NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761055 S-031
Priority or Standard	Standard
Submit Date(s)	December 21, 2020
Received Date(s)	December 21, 2020
PDUFA Goal Date	October 21, 2021
Division/Office	Division of Pulmonology, Allergy, and Critical Care (DPACC), Office of Immunology and Inflammation (OII)
Review Completion Date	October 21, 2021
Established/Proper Name	Dupilumab
(Proposed) Trade Name	Dupixent
Pharmacologic Class	Interleukin-4 receptor alpha antagonist
Applicant	Regeneron
Dosage form	Injection
Applicant proposed Dosing Regimen	100 mg every 2 weeks subcutaneous or 300 mg every 4 weeks subcutaneous for 15 to < 30 kg 200 mg every 2 weeks subcutaneous (b) (4)
Applicant Proposed Indication(s)/Population(s)	Add-on maintenance treatment in patients aged 6 years and older with moderate-to-severe asthma with (b) (4) an eosinophilic phenotype (b) (4) or with oral corticosteroid dependent asthma
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Add-on maintenance treatment in patients aged 6 years and older with moderate-to-severe asthma (b) (4) an eosinophilic phenotype or with oral corticosteroid dependent asthma
Recommended Dosing Regimen	100 mg every 2 weeks or 300 mg every 4 weeks subcutaneous for 15 to < 30 kg 200 mg every 2 weeks for ≥ 30 kg

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OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
PLT= Patient Labeling Team

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1 Executive Summary

1.1. Product Introduction

Regeneron submitted an efficacy supplement, S-031, for biologic license application (BLA) 761055 to expand the asthma indication from 12 years of age down to 6 years of age, which fulfills PREA PMR 3508-1. Regeneron also proposed to modify the overall asthma indication with the proposed indication of 'add-on maintenance treatment in patients with moderate-to-severe asthma aged 6 years and older with (b) (4) an eosinophilic phenotype (b) (4) or with oral corticosteroid dependent asthma'.

Dupilumab is human monoclonal IgG4 interleukin-4 receptor alpha (IL-4Rα) antagonist that inhibits IL-4 and IL-13 signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes.

Dupilumab was first approved in March 2017 for treatment of adult patients with moderate-to-severe atopic dermatitis (AD). Currently dupilumab is approved for atopic dermatitis in patients 6 years of age and older, asthma in patients 12 years of age and older, and adults with chronic rhinosinusitis with nasal polyps as follows:

- moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable in patients 6 years and older
- 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
- add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)

The labeled dosage by indication is listed in Table 1.

Table 1. Dupilumab dosage by indication

Indication	Dose (Subcutaneous)
Atopic dermatitis in adults	600 mg followed by 300 mg every 2 weeks
Atopic dermatitis in pediatric patients	600 mg followed by 300 mg every 4 weeks (15 to < 30 kg) 400 mg followed by 200 mg every 2 weeks (30 to < 60 kg) 600 mg followed by 300 mg every 2 weeks (≥60 kg)
Asthma in adults and adolescents (12 years and older)	400 mg followed by 200 mg every 2 weeks or 600 mg followed by 300 mg every 2 weeks
Chronic rhinosinusitis with nasal polyps in adults	300 mg every other week

There are two approved presentations for dupilumab, a pre-filled syringe with needle shield and a pre-filled pen, included in a single USPI. The application proposes a new 100 mg dose, which is only available as a pre-filled syringe.

With this sBLA submission, the Applicant requested Priority Review. Priority review was not granted. Although asthma is a serious condition, dupilumab would not provide a significant improvement in safety or effectiveness over current available treatments[1].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is approval of dupilumab for use as add-on maintenance treatment in patients 6 years of age and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.

To support expanding the asthma indication to patients 6 to < 12 years of age, the Applicant completed a 1-year, randomized, double-blind, placebo-controlled safety and efficacy trial (EFC14153) in 408 subjects with moderate-to-severe asthma treated with dupilumab or placebo every two weeks (Q2W) based on body weight 15 to < 30 kg (100 mg Q2W) or ≥ 30 kg (200 mg Q2W). Unlike the adolescent and adult asthma trials, a loading dose was not included. This trial demonstrated a statistically significant and clinically relevant improvement on the primary endpoint of annualized rate of severe asthma exacerbations events and for the key secondary endpoint of change from baseline in pre-bronchodilator percent-predicted FEV1 at Week 12 in subjects with moderate-to-severe asthma with an eosinophilic phenotype for both the 100 mg subcutaneous (SC) Q2W (15 to < 30 kg) and 200mg SC Q2W dose (≥30 kg).

An oral corticosteroid reduction trial was not conducted in subjects 6 to < 12 years of age as oral corticosteroid dependence is rare in the pediatric population. Expanding the "oral corticosteroid dependent" portion of the indication to 6 to < 12 years of age is supported by extrapolation of efficacy from the adult and adolescent oral corticosteroid reduction trial based on the overlap in the clinical presentation of both adult and pediatric oral corticosteroid dependent asthma, consistency in the therapeutic approach, consistency of the dupilumab mechanism of action, and relevance of the clinical endpoints.

This application supports the 100 mg SC Q2W or 300 mg SC every 4 weeks (Q4W; 15 to < 30 kg) and 200 mg SC Q2W (≥30kg) dosage for the new pediatric age group (6 to < 12 years of age). The 100 mg SC Q2W and 200 mg SC Q2W doses were included in Study EFC14153. The 300mg SC Q4W dose is supported for the 15 to < 30 kg group due to the higher exposure (supported by modeling and exposure response analysis) compared to the 200 mg SC Q2W dose in this weight group and safety information in some subjects who received this dose in the open-label extension study (LTS14424). Additional safety support is provided by trials in atopic dermatitis

[1] Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics; May 2014

which included this dose in the same age and weight group. (b) (4) [redacted]

Substantial evidence of effectiveness is based on Study EFC14153, an adequate and well-controlled trial in a discrete population of asthma subjects (eosinophilic phenotype or oral corticosteroid dependent asthma) 6 to < 12 years of age supported by existing adequate and well-controlled clinical investigations that demonstrated effectiveness in adults and adolescents with eosinophilic phenotype or oral corticosteroid dependent asthma[2].

[2] Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

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 approved for add-on maintenance in moderate-to-severe asthma in patients ≥12 years with an eosinophilic subtype or oral corticosteroid-dependent asthma. This efficacy supplement proposes to expand the asthma indication from 12 years of age down to 6 years of age. The Applicant also proposes to modify the overall asthma indication with the proposed indication of add-on maintenance treatment in patients with moderate-to-severe asthma aged 6 years and older with [redacted] (b) (4) an eosinophilic phenotype [redacted] (b) (4) or with oral corticosteroid dependent asthma.

Dupilumab was originally 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. The atopic dermatitis indication has since been expanded to include patients down to 6 years of age. Dupilumab is also approved for add-on maintenance of adults with inadequately controlled chronic rhinosinusitis with nasal polyps (CRSwNP).

The efficacy and safety of dupilumab in subjects 6 to < 12 years of age with an eosinophilic phenotype was evaluated in a well-controlled and adequately designed 1-year safety and efficacy trial. This trial demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations and lung function for subjects with moderate-to-severe asthma with an eosinophilic phenotype for the 100 mg SC Q2W (15 to < 30 kg) and the 200 mg SC Q2W (≥30 kg) doses. Support for the 300 mg SC Q4W in pediatric subjects 15 to < 30 kg dose relies on a higher exposure compared to 200 mg SC Q2W and safety experience from the open-label extension trial (LTS14424) in the same age and weight group. An oral corticosteroid reduction trial was not conducted in subjects 6 to < 12 years of age as oral corticosteroid dependence is rare in the pediatric population. Expanding the "oral corticosteroid dependent" portion of the indication to 6 to < 12 years of age is supported by extrapolation of efficacy from the adult and adolescent oral corticosteroid reduction trial.

[redacted] (b) (4)

(b) (4) However, this submission did support inclusion of efficacy by FeNO in the adult/adolescent and pediatric studies in labeling.

Overall the safety profile in the clinical trial for subjects 6 to 11 years of age was similar to the adult and adolescent asthma program. Unlike the adult and adolescent asthma program, parasitic infections were reported. There were no cases of anaphylaxis in the dupilumab group. The ocular safety issues seen in the atopic dermatitis program were not identified in the asthma program. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

Overall, the benefit-risk assessment for dupilumab in patients 6 years of age and older with moderate-to-severe asthma and an eosinophilic phenotype for the proposed doses is favorable. Efficacy and safety findings support expanding the current asthma indication for dupilumab down to 6 years of age.

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. It is the most common chronic disease of childhood. While most children have mild disease that is well-controlled, many have disease that can be characterized as moderate to severe. Uncontrolled disease, including frequent hospitalizations and emergency room visits is present in many children with asthma. Although airway obstruction is often reversible, long-term consequences of uncontrolled asthma include progressive airway obstruction which may persist into adulthood.	Asthma is a common condition in pediatric patients. While most patients can be treated with existing therapies, a small percentage of the pediatric asthma population with uncontrolled asthma continues to experience significant morbidity and the potential for mortality from this condition.
Current Treatment Options	There are three biologics currently approved for the treatment of pediatric asthma. Omalizumab is an anti-immunoglobulin E (IgE) for treatment of allergic asthma and approved down to 6 years of age for moderate-to-severe persistent asthma. For severe eosinophilic asthma, there are two additional approved biologics (anti-IL-5): mepolizumab	While there is an anti-IgE approved for moderate-to-severe asthma, it is limited to allergic asthma (defined by perennial aeroallergen sensitivity) and dosed by weight and serum IgE restrictions. There are also two

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	for 6 years of age or older and benralizumab for 12 years of age or older.	approved therapies for pediatric asthma with an eosinophilic phenotype; however, these are limited to severe asthma and have distinct safety profiles due to the different mechanism of action (anti-IL5). Additional treatment options are needed for those who are ineligible for existing treatments, or unable to tolerate them.
Benefit	• In an adequate and well-controlled trial, dupilumab demonstrated a statistically significant and clinically relevant improvement in asthma exacerbations and lung function in patients 6 to <12 years of age with moderate-to-severe asthma with an eosinophilic phenotype.	Dupilumab demonstrated substantial evidence of effectiveness in reducing asthma exacerbations and improving lung function in subjects ≥6 years of age with moderate-to-severe asthma with an eosinophilic phenotype.
Risk and Risk Management	• Unlike the adolescent and adult clinical trials, the trial in patients 6 to < 12 years of age was notable for parasitic infections. • Injection site reactions were the most common adverse events and were dose-related. • No anaphylaxis cases in the dupilumab groups were reported. • Similar to the adolescent and adult trials, ocular safety issues seen in the atopic dermatitis program were not identified in the asthma studies.	• The program does not demonstrate any safety findings that outweighed the benefit. • The safety findings that were seen in the program can be managed through labeling and routine pharmacovigilance. • No risk evaluation and mitigation strategies are needed.

1.4. Patient Experience Data

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

X	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	8.1.1.3.6, 8.1.1.3.8, 8.1.2
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
□	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	□	Input informed from participation in meetings with patient stakeholders		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1.Analysis of Condition

Asthma is characterized by recurring symptoms of wheezing, breathlessness, chest tightness, and coughing caused by underlying airway inflammation and airway hyper-responsiveness. It is the most common chronic disease of childhood, with a worldwide prevalence of almost 12%[3]. While most children have mild disease that is well-controlled, over one third of children with asthma in the US and Western Europe have disease that can be characterized as moderate to severe. Uncontrolled disease, including frequent hospitalizations and emergency room visits is present in half of all children with asthma[4]. Although airway obstruction is often reversible, long-term consequences of uncontrolled asthma include progressive airway obstruction which may persist into adulthood[5].

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)[6]. 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[7]. Together, IL-4 and IL-13 play a role in the pathogenesis of asthma.

The diagnosis and management of this common condition are outlined in the NAEPP[8] and Global Initiative for Asthma (GINA)[9] 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.

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[3] Pearce N, et al., 2007, Worldwide trends in the prevalence of asthma symptoms: Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax, 62(9): 758-66.
[4] Rabe KF, et al., 2000, Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. Eur Respir J, 16(5): 802-7.
[5] Asthma. World Health Organization, 3 May 2021. https://www.who.int/news-room/fact-sheets/detail/asthma
[6] Brandt EB, et al., 2011, Th2 Cytokines and Atopic Dermatitis. J Clin Cell Immunol, 2(3): 110.
[7] Corren J, 2013, Role of interleukin-13 in asthma, Curr Allergy Asthma Rep, 13(5): 415-420.
[8] National Institutes of Health (NIH) and National Heart, Lung, and Blood Institute (NHLBI), National Asthma Education and Prevention Program. Expert Panel Report 3: 2020 Focused Updates to the Asthma Management Guidelines.
[9] Global Initiative for Asthma (GINA), 2021 GINA Report, Global Strategy for Asthma Management and Prevention, http://www.ginasthma.org/.

2.2. Analysis of Current Treatment Options

Dupilumab is the first and only anti-IL-4Rα approved for the treatment of asthma. Three other biologics are approved for pediatric asthma: omalizumab and mepolizumab for 6 years of age and older, and benralizumab for 12 years of age as outlined in Table 2. Omalizumab is an anti-IgE monoclonal antibody, however its indication is limited to allergic asthma defined by a positive skin test or in vitro reactivity to a perennial aeroallergen. Mepolizumab and benralizumab, both anti-IL-5, are limited to severe asthma with an eosinophilic phenotype. Dupilumab is approved for moderate-to-severe asthma with an eosinophilic phenotype and the Applicant is seeking to expand this indication to subjects 6 years of age and older, which would make dupilumab the only biologic option for pediatric patients 6 to <12 years of age with moderate-to-severe asthma with an eosinophilic phenotype.

Table 2 Summary of Treatments Relevant to Proposed Indication

Product Name	Indication	Dose	Efficacy Information & Population Studied
Omalizumab (Approved 2003)	Moderate-to-severe persistent asthma in patients ≥6 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms inadequately controlled with inhaled corticosteroids	75 to 375 mg SC every 2 to 4 weeks depending on weight and serum IgE	*Exacerbations* Omalizumab demonstrated a significantly lower rate of asthma exacerbations when compared to placebo in two trials in pediatric subjects ages 6 to <12 years. *Lung function* FEV1 was not significantly different in omalizumab-treated subjects compared to placebo.
Mepolizumab (Approved 2015)	Add-on maintenance treatment in patients ≥6 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 subjects meeting criteria believed to identify an eosinophilic phenotype. These criteria included peripheral blood eosinophil counts≥ 300 cells/uL, sputum eosinophil counts > 3%, FeNO >50 ppm or

			loss of control with OCS dose reduction. One pivotal exacerbation trial demonstrated a reduction in exacerbations in severe asthma subjects on background standard of care with peripheral blood eosinophil count ≥150 cells/µl (within 6 weeks of dosing) or historical count ≥300 cells/µl (within 12 calendar months of enrollment) with a history of two exacerbations in the prior 12 months. *Adolescents* 28 adolescents were evaluated in the program with a trend toward exacerbation reduction. *Oral Corticosteroid Reduction* One trial demonstrated an ability to reduce oral corticosteroids dosage in severe asthma subjects with peripheral blood eosinophil count ≥150 cells/µl or historical count ≥300 cells/µl. *Lung function* No consistent improvement in lung function was seen in this development program. *Approval in subjects 6 to < 12 years of age* Based on 1-year PK/PD/safety in 36 pediatric subjects with severe eosinophilic asthma.

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 subjects with a peripheral blood eosinophil count ≥300 cells/µl within 3-4 weeks of dosing (primary analysis population) and a history of ≥2 asthma exacerbations in the prior year. OCS use was allowed. Subjects with a baseline eosinophil count of ≥ 300 cells/µL showed a numerically greater response than those with <300 cells/µL . The exacerbation benefit was not statistically significant in those with < 300 cells/µL. *Lung function* One dose-ranging and two exacerbation trials demonstrated an improvement in lung function in subjects with a baseline eosinophil count ≥ 300 cells/uL. *Adolescents* 108 adolescents were evaluated in the program with similar PK and PD to adults. *Oral corticosteroid reduction* One trial demonstrated an ability to reduce oral corticosteroid dosage in severe asthma subjects with peripheral blood eosinophil count ≥150 cells/µl (within 6 weeks of dosing).

FeNO= fractional exhaled nitric oxide; OCS= oral corticosteroids; SC= subcutaneous; PK=pharmacokinetics; PD=pharmacodynamics. Source: Reviewer

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Dupilumab has been developed under IND 105379 (for asthma and CRSwNP) and IND 107969 (atopic dermatitis) and was initially approved in March of 2017, under BLA 761055, for the add-on maintenance 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.

Since 2017, the Applicant has submitted supplements for the following indications: add-on maintenance treatment of adolescent patients aged 12 to 17 with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable (approved March 2019 and extended down to 6 years of age May 2020), 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 (approved October 2018), and add-on maintenance treatment in adult patients with inadequately controlled CRSwNP (approved June 2019). At the time of approval for adult and adolescent asthma, two PREA PMRs were issued (3508-1 and 3508-2) for pediatric patients 6 to < 12 years of age and 2 to 5 years of age with asthma. This approval will fulfill PMR 3508-1. A waiver was granted for < 2 years of age as studies in this age group were considered impossible or highly impracticable.

Reviewer comment: The PREA PMRs aligned with the trials proposed by the Applicant in the initial Pediatric Study Plan. Mepolizumab, in contrast, was approved for severe eosinophilic asthma in patients 6 to < 12 years of age based on a PK/PD/safety trial with a PD marker of eosinophils. There were also feasibility concerns with recruiting pediatric subjects down to 6 years of age with severe eosinophilic asthma.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 3 Summary of Presubmission/Submission Regulatory Activity

Interaction	Date	Remarks
Agreed iPSP	April 2, 2015	-Deferral < 12 years
Pre-sBLA	June 26, 2020	-Disagreed with (b) (4) [redacted] -Primary analysis should occur in subjects with eosinophils 300 cells/µL -"OCS dependent" reasonable to include in indication as

		steroid use rare in pediatric population -Questioned whether baseline FeNO adds additional value beyond eosinophil levels -FeNO should be treated as a continuous variable -Exploratory analysis should include both continuous eosinophil-by-treatment and FeNO-by-treatment interactions (along with main effects for FeNO, eosinophil, and treatment) -The results in subjects with low eosinophil levels but high FeNO levels will also be important -Consider post-hoc analysis for completed studies

EOP2 = end of phase 2; FeNO= fractional exhaled nitric oxide; iPSP= initial pediatric study plan; OCS= oral corticosteroid; sBLA= supplemental biologics license application; Source: Reviewer

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

4.1. Office of Scientific Investigations (OSI)

The clinical trials conducted to support this sBLA included both foreign and domestic sites. Due to the COVID-19 pandemic, OSI was not conducting foreign inspections for non-mission critical applications. This efficacy supplement did not qualify as a mission critical application.

Efficacy by site was analyzed and one domestic site, 840002, was notable as there was one placebo subject with exacerbation data that seemed to be an outlier, however it was concluded that this may be due to small sample size at the site, and the overall estimate was not impacted. Thus the Division deferred domestic inspections after this analysis.

Reviewer comment: Mission critical applications include public health emergency (including COVID-19 response activities, life saving/extending, new molecular/chemical entity, rare diseases/orphan products, opioid study, human and/or animal food safety, human subject protection concerns, serious data integrity concerns, drug shortage, first generic, or products with Medical Countermeasures (MCM) designation.

4.2. Product Quality

With this supplement, the Applicant introduced a new presentation of dupilumab (100 mg /0.67 mL in a single-dose pre-filled syringe in a safety system). The manufacturing of the new presentation is similar to the approved processes with exception of (b) (4) are specific for the 100 mg presentation as they relate to (b) (4). The data provided in the supplement support the conclusion that the proposed control strategy for the new 100 mg/0.67 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.

4.3. 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. Richard Ledwidge.

4.4. Devices and Companion Diagnostic Issues

There is no companion diagnostic test for review in support of this sBLA. A new presentation was introduced in this supplement, 100 mg pre-filled syringe. The dupilumab pre-filled syringe

is supplied as a ready-to-use, sterile, single dose, prefilled syringe and disposable glass syringe assembled with a plunger rod and inserted within a safety system preassembled with a finger flange.

Needle shield removal force across all concentrations was identified as an on-going issue in a small number of tested samples. The benefit of dupilumab treatment outweighs the risk of inability to access medication for a small amount of users. The Sponsor is addressing this issue through Biological Product Deviation Reports (BPDRs) and CDRH and DMEPA will continue discussion with the Sponsor regarding resolution of this issue. The Center for Devices and Radiological Health reviewed the device constituents and recommends approval.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical studies were conducted to support the approval of dupilumab 100 mg SC Q2W or 300 mg SC Q4W (15 to < 30 kg) and 200 mg SC Q2W (≥30kg) for use as add-on maintenance treatment in patients 6 years of age and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma. No additional toxicology studies were considered necessary as it was decided in conjunction with the Division of Dermatology and Dentistry that: no effects were identified in an enhanced pre- and post-natal development (ePPND) study in monkeys, no target organs of concern were identified in adult animals, and there are no additional concerns based on the drug's pharmacology.

6 Clinical Pharmacology

6.1.Executive Summary

This is a pediatric BLA supplement seeking to expand the approved asthma indication of dupilumab to include children aged 6 to < 12 years old with moderate to severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma. Dupilumab is a human monoclonal IgG4 antibody that is approved for the treatment of patients aged 6 years and older with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable and for add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with oral corticosteroid dependent asthma in the United States.

The proposed doses of dupilumab for children 6 to less than 12 years old of age are:

- 15 kg to less than 30 kg: 100 mg Q2W or 300 mg Q4W
- (b) (4) 200 mg Q2W (b) (4)
- (b) (4)

The efficacy and safety of the proposed 100 mg Q2W and 200 mg Q2W dosing regimens were evaluated in Study EFC14153 (see clinical review in Section 8). The efficacy of 300 mg Q4W dosing regimen is extrapolated based on exposure matching.

The clinical pharmacology review for this sBLA focused on the pharmacokinetics, pharmacodynamics, exposure response relationship in children 6 to less than 12 years old with persistent asthma to support the proposed dosing regimen. The major clinical pharmacology findings for this submission are as follows:

- Following 100mg/200 mg Q2W dosing regimen, the observed trough concentration values in children 6 to less than 12 years old were comparable to the observed trough concentration values in adults and adolescents following 200 mg/300 mg Q2W dosing regimen.

- The pharmacodynamic responses, including IgE, FeNO (fractional exhaled nitric oxide), and TARC (thymus and activation regulated chemokine), supported effectiveness of dupilumab 100mg/200 mg Q2W dosing regimen in children 6 to less than 12 years old.

- The exposure response relationship in percent predicted FEV1 (FEV1pp) and severe asthma exacerbation observed in children 6 to less than 12 years old supported 100 mg/200 mg Q2W dosing regimen as the optimized dosing regimen.

- The exposure response relationship supported 300 mg Q4W as an alternative dosing regimen in children 6 to less than 12 years old with a body weight of 15 kg to less than 30 kg.

- (b) (4)

6.1.1. Recommendations

The Office of Clinical Pharmacology Division of Immune and Inflammation Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the information submitted under sBLA 761055/S-31. This efficacy supplement and the proposed dosing regimen of 100mg/200 mg Q2W for children 6 to less than 12 years old are approvable from a clinical pharmacology perspective. In addition, the proposed alternative dosing regimen of 300 mg Q4W for children 15 kg to less than 30 kg is supported by exposure response analysis and approvable. (b) (4)

6.2.Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Dupilumab is a human monoclonal IgG4 antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. The general clinical pharmacology information for dupilumab was reviewed by Dr. Jie Wang during the original application (DARRTS date 12/19/2016).

EFC14153 is the pivotal clinical trial submitted under BLA 761055 S-031. Study EFC14153 is a randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma. Subjects were randomized in a 2:1 ratio to receive 100 mg (15 kg to less than 30 kg) or 200 mg (30 kg and above) SC injection of dupilumab or placebo every 2 weeks for 52 weeks. In total 405 subjects were randomized and treated. The observed PK mean ± SD steady-state trough concentration in children 15 to <30 kg (N=91) and ≥30 kg (N=179) was 58.4±28.0 mcg/mL and 85.1±44.9 mcg/mL, respectively. Simulation of a 300 mg Q4W subcutaneous dose in children aged 6 to < 12 years with body weight of 15 to <30 kg resulted in predicted steady-state trough concentrations and average concentrations higher than the observed trough concentrations and average concentrations following 100 mg Q2W (<30 kg) in this pediatric population.

FeNO, IgE, and TARC responses in children 6 to less than 12 years old following the studied dosing regimen were similar to adult and adolescent subjects with moderate to severe asthma.

In children with persistent asthma receiving dupilumab 100mg/200mg Q2W, treatment-emergent positive ADA responses were observed in 17 (6.3%) subjects in the dupilumab group compared to 4 (3.0%) subjects in the placebo group. The proportion of subjects positive in the NAb assay was 6 (2.2%) in the dupilumab group and 1 (0.8%) in the placebo group.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen of 100 mg/200 mg Q2W SC administration was evaluated in children 6 to less than 12 years old in the pivotal clinical Study EFC14153. The recommended alternative dosing regimen of 300 mg Q4W was not evaluated in a double-blinded placebo-control study; and was mainly supported by modeling and exposure response analysis.

The recommended dosing regimens in children 6 years to less than 12 years are:

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

Therapeutic Individualization

None.

Outstanding Issues

None.

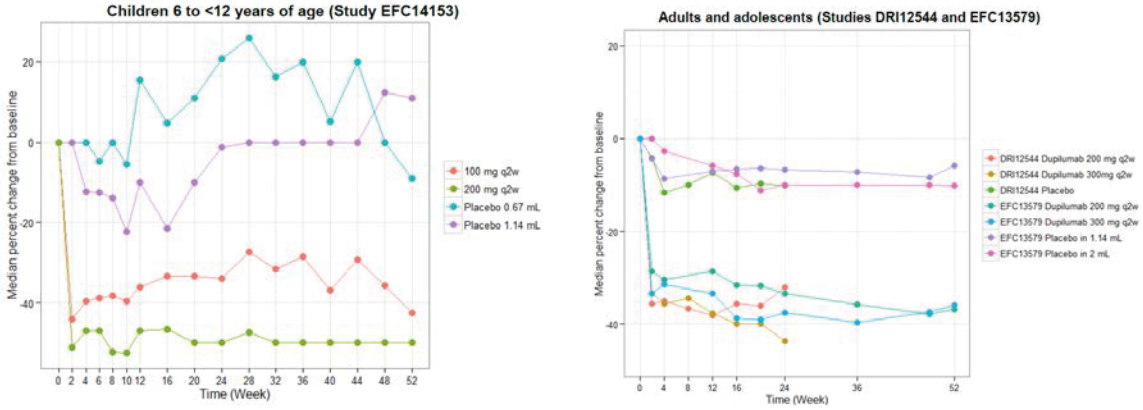
6.3.Comprehensive Clinical Pharmacology Review

6.3.1. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

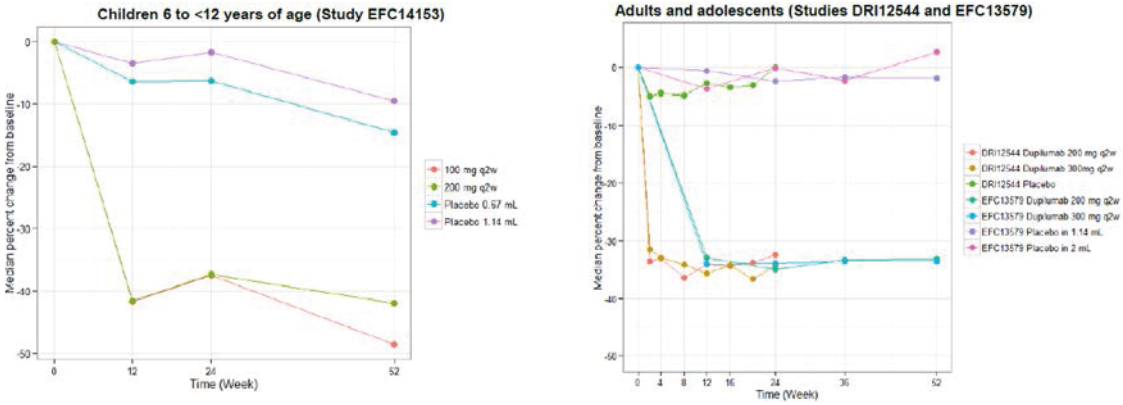
Yes, pharmacodynamic endpoints, including FeNO, IgE, and serum TARC, supported the effectiveness of dupilumab in children 6 to less than 12 years old with persistent asthma. In Study EFC14153, children 6 to less than 12 years old showed comparable responses in FeNO, IgE, and serum TARC, compared to adults and adolescents in Studies DRI12544 and EFC13579 (Figure 1 to Figure 3).

Figure 1 Median percent change in FeNO from baseline over time following dupilumab or placebo in children 6 to <12 years of age with asthma (left panel, Study EFC14153; without a loading dose) and adolescents and adults with asthma (right panel, Study DRI12544 and EFC13579; with a loading dose)



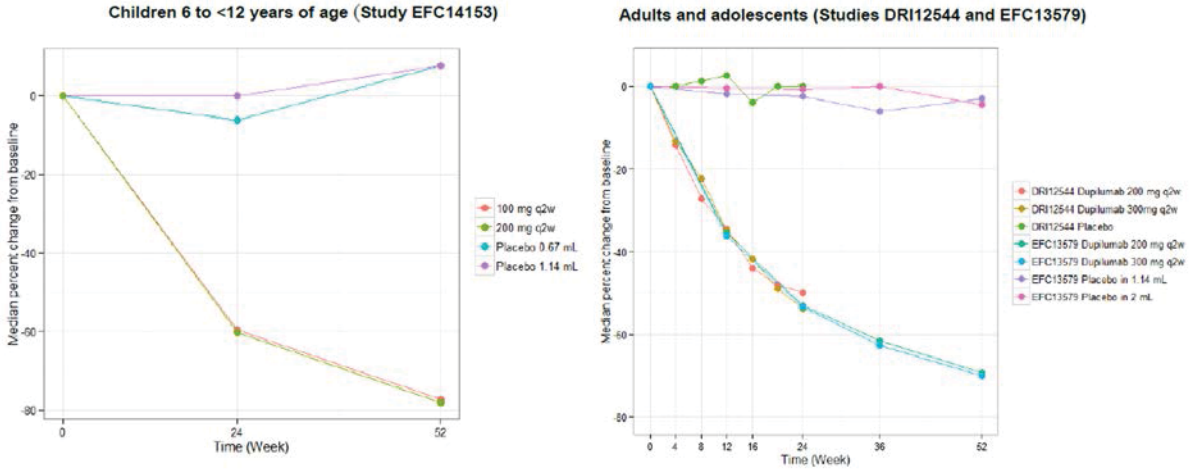
Source: Figure 4 in 2.7.2 Summary of Clinical Pharmacology Studies

Figure 2 Median percent change in serum TARC from baseline over time following dupilumab or placebo in children 6 to <12 years of age with asthma (left panel, Study EFC14153; without a loading dose) and adolescents and adults with asthma (right panel, Study DRI12544 and EFC13579; with a loading dose)



Source: Figure 5 in 2.7.2 Summary of Clinical Pharmacology Studies

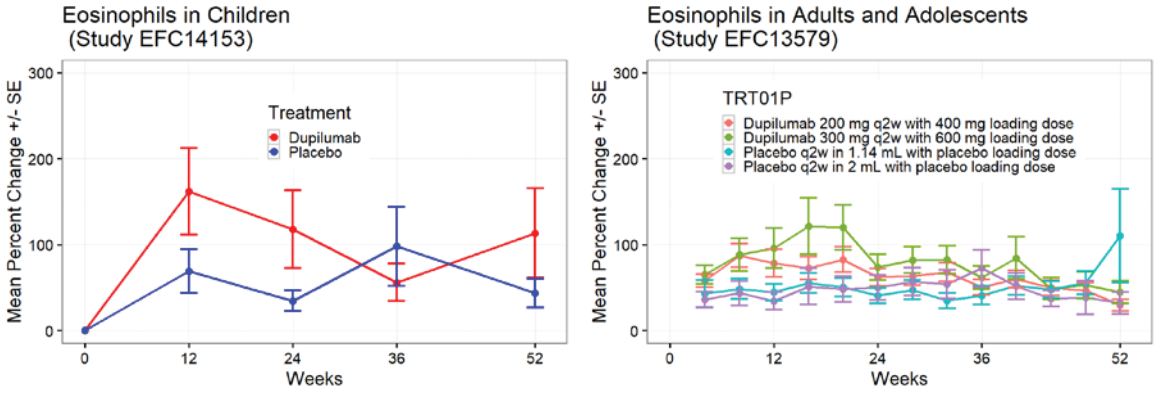
Figure 3 Median percent change in serum IgE change from baseline over time following dupilumab or placebo in children 6 to <12 years of age with asthma (left panel, Study EFC14153; without a loading dose) and adolescents and adults with asthma (right panel, Study DRI12544 and EFC13579; with a loading dose)



Source: Figure 6 in 2.7.2 Summary of Clinical Pharmacology Studies

Eosinophil count in Study EFC14153 was also evaluated as part of the clinical laboratory assessment. The mean (±standard error) percent change from baseline in eosinophil count is depicted in Figure 4. A similar elevation of blood eosinophil count during early dupilumab treatment phase was observed in both adults and children.

Figure 4 Mean percent change from baseline in blood eosinophil count over time following dupilumab or placebo in children 6 to <12 years of age with asthma (left panel, Study EFC14153; without a loading dose, excluding three observations with blood eosinophil count increase > 30800% from baseline) and adolescents and adults with asthma (right panel EFC13579; with a loading dose)

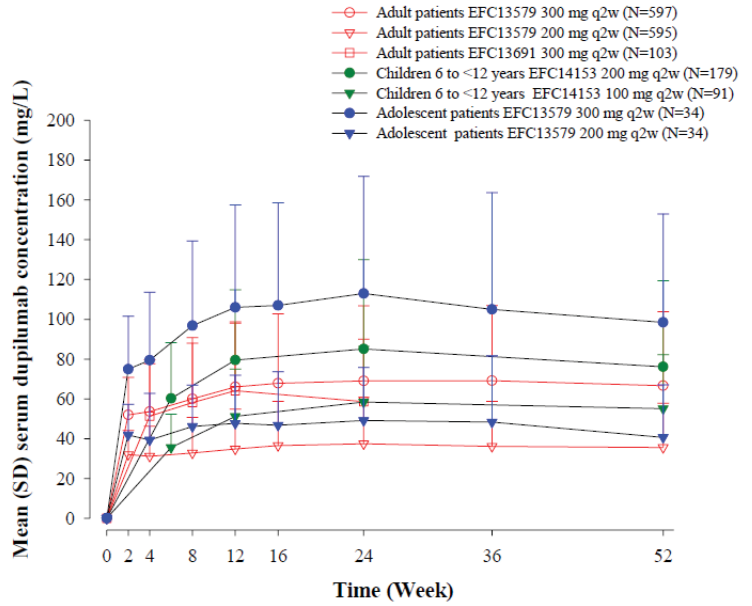


Source: Reviewer's analysis

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

The pharmacokinetics of dupilumab in children 6 to less than 12 years old were characterized in Study EFC14153. Trough PK samples were collected at pre-dose, Week 2, 4, 8, 12, 16, 24, 36, and 52. A comparison of trough concentration in children 6 to less than 12 years following 100 mg Q2W/200 mg Q2W and trough concentrations in adults and adolescents following 200 mg Q2W/300 mg Q2W are depicted in Figure 5. The observed trough concentrations in children 6 to less than 12 years old following 100/200 mg Q2W dosing were similar to the observed trough concentrations in adults (Study EFC13579) and adolescents (Study EFC13691) following the approved dosing regimen of 200/300 mg Q2W. Following the same dosing regimen (100mg/200mg Q2W), the observed trough concentrations in children with asthma were also comparable to the previously reported trough concentrations in children with atopic dermatitis. (see Clinical Pharmacology Review by Dr. Luke Oh for BLA 761055/S20, DARRTS date 05/22/2020)

Figure 5 Mean (SD) trough concentration-time profiles of dupilumab in children 6 to <12 years of age (Study EFC14153) and adults and adolescents with asthma (Study EFC13579 and Study EFC13691)

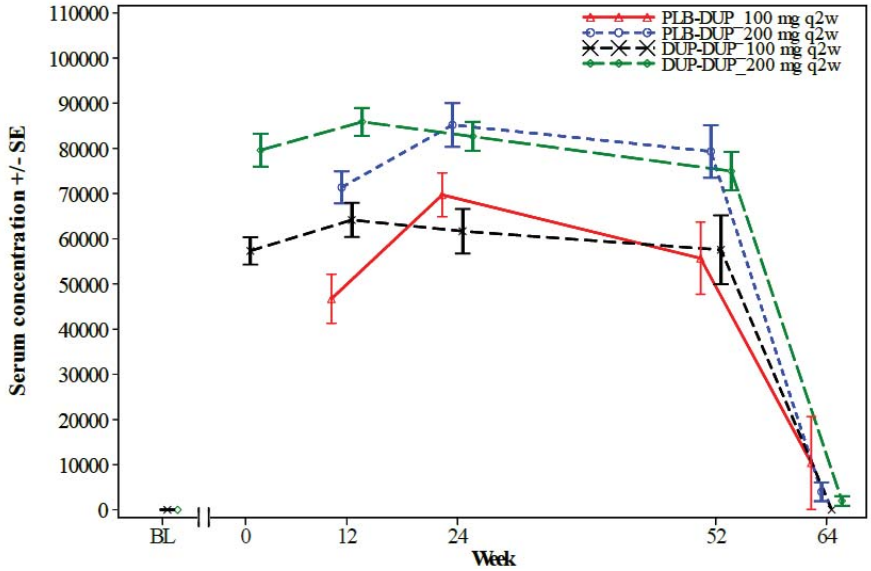


Loading dose of 400 mg and 600 mg for 200 mg q2w and 300 mg q2w, respectively, in adults and adolescents
Sources: 5.3.5.1 Study EFC14153, Appendix 16.2.5 Compliance and drug concentration data [16.2.5.4.1.1]; 5.3.5.1 Study EFC13579, Appendix 16.2.5 Compliance and drug concentration data (16.2.5.4.1.1) and 5.3.5.1 Study EFC13691, Appendix 16.2.5 Compliance and drug concentration data (16.2.5.4.1.1), previously submitted in the marketing application for adults and adolescents with asthma

Source: Figure 3 in 2.7.2 Summary of Clinical Pharmacology Studies

In the open label extension study LTS14424, children received either 100 mg Q2W or 200 mg Q2W dosing regimen based on their bodyweight. The observed trough concentrations are depicted in **Figure 6**.

Figure 6 Serum concentrations (ng/mL) of dupilumab over time - PK population – Modified analysis set



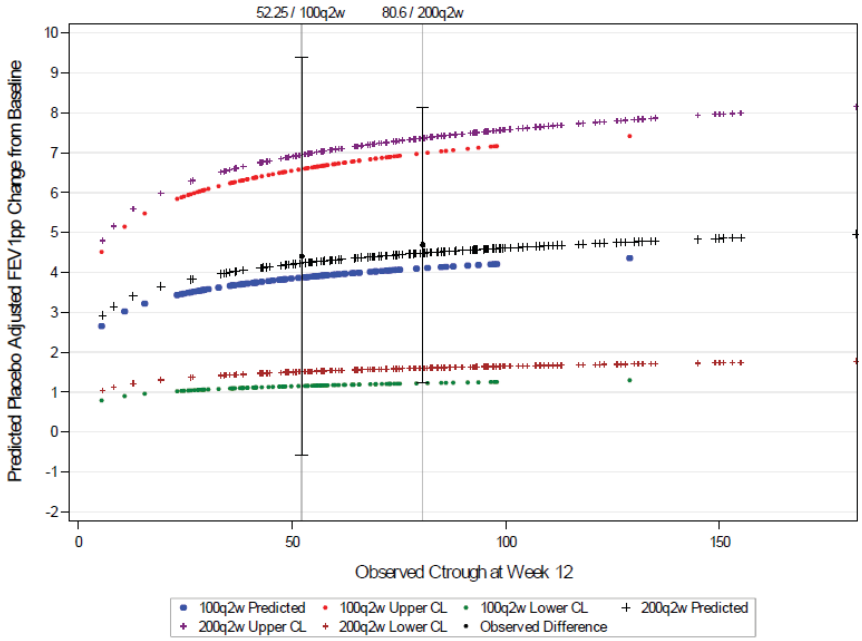
Source: Study EFC14153 CSR (interim analysis) Figure 9

A protocol amendment to Study LTS14424 was made to introduce 300 mg Q4W in children 15 to 30 kg to replace 100 mg Q2W dosing regimen on 10/18/2019. Eighteen children were exposed to the 300 mg Q4W dosing regimen, including 11 subjects who switched to 300 mg Q4W from 100 mg Q2W during the study and 3 subjects who started the study with 300 mg Q4W on Day 1. Of these 18 children, only 2 PK samples from 2 children were collected. The limited PK data cannot support an evaluation of PK characteristics following 300 mg Q4W dosing regimen directly. To support the PK evaluation of 300 mg Q4W dosing regimen, PK profiles were simulated based on the PopPK model. See below for the evaluation of alternative dosing regimen.

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

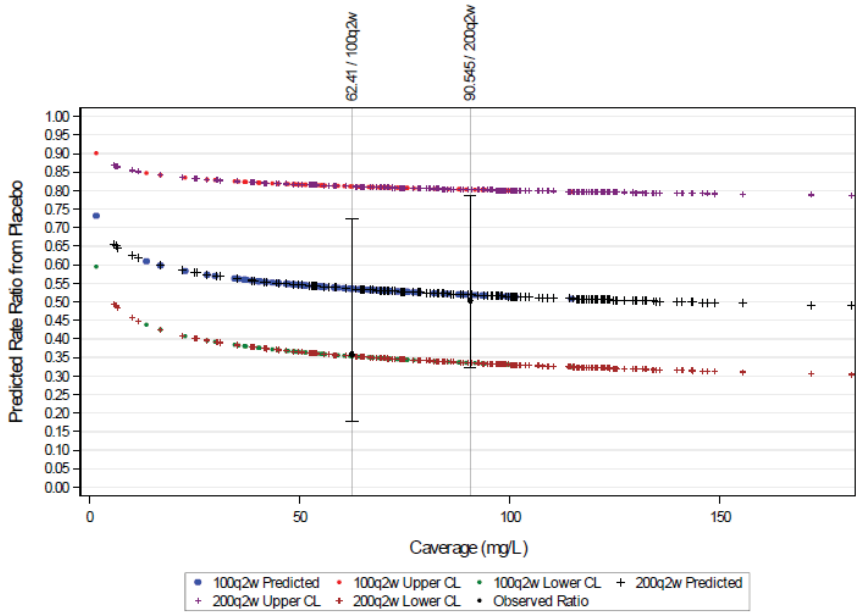
The primary efficacy endpoint in Study EFC14153 was the annualized rate of severe asthma exacerbation events during the 52-week treatment period. The key secondary efficacy endpoint was the change from baseline in pre-bronchodilator FEV1pp at Week 12. The Applicant conducted exposure response (ER) analyses to support the selection of 100/200 mg Q2W dosing regimen. The major findings in the ER analyses based on FEV1pp and severe asthma exacerbation are depicted in Figure 7 and Figure 8 below. See Section 15.2.2 for details of the Applicant's ER analyses.

Figure 7 PK/PD model-predicted FEV1pp change from baseline versus observed Ctrough (mg/L) at Week 12 in children 6 to <12 years of age



Source: Figure 8 in 2.7.2 Summary of Clinical Pharmacology Studies

Figure 8 PK/PD model predicted severe exacerbation event ratio from placebo (relative risk) for children 6 to <12 years of age

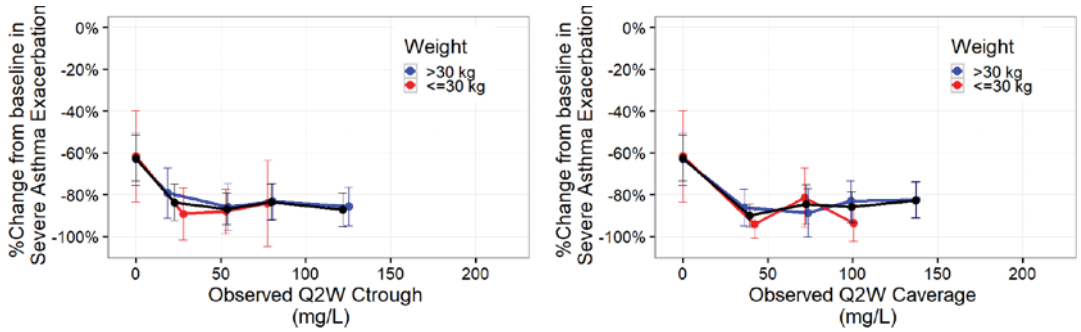


Source: Figure 9 in 2.7.2 Summary of Clinical Pharmacology Studies

While the between-subject variability at baseline was adjusted for FEV1pp ER analysis, heterogenicity in severe asthma exacerbation at baseline was not balanced and adjusted between bodyweight subgroups and different dosing regimens. As a result, the Applicant's exposure response analysis on the reduction of severe asthma exacerbation (vs placebo) showed inconsistent response between 100 mg Q2W and 200 mg Q2W dosing regimens (Figure 8). Children with body weight 15 to <30 kg on 100 mgQ2W treatment had more reduction in severe exacerbations than children ≥30 kg on 200 mg Q2W treatment.

To account for the differences in disease characteristics at baseline, the annualized rate of severe asthma exacerbation in the previous year was taken into consideration, and percent change from baseline in the annualized rate of severe asthma exacerbation was used as the efficacy endpoint in exposure response analysis instead of the annualized rate of severe asthma exacerbation. (Figure 9)

Figure 9 Reviewer's exposure response analyses on percent change from baseline (placebo unadjusted) in severe asthma exacerbation by Ctrough (left panel) and Caverage (right panel) quartiles



Source: Reviewer's analysis

The ER analyses showed similar responses in percent change from baseline in severe asthma exacerbation (placebo unadjusted) across different exposure levels for both Ctrough and Caverage observed in Study EFC14153. Also, patients with different bodyweight (below and above 30 kg) showed similar responses. These results supported the proposed dosing regimen of (100 mg /200 mg Q2W) as the optimized dosing regimen in 6 to less than 12 years old children with persistent asthma.

Although subjects were not stratified to the exposure quartiles, demographics, disease characteristics, and the use of background therapies were similar across different exposure quartiles and placebo group.

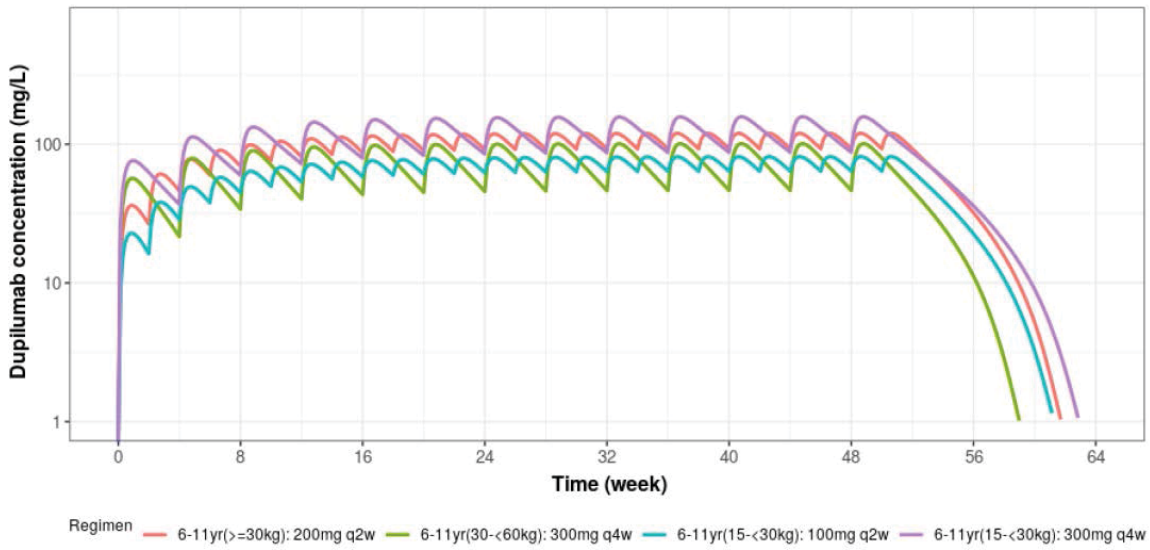
Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

(b) (4)

No PK samples following 300 mg Q4W dosing were collected in Study EFC14153, and only 2 PK samples were available from 2 subjects (15 to <30 kg) on 300 mg Q4W treatment in Study LTS14424. PK profiles following 300 mg Q4W dosing regimen were not characterized based on the limited sample size of PK samples. The Applicant developed a population pharmacokinetic (PopPK) model in children 6 to less than 12 years old based on dupilumab plasma concentrations obtained from Study EFC14153 and LTS14424. A previously developed global PopPK model in healthy subjects, subjects with asthma and/or atopic dermatitis (including both adults and children) was used as base model. The base model was previously reviewed by Dr. Dipak Pisal under BLA 761055 Supplement 14 (DARRTS date 06/25/2019). Some key PK parameters of the asthma pediatric PopPK model were fixed from the values estimated by the global PopPK base model. The basic model/model structure and some basic PK parameters were all shared by these models. The estimated PK parameters in children with asthma were also comparable to the estimated PK parameters in children with atopic dermatitis. Along with the comparable trough concentration, the pharmacokinetics data suggested similar PK characteristics in children with asthma and atopic dermatitis.

Based on this pediatric PopPK model in children with asthma, the Applicant simulated typical concentration time profiles following 100 mg Q2W in children 15 to 30 kg, 200 mg Q2W in children 30 kg and above, 300 mg Q4W in children 15 to 30 kg and 30 kg and above. The simulated PK profiles are depicted in Figure 10 below.

Figure 10 Comparison of Pop PK model-predicted typical concentration-time profiles of dupilumab in children 30 to < 60 kg following 200 mg Q2W, children 15 to < 30 kg on 100 mg Q2W, and 300 mg Q4W by body weight group



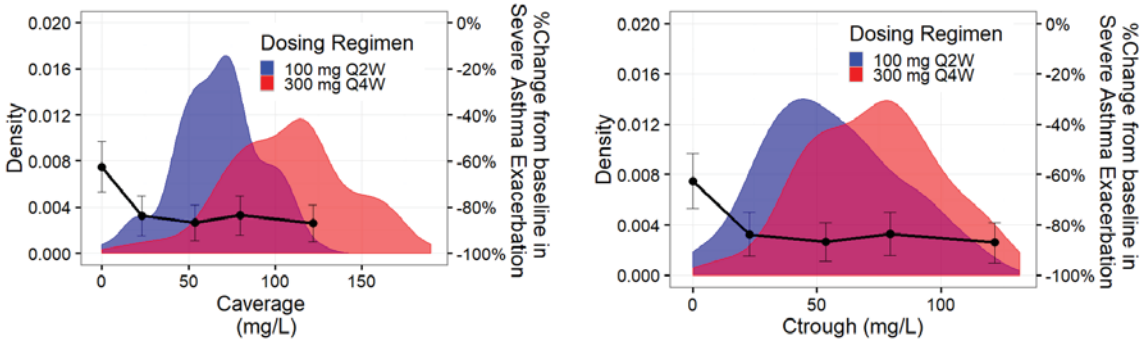
Source: Figure 11 in 2.7.2 Summary of Clinical Pharmacology Studies

According to the Applicant's simulation depicted in Figure 10 above, the exposure of 300 mg Q4W dosing regimen in children 15 kg to 30 kg is consistently higher than the 100 mg Q2W dosing regimen, and the exposure of 300 mg Q4W dosing regimen in children 30 kg and above is consistently lower than the 200 mg Q2W dosing regimen.

The impact of the exposure differences on efficacy between the Q4W dosing regimen and Q2W dosing regimen was evaluated by the reviewer. Individual Ctrough and Caverage following 300 mg Q4W dosing regimen were simulated based on PopPK model developed by the Applicant.

For children 15 kg to 30 kg, projecting the predicted exposure in 300 mg Q4W onto the ER relationship (Figure 11), fewer subjects are expected to fall in the exposure range between placebo and the lowest quartile of systemic exposure following the 100 mg Q2W dosing regimen, and the proposed 300 Q4W dosing regimen in children 15 kg to 30 kg is expected to maintain the overall efficacy observed in Study EFC14153.

Figure 11 Q4W dosing regimen impact on exposure and efficacy in patients 15 to < 30 kg



Source: Reviewer's analysis

(b) (4)

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What is the incidence of the formation of ADA and the impact of immunogenicity on dupilumab exposure?

Blood samples for anti-dupilumab antibody analysis were collected at Baseline, Week 12, Week 24, and Week 52 (four weeks after last dose), and early withdrawal (if applicable) in Study EFC14153. The same bioanalytical method was used for anti-drug antibodies (ADA) and neutralizing antibodies (NAb) assay in Study EFC14153 and the adult and adolescent asthma program. For ADA determination, a non-quantitative, titer-based, electrochemiluminescence bridging immunoassay using a modified REGN668 (REGN3432) has been developed. For NAb determination, a competitive ligand binding assay has been developed to detect anti-REGN668 NAb in human serum samples using electrochemiluminescence.

Treatment-emergent positive ADA responses were observed in 17 (6.3%) subjects in the dupilumab group and 4 (3.0%) subjects in the placebo group. There were no subjects with treatment-boosted ADA responses from positive baseline. Persistent ADA responses were observed in 9 (3.3%) subjects in the dupilumab group and 1 (0.8%) in the placebo group. The proportion of subjects who were positive in the NAb assay was 6 (2.2%) in the dupilumab group and 1 (0.8%) in the placebo group.

Due to the small sample size of ADA-positive subjects in Study EFC14153, no formal analysis was conducted to evaluate the effect of ADA on PK, efficacy, and safety.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 6: Listing of Clinical Trials Relevant to This sBLA

Trial Date	Trial Design/ Duration	Regimen/ schedule/ route	N[ϰ]	Population	Primary Endpoint	No. of Centers/ Countries
EFC14153 April 2017 - Aug 2020	R, DB, PC phase 3 52 weeks	100 mg Q2W[γ] 200 mg Q2W[γ] Placebo	273 135	Subjects with uncontrolled moderate-to-severe asthma on background therapy[†]	Annualized rate of severe exacerbation events	90 sites/17 countries (Argentina, Australia, Brazil, Canada, Chile, Colombia, Hungary, Italy, Lithuania, Mexico, Poland, Russia, South Africa, Spain, Turkey, Ukraine, United States)
LTS14424 Jun 2018- Present	OLE phase 3 52 weeks	100mg Q2W[γ] 200mg Q2W[γ] 300mg Q4W[∞] Placebo	240 18 125	Subjects with uncontrolled moderate-to-severe asthma on background therapy[†]	Safety	90 sites/17 countries (Argentina, Australia, Brazil, Canada, Chile, Colombia, Hungary, Italy, Lithuania, Mexico, Poland, Russia, South Africa, Spain, Turkey, Ukraine, United States)

γ: 100mg SC Q2W for body weight < 30kg or 200mg Q2W for body weight ≥30kg ; ϰ: Randomized population; †: high-dose inhaled corticosteroid or medium-dose or high-dose inhaled corticosteroid in combination with a second controller (long-acting β-agonist/long-acting muscarinic antagonist/leukotriene receptor antagonist/methylxanthine); ∞ Introduced as a protocol amendment, a total of 18 subjects received this dose
R = randomized, DB = double-blind, OLE = open-label extension, PC = placebo-controlled, Q2W= every 2 weeks, Q4W= every 4 weeks
Source: EFC14153 CSR Synopsis

7.2.Review Strategy

This sBLA contained one randomized, double-blind, placebo-controlled study of 52 week duration (EFC14153) that was evaluated for efficacy and safety. Section 8.1 includes a summary of the protocol, and the efficacy and safety results. Additionally, safety results from the Applicant's one year open-label extension study (LTS14424) are included throughout the review.

Data Sources

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

8 Statistical and Clinical Evaluation

8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. EFC14153

8.1.1.1 Administrative Information

- **Study title:** A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma
- **Study dates:** April 27, 2017-August 26, 2020
- **Study sites:** Argentina, Australia, Brazil, Canada, Chile, Colombia, Hungary, Italy, Lithuania, Mexico, Poland, Russia, South Africa, Spain, Turkey, Ukraine, and United States
- **Study report date:** December 7, 2020

Reviewer comment: Although the Applicant refers to the target disease as "persistent" asthma, the Division maintains that moderate-to-severe asthma, as used in the indication statement, most accurately reflects the study population. Patients who have "moderate persistent" asthma and are uncontrolled on background therapy would technically classify as "severe" asthma, however, in contrast to the anti-IL-5s for severe asthma, dupilumab's asthma program only required 1 asthma exacerbation for study enrollment and did not permit patients to enter the study on systemic corticosteroids.

8.1.1.2 Objectives

Primary

- Evaluate efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma

Secondary

- Assess the safety and tolerability of dupilumab
- Evaluate the effect of dupilumab in improving patient reported outcomes (PROs); including health related quality of life (HRQoL)
- Assess the dupilumab systemic exposure and incidence of ADA
- Evaluate the association between dupilumab treatment and pediatric immune responses to vaccines; any vaccination for tetanus, diptheria, pertussis and/or seasonal trivalent/quadrivalent influenza vaccine

Other

- Explore baseline and on-treatment levels of biomarkers for their potential to predict and to associate with a treatment response
- Explore the association of genetic profiles (optional) with treatment response or airway disease
- Evaluate the proportion of patients requiring increased dose of ICS or step up in the second controller medication regimen
- Evaluate the effect of dupilumab on additional PROs

Reviewer comment: Regarding humoral responses to vaccination, the Applicant notes that the number of patients with tetanus, yellow fever, and pertussis vaccinations was insufficient to conduct treatment comparisons. Regarding the influenza vaccine, results were comparable between treatment groups. The label notes to avoid live vaccines during DUPIXENT treatment and limited data are available regarding co-administration of DUPIXENT with non-live vaccines.

8.1.1.3 Study Design and Conduct

Study EFC14153 was a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study comparing 100 mg every 2 weeks (15 to <30 kg), and 200 mg every 2 weeks (≥ 30 kg) of dupilumab administered subcutaneously (SC) to placebo for a 52-week treatment period in children 6 years to <12 years of age with moderate to severe uncontrolled asthma, regardless of baseline serum eosinophils. Dupilumab was administered as

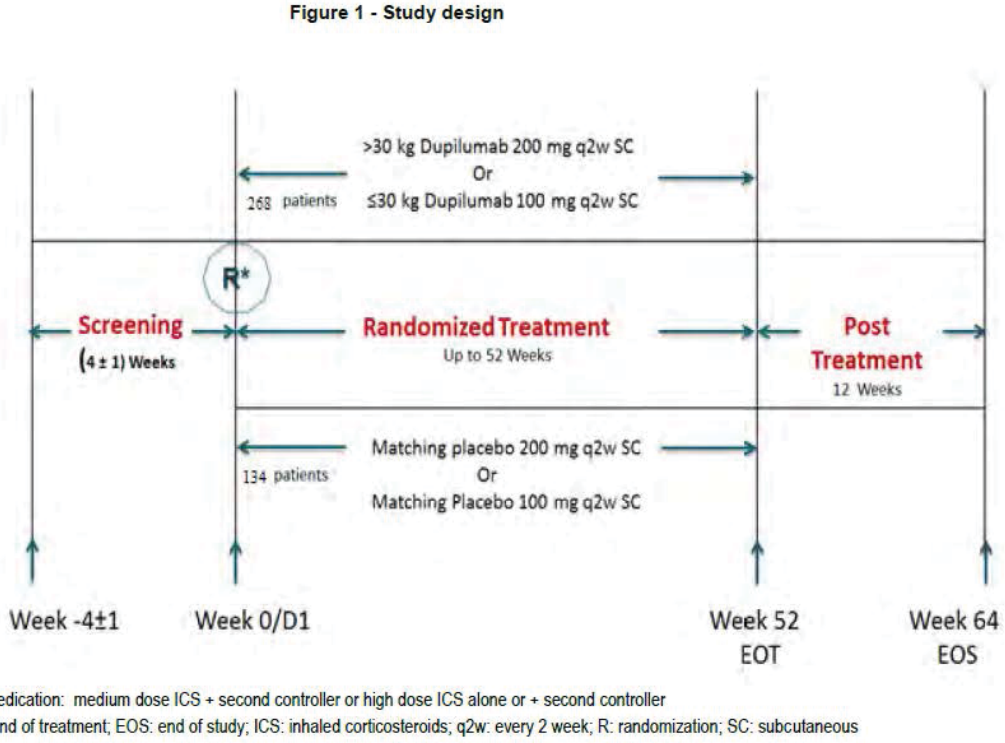
add-on therapy to high-dose ICS alone or medium-dose or high-dose ICS in combination with a second controller (e.g. long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), leukotriene receptor antagonist (LTRA), or methylxanthines).

The primary efficacy population in the US was subjects with a baseline blood eosinophil count ≥0.3 Giga/L. Subjects were randomized 2:1 to receive SC dupilumab or placebo every 2 weeks.

Randomization was stratified by ICS dose level (medium,high) at screening, blood eosinophil count (<0.3 Giga/L and ≥ 0.3 Giga/L) at screening, and region (Latin America, Eastern Europe, and Western countries). Dose levels considered as medium-or high-dose ICS in children 6 to <12 years old were adapted from the GINA guidelines 2015, applicable at the time of study initiation.

The study schematic is shown in **Figure 13**

Figure 13 EFC14153 Study Schematic



Background medication: medium dose ICS + second controller or high dose ICS alone or + second controller
D: day; EOT: end of treatment; EOS: end of study; ICS: inhaled corticosteroids; q2w: every 2 week; R: randomization; SC: subcutaneous

Source: Study EFC14153 CSR, Figure 1, p.27

8.1.1.3.2 Procedures

The study consisted of 3 periods with a total duration of 68±1 weeks for each subject:

- Screening period (4±1 weeks)

- Randomized double-blind treatment period (up to 52 weeks) during which subjects received dupilumab or placebo administered as SC injections

- Post-treatment period (12 weeks) for subjects who did not participate in the 1-year long-term extension study (LTS14424)

A schedule of assessments is provided in **Figure 14**

Figure 14 Schedule of Assessments

	SCR[a]	Randomized Treatment Period																										Post-treatment Period[d]		
		RND[b]																									EOT[c]			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[e]	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
Informed Consent/Assent[f]	x																														
Inclusion/Exclusion Criteria	x	x																													
Patient Demography	x																														
Medical/Surgical History[g], and Reversibility[h]	x																														
Physical Examination	x													x														x			x
Menstruation status[i]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x			x
Vital Signs[j] (including height and weight)	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Dispense or download electronic diary/ PEF meter[k]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Health Care Resource Utilization (HCRU)		x						x						x						x						x		x			x
Randomization[b]		x																													
Call IVRS/IWRS	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x			x
Treatment																															
Investigational Product Administration[l]		x	x	x	x	x	x	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]	x	x[m]				
Dispense/review of diary for Home Dosing[m] (optional) by parent/caregiver								x		x		x		x		x		x		x		x		x		x		x			
Efficacy Assessments																															
Spirometry[n]	x	x[o]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Post-bronchodilator FEV1[n]		x	x	x		x		x						x						x								x			x
Patient Reported Outcomes / HRQoL																															
ACQ-IA[p]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x			x
PAQLQ(S)-IA (for patients ≥7 years old at Randomization V2)[p]		x						x						x						x								x			x
PRQLQ-IA [q]		x						x						x						x								x			x
EQ-5D-Y		x												x														x			x
Patient Reported Outcomes (Caregiver)																															
PACQLQ (for caregivers of patients ≥7 years old at Randomization V2)		x						x						x						x								x			x
PK, PD, Pharmacogenetics																															
Blood biomarkers[r]		x						x						x														x			
Total IgE, and antigen-specific IgE[s]		x												x														x			
Antigen-specific IgG4 panel[s]		x												x														x			
Systemic drug concentration[t]		x			x			x						x														x			x
Exhaled NO[u]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x	x	x
Blood for DNA extraction (optional) [v]		<—													X													—>			
Safety Assessments																															
Total IgG, IgG subclasses, IgM, IgA		x												x														x			x
Anti-drug antibodies[w]		x						x						x														x			x
Pregnancy test for girls who are menstruating[x]	x	x		x		x		x		x		x		x		x		x		x		x		x		x		x			x
Prior and concomitant medications	x	x	x	x	x	x	x	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		x		x		x		x	x	x	x
Clinical lab testing[y] (hematology/biochemistry)	x	x						x						x						x								x			x
Urinalysis	x							x						x						x								x			x
ECG	x																											x			x
Archival serum (optional)		x						x						x						x								x			

Vaccines Record Review / Scheduling[z,aa]	X																												
Any planned vaccination for tetanus, diphtheria, pertussis[z]												<———	Xz	———>	- - - - - - - - - - - - - - - - - >														
Any planned vaccination for seasonal trivalent / quadrivalent influenza[z]						<———							Xz			———>	- - - - - - - - - - - - - - - - - >												
Blood sample collection[aa] for assessment of IgG response to vaccination					Xaa			Xaa						Xaa					Xaa							Xaa				

AE: Adverse event; AESI: Adverse Events of Special Interest ; EQ-5D-Y: EuroQol 5 Dimension Youth instrument; ETD: early treatment discontinuation visit; FEV_1: Forced expiratory volume in 1 second; HRQol: health-related quality of life; IgA: Immunoglobulin A; IgE: IgG: Immunoglobulin E; Immunoglobulin G; IgM: Immunoglobulin M; IVRS: Interactive voice response system; IWRS: Interactive web response system, NO: Nitric oxide; ACQ-IA: Asthma Control Questionnaire–Interviewer Administered; PACQLQ: Pediatric Asthma Caregivers Quality of Life Questionnaire; PAQLQ(S)-IA: Pediatric Asthma Quality of Life Questionnaire With Standardised Activities–Interviewer Administered; PD: Pharmacodynamics; PK: Pharmacokinetics; PRQLQ-IA: Pediatric Rhinoconjunctivitis Quality of Life Questionnaire–Interviewer Administered; PEF: Peak expiratory flow; SAE: Serious adverse event;

Source: EFC14153 CSR Table 2, p. 39

8.1.1.3.3 Patient Population

Key Inclusion Criteria

- Children 6 to < 12 years of age with physician diagnosis of persistent asthma for ≥12 months prior to screening based on clinical history and examination, pulmonary function parameters according to Global Initiative for Asthma (GINA) 2015 Guidelines and the following criteria:
    - Existing background therapy of medium-dose ICS with a second controller medication (LABA, LTRA, LAMA, or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for ≥ 3 months with a stable dose 1 month prior to Screening Visit 1
    - Pre-bronchodilator FEV1 ≤95% of predicted normal or pre-bronchodilator FEV1/FVC ratio < 0.85 at screening and baseline
    - Reversibility of at least 10% in FEV1 after the administration of 200 to 400 mcg 2 to 4 puffs with metered-dose inhaler (MDI) of albuterol/salbutamol or 45 to 90 mcg (2 to 4 puffs with MDI) of levalbuterol/levosalbutamol reliever medication before randomization (up to 3 opportunities during the same visit were allowed with a maximum of 12 puffs of reliever medication if tolerated by the subject)
    - Must have experienced within 1 year prior to screening Visit 1, any of the following events:
        - Treatment with a systemic corticosteroid (oral or parenteral) prescribed by a healthcare professional for worsening asthma at least once or
        - Hospitalization or emergency medical care visit for worsening asthma
    - Evidence of uncontrolled asthma, with at least one of the following criteria during the 4 (±1)-week screening period:

- ACQ-5-IA score ≥1.5 on at least one day of the screening period including Visit 2.
- Use of reliever medication (albuterol/salbutamol or levalbuterol/levosalbutamol) other than as a preventive for exercise induced bronchospasm, on 3 or more days/per week on at least one week during the screening period.
- Sleep awakening due to asthma that required the use of reliever medication at least once during the screening period
- Asthma symptoms 3 or more days/week on at least one week during the screening period.

Reviewer comment: A maximum of 3 visits to meet the qualifying criterion of reversibility was allowed during the screening period and prior to randomization. For patients that had an additional and last attempt of reversibility testing at the baseline Visit 2 before patients' randomization into the interactive response technology, the post-bronchodilator FEV1 came from the result of this reversibility test. Additionally, documented reversibility or positive airway hyper-responsiveness to methacholine within 12 months prior to screening Visit 1 was considered acceptable.

Key Exclusion Criteria

- Patients < 6 or ≥12 years of age
- Patients < 16 kg body weight
- Any other chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia, etc.) which may impair lung function
- History of life-threatening asthma (e.g. requiring intubation)
- Co-morbid disease interfering with the evaluation of IMP (investigational medicinal product)
- History of malignancy of any kind
- Inability to follow study procedures (e.g. due to language barrier or psychological disorder)
- Anti-IgE therapy (omalizumab) within 130 days prior to Visit 1 or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease (e.g. rheumatoid arthritis, inflammatory bowel disease or autoimmune disease (e.g. rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus as well as other diseases) within 2 months or 5 half-lives prior to Visit 1, whichever was longer.
- Initiation of allergen immunotherapy within 3 months prior to Visit 1 or dose change from 1

month prior to Visit 1 or a plan to begin allergen immunotherapy or to change its dose during the screening period or the randomized treatment period.

- Exposure to another investigative antibody within a time period prior to Visit 1 that was less than 5 half-lives of the antibody. In case the half-life was not known, then the minimum interval since exposure to the prior investigative antibody was 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication was 30 days prior to Visit 1.
- Patients receiving medications or therapy that were prohibited as concomitant medications
- Patients previously treated in any clinical trial of dupilumab
- Patients or caregivers related to the Investigator or other study staff
- Non-compliance with the use of mandatory background therapy during screening, as defined as < 80% of total number of prescribed doses of background medication taken during screening.
- Patient treated with systemic corticosteroids (SCS) for diagnoses other than severe exacerbation of asthma and/or high-potency topical steroids within 30 days before screening Visit 1, during screening, and/or during randomized treatment phase.
- History of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular, or other significant medical illness or disorder.
- Positive urine pregnancy test or sexually active not using acceptable contraception (oral, injected, inserted, or implanted hormonal contraceptive, intrauterine device, barrier contraceptive used with spermicide).
- Active parasitic infection or high risk of parasitic infection
- History of human immunodeficiency virus (HIV) or positive HIV serology at Visit 1
- Known or suspected history of immunosuppression, including history of invasive opportunistic infections (histoplasmosis, listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections.
- Acute or chronic infection requiring systemic treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1 or during the Screening period, significant viral infections within 4 weeks before Visit 1 or during the Screening period that may not have received antiviral treatment.
- Active autoimmune disease or patients using immunosuppressive therapy for autoimmune

disease or patients with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or Sponsor

- History of hypersensitivity reaction, other than localized injection site reaction, to any biologic drug
- Positive or indeterminate test for hepatitis B surface antigen (HBs-Ag); positive immunoglobulin M (IgM) hepatitis B core antibody; positive total hepatitis B core antibody (HBc-Ab) confirmed by positive hepatitis B virus DNA (HBV DNA); positive hepatitis C virus antibody (HCV-Ab) confirmed by positive hepatitis C virus RNA (HCV RNA).
- Clinically significant hepatobiliary disease or elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3x ULN
- Abnormal lab values at screening (creatine phosphokinase (CPK) > 3x ULN or platelets < 100,000 cells/mm^3 or eosinophils > 1500 cells/mm^3
- Patients receiving live (attenuated) vaccines within 4 weeks before the baseline visit

Reviewer comment: During a yellow fever outbreak in Brazil, via local protocol amendment 2, any patient not previously vaccinated with the yellow fever vaccine was unblinded and permanently discontinued from IMP. All patients continued to be followed until the end-of-study visit. Patients remained eligible for the 1-year long-term extension study. Four patients who were not previously vaccinated with the yellow fever vaccine were unblinded and permanently discontinued from IMP; 3 of them received the vaccine.

8.1.1.3.4 Treatment

Eligible patients received dupilumab or placebo administered SC Q2W as follows:

Dupilumab 100 mg Q2W or matching placebo for children with a body weight at randomization of 15 to <30 kg

Dupilumab 200 mg Q2W or matching placebo for children with a body weight at randomization of ≥30 kg

The Investigator or delegate trained the parent(s)/caregiver(s) on how to inject IMP. Injections could be performed at home after Week 12.

Sterile dupilumab was supplied as a 150 mg/mL solution in a prefilled syringe to deliver one Q2W dose of 100 mg in a 0.67 mL SC injection or as a 175 mg/mL solution in a prefilled syringe to deliver a Q2w dose of 200 mg in a 1.14 mL SC injection. Matching placebo was supplied in a prefilled syringe to deliver one q2w dose of placebo in a 0.67 mL or 1.14 mL SC injection.

8.1.1.3.5 Efficacy Endpoints

Primary:

- Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period

Secondary:

- Change from baseline in pre-bronchodilator FEV1pp at Week 12
- Change from baseline in pre-bronchodilator FEV1pp at Weeks 2, 4, 8, 24, 36, and 52 and other time points assessed
- Change from baseline in ACQ-7-IA Week 24
- Proportion of participants who reached the minimally important clinical difference (MCID) defined as change from baseline in ACQ-7 ≤ -0.5 at Week 12, 24, 36 or 52
- Change from baseline in FeNO at Week 12

8.1.1.3.6 Efficacy Parameters

Severe exacerbation was defined as deterioration of asthma requiring:

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

A loss of asthma control event was defined as deterioration of asthma requiring:

- 6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days;
- Increase in ICS dose 4 times than the dose at Visit 2;
- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The treatment period stability limit was defined as the respective mean AM or PM peak expiratory flow obtained over the last 7 days prior to randomization (Day 1);
- Severe exacerbation event

Events were considered as different if the time interval between their start dates was ≥28 days.

Asthma Control Questionnaire–Interviewer Administered, 5-question version (ACQ-5-IA)

This patient-reported outcome measures the adequacy of asthma control and change in asthma control. The questionnaire consists of five items that are administered by an interviewer 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?
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 MCID is a change in score of 0.5.

Asthma Control Questionnaire–Interviewer Administered, 7-question version (ACQ-7-IA)

The questionnaire consists of seven items that are administered by an interviewer queried over a 1-week recall period. The items additional to the 5 questions in the ACQ-5-IA include FEV1pp and daily rescue bronchodilator use. The MCID is a change in score of 0.5.

Paediatric Asthma Quality of Life Questionnaire With Standardised Activities – Interviewer Administered (PAQLQ(S)-IA)

The PAQLQ(S)-IA has 23 questions in 3 domains (symptoms, activity limitation, and emotional function) administered by an interviewer queried over a 1-week recall period. The activity limitation domain contains generic activity questions (in contrast to the original PAQLQ which contains three patient-specific activity questions). Items are scored on a 7-point scale (1= extremely bothered and 7=not bothered at all). The overall score is the mean of all 23 responses. The MCID is a change in score of 0.5.

Reviewer comment: Although the Applicant also included PACQLQ , the Division of Clinical Outcome Assessment was consulted and felt this was not appropriate to include in the label. PACQLQ assesses the health-related quality of life of the caregiver of children with asthma.This is a distal concept as it measures health-related quality of life of the caregiver. Health-related quality of life is already a distal concept compared to direct signs and symptoms of asthma. Additionally, this instrument was not multiplicity controlled.

Of note, interviewer administered versions of ACQ and PAQLQ were developed for children 6-10 years of age as initial cognitive debriefing studies provided evidence that only children 11 years and older could understand ACQs accurately and unaided.

8.1.1.3.7 Safety Parameters

Safety parameters included clinical labs (hematology, serum chemistry, urinalysis, serum immunoglobulins, anti-nuclear antibodies, hepatitis and HIV screening, pregnancy testing, vital signs (blood pressure, heart rate, respiratory rate, temperature, and height/weight), physical examinations, and electrocardiograms.

8.1.1.3.8 Statistical Analysis Plan

Analysis Populations

The randomized population included any patient who had been allocated to a randomized treatment regardless of whether the treatment kit was used. For efficacy populations, the full intent-to-treat (ITT) population was defined as all randomized pateints. Patients were analyzed in the treatment group to which they are randomized. The key efficacy endpoints were further analyzed on the following analysis populations:

- Baseline blood eosinophils ≥0.3 Giga/L population (primary analysis population)
- Baseline blood eosinophils ≥0.15 Giga/L population
- Type 2 inflammatory asthma phenotype population (defined as randomized patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb)
- Baseline FeNO ≥20 ppb population

Reviewer comment: At the pre-sBLA meeting, the Applicant proposed a primary analysis population of type 2 inflammatory phenotype (eosinophils ≥150 cells or FeNO ≥20). We noted uncertainty in what additional information was added by including elevated FeNO in the study population and recommended that the primary analysis population remain similar to adult and adolescent asthma (baseline eosinophils ≥ 0.3 Giga/L). Based on this feedback, the Applicant included baseline eosinophils ≥ 0.3 Giga/L as the primary analysis population at the top of the hierarchy for the United States. (b) (4) .

Due to the concerns outlined for the type 2 inflammatory phenotype population, the remainder of the efficacy section will not include results for this population and this population will only be mentioned where applicable.

(b) (4)

The safety population was defined as all patients who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment patients actually received.

Sample Size Considerations

For patients with baseline blood eosinophils ≥0.3 Giga/L assuming a placebo annualized severe exacerbation rate of 0.8 and a dispersion parameter of 1.5, with approximately 255 patients randomized (170 for dupilumab and 85 for matching placebo group), this study was to have approximately 96% power to detect a 60% relative risk reduction (ie, annualized rate of 0.32 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05 among these subjects. The sample size calculation assumed a linear

discontinuation rate (20% at 1 year), thus the average exposure duration for subjects was 0.9 years. The assumed relative risk reductions were based on the results in the phase 3 asthma study EFC13579.

To achieve target sample size for each of the two main efficacy populations of interest (baseline blood eosinophils ≥0.3 Giga/L and baseline blood eosinophils ≥0.15 Giga/L populations), at least a total of 402 patients in the overall population (268 for dupilumab and 134 for placebo) need to be randomized assuming approximately 81% of the randomized patients have the baseline blood eosinophils ≥0.15 Giga/L, and approximately 64% of the randomized patients have the baseline blood eosinophils ≥0.3 Giga/L.

Multiple Testing

To control the type-I error rate for the analysis of efficacy endpoint, a hierarchical testing procedure was applied at a 2-sided 5% significance level (i.e., each hypothesis was formally tested only if the preceding one is significant at the 2-sided 5% level). To match the approved indication in adults and adolescents, for the US and US reference countries, the testing hierarchy started with baseline blood eosinophils ≥0.3 Giga/L population. The complete list of the endpoints with their testing order is specified in Table 5.

Table 7: Hierarchical testing order for US and US reference countries

Test Order	Endpoints	Population
1st	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.3 Giga/L
2nd	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L
3rd	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb
4th	Change from baseline in FEV1pp at Week 12	Patients with baseline blood eosinophils ≥0.3 Giga/L
5th	Change from baseline in FEV1pp at Week 12	Patients with baseline blood eosinophils ≥0.15 Giga/L
6th	Change from baseline in FEV1pp at Week 12	Patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb
7th	Change in ACQ-7-IA at Week 24	Patients with baseline blood eosinophils ≥0.3 Giga/L
8th	Change in ACQ-7-IA at Week 24	Patients with baseline blood eosinophils ≥0.15 Giga/L
9th	Change in ACQ-7-IA at Week 24	Patients with baseline blood

		eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb
10th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Baseline FeNO ≥20 ppb
11th	Change from baseline in FEV1pp at Week 12	Baseline FeNO ≥20 ppb
12th	Change in ACQ-7-IA at Week 24	Baseline FeNO ≥20 ppb
13th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Full ITT
14th	Change from baseline in FEV1pp at Week 12	Full ITT
15th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.3 Giga/L and High ICS at baseline
16th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L and High ICS at baseline
17th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb with High ICS at baseline
18th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Baseline FeNO ≥20 ppb with High ICS at baseline
19th	Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period	Full ITT with High ICS at baseline
20th	Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.3 Giga/L
21st	Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.15 Giga/L
22nd	Change from baseline in FeNO at Week 12	Patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb
23rd	Change from baseline in FeNO at Week 12	Baseline FeNO ≥20 ppb
24th	Change from baseline in FeNO at Week 12	Full ITT

Source: Modified from the Applicant's Statistical Analysis Plan Table 9, p.58

Estimand

The primary estimand for the primary endpoint utilized a treatment policy strategy. In this approach, the severe exacerbation events reported after the premature treatment discontinuation were included in the analysis. Any exacerbation obtained after the first permanent stepping-up of background asthma medication (following at least two severe exacerbations per protocol) was also included in the analysis.

A supportive analysis to assess the efficacy of dupilumab if subjects adhere to the treatment as directed was also specified (on-treatment analysis). In this approach, the severe exacerbation events reported after the premature treatment discontinuation were excluded from the analysis. Any exacerbation obtained after the first permanent stepping-up of background asthma medication (following at least two severe exacerbation per protocol) was also to be excluded from the analysis.

Estimators

A negative binomial model was used with the treatment arm, age, baseline weight (≤30kg, >30kg), region, baseline eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration was used as an offset variable. When performing the primary endpoint analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level was removed from the model covariates. When performing the primary endpoint analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level was removed from the model covariates. Comparisons of the annualized event rates between dupilumab and placebo were derived by testing the dupilumab group versus placebo. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals were derived from the negative binominal model.

The absolute change from baseline in FEV1pp at Week 12 was analyzed using a mixed-effect model with repeated measures (MMRM) approach. The analysis for change from baseline in FEV1pp was performed in the baseline blood eosinophils ≥0.3 Giga/L, baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20 ppb and full ITT populations. When performing the key secondary endpoint analysis in the baseline blood eosinophils ≥0.15 Giga/L and full ITT populations, the model included change from baseline in FEV1pp values up to Week 12 as response variables, and treatment, baseline weight, region, ethnicity, baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1pp value and baseline-by-visit interaction as covariates. When performing the key secondary endpoint analysis in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level was removed from the model covariates. When performing the key secondary endpoint analysis in the baseline FeNO ≥20 ppb population, the baseline FeNO level was removed from the model covariates.

Change from baseline in ACQ-7-IA Week 24 was analyzed using MMRM model including change from baseline up to Week 24 as response variables, regardless of whether the subject was on treatment or not when the endpoint was measured. Change from baseline in FeNO at Week 12 was analyzed using MMRM including change from baseline up to Week 12 as response variables, regardless of whether the subject was on treatment when the endpoint was measured. The analyses for the secondary endpoints of ACQ-7-IA and FeNO were performed in

the baseline blood eosinophils ≥0.3 Giga/L, baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20 ppb and full ITT populations. When performing these analyses in the baseline blood eosinophils ≥0.15 Giga/L or full ITT population, the MMRM models included treatment, age, baseline weight, region (pooled country), baseline eosinophil level, baseline FeNO level, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value, and baseline-by-visit interaction as covariates. When performing these analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level was removed from the model covariates. When performing these analyses in the baseline FeNO ≥20 ppb population, the baseline FeNO level was removed from the model covariates.

In addition to the MMRM analyses for change from baseline in ACQ-7, a responder analysis was also performed for the endpoint at Week 12, 24, 36 and 52, in the baseline blood eosinophils ≥0.3 Giga/L populations. A logistic regression model was used to compare percentage of subjects who reached MCID (responders) in the dupilumab and placebo group at the time points aforementioned, respectively. Subjects with change from baseline in ACQ-7 ≤ -0.5 were considered to be responders. Subjects with change from baseline in ACQ-7 > -0.5 or with missing value were considered to be non-responders. When performing the analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level was removed from the model covariates. Odds ratio of being a responder comparing dupilumab and placebo group was provided along with the corresponding 95% CI and p-value.

Missing Data Handling

If subjects withdrew from the study before Visit 28 (Week 52), severe exacerbation events that may occur after study discontinuation were not observed. These subjects were considered as subjects with missing data for the severe exacerbation endpoint. The number of subjects with missing data, reasons and timing for subject withdrawals were summarized by treatment groups. The following sensitivity analyses were conducted to assess the robustness of the conclusion drawn based on the main model for the primary analysis to the missing data:

- Pattern mixture model (PMM-MI with logistic regression model)
- Control-based PMM
- Tipping point analysis

The missing data sensitivity analyses for the primary endpoint analysis were performed in the baseline blood eosinophils ≥0.3 Giga/L population.

Pre-specified Subgroup Analyses

To assess the consistency of treatment effects across the subgroup levels, subgroup analyses were performed for the annualized rate of severe exacerbation events during the 52-week treatment period and FEV1pp at Week 12 by:

- Gender (Male, Female)
- Region (Latin America, Eastern Europe, and Western Countries)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other)
- Background ICS dose levels at randomization (medium, high)
- Baseline blood eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L; <0.15 Giga/L, ≥0.15 Giga/L; <0.15 Giga/L, ≥0.15 - <0.3 Giga/L, ≥0.3 - <0.5 cells/µL, ≥0.5 cells/µL)
- Baseline FeNO level (<20 ppb, ≥20 – <35 ppb, ≥35 ppb)

In addition, quadrant analyses were performed to descriptively demonstrate that elevated blood eosinophils (</>=0.15 Giga/L) and/or FeNO (</>=20 ppb) predict efficacy. The following subgroup analyses were performed for the quadrant analyses:

- Eos-FeNO Quadrant (0.15-20) 1 (H-H): Baseline blood eosinophil level ≥0.15 Giga/L and Baseline FeNO ≥20 ppb
- Eos-FeNO Quadrant (0.15-20) 2 (H-L): Baseline blood eosinophil level ≥0.15 Giga/L and Baseline FeNO <20 ppb
- Eos-FeNO Quadrant (0.15-20) 3 (L-H): Baseline blood eosinophil level <0.15 Giga/L and Baseline FeNO >=20 ppb
- Eos-FeNO Quadrant (0.15-20) 4 (L-L): Baseline blood eosinophil level <0.15 Giga/L and Baseline FeNO <20 ppb

Treatment-by-Biomarker Interaction Analysis

To examine the ability of FeNO to predict the treatment effect of dupilumab independent of blood eosinophil levels for the primary endpoint, pre-specified treatment-by-biomarker interactions were tested using negative binomial regression models that include the total number of severe exacerbation events during the 52-week treatment period as the response variable, and with the following different sets of model covariates, respectively (Table 6). Common covariates shared across all models were treatment group, age, baseline weight group, region, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study.

To examine the ability of FeNO to predict the treatment effect of dupilumab independent of blood eosinophil levels for the key secondary endpoint, the treatment-by-biomarker interactions were tested with MMRM model, which included change from baseline in FEV1pp values up to Week 12 as response variables, and with the following different sets of model covariates, respectively (Table 6). Common covariates shared across all models were treatment group, baseline weight group, region, ethnicity, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV1pp value and baseline-by-visit interaction.

A threshold value of 0.15 was utilized for the nominal p-value of interaction test.

Table 8: Planned Biomarker Analysis and Biomarker Covariate and Treatment-by-Biomarker Interaction

Biomarker analysis	Biomarker covariate and treatment -by-biomarker interaction
FeNO's predictability (unadjusted for baseline eosinophil group)	Baseline FeNO group (<20 ppb, >=20 ppb), and treatment-by-baseline FeNO group interaction
FeNO's predictability (adjusted for baseline eosinophil group)	Baseline eosinophil group (<0.15 Giga/L, >=0.15 Giga/L), baseline FeNO group (<20 ppb, >=20 ppb), and treatment-by-baseline FeNO group (<20 ppb, >=20 ppb) interaction
FeNO's predictability (adjusted for baseline eosinophil group and baseline eosinophil group-by-treatment interaction)	Baseline FeNO group (<20 ppb, >=20 ppb), baseline eosinophil group (<0.15 Giga/L, >=0.15 Giga/L), treatment-by-baseline eosinophil Group (<0.15 Giga/L, >=0.15 Giga/L) interaction and treatment-by-baseline FeNO group (<20 ppb, >=20 ppb) interaction

Source: Modified from the Applicant's Statistical Analysis Plan p. 47

Protocol Amendments

Table 9 Summary of protocol amendments

Amendment No./Amended Protocol No.	Date	Purpose of amendments
1 Global/Amended protocol 1	March 10, 2017	-FeNO results not blinded to investigators or site personnel -To add exclusion criterion to clearly define the interval between live (attenuated) vaccines administration and IMP administration and be consistent with other dupilumab trials -To correct the description of PAQLQ domains and PAQLQ(S)-IA periodicity -To correct the values for medium and high dose of beclomethasone dipropionate and budesonide

		-Clarification of PEF meter -To add IMP compliance check -To clarify that a separate informed assent form had to be obtained from female patients who started menstruating -Clarification of patient monitoring -Clarification of PK sample blood volume for pediatric study -Clarification of vaccination response -To remove suicidal behavior from the list of AESIs
Protocol Amendment 02 (Local for Brazil)	February 2, 2018	-To include guidance for the investigators with patients participating in ongoing dupilumab studies in Brazil during the yellow fever outbreak
Protocol Amendment 03 Global Amended protocol 02	June 18, 2018	-To increase sample size due to an update on the assumptions based on the concluded phase 3 dupilumab clinical trial in adult and adolescent patients with asthma -Clarification of an inclusion criterion: reversibility attempts definition during the screening period -To include new countries/sites in the trial -Change in schedule of collection of blood samples: change of last possible date for post vaccination sample collection from Week 48 to Week 50 -Clarification that potent dermatological topical corticosteroids are prohibited concomitant medications -Removal of using prior assessments for re-screening -To include reliever medication baseline definition -Change of safety monitoring parameter: to adjust the neutrophil count defining neutropenia (<1000/mm3) in the study population age group

Amended protocol 03 Global	October 18, 2019	-To change the study primary efficacy analysis population from an overall uncontrolled persistent asthma population to the population with evidence of either asthma with baseline eosinophil count 0.3 Giga/L or, more broadly, asthma with the type 2 inflammatory asthma phenotype -To change the sample size -To specify the different hierarchy orders used for US and US reference countries and EU and EU reference countries -Removal of the limit in enrolling patients according to background therapy with medium-dose ICS or blood eosinophil count level -To describe the planned database lock -To classify FeNO as a secondary endpoint instead of an exploratory endpoint -To describe the fasting status -To allow for home dosing start after Visit 9 -To clarify that ACQ-5 data collected on V2 can be used for inclusion criterion 01 -To clarify how ACQ-7 value is calculated for statistical analysis -To clarify DNA sample collection timeline -To remove a sentence on the possible hurdle to public health value of the study in case of study withdrawal

Source: EFC14153 CSR Table 6 p.61

8.1.2. Study Results

Compliance with Good Clinical Practices

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.

Financial Disclosure

See Financial Disclosure 15.1

Patient Disposition

Patient disposition is summarized in Table 8. Among the 405 patients of the ITT population who were randomized and treated, the overall early study discontinuation rate was low (4%), however, the discontinuation rate was slightly higher in the dupliumab arm compared to the placebo arm (5% vs 2%). Only 2 patients (1%) in the dupilumab arm discontinued the study to adverse events.

Table 10: Patient Disposition (ITT)

Status	Number of Participants, n (%)		
	Placebo	**Dupliumab**	**Total**
Randomized (ITT)	135 (100%)	273 (100%)	408 (100%)
Randomized and treated	135 (100%)	270 (99%)	405 (99%)
Discontinued study treatment	5 (4%)	22 (8%)	27 (7%)
Adverse event	2 (2%)	5 (2%)	7 (2%)
Poor compliance to protocol	0 (0%)	2 (1%)	2 (<1%)
Other reason	3 (2%)	15 (6%)	18 (4%)
Discontinued from the study prior to Week 52	3 (2%)	13 (5%)	16 (4%)
Adverse event	0 (0%)	2 (1%)	2 (<1%)
Poor compliance to protocol	0 (0%)	1 (<1%)	1 (<1%)
Other reason	3 (2%)	10 (4%)	13 (4%)

Source: Statistical Reviewer

Protocol Violations/Deviations

In the population with baseline blood eosinophils ≥0.3 Giga/L, 3 patients (1.2%) were on low dose ICS, in violation of the protocol. Two patients in the dupilumab group were using 3 controller medications, also in violation of the protocol.

Demographic characteristics are summarized in Table 9. Baseline demographics were balanced between arms. The majority of patients were white (88%) and male (64%) with a mean age of 8.9 years with more than half of subjects in the 6-8 year age group.

Table 11: Demographic Characteristics – ITT Population

	Placebo (N = 135)	Dupilumab (N = 273)	Total (N = 408)
Age (years)			
Mean (SD)	8.9 (1.6)	8.9 (1.7)	8.9 (1.6)
Min	6	6	6
Max	11	11	11
Age group, n (%)			
6-8 years	53 (39%)	113 (41%)	242 (59%)
9-11 years	82 (61%)	160 (59%)	166 (41%)
Sex, n (%)			
Female	48 (36%)	98 (36%)	146 (36%)
Male	87 (64%)	175 (64%)	262 (64%)
Race, n (%)			
Caucasian/White	118 (87%)	242 (89%)	360 (88%)
Black/of African descent	9 (7%)	11 (4%)	20 (5%)
Asian/Oriental	0 (0%)	2 (1%)	2 (1%)
All the other	8 (6%)	18 (6%))	26 (6%)
Ethnicity, n(%)			
Hispanic or Latino	60 (44%)	118 (43%)	178 (44%)
Not Hispanic or Latino	75 (56%)	155 (57%)	230 (56%)
Region, n(%)			
Eastern Europe	49 (36%)	94 (34%)	143 (35%)
Latin America	60 (45%)	123 (45%)	183 (45%)
Western countries	26 (19%)	56 (21%)	82 (20%)

Source: Statistical Reviewer

Baseline disease characteristics are summarized in Table 10. The baseline characteristics were balanced between arms. The average age at onset of asthma was 3.4 years, with 5.6 years since diagnosis (which coincides with the mean study age of 8.9 years). The majority (87%) of

patients had an atopic history. The mean FEV1 was 1.5 L and 78.1% predicted, with 19.6% reversibility. About 36% of patients had one exacerbation within the past year, with a mean of 2.4 exacerbations per year. About 55% and 45% of patients had medium- and high-dose ICS/LABA baseline use, respectively. The mean blood eosinophil count was 0.5 Giga/L and about 63% of patients had a blood eosinophil count of ≥0.3 Giga/L. The mean FeNO was 28 ppb and approximately half of the subjects had a FeNO under 20 ppb. Mean ACQ-7-IA and PAQLQ-(S)-IA scores were 2.1 and 5.0, respectively. The mean number of puffs of rescue short-acting bronchodilator (albuterol) per day was 2.4.

Table 12: Baseline Disease Characteristics – ITT Population

	Placebo (N = 135)	**Dupilumab (N = 273)**	**Total (N = 408)**
Age at onset of asthma (Years)			
Mean (SD)	3.8 (2.5)	3.2 (2.5)	3.4 (2.6)
Min	0	0	0
Max	10	10	10
Time since first diagnosis of asthma (years)			
Mean (SD)	5.2 (2.6)	5.8 (2.6)	5.6 (2.6)
Min	1.0	1.2	1
Max	11.4	11.9	11.9
Atopic history, n (%)			
Yes	111 (82%)	245 (90%)	356 (87%)
No	24 (18%)	28 (10%)	52 (13%)
FEV1 (L)			
Mean (SD)	1.5 (0.5)	1.5 (0.4)	1.5 (0.4)
Min	0.6	0.4	0.4
Max	3.1	2.5	3.1
Percent predicted FEV1 (FEV1pp) (%)			
Mean (SD)	79.0 (14.7)	77.6 (14.7)	78.1 (14.7)
Min	31	24	24
Max	110	112	112
FEV1 reversibility (%)			
Mean (SD)	15.6 (16.3)	21.6 (22.4)	19.6 (20.8)
Min	-12	-9	-12
Max	95	140	140
Number of asthma exacerbations in past year			

Mean (SD)	2.2 (1.5)	2.6 (2.4)	2.4 (2.2)
Min	1	1	1
Max	12	24	24
1	53 (39%)	96 (35%)	149 (36%)
2	42 (31%)	87 (32%)	129 (32%)
3	23 (17%)	38 (14%)	61 (15%)
≥4	17 (13%)	52 (19%)	69 (17%)
ACQ-5-IA			
Mean (SD)	2.2 (0.8)	2.2 (0.9)	2.2 (0.8)
Min	0	0	0
Max	5.6	5	5.6
ACQ-7-IA			
Mean (SD)	2.1 (0.8)	2.1 (0.7)	2.1 (0.7)
Min	0.1	0	0
Max	4.6	5.1	5.1
PAQLQ-(S)-IA			
Mean (SD)	4.9 (1.2)	5.0 (1.1)	5.0 (1.1)
Min	1.8	1.2	1.2
Max	6.9	7.0	7.0
Number of puffs of albuterol (in 24 hours)			
Mean (SD)	2.7 (3.3)	2.3 (2.5)	2.4 (2.8)
Min	0	0	0
Max	23.7	14.3	23.7
ICS/LABA dose			
High	60 (44%)	120 (44%)	180 (45%)
Medium	75 (56%)	153 (56%)	228 (55%)
Blood eosinophil (Giga/L)			
Mean (SD)	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)
Min	0.02	0.01	0.01
Max	2.47	2.06	2.47
>=0.3	84 (62%)	175 (64%)	259 (63%)
<0.3	51 (38%)	98 (36%)	149 (37%)
Baseline FeNO (ppb)			
Mean (SD)	28.8 (24.4)	25.4 (22.5)	27.7 (23.8)
Min	1	3	1
Max	139	123	139
<20	124 (47%)	69 (53%)	193 (49%)
≥20-<35	63 (24%)	37 (28%)	100 (25%)
≥35	78 (29%)	25 (19%)	103 (26%)

Source: Statistical Reviewer

Other Baseline Characteristics (important concomitant drugs)

At baseline, most patients (96.9%) were using two types of controller medications, the majority were receiving medium or high-dose ICS in combination with LABA (83.8%) and only a few patients used high-dose ICS alone (2.3%). Two patients (0.8%), both in the dupilumab group, were using 3 controller medications, in violation of the protocol.

Treatment Compliance

In the safety population, mean compliance with administration of IMP was approximately 99%. Only 1 patient (0.4%) in the dupilumab group and 2 patients in the placebo group had a compliance of <80%. In the primary analysis population (baseline blood eosinophils ≥0.3 Giga/L, mean compliance with administration of IMP was also approximately 99%.

Data Quality and Integrity

No data quality issues as they relate to efficacy were identified in the review of this sBLA.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the annualized rate of severe exacerbations over 52 weeks of treatment. Dupilumab demonstrated a significant reduction in the primary efficacy endpoint compared to placebo in the primary analysis population with baseline blood eosinophil count ≥0.3 Giga/L (relative risk: 0.35 [95% CI: 0.22, 0.56]; p<0.01) (Table 11).

The supportive analyses for the primary efficacy endpoint performed in subjects with baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20 ppb and ITT populations demonstrated results similar to the primary efficacy population (Table 11).

Table 13: Primary endpoint analysis: Annualized rate of severe exacerbation events during the 52-week treatment period

Test Order	Popuation	Adjusted[1] Annualized Rate of Exacerbation Events		
	Randomized	**Placebo (N = 135[2])** **N** **Rate (95% CI)**	**Dupliumab (N = 273[2])** **N** **Rate (95% CI)**	**Rate Ratio (95% CI)** **p-value**
1	**Baseline blood eosinophils >= 0.3 Giga/L**	84 0.67 (0.47, 0.95)	175 0.24 (0.16, 0.34)	0.35 (0.22, 0.56) <0.01
2	**Baseline blood eosinophils >= 0.15 Giga/L**	108 0.82 (0.59, 1.14)	223 0.32 (0.23, 0.44)	0.39 (0.26, 0.59) <0.01

10	**FeNO >= 20 ppb**	62 0.70 (0.42, 1.65)	141 0.27 (0.17, 0.43)	0.39 (0.23, 0.66) <0.01
13	**ITT**	135 0.61 (0.45, 0.82)	273 0.28 (0.21, 0.37)	0.46 (0.32, 0.67) <0.01

[1] Adjusted rates and rate ratios vs placebo were derived using negative binomial model with the total number of events onset from randomization up to Week 52 visit or last contact date (whichever comes earlier) as the response variable, with the treatment group, age, baseline weight group (≤30kg, >30kg), region, baseline eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high) and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable. In patients with baseline blood eosinophils ≥0.3 Giga/L, the covariate of baseline eosinophil level was removed.
[2] Number of subjects in the randomized population.
N = number of subjects in the population
Source: Statistical Reviewer

Efficacy Results – Secondary and other relevant endpoints

The key secondary efficacy endpoint was the change from baseline in FEV1pp at Week 12. Dupilumab demonstrated a statistically significant improvement in the FEV1pp at Week 12 compared with placebo in the primary analysis population with baseline blood eosinophil count ≥0.3 Giga/L (LS mean difference: 5.29% [95% CI: 1.73, 8.85]; p<0.01). The analyses performed in baseline blood eosinophils ≥0.15 Giga/L, baseline FeNO ≥20ppb and ITT populations demonstrated similar results (Table 12).

Table 14: Key secondary endpoint analysis: Change from baseline in FEV1pp at Week 12

Test Order	Popuation	Adjusted[1] pFEV1pp Mean change from baseline at week 12		
	Randomized	**Placebo (N = 135)** **N** **LS Mean (95% CI)**	**Dupliumab (N = 273)** **N** **LS Mean (95% CI)**	**LS Mean Diff (95% CI)** **p-value**
4	**Baseline blood eosinophils >= 0.3 Giga/L**	81 6.44 (0.70, 12.19)	168 11.73 (6.51, 16.95)	5.29 (1.73, 8.85) <0.01
5	**Baseline blood eosinophils >= 0.15 Giga/L**	105 7.04 (1.40, 12.69)	216 12.00 (6.78, 17.22)	4.96 (1.81, 8.11) <0.01
11	**FeNO >= 20 ppb**	59 2.52 (-5.49, 10.53)	139 9.31 (1.88, 16.73)	6.79 (2.58, 10.99) <0.01
14	**ITT**	132 6.39 (0.81, 11.98)	264 11.06 (5.81, 16.31)	4.66 (1.85, 7.48) <0.01

[1] Least squares (LS) means (95% CI) and LS mean differences vs placebo (95% CI) were derived from MMRM model with change from baseline in FEV1pp values up to Week 12 as the response variable, and treatment, baseline weight group (≤30kg, >30kg), region, ethnicity, baseline eosinophil level (<0.3 Giga/L, ≥0.3 Giga/L), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose

level (medium/high), visit, treatment by-visit interaction, baseline FEV1pp value and baseline-by-visit interaction as covariates. In patients with baseline blood eosinophils ≥0.3 Giga/L, the covariate of baseline eosinophil level was removed.
N = Number of subjects in the randomized population; n = number of evaluable subjects at Week 12
Source: Statistical Reviewer

Reviewer comment: In the adult and adolescent asthma studies, the co-primary endpoints were annualized rate of severe exacerbation events and change from baseline in FEV1 at Week 12 in the overall population. Both dupilumab arms (200 mg Q2W and 300 mg Q2W) showed an approximate 50% reduction compared to placebo during the 1-year study period. Change from baseline in FEV1 at Week 12 in the overall population was higher for both dupilumab doses with similar mean treatment differences for both dose groups. Generally the efficacy demonostrated in this pediatric study is comparable to the the efficacy demonostrated in the adult and adolescent trials.

Durability of Response

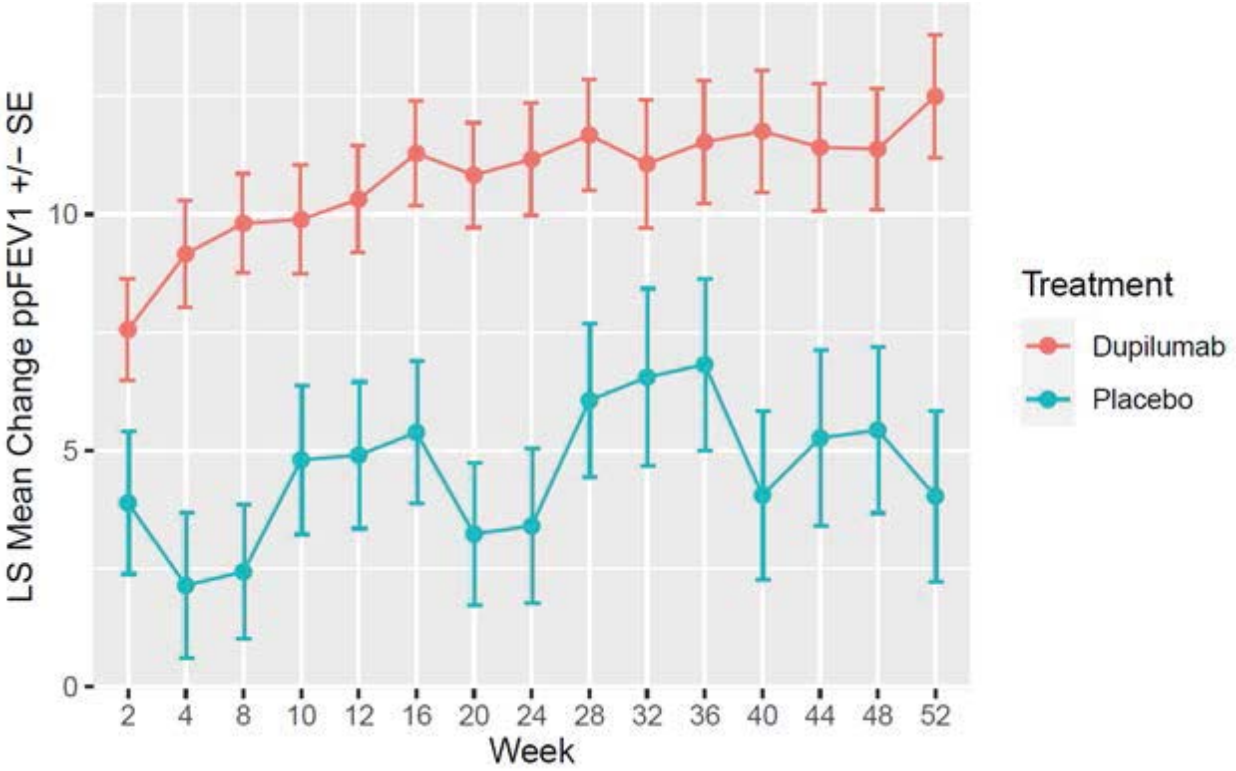
The improvement in FEV1pp was present (onset of a treatment difference was observed as early as Week 2) and sustained through Week 52 in the primary efficacy population (Figure 15). In the population with baseline blood eosinophil count ≥0.3 Giga/L, the LS mean change in FEV1pp from baseline to Week 52 was 12.50% in the dupilumab group and 4.03% in the placebo group, resulting in an LS mean difference versus placebo of 8.47% (nominal p<0.0001) (Table 13).

Table 15: Changes from baseline in FEV1pp over time up to Week 52 – Baseline blood eosinophils ≥0.3 Giga/L population

Weeks	Adjusted[1] FEV1pp mean change from baseline		
	Placebo (N=84) LS Mean (SE)	Dupliumab (N=175) LS Mean (SE)	LS Mean Diff (95% CI)
Week 2	3.89 (1.51)	7.56 (1.08)	3.67 (0.21, 7.14)
Week 4	2.14 (1.54)	9.16 (1.13)	7.02 (3.46, 10.58)
Week 8	2.43 (1.42)	9.81 (1.05)	7.39 (4.11, 10.67)
Week 10	4.80 (1.58)	9.89 (1.15)	5.09 (1.43, 8.74)
Week 12	4.90 (1.55)	10.32 (1.13)	5.42 (1.85, 9.00)
Week 16	5.38 (1.51)	11.29 (1.11)	5.91 (2.41, 9.40)
Week 20	3.23 (1.51)	10.83 (1.11)	7.60 (4.10, 11.10)
Week 24	3.40 (1.63)	11.17 (1.19)	7.77 (4.00, 11.56)
Week 28	6.06 (1.63)	11.68 (1.18)	5.62 (1.83, 9.41)
Week 32	6.55 (1.88)	11.07 (1.36)	4.52 (0.10, 8.94)
Week 36	6.82 (1.82)	11.53 (1.31)	4.72 (0.46, 8.98)
Week 40	4.05 (1.79)	11.76 (1.29)	7.71 (3.52, 11.90)
Week 44	5.26 (1.86)	11.42 (1.34)	6.16 (1.80, 10.51)
Week 48	5.43 (1.76)	11.38 (1.28)	5.96 (1.85, 10.07)
Week 52	4.03 (1.81)	12.50 (1.30)	8.47 (4.25, 12.70)

[1] Least squares (LS) means (SE) and LS mean differences vs placebo (95% CI) were derived from MMRM model with change from baseline in FEV1pp values up to Week 52 as the response variable, and treatment, baseline weight group (≤30kg, >30kg), region, ethnicity, baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline FEV1pp value and baseline-by-visit interaction as covariates.
Source: Statistical Reviewer

Figure 15: LS mean change from baseline in FEV1pp over time up to Week 52– Baseline blood eosinophils ≥0.3 Giga/L population



Least squares means and standard errors (SE) in each arm were derived from MMRM model with change from baseline in FEV1pp values up to Week 52 as the response variable, and treatment, baseline weight group (≤30kg, >30kg), region, ethnicity, baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline FEV1pp value and baseline-by-visit interaction as covariates.
Source: Statistical Reviewer

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Statistically significant improvements in the ACQ-7-IA at Week 24 were observed for the primary efficacy population as well as the other multiplicity controlled populations (Table 14).

Table 16: Other multiplicity-controlled secondary endpoint: Change from baseline in ACQ-7-IA at week 24

Test Order	Popuation	Adjusted[1] ACQ-7-IA Mean Change from Baseline at Week 24		
		Placebo (N = 135) n	Dupliumab (N = 273) n	

		LS Mean (95% CI)	LS Mean (95% CI)	LS Mean Diff (95% CI) p-value
7	**Baseline blood eosinophils >= 0.3 Giga/L**	82 -0.88 (-1.05, -0.71)	168 -1.34 (-1.47, -1.22)	-0.47 (-0.67, -0.27) <0.01
8	**Baseline blood eosinophils >= 0.15 Giga/L**	216 -1.34 (-1.45, -1.22)	106 -0.98 (-1.13, -0.82)	-0.36 (-0.53, -0.19) <0.01
12	**FeNO >= 20 ppb**	139 -0.91 (-1.11, -0.71)	61 -1.33 (-1.47, -1.19)	-0.42 (-0.65, -0.19) <0.01

[1] Least squares (LS) means (95% CI) and LS mean differences vs placebo (95% CI) were derived from MMRM model which included treatment, age, baseline weight group (≤30kg, >30kg), region (pooled country), baseline FeNO level (<20 ppb, ≥20 ppb), baseline ICS dose level (medium/high), visit, treatment by-visit interaction, baseline endpoint value and baseline-by-visit interaction as covariates. When performing these analyses in the baseline blood eosinophils ≥0.3 Giga/L population, the baseline eosinophil level was removed from the model covariates.
N = Number of subjects in the randomized population; n = number of evaluable subjects at Week 24
Source: Statistical Reviewer

A responder was defined as a patient with a reduction from baseline in ACQ-7-IA score ≥0.5 which is considered the MCID for this outcome. In the population with baseline blood eosinophil count ≥0.3 Giga/L, the proportion of patients who reached the MCID at Week 24 was higher in the dupilumab group compared with the placebo group (80.6% versus 64.3%), with an odds ratio versus placebo of 2.64 (95% CI: 1.36 to 5.12) (Table 15).

Table 17: Responder analysis for change from baseline in ACQ-7-IA over time – Baseline blood eosinophils ≥0.3 Giga/L population

Weeks	Response defined by improvement from baseline in ACQ-7-IA >=0.5		
	Placebo (N=84)	**Dupliumab (N=175)**	**Odds Ratio[1] (95% CI)**
12	57/84 (67.9%)	142/175 (81.1%)	2.28 (1.18, 4.41)
24	54/84 (64.3%)	141/175 (80.6%)	2.64 (1.36, 5.12)
36	61/84 (72.6%)	141/175 (80.6%)	1.78 (0.88, 3.61)
52	59/84 (70.2%)	152/175 (86.9%)	3.65 (1.69, 7.87)

[1] Odds ratios vs placebo were based on logistic regression with treatment, age, weight group, region, baseline FeNO level, baseline ICS dose level, and baseline ACQ-7-IA score as covariates. Patients who did not meet the criterion or had missing value are considered as non-responders.
Source: Statistical Reviewer

In the population with baseline blood eosinophil count ≥0.3 Giga/L, the proportion of patients who reached the MCID (≥0.5) in PAQLQ(S)-IA at Week 24 was higher in the dupilumab group compared with the placebo group (72.8% versus 63.0%), with an odds ratio versus placebo of 1.83 (95% CI: 0.92 to 3.64) (Table 16).

Table 18. Responder analysis for change from baseline in PAQLQ(S)-IA over time – Baseline blood eosinophils ≥0.3 Giga/L population

Weeks	Response defined by improvement from baseline in PAQLQ(S)-IA >=0.5		
	Placebo (N[1]=81)	Dupliumab (N[1]=158)	Odds Ratio[2] (95% CI)
12	49/81 (60.5%)	101/158 (63.9%)	1.54 (0.79, 3.01)
24	51/81 (63.0%)	115/158 (72.8%)	1.83 (0.92, 3.64)
36	52/81 (64.2%)	112/158 (70.9%)	1.98 (0.97, 4.03)
52	54/81 (66.7%)	118/158 (74.7%)	1.88 (0.92, 3.88)

[1] Among the baseline blood eosinophils ≥0.3 Giga/L population, only subjects of age >=7 years old were included in the analysis.
[2] Odds ratios vs placebo were based on logistic regression with treatment, age, weight group, region, baseline FeNO level, baseline ICS dose level, and baseline PAQLQ(S)-IA Global score as covariates. Patients who did not meet the criterion or had missing value are considered as non-responders.
Source: Statistical Reviewer

Additional Analyses Conducted on the Individual Trial – FeNO

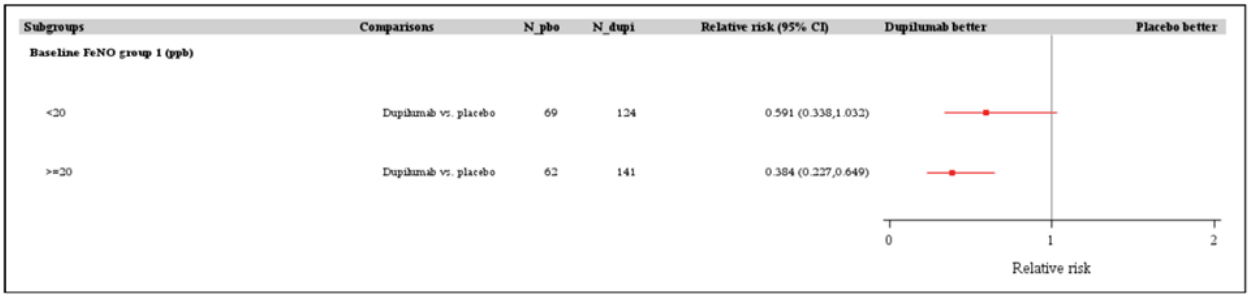
Trial EFC14153 – 6 to < 12 years of age

To examine baseline FeNO as a predictor of efficacy, prespecified analyses were conducted for the primary endpoint for different FeNO subgroups.

The effect of dupilumab on the annualized rate of severe exacerbation events was evaluated in the ITT population across subgroups defined by baseline FeNO level (<20 ppb and ≥20 ppb). The FeNO ≥20 ppb subgroup analysis was multiplicity controlled. In Figure 16, the baseline FeNO ≥20 ppb subgroup excluded the null and demonstrated a higher relative risk reduction compared with the baseline FeNO <20 ppb subgroup (62% versus 41%, respectively), although there was no clear separation in the confidence intervals.

Reviewer comment: The cutoffs of ≥20 ppb and ≥25 ppb were chosen for the pediatric population and adults respectively based on the literature and guidelines.

Figure 16: Subgroup analysis: Forest plot of relative risk in annualized event rate of severe exacerbation by baseline FeNO (<20 ppb and ≥20 ppb) - ITT population

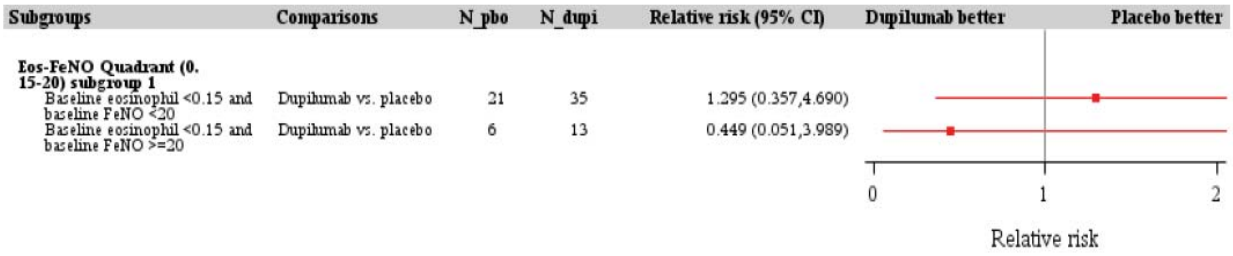


Source: Modified from EFC14153 Clinical Study Report Figure 8, p.131

In a pre-specified analysis, subgroups defined by baseline FeNO level (<20 ppb and ≥20 ppb)

were further evaluated, conditioning on low baseline blood eosinophil count group (<0.15 Giga/L) (Figure 17). Both subgroups included the null for the relative risk in the annualized rate of severe exacerbation events.

Figure 17: Subgroup analysis: Forest plot of relative risk in annualized event rate of severe exacerbation by baseline FeNO (<20 ppb and ≥20 ppb) conditioning on low baseline eosinophilic level (<0.15 Giga/L) - ITT population



Source: Modified from the Applicant's Appendix 16.2.6 Efficacy Response Data Figure 16.2.6.1.29, p.158

To examine baseline FeNO group predictability as an independent biomarker, a treatment-by-biomarker interaction analysis was performed, adjusting for baseline eosinophil count and a treatment-by-baseline eosinophil count interaction term (FeNO biomarker interaction analysis #3 in Table 17). The analysis did not show statistical relevance (nominal p=0.55), indicating that there is not enough statistical evidence that baseline FeNO predicts a reduction in the annualized rate of severe exacerbation events independent of baseline eosinophil count. On the other hand, there was evidence that baseline FeNO group can support an effect for the key secondary endpoint, change from baseline in FEV1pp at Week 12.

Table 19: FeNO biomarker interaction analysis (treatment-by-baseline FeNO interaction effect) on the primary and key secondary efficacy endpoints – ITT population

Biomarker analysis[1]	**Biomarker covariates and treatment -by-biomarker interaction**	**Treatment-by-baseline FeNO group interaction term p-value**[2]	
		Annualized rate of severe exacerbation during the 52-week treatment period	**FEV1pp change from baseline at week 12**
1. FeNO's predictability (unadjusted for baseline EOS)	Baseline FeNO group (<20 ppb, >=20 ppb), and treatment-by-baseline FeNO group interaction	**0.31**	**<0.01**
2. FeNO's	Baseline eosinophil group		

predictability (adjusted for baseline EOS)	(<0.15 Giga/L, >=0.15 Giga/L), baseline FeNO group (<20 ppb, >=20 ppb), and treatment-by-baseline FeNO group interaction	**0.31**	**<0.01**
3. FeNO's predictability (adjusted for baseline EOS and baseline EOS-by-treatment interaction)	Baseline FeNO group (<20 ppb, >=20 ppb), baseline eosinophil group (<0.15 Giga/L, >=0.15 Giga/L), treatment-by-baseline eosinophil group interaction and treatment-by-baseline FeNO group interaction	**0.55**	**<0.01**

[1] Each biomarker was treated as a categorical variable
[2] A p-value threshold of 0.15 was prespecified to establish statistical relevance for the interaction tests
Source: Statistical Reviewer

Trial EFC13579 – Adults and Adolescents

(b) (4)

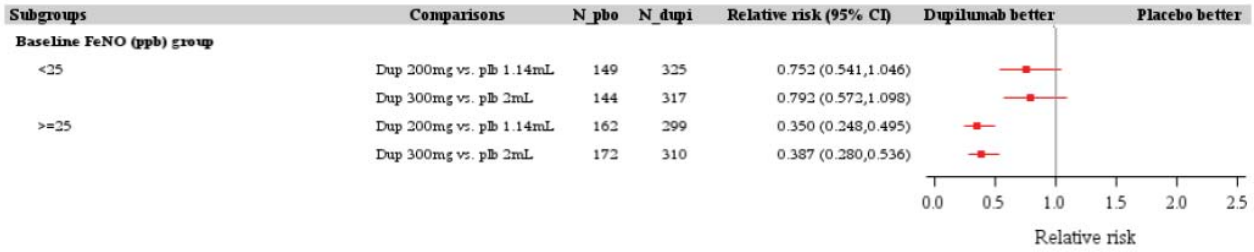
. This review focused on the longest and largest safety and efficacy study (EFC13579) for the FeNO analysis as the FeNO results for the dose-ranging trial (DRI12544) were limited based on smaller sample size. For further details on the adolescent and adult clinical trials, see review for S-007 DARRTs submission dated October 19, 2018.

Trial EFC13579 was a randomized, double-blind, placebo-controlled safety and efficacy study consisting of 1902 subjects ≥12 years old with moderate-to-severe asthma, regardless of baseline eosinophil level, who were uncontrolled on medium-high dose ICS/LABA with history of ≥1 exacerbation in the past year.

The effect of dupilumab on the annualized rate of severe exacerbation events was evaluated in a pre-specified analysis of the ITT population across subgroups defined by baseline FeNO level (<25 ppb and ≥25 ppb). These subgroup analyses were not multiplicity controlled. In Figure 18,

(b) (4)

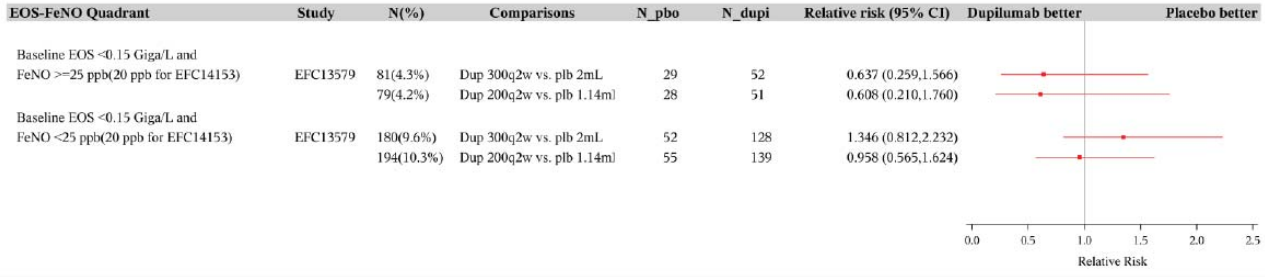
Figure 18: Subgroup analysis: Forest plot of relative risk in annualized event rate of severe exacerbation by baseline FeNO (<25 ppb and ≥25 ppb) - ITT population of EFC13579 study



Source: Modified from the Applicant's Clinical Overview Figure 12, p.68

A post-hoc analysis of subgroups defined by baseline FeNO groups (<25 ppb and ≥25 ppb) were further evaluated, conditioning on low baseline blood eosinophil count group (<0.15 Giga/L) (Figure 19). Both subgroups included the null for the relative risk in the annualized rate of severe exacerbation events.

Figure 19: Subgroup analysis: Forest plot of relative risk in annualized event rate of severe exacerbation by baseline FeNO (<25 ppb and ≥25 ppb) conditioning on low baseline eosinophilic level (<0.15 Giga/L) - ITT population of EFC13579 study



Source: Modified from the Applicant's Response to Information Request Figure 3, p.13

Additionally, a treatment-by-biomarker interaction analysis was performed, adjusting for baseline eosinophil count and a treatment-by-baseline eosinophil count interaction term (FeNO biomarker interaction analysis #3 in Table 18). The analysis did show that there is statistical evidence that baseline FeNO level predicts improvement in the key efficacy endpoints independent of baseline eosinophil count in the adult/adolescent population.

Table 20: FeNO biomarker interaction analysis (treatment-by-baseline FeNO interaction effect) on the co-primary efficacy endpoints - ITT population of EFC13579 study (300mg Q2W)

Biomarker	Biomarker covariates and	Treatment-by-baseline FeNO group interaction

analysis[1]	treatment -by-biomarker interaction	term p-value[2]	
		Annualized rate of severe exacerbation during the 52-week treatment period	FEV1pp change from baseline at week 12
1. FeNO's predictability (unadjusted for baseline EOS)	Baseline FeNO value, and treatment-by-baseline FeNO value interaction	**<0.01**	**<0.01**
2. FeNO's predictability (adjusted for baseline EOS)	Baseline eosinophil value, baseline FeNO value, and treatment-by- baseline FeNO value interaction	**<0.01**	**<0.01**
3. FeNO's predictability (adjusted for baseline EOS and baseline EOS-by-treatment interaction)	Baseline FeNO value, baseline eosinophil value, treatment-by- baseline eosinophil value interaction and treatment-by-baseline FeNO value interaction	**0.09**	**<0.01**

[1] Each biomarker was treated as a continuous variable
[2] A p-value threshold of 0.15 was prespecified to establish statistical relevance for the interaction tests
Source: Modified from the Applicant's Response to Information Request Table 1, p.8

FeNO Conclusions

Overall, the efficacy results by FeNO subgroup for the overall population across asthma trials supports inclusion in Section 14 of the label. Elevation of FeNO can be a marker of the eosinophilic asthma phenotype and based on the submitted data, may be important information for prescribers.

(b) (4)

(b) (4)

Generally, the Division also had concerns with variability in the measurement of FeNO in clinical practice. Isolated elevated FeNO may occur due to various conditions outside of the eosinophilc asthma phenotype (viral infection, high-nitrate foods, physical activity, and oral/inhaled corticosteroid use, etc.). This could result in patients being erroneously identified as patients that will benefit from treatment with dupilumab. Although these factors were generally controlled for in the clinical trial[10], controlling for these factors is more challenging in clinical practice. Professional guidelines maintain that FeNO should not be used in isolation, but instead as an adjunct to the evaluation process[8,9] (b) (4)

(b) (4)

(b) (4)

Due to the complexities with the proposal to include FeNO in the prescribing information, the Division consulted with the Medical Policy and Program Review Council (MPPRC) on July 7, 2021. The MPPRC generally (b) (4) agreed that efficacy by FeNO subgroup was appropriate for inclusion in Section 14 of the prescribing information. It was suggested that limitations and clarifying details for FeNO be included in the prescribing information. During the labeling teleconference with the Applicant September 29, 2021, the Applicant agreed with the Division's stance on (b) (4)

(b) (4) Additionally, it was mutually agreed upon that a statement regarding

[10] The Applicant notes the use of NIOX 510(k) cleared devices and followed ATS/ERS recommendations for FeNO measurement

FeNO being a component of the eosinophilic phenotype (originally proposed by the Division) should be added.

8.1.3. Integrated Assessment of Effectiveness

The efficacy of dupilumab doses (100 mg Q2W or 300 mg Q4W for 15 to < 30 kg and 200 mg Q2W for ≥30 kg) was demonstrated for add-on maintenance treatment of moderate-to-severe asthma in subjects ≥6 years of age with an eosinophilic phenotype or with oral corticosteroid dependent asthma. The 300 mg Q4W dose is supported for the 15 to < 30 kg weight group because higher exposure covers efficacy concerns and safety is supported by 18 subjects in the 1-year open-label extension study (LTS14424) who received this dose. The 1-year safety and efficacy study demonstrated a statistically significant difference in the annualized rate of severe exacerbation in the primary analysis population of baseline blood eosinophil count ≥0.3 Giga/L eosinophils (approximate 35% reduction (0.22, 0.56), p<0.01). Efficacy is further supported by change from baseline in percent predicted pre-bronchodilator FEV1 at Week 12 (LS mean difference: 5.29% [95% CI: 1.73, 8.85]; p<0.01) and favorable ACQ-5-IA, ACQ-7-IA, and PAQLQ(S)-IA responder rates compared to placebo.

Based on the pre-specified FeNO subgroup efficacy analysis from the pediatric trial (EFC14153) and additional FeNO analyses from the adolescent and adult asthma trial (EFC13579), efficacy results by FeNO subgroup were considered appropriate for inclusion in Section 14 of the prescribing information.

8.2.Review of Safety

8.2.1. Safety Review Approach

The 52-week safety and efficacy study (EFC14153) was evaluated for safety. Safety is also supported by findings from the open-label extension study (LTS14424) which enrolled subjects who participated in Study EFC14153. Study LTS14424 is reviewed separately in Section 8.2.7. The review tools used to conduct independent reviewer analyses included JMP Clinical, JMP, and the clinical investigator site selection tool.

8.2.2. Review of the Safety Database

Overall Exposure

The overall exposure for Study EFC14153 is summarized in Table 19.

Table 21 Overall Exposure Safety Population

	Placebo N=134	Dupilumab N=271
Mean (SD) (Days)	357 (43)	345 (73)
Min:Max (Days)	55:386	14:384
Exposure categories		

n (%)		
>4 weeks	134 (100%)	267 (99%)
>8 weeks	133 (99%)	262 (97%)
>12 weeks	133 (99%)	259 (96%)
>16 weeks	132 (99%)	257 (95%)
>24 weeks	131 (98%)	256 (95%)
>36 weeks	130 (97%)	252 (93%)
>44 weeks	130 (97%)	251 (93%)
>52 weeks	42 (31%)	93 (34%)

Source: EFC14153 CSR Table 48 p. 252

The exposure was balanced across treatment groups. A total of 251 subjects were treated with dupilumab for at least 44 weeks. The lower exposure at > 52 weeks is expected as the trial completed at 52 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 indications of adult and adolescent asthma (≥12 years of age) and atopic dermatitis (≥6 years of age).

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

No data quality issues were identified in the review of this supplemental BLA.

Categorization of Adverse Events

The Applicant provided accurate definitions of adverse events (AEs) and serious adverse events (SAEs) in the protocols. AEs were captured from signing of informed consent through the final follow up visit. Treatment emergent adverse events (TEAEs) 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 MedDRA dictionary version 23.0.

The Applicant's coding of verbatim terms to preferred terms (PTs) was appropriate. Adverse events of special interest (AESIs) included anaphylaxis, hypersensitivity, serious injection site reactions or severe injection site reactions that last longer than 24 hours, severe or serious infection, parasitic infection, opportunistic infection, drug-related liver disorder, pregnancy, and symptomatic overdose. Other selected AE groups included injection site reaction, malignancy, partner pregnancy, conjunctivitis, and eosinophilia. The Applicant analyzed Standardized MedDRA Queries (SMQs) for anaphylaxis and hypersensitivity events, and drug-related hepatic disorders.

8.2.4. Safety Results

Deaths

No deaths occurred in the 52-week safety and efficacy study (EFC14153).

Serious Adverse Events

Serious adverse events are summarized in Table 20.

Table 22 Study EFC14153: SAEs Greater than Placebo (Safety Population)

SOC PT	Placebo N=134 n (%)	Dupilumab 100 mg SC Q2W N=91 n (%)	Dupilumab 200mg SC Q2W N=180 n (%)	Dupilumab N=271 n (%)
Respiratory, thoracic and mediastinal disorders				
Asthma	0	2 (2)	2(1)	4(2)
Blood and lymphatic system disorders				
Eosinophilia	0	0	2(1)	2(1)
Infections and infestations				
Pneumonia	0	0	1(1)	1(1)
Pharyngitis	0	1(1)	0	1(1)
Furuncle	0	0	1(1)	1(1)
Immune system disorders				
Drug hypersensitivity	0	0	1(1)	1(1)
Milk allergy	0	0	1(1)	1(1)
Allergy to chemicals	0	0	1(1)	1(1)
Eye disorders				
Vision blurred	0	0	1(1)	1(1)
Nervous system disorders				
Headache	0	0	1(1)	1(1)
Injury, poisoning, and procedural complications				
Hand fracture	0	0	1(1)	1(1)

PT=preferred term; Q2W= once every 2 weeks; SAE= serious adverse event; SC= subcutaneous; SOC= system organ class
Source: Reviewer generated table in JMP using ADSL and ADAE dataset (TRT01A, TRETEMFL, AESER, PSOCFL, AEDECOD)

The only SAEs that occurred in more than one subject in the dupilumab treatment arms were

eosinophilia (n=2) and asthma (n=4) compared to no events in placebo treated subjects. The four subjects who experienced SAEs of asthma reported trigger factors for asthma exacerbation: infection, change in temperature, and exercise. None of these subjects discontinued treatment permanently and all four subjects recovered. Eosinophilia and drug hypersensitivity are discussed further in Section 8.2.5.2 Eosinophilia and Section 8.2.5.3 Drug hypersensitivity.

Pneumonia and eosinophilia were also SAEs in the adult and adolescent studies.

Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events leading to discontinuation for Study EFC14153 are summarized in Table 21.

Table 23 Adverse events Leading to Discontinuation > Placebo (Safety Population)

SOC PT	Placebo N=134 n (%)	Dupilumab 100 mg SC Q2W N=91 n (%)	Dupilumab 200mg SC Q2W N=180 n (%)	Dupilumab N=271 n (%)
General disorders and administration site conditions				
Injection site erythema	0	0	2(1)	2(1)
Injection site edema	0	0	2(1)	2(1)
Injection site discoloration	0	0	1(1)	1(1)
Injection site inflammation	0	0	1(1)	1(1)
Injection site pain	0	0	1(1)	1(1)
Injection site pruritus	0	0	1(1)	1(1)
Injection site urticaria	0	0	1(1)	1(1)
Blood and lympatic system disorders				
Eosinophilia	0	0	1(1)	1(1)
Skin and subcutaneous tissue disorders				
Erythema multiforme	0	0	1(1)	1(1)

PT=preferred term; Q2W= once every 2 weeks; SC= subcutaneous; SOC= system organ class
Source: Reviewer generated table in JMP

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. Eosinophilia and erythema multiforme will be discussed further in 8.2.5.2 Eosinophilia and 8.2.5.3 Hypersensitivity.

Adverse events leading to discontinuation in EFC14153 were similar to the adult and adolescent studies with a unique event of erythema multiforme.

Significant Adverse Events

Adverse events of special interest for Study EFC14153 that occurred more often in subjects on dupilumab compared to placebo are summarized in Table 22**.**

Table 24 AESI > Placebo (Safety Population)

Preferred Term	Placebo N=134 n (%)	Dupilumab 100 mg SC Q2W N=91 n (%)	Dupilumab 200mg SC Q2W N=180 n (%)	Dupilumab N=271 n (%)
Injection site reaction	18(13)	12(13)	36(20)	48(18)
Serious injection site reaction	0	0	2(1)	2(1)
Eosinophilia	1(1)	9(10)	9(5)	18(7)
Parasitic infection	1(1)	5(5)	2(1)	7(3)

AESI=adverse event of special interest ; Q2W= once every 2 weeks; SAE= serious adverse event; SC= subcutaneous
Source: Reviewer generated table in JMP

AESIs included anaphylaxis, hypersensitivity, serious injection site reactions, severe/serious infection, parasitic infection, opportunistic infection, drug-related liver disorder, pregnancy, and symptomatic overdose. Other selected AE groups included malignancy, partner pregnancy, conjunctivitis, and eosinophilia. The most common AESI that occurred more in the dupilumab group than placebo was injection site reactions. Eosinophilia and parasitic infection will be discussed further in 8.2.5.1 Eosinophilia and 8.2.5.2 Parasitic infection. There were no pregnancies, malignancies, opportunistic infections, or symptomatic overdoses.

Anaphylaxis triggered by peanut ingestion occurred in one subject in the placebo group who had a history of peanut allergy. Another subject in the placebo group experienced a hypersensitivity event (edema of ears, eyelids, redness on body that did not fulfill Sampson's criteria) 12 days after their 8th injection that resolved on the same day and did not recur.

Only one patient in the dupilumab group (200 mg Q2W) reported aspartate aminotransferase increase on Day 224. The highest reported value on Day 255 was 2.12 times the upper limit of normal. The patient self-recovered on Day 284.

Similar to the adult and adolescent asthma studies, injection site reactions occurred more often in the dupilumab group compared to placebo. Serious injection site reactions (lasting more than 24 hours) occurred more frequently in the dupilumab group when compared to placebo and were dose-dependent.

Although injection site reactions and eosinophilia were common to the adult and adolescent asthma program, no cases of eosinophilia progressed to EGPA in the pediatric asthma program. An imbalance in parasitic infections was unique to the pediatric asthma program.

Common Adverse Events

Adverse events that occurred in at least 5% of subjects and occurred more often in any treatment group compared to placebo are summarized in Table 23**.**

Table 25 Common Adverse Events ≥ 5% and > Placebo (Safety Population)

Preferred Term	Placebo N=134 n (%)	Dupilumab 100 mg SC Q2W N=91 n (%)	Dupilumab 200mg SC Q2W N=180 n (%)	Dupilumab N=271 n (%)
Injection site reaction	18 (13)	12 (13)	36 (20)	48 (18)
Eosinophilia	1 (1)	8 (9)	8 (4)	16 (6)

SC= subcutaneous, Q2W= every two weeks Source: Reviewer generated table in JMP Clinical

Similar to the adult and adolescent asthma program, the most common adverse event was injection site reactions (injection site edema, injection site nodule, injection site erythema) followed by eosinophilia.

Reviewer comment: The cutoff of ≥5% was chosen for common adverse event frequency as the events that occurred under this frequency were generally similar between treatment groups, with the difference between dupilumab and placebo being small (≤1%). Tonsillitis (4.1% dupilumab versus 3% placebo), gastroenteritis (3.7% dupilumab versus 3% placebo), and diarrhea (4.4% dupilumab versus 3.7% placebo) were events that occurred at the ≥4% cutoff.

An imbalance was noted for upper respiratory tract infections. When combining Preferred Terms of viral upper respiratory tract infections and upper respiratory tract infections, this adverse event occurred in n=31 (23.1%) of the placebo group and n=68 (25.1%) of the dupilumab group. For completeness, the Applicant's analysis combined four High Level Terms per MedDRA version 23.0 (upper respiratory tract infections NEC, viral upper respiratory tract infections, bacterial upper respiratory tract infections and fungal respiratory tract infections), which demonstrated an incidence higher in the placebo arm (62%) when compared to the dupilumab arm (56%), thus (b) (4) *It is possible that the high overall incidence of upper respiratory tract infections in EFC14153 is inherent to the pediatric study population which frequently experience upper respiratory tract infections.*

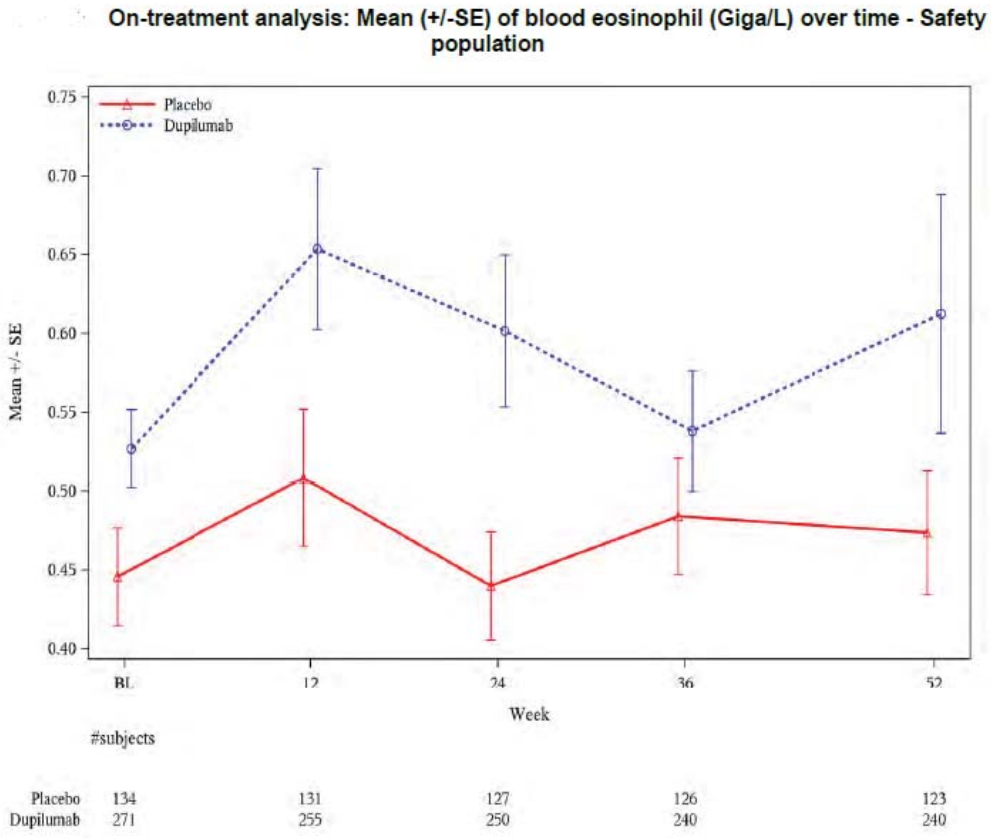
Laboratory Findings

Eosinophilia

Similar to the adult and adolescent clinical trials, eosinophils increased in subjects treated with dupilumab compared to placebo in EFC14153. Over time, eosinophils returned to baseline. The Applicant hypothesizes that this is due to the reduction of lung eosinophils, which results in an increase in serum eosinophils.

For EFC14153, the mean eosinophil count over time is shown in Figure 19. In the dupilumab treatment group, eosinophilia peak occurred around 12 weeks after the first dose and slowly decreased to close to baseline at the end of 36 weeks. The mean baseline eosinophilia was 0.527 Giga/L (527 cells/mcL) in the dupilumab group which increased to a mean of 0.65 Giga/L (650 cells/mcL) by Week 12. By Week 52 the mean eosinophilia was 0.60 Giga/L (600 cells/mcL) and the Applicant notes this higher level was due to a single outlier patient who had asyptomatic eosinophilia to 12.6 Giga/L (12,600 cells/mcL) at Week 52. Subjects were excluded from the clinical studies for eosinophilia greater than 1.5 Giga/L (1500 cells/mcL). Eosinophilia AEs were reported for elevations above 3.0 Giga/L (3000 cells/mcL).

Figure 20 Mean blood eosinophil (Giga/L) over time



BL=Baseline
Only baseline and on-treatment post-baseline values (from first IMP to end of treatment or last IMP +14 days) are included.

Source: EFC14153 CSR Figure 63 p. 287

Vital Signs

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

Electrocardiograms (ECGs)

ECGs were assessed at baseline and Week 52. Overall, no ECG parameters showed a clinically relevant trend over time.

Immunogenicity

Positive ADA responses were observed in 17 (6%) patients in the dupilumab group compared to 4 (3%) patients in the placebo group. Persistent ADA responses were observed in 9 (3%) patients in the dupilumab group compared to 1 (0.8%) patient in the placebo group. No patient

exhibited high titers. Moderate titers were observed in 1 patient in the dupilumab group and 1 patient in the placebo group. The ADA incidence was numerically greater in the higher dose group (7%) versus the lower dose groups (4%). No difference in the incidence of persistent ADA response was observed between these dose groups. See Clinical Pharmacology Section 6 for more details.

8.2.5. Analysis of Submission-Specific Safety Issues

8.2.5.1. Parasitic Infections

There were a total of 7 parasitic infections (3%) in the dupilumab group. The most frequently reported parasitic infection was enterobiasis (n=5). One patient in the dupilumab group experienced ascariasis and the remaining patient experienced lice infestation. Four of the patients with enterobiasis and ascariasis were from Argentina or Poland which are considered endemic zones for soil transmitted helminthic infection. For 3 out of the 6 cases, no confirmatory test was performed. All patients received treatment and recovered. One patient experienced parasitic gastroenteritis in the placebo group (erroneously not recorded as an AESI).

Below are details of the patients in the dupilumab group with parasitic infections:

1. A male in the 6-8 years age group on dupilumab 100 mg Q2W with a previous history of ascariasis experienced eosinophilia on Day 84 (4.33 Giga/L or 4330 cells/mcL) and on Day 181 was diagnosed with enterobiasis when his mother noticed an anal pinworm. He was treated with oral pyrantel and recovered.
2. A female in the 6-8 years age group on dupilumab 100 mg Q2W was diagnosed with enterobiasis on Day 311. Her mother observed parasites in her stool after she complained of anal itching. The patient had eosinophilia to 4.62 Giga/L (4620 cells/mcL). She recovered after a single dose of mebendazole.
3. A female in the 9-11 years age group was diagnosed with enterobiasis on Day 179 based on stool culture. The patient had an eosinophil count of 1.4 Giga/L (1440 cells/mcL). She recovered after treatment with mebendazole followed by tinidazole.
4. A female in the 9-11 years age group on dupilumab 100 mg Q2W was diagnosed with enterobiasis after parasites were visible in the stool on Day 87. Her eosinophil count was 2.56 Giga/L (2560 cells/mcL). The patient recovered after 3 daily doses of mebendazole.
5. A female in the 6-8 years age group experienced ascariasis on Day 371, 14 days after the last IMP. Eosinophil count was 3.59 Giga/L (3590 cells/mcL) and the patient had a positive serum IgG for *Ascaris lumbricoides*. She received albendazole and recovered.
6. A female in the 9-11 years age group had lice infestation on Day 422. She was treated with topical permethrin and recovered.
7. A male in 6-8 years age group on dupilumab 100mg Q2W was diagnosed with enterobiasis and had eosinophilia on Day 169 (5.97 Giga/L or 5970 cells/mcL). See 8.2.5.2 below for further details.

8.2.5.2. Eosinophilia

There were 18 patients in the dupilumab group and 1 patient in the placebo group with eosinophilia (above 3.0 Giga/L or 3000 cells/mcL). Most cases of eosinophilia (16 out of 18) were self-limiting laboratory findings without associated symptoms. Similar to previous programs, eosinophilia and progression to EGPA remains a concern in the pediatric asthma program. Two cases of symptomatic eosinophilia were appropriately monitored for symptoms of EGPA, however none of these cases progressed to EGPA. Instead, they reached a peak eosinophil level and then self-resolved (see below). Mean and median increases in blood eosinophils from baseline to Week 12 were 124 cells/mcL and 0 cells/mcL, respectively.

Four patients had eosinophilia associated with a parasitic infection (See 8.2.5.1). Two patients had eosinophilia associated with clinical symptoms which qualified as serious adverse events that required treatment discontinuation:

- A male patient in the 6-8 years age group on dupilumab 100mg Q2W had eosinophilia on Day 169 (5.97 Giga/L or 5970 cells/mcL) with generalized myalgia and arthralgia. He was diagnosed with enterobiasis via stool analysis. He was treated with mebendazole and dupilumab was discontinued on Day 182 and restarted on Day 224.
- A female patient in the 9-11 years age group on dupilumab 200mg Q2W had asymptomatic eosinophilia on Day 15 (3.09 Giga/L or 3090 cells/mcL). On Day 73 the patient had blurred vision and headache. On Day 74, two days after the sixth dupilumab injection, the patient had worsening eosinophilia that required hospitalization. Hypereosinophilic syndrome was ruled out based on ECG, transthoracic echocardiogram, MRI brain, and lumbar puncture which were all normal. Dupilumab was permanently discontinued.

8.2.5.3. Hypersensitivity

Hypersensitivity occurred more frequently in the placebo group (n=5 ,4%) compared to the dupilumab group (n=5, 3%). Two of the 10 subjects who experienced hypersensitivity reactions, experienced anaphylaxis. Both of these subjects were treated with placebo:

1. One patient (a 7-year-old male) had a history of peanut allergy and experienced anaphylaxis triggered by peanut ingestion.
2. The other patient (a 9-year-old male) experienced a hypersensitivity reaction (edema of ears, eyelids, and erythema on their body) that did not meet Sampson's criteria 12 days after their 8th injection which self-resolved that same day.

In the dupilumab group a total of 5 subjects experienced hypersensitivity reactions. Hypersenstivity reactions included erythema multiforme, asthma, urticaria, angioedema, and rash. One out of 5 subjects discontinued treatment as a result of the hypersensitivity reaction.

In the remaining 4 subjects, the hypersensitivity events resolved despite continuing dupilumab, as outlined below:

1. One patient in the dupilumab group (200mg Q2W), a male in the 9-11 years age group, experienced erythema multiforme on Day 10, which led to permanent treatment discontinuation.
2. A male patient in the 9-11 years age group on dupilumab was receiving allergen immunotherapy for allergic rhinitis. He experienced worsening of asthma in relation to allergen immunotherapy and recovered the same day after oral antihistamines and short acting bronchodilator.
3. A male patient in the 9-11 years age group on dupilumab with a history of urticaria experienced urticaria and angioedema on Day 157 which resolved after the patient took antihistamines.
4. A female in the 9-11 years age group on dupilumab experienced a full body rash of moderate intensity on Day 28 that resolved.
5. A male in the 9-11 years age group on dupilumab experienced diffuse urticaria on Day 31 that resolved.

8.2.6. Safety Analyses by Demographic Subgroups

No safety differences were noted in subgroups based on demographics.

8.2.7. Specific Safety Studies/Clinical Trials LTS14424

Study LTS14424 was a multinational, multicenter, 1-year open-label extension study evaluating the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in the dupilumab asthma clinical study (EFC14153). Patients were required to be on background therapy (medium-high dose ICS alone or with a second controller) as used at the end of treatment visit of the parent study EFC14153. During the open-label treatment period, patients continued to take their controller medication(s) at the stable dose. Patients were allowed to use albuterol/salbutamol or levalbuterol/levosalbutamol as reliever medication as needed during the study. An additional dose regimen of 300 mg Q4W was introduced per protocol amendment (December 12, 2019) to replace 100 mg Q2W for patients with body weight ≤30 kg with ≥8 weeks remaining in the study, based on the overall efficacy, PK, safety and tolerability observed for this dosing regimen in the pediatric atopic dermatitis study (6 to < 12 years, R668-AD-1652). In total, at the cutoff date, there were 18 patients (8 from the placebo group of the parent study and 10 from the dupilumab group of the parent study) exposed to the dupilumab 300 mg Q4W dose regimen for a cumulative exposure of 7.4 PY (mean [SD] duration of exposure: 149.7[67.8] days). Twelve of the 18 patients (6 from the placebo group of the parent study and 6 from the dupilumab group of the parent study) had more than 20 weeks of exposure to the 300 mg Q4W dose.

Study LTS14424 was initiated on June 21, 2018. The 120-Day safety update report provided additional safety data that was ongoing during the period from the original sBLA cutoff date (August 26, 2020 for EFC14153 and August 18, 2020 for Study LTS14424) until the cutoff date of January 26, 2021. At the time of the cutoff date (January 26, 2021), a total of 365 patients were enrolled into Study LTS14424 and were exposed to open-label treatment with dupilumab. Of these, 285 (78%) patients completed the 52-week open-label study treatment period, 65 (18%) were still ongoing, and 15 (4%) patients prematurely discontinued study treatment. Since the sBLA cutoff, 89 additional patients completed the 52-week study treatment period and one prematurely discontinued study treatment due to AE.

Cumulative exposure was 333 patient-years with an additional 49 patient-years of exposure since the sBLA cutoff. Demographics were similar to the parent studies.

The safety profile of the open-label safety study included in the 120-day safety update included the following adverse events. No new safety concerns were identified. There were no deaths during the open-label extension study LTS14424. Upper respiratory tract infection was the most frequently occurring common adverse event that occurred more frequently in subjects previously treated with dupilumab (n=17, 7%) versus subjects previously treated with placebo (n=5, 4%). SAEs in the dupilumab group through the 120-Day SUR cutoff in LTS14424 included included hospitalization for radius fracture due to an accidental fall, complicated appendicitis, pulmonary tuberculosis, upper respiratory tract infection, and atelectasis (all n=1, 0.4%). TEAEs leading to permanent treatment discontinuation through the 120-Day SUR cutoff include ascariasis, pulmonary tuberculosis, and allergic conjunctivitis (all n=1, 0.4%). The following AESIs occurred: anaphylaxis (n=2, 0.8%) likely due to peanut exposure, angioedema (n=2, 0.8%), urticaria (n=2, 0.8%), rash (n=1, 0.4%), appendicitis (n=1, 0.4%), pulmonary tuberculosis (n=1, 0.4%), upper respiratory tract infection (n=1, 0.4%), enterobiasis (n=3, 1.3%), ascariasis (n=1, 0.4%), injection site reaction (n=21, 9%), conjuncitivitis (n=10, 4%), and eosinophilia (n=8, 3%).

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No malignancies were reported in EFC14153.

Human Reproduction and Pregnancy

No pregnancies occurred in EFC14153; a pregnancy registry for the atopic dermatitis indication is in place.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose with IMP (accidental or intentional) that was suspected by the Investigator or spontaneously notified by the patient was defined as at least twice the planned dose during an interval of less than 11 days. In the safety population, 3 (1.1%) patients in the dupilumab group

and 5 (3.7%) in the placebo group met the criteria for overdose at least once, with 1 (0.7%) patient in the placebo group having more than one overdose. No patients experienced a symptomatic overdose.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

A labeling supplement to sBLA 761055 S-021/S-027 is currently under review in conjunction with the Division of Dermatology and Dentistry. Postmarketing experience has revealed additional adverse reactions of angioedema and arthralgia. See supplement S-021/S-027 for further details.

8.2.10. Integrated Assessment of Safety

Safety analysis was based on a 1-year safety and efficacy study (EFC14153) with support from a 1-year open-label extension study (LTS14424). No deaths were reported in EFC14153. SAEs were reported more frequently in the dupilumab 200 mg Q2W group (n=10, 6%) compared to the 100 mg Q2W group (n=3, 3%) and placebo (n=6, 5%). Asthma was the most commonly reported SAE, with a higher incidence in the 100 mg Q2W group (n=2, 2%) compared to the 200 mg Q2W group (n=2, 1%) and compared to placebo (n=0). Eosinophilia was the only other SAE reported in more than one subject (n=2, 1% in the 200 mg Q2W group). No additional consistent treatment related safety findings are seen from a review of SAE data.

Eleven subjects had AEs leading to discontinuation of investigational product, all of which were on dupilumab 200 mg Q2W. The most common AE leading to discontinuation was injection-site reactions (n=9, 5%) with a clear dose-response as all of these subjects were in the 200 mg Q2W dose group. Other AEs leading to discontinuation included eosinophilia (n=1,1%) and erythema multiforme (n=1, 1%). No additional consistent treatment related safety findings are seen from a review of AEs leading to discontinuation.

The overall common adverse event incidence was similar across treatment groups. The most common adverse event was injection site reaction occurring in 36 (20%) of subjects on 200 mg Q2W of dupilumab and 12 (13%) on 100 mg Q2W of dupilumab compared to 18 (13%) on placebo. The other common AE of eosinophilia was reported at a higher incidence than placebo.

In EFC14153, eosinophils peaked around 12 weeks after the first dose and slowly decreased to close to baseline at the end of 36 weeks. The mean baseline eosinophilia was 0.527 Giga/L in the dupilumab group which increased to a mean of 0.65 Giga/L by Week 12. By Week 52 the mean eosinophilia was 0.60 Giga/L and the Applicant notes this higher level was due to a single outlier patient who had asyptomatic eosinophilia to 12.6 Giga/L at Week 52.

Parasitic infections emerged as an adverse event of special interest. No pregnancies,

opportunistic infections, or malignancies were reported in the pediatric asthma program. Similar to the adult and adolescent asthma program, the ocular safety issues that were identified in the atopic dermatitis program were also not identified in the pediatric asthma study.

Overall, the safety profile in moderate-to-severe asthma in subjects ≥6 years of age is favorable.

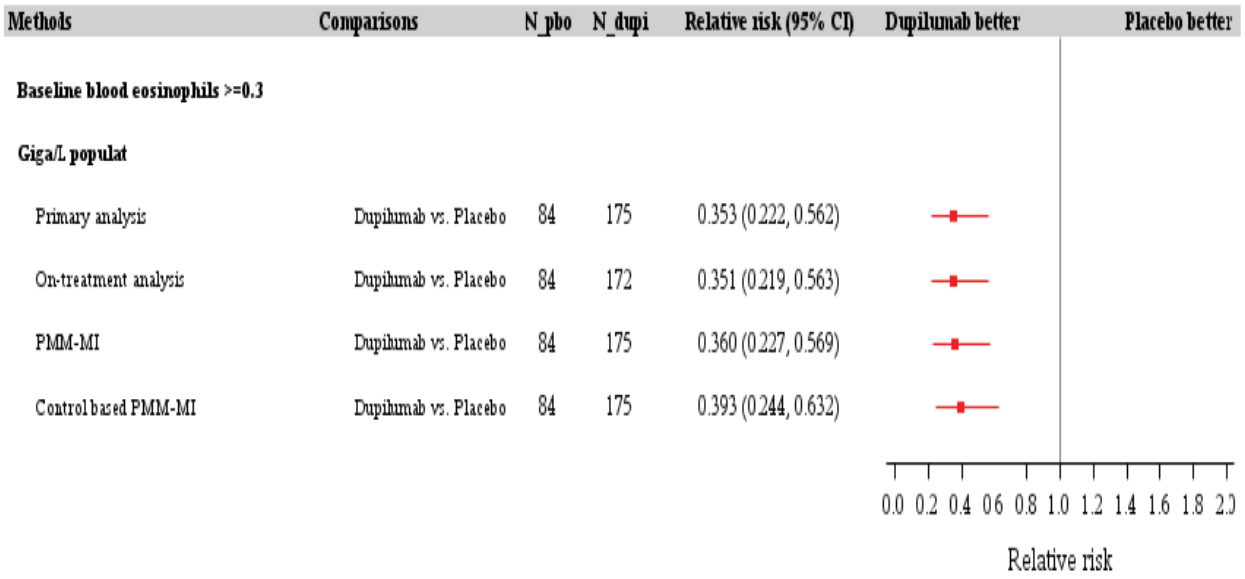
8.3. Statistical Issues

Robustness of Efficacy Data

In Study EFC 14153, there were 16 (3.9%) patients (13 dupliumab (4.8%) and 3 placebo (2.2%)) who discontinued the 52-week treatment as planned, and these subjects were considered as subjects with missing data for the severe exacerbation endpoint, under the primary estimand defined by the applicant. To assess the robustness to variations of the missing data assumptions underlying the primary analysis on the primary efficacy endpoint, sensitivity analyses using a pattern mixture model multiple imputation (PMM-MI) and control-based PMM-MI were performed by the Applicant (Figure 20). The amount of missing data was small and the sensitivity analyses demonstrated a similar treatment effect compared to the primary analysis and supported the robustness of the primary analysis in the population with baseline blood eosinophils ≥0.3 Giga/L. Furthermore, on-treatment analysis was performed as a supplementary analysis to explore alternative estimand considering the first permanent stepping-up of background asthma medication and treatment discontinuation as intercurrent events with a while-on-treatment strategy. The on-treatment analysis supported treatment effects on the primary endpoint, therefore, the results of effectiveness are considered reasonably robust against the alternative estimand in the population with baseline blood eosinophils ≥0.3 Giga/L.

The applicant also conducted the tipping point analysis which showed that the treatment effect remained significant (nominal $p<0.05$) even when using some extreme implausible conditions, confirming the robustness of the study results in the population with baseline blood eosinophils ≥0.3 Giga/L (table not shown).

Figure 21: Sensitivity analysis: Forest plot of relative risk in annualized event rate of severe exacerbation by analysis methods - Baseline blood eosinophils >=0.3 Giga/L population



Source: Modified from the Applicant's Clinical Overview Figure 2, p.44

8.4. Conclusions and Recommendations

The recommended regulatory action from a clinical perspective is approval of dupilumab 100mg SC Q2W, 300mg SC Q4W (for 15 to < 30 kg), and 200mg SC Q2W (for ≥30 kg) for use as add-on maintenance treatment in patients 6 years of age and older with moderate-to-severe asthma and an eosinophilic phenotype or oral corticosteroid-dependent asthma as efficacy was demonstrated for these doses and there were no major dose-related safety concerns.

To support expanding the asthma indication to patients 6 to < 12 years of age, the Applicant completed a 1-year safety and efficacy trial. This trial demonstrated a statistically significant and clinically relevant improvements in asthma exacerbations and lung function in subjects with moderate-to-severe asthma with an eosinophilic phenotype for the 100 mg SC Q2W and 200 mg SC Q4W doses. Support for the 300 mg SC Q4W dose for the 15 to < 30 kg relies on the higher exposure compared to the 200 mg SC Q2W dose in this weight group and safety experience from 18 subjects enrolled in the 1-year open-label extension study (LTS14424) that received this dose and were within the same weight group. Additional safety support is provided by trials in atopic dermatitis which included this dose in the same age and weight group.

Overall the safety profile in the clinical trial for subjects 6 to < 12 years of age was similar to the adult and adolescent asthma program. Injection-site reactions were the most common adverse event and were dose-related. Parasitic infections were an adverse event of special interest that emerged during the pediatric asthma program and the label has been updated to reflect this. The ocular safety issues seen in the atopic dermatitis program were not identified in the pediatric asthma study. There were no cases of anaphylaxis in the dupilumab group. No safety

concerns that offset the efficacy benefits provided by dupilumab were identified. The safety findings that were seen in the program can be adequately addressed through labeling and should continue to be followed with routine pharmacovigilance.

9 Advisory Committee Meeting and Other External Consultations

There were no safety or efficacy concerns requiring an Advisory Committee meeting for dupilumab for pediatric asthma.

Due to complexities regarding inclusion of FeNO and Type 2 Inflammation in the prescribing information, the Division sought input from the MPPRC on July 7, 2021. For details regarding the discussion that occurred during the MPPRC meeting, see Additional Analyses Conducted on the Individual Trial – FeNO and the Labeling Recommendations in Section 11.

10 Pediatrics

At the time of approval of the adolescent and adult asthma supplement (2018), a waiver for children < 2 years of age was granted as studies are impossible or highly impractical as moderate to severe asthma with eosinophilic phenotype requiring add-on treatment is unlikely to exist in sufficient numbers of patients to allow for a study to be conducted.

Two PREA PMRs were also issued with the 2018 approval:

3508-1 Complete the ongoing 52-week efficacy and safety trial in children 6 to < 12 years of age with moderate to severe asthma (Study EFC14153).

3508-2 Conduct a safety and efficacy study with dupilumab in children 2 years to < 6 years of age with moderate to severe asthma with a continued safety evaluation out to a minimum of 52 weeks (Study EFC14771).

Efficacy and safety information for the 6 to < 12 year old pediatric population in Study EFC14153 is presented throughout this review; Study EFC14153 satisfies PREA PMR 3508-1.

A randomized, double-blind, placebo-controlled safety and efficacy study in subjects age 2 to < 6 years of age was submitted September 2020 with an expected submission date of June 2027 (which aligns with the agreed upon timeline) in order to satisfy PREA PMR 3508-2.

The Pediatric Review Committee discussed this supplemental BLA on September 14, 2021 and agreed with the pediatric waivers and PMRs outlined in the 2018 approval letter.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The label submitted by the Applicant on October 19, 2021 is the finalized accepted version of the label.

Section	Proposed Labeling	Approved Labeling
1	• As an add-on maintenance treatment in patients aged 6 years and older with moderate-to-severe asthma with (b) (4) an eosinophilic phenotype (b) (4) or with oral corticosteroid dependent asthma	• As an add-on maintenance treatment in patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma
2	• 100 mg every 2 weeks or 300 mg every 4 weeks SC for 15 to < 30 kg • 200 mg every 2 weeks (b) (4)	• 100 mg every 2 weeks or 300 mg every 4 weeks SC for 15 to < 30 kg • 200 mg every 2 weeks SC for ≥30 kg • Added that no loading dose is recommended for patients 6 to 11 years of age.
5		• Erythema multiforme added to Warnings and Precautions under Hypersensitivity • Enterobiasis changed to Parasitic infections
8		• Removed (b) (4) and (b) (4) • Added supporting information for 300 mg every 4 weeks dose
12		• Removed (b) (4)
14		• Added FeNO can be a marker of the eosinophilic asthma phenotype when supported by clinical data • Removed (b) (4)

	• (b) (4)	
	• (b) (4)	• Changed to DUPIXENT significantly reduced the annualized rate of severe asthma exacerbation events during the 52-week treatment period compared to placebo in populations with an eosinophilic phenotype as indicated by elevated blood eosinophils and/or the population with elevated FeNO.
	• (b) (4)	• (b) (4) noted that subgroup analyses for results of DUPIXENT treatment based upon baseline eosinophil level and baseline FeNO level were similar to the adolescent and adult trials • (b) (4)
	• (b) (4)	• (b) (4)

	• (b) (4) [redacted]	• Retained Figure 12 Mean Change from Baseline in Percent Predicted Pre-bronchodilator FEV1 (L) Over Time in AS Trial 4 (Baseline Blood Eosinophils ≥300 cells/mcL)

AS Trial 1 = DRI12544; AS Trial 2 = EFC13579; AS Trial 4 = EFC14153

Reviewer comment: Initially the Applicant proposed to (b) (4) [redacted] *This proposal was rejected by the Division.* (b) (4) [redacted]

12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

13 Postmarketing Requirements and Commitment

At the time of approval of the adult and adolescent asthma supplement (2018), a PREA PMR was issued:

3508-2 Conduct a safety and efficacy study with dupilumab in children 2 years to < 6 years of age with moderate to severe asthma with a continued safety evaluation out to a minimum of 52 weeks (Study EFC14771).

This review also recommends that the Applicant conduct the trial outlined in the PMR. At the time the PREA PMR was issued, the Applicant agreed to the timelines below:

Final protocol submission: 9/2020 (received 9/23/2020)

Study completion: 12/2026

Final report submission: 6/2027

14 Division Director Comments

Regeneron submitted this efficacy supplement to expand the asthma indication from 12 years of age down to 6 years of age. The current indication is 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.

To support the expansion of the indication, the Applicant conducted a one year, randomized, double-blind, placebo-controlled safety and efficacy trial (EFC14153) in 408 children with moderate-to-severe asthma. There were two dupilumab dose groups based on body weight: 15 to < 30 kg (100 mg dupilumab Q2W) or ≥ 30 kg (200 mg dupilumab Q2W). Results of the trial showed a statistically significant improvement on the primary endpoint of annualized rate of severe asthma exacerbations and for the important secondary endpoint of change from baseline in pre-bronchodilator percent-predicted FEV1 at Week 12 in children with moderate-to-severe asthma with an eosinophilic phenotype. Both dose groups showed a significant response, which supports the efficacy of the 100 mg SC Q2W (15 to < 30 kg) and 200 mg SC Q2W (≥ 30 kg) proposed doses. Review of the safety data did not identify any new or unique safety signals in the pediatric population. Substantial evidence of effectiveness is based upon this single adequate and well-controlled trial plus confirmatory evidence of the established effectiveness of dupilumab in adults and adolescents with moderate-to-severe asthma with an eosinophilic phenotype.

The Applicant also proposed a 300mg SC Q4W dose of dupilumab based upon PK modeling. To support the safety of the 300mg SC Q4W dose, there is some limited safety data from the open label extension study in children with asthma, but more extensive safety data from the pediatric atopic dermatitis program.

The team and Applicant have agreed upon labeling. Refer to the review for a discussion of the major labeling issues. The regulatory action is approval of dupilumab for use as add-on maintenance treatment in patients 6 years of age and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma.

15 Appendices

15.1. Financial Disclosure

- The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this biologics license application (BLA). Details of the financial disclosure are outlined below.
- The Applicant submitted Food and Drug Administration (FDA) form 3454 certifying investigators and their spouses/dependents were in compliance with 21 Code of Federal Regulations (CFR) Part 54.
- The 10 investigators disclosed their financial interests/arrangements and implemented appropriate actions to protect the studies from potential bias.

Covered Clinical Study (Name and/or Number): EFC14153, LTS14424

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 332		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 10		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 10 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

15.2. OCP Appendices (Technical documents supporting OCP recommendations)

15.2.1. Population Pharmacokinetics Model

The PK of dupilumab in children with asthma was described by a two compartment model with a first order absorption, and parallel linear and nonlinear elimination. Taking into account the sparse nature of the PK data in children 6 to <12 years of age with asthma, the PopPK base model was fitted to asthma pediatric PK data with most PK parameters (except for key PK parameters, such as V2 and Ke, IIV and weight exponents on V2 and Ke) fixed to values estimated with large dataset from clinical studies in HV, AD and asthma patients.

The demographics, disease characteristics, concomitant medications are summarized in Table 25 and Table 26 below.

Table 26 Descriptive statistics of continuous covariates for children 6 to <12 years of age with asthma in the final dataset

Covariate candidates	EFC14153 (N=268)		LTS14424 (N=109)[a]		Total (N=377)	
	Mean (SD)	Median (min, max)	Mean (SD)	Median (min, max)	Mean (SD)	Median (min, max)
Weight (kg)	35.5 (10.2)	35 (16.4, 67)	36.3 (10.5)	35 (18.2, 67.2)	35.7 (10.3)	35 (16.4, 67.2)
WT <= 30kg	25.2 (3.42)	26.0 (16.4, 30.0)	23.3 (2.76)	24.0 (18.2, 28.0)	24.9 (3.38)	25.2 (16.4, 30.0)
WT > 30kg	40.7 (8.30)	38.6 (30.1, 67.0)	38.4 (9.77)	37.9 (20.7, 67.2)	39.9 (8.89)	38.2 (20.7, 6.27)
Age (Year)	8.88 (1.65)	9 (6, 11)	8.84 (1.6)	9 (6, 11)	8.87 (1.63)	9 (6, 11)
CLCR (mL/min)	128 (37.7)	121 (66.0, 315)	126 (36.2)	121 (53.6, 267)	127 (37.2)	121 (53.6, 315)
CLCRN (mL/min/1.73 m^2)	191 (37.7)	186 (91.1, 410)	187 (36.2)	182 (90.1, 330)	190 (37.2)	184 (90.1, 410)
Albumin (g/L)	46.8 (2.85)	47 (35, 54)	46.8 (3.1)	47 (36, 54)	46.8 (2.92)	47 (35, 54)
EoS (cells/mm^3)	524 (407)	470 (10, 2060)	458 (384)	380 (20, 2470)	505 (401)	420 (10, 2470)
FENO	29.0 (24.2)	23 (1, 139)	24.8 (23.3)	18 (3, 123)	27.8 (24.0)	21 (1, 139)
FEV_1pp	77.5 (14.6)	80 (24, 112)	80.2 (14.5)	81 (39, 110)	78.3 (14.6)	80 (24, 112)
TRAC (ng/L)	497 (484)	375 (36.5, 5640)	575 (673)	416 (67.8, 5990)	519 (546)	391 (36.5, 5990)
IgE (IU/mL)	822 (1100)	430 (1, 5000)	650 (1060)	311 (3, 5000)	772 (1090)	375 (1, 5000)

Abbreviation: CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by body surface area (BSA); EoS: eosinophil; FENO: Fraction of exhaled nitric oxide; FEV_1pp: percent predicted forced expiratory volume in 1 second; IgE: immunoglobulin E; N: subject number; SD: standard deviation; TARC: thymus and activation regulated chemokine.

[a] In study LTS14424, only the 109 placebo patients who rolled over from study EFC14153 are summarized in this table, as the other 210 patients in LTS14424 study were from dupilumab treatment group of EFC14153 study and are summarized within EFC14153 study in this table.

Source: Table 5 in Population Pharmacokinetics Study Report POH0766

Table 27 Descriptive statistics of categorical covariates for children 6 to <12 years of age with asthma in the final dataset

Covariate candidates	Subgroup	EFC14153 (N=268) Count (%)	LTS14424 (N=109)[a] Count (%)	Total (N=377) Count (%)
Weight (kg)	<= 30	90 (33.6%)	15 (13.8%)	105 (27.9%)
	> 30	178 (66.4%)	94 (86.2%)	272 (72.1%)
Gender	Male	173 (64.6%)	69 (63.3%)	242 (64%)
	Female	95 (35.4%)	40 (36.7%)	135 (36%)
Race[b]	Caucasian	239 (89.2%)	98 (89.9%)	337 (89.4%)
	Black	11 (4.1%)	6 (5.5%)	17 (4.5%)
	Asian	2 (0.7%)	0 (0%)	2 (0.5%)
	Other	16 (6%)	5 (4.6%)	21 (5.6%)
Stationary ADA[c]	Negative	248 (92.5%)	98 (89.9%)	346 (91.8%)
	Pre-existing	3 (1.1%)	1 (0.9%)	4 (1.1%)
	Treatment-emergent	17 (6.3%)	9 (8.3%)	26 (6.9%)
	Treatment-boosted	0 (0%)	1 (0.9%)	1 (0.3%)
Stationary ADA[c]	Negative	248 (92.5%)	98 (89.9%)	346 (91.8%)
	Positive	20 (7.5%)	11 (10.1%)	31 (8.2%)
LABA	With	22 (8.2%)	20 (18.3%)	42 (11.1%)
	Without	246 (91.8%)	89 (81.7%)	335 (88.9%)
SCS	With	79 (29.5%)	20 (18.3%)	99 (26.3%)
	Without	189 (70.5%)	89 (81.7%)	278 (73.7%)
XANT	With	1 (0.4%)	0 (0%)	1 (0.3%)
	Without	267 (99.6%)	109 (100.%)	376 (99.7%)
LTRA	With	1 (0.4%)	1 (0.9%)	2 (.5%)
	Without	267 (99.6%)	108 (99.1%)	375 (99.5%)

Abbreviation: ADA:anti-drug antibody; LABA: long-acting beta agonists; LTRA: leukotriene antagonists; SCS: systemic corticosteroids; XANT: methylxanthines.

[a] In study LTS14424, only 109 placebo patients who rolled over from study EFC14153 are summarized in this table, as the other 210 patients in LTS14424 study were from dupilumab treatment group of EFC14153 study and are summarized within EFC14153 study in this table.

[b] One patient from study EFC14153 had missing information for race. In Pop PK analysis, any missing race value was imputed using the categorical value of the majority of the population (i.e., Caucasian).

[c] One patient from study EFC14153 had missing information for stationary ADA. In Pop PK analysis, any missing ADA value was imputed using the categorical value of the majority of the population (i.e., negative). In addition, five patients from study EFC14153 had missing information for time-varying ADA. In Pop PK analysis, any missing ADA value was imputed using the categorical value of the majority of the population (i.e., negative).

Source: Table 6 in Population Pharmacokinetics Study Report POH0766

Body weight was identified as the only statistically significant covaraite on dupilumab PK parameters. The final PK parameter estimates are given in Table 27.

Table 28 Parameter estimates for final Pop PK model for children 6 to <12 years of age with asthma

Parameter	Estimate	% RSE	[95%CI]
Typical value of K_e (θ_1, 1/day)	0.0564	8.31%	[0.0470, 0.0657]
Typical value of V_2 (θ_2, L)	2.35	6.41%	[2.05, 2.65]
Typical value of K_{23} (θ_3, 1/day)	0.089 (fix)	--	--
Typical value of K_{32} (θ_4, 1/day)	0.150 (fix)	--	--
Typical value of V_{max} (θ_5, mg/L/day)	1.48 (fix)	--	--
Typical value of K_m (θ_6, mg/L)	2.52 (fix)	--	--
Typical value of K_a (θ_7, 1/day)	0.252 (fix)	--	--
Typical value of F_{sc} (θ_8, %)	63 (fix)	--	--
Power coefficient of weight on K_e	0.416	23.8%	[0.218, 0.613]
Power coefficient of weight on V_2	0.616	11.7%	[0.473, 0.760]
Power coefficient of weight on V_{max}	0.33 (fix)	--	--
Inter-individual variability (CV%)			
Parameter	**Estimate**	**% RSE**	**[95%CI]** (Shrinkage %)
K_e	25.4	12.2%	[22.1, 28.3] (24.3%)
V_2	16.1	19.3%	[12.7,19.0] (34.9%)
Residual variability (RV)			
Proportional term	0.159	4.38%	[0.152, 0.165]
Additive term (mg/L)	7.43	6.77%	[6.91, 7.91]
Derived Parameters			
CL (L/day)	0.133	--	--
Q (L/day)	0.209	--	--
V_3 (L)	1.39	--	--
V_{ss} (L)	3.74	--	--

Abbreviation: CI: confidence interval; CL: linear clearance; CV: coefficient of variation; F_{sc}: bioavailability following SC administration; K_{23}, K_{32}: inter-compartment distribution rate constants; K_a : absorption rate constant ; K_e: linear elimination rate constant; K_m: Michaelis constant; Q: inter-compartment distribution clearance; V_2:volume of central compartment; V_3: volume of peripheral compartment; V_{max}: maximum target-mediated rate of elimination; V_{ss}: volume distribution at steady state; RSE: percentage of relative standard error (100% * SE / estimate); SC: subcutaneous; θ: estimate of a Pop PK parameter.

Source: Table 9 in Population Pharmacokinetics Study Report POH0766

The apparent difference in PK exposures across age and race was mainly explained by the difference in the body weight. The impact of concomitant medications (SCS and LABA) on dupilumab PK exposures had no apparent effect on dupilumab PK.

The Applicant's overall modeling strategy is reasonable, and the modeling results are replicable.

15.2.2. Exposure Response Relationship (FEV1pp and Severe Asthma Exacerbation)

Exposure response analyses were perfomed the Applicant to support the proposed dosing regimen of 100mg/200mg Q2W in children 6 to less than 12 years old. Exposure metrics including average concentration at steady state and trough concentration at steady state were predicted based on the PopPK model described in Section 15.2.1 above.

A summary of FEV1pp change of baseline by quartiles of Ctrough is given in Table 28.

Table 29 Summary of FEV1pp Change from Baseline by Combined 100 mg Q2W and 200 mg Q2W Observed Ctrough (mg/L) Quartile at Week 12

Quartile	Number of patients	FEV1 Change Mean	FEV1 Change Range	FEV1 Change Standard Error	C_{trough} (mg/L) Mean	C_{trough} (mg/L) Range	Ctrough Standard Error	Number of patients: 100q2w:200q2w
1	64	12.078	(-34.00,77.000)	2.382	33.07	(0.04,47.90)	1.40	40:24
2	64	11.578	(-23.00,56.000)	2.042	57.55	(48.20,68.30)	0.71	28:36
3	64	6.656	(-22.00,44.000)	1.981	80.01	(68.80,93.10)	0.91	15:49
4	63	11.825	(-15.00,56.000)	1.754	116.2	(93.20,219.0)	2.92	5:58

Quartile values: Q1= 47.9; Q2= 68.3; Q3= 93.1

Source: Table 4 in Pharmacokinetics/Pharmacodynamic Report CTS0077

A log-linear model was selected to describe the relationship between FEV1pp and C_{trough}. Baseline covariates including FEV1pp, ethnicity, age at onset of asthma and TARC were identified as having a significant interaction (P value < 0.05) with the concentration. For the main effect (placebo effect), in addition to baseline FEV1pp, baseline weight, baseline EOS, baseline FeNO, ICS dose group, ethnicity and regions which were baseline covariates that already included in the base model, age effect was also identified to be associated with background FEV1pp effects (placebo rate) regardless of the treatment. Older patients have worse background FEV1pp effects.

The final PK/PD model for FEV1pp and the corresponding parameter estimates are given in Table 29, and the model predicted exposure response relationship for FEV1pp with the overlaid observed data is depicted in Figure 7 in Section 6.2.2 above.

Table 30 FEV1pp Change from Baseline at Week 12: the PK/PD Model Parameter Estimations

Parameter	Estimate	95% CI	Standard Error	P-value
b0	3.555	-0.243 , 7.354	1.932	0.0665
b1: baseline FEV_1pp	-0.485	-0.584 , -0.385	0.051	<.0001
b2: baseline weight	0.053	-0.091 , 0.197	0.073	0.4701
b3: log baseline eos	0.242	-1.212 , 1.697	0.740	0.7436
b4: log baseline feno	0.995	-0.851 , 2.84	0.939	0.2900
b5: baseline ICS	0.992	-1.684 , 3.667	1.361	0.4666
b6: HISPANIC vs NON HISPANIC	1.109	-3.261 , 5.479	2.222	0.6180
b7: Latin America vs Western	0.531	-4.036 , 5.099	2.323	0.8192
b8: East Europe vs Western	4.321	0.153 , 8.489	2.120	0.0422
b9: log age at onset of asthma	0.427	-1.387 , 2.241	0.923	0.6438
b10: age	-1.192	-2.203 , -0.18	0.515	0.0211
bpk1	0.642	0.265 , 1.02	0.192	0.0009
bpk2: baseline FEV_1pp	-0.031	-0.056 , -0.005	0.013	0.0182
bpk3: log age at onset of asthma	0.440	0.018 , 0.863	0.215	0.0410
sigma**2	161.456	138.302 , 184.61	11.775	<.0001

FEV_1pp change = b0 + b1*(baseline FEV_1pp -median baseline FEV_1pp) + b2*(baseline weight-median baseline weight) + b3*(log baseline EOS-median log baseline EOS) + b4*(log baseline FeNO-median log baseline FeNO) + b5*(baseline ICS='MEDIUM') + b6*(ethnic='HISPANIC OR LATINO') + b7*(Region='Latin America' vs. 'Western Countries') + b8*(Region='East Europe' vs. 'Western Countries') +b9*(log age of onset asthma – median log age of onset asthma)+b10*(age-median age)+ (bpk1 + bpk2*(baseline FEV_1pp -median baseline FEV_1pp) + bpk3*(log age of onset asthma – median log age of onset asthma))*log(C_{trough}).

Source: Table 5 in Pharmacokinetics/Pharmacodynamic Report CTS0077

A summary of the annualized severe exacerbation event rate by quartiles of coverage is given in Table 30.

Table 31 Summary of Mean Annualized Severe Exacerbation Event Rate by combined 100 mg Q2W and 200 mg Q2W Coverage (mg/L) Quartile

Treatment	Quartile	Event Rate Mean	Event Rate Range	Event Rate Standard Error	$C_{average}$ (mg/L) Mean	$C_{average}$ (mg/L) Range	$C_{average}$ Standard Error	Number of patients
1	67	0.298	(0.000,3.010)	0.085	37.93	(1.55,53.80)	1.71	33:34
2	67	0.418	(0.000,4.990)	0.113	66.15	(53.90,75.55)	0.74	36:31
3	67	0.268	(0.000,4.014)	0.078	90.10	(75.63,101.7)	0.98	20:47
4	67	0.388	(0.000,3.002)	0.085	125.4	(102.4,197.2)	2.11	1:66

Quartile values: Q1= 53.85; Q2= 75.59; Q3= 102.06
Severe exacerbation events from ITT analysis were used. $C_{average}$ is calculated by PopPK model estimated AUC during the ITT period standardized by exposure days.

Source: Table 1 in Pharmacokinetics/Pharmacodynamic Report CTS0077

A log-linear model was selected to describe the relationship between the annualized severe asthma exacerbation event rate and $C_{average}$. In addition to baseline eosinophils, gender was identified as having a significant interaction (P value < 0.05) with the concentration, i.e. influencing the treatment difference. Male patients have better treatment effects than female patients. For the main effect (placebo effect), in addition to baseline number of prior events, age, ICS dose group, regions, baseline weight, baseline EOS and baseline FeNO which are the baseline covariates already included in the base model, gender and background controller type were identified. These are the effects associated with background event rate (placebo rate) regardless of the treatment. Female patients have lower background severe exacerbation event rate compared to male patients. Patients who took ICS+LABA as background controller have higher background severe exacerbation event rate compared to patients who took ICS only.

The final PK/PD model for severe asthma exacerbation and the corresponding parameter estimates are given in Table 31, and the model predicted exposure response relationship for annualized severe asthma exacerbation event rate with the overlaid observed data is depicted in Figure 8 in Section 6.2.2 above.

Table 32 Severe Exacerbation Event: the PK/PD Model Parameter Estimations

Parameter	Estimate	95% CI	Standard Error	P-value
b0	-1.244	-2.093 , -0.396	0.432	0.0042
b1: age	-6.318	-20.184 , 7.549	7.053	0.3709
b2: baseline weight	1.310	-0.498 , 3.118	0.920	0.1550
b3: log baseline eos	0.165	-0.054 , 0.385	0.112	0.1398
b4: log baseline feno	0.080	-0.166 , 0.326	0.125	0.5224
b5: baseline ICS	-0.395	-0.769 , -0.021	0.190	0.0384
b6: # prior severe exacerbation event	0.457	0.171 , 0.743	0.145	0.0018
b7: Latin America vs Western	-0.047	-0.496 , 0.401	0.228	0.8354
b8: East Europe vs Western	-0.799	-1.347 , -0.251	0.279	0.0044
b9: female vs male	-0.554	-0.976 , -0.133	0.214	0.0100
b10: Background controller (ICS+LABA vs. ICS only)	1.136	0.331 , 1.942	0.410	0.0058
bpk1	-0.129	-0.185 , -0.072	0.029	<.0001
bpk2: log baseline EOS	-0.052	-0.103 , -0.001	0.026	0.0449
bpk3: female vs male	0.123	0.016 , 0.23	0.054	0.0243
Over dispersion	2.211	-0.058 , 4.481	1.154	0.0562

log(Event count) = b0 + b1*(age-median age)/100 + b2*(baseline weight-median baseline weight)/100 + b3*(log baseline EOS-median log baseline EOS) + b4*(log baseline FeNO-median log baseline FeNO) + b5*(baseline ICS='MEDIUM') + b6*(log # prior event- median log # prior event) + b7*(Region='Latin America' vs. 'Western Countries') + b8*(Region='East Europe' vs. 'Western Countries') + b9*(Gender=Female') + b10*(Background controller=ICS+LABA)+(bpk1 + bpk2*(log baseline EOS-median log baseline EOS) + bpk3*(Gender=Female))*log($C_{average}$) + log(duration)

Source: Table 2 in Pharmacokinetics/Pharmacodynamic Report CTS0077

The Applicant's exposure response analyses are replicable. The overall modeling results and conclusion supported the proposed dosing regimen in children 6 to less than 12 years old. See the reviewer's comments in Section 6.2.2 for additional discussion on dose selection.

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/s/

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