visit 18 were included in the primary analysis, whether the patient was on treatment or not, and the observation duration was defined as from randomization to visit 18. If a patient withdrew from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date were included in the analysis, and the observation duration was defined as from randomization to the last contact date. No imputation was performed for the unobserved events that might happen after study discontinuation and up to Week 52. This estimand compared the rate of severe exacerbation for the patients randomized to

the dupilumab and placebo arms, regardless of what treatment patients received. It assessed the benefits of the treatment policy or strategy relative to placebo.

Off study-treatment pre-BD FEV1 values measured up to Week 12 were included in the primary analysis. For patients who withdrew from the study before week 12, pre-BD FEV1 values were considered missing after study discontinuation. No imputation was performed for missing values in the primary analysis. This estimand compared the change from baseline in pre-BD FEV1 for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients received. It assessed the benefits of the treatment policy or strategy relative to placebo.

Patients who withdrew from the study before week 52 were considered as patients with missing data in the study. The models assume that these missing data are missing at random (MAR). The Applicant conducted the following sensitivity analyses to assess the robustness of the primary analysis results to violations in the MAR assumption. For each of the methods given below, a negative binomial model was fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates.

PMM-MI:

For each patient with missing data of severe exacerbation events, an individual monthly event probability was estimated using observed data with adjustment for the planned treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1one year prior to the study.

A binary event was imputed on a monthly basis using multiple imputation. Within each month, the logistic regression model was fitted to the observed data to model coefficient estimates and the estimated variance-covariance matrix, with adjustment for the planned treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. From the posterior distribution of the model coefficients, 40 sets of independent samples were generated. As a result, for each patient and in each month, 40 estimated probabilities can be obtained by using the 40 samples of coefficients and the patients' covariate values. A negative binomial model with the same set of covariates as in the primary analysis was fitted with 40 sets of complete datasets, so as to obtain 40 sets of treatment effect estimates and p-values accordingly.

Missing pre-BD FEV1 values were imputed multiple times with adjustment for covariates including treatment group, baseline eosinophil group, age, sex, height, region, baseline ICS dose level, and reason for treatment discontinuation. Each of the complete datasets were analyzed using the analysis of covariance (ANCOVA) model with change from baseline in pre-BD FEV1 at week 12 as the response variable, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline pre-BD FEV1 value as covariates.

For both primary endpoints, the statistical inferences were obtained by combining results from the 40 analyses using Rubin's formula.

Control-based PMM-MI:

For each patient with missing data of severe exacerbation events, an individual monthly event probability was estimated using observations in the matching placebo arms only, with adjustment for age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. And a binary event was imputed monthly using the multiple imputation method explained in the PMM-MI. A similar approach was used for imputing missing pre-BD FEV1 values.

Tipping point analysis:

For each patient with missing data of severe exacerbation events, the monthly event data was imputed in a similar fashion as PMM-MI based on various odds values. Within each month up to week 52, the logistic regression model was fitted to the observed data to obtain the model coefficient estimates and the estimated variance-covariance matrix, adjusting for the planned treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. From the posterior distribution for the model coefficients, 40 sets of independent samples were randomly drawn. Within each month for the patients from the placebo group(s) with missing data in that month, the estimated odds for binary event were deflated by decreasing a positive amount. For the patients from the treatment group(s) with missing data in that month, the estimated odds for binary event were inflated by increasing a positive amount. After the deflation/inflation, 40 sets of binary event probabilities were obtained for the placebo and treatment groups.

A negative binomial model with the same set of covariates as in the primary analysis was fitted to the 40 sets of complete datasets, and 40 sets of treatment effect estimates, and p-values were obtained accordingly. Log transformed observation duration was the offset variable for patients who complete the 52-week treatment/study period, and log transformed 52 weeks was the offset variable for patients who discontinue the study before visit 18 (week 52). The results were combined from the 40 analyses using Rubin's formula.

For the pre-BD FEV1 endpoint, the imputed values in the placebo group were obtained by adding a sequence of positive values; the imputed values in the dupilumab groups were obtained by subtracting a sequence of positive values. For each combination of the shift parameters, the imputed and shifted datasets were analyzed with the ANCOVA model, and the results were combined using Rubin's formula to generate statistical inference.

8.2.2.5. Multiple Comparisons and Multiplicity

In Study EFC13579, the family wise type I error for the primary family (two primary endpoints and two doses) was controlled using a hierarchical testing procedure at a two-sided 5% significance level starting with the two primary endpoint analyses of the 300 mg q2w dose; i.e., each hypothesis was formally tested only if the preceding one was significant at the 5% level. The Applicant provided a selective set of secondary endpoints which would be tested in a pre-specified hierarchical testing order (Table 42) only if both the primary endpoints established statistical significance.

Table 42: Multiple Testing Hierarchy for Primary and Selected Secondary Endpoints

	Endpoints	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Primary endpoints	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population	3	1
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population	4	2
Secondary endpoints	Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population	11	5
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil >=0.15 Giga/L	12	6
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline eosinophil >=0.15 Giga/L	13	7
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil >= 0.3 Giga/L	14	8
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline eosinophil >= 0.3 Giga/L	15	9
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil <0.3Giga/L	16	10
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with high dose ICS at baseline	22	17
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with high dose ICS/LABA at baseline	23	18
	Change from baseline in AQLQ global score at Week 24 - ITT population	24	19
	Change from baseline in AQLQ global score at Week 24 - ITT population with baseline eosinophil >= 0.3 Giga/L	25	20
	Change from baseline in ACQ-5 score at Week 24 - ITT population	26	21
	Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week treatment period - ITT population	28	27
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline blood eosinophil <0.3 Giga/L	30	29

ACQ = Juniper Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; FEV1 = forced expiratory volume in 1 second; HEos = high eosinophil; ICS = inhaled corticosteroids; ITT = intention to treat; LABA = long-acting beta agonist; q2w = once every 2 weeks
Source: Study EFC13579 CSR, Table 2, page 56

The Applicant also presented results from Study DRI12544 of the primary endpoints and selected secondary endpoints based on the hierarchical order defined for Study EFC13579 at α=0.05 for the 300 mg q2w and 200 mg q2w dose groups to make a side-by-side comparison of results from the two studies.

8.2.3. Study EFC13691

8.2.3.1. Trial Design and Endpoints

The study design and endpoints of Study EFC13691 are described in the clinical section (Section 7.5.3).

8.2.3.2. Sample Size Calculations

In Study EFC13691, the Applicant's sample size estimation was based on the comparison between dupilumab versus placebo with regard to the primary endpoint and the key secondary endpoints. For the primary endpoint of the percent reduction of OCS dose, assuming a common standard deviation of 50%, with 90 randomized patients per group, the Applicant computed that the study would have 94% power to detect a treatment difference of 27% at the two-tailed significance level of α=0.05.

8.2.3.3. Statistical Methodologies

In Study EFC13691, the primary estimand was the ITT or treatment policy estimand, i.e., the absolute difference between dupilumab and control in the mean percentage reduction of OCS dose at week 24 while maintaining asthma control in all patients in the ITT population, whether patients discontinued treatment before week 24 or not. The percent reduction in OCS dose was be calculated as: (optimized OCS dose at baseline – final OCS dose at Week 24)/optimized OCS dose at baseline × 100. A patient was considered as having maintained asthma control between Week 20 and Week 24 if he/she did not have a clinically significant event, based on investigator judgment that requires treatment by OCS dose adjustment during this period. For those patients who experienced an exacerbation, the final OCS dose was considered to be one step higher than the dose they were receiving at the time of the exacerbation.

The primary efficacy endpoint was analyzed using an ANCOVA model. The model included the percentage reduction of OCS dose at week 24 as the response variable, and the treatment group, optimized OCS dose at baseline, region (pooled countries), and baseline eosinophil level subgroups (<0.15 Giga/L, ≥0.15 Giga/L) as covariates. The treatment difference was tested at the two-sided significance level of α=0.05.

8.2.3.4. Handling Missing Data and Sensitivity Analysis

The primary analysis was based on all patients in the ITT population no matter whether the patients discontinue treatment before week 24. The primary missing data handling approach was PMM-MI. This approach imputed missing percent reduction of OCS dose at visits 5 (week 4), 7 (week 8), 8 (week 12), 9 (week 16), 10 (week 20), and 11 (week 24), using multiple regression models. Imputation was conducted sequentially by visit. For each visit, the imputation model used the percent reduction of OCS dose at the visit as the response variable and included the following predictors: the covariates incorporated in the ANCOVA model above, and the percent reduction of OCS dose from baseline at all the prior visits. Forty imputations were performed. For each imputation, the complete percent reduction of OCS dose at week 24 was analyzed using

the ANCOVA model above, and Rubin's rule was used to combine results from all the imputations. In addition, the Applicant conducted two sensitivity analyses, tipping point analysis and worse of the last two observations carried forward analysis to assess the robustness of the conclusion of the main model.

8.2.3.5. Multiple Comparisons and Multiplicity

For Study EFC13691, the primary endpoint was tested at a two-sided 5% significance level. If the primary endpoint met the significance level, the following secondary endpoints were tested at a two-sided 5% significance level in the hierarchical order defined below:

i. Proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at week 24 while maintaining asthma control;
ii. Proportion of patients achieving a reduction of OCS dose to <5 mg/day at week 24 while maintaining asthma control;
iii. Proportion of patients achieving their maximum possible reduction of OCS dose per protocol at week 24 while maintaining asthma control;
iv. Proportion of patients no longer requiring OCS at week 24 while maintaining asthma control.

No multiple testing adjustments were performed for the other efficacy endpoints.

8.3. Study Results

8.3.1. Patient Disposition

Patient disposition is described in the clinical section (Section 7).

8.3.2. Table of Demographic Characteristics

Please refer clinical section (Section 7) for demographic characteristics of patients in the clinical studies.

8.3.3. Results and Conclusions

8.3.4. Study DRI12544

The primary endpoint of study DRI12544 was the absolute change from baseline FEV1 at week 12. The secondary endpoints included annualized event rate of severe exacerbation events during the treatment period, percentage change from baseline in pre-BD FEV1 at week 12 and change from baseline in ACQ-5 and AQLQ at various time points. The pre-specified primary analysis population was the subset of the ITT population with baseline blood eosinophils ≥0.3 Giga/L (HEos patients), and all of the efficacy endpoints were analyzed using both the HEos population and the overall ITT population, including patients with eosinophils <0.3 Giga/L.

8.3.4.1. Primary Efficacy Analysis

The primary endpoint, absolute change from baseline FEV1 at week 12, was analyzed using the HEos population. The three highest doses of dupilumab (200 mg q2w, 300 mg q2w, 300 mg q4w) showed a statistically significant improvement in FEV1 (L) at week 12 in comparison with placebo (Table 43). The mean differences from placebo at week 12 were 0.26 (95% CI: 0.11, 0.40) for 200 mg q2w and 0.21 (95% CI: 0.06, 0.36) for 300 mg q2w. Among the two q2w dosing regimens, the dupilumab 200-mg dose had a slightly better estimated effect compared to the 300-mg dose. Mean changes over time by treatment group in the high eosinophil subgroup are displayed in Figure 15.

Table 43: DRI125544 - Primary Analysis: Change from Baseline in Pre-BD FEV1 (L) to Week 12 – ITT Population With Baseline Blood Eosinophil ≥0.3 G/L

		Dupilumab			
Statistic	**Placebo (N=68)**	**200 mg q4w (N=62)**	**300 mg q4w (N=66)**	**200 mg q2w (N=65)**	**300 mg q2w (N=64)**
LS Mean (SE)	0.18 (0.05)	0.26 (0.06)	0.35 (0.05)	0.43 (0.05)	0.39 (0.05)
LS mean difference (95% CI)		0.08 (-0.07, 0.23)	0.17 (0.03, 0.32)	0.26 (0.11, 0.40)	0.21 (0.06, 0.36)
p-value vs. placebo		0.28	0.02	<.001	<.001

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; LS = least squares; q2w = once every 2 weeks; q4w = once every 4 weeks
Source: Statistical Reviewer

Analysis of the primary endpoint in the overall population (including patients with eosinophils <0.3 Giga/L) shows that all dose regimens of dupilumab resulted in statistically significant improvement in pre-BD FEV1 at week 12 in comparison with placebo. In particular, the treatment effect was larger for both q2w doses compared to the two q4w dose regimens (Table 44). The LS mean differences from placebo at week 12 were 0.20 L (95% CI: 0.11, 0.28) for 200 mg q2w and 0.16 L (95% CI: 0.08, 0.25) for 300 mg q2w.

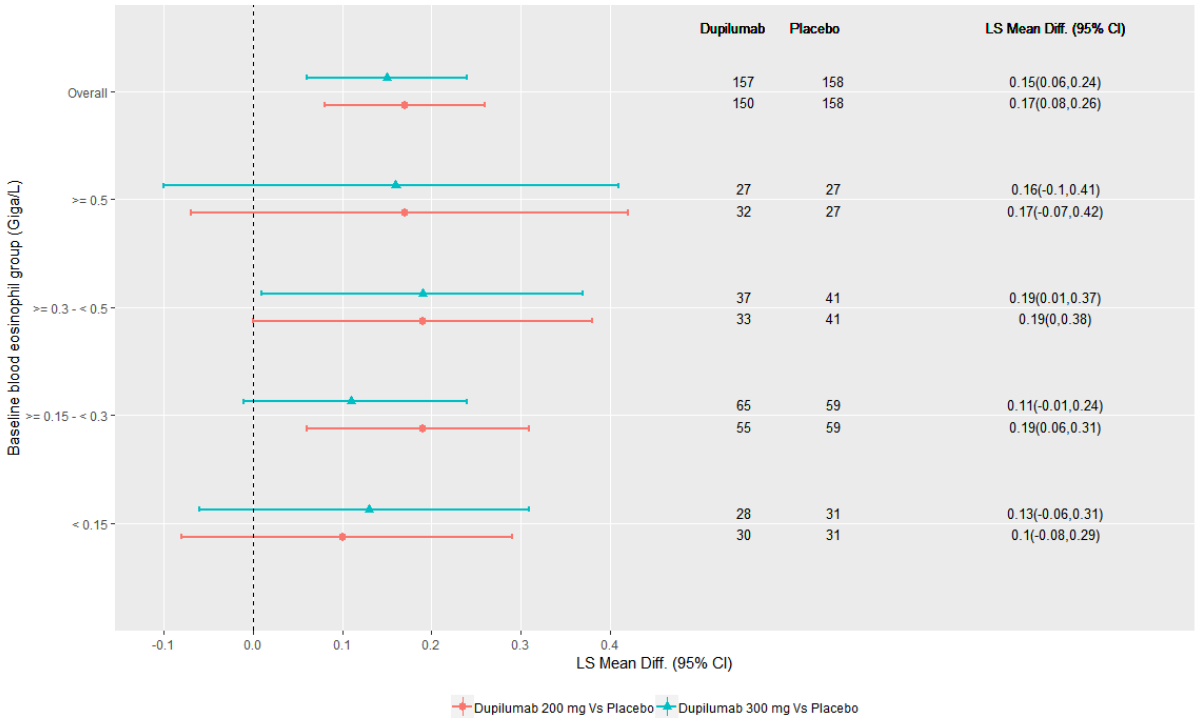
Table 44: DRI125544 - Change from Baseline in Pre-BD FEV1 (L) to Week 12 – ITT Population

		Dupilumab			
Statistic	**Placebo (N=158)**	**200 mg q4w (N=154)**	**300 mg q4w (N=157)**	**200 mg q2w (N=150)**	**300 mg q2w (N=157)**
LS Mean (SE)	0.12 (0.03)	0.21 (0.03)	0.24 (0.03)	0.31 (0.03)	0.28 (0.03)
LS mean difference (95% CI)		0.10 (0.01, 0.18)	0.12 (0.04, 0.21)	0.20 (0.11, 0.28)	0.16 (0.08, 0.25)
p-value vs. placebo		0.03	<.001	<.001	<.001

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; LS = least squares; q2w = once every 2 weeks; q4w = once every 4 weeks; SE = standard error
Source: Statistical Reviewer

Subgroup analysis showed that dupilumab patients in the lower eosinophilic group (<0.15) did not demonstrate significant improvement in lung function (Figure 14) compared to the placebo group.

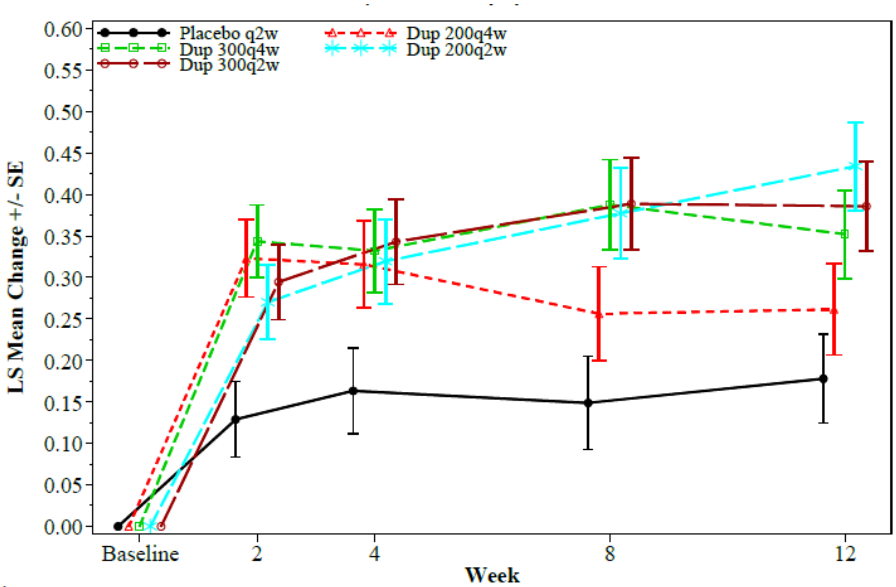
Figure 14: DRI125544 - Change from Baseline in Pre-BD FEV1 (L) at Week 12 by Eosinophil Subgroups



BD = bronchodilator; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

Mean change from baseline over time plot in the HEos population showed that an improvement in FEV1 for dupilumab as compared to placebo was identified from Week 2 and reached a plateau from Week 8 onward (Figure 15).

Figure 15. DRI125544 - LS Mean Change from Baseline in FEV1 (L) Over Time – ITT Population with Baseline Blood Eosinophil >0.3 G/L



# subjects					
Placebo q2w	68	59	57	54	58
Dup 200q4w	62	56	57	56	53
Dup 300q4w	66	66	61	59	55
Dup 200q2w	65	64	62	60	57
Dup 300q2w	64	60	59	57	59

FEV1 = forced expiratory volume in 1 second; HEos = high eosinophil; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; q4w = once every 4 weeks; SE =
Source: Statistical Reviewer

8.3.4.2. Sensitivity Analysis

To examine the robustness of the primary analysis to violations in missing data assumptions, sensitivity analyses were conducted using all on-study data regardless if the patient was on treatment, a pattern-mixture model with multiple imputation, and a control-based pattern mixture model. All sensitivity analyses showed consistent results, with a statistically significant improvement in FEV1 at week 12 for dupilumab 300 mg q4w, 200 mg q2w, and 300 mg q2w doses as compared to placebo. The results in the overall ITT population are given in Table 45.

Table 45: Sensitivity Analyses of Change From Baseline in FEV1 at Week 12– ITT Population					
	Placebo	Dupilumab			
		200 mg q4w	300 mg q4w	200 mg q2w	300 mg q2w
Analysis using all on-study data up to Week 12					
N	153	142	151	147	151
LS Mean	0.13	0.21	0.23	0.30	0.29
LS Mean Diff. (95% CI)		0.07 (-0.01, 0.16)	0.09 (0.01, 0.18)	0.17 (0.08, 0.26)	0.15 (0.06, 0.24)
p-value vs placebo		0.09	0.03	<0.001	<0.001
PMM-MI					
N	158	154	157	150	157
LS Mean	0.13	0.22	0.23	0.31	0.29
LS Mean Diff. (95% CI)		0.08 (-0.01, 0.17)	0.09 (0.01, 0.18)	0.17 (0.09, 0.26)	0.15 (0.07, 0.24)
p-value vs placebo		0.07	0.03	<0.001	<0.001
Control based PMM					
N	158	154	157	150	157
LS Mean	0.14	0.21	0.23	0.30	0.29
LS Mean Diff. (95% CI)		0.08 (-0.02, 0.16)	0.09 (0.01, 0.18)	0.16 (0.09, 0.25)	0.15 (0.06, 0.24)
p-value vs placebo		0.13	0.03	<0.001	<0.001

CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; LS = least squares; PMM-MI = pattern mixture model-multiple imputation; q2w = once every 2 weeks; q4w = once every 4 weeks
Source: Statistical Reviewer

8.3.4.3. Secondary Efficacy Analysis

In the HEos population, all doses except 300 mg q4w demonstrated a significant reduction in the annualized rate of severe asthma exacerbations (Table 46). In particular, dupilumab 300 mg q2w dose had the lowest rate with a rate ratio of 0.19 compared to placebo (95% CI: 0.07, 0.56).

Table 46: DRI125544 - Analysis of Annualized Event Rate of Severe Exacerbation Over the Treatment Period – ITT Population With Baseline Blood Eosinophil >0.3 G/L					
		Dupilumab			
Statistic	Placebo (N=68)	200 mg q4w (N=62)	300 mg q4w (N=66)	200 mg q2w (N=65)	300 mg q2w (N=64)
Estimate	1.0	0.36	0.68	0.30	0.20
Rate ratio (95% CI)		0.34 (0.13, 0.92)	0.65 (0.28, 1.50)	0.29 (0.11, 0.76)	0.19 (0.07, 0.56)
p-value vs placebo		0.03	0.31	0.01	0.002

CI = confidence interval; ITT = intention to treat; q2w = once every 2 weeks; q4w = once every 4 weeks
Source: Statistical Reviewer

The reduction of annualized rate of severe asthma exacerbations was largely similar in the overall population compared to the HEos subgroup (Table 47). The 300 mg q4w dose did not demonstrate statistical significance in either the overall population or in the HEos subgroup.

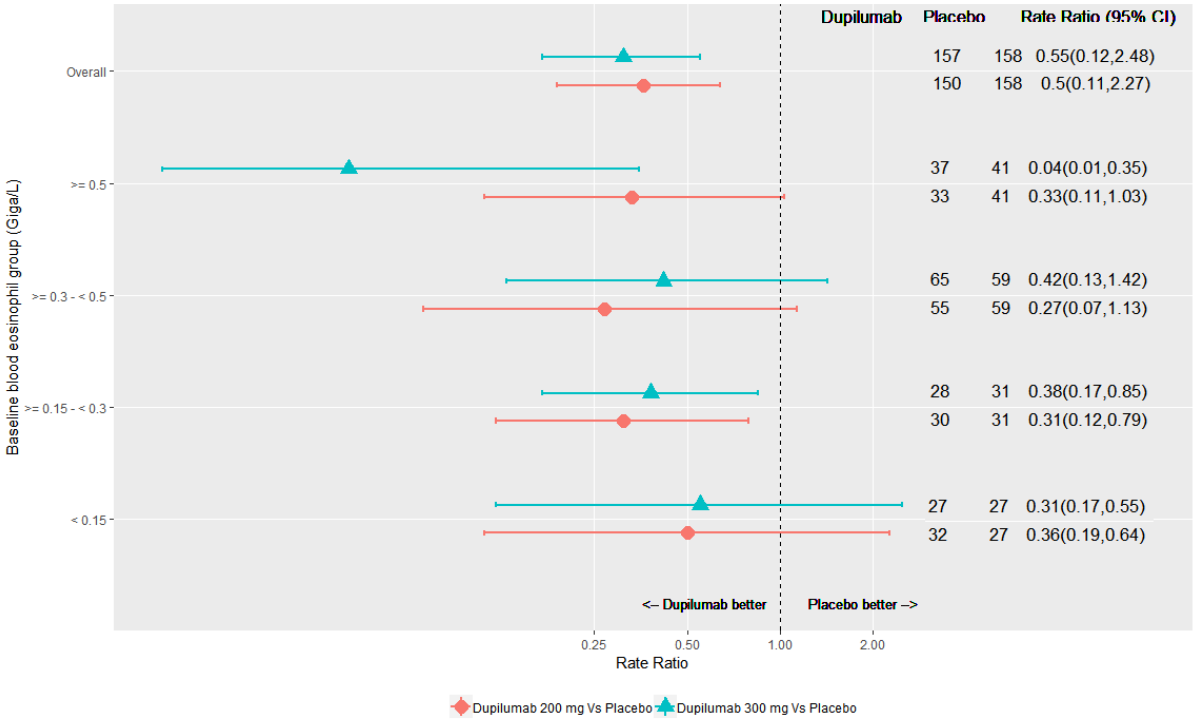
Table 47: DRI125544 - Analysis of Annualized Event Rate of Severe Exacerbation Through Week 12 – ITT Population

		Dupilumab			
Statistic	**Placebo (N=158)**	**200 mg q4w (N=154)**	**300 mg q4w (N=157)**	**200 mg q2w (N=150)**	**300 mg q2w (N=157)**
Estimate	0.90	0.41	0.60	0.27	0.27
Rate Ratio (95% CI)		0.46 (0.26, 0.83)	0.67 (0.40, 1.14)	0.30 (0.16, 0.57)	0.30 (0.16, 0.55)
p-value vs placebo		0.009	0.13	<.001	<.001

CI = confidence interval; ITT = intention to treat; q2w = once every 2 weeks; q4w = once every 4 weeks
Source: Statistical Reviewer

Subgroup analysis by the Applicant showed dupilumab patients in lower eosinophilic group (<0.15) did not demonstrate significant reduction of severe exacerbation event (Figure 16) compared to placebo group.

Figure 16. DRI125544 Relative Risk in Annualized Event Rate of Severe Exacerbation by Eosinophil Subgroups



CI = confidence interval; ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.5. Study EFC13579

Study EFC13579 had two primary endpoints: the annualized event rate of severe exacerbations during the 52-week treatment period, and the absolute change from baseline in pre-BD FEV1 at week 12.

8.3.5.1. Primary Efficacy Analysis on the Annualized Event Rate of Severe Exacerbation

Results from the primary efficacy analyses on the annualized event rate of severe exacerbations showed both dupilumab dose groups had a statistically significant lower event rate compared to the placebo group in the overall population (Table 48). In particular, patients in the dupilumab groups experienced a roughly 50% reduction compared to their matching placebo groups in the severe exacerbation rate during the study period (200 mg: rate ratio: 0.52, CI: 0.41, 0.66; 300 mg: rate ratio: 0.54, CI: 0.43, 0.68).

Table 48: EFC13579 - Efficacy Analysis of Primary Endpoints – ITT Population

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
Annualized event rate of severe exacerbation	**Placebo, N=317**	**Dupilumab, N=631**	**Placebo, N=321**	**Dupilumab, N=633**
Estimate	0.87	0.46	0.97	0.52
Rate Ratio		0.52		0.54
(95% CI)		(0.41, 0.66)		(0.43, 0.68)
p-value vs placebo		<.0001		<.0001

CI = confidence interval; ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.5.2. Sensitivity Analyses on the Annualized Event Rate of Severe Exacerbation

Consistent results obtained from sensitivity analyses on the primary endpoint, annualized event rate of severe exacerbation showed that the primary efficacy results were robust and unaffected by the missing data in both treatment arms. On-treatment analysis, PMM-MI and control based PMM-MI provided comparable results as given in Table 49. However, these analyses each consider only one alternative missing data assumption. Therefore, tipping point analysis that more comprehensively explore the plausible space of missing data assumptions were also considered important.

Table 49: Sensitivity Analysis on Annualized Event Rate of Severe Exacerbation During 52-week Treatment Period

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo	Dupilumab	Placebo	Dupilumab
On-treatment analysis				
N	315	629	321	632
Estimate	0.87	0.45	0.97	0.52
Rate Ratio		0.51		0.52
(95% CI)		(0.40, 0.66)		(0.41, 0.66)
p-value vs placebo		<.0001		<.0001
PMM-MI				
N	317	631	321	633
Estimate	0.87	0.46	0.96	0.52
Relative risk		0.52		0.55
(95% CI)		(0.41, 0.66)		(0.44, 0.68)
p-value vs placebo		<.0001		<.0001
Control based PMM-MI				
N	317	631	321	633
Estimate	0.87	0.46	0.97	0.52
Rate Ratio		0.52		0.54
(95% CI)		(0.41, 0.66)		(0.43, 0.68)
p-value vs placebo		<.0001		<.0001

CI = confidence interval; ITT = intention to treat; PMM-MI = pattern mixture model-multiple imputation; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.5.3. Tipping Point Analysis on the Annualized Event Rate of Severe Exacerbation

In this study, 1,434 patients completed the treatment and 228 patients discontinued treatment (73 (11.4%) in combined placebo group and 155 (12.3%) in combined dupilumab group); 103 patients discontinued from the study - placebo (1.14mL): 17 (5.4%), dupilumab 200 mg: 28 (4.4%), placebo (2 mL): 17 (5.3%) and dupilumab 300 mg: 41 (6.5%). Among the patients who discontinued from the study, 84 patients withdrew from the study due to patient's request (30 (4.7%) in combined placebo group and 54 (4.3%) in combined dupilumab group)

To check the robustness of study results, the tipping point analyses were performed on both dupilumab dose groups and the comparable placebo groups. The tipping point analyses targeted the de facto estimand, i.e., the ratio of annualized event rates of severe exacerbation between the treatment and placebo groups regardless of adherence, and therefore included all observed data regardless of treatment adherence. The predicted odds of having a severe exacerbation in each month for the dupilumab groups were inflated from an MAR assumption by the inflation ratio, whereas the predicted odds were deflated by a deflation ratio in the placebo groups. The results from the tipping point analyses showed that, under all assumptions that were considered, including some implausible situations, the treatment effect remained significant ($p<0.05$), which provided additional support for the robustness of the study result (Table 50, Table 51).

Table 50: EFC13579 - Tipping Point Analysis of Annualized Rate of Severe Exacerbations - Dupilumab 200 mg q2w vs. Placebo in 1.14 mL q2w

	Deflation Ratio on the Monthly Odds[b] for Early-Study-Withdrawal Patients in Matching Placebo

		1	0.8	0.5	0.25	0.1	0.05
Inflation ratio on the monthly odds for early-study-withdrawal patients in 200q2w arm[a]	1	0.524 (<.0001)	0.529 (<.0001)	0.536 (<.0001)	0.543 (<.0001)	0.548 (<.0001)	0.55 (<.0001)
	1.25	0.526 (<.0001)	0.529 (<.0001)	0.54 (<.0001)	0.548 (<.0001)	0.554 (<.0001)	0.553 (<.0001)
	2	0.539 (<.0001)	0.542 (<.0001)	0.551 (<.0001)	0.56 (<.0001)	0.566 (<.0001)	0.565 (<.0001)
	4	0.565 (<.0001)	0.572 (<.0001)	0.579 (<.0001)	0.587 (<.0001)	0.59 (<.0001)	0.589 (<.0001)
	10	0.629 (<.0001)	0.634 (0.0001)	0.645 (0.0002)	0.654 (0.0003)	0.658 (0.0004)	0.662 (0.0005)
	20	0.7 (0.0023)	0.705 (0.0037)	0.717 (0.0055)	0.73 (0.0089)	0.733 (0.0098)	0.73 (0.0090)

[a] Predicted odds of having severe exacerbation in each month for the dupilumab groups is inflated by the inflation ratio.
[b] Predicted odds of having severe exacerbation in each month for the placebo groups is deflated by the deflation ratio.
q2w = once every 2 weeks
Source: Adapted from Applicant's Analysis

Table 51:EFC13579 - Tipping Point Analysis of Annualized Rate of Severe Exacerbations - Dupilumab 300 mg q2w vs. Placebo in 1.14 mL q2w

		Deflation Ratio on the Monthly Odds[b] for Early-Study-Withdrawal Patients in Matching Placebo					
		1	0.8	0.5	0.25	0.1	0.05
Inflation Ratio on the Monthly Odds for Early-study-withdrawal Patients in 300q2w arm [a]	1	0.55 (<.0001)	0.55 (<.0001)	0.55 (<.0001)	0.55(<.0001)	0.56 (<.0001)	0.56 (<.0001)
	1.25	0.55 (<.0001)	0.55 (<.0001)	0.56 (<.0001)	0.56 (<.0001)	0.56 (<.0001)	0.56 (<.0001)
	2	0.56 (<.0001)	0.57 (<.0001)	0.57 (<.0001)	0.57 (<.0001)	0.57 (<.0001)	0.57 (<.0001)
	4	0.59 (<.0001)	0.59 (<.0001)	0.60 (<.0001)	0.61 (<.0001)	0.61 (<.0001)	0.61 (<.0001)
	10	0.66 (0.0002)	0.67 (0.0004)	0.67 (0.0005)	0.68 (0.0007)	0.68 (0.0008)	0.68 (0.0009)
	20	0.71 (0.0092)	0.74 (0.0110)	0.75 (0.0129)	0.75 (0.0144)	0.75 (0.0147)	0.75 (0.0159)

[a] Predicted odds of having severe exacerbation in each month for the dupilumab groups is inflated by the inflation ratio.
[b] Predicted odds of having severe exacerbation in each month for the placebo groups is deflated by the deflation ratio.
q2w = once every 2 weeks
Source: Adapted from Applicant's Analysis

8.3.5.4. Primary Efficacy Analysis on Mean Change in pre-BD FEV1 (L) from Baseline

Results from the primary analysis on mean change in pre-BD FEV1 from baseline showed that both doses of dupilumab significantly improved lung function compared with matching placebo treatment, without obvious difference observed between the two dupilumab dose groups. In particular, the mean change in pre-BD FEV1 (L) from baseline was significantly higher for both dupilumab doses, with a mean difference of 0.14 (CI: 0.08, 0.19) for the 200-mg dose and 0.13 (CI: 0.08, 0.18) for the 300-mg dose, relative to the respective matching placebo group.

Table 52: EFC13579 - LS Mean Change in Pre-BD FEV1 (L) From Baseline to Week 12				
	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)
Estimate	0.18	0.32	0.21	0.34
LS mean difference		0.14		0.13
(95% CI)		(0.08, 0.19)		(0.08, 0.18)
p-value vs placebo		<.0001		<.0001

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.5.5. Sensitivity Analyses Mean Change in pre-BD FEV1 (L) from Baseline

Sensitivity analyses using different missing data handling methods provided similar results compared to the primary analysis. Results from an on-treatment analysis, PMM-MI, and control based PMM-MI are given in Table 53.

Table 53: Sensitivity Analysis on Change from Baseline in Pre-BD FEV1 (L) at Week 12				
	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo	Dupilumab	Placebo	Dupilumab
On-treatment analysis				
N	306	605	312	595
Estimate	0.18	0.32	0.21	0.34
LS mean difference		0.14		0.13
(95% CI)		(0.09, 0.19)		(0.08, 0.18)
p-value vs placebo		<.0001		<.0001
PMM-MI				
N	317	630	320	633
Estimate	0.19	0.33	0.22	0.34
LS mean difference		0.14		0.13
(95% CI)		(0.09, 0.19)		(0.08, 0.18)
p-value vs placebo		<.0001		<.0001
Control based PMM-MI				
N	317	630	320	633
Estimate	0.19	0.33	0.22	0.34
LS mean difference		0.14		0.13
(95% CI)		(0.08, 0.19)		(0.07, 0.18)
p-value vs placebo		<.0001		<.0001

CI = confidence interval; FEV1 = forced expiratory volume in 1 second; LS = least squares; PMM-MI = pattern mixture model-multiple imputation; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.5.6. Tipping Point Analysis Mean Change in pre-BD FEV1 (L) from Baseline

The Applicant's tipping point analyses assessed the treatment effect using multiple imputation under various missing not at random assumptions. For the FEV1 (L) endpoint, the imputed FEV1 values in the dupilumab groups (originally imputed under a MAR assumption) were subtracted by the shifting value, and imputed FEV1 values in the placebo groups were increased by the

shifting value. Tipping point analysis (Table 54 and Table 55) showed that the treatment effect remained significant ($p<0.05$) at various shifting values and confirmed the robustness of the study results.

Table 54: EFC13579 - Tipping Point Analysis of Change from Baseline in Pre-BD FEV1 (L) at Week 12 in Dupilumab 200 mg q2w vs. Placebo in 1.14 mL q2w

Shift in Dupilumab (L)[a]	Shift in Placebo (L)[b]									
	0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.8**	**1.0**
-0.1	0.13 (<.0001)	0.13 (<.0001)	0.13 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0002)
-0.2	0.13 (<.0001)	0.13 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0002)	0.10 (0.0003)
-0.3	0.13 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0001)	0.10 (0.0003)	0.10 (0.0004)
-0.4	0.12 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0001)	0.10 (0.0002)	0.10 (0.0004)	0.09 (0.0007)
-0.5	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0004)	0.09 (0.0007)	0.09 (0.0011)
-0.6	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0004)	0.09 (0.0007)	0.09 (0.0011)	0.09 (0.0017)
-0.7	0.11 (<.0001)	0.11 (<.0001)	0.11 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0005)	0.09 (0.0007)	0.09 (0.0011)	0.09 (0.0018)	0.08 (0.0027)
-0.8	0.11 (<.0001)	0.11 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0005)	0.09 (0.0008)	0.09 (0.0012)	0.09 (0.0018)	0.08 (0.0028)	0.08 (0.0042)
-0.9	0.11 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0005)	0.09 (0.0008)	0.09 (0.0013)	0.09 (0.0019)	0.08 (0.0029)	0.08 (0.0043)	0.08 (0.0064)
-1.0	0.10 (0.0003)	0.10 (0.0004)	0.10 (0.0006)	0.09 (0.0009)	0.09 (0.0014)	0.09 (0.0021)	0.08 (0.0031)	0.08 (0.0046)	0.08 (0.0066)	0.08 (0.0095)

[a] Imputed FEV1 values in dupilumab groups are subtracted by the shifting value.
[b] Imputed FEV1 values in placebo group are increased by the shifting value.
FEV1 = forced expiratory volume in 1 second; q2w = once every 2 weeks
Source: Adapted from Applicant's Analysis

Table 55: EFC13579 - Tipping Point Analysis of Change From Baseline in Pre-BD FEV1 (L) at Week 12 in Dupilumab 300 mg q2w vs. Placebo in 1.14 mL q2w

Shift in Dupilumab (L)[a]	Shift in Placebo (L)[b]									
	0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.8**	**1.0**
-0.1	0.12 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (0.0001)	0.10 (0.0002)	0.10 (0.0003)
-0.2	0.12 (<.0001)	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0004)
-0.3	0.12 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0005)	0.09 (0.0007)
-0.4	0.11 (<.0001)	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0001)	0.10 (0.0002)	0.10 (0.0002)	0.10 (0.0004)	0.09 (0.0006)	0.09 (0.0008)	0.09 (0.0012)
-0.5	0.11 (<.0001)	0.11 (<.0001)	0.10 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0004)	0.09 (0.0007)	0.09 (0.0010)	0.09 (0.0014)	0.09 (0.0020)
-0.6	0.10 (0.0001)	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0004)	0.09 (0.0005)	0.09 (0.0008)	0.09 (0.0011)	0.09 (0.0016)	0.08 (0.0023)	0.08 (0.0033)
-0.7	0.10 (0.0002)	0.10 (0.0003)	0.10 (0.0005)	0.09 (0.0007)	0.09 (0.0010)	0.09 (0.0014)	0.09 (0.0019)	0.08 (0.0027)	0.08 (0.0038)	0.08 (0.0053)
-0.8	0.10 (0.0004)	0.10 (0.0006)	0.09 (0.0009)	0.09 (0.0012)	0.09 (0.0017)	0.09 (0.0023)	0.08 (0.0033)	0.08 (0.0045)	0.08 (0.0061)	0.08 (0.0083)
-0.9	0.09 (0.0008)	0.09 (0.0011)	0.09 (0.0015)	0.09 (0.0021)	0.08 (0.0028)	0.08 (0.0039)	0.08 (0.0053)	0.08 (0.0072)	0.07 (0.0096)	0.07 (0.0128)
-1.0	0.09 (0.0014)	0.09 (0.0019)	0.09 (0.0026)	0.08 (0.0035)	0.08 (0.0047)	0.08 (0.0063)	0.08 (0.0084)	0.07 (0.0112)	0.07 (0.0147)	0.07 (0.0192)

[a] Imputed FEV1 values in dupilumab groups are subtracted by the shifting value.
[b] Imputed FEV1 values in placebo group are increased by the shifting value.
FEV1 = forced expiratory volume in 1 second; q2w = once every 2 weeks
Source: Adapted from Applicant's Analysis

8.3.5.7. Secondary Efficacy Analysis

The secondary efficacy endpoints were tested according to the pre-specified hierarchical order to control the overall type 1 error. Some of the key secondary endpoints in the study were: the annualized event rate of severe exacerbation and the absolute change from baseline in pre-BD FEV1 at week 12 in subgroups defined by different baseline eosinophil thresholds (0.15 Giga/L, 0.3 Giga/L); percentage change from baseline in pre-BDFEV1 at week 12; change from baseline in ACQ-5 at various time points; and change from baseline in AQLQ at various time points.

In patients with baseline blood eosinophil ≥0.3 Giga/L, both dupilumab dose groups exhibited a significant reduction in severe exacerbation rate (200 mg: 0.34, 95% CI: 0.24, 0.48; 300 mg: 0.32, 95% CI: 0.23, 0.45) and significantly greater mean change in pre-BD FEV1 (200 mg: 0.21, 95% CI: 0.13, 0.29; 300 mg: 0.24, 95% CI: 0.16, 0.32) compared to the matching placebo group (Table 56). Among the dupilumab dose groups, the treatment effect estimates were slightly higher for the 300 mg q2w dose compared to the 200 mg q2w dose.

Table 56: EFC13579 - Efficacy Analysis of Secondary Endpoints – ITT Population With Baseline Blood Eosinophil ≥0.3 Giga/L

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
Annualized event rate of severe exacerbation	**Placebo (N=148)**	**Dupilumab (N=264)**	**Placebo (N=142)**	**Dupilumab (N=277)**
Estimate	1.08	0.37	1.23	0.4
Rate Ratio		0.34		0.32
(95% CI)		(0.24, 0.48)		(0.23, 0.45)
p-value vs placebo		<.0001		<.0001
LS mean change in pre-BD FEV1 (L) from baseline to week 12				
Estimate	0.21	0.43	0.22	0.47
LS mean difference		0.21		0.24
(95% CI)		(0.13, 0.29)		(0.16, 0.32)
p-value vs. placebo		<.0001		<.0001

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

The analysis of secondary endpoint, annualized event rate of severe exacerbation defined on eosinophil thresholds 0.15 Giga/L showed that significant treatment difference was found in both dupilumab dose groups (Table 57). There was not a clear dose response comparing the 300 mg q2w dose and the 200 mg q2w dose.

Table 57: EFC13579 - Efficacy Analysis of Secondary Endpoints – ITT Population With Baseline Blood Eosinophil ≥0.15 Giga/L

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
Annualized event rate of severe exacerbation	**Placebo (N=232)**	**Dupilumab (N=437)**	**Placebo (N=237)**	**Dupilumab (N=452)**
Estimate	1.00	0.45	1.08	0.43
Rate Ratio		0.44		0.41
(95% CI)		(0.34, 0.58)		(0.31, 0.53)
p-value vs placebo		<.0001		<.0001
LS mean change in pre-BD FEV1 (L) from baseline to week 12				
Estimate	0.18	0.36	0.22	0.37
LS mean difference		0.17		0.15
(95% CI)		(0.11, 0.23)		(0.09, 0.21)
p-value vs. placebo		<.0001		<.0001

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

However, the reduction in the annualized event rate of severe exacerbation did not achieve statistical significance with either dose in patients with less than 0.3 Giga/L eosinophil level at baseline (Table 58). The rate ratio versus matching placebo in this subgroup was 0.76 (95% CI: 0.54, 1.05) for the 200 mg q2w dose and 0.83 (95% CI: 0.61, 1.14) for the 300 mg q2w dose. As a consequence, the hierarchical testing procedure broke at this endpoint, such that the p-values of remaining secondary endpoints should be considered not statistically significant.

Table 58: EFC13579 - Efficacy Analysis of Secondary Endpoints – ITT Population With Baseline Blood Eosinophil <0.3 Giga/L

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
Annualized event rate of severe exacerbation	**Placebo (N=156)**	**Dupilumab (N=340)**	**Placebo (N=167)**	**Dupilumab (N=332)**
Estimate	0.67	0.51	0.73	0.61
Rate Ratio		0.76		0.83
(95% CI)		(0.54, 1.05)		(0.61, 1.14)
p-value vs placebo		0.09		0.25
LS mean change in pre-BD FEV1 (L) from baseline to week 12				
Estimate	0.15	0.23	0.18	0.22
LS mean difference		0.08		0.04
(95% CI)		(0.01, 0.15)		(-0.03, 0.11)
p-value vs placebo		0.02		0.25

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

Results obtained for the subgroup of patients having a baseline eosinophil level less than 0.15 Giga/L were even less favorable. In this subgroup, there was no evidence of a treatment effect for either dose of dupilumab compared to matching placebo (Table 59). Furthermore, the rate ratios for the annualized event rate of severe exacerbation for dupilumab compared to matching placebo were near 1, with estimates of 0.92 (95% CI: 0.58, 1.47) for the 200 mg q2w dose and 1.14 (95% CI: 0.74, 1.76) for the 300 mg q2w dose. Similar results were obtained for the other primary endpoint, mean change in pre-BD FEV1 (L) from baseline to week 12. The estimated mean difference between the dupilumab group and the matching placebo group was 0.06 (95% CI: -0.04, 0.15) for the 200 mg q2w dose and 0.09 (95% CI: -0.01, 0.18) for the 300 mg q2w dose.

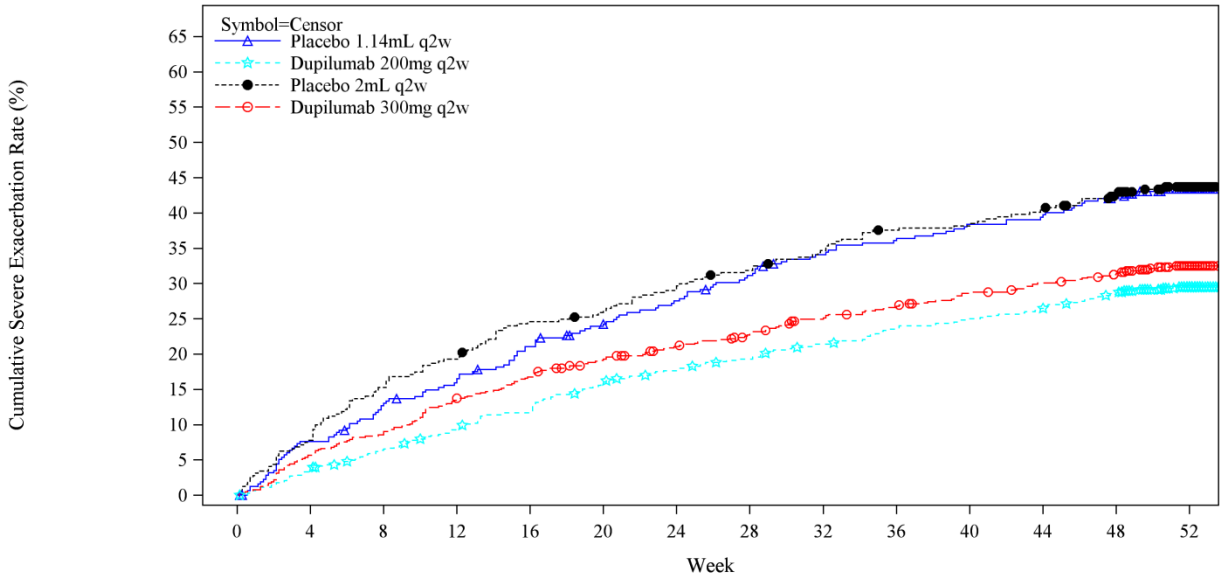
Table 59: EFC13579 - Efficacy Analysis of Secondary Endpoints – ITT Population With Baseline Blood Eosinophil <0.15 Giga/L

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
Annualized event rate of severe exacerbation	**Placebo (N=85)**	**Dupilumab (N=193)**	**Placebo (N=83)**	**Dupilumab (N=181)**
Estimate	0.51	0.47	0.64	0.73
Rate Ratio		0.92		1.14
(95% CI)		(0.58, 1.47)		(0.74, 1.76)
p-value vs placebo		0.74		0.52
LS mean change in pre-BD FEV1 (L) from baseline to week 12				
Estimate	0.13	0.18	0.11	0.19
LS mean difference		0.06		0.09
(95% CI)		(-0.04, 0.15)		(-0.01, 0.18)
p-value vs placebo		0.26		0.08

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

Kaplan-Meier analysis on the time to first severe exacerbation event during the 52-week treatment period in the ITT population showed that the dupilumab treatment groups had delayed exacerbation events compared to the placebo groups (Figure 17).

Figure 17: EFC13579 - Time to First Severe Exacerbation Event During 52-Week Treatment- ITT Population



Number at Risk

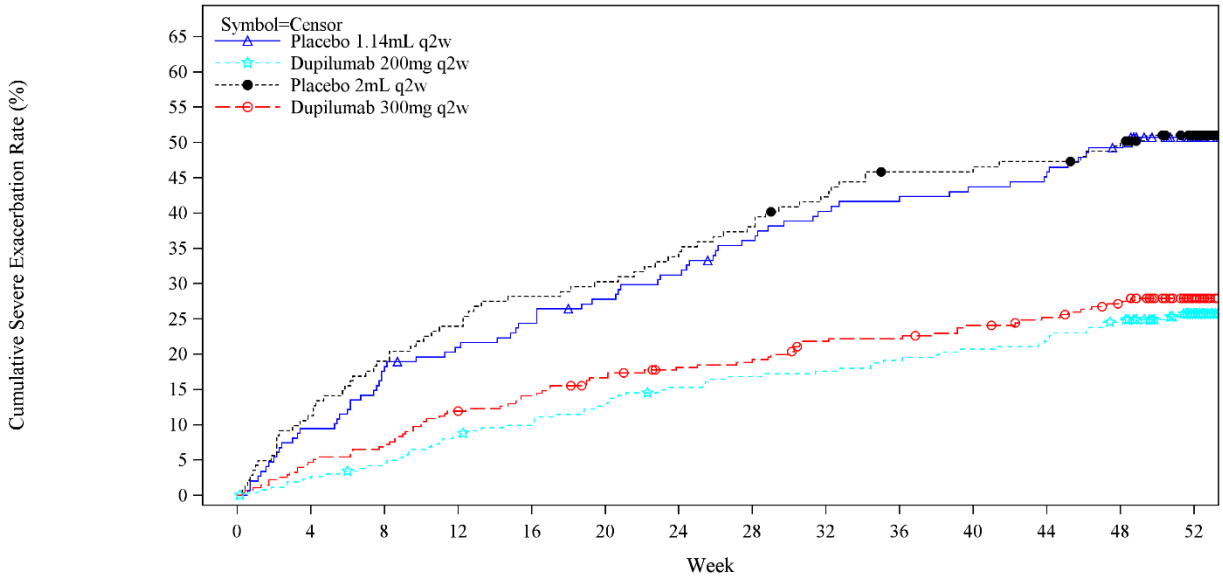
Placebo 1.14mL q2w	317	291	274	263	246	234	222	210	199	193	186	183	173	134
Dupilumab 200mg q2w	631	608	584	564	548	521	507	495	480	466	458	448	433	338
Placebo 2mL q2w	321	296	272	259	241	236	226	216	206	196	194	187	175	131
Dupilumab 300mg q2w	633	597	579	548	526	506	489	475	457	446	431	420	408	312

q2w = once every 2 weeks
Source: Statistical Reviewer

In addition, the Kaplan-Meier plot in the subgroup of patients with baseline blood eosinophils ≥0.3 Gig/L showed that the time to first severe exacerbation event during the treatment period

was delayed for the dupilumab 200 mg q2w group and 300 mg q2w group compared with the respective placebo groups (Figure 18).

Figure 18: EFC13579 - Time to First Severe Exacerbation Event During 52-week Treatment- ITT Population with Baseline Blood Eosinophil ≥0.3 Giga/L



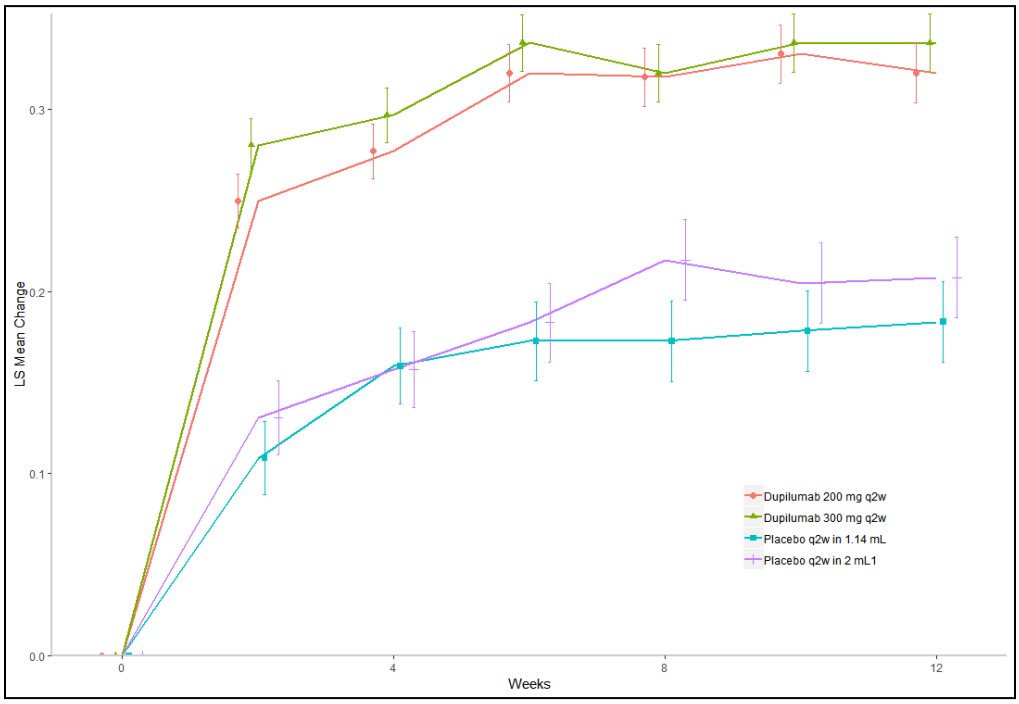
Number at Risk

Placebo 1.14mL q2w	148	134	122	116	111	105	100	92	86	84	81	79	72	52
Dupilumab 200mg q2w	264	257	250	240	235	227	220	216	214	210	206	203	195	154
Placebo 2mL q2w	142	126	115	108	102	99	94	88	81	75	75	73	69	54
Dupilumab 300mg q2w	277	264	258	244	237	228	221	219	209	208	202	197	189	145

ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

Mean change from baseline in pre-BD FEV1 over time was higher for the dupilumab groups than the placebo groups and the improvements were observed from week 2 onward and sustained through week 12 (Figure 19).

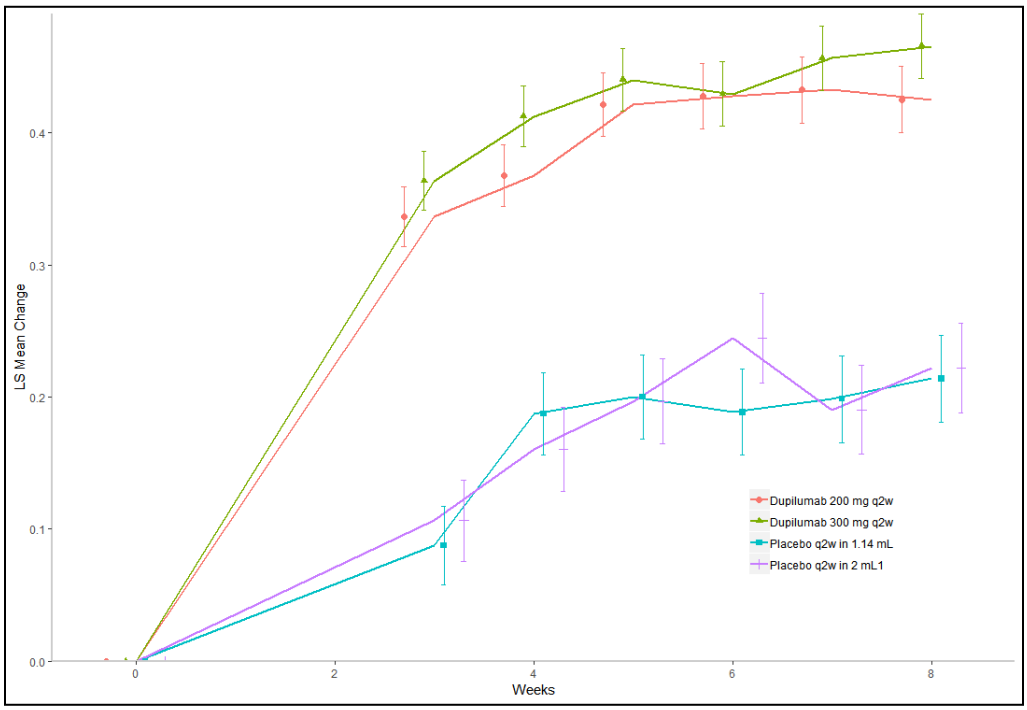
Figure 19: EFC13579 - LS Mean Change From Baseline in Pre-BD FEV1 (L) Over Time- ITT Population



FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

Similarly, the results were consistent in the subgroup of patients with baseline blood eosinophils ≥0.3 Gig/L (Figure 20).

Figure 20: EFC13579 - LS Mean Change from Baseline in Pre-BD FEV1 (L) Over Time - ITT Population with Baseline Blood Eosinophil ≥0.3 Giga/L



FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.6. Study EFC13691

The primary objective of study EFC13691 was to evaluate the efficacy of dupilumab 300 mg q2w, compared with placebo, for reducing the use of maintenance OCS in patients with severe steroid-dependent asthma. The primary endpoint was the percentage reduction of investigator prescribed OCS dose at week 24 compared with the baseline dose, while maintaining asthma control. The key secondary endpoints were: proportion of patients achieving a reduction of 50% or greater in their OCS dose at week 24 compared with baseline; and proportion of patients achieving a reduction of OCS dose to <5 mg/day at week 24 while maintaining asthma control.

8.3.6.1. Primary Efficacy Analysis

The primary analysis results (Table 60) show that the mean percent reduction in OCS dose at week 24 was greater in the dupilumab group (LS mean: 73.9%) compared with the placebo group (LS mean: 45.3%) with an absolute difference of 28.2% (95% CI: 15.81, 40.67).

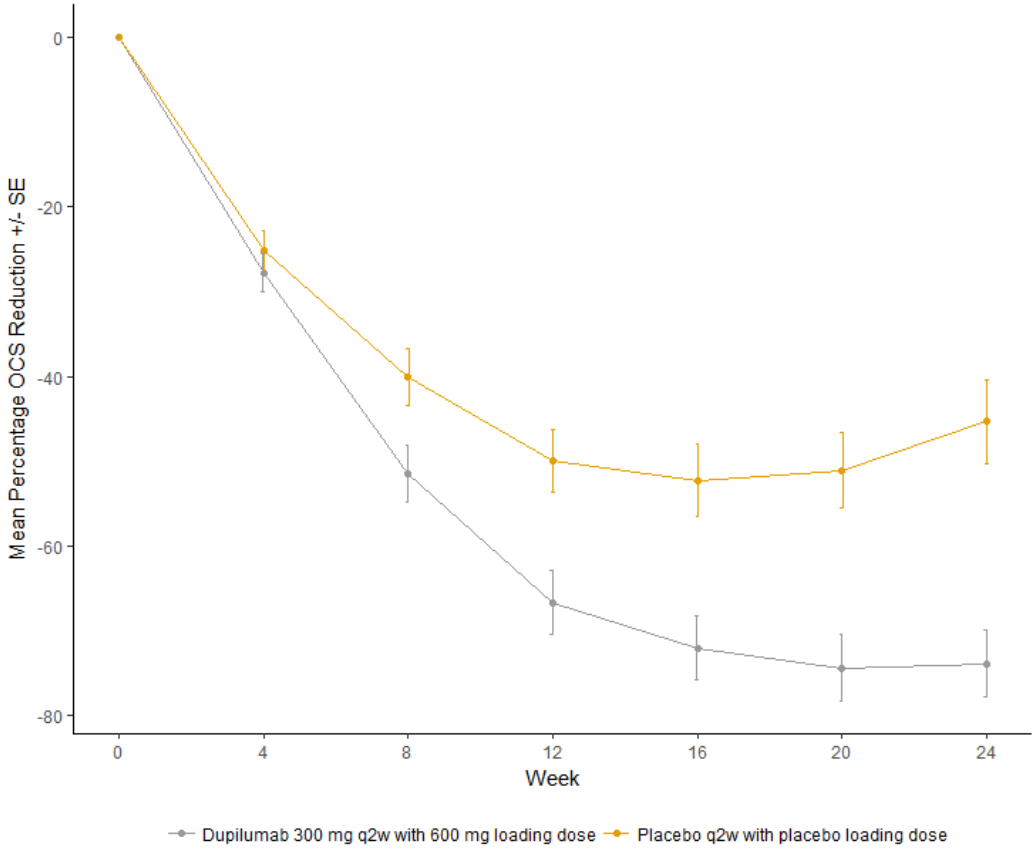
Table 60: EFC13691 - Percentage Reduction of OCS Dose (Mg/Day) at Week 24 – ITT Population

Percentage reduction from baseline	Placebo (N=107)	Dupilumab 300 mg q2w (N=103)
Mean (SD)	45.28 (50.73)	73.85 (39.78)
LS Mean (SE)	41.85 (4.57)	70.09 (4.90)
LS Mean Diff (95% CI)		28.24 (15.81, 40.67)
P-value		<.0001

CI = confidence interval; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks; SD = standard deviation; SE = standard error
Source: Statistical Reviewer

The mean percentage OCS reduction over time was greater for the dupilumab group compared to the placebo group (Figure 21).

Figure 21: EFC13691 - Mean Percentage Change OCS Reduction Over Time



OCS = oral corticosteroids; q2w = once every 2 weeks; SE =
Source: Statistical Reviewer

8.3.6.2. Sensitivity Analysis

There were only two patients in the dupilumab group and one in the placebo group who had missing data due to study discontinuation. The Applicant's sensitivity analyses using different

missing data handling approaches provided similar results compared to the primary analysis and confirmed the robustness of the conclusions to potential violations in missing data assumptions (data not shown).

8.3.6.3. Secondary Efficacy Analysis

The proportion of patients with ≥50% reduction in OCS dose compared with baseline at week 24 was significantly greater in the dupilumab group (80%) than in the placebo group (50%) (Table 61). The odds of a ≥50% reduction in the OCS dose was 3.9 times (95% CI: 2.1, 7.7) as high with dupilumab as compared to placebo (p<0.001).

Table 61: EFC13691 - Proportion of Patients With ≥50% Reduction OCS Dose Compared With Baseline at Week 24– ITT Population

Proportion of reduction from baseline	Placebo (N=107)	Dupilumab 300 mg q2w (N=103)
Estimate	**0.5**	**0.8**
Odds ratio vs. placebo (95% CI)		3.9 (2.1, 7.7)
P-value		<.001

ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

The proportion of patients achieving a reduction in OCS dose to <5 mg/day at week 24 was significantly greater in the dupilumab group (70%) than in the placebo group (30%) (Table 62). The odds of OCS dose reduction were 4.5 times (95% CI: 2.4, 8.4) higher with dupilumab as compared to placebo (p<0.001).

Table 62: EFC13691 - Proportion of Patients Achieving a Reduction of OCS Dose to <5 Mg/Day at Week 24– ITT Population

Proportion of reduction from baseline	Placebo (N=107)	Dupilumab 300 mg q2w (N=103)
Estimate	**0.3**	**0.7**
Odds ratio vs. placebo (95% CI)		4.5 (2.4, 8.4)
P-value		<.001

CI = confidence interval; ITT = intention to treat; OCS = oral corticosteroids; q2w = once every 2 weeks
Source: Statistical Reviewer

The dupilumab group also had a significant reduction in the annualized event rate of severe exacerbation compared to the placebo group (rate ratio: 0.41, CI: 0.26, 0.63) (Table 63).

Table 63: EFC13691- Annualized Event Rate of Severe Exacerbation – ITT Population		
	Placebo (N=107)	**Dupilumab 300 mg q2w (N=103)**
Number of Events	**78**	**31**
Estimate	1.60	0.65
Relative risk		0.41
(95% CI)		(0.26, 0.63)
p-value vs placebo		<.001

CI = confidence interval; ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

In addition, the mean change in pre-BD FEV1 from baseline was significantly higher (Table 64) for the dupilumab group with a mean difference of 0.22 (CI: 0.09, 0.34).

Table 64: EFC13691- Mean Change in Pre-BD FEV1 (L) From Baseline – ITT Population		
	Placebo (N=107)	**Dupilumab 300 mg q2w (N=103)**
LS Mean	0.01	0.22
Mean Difference		0.22
(95% CI)		(0.09, 0.34)
p-value vs placebo		<.001

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intention to treat; LS = least squares; q2w = once every 2 weeks
Source: Statistical Reviewer

8.3.7. Findings in Special/Subgroup Populations

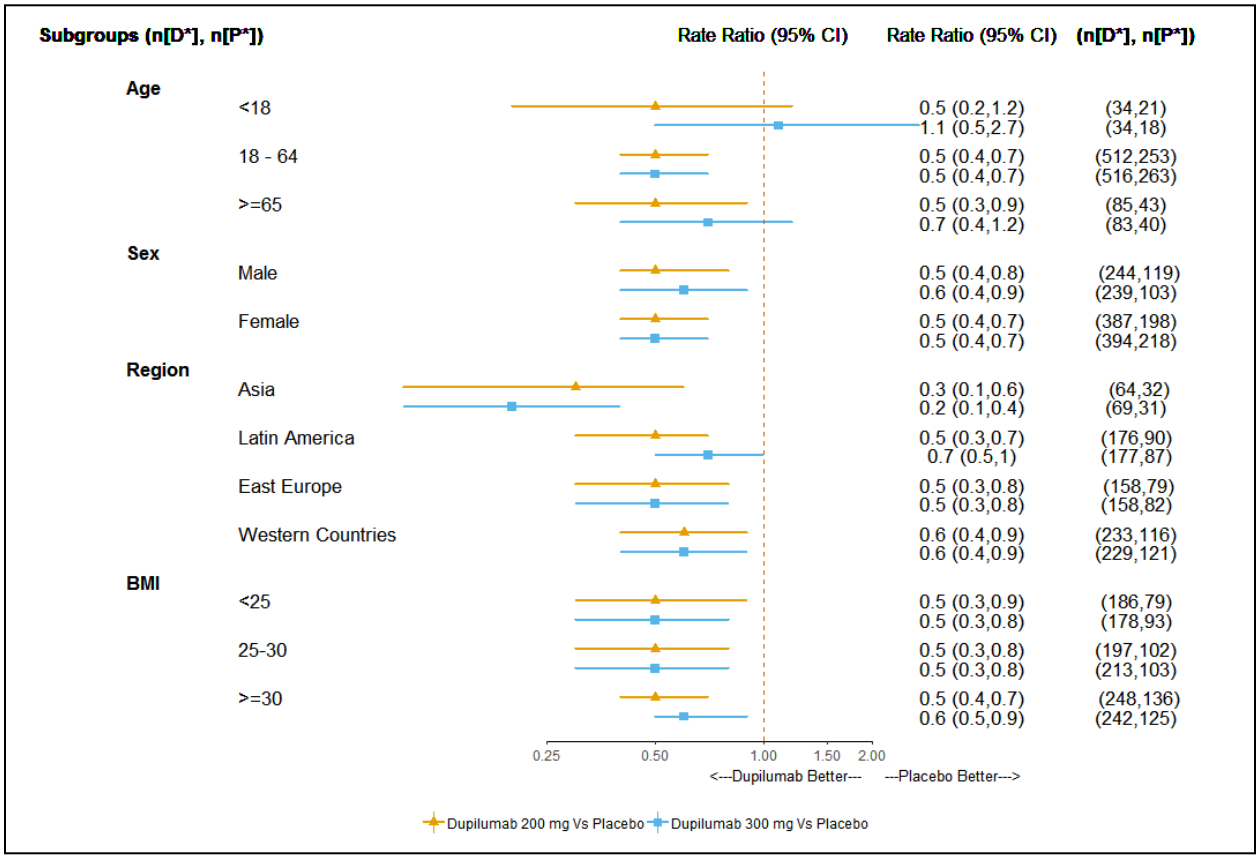
The subgroup analyses compared efficacy results across different subgroups defined by sex, region, age, race, baseline BMI values, FeNO, ICS dose levels, ACQ-5 score, number of prior exacerbations, and age of onset asthma. The consistency of the treatment effect on the primary efficacy endpoint across subgroups was analyzed using primary analysis methods.

8.3.7.1. Demographic and Baseline Disease Characteristics

Forest plots of rate ratios for the primary endpoint, annualized event rate of severe exacerbation, by various subgroups are presented in this section. Estimated effects were largely consistent across the subgroups. Of note, the reduction in the rate of severe exacerbation in the adolescent population (<18 years) was not statistically significant for either dose group (Figure 22). In addition, the rate was slightly higher for the 300 mg q2w dose group compared to the matching placebo group. However, the subgroup analyses in the adolescent population are subject to considerable uncertainty due to the small sample size (resulting in very wide confidence intervals). There was a large imbalance in the number of severe exacerbations in the prior year

(mean of 1.53 versus 2.22) between the dupilumab 300 mg q2w group and the matching placebo group.

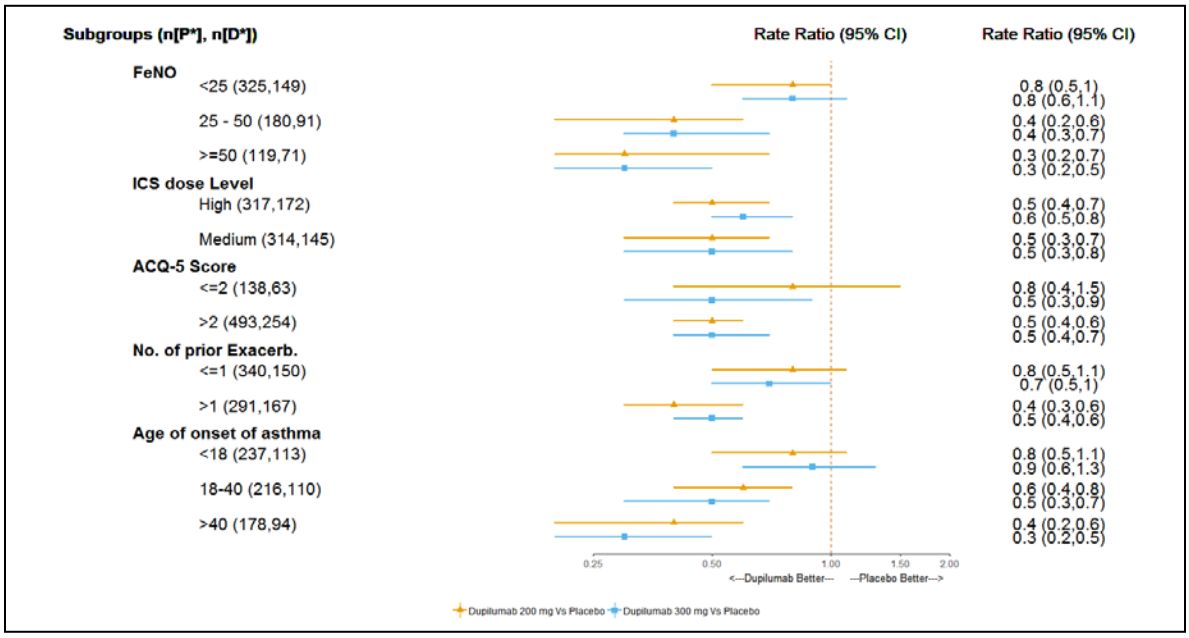
Figure 22: EFC13579 – Rate Ratio for Annualized Event Rate of Severe Exacerbation by Demographic Subgroups



n[D] = number of patients in the dupilumab group; n[P] = number of patients in the placebo group; BMI = body mass index; CI = confidence interval
Source: Statistical Reviewer

Among various subgroups defined by baseline disease characteristics, both dupilumab doses demonstrated largely consistent improvement over the matching placebo (Figure 23).

Figure 23: EFC13579 – Rate Ratio for Annualized Event Rate of Severe Exacerbation by Disease Subgroups

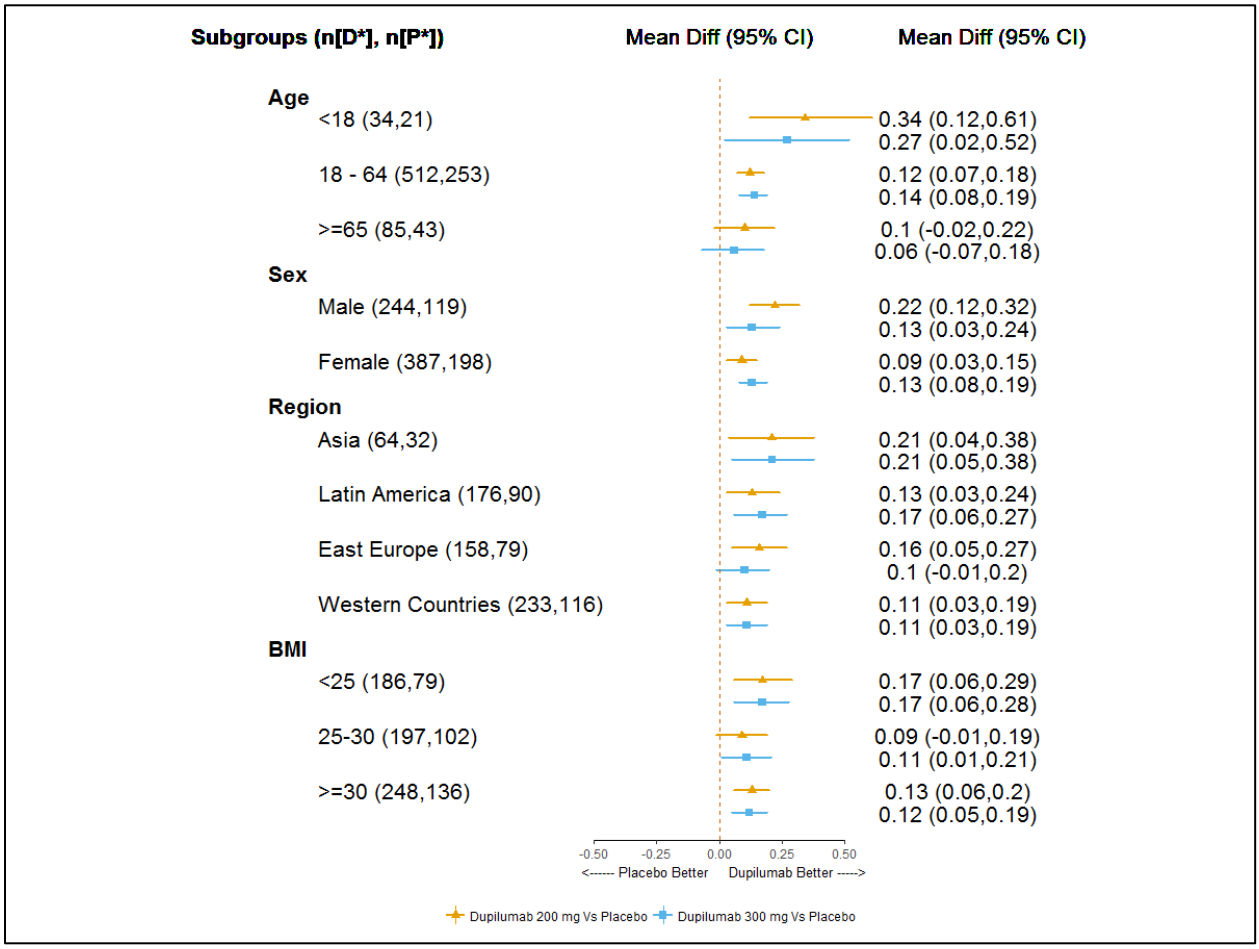


ACQ = Juniper Asthma Control Questionnaire; CI = confidence interval; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroids; n[D] = number of patients in the dupilumab group; n[P] = number of patients in the placebo group
Source: Statistical Reviewer

Patients in both dupilumab dose groups showed significant improvement in pre-BD FEV1 endpoint in the adolescent subgroup. Efficacy analysis on other demographic subgroups showed

that the improvement in lung function was consistently greater for the patients in the dupilumab dose groups compared to the matching placebo groups (Figure 24).

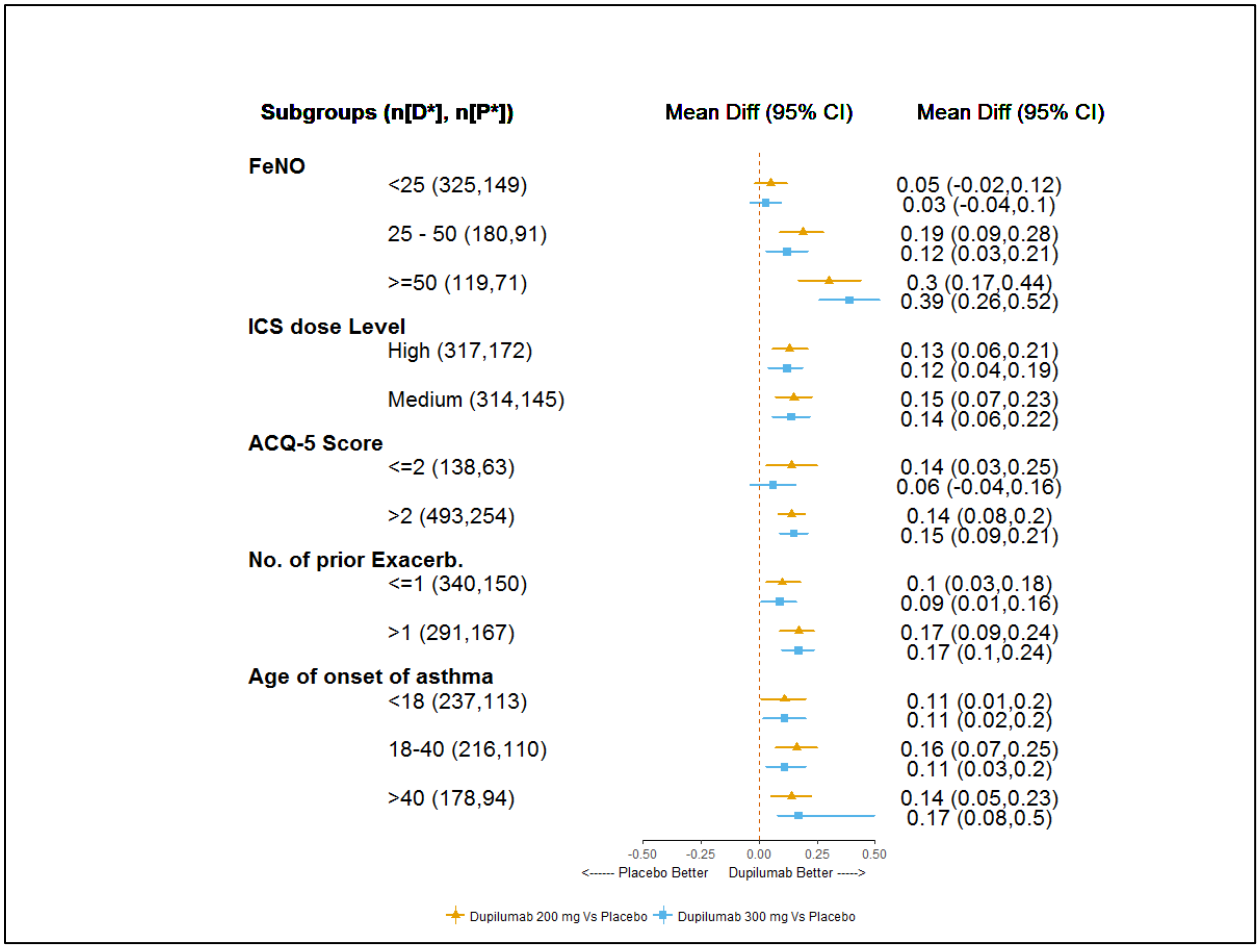
Figure 24: EFC13579 – Mean Change from Baseline in Pre-BD FEV1 (L) by Demographic Subgroups



n[D] =- number of patients in the dupilumab group; n[P] =- number of patients in the placebo group; BMI = body mass index; CI = confidence interval
Source: Statistical Reviewer

Both dupilumab doses demonstrated largely consistent improvement over the matching placebo in various subgroups defined by baseline disease characteristics (Figure 25).

Figure 25. EFC13579 – Mean Change from Baseline in Pre-BD FEV1 (L) by Disease Subgroups



n[D] = number of patients in the dupilumab group; n[P] = number of patients in the placebo group; BMI = body mass index; CI = confidence interval; ACQ = Juniper Asthma Control Questionnaire; FeNO = fractional exhaled nitric oxide; ICS = inhaled corticosteroids
Source: Statistical Reviewer

In summary, no significant treatment-by-subgroup interactions were observed for demographic subgroups including age, gender, region, race, and baseline weight and BMI, and estimates were largely consistent across the subgroups. Significant treatment-by-fractional exhaled nitric oxide subgroup interaction on severe exacerbation rate was observed (p=0.003 and 0.004 for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with matching placebo groups). For FEV1 endpoint, a significant quantitative treatment-by-fractional exhaled nitric oxide subgroup interaction was observed (p<0.001 and p<0.001 for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with matching placebo groups). Detailed analyses of eosinophil subgroups are discussed in 8.4.1.2.1.

8.4. Summary and Conclusions

This sBLA submission is a supplement to the original marketing application for the atopic dermatitis indication, supporting the addition of the asthma indication. Three efficacy studies were presented in this submission: phase 2b study DRI12544; phase 3 study EFC13579 in patients with moderate-to-severe persistent asthma; and phase 3 study EFC13691 in patients with OCS-dependent severe asthma.

8.4.1. Statistical Issues

The following statistical issues have been identified during the review process.

8.4.1.1. Missing Data and Sensitivity Analyses

In study DRI12544, 732 (94.3%) patients completed the 12-week primary efficacy endpoint treatment period, and 709 (91.4%) patients completed the entire treatment period (24 weeks). Percentages of patients who completed the entire treatment period were comparable across the five treatment groups and ranged between 135 (87.7%) and 149 (94.9%) patients. Discontinuation from the study was lower for dupilumab 300 mg q2w (7 (4.5%)) compared to other treatment arms (placebo:12 (7.6%), dupilumab 200 mg q4w: 15 (9.7%), dupilumab 300 mg q4w: 15 (9.6%), dupilumab 200 mg q2w: 11 (7.3%)). Withdrawal from the study due to patient's request was largely similar across the studies. In the primary analyses, data collected after treatment discontinuation was set as missing, and no imputation was performed for the MMRM model. However, sensitivity analyses showed consistent results, with a statistically significant improvement in FEV1 at week 12 for dupilumab 300 mg q4w, 200 mg q2w, and 300 mg q2w doses as compared to placebo.

In study EFC13579, there were 1,897 randomized and treated patients, and 228 (11.9%) patients discontinued the treatment (placebo (combined): 73 (11.4%), dupilumab (combined): 155 (12.3%)). Early treatment discontinuation was balanced across treatment groups, with a slightly higher percentage of patients discontinuing in the dupilumab 300 mg q2w (13.4%) compared to the dupilumab 200 mg q2w group (11.1%); treatment discontinuations in the placebo groups were reported in 10.9% and 12.0% of patients. In addtion,103 patients discontinued from the study prior to Week 52 - placebo (1.14mL): 17 (5.4%), dupilumab 200 mg: 28 (4.4%), placebo (2mL): 17 (5.3%) and dupilumab 300 mg: 41 (6.5%). Discontinuation from study was similar across the treatment arms (placebo (combined): 34 (5.3%), dupilumab (combined): 69 (5.5%)).

Out of 103 patients discontinued from the study, 84 patients (placebo (combined): 30 (4.7%), dupilumab (combined): 54 (4.3%)) discontinued upon patient's request. Study discontinuation due to patient's request was largely similar across the treatment arms: placebo (1.14mL): 1 14 (4.4%), dupilumab 200 mg: 23 (3.6%), placebo (2mL): 16 (5.0%) and dupilumab 300 mg: 31 (4.9%)

The primary analyses targeted the de-facto estimand, i.e., compared outcomes between patients randomized to the dupilumab and placebo arms, regardless of adherence to assigned treatments

or ancillary therapies. The primary analyses relied on a missing-at-random assumption. Tipping point analyses were performed to gauge the extent to which the demonstration of a treatment effect was dependent on the missing at random assumption. In this study, tipping point analysis and different sensitivity analyses showed consistent evidence of effects under varying missing data assumptions and therefore supported the findings of the key efficacy analyses.

In study EFC13691, early treatment discontinuation was generally low, with frequencies of two (1.9%) for the dupilumab group versus five (4.7%) for the placebo group. One patient in the dupilumab group discontinued from the study prior to week 24, and no patient discontinued from the study prior to week 24 in the placebo group. Moreover, the Applicant's sensitivity analysis supported the robustness of the primary analysis.

In summary, the key conclusions from the three studies are considered convincing notwithstanding the missing data.

8.4.1.2. Interpretation of Subgroup Analysis Finding

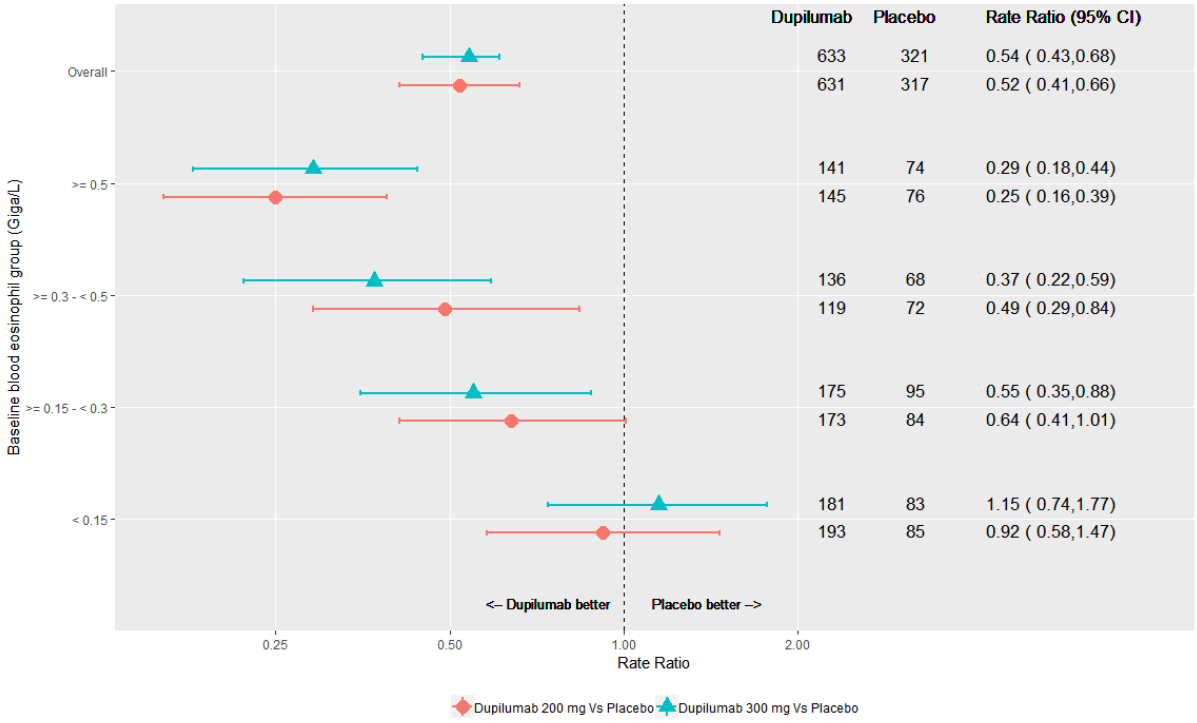
8.4.1.2.1. Eosinophil subgroups

The proposed indication for dupilumab was as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, (b) (4) . However, subgroup analyses based on various baseline eosinophil categories suggested that eosinophilia may modify the effect of dupilumab on both primary endpoints of annualized rate of severe exacerbation and change in FEV1 at week 12. Considering that the phase 2 study was designed to show efficacy in the high baseline eosinophilic population, there was a priori and plausible expectation of interaction between treatment and eosinophilic level. In fact, there was statistical evidence of interaction and there was lack of benefit or even consistent trends toward benefit in low eosinophilic group (e.g., <0.15 Giga/L).

In the large phase 3 study, EFC13579, the reduction of exacerbation events was not statistically significant in either dose group in the low baseline eosinophil subgroup (<0.15 Giga/L) with rate ratios (200 mg: 0.92, CI: 0.58, 1.47; 300 mg: 1.15, CI: 0.74, 1.77). Importantly, the estimated rate ratios were near 1, with the estimated event rate on the dupilumab 300 mg q2w dose group actually slightly higher than the estimated event rate on the matching placebo. In general, trends toward higher reductions in exacerbation rates on dupilumab were observed in patients with higher baseline eosinophil counts (Figure 26).

Treatment by interaction tests on the annualized rate of severe exacerbation events across baseline blood eosinophil categories showed significant results. In particular, a significant quantitative treatment-by subgroup interaction was observed ($p<0.001$ and $p<0.001$ for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with matching placebo groups comparing subgroups with baseline blood eosinophils ≥0.3 Giga/L versus <0.3 Giga/L). In addition, an interaction test on a four-category eosinophil subgroup variable (<0.15 Giga/L, ≥0.15 to <0.3 Giga/L, ≥0.3 to <0.5 Giga/L, ≥0.5 Giga/L) showed a significant treatment-by-subgroup interaction ($p<0.001$ and $p<0.001$ for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively). Significant results were also obtained in the interaction test between treatment and observed eosinophil measurement at baseline as a continuous variable ($p<0.001$).

Figure 26: EFC13579 - Annualized Event Rate of Severe Exacerbation by Subgroups Defined by Baseline Blood Eosinophil (Giga/L)

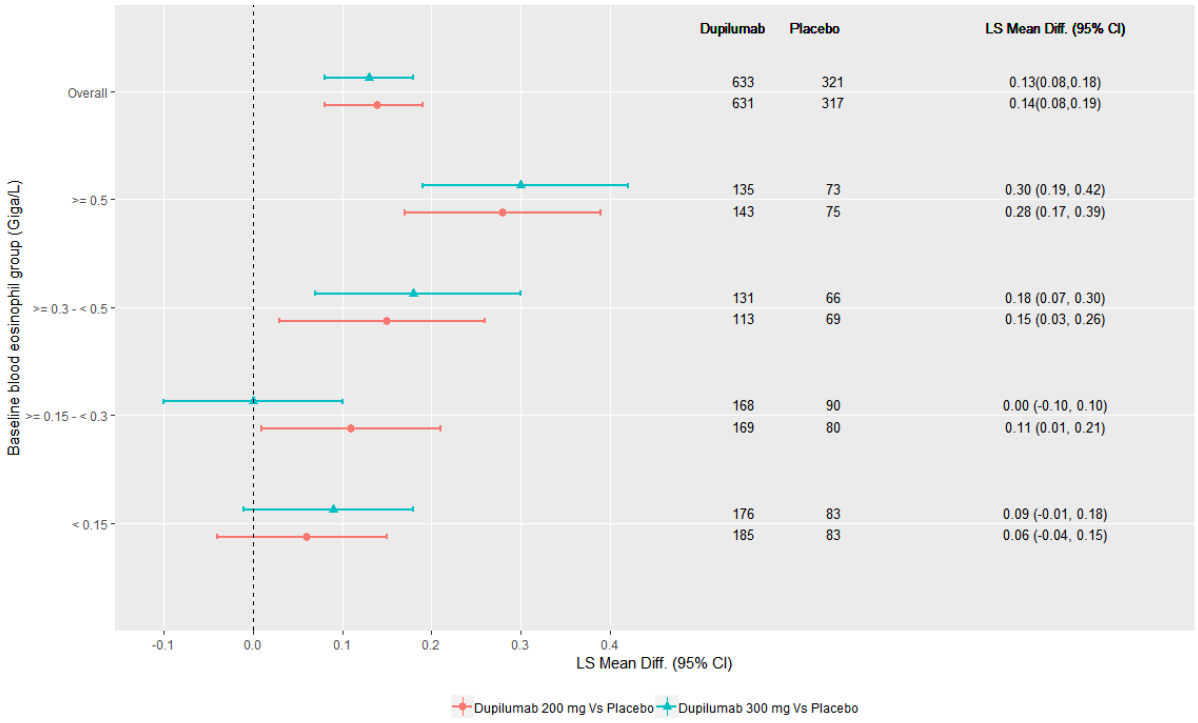


CI = confidence interval
Source: Statistical Reviewer

Similar results were obtained for the other primary endpoint; change from baseline in pre-BD FEV1 at Week 12. The improvement in FEV1 was not statistically significant in either dose group in the low baseline eosinophil subgroup (<0.15 Giga/L) (200 mg: 0.09, CI: -0.01, 0.18; 300 mg: 0.06, CI: -0.04, 0.15). Higher improvements in FEV1 on dupilumab compared to placebo were observed in patients with higher baseline eosinophil counts (Figure 27). Treatment by interaction tests on change from baseline in pre-BD FEV1 endpoint demonstrated statistically significant interaction between treatment groups and baseline eosinophil level. For example, comparing subgroups with baseline blood eosinophils ≥0.3 Giga/L versus <0.3 Giga/L, a significant quantitative treatment-by-subgroup interaction was observed (p=0.02 and p<0.001 for

the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with matching placebo groups).

Figure 27: EFC13579 Change from Baseline in Pre-BD FEV1 (L) at Week 12 by Subgroups Defined by Baseline Blood Eosinophil (Giga/L)

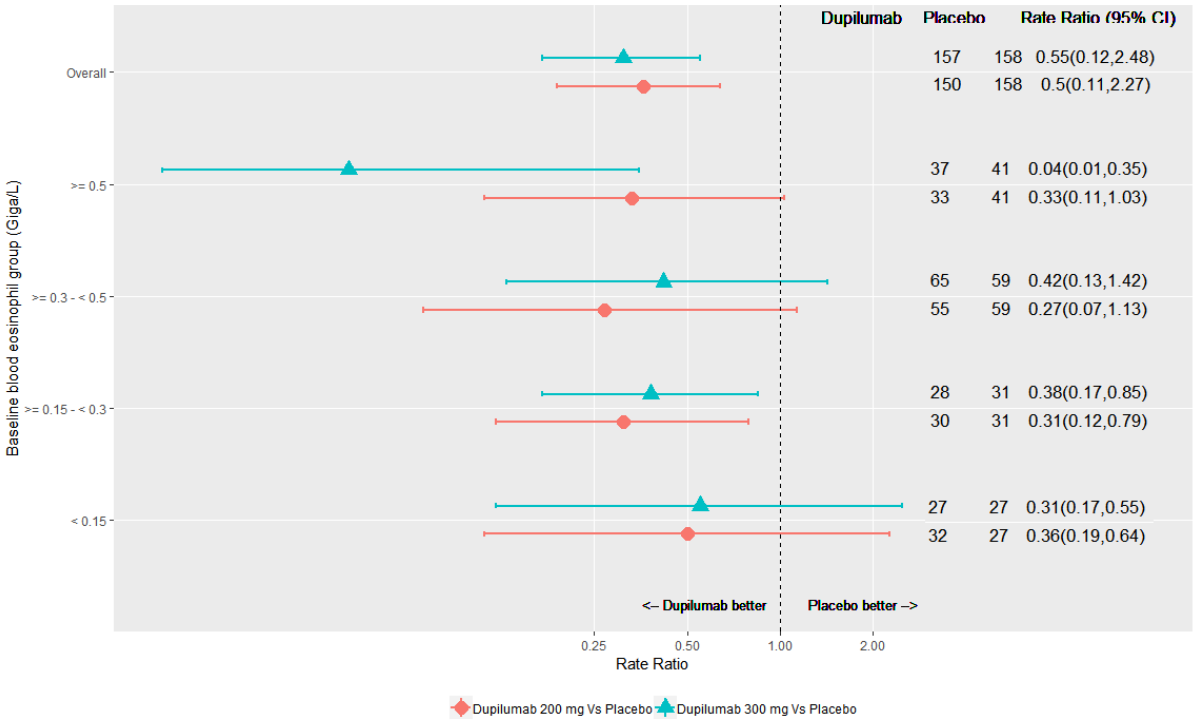


CI = confidence interval; FEV1 = forced expiratory volume in 1 second; LS = least squares
Source: Statistical Reviewer

The results for severe exacerbation rates were somewhat similar in study DRI12544, with some trends toward smaller estimated effects in the subgroups with lower baseline eosinophil levels

(Figure 28). Sample sizes within subgroups were smaller in this phase 2 study, leading to greater uncertainty around subgroup estimates than in the phase 3 study.

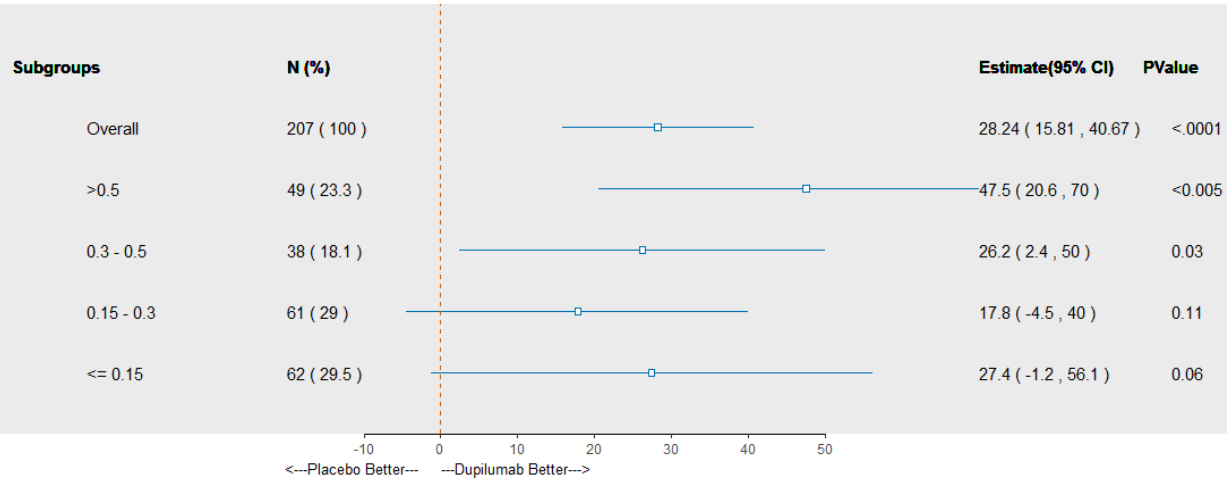
Figure 28: DRI12544 Annualized Event Rate of Severe Exacerbation by Subgroups Defined by Baseline Blood Eosinophil (Giga/L)



CI = confidence interval; ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

However, the subgroup analysis of percentage of OCS reduction in Study EFC139 did not demonstrate a clear association with eosinophil level (interaction p-value= 0.33). The percentage reduction of OCS dose across eosinophil subgroups is displayed below (Figure 29).

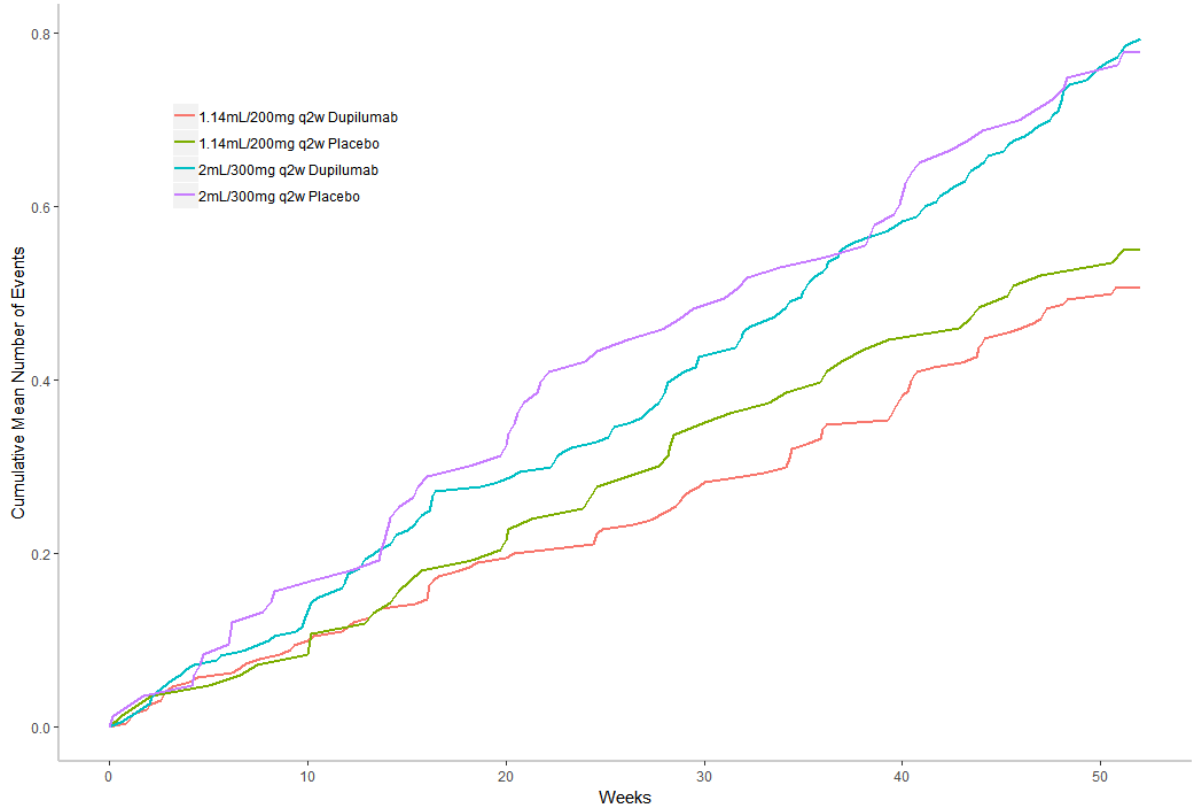
Figure 29: EFC13696: Percentage Reduction of OCS dose at Week 24 by eosinophil subgroups



Source: Statistical reviewer

The cumulative mean number of severe exacerbation events over time for the low baseline eosinophilic subgroup (<0.15 Giga/L) in study EFC13579 is shown in Figure 30. This plot also shows a lack of consistent separation between the dupilumab and matching placebo groups.

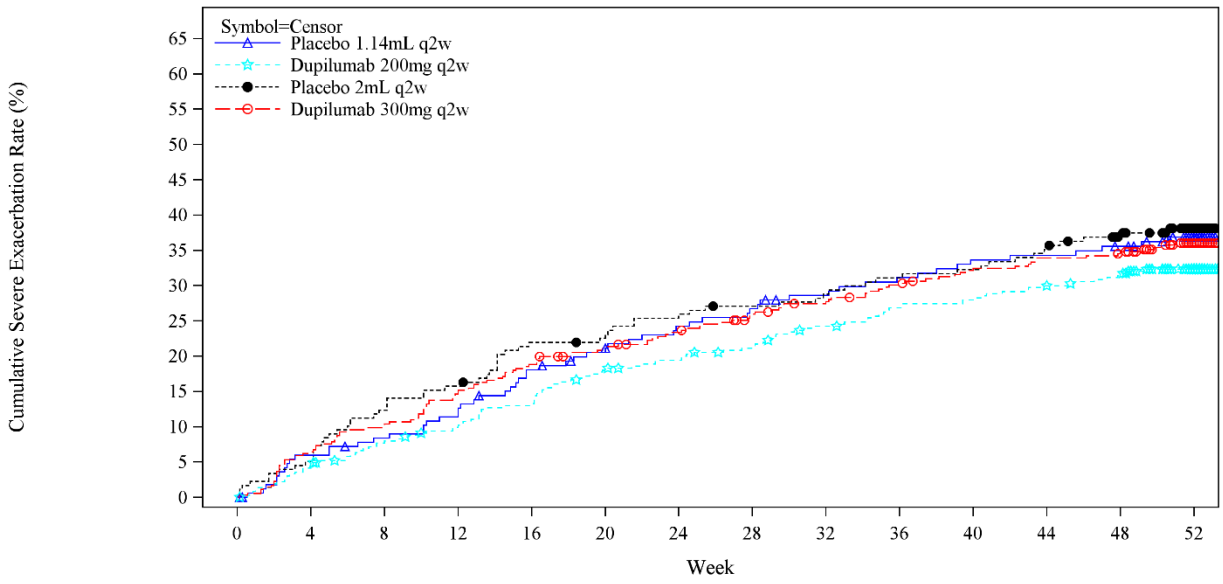
Figure 30: EFC13579- Cumulative Mean Functions for the Number Of Severe Exacerbation Events- ITT Population with Baseline Blood Eosinophil <0.15 Giga/L



ITT = intention to treat; q2w = once every 2 weeks
Source: Statistical Reviewer

Kaplan- Meier analysis on the time to first exacerbation event during the 52-week treatment period in the low eosinophil population (<0.15 Giga/L) did not show that the dupilumab treatment groups delayed exacerbation events compared to the placebo groups (Figure 31).

Figure 31: EFC13579- Time to First Severe Exacerbation Event During 52-Week Treatment - ITT Population with Baseline Blood Eosinophil <0.3 Giga/L



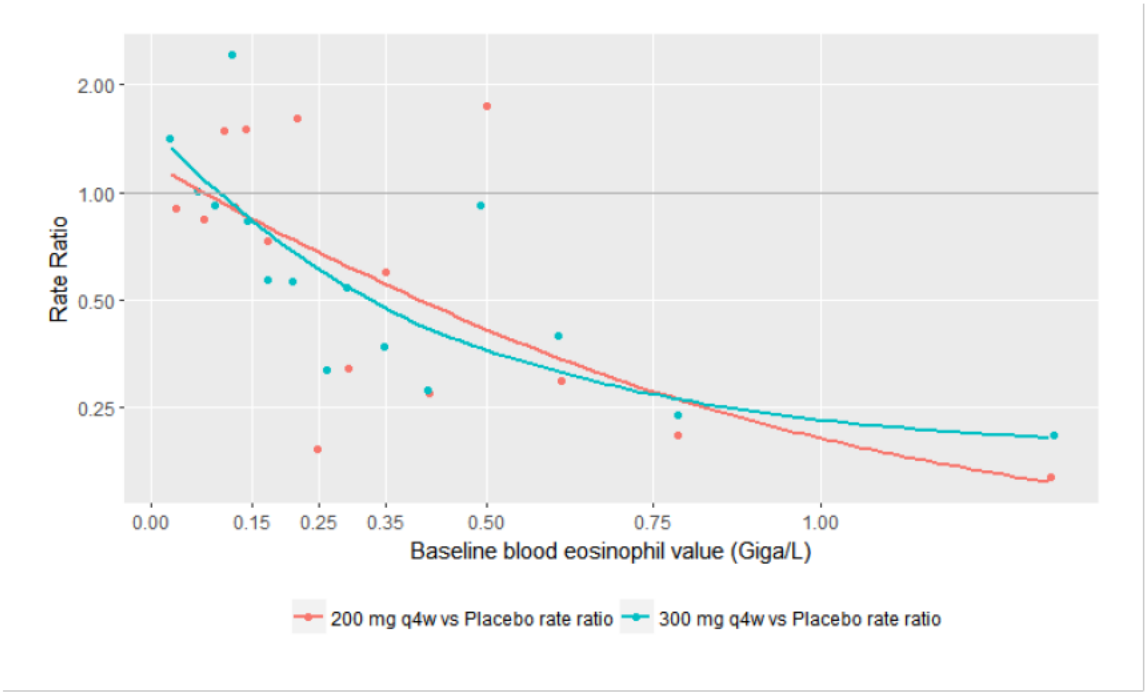
Number at Risk

Placebo 1.14mL q2w	169	157	152	147	135	129	122	118	113	109	105	104	101	82
Dupilumab 200mg q2w	366	350	333	323	312	293	286	278	265	255	251	244	237	183
Placebo 2mL q2w	178	169	156	150	138	136	131	127	124	120	118	113	105	76
Dupilumab 300mg q2w	356	333	321	304	289	278	268	256	248	238	229	223	219	167

q2w = once every 2 weeks
Source: Statistical Reviewer

Spline regression analysis to estimate rate ratios across different baseline eosinophil values provided similar results. Estimated rate ratios for both doses versus placebo approached one (equivalence with placebo) in patients with lower eosinophil values (Figure 32).

Figure 32: EFC13579- Spline Regression of Rate Ratio Across Baseline Eosinophil Values



q4w = once every 4 weeks
Source: Statistical Reviewer

An information request was issued on June 18, 2018, asking the Applicant to provide further justification for (b) (4) [redacted]. Therefore, the Applicant's claim (b) (4) [redacted] is not supported by statistical evidence.

8.4.1.2.2. Efficacy in the adolescent subgroup

Studies EFC13579 and EFC13691 included adolescent patients, with 107 (5.6%) and three (1.4%) patients respectively. In study EFC13579, the rate of severe exacerbations in the adolescents was slightly higher for the dupilumab 300-mg dose compared to matching placebo. However, there was a favorable trend for the dupilumab 200 mg q2w dose compared to the matching placebo, and improvement in lung function was found in this subgroup with both dose groups. The inconsistency of results in exacerbation rate could be due to the small sample size in the adolescent population (confidence intervals are very wide) and/or a large imbalance in the number of severe exacerbations in the prior year (mean of 1.53 versus 2.22) between the dupilumab 300 mg q2w group and the matching placebo group. In addition, the approval decision in 12 to 17 age group can be made considering the clinical team's benefit-risk assessment given in Section 1.3 .

8.4.1.3. Hierarchical Testing and multiple endpoints

The Applicant used a hierarchical sequential testing procedure to control the overall type 1 error rate for the analysis of the primary and the key secondary efficacy endpoints. The analysis of both primary endpoints was found to be statistically significant. However, the secondary analysis of the annualized exacerbation rate in the subgroup of low eosinophilic patients was not statistically significant, hence, the additional analyses in the hierarchy are considered nominal. However, (b) (4)

8.4.1.4. Patients who were ongoing in the study

The applicant amended the protocol to add approximately 220 patients to provide additional exposure to dupilumab manufactured with the intended commercial process. At the time of the data cutoff date, 235 patients with ongoing treatment had completed at least 47 weeks of the 52-week treatment period. Analysis on the patients who were treated with the new process showed that there was no noticeable difference in the efficacy estimates compared to the ITT analysis (Table 65). In addition, the results obtained from the efficacy analysis of primary endpoints after excluding the patients ongoing in the study were similar to the results obtained from the analysis of ITT population. Although the study was not intended to compare the efficacy of manufacturing processes, the statistical analysis showed that there were no apparent reasons to question the efficacy of dupilumab manufactured with the intended commercial process.

Table 65: EFC13579 - Efficacy Analysis of Primary Endpoints (New Commercial Process)				
	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
Annualized event rate of severe exacerbation	Placebo (N=85)	Dupilumab (N=193)	Placebo (N=83)	Dupilumab (N=181)
Estimate	0.85	0.45	1.18	0.50
Rate Ratio		0.53		0.42
LS mean change in pre-BD FEV1 (L) from baseline to week 12				
Estimate	0.22	0.37	0.19	0.39
LS mean difference		0.15		0.24

BD = bronchodilator; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; LS = least squares
Source: Statistical Reviewer

8.4.2. Collective Evidence

Results from the primary efficacy analyses showed that both dupilumab dose groups had a statistically significant lower severe exacerbation event rate than their matching placebo groups. In study EFC13579, patients in the dupilumab groups experienced a roughly 50% reduction compared to placebo in severe exacerbation rate during the study period (200 mg: 0.52, 95% CI: 0.41, 0.66; 300 mg: 0.54, 95% CI: 0.43, 0.68). The mean change in pre-BD FEV1 (L) from baseline was significantly higher for both doses of dupilumab, with a mean difference versus placebo of 0.14 (95% CI: 0.08, 0.19) for the 200-mg dose and 0.13 (95% CI: 0.08, 0.18) for the 300-mg dose. The results from the analyses of the other studies and secondary endpoints were generally supportive to those of the primary analysis of study EFC13579.

The results from study DRI12544 showed that the three highest doses of dupilumab (200 mg q2w, 300 mg q2w, 300 mg q4w) demonstrated a statistically significant improvement in FEV1 (L) at week 12 in comparison with placebo. The LS mean differences from placebo at week 12 were 0.26 (95% CI: 0.11, 0.40) for 200 mg q2w and 0.21 (95% CI: 0.06, 0.36) for 300 mg q2w. Moreover, the primary analysis results from study EFC13691 showed that the mean percent reduction in OCS dose at week 24 was greater in the dupilumab group (LS mean: 73.9%) compared with the placebo group (LS mean: 45.3%) with a difference of 28.2% (95% CI: 15.8, 40.7). Furthermore, the missing data in important analyses was not a major issue, given that tipping point analyses and other sensitivity analyses largely supported the key efficacy results in the studies.

The Applicant's proposal to (b) (4)

(b) (4)

Therefore, is not recommended.

Thus, the collective evidence from the clinical studies supports the efficacy of dupilumab in patients with moderate-to-severe asthma, and with an eosinophilic phenotype.

8.4.3. Conclusions and Recommendations

In summary, there was evidence of efficacy for dupilumab from the three studies that were reviewed under this supplemental application. Therefore, the overall package provides substantial evidence of efficacy of dupilumab as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, and with an eosinophilic phenotype.

8.4.4. Labeling Recommendations (as applicable)

The focus of the labeling review will be on Section 14 Clinical Studies. Edits to the labeling are pending. (b) (4) .

See signature page	See signature page
X	X
Primary Statistical Reviewer	Statistical Team Leader
Ginto Pottackal	Youngman Kim

9. Pediatrics

Efficacy and safety information for the adolescent population 12 to 17 years of age is presented throughout this review. For the population of 6- to 11-year-olds, the Applicant submitted its amended initial pediatric study protocol in December 2016, and it was agreed to in March 2017. The initial pediatric study protocol includes a deferral for <12 years. Previously, the Applicant had requested a waiver for <6 months; however, the Division advised the Applicant to remove the waiver request as the Division has not determined the appropriate age cut-off for a waiver as this would likely be driven by the phase 3 efficacy/safety results in adolescents/adults as well as the severity of asthma targeted.

The Applicant is requesting a deferral for the planned pediatric clinical studies in asthma patients <12 years of age as they will not be completed at the time of the asthma sBLA submission for

adults and adolescents (12 to 18 years of age). A randomized, placebo-controlled, double-blind study efficacy and safety study in 470 subjects age 6 to 11 years old was initiated April 2017, with an expected submission date of August 2022. The sponsor also proposes to conduct an efficacy and safety trial in children <6 years of age with asthma. No waiver is requested with this supplemental BLA. Per the Applicant, the definition and prevalence of the proposed asthma phenotype in children is unclear, making it difficult to confirm the appropriate cut-off age for which pediatric studies should be waived. This review is recommending a safety and efficacy study in children aged 2 to < 6 years of age with a continued safety evaluation out to a minimum of 52 weeks.

The atopic dermatitis approval included post-marketing requirements for a 1-year, open-label, long-term safety and safety, PK, and efficacy study in children down to 6 months of age.

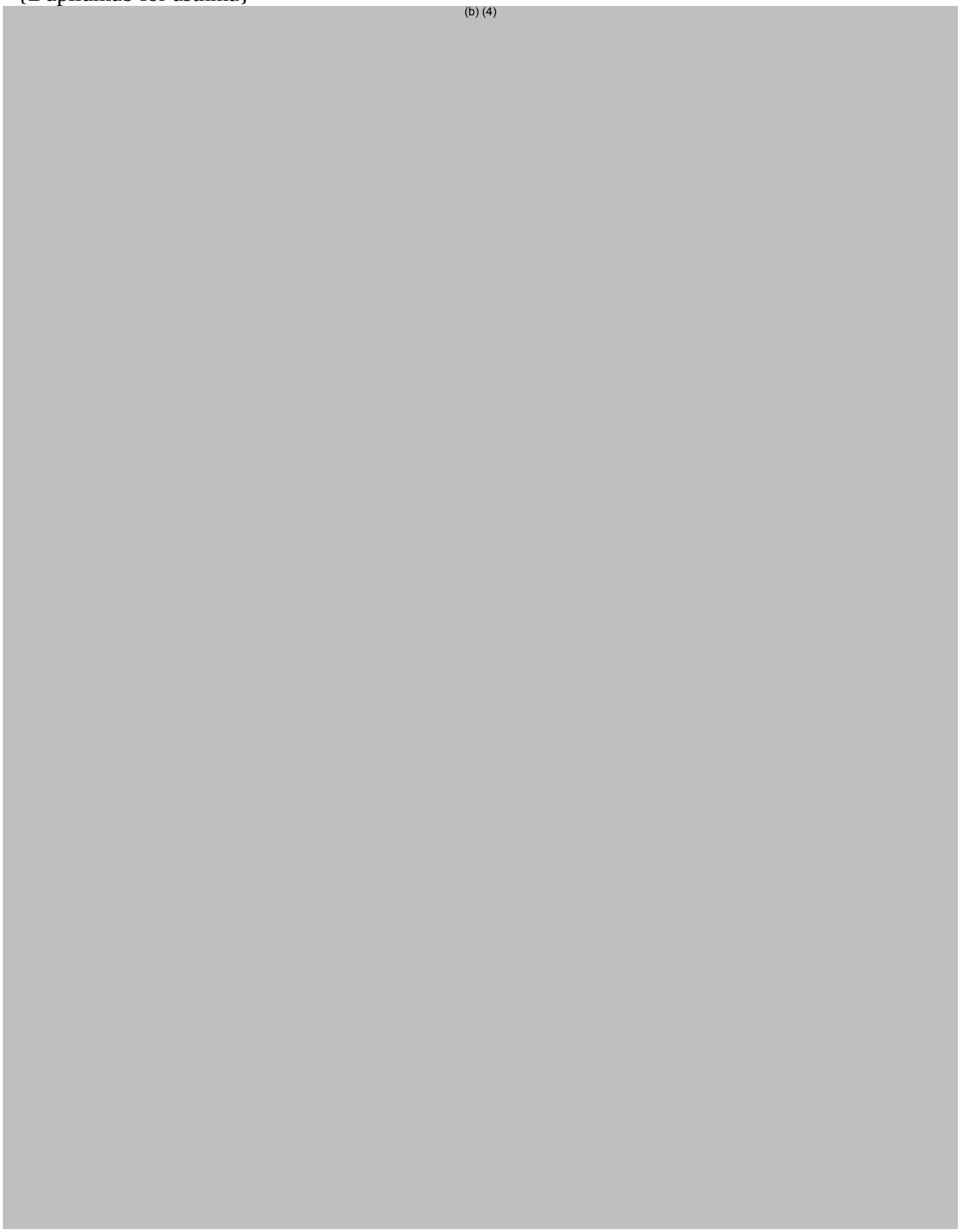
This review recommends a waiver in <2 years of age as asthma the diagnosis of asthma is not clearly established in this age group making studies impossible or highly impractical.

The Pediatric Review Committee discussed this supplemental BLA on October 10, 2018 and agreed with the waiver for children <2 years of age as studies are impossible or highly impractical and of age and the deferral for patients 2 to 11 years. The Pediatric Review Committee was also in agreement with the proposed pediatric studies outlined above.

10. Labeling Recommendations

10.1. Prescribing Information

(b) (4)



(b) (4)

Reviewer comment: During labeling discussion with the sponsor several issues were addressed.

(b) (4)

11. Postmarketing Requirements and Commitments

This review recommends that the sponsor complete the ongoing 52-week efficacy and safety trial in children 6 to < 12 years of age with moderate to severe asthma (Study EFC14153). The sponsor agreed to the timelines below:

Final Protocol Submission:	10/16
Study/Trial Completion:	01/22
Final Report Submission:	08 /22

This review also recommends that the sponsor 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). The sponsor agreed to the timelines below:

Final Protocol Submission:	09/20
Study/Trial Completion:	12/26
Final Report Submission:	06/27

12. Appendices

12.1. Appendix 1: Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

NDA/BLA Number	BLA761055
Generic Name	Dupilumab
Trade Name	DUPIXENT
Submission Type	Supplemental NDA (Supplement 7 - Efficacy)
Sponsor	Regeneron Pharmaceuticals, Inc.
Dosage Form and Strengths	300 mg/2 mL solution and 200 mg/1.14 mL solution in a single-dose pre-filled syringe with needle shield
Proposed Indication (current submission)	• as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older. (b) (4) • as maintenance therapy to improve lung function. • as maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients.
Proposed Dose Regimen (current submission)	The recommended dose of dupilumab for adults and adolescents (12 years of age and older) is: • an initial dose of 400 mg (two 200 mg injections) followed by 200 mg given every other week. The dose may be increased to 300 mg every other week based on physician assessment • an initial dose of 600 mg (two 300 mg injections) followed by 300 mg given every other week for patients requiring concomitant oral corticosteroids or with co-morbid moderate-to-severe atopic dermatitis for which dupilumab is indicated
Pharmacometrics Reviewer	Nan Zheng, Ph.D.
Pharmacometrics Team Lead	Jingyu Yu, Ph.D.

12.1.1. Summary of Findings

12.1.1.1. Key Review Questions

The purpose of this review is to address the following key question:

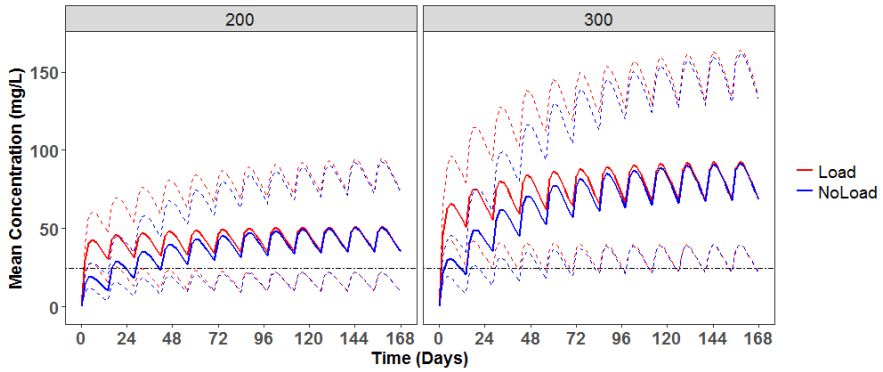
Does population pharmacokinetics (PPK) analysis and exposure response analysis support the proposed dosing regimens including a loading dose of dupilumab for the treatment in patients with moderate-to-severe asthma aged 12 years and older?

Yes.

Dose selection: Clinical efficacy of the proposed 200 mg q2w and 300 mg q2w dosing regimens are demonstrated in studies DRI12544 and EFC13579. The incidence of safety events was too low to support meaningful ER analysis for safety. Body weight exerted a signifiant effect on dupilumab exposure. Steady state exposure in patients with a body weight higher than 100 kg (approximately 10% of the study population) is half of that in patients with a body weight less than 100 kg. Cinical observations from study EFC13579 did not support better efficacy from the 300 mg dose than the 200 mg dose in high body weight patients. Therefore, no dose adjustment is needed for body weight. Age was not a significant covariate on dupilumab exposure or efficacy after adjusting for the effect by body weight. Overall, both 200 mg q2w and 300 mg q2w appear acceptable for the proposed indication in adult and adolescent.

Loading dose: PPK and ER analyses supported the use of a loading dose, as a loading dose helps achieve target exposure sooner.

Figure 33: Simulated Dupilumab Exposure in Asthma Patients on 200 mg q2w (Left) or 300 mg q2w (Right) Treatment



Sources: Reviewer's analysis.
Red lines: with a loading dose. Blue lines: without a loading dose. Solid line and dashed lines represent the median, 5th quantile, and 95th quantile concentration in the PPK study population. Horizontal line represents the target daily exposure to achieve 90% maximum effect in FEV1 change from baseline.

Other factors: ADA was identified as a statistically significant covariate, but the magnitude of ADA effect on dupilumab exposure is small (i.e., less than 20% increase in overall clearance). In reviewer's analyses, high tier ADA response (>480) was identified as a statistically significant covariate and increased overall clearance by up to 57%. These findings are consistent with the observation of substantially lower dupilumab concentration in the presence of high tier ADA response.

12.1.2. Sponsor's Population Pharmacokinetics and ER Analysis

12.1.2.1. PPK Analysis

12.1.2.1.1. Objectives

- To develop a PPK model for dupilumab using pooled data from healthy adult subjects and adult and adolescent patients with asthma;
- To assess the influence of intrinsic and extrinsic factors on dupilumab PK in asthma patients;
- To evaluate PK data for study EFC13691 (not included in PPK model development) with maximum a posteriori probability Bayesian analysis.

12.1.2.1.2. Data, Software, Methods

Concentrations of functional dupilumab in serum from nine phase 1, 2 and 3 studies were included in the PPK analysis (Table 72).

Based on prior knowledge, a two-compartment model with parallel linear and non-linear elimination was evaluated as the base model with two options of absorption processes (i.e., transit compartment and first-order) evaluated. Body weight was included as a covariate on central volume in the base model for asthma patients.

The following covariates were tested in a step-wise covariate search (forward $p<0.01$ and backward $p<0.001$): demographics (gender, age, and race), lab parameters (creatinine clearance, albumin, alanine amino transferase, aspartate amino transferase, alkaline phosphatase), baseline biomarkers (EOS, FeNO), FEV1 % of predicted normal, immunogenicity, and population. The effect of concomitant medication (leukotriene antagonists, systemic corticosteroids, long-acting beta agonist, and methylxanthines) was tested by the comparison of post hoc PK parameters.

The final model performance was evaluated by visual predictive check (VPC) and bootstrapping. The final PPK model was used to generate post hoc estimates of individual PK parameters and steady-state exposure for each asthma patient. It was also used to generate maximum a posteriori probability Bayesian estimate of dupilumab exposure for patients with severe steroid dependent asthma in study EFC13691 and model predictive performance were assessed by standard diagnostic criteria.

The PPK analysis was performed with NONMEM (version 7.3).

12.1.2.1.3. Results

The final PPK dataset contained 14,584 dupilumab concentrations from 202 healthy subjects and 1,912 asthma patients including 68 adolescents (≥12 to <18 year old).

The base model was determined to be a two-compartment model with a first order absorption from the depot to the central compartment, parameterized in terms of absorption rate constant (K_a), a first order elimination rate constant (K_e), Michaelis-Menten parameters (V_{max} and K_m), a distribution volume of central compartment (V_2), and inter-compartment distribution rate constants (K_{23} and K_{32}). Inter-individual variability was estimated for K_e, V_2, V_{max}, K_a, and absorption bioavailability. Residual error was described using a combined proportional and additive error model.

Among the tested covariates, body weight (WT), presence of anti-drug antibody during treatment (ADA), albumin, and creatinine clearance normalized to body surface area (CLCRN) were identified to be statistical significant covariates on dupilumab PK in asthma patients. All other covariates had no statistically significant effect on dupilumab PK in asthma patients.

$V_2 = 2.76 \times (WT/78)^{0.667} \times (ALB/44)^{-0.484}$

$K_e = (0.0418 + 0.0418 \times 0.191 \times ADA) \times (WT/78)^{0.222} \times (CLCRN/111)^{0.217}$

$V_{max} = 1.39 \times (WT/78)^{0.224}$

* The median values of WT, albumin, and CLCRN in the dataset are 78 kg, 44 g/L, 111 mL/min/1.73 m^2, respectively. ADA is 0 for patients with negative ADA and 1 for patients with non-negative ADA.

No important systematic deviations or major bias in any of the goodness of fit plots were observed, and the predictive performance of model was acceptable based on bootstrap and VPC.

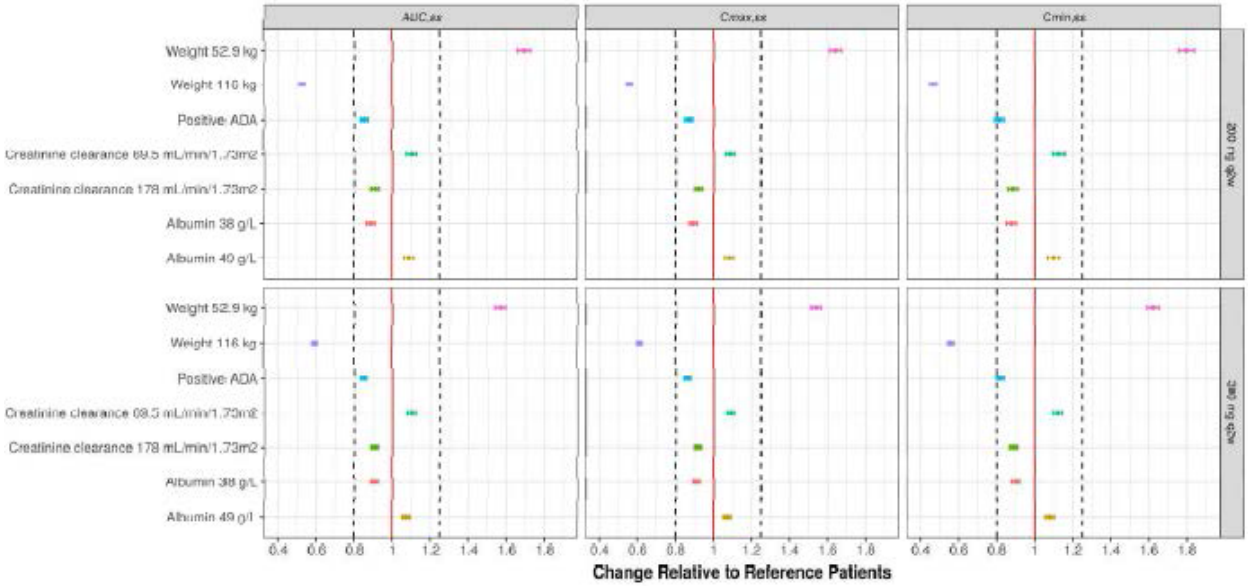
Table 66: Final Asthma PPK Model Parameters

	Parameter	**Estimate**	**% RSE**	**[95%CI]**
	Typical value of K_e (1/day)	0.0418	2.77%	[0.0395; 0.0442]
	Typical value of V_2 (L)	2.76	2.43%	[2.63; 2.90]
	Typical value of K_{23} (1/day)	0.0952	6.97%	[0.0819; 0.108]
	Typical value of K_{32} (1/day)	0.163	4.36%	[0.148; 0.177]
	Typical value of V_{max} (mg/L/day)	1.39	3.80%	[1.28; 1.49]
	Typical value of K_m (mg/L)	2.08	13.6%	[1.52; 2.65]
	Typical value of K_a (1/day)	0.263	3.80%	[0.243; 0.283]
	Typical value of Fsc (1/day)	0.609	3.27%	[0.569; 0.649]
	Power coefficient of weight on K_e	0.222	22.5%	[0.122; 0.321]
	Proportional coefficient of positive ADA on K_e	0.191	13.6%	[0.139; 0.243]
	Power coefficient of creatinine clearance on K_e	0.217	12.1%	[0.164; 0.269]
	Power coefficient of weight on V_2	0.667	3.89%	[0.615; 0.719]
	Power coefficient of albumin on V_2	-0.484	12.3%	[-0.604; -0.365]
	Power coefficient of weight on V_{max}	0.224	24.0%	[0.117; 0.332]
	Parameter	**Estimate**	**% RSE**	**[95%CI] (Shrinkage %)**
Inter-individual variability (CV%)	K_e	0.0385 (19.6%)	10.6%	[0.0303; 0.0466] (47.3%)
	V_2	0.00834 (9.13%)	18.2%	[0.00530; 0.0114] (57.7%)
	V_{max}	0.0589 (24.3%)	7.69%	[0.0499; 0.0680] (44.2%)
	K_a	0.243 (49.2%)	7.68%	[0.205; 0.280] (57.6%)
	Fsc	0.132 (36.3%)	11.9%	[0.100; 0.163] (36.3%)
Residual variability	Proportional term (CV%)	0.0388 (19.7%)	0.880%	[0.0381; 0.0395]
	Additive term (mg/L) (SD)	2.98 (1.73)	2.86%	[2.81; 3.16]

Source: PPK Study Report, Table 4
RSE = relative standard error; SD = standard deviation; CI = confidence interval; CV% = coefficient of variance; ADA = anti-drug antibody; PPK = population pharmacokinetics; Fsc = absorption bioavailability

Simulations using the final model revealed that only body weight exerted a notable effect explaining between-subject variability of dupilumab PK parameters as well as steady-state exposure in asthma patients (
Figure 34).

Figure 34: Forest Plot of Covariate Effect on Dupilumab Steady State Exposure in Asthma Patients



Source: PPK Study Report, Figure 18
The covariate value for simulation represented 5th and 95th percentile of covariate distribution in PPK dataset.

The final EFC13691 dataset contained 483 dupilumab samples from 103 asthma patients. Both intrinsic and extrinsic factors are generally comparable between asthma patients in EFC13691 and asthma patients in the final dataset for PPK model development. Goodness-of-fit plots demonstrated a reasonable fit in the EFC13691 population. Descriptive statistics of predicted individual steady-state exposures for asthma patients are highly comparable between the two phase 3 studies EFC13579 and EFC13691 (Table 67).

Table 67: Mean (SD) [CV%] Dupilumab Steady-State Exposures in Asthma Patients - 300 mg q2w

Study	Phase	Dose	N	$AUC_{T,ss}$ (mg day/L)	$C_{max,ss}$(mg/L)	$C_{min,ss}$ (mg/L)
DRI12544	2b	300 mg q2w	154	983 (526) [53.4%]	78.6 (39.2) [49.9%]	58.9 (34.7) [58.9%]
EFC13579	3	300 mg q2w	630	1090 (593) [54.4%]	86.9 (44.8) [51.6%]	70.0 (40.9) [58.5%]
EFC13691	3	300 mg q2w	102	1064 (511) [48.0%]	85.4 (38.3) [44.8%]	64.5 (33.9) [52.6%]

Source: PPK Study Report, Table 23
AUC = area under the curve; $C_{max,ss}$, $C_{min,ss}$ = maximum and minimum steady-state plasma drug concentration, respectively; CV% = coefficient of variance; SD = standard deviation

Reviewer's Comments:

a. *Reviewer agreed that dupilumab PK was similar between OCS-dependent and non-OCS dependent asthma patients and that the final model adequately described the PK data in study EFC13691.*

b. *Sponsor's model was found acceptable to simulate exposure metrics in ER analyses.*

12.1.2.2. Exposure-Response Analysis

12.1.2.2.1. Objectives

- To conduct ER analyses of severe exacerbation rate and pre-BD FEV1 at week 12 (FEV1-12wk) in studies DRI12544 and EFC13579.
- To develop and qualify a population PK/PD model that characterized the time course of pre-BD FEV1 in adult and adolescent asthma patients in studies DRI12544 and EFC13579

12.1.2.2.2. Data, Software, and Methods

The number of severe exacerbation events was assumed to follow a negative binomial distribution. The PPK model estimated average dupilumab concentration during the event observation period (up to 52 weeks for EFC13579 and up to 24 weeks for DRI12544) was used as the exposure metric. The relationship between dupilumab exposure and the log number of events was fitted with linear, log-linear, or Emax models using the log treatment duration as the offset. The base model included the number of prior severe exacerbation events, age, ICS dose group (high versus medium), region (Asia, Latin America, east Europe, and Western countries), and log of baseline EOS as main effects (placebo effect), and it included a log baseline EOS by concentration interaction term.

FEV1-12wk was assumed to follow a normal distribution. The observed trough concentration at week 12 was used as the exposure metric. The base model included baseline FEV1, age, sex, baseline height, ICS dose group, region, and log of baseline EOS as main effects. It also included a log baseline EOS by concentration interaction as covariate.

In the exacerbation event and FEV1-12wk model development, the effects of additional baseline covariates, either as a main effect or an interaction effect, were explored using a forward selection approach (p-value <0.05).

In addition, the time course of pre-BD FEV1 measurements from patients in studies DRI12544 and EFC13579 were combined for the population PK/PD analysis. PPK model derived dupilumab concentrations were used as the exposure metric. Based on prior knowledge, a dupilumab concentration-dependent sigmoidal Emax model was used for base model development. Relevant intrinsic/extrinsic factors, including demographic variables (e.g., age, body weight, gender, race, and region), baseline disease characteristics and medical history (e.g., FEV1, number of exacerbations in the past year, smoking history, asthma onset age, background inhaled corticosteroids dose level, ACQ5, and atopic medical condition), baseline T-helper 2 inflammation biomarkers (e.g., EOS, FeNO, periostin, TARC, and IgE), and immunogenicity were tested to assess their potential influence on pre-BD FEV1 response. A typical step-wise forward selection (p=0.01) and backward elimination (p=0.001) method was implemented in

covariate search. Model validation was performed using VPC and bootstrap. The analysis was performed with NONMEM (version 7.4)

12.1.2.2.3. Results

An Emax model was selected as the best base model for both the exacerbation event and FEV1-12wk models. In the final exposure-exacerbation event model, baseline EOS, baseline FeNO, asthma age onset, and study (DRI12544 versus EFC13579) were identified as significant covariate on Emax, while study effect (even though not significant) was added on EC_{50} (Table 68). Percent predicted FEV1 at baseline, ACQ5, time since last event, and smoking were identified as significant in addition to the pre-selected main effects. In the final FEV1-12wk model, baseline FeNO, prior severe exacerbation events, baseline periostin, baseline height, and baseline predicted FEV1 were identified as significant covariate on Emax (EOS = eosinophil; FeNO = fractional exhaled nitric oxide

); baseline weight, percent predicted FEV1, asthma age onset, FeNO, eosinophil cationic protein, periostin, eotaxin-3, and race were identified as significant in addition to the pre-selected main effect. A significant ADA status by the concentration interaction was not identified in either model.

Table 68: Parameter Estimates in the Exposure-Exacerbation Event Model (Interaction Effect Only)

Parameter	Estimate	95% CI	Standard Error	P-value
Emax0	-1.525	-2.284, -0.766	0.387	<.0001
Emax1:ln(baseline EOS)-median ln(baseline EOS)	-0.396	-0.621, -0.172	0.115	0.0006
Emax2:ln(Asthma age onset)-median ln(age onset)	-0.321	-0.488, -0.154	0.085	0.0002
Emax3:ln(base FeNO)-median ln(base FeNO)	-0.439	-0.715, -0.162	0.141	0.0019
Emax4:Study = EFC13579	0.593	-0.176, 1.362	0.392	0.1304
EFC13579 EC_{50}	8.536	-4.895, 21.966	6.849	0.2128
DRI12544 EC_{50}	17.358	-2.417, 37.134	10.085	0.0853

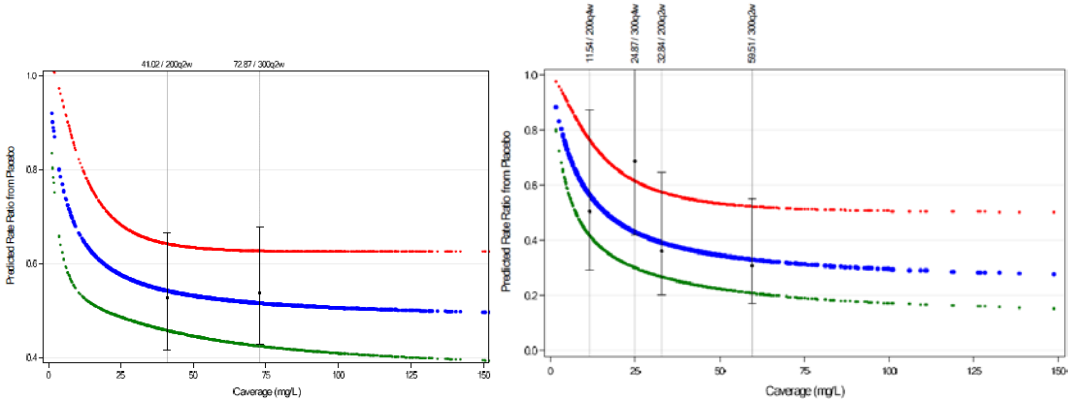
Sources: Exposure-response analysis report, Table 2.
EOS = eosinophil; FeNO = fractional exhaled nitric oxide

Table 69: Parameter Estimates in the Exposure – FEV1-12-wk Model (Interaction Effect Only)

Parameter	Estimate	95% CI	Standard Error	P-value
Emax0	0.121	0.051, 0.191	0.036	0.0007
Emax1:ln(base FeNO)-median ln(base FeNO)	0.140	0.065, 0.215	0.038	0.0002
Emax2:ln(prior # severe exacerbation events)	0.107	0.027, 0.188	0.041	0.0089
Emax3:ln(base Periostin)-median ln(base Periostin)	0.122	0.01, 0.232	0.056	0.0283
Emax4:Baseline FEV1%-median FEV1%	-0.004	-0.007, 0	0.002	0.0458
Emax5:Baseline height-median height	0.005	0, 0.011	0.003	0.0398
EC_{50}	4.661	-5.447, 14.768	5.154	0.3660
Hill	0.659	0.112, 1.206	0.279	0.0183
sigma**2	0.134	0.126, 0.141	0.004	<.0001

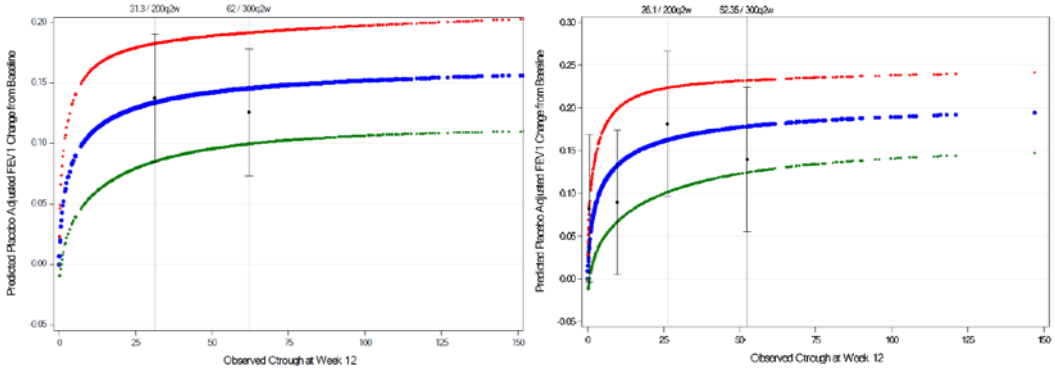
Sources: Exposure-response analysis report, Table 6.
FeNO = fractional exhaled nitric oxide; FEV1 = forced expiratory volume in 1 second

Figure 35: Predicted and Observed Severe Exacerbation Event Ratio From Placebo in EFC13579 (Left) and DRI12544 (Right)



Sources: Exposure-response analysis report, Figure 2 and Figure 3.

Figure 36: Predicted and Observed FEV1 Change From Baseline at Week 12 in EFC13579 (Left) and DRI12544 (Right)



Sources: Exposure-response analysis report, Figure 6 and Figure 7.

The population PK/PD model was developed using 39,325 FEV1 observations from 2,654 asthma patients (N=794 treated with placebo, N=1,860 treated with dupilumab). The placebo effect was described by an empirical time-dependent function in terms of maximum placebo effect and time-dependent improvement rate constant. In the final model, Emax was positively related to baseline EOS and FeNO. Important systematic deviations or major bias were not observed in the goodness of fit plots, and the predictive performance of model was acceptable based on bootstrap and VPC. Simulations suggested that baseline EOS and FeNO concentration exerted a notable effect, explaining between-subject variability of Emax, with larger treatment effect in patients with elevated biomarker levels.

Table 70: Final Population PK/PD Model Parameter Estimates			
Parameter	**Estimate**	**%RSE**	**[95%CI]**
Typical value of Base for males (L)	1.93	0.94	[1.89, 1.96]
Typical value of Base for females (L)	1.54	1.05	[1.47, 1.59]
Typical value of P_{max} (L)	0.172	3.91	[0.158, 0.185]
Typical value of K_{plb} (day^{-1})	0.0322	6.83	[0.0278, 0.0366]
Typical value of EC_{50} (mg/L)	0.713	20.7	[0.418, 1.01]
Typical value of E_{max} (L)	0.104	5.25	[0.0933, 0.115]
Power coefficient of AGEY on Base	-0.423	3.03	[-0.449, -0.397]
Power coefficient of FeNO on E_{max}	0.682	7.55	[0.579, 0.785]
Power coefficient of WT on Base	0.259	7.95	[0.218, 0.300]
Power coefficient of EOS on E_{max}	0.334	13.5	[0.244, 0.424]
Power coefficient of PREEXAC on Base	-0.0411	20.1	[-0.0576, -0.0246]
Inter-individual variability (CV%)			
Base	0.0588 (24.2%)	3.08	[0.0552, 0.0625] (5.48%)
P_{max}	0.0924 (30.4%)	2.82	[0.0872, 0.0976] (8.49%)
K_{plb}	1.64 (128%)	8.40	[1.37, 1.92] (48.7%)
EC_{50}	3.72 (193%)	15.5	[2.56, 4.87] (80.3%)
E_{max}	0.710 (84.3%)	7.57	[0.602, 0.817] (52.2%)
Residual variability			
Proportional term	0.00419 (6.47%)	0.91	[0.00411, 0.00427]
Additive term (L)	0.0144 (0.12)	1.03	[0.0141, 0.0147]

Sources: Population PK/PD modeling report, Table 8.
CV% = coefficient of variance; EOS = eosinophil; FeNO = fractional exhaled nitric oxide; PD = pharmacodynamic; PK = pharmacokinetic; RSE = relative standard error; WT = body weight

Reviewer's Comments:

a. *Sponsor's exacerbation event model and FEV1-12wk model suggested positive ER relationship between dupilumab exposure and efficacy linked as by a saturable, Emax model. Dupilumab efficacy appeared to have reached plateau at the 200 mg q2w level. EC_{50} values were estimated with large uncertainty. Even though studies DRI12544 and EFC13579 had somewhat different efficacy in the 200 mg q2w and 300 mg q2w treatment arms, ER analyses in EFC13579 alone were not pursued due to limited data in the low exposure range and consequently difficulties in the estimation of EC_{50} values.*
b. *Body weight exerted a signifiant effect on dupilumab exposure. Steady state exposure in patients with a body weight higher than 100 kg (approximately 10% of the study population) is half of that in patients with a body weight less than 100 kg. However, clinical observations from study EFC13579 did not suggest better efficacy from the 300 mg dose than the 200 mg dose in high-body weight patients. Therefore, no dose adjustment is needed for body weight.*
c. *Sponsor did not conduct exposure-response analysis for safety. In study EFC13579, the incidence rates of most serious events in dupilumab treatment arms were too low to support meaningful ER analysis for safety. An apparent dose-response was observed for any grade injection-site reaction. However, injection-site reaction is a local effect that is rarely driven by systemic exposure. Reviewer agreed that ER analysis for safety would not provide useful information to support dupilumab dose selection.*

12.1.3. Reviewer's Analysis

12.1.3.1. Objectives

- Evaluate the effect of a loading dose on dupilumab PK/efficacy in asthma patients
- Evaluate the effect of immunogenicity on dupilumab PK/efficacy in asthma patients

12.1.3.2. Methods And Results

To evaluate the effect of a loading dose on dupilumab PK and efficacy in asthma patients, the reviewer used individual post hoc estimates of PK parameters from Applicant's final PPK model to predict the average concentration in the two weeks ($C_{ave.2wk}$) prior to each pre-BD FEV1 measurements, then developed a population PK/PD model between $C_{ave.2wk}$ and pre-BD FEV1. PK profiles in asthma patients in Study EFC13579 were simulated based on Applicant's final PPK model with or without a loading dose. The predicted exposure is compared with the target $C_{ave.2wk}$ to reach 90% of maximum effect.

To evaluate the effect of immunogenicity on PK, reviewer tested the effect of time-invariant ADA parameter (i.e., negative versus transit versus intermediate versus persistent ADA) or time-variant ADA parameters (i.e., negative versus ADA tier between 0 and 480 versus ADA tier greater than 480) on dupilumab elimination in PPK model.

NONMEM (v7.3), Pirana (2.9.0), and R (v3.3.1) were used for the FDA reviewer's analysis.

12.1.3.3. Results and Discussion

Reviewer's analysis confirmed a positive ER relationship between dupilumab exposure and pre-BD FEV1 with a relatively low EC_{50} for $C_{ave.2wk}$ (6.24 mg/mL). An average exposure of 24.7 mg/mL could ensure 90% maximum effect in the study population. Simulation of dupilumab exposure using post hoc estimates of individual PK parameters suggested that a loading dose could help achieving high exposure as quickly as within 2 weeks (Figure 33 and Table 71). A loading dose is favorable for early onset of clinical efficacy.

Table 71: Predicted Median $C_{ave.2wk}$ During the First 2 Weeks in PPK Dataset

	predicted median $C_{ave,2wk}$ during the first 2 weeks (mg/L)
200 mg (Load / No Load)	35.2 / 15.1
300 mg (Load / No Load)	55.9 / 25.2

In Applicant's analysis, time-invariant ADA parameter, negative versus ever-positive, was used in Applicant's PPK analysis. ADA was identified as a statistically significant covariate but the magnitude of ADA effect on dupilumab expsorue is small (i.e. less than 20% increase in overall clearance).

In reviewer's analyses, high tier ADA response (>480), a time-variant ADA parameter, was identified as statistically significant covariates (e.g., ΔOFV: -34) and it increased overall clearance by up to 57%. Reviewer's PPK model appears to be more consistent with visual presentation of individual PK data, which showed substantially lower dupilumab concentration in the presence of high tier ADA response (Figure 39).

12.2. Appendix 2: PPK data

Table 72: Summary of Clinical Studies Included in the PPK Analysis

Phase	Study	Dupilumab Dose Regimens	Treatment Duration	Population	PK Sampling	N[a]
1	AS-0907	IV: 1, 3, 8 and 12 mg/kg; SC : 150 and 300 mg	Single dose	Healthy adults	Dense	36
1	HV-1108	SC: 300 mg	Single dose	Healthy adults	Dense	36
1	TDU12265	SC: 75, 150, 300 and 600 mg	Single dose	Healthy adults (Japanese)	Dense	24
1	PKM12350	SC: 300 mg	Single dose	Healthy adults	Dense	24
1	PKM14161	SC: 300 mg	Single dose	Healthy adults	Dense	38
1	PKM14271	SC: 200 mg	Single dose	Healthy adults	Dense	38
2a	ACT11457	SC: 300 mg qw	12 weeks	Adult patients with persistent moderate-to-severe eosinophilic asthma	Sparse	52
2b	DRI12544	SC: 300mg q2w, q4w (with a 600 mg loading dose) and 200 mg q2w, q4w	24 weeks	Adult patients with persistent moderate-to-severe uncontrolled asthma	Sparse	611
3	EFC13579	SC: 300 mg q2w (with a 600 mg loading dose) and 200 mg q2w (with a 400 mg loading dose)	52 weeks	Adult and adolescent patients with persistent asthma	Sparse	1260[b]
3	EFC13691[c]	SC: 300 mg q2w (with a 600 mg loading dose)	24 weeks	Adult and adolescent patients with severe, steroid-dependent asthma	Sparse	103

[a] Number exposed to dupilumab in each study; total N=2125, with 202 adult healthy subjects and 1923 asthma patients (1855 adults and 68 adolescents).
[b] In phase 3 study EFC13579, 1186 (94%), 1171 (93%), 805 (64%) and 388 (31%) patients treated up to Weeks 16, 24, 36, and 52, respectively.
[c] Data from study EFC13691 not included in population PK model development, but evaluated using maximum a posteriori probability Bayesian approach on the basis of the established asthma PPK model.
Source: Population PK report, Table 1
SC = subcutaneous; PK = pharmacokinetics; PPK = population pharmacokinetics; qw = every week

Table 73: Summary of Baseline Demographic Information (Continuous) in the PPK Dataset

	Healthy subjects (N=202)		Asthma patients (N=1912)		Total (N=2114)	
Covariates	**Mean (SD)**	**Median (min-max)**	**Mean (SD)**	**Median (min-max)**	**Mean (SD)**	**Median (min-max)**
Age (Year)	34.6 (11.5)	32 (18-63)	47.8 (14.8)	49 (12-83)	46.5 (15.0)	48 (12-83)
Weight (kg)	76.0 (9.9)	77.3 (52-95)	80.0 (19.8)	78.0 (32-86)	79.6 (19.1)	78.0 (32-186)
Weight of adolescents (<18 year) (kg)	NA (NA)	NA (NA)	59.8 (18.3)	56.0 (32-122)	59.8 (18.3)	56.0 (32-122)
Weight of adults (>=18 year) (kg)	76.0 (9.90)	77.3 (52-95)	80.8 (19.4)	78.0 (39-186)	80.3 (18.8)	78.0 (39.0-186)
Albumin (g/L)	43.9 (3.4)	44.0 (33-53)	43.8 (3.5)	44.0 (30-55)	43.8 (3.5)	44.0 (30-55)
ALP (IU/L)	81.6 (48.0)	67.0 (21-285)	82.4 (40.8)	75.0 (7.0-546)	82.3 (41.5)	75.0 (7.0 -546)
ALT (IU/L)	20.8 (9.9)	19.0 (6.0-60)	23.2 (14.8)	20.0 (5.0-244)	23.0 (14.4)	20.0 (5.0-244)
AST (IU/L)	20.6 (8.5)	19.0 (10-101)	21.6 (11.2)	20.0 (8.0-278)	21.5 (10.9)	20.0 (8.0-278)
CLCR[a] (mL/min)	125.7 (24.4)	125.4 (74.3-191)	125.8 (44.7)	118.2 (30.2-385)	125.8 (43.1)	119.2 (30.2-385)
CLCRN[b] (mL/min/1.73 m^2)	116 (22.3)	114 (68.8-186)	116 (37.1)	111 (30.1-377)	116 (36.0)	111 (30.1-377)
Eosinophils (cells/uL)	154 (116)	110 (0-900)	356.2 (391)	260 (0-8750)	337 (378)	240 (0-8750)
FeNO (ppb)	16.0 (0)	16.0 (16.0-16.0)	35.4 (32.7)	25.0 (3-387)	33.5 (31.6)	24.0 (3.0-387)
FEV1 of predicted normal (%)	100.0 (0)	100.0 (100.0-100.0)	64.7 (14.7)	65.0 (17-125)	68.1 (17.4)	67.0 (17-125)

Source: Population PK report, Table 4
Abbreviation: ALP = a kaline phosphatase; ALT = alanine amino transferase; AST = aspartate amino transferase; CLCRN = creatinine clearance normalized by body surface area (BSA); FeNO = fractional exhaled nitric oxide; FEV1 = forced expiratory volume in 1 second; N = subject number; PPK = population pharmacokinetics; SD = standard deviation.
[a] The percentages (N) of total subjects with CLCR ≥90, 60 to 90, and 30 to 60 mL/min are 80.9% (1711), 17.4% (368) and 1.7% (35), respectively.
[b] The percentages (N) of total subjects with CLCRN≥90, 60 to 90, and 30 to 60 mL/min/1.73 m2 are 77.3% (1635) and 21.1% (447), 1.51% (32), respectively.

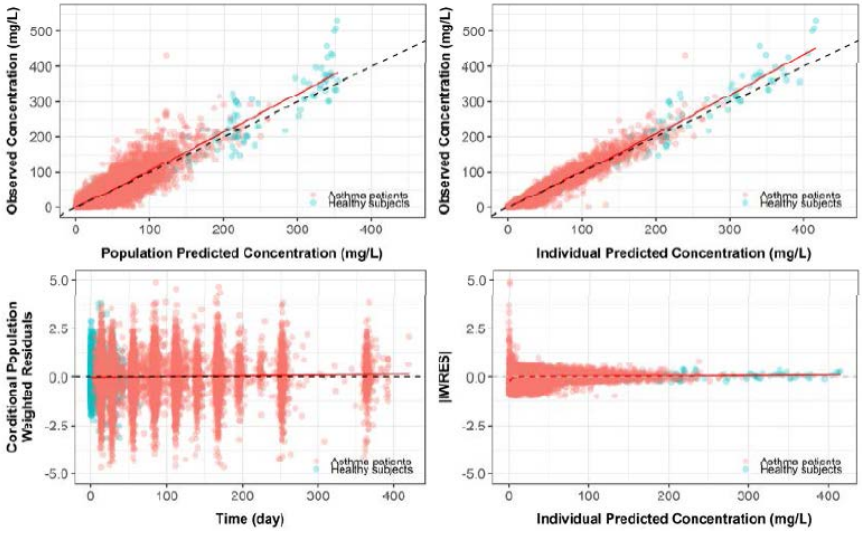
Table 74: Summary of Baseline Demographic Information (Categorical, Count [%]) in the PPK Dataset

Covariates	Subgroup	Healthy subjects Count (%)	Asthma patients Count (%)	Total Count (%)
Adolescents	Adolescents (<18 year)	0	68 (3.6%)	68 (3.2%)
	Adults (>= 18 year)	202 (100%)	1844 (96.4 %)	2046 (96.8%)
Gender	Male	121 (59.9%)	734 (38.4%)	855 (40.4%)
	Female	81 (40.1%)	1178 (61.6%)	1259 (59.6%)
Race	Caucasian	128 (63.4%)	1550 (81.1%)	1678 (79.4%)
	Black	43 (21.3%)	93 (4.86%)	136 (6.43%)
	Asian	25 (12.4%)	247 (12.9%)	272 (12.9%)
	Other	6 (2.97%)	22 (1.15%)	28 (1.32%)
ADA	Negative	135 (66.8%)	1635 (85.5%)	1770 (83.7%)
	Pre-existing	4 (1.98%)	28 (1.46%)	32 (1.51%)
	Treatment-emergent	60 (29.7%)	247 (12.9%)	307 (14.5%)
	Treatment-boosted	3 (1.49%)	2 (0.10%)	5 (0.24%)
LTRA	With	0 (0.00%)	482 (25.2%)	482 (22.8%)
	Without	202 (100%)	1430 (74.8%)	1632 (77.2%)
LABA	With	0 (0.00%)	1850 (96.8%)	1850 (87.5%)
	Without	202 (100%)	62 (3.24%)	264 (12.5%)
SCS	With	2 (0.99%)	744 (38.9%)	746 (35.3%)
	Without	200 (99.0%)	1168 (61.1%)	1368 (64.7%)
XANT	With	0 (0.00%)	87 (4.55%)	87 (4.12%)
	Without	202 (100%)	1825 (95.5%)	2027 (95.9%)

Abbreviation: ADA: anti-drug antibody; LTRA: leukotriene receptor antagonist; LABA: long-acting beta agonist; SCS: systemic corticosteroid; XANT: methylxanthines.

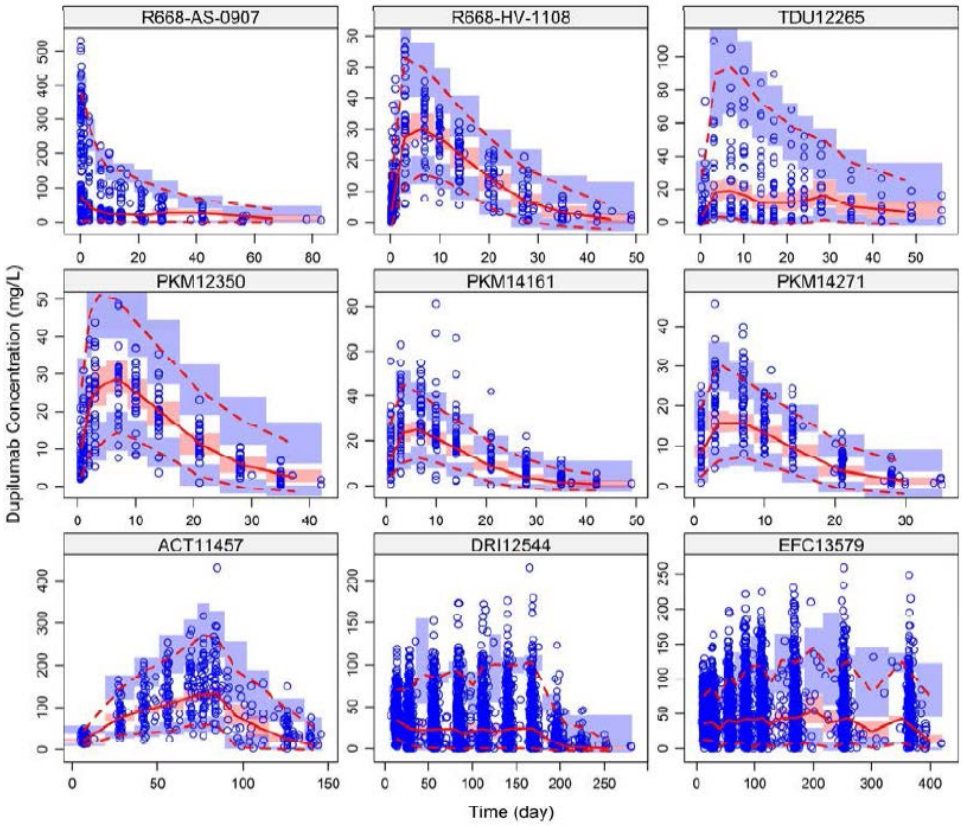
Source: Population PK report, Table 5
PPK = population pharmacokinetics

Figure 37: Goodness-of-Fit Plots From Asthma Final PPK Model



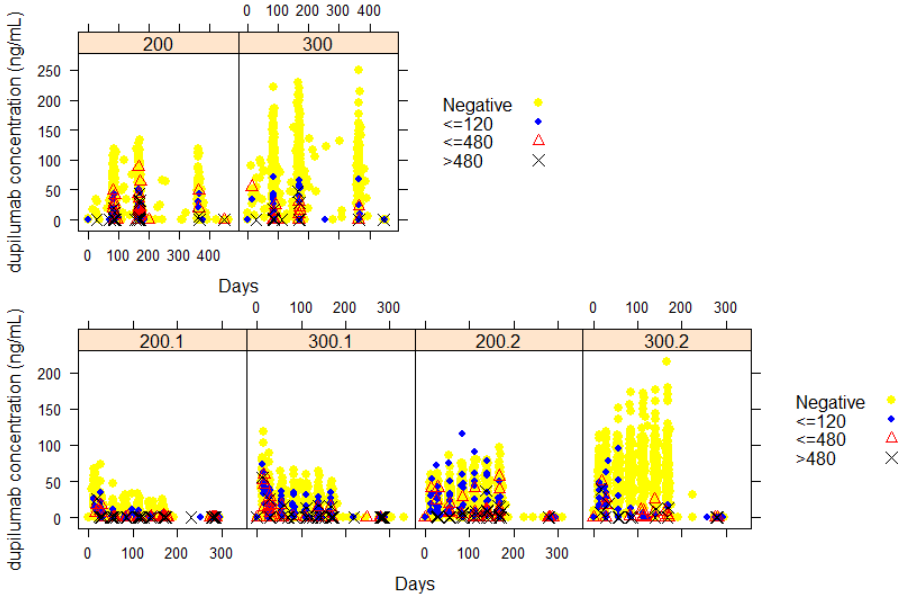
Source: Population PK report, Figure 11
PPK = population pharmacokinetics

Figure 38: Visual Predictive Checks for Final PPK Model by Study



Source: Population PK report, Figure 12
PPK = population pharmacokinetics

Figure 39: Dupilumab Concentration in Study EFC13579 (Upper) and DRI12544 (Lower) Plotted against ADA Tier



200.1 and 300.1 refers to the 200 or 300 mg q4w dosing regimen; the rest were for the q2w dosing regimen.
ADA = anti-drug ant bodies

13. References

See footnotes.

14. Division Director (DPARP)

Dupilumab is a first-in-class monoclonal antibody proposed for an asthma indication. Dupilumab targets the IL-4Rα subunit, which is shared by the IL-4 and IL-13 receptor complexes, and therefore, inhibits IL-4 and IL-13 signaling. Dupilumab was approved in March 2017 for adult patients with atopic dermatitis.

There are several monoclonal antibodies currently approved for asthma. These products target IL-5, which is a key cytokine in the regulation of eosinophils and thus, the IL-5 products cause a reduction in eosinophils. Based upon the development programs for these products, they are approved for patients with severe asthma with an eosinophilic phenotype. The indication "eosinophil phenotype" reflects the data from the development programs which primarily focused on enrollment of patients with elevated eosinophil levels and/or the data showed that baseline eosinophil level is a predictor of treatment response. These programs also focused on patients with severe asthma and the approval was based upon a reduction in asthma exacerbations. Some of these programs also showed an improvement in lung function and reduction in OCS use.

Since dupilumab has a different mechanism of action through targeting of IL-4Ra, the sponsor focused on a broader asthma population – patients with moderate to severe asthma and patients were not required to have elevated eosinophil levels to enroll in the clinical trials. However, randomization was stratified by eosinophils and analysis of patients with high eosinophils was prespecified. Patients treated with dupilumab in the asthma program showed an initial increase in eosinophil levels that over time returned close to baseline. This is a different PD effect on eosinophils compared to the IL-5 products. The mechanism of action for this increase in eosinophils with dupilumab is not entirely clear but may be related to blocking of recruitment/migration of serum eosinophils into tissues.

The asthma program consists of 3 clinical trials: a 6-month dose-ranging trial, a 1-year efficacy and safety trial, and one OCS reduction trial. Based upon the dose ranging trial, the sponsor evaluated two doses of dupilumab in the pivotal 1-year clinical trial: dupilumab 200 mg SC q2w with an initial loading dose of 400 mg and 300 mg SC q2w with an initial loading dose of 600 mg.

The 6-month dose-ranging trial and the 1-year efficacy and safety trial demonstrated a statistically significant reduction in asthma exacerbations and improvement in lung function for patients with moderate-to-severe asthma with increased eosinophil levels for both dupilumab dose groups (200 mg SC q2w and 300 mg SC q2w) compared to placebo. While both studies enrolled subjects regardless of baseline blood eosinophil level, analysis by eosinophil subgroup demonstrated clearly that drug effects tend to be greater in patients with higher eosinophil levels and did not provide convincing evidence of drug effects in patients with lower eosinophil levels. Therefore, the indication for dupilumab is for patients with moderate-severe asthma with an eosinophilic phenotype.

The third pivotal trial in patients with severe asthma that were OCS dependent showed that dupilumab 300 mg SC q2w provided for a greater reduction in OCS use and rate of severe exacerbations, in addition to improvement in lung function compared to placebo. Unlike the dose ranging and 1-year efficacy trial, analysis by eosinophil subgroup did not demonstrate a clear correlation with eosinophil level. OCS can affect the eosinophil level and thus the eosinophil level in this patient population may not reflect the patient's baseline eosinophil level when not on OCS. Given that efficacy was not correlated with eosinophil level, the indication for patients with OCS dependent asthma is not limited to the eosinophil phenotype. Therefore, the indication for dupilumab is as follows: add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma.

The safety of dupilumab was adequately assessed in the asthma development program. In addition, safety data are available from the atopic dermatitis program, which is relevant as there are patients who would be expected to have both atopic dermatitis and asthma. Injection site reactions were the most common AE and were dose related. There was one case of anaphylaxis reported with dupilumab. AEs related to eosinophilia were noted, including eosinophilic granulomatosis with polyangiitis and one case of eosinophilic pneumonia were reported. While it is not clear if there is causal relationship with dupilumab, these events are described in the product label. The ocular safety issues seen in the atopic dermatitis program were not identified in the asthma studies. Cardiovascular events were noted during the review. The overall number of MACE is low and reported at a slightly higher frequency in the 300 mg q2w dose group compared to placebo, but not in the 200 mg q2w dose group. These data are included in the product label. Overall, the safety data do not raise safety concerns that outweigh the benefits of dupilumab for the treatment of patients with asthma.

Both doses of dupilumab were effective and there was no clear dose response between doses. Only the higher dose of 300 mg SC q2w was included in the OCS reduction trial and the 300 mg SC q2w dose is approved for patients with atopic dermatitis. There were dose related AEs noted, particularly injection site reactions, so availability of the lower dose (200 mg q2w) for patients is appropriate. The 300 mg SC q2w dose is recommended as the starting dose for patients requiring concomitant oral corticosteroids or with comorbid moderate-to-severe atopic dermatitis.

Adolescents down to 12 years of age were included in the phase 3 program. The adolescent subgroup demonstrated a statistically significant improvement in lung function for both dose groups; however, the exacerbation benefit was not clearly demonstrated for either dose group. There are no age-related differences in the PK (after adjusting for the effect by bodyweight) and PD for the use of dupilumab in adolescent patients and no unique safety concerns. Given the mechanism of action of dupilumab, the similar PK in this age group (compared to adults) and the similarity of disease (compared to adults) in this age group, the submitted data are sufficient to include approval for patients down to 12 years of age. The sponsor has agreed to additional pediatric studies to address PREA.

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

See signature page

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Sally Seymour, Division Director

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Division Director

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/s/

MIYA O PATERNITI
10/19/2018