27 January 2022
EMA/98744/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: dupilumab

Procedure No. EMEA/H/C/004390/X/0045/G

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AD: atopic dermatitis
ADA: anti-drug antibody
AM: morning
ATS: American Thoracic Society
BD: bronchodilator
BLQ: below limit of quantification
CI: confidence interval
CSR: Clinical study report
CRSwNP: chronic rhinosinusitis with nasal polyposis
EOT: end of treatment
EQ-VAS: European Quality of Life Visual Analog Scale
ERS: European Respiratory Society
EU: European Union
FEF: forced expiratory flow
FeNO: fractional exhaled nitric oxide
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GINA: Global Initiative for Asthma
HR: hazard ratio
ICS: inhaled corticosteroids
SCS:systemic corticosteroids
IgE: immunoglobulin E
IgG: immunoglobulin G
IL: interleukin
IL-4Rα: IL-4 receptor alpha subunit
IMP: investigational medicinal product
ISR: injection site reactions
ITT: intent-to-treat
LABA: long-acting β2 agonist
LAMA: long-acting muscarinic antagonist
LOAC: loss of asthma control
LS: least square
LTRA: leukotriene receptor antagonist
mAb: monoclonal antibody
MCID: minimal clinically important difference
MMRM: mixed-effect model with repeated measures
OCS: oral corticosteroids
OLE: open-label extension
PACQLQ: Paediatric Asthma Caregiver's Quality of Life Questionnaire
PAQLQ(S)-IA: Paediatric Asthma Quality of Life Questionnaire with Standardized Activities-IA:interviewer Administered
PD: pharmacodynamic(s)
PK: pharmacokinetic(s)
PM: evening
PMM: pattern mixture modelling
PRQLQ-IA: Paediatric Rhinoconjunctivitis Quality of Life Questionnaire-Interviewer Administered
q2w: every 2 weeks
q4w: every 4 weeks
SAP: statistical analysis plan
SCS: systemic corticosteroids

SD: standard deviation
SE: standard error
TARC: thymus and activation-regulated chemokine
TEAE: treatment-emergent adverse event
US: United States

1. Background information on the procedure

1.1. Submission of the dossier

Sanofi-aventis groupe submitted on 5 March 2021 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

1- Extension of a marketing authorisation for Dupixent to add a new strength, 100 mg solution for injection.
The presentations proposed for dupilumab 100 mg strength are the following: 1 presentations containing 2 pre-filled syringes and 1 presentation containing 6 pre-filled syringes (multipack of 3 packs of 2).
2- Type II (C.I.6) - Extension of indication to include treatment of paediatric patients with severe asthma with type 2 inflammation aged 6 to 11 years old.

Version 6.0 of the RMP has also been submitted.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0404/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0404/2020 was not yet completed as some measures were deferred.

1.3.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.4. Scientific advice

The MAH received Scientific Advice from the CHMP on 14 September 2017 (EMEA/H/SA/2744/6/2017/I) pertained to quality aspects of the dossier, on 28 June 2018 pertained to the clinical aspects of the dossier (EMEA/H/SA/2744/7/2018/II), on 31 January 2019 pertained to

clinical aspects of the dossier (EMEA/H/SA/2744/8/2018/II), on 14 November 2019 pertained to clinical aspects of the dossier (EMEA/H/SA/2744/9/2019/II), on 26 March 2020 pertained to clinical aspects of the dossier (EMEA/H/SA/2744/10/2020/II), on 27 February 2020 pertained to clinical aspects of the dossier (EMEA/H/SA/2744/11/2020/II) and also on 15 October 2020 pertained to clinical aspects of the dossier (EMEA/H/SA/2744/12/2020/II).

1.5. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

CHMP Rapporteur: Jan Mueller-Berghaus

The application was received by the EMA on	5 March 2021
The procedure started on	25 March 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 June 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 July 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 July 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	07 September 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	12 October 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on	11 November 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	20 December 2021
The CHMP Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 January 2021
The CHMP Rapporteur circulated the updated Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	20 January 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Dupixent on	27 January 2022

2. Scientific discussion

2.1. Problem statement

The purpose of this application is to extend the initially authorised indication of Dupixent to include the treatment of Asthma in children from 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment. The MAH also applied for a new strength (100mg) to be used in the posologic regimen proposed for this new indication.

2.1.1. Disease or condition

Asthma is a complex, heterogeneous disease that can affect persons of all ages. Asthma is characterized by chronic airway inflammation and variable expiratory airflow limitation that is often reversible. Symptoms vary over time and in intensity and can include wheezing, shortness of breath, chest tightness, and cough. Children with uncontrolled moderate-to-severe asthma are at risk for future respiratory complications, including asthma exacerbations, which can be life-threatening at times, and progressive lung function decline. These children are at increased risk for abnormal patterns of lung growth, including reductions in maximal lung function achieved or early decline in lung function. Progressive lung function decline can lead to fixed airflow obstruction or even the development of chronic obstructive pulmonary disease at a young age.

2.1.2. Epidemiology

Asthma is the most common chronic disease of childhood, affecting over 8% of children in the United States (US), and over 9% of children in the European Union (EU), with a worldwide prevalence estimated at almost 12%. Over one-third of children with asthma in the US and Western Europe have a disease that can be characterized as moderate-to-severe, with around 19% of children having a disease characterized as moderate, and around 2% with severe disease.

2.1.3. Biologic features

While asthma is heterogeneous with multiple environmental and intrinsic causes, the most common driver in children is type 2 inflammation. Type 2 inflammation is the most common underlying driver of asthma and is present in up to 80% of children and half of all adults with asthma. This inflammatory process involves the downstream effects of both type 2 innate lymphoid cells (ILC2) and T-helper type 2 (Th2) cell activation and is characterized by the release of signature cytokines interleukin (IL)-4, IL-13, and IL-5. IL-5 plays a role in type 2 inflammation by promoting eosinophil maturation, proliferation, as well as activation and migration. IL-4 is a key driver of T-cell differentiation and induces the production of type-2-associated cytokines and chemokines. Both IL-4 and IL-13 are involved in B cell class switching from immunoglobulin G (IgG) to immunoglobulin E (IgE), and activation of mast cells, basophils, eosinophils, and IgE-producing plasma cells. Interleukin-13 additionally mediates goblet cell hyperplasia, mucus production, and airway hyper-responsiveness. IL-13 upregulates inducible nitric oxide synthase (iNOS) gene expression, leading to increased nitric oxide (NO) release from respiratory epithelium, which can then be measured as fractional exhaled nitric oxide (FeNO), reflecting the degree of airway inflammation. In concert, these inflammatory pathways

produce the clinical features of asthma, including variable airflow obstruction, airway hyper-responsiveness, and mucus production.

2.1.4. Clinical presentation

Asthma is characterized by airway inflammation with edema, cellular infiltrations and mucus plugging, variable airway obstruction and bronchial hyperresponsiveness in response to various triggers. Typical symptoms of asthma are wheezing, chest tightness, shortness of breath, and cough, especially nocturnal. Asthma is increasingly recognized as a heterogeneous disease and not all patients may respond similarly to current therapies or have the same clinical course. While current treatment options are fairly satisfactory for patients with milder disease, they are insufficient for 50% of adult asthma patients with moderate-to-severe uncontrolled disease. Low forced expiratory volume in 1 second (FEV1) is a strong predictor of asthma exacerbations and progressive lung function decline, independent of symptom levels, especially if FEV1 is <60% predicted. FEV1 is a powerful predictor of general, pulmonary, and cardiovascular mortality. Research indicates that asthma itself and the use of asthma medications may be independently associated with increased cardiovascular risk. Studies of patients with asthma selected from the general population have shown increased all-cause mortality due to pulmonary causes, especially in patients with reduced lung function. These findings underscore the importance of preserving normal lung function in the management of asthma.

2.1.5. Management

Current treatment guidelines

The primary goal of asthma management in children is to achieve control of symptoms, optimize lung function, and decrease or eliminate asthma exacerbations while balancing the potential side effects of therapy. In addition, management of childhood asthma aims to reduce chronic underlying inflammation that, if left uncontrolled, may lead to non-reversible airflow limitation. The Global Initiative for Asthma (GINA) guidelines for the management of asthma in children age 6 to <12 years old centre on a stepwise approach to therapy, with incremental adjustments in controller therapy for each step (1-5) reflecting the frequency and extent of underlying symptoms. Inhaled corticosteroids (ICS) are the primary controller medication, and additional controllers include long-acting β2 agonists (LABAs), leukotriene receptor antagonists (LTRAs), or long-acting muscarinic antagonists (LAMAs). Short-acting beta-2 agonists are used as-needed for rescue medication. Children meeting criteria for Step 4 and 5 therapy experience symptoms most days, and standard of care treatment as of the GINA 2020 includes medium-dose ICS plus a LABA, with other options including a high-dose ICS alone or with a second controller therapy. For children uncontrolled with this approach, additional add-on therapy options at Step 5 include systemic corticosteroids (SCS), anti-IgE (omalizumab) for patients with moderate-to-severe persistent or allergic asthma and elevated IgE, or anti-IL-5 (mepolizumab) for patients with elevated blood eosinophils.

Inhaled corticosteroids(ICS) and Systemic Corticosteroids (SCS) carry known side effects, and therefore guidelines recommend using the minimum effective dose to maintain asthma control. While there is strong evidence that both ICS and SCS can prevent exacerbations and preserve lung function, there is little data to support added clinical benefit from increasing ICS above medium dose in children. In children, the long-term use of ICS can have negative impacts on growth, bone metabolism, and adrenal function. In addition to these adverse effects, short courses of SCS are additionally associated with acute mood changes and sleep disturbances.

Biomarker-led management approaches

Predictive response biomarkers can aid in the diagnosis of asthma as well as the selection of appropriate targeted therapies for appropriate patients. The GINA guidelines for the management of asthma recommend using blood or sputum eosinophils, fractional exhaled nitric oxide (FeNO), or other clinical characteristics to select the appropriate biologic therapy for patients with severe type 2 asthma that is not responding to the standard of care therapies. FeNO is produced at the respiratory epithelium as a direct result of IL-13 activation, and therefore uniquely reflects the level of type 2 inflammation in the airways. FeNO levels have been associated with disease severity including exacerbation frequency, lung function, and mucosal airway inflammation. FeNO levels not only support the diagnosis of asthma in children and adults but can also identify patients that are likely to respond to ICS therapy. FeNO testing is simple, safe, and well-tolerated, even in patients with severe airflow obstruction and can be easily measured in children as young as 4 years old. FeNO levels ≥20 ppb are considered the cut-off for characterizing type 2 inflammation in paediatric and adult patients with asthma. American Thoracic Society (ATS)/European Respiratory Society (ERS) recommends a similar cut-point of 20 ppb in children (25 ppb in adults) to identify the upper limit of "normal" FeNO values.

Unmet medical need

For paediatric patients with uncontrolled asthma, the options for add-on therapies beyond the standard of care therapies are relatively limited. A few targeted biologic therapies are available; however, the intended patient population for these therapeutics may be narrow, or clinical efficacy has yet to be demonstrated in randomized-controlled trials. The anti-IgE omalizumab has been approved for patients aged 6 years and older with moderate-to-severe persistent asthma (US), severe allergic asthma (EU), and evidence of positive skin test or in vitro reactivity to a perennial aeroallergen. In clinical trials, omalizumab reduced the annualized rate of exacerbation events in this population by 31%. The applicant states that the anti-IL-5 antibody mepolizumab has been approved in the US and EU for patients 6 to <12 years of age with severe refractory asthma and an eosinophilic phenotype and that this approval was based on a partial extrapolation approach from the adult population with limited placebo-controlled efficacy and safety data in the paediatric population. However, severe eosinophilic asthma is a rare disease (see also conclusion B/R) which hampers the recruitment for clinical studies and therefore extrapolation was performed. While it is known that children who have impaired lung function have a higher risk of significant fixed airflow obstruction as adults, neither anti-IgE nor anti-IL-5 therapeutics has demonstrated a sustained ability to improve lung function in paediatric populations. Therefore, for patients with moderate-to-severe asthma who remain uncontrolled despite standard of care therapy, there is a need for a safe and effective therapy that can both effectively reduce exacerbations and improve lung function.

2.2. About the product

Dupilumab is a human monoclonal antibody (mAb) directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 heterodimeric Type I (IL-4-ligand only) and Type II (both IL-4 and IL-13 ligands) receptors. The binding of dupilumab to IL-4Rα results in blockade of downstream signalling initiated by both IL-4 and IL-13. IL-4 and IL-13 are key type 2 cytokines involved in type 2 inflammatory diseases.

Dupilumab is authorized for marketing in the US for use as an add-on maintenance treatment in patients aged 12 years and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroids (OCS)-dependent asthma; in the EU as an add-on maintenance treatment for adult and adolescent (12 years and older) patients with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO who are inadequately controlled with high-dose ICS plus another medicinal product, and in Japan for use in adults and adolescents (≥12

years of age) with severe or refractory bronchial asthma. Dupilumab is also approved in multiple regions for the treatment of adults and adolescents with moderate-to-severe atopic dermatitis (AD) and the treatment of patients aged 6 to <12 years old with moderate-to-severe AD in the US or with severe AD in the EU. In addition, dupilumab is approved for the treatment of adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP) in the US, EU, and Japan.

It is of note that Regeneron Pharmaceuticals and Sanofi continue to explore dupilumab as a potential treatment for additional type 2 inflammation-mediated disorders.

2.3. Type of Application and aspects on development

The current submission dossier is an extension of the Marketing Authorization application for asthma patients 6 to <12 years of age. The results of the completed Phase 3 efficacy/safety study (EFC14153) and the ongoing open-label extension study (LTS14424) in patients aged 6 to <12 years are presented in this application.

In the EFC14153 study, patients with asthma aged 6 to <12 years on background controller therapy with medium or high dose ICS in combination with a second controller or with high dose ICS alone were evaluated. The clinical benefits of dupilumab were observed both for patients on medium or high dose ICS at baseline. In children, providers must limit the use of high dose ICS unless clearly indicated. Studies have demonstrated that there is limited data to support additional clinical benefit with increasing ICS from medium to high dose ICS in this population, while side effects of higher dose ICS can include reduced growth velocity and impact on the HPA axis. Hence, the applicant is proposing for this extension an indication similar to the adults and adolescents in severe asthma with type 2 inflammation with the exception that the population 6 to <12 years of age includes patients on medium to high dose ICS; ie, Dupixent is indicated in children aged 6 to <12 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or FeNO, who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment. According to GINA severe asthma is a condition that remains uncontrolled despite high dose ICS-LABA or that requires high dose ICS-LABA to prevent becoming uncontrolled.

Finally, the submission dossier, written in a global context, proposes to update the adult and adolescent US and US reference countries' indication statement to reflect the demonstration of both blood eosinophils and FeNO as predictive biomarkers. Both of these biomarkers are already incorporated into the approved indication statement in the EU and EU reference countries.

Dupilumab was approved by the US FDA on 19 October 2018 for the treatment of adults and adolescents with moderate-to-severe asthma with an eosinophilic phenotype or with OCS-dependent asthma. Dupilumab was also approved by the European Commission (EC) on 6 May 2019 for use in adults and adolescents 12 years and older as an add-on maintenance treatment for severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment, and in Japan on 26 March 2019, for use in adults and adolescents (≥12 years) with severe or refractory bronchial asthma.

2.4. Quality aspects

2.4.1. Introduction

The proposed finished product is presented as a solution for subcutaneous injection containing 100 mg of dupilumab (150 mg/mL) as active substance.

Other ingredients are: arginine hydrochloride, histidine, polysorbate 80 (E433), sodium acetate trihydrate, glacial acetic acid (E260), sucrose and water for injections.

The product is available in a siliconised type-1 clear glass pre-filled syringe (PFS) with needle shield, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

There is no change to the active substance information or quality. The authorised formulated active substance dupilumab 150 mg/mL is used for the manufacture of the proposed new dose Dupixent 100 mg and is the same as used for the manufacture of the authorised dose Dupixent 300 mg. Therefore, the approved active substance and formulated active substance sections are applicable and no additional sections are needed to support the present submission.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

This line extension application includes the addition of the new dosage strength 100 mg in a pre-filled syringe with safety system (PFS-S). The same active substance and 150 mg/mL dupilumab formulated active substance is used to manufacture 100 mg Dupixent as is currently authorised for the manufacture of 300 mg Dupixent. Essentially, the 150 mg/mL dupilumab formulated active substance is aseptically filled at a lower volume (0.67 mL) in a smaller primary container to yield the new 100 mg dose.

The filled volume and the syringe size (1 mL) have been adjusted for the lower volume (0.67 mL) used for the 100 mg dose.

The 100 mg bulk PFS uses the same primary container closure components (syringe, needle shield, and plunger stopper) as the authorised 200 mg bulk PFS which uses the 175 mg/mL dupilumab concentration with a slightly different formulation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. Dupilumab finished product contains no excipients of human or animal origin.

The primary packaging is a siliconised type-1 clear glass pre-filled syringe (PFS) with needle shield, with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The primary packaging of the 100 mg bulk PFS with rigid needle shield (RNS) is the same as the 200 mg bulk PFS with RNS. Device constituent parts of the PFS-S for the 100 mg dupilumab PFS-S are the same as for the commercialized 200 mg dupilumab PFS-S: syringe glass barrel with staked needle and RNS, plunger stopper, plunger rod, finger flange, safety system. The device has no CE mark.

The applicant confirmed that the pre-filled syringe used for the delivery of dupilumab 100 mg is a device that is fully integrated at the time of placing on the market (i.e. no assembly of the medicine part is needed before administration).

This device has been developed under applicable good manufacturing practice (GMP) and all applicable medical device regulations including design control, risk management and relevant purchasing control provisions such as 21 CFR part 4 – Regulation of Combination Products and applicable parts of ISO-13485 Medical devices – Quality management systems – Requirements for regulatory purposes.

Device requirements of the device constituent parts of the bulk PFS with RNS fulfill ISO 11040 – Pre-filled Syringes Part 4: Glass Barrels for injectables and sterilized sub-assembled syringes ready for filling and FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics; and are classified according to the five categories as described per FDA Guidance plus sterilisation item.

The leachable evaluation of the bulk PFS container closure did not identify any leachables of toxicological concern.

Manufacturing process development

Dupilumab 150 mg/mL is currently filled into a 2.25 mL syringe (300 mg dose) ; the dupilumab 100 mg dose (0.67 mL of dupilumab 150 mg/mL in 1 mL syringe) is introduced with the same manufacturing process.

The current manufacturing process of dupilumab 150 mg/mL consists of the following steps:

- Step I - Thawing of dupilumab 150 mg/mL formulated drug substance
- Step II - Pooling and mixing of dupilumab 150 mg/mL formulated drug substance
- Step III - Prefiltration of formulated drug substance
- Step IVa - In-line sterilizing filtration
- Step IVb - Filling and stoppering
- Step V - 100% Visual Inspection

Manufacturing operations of thawing, pooling and mixing, prefiltration and in-line sterilisation remain the same. There is no change to the currently approved areas, equipment and process parameters of these manufacturing steps.

The filling and stoppering process for the 100 mg dose syringe uses the same trained pool of personnel; the 100 mg dose consists of filling and stoppering a new volume of dupilumab 150 mg/mL in a new container closure system.

Capability studies demonstrated the ability of the filling machine to meet the defined filling volume specifications.

The presented data of the dupilumab bulk PFS lots filled showed similar stability profiles under long-term storage conditions, thereby confirming the similar nature of the material and that the differences between processes at the two sites did not affect protein quality up to 36 months under long-term storage conditions. In the D120 response document, the MAH provided a comparison of the

degradation profiles of the 100 mg dupilumab bulk PFS lots filled after storage at accelerated conditions which demonstrated that finished product manufactured degraded as expected and had similar degradation profiles to one another during the accelerated stability studies.

Manufacture of the product and process controls

The finished product manufacturers involved in the manufacture of 100 mg Dupixent are authorised finished product manufacturers currently involved in the manufacture of the authorised doses of Dupixent 300 mg and 200 mg. There are no new active substance, formulated active substance or finished product manufacturers involved in the manufacture of 100 mg Dupixent.

Compared with the batch size for 300 mg Dupixent, the batch size for the manufacture of 100 mg Dupixent is smaller. A batch size range of, expressed as the amount of 150 mg/mL formulated drug substance (FDS) used to manufacture a batch of 100 mg bulk PFS has been defined based on validation studies. Mixing of more than one batch of FDS is allowed to reach the batch size.

The differences in manufacturing process conditions (Critical Process Parameters (CPPs), Critical in-process controls (CIPCs), Holding times (HTs) and Time out of refrigeration (TOR)) between the 100 mg dose and the 300 mg dose were adequately described and defined/verified following process validation.

The manufacturing process and process controls for the dupilumab 100 mg PFS-S assembly process is the same as for the authorised dupilumab 200 mg PFS-S. There is no change to the currently approved process parameters and in-process controls (IPC) of these manufacturing steps except for the global time out of refrigeration (TOR) validated for the 100 mg PFS-S during the assembly process validation and applicable in routine manufacturing.

Validation of manufacturing occurred on three batches of dupilumab 100 mg solution in bulk PFS followed by assembly process validation on three batches. The collection and evaluation of in-process controls and release testing data from the validation batches of dupilumab demonstrated that the process operated within the defined process parameters while applying maximum hold times and time out of refrigeration. All validation batches confirmed that the process can consistently produce bulk PFS and final finished product as PFS-S in a robust manner, meeting quality release specifications.

Filled bulk PFS (RNS) syringes were used for the assembly of the PFS-S. The PFS-S validation batches confirmed that the process can consistently reproduce assembly operations and is capable of producing finished product in PFS-S in a robust manner thus meeting quality release specifications.

Release results of the 100 mg Bulk PFS and PFS-S process validation (PV) batches met the specifications valid at time of validation runs and the stricter acceptance criteria of current specifications and demonstrated satisfactory consistency among the three batches.

The dupilumab 300 mg critical process parameters have been confirmed to also be appropriate for dupilumab 100 mg with a lower batch size and lower filling volume with a different plunger stopper position.

Studies have been conducted to provide evidence for manufacturing process asepsis of 100 mg bulk PFS. Validation of aseptic processing filling lines includes a process simulation test using microbial growth medium (Media Fill Tests). The maximum holding time of the prefiltered solution storage into the single-use bag assembly applicable for commercial production is limited by storage holding time validated during aseptic process simulation runs (Media Fill).

As part of microbiological attributes, the sterility (in conjunction with the Container Closure Integrity Test (CCIT) is monitored as part of batch release and stability testing.

The 100 mg PFS-S simulated shipping validation studies were performed according to ASTM D4169 Standard Practices for Performance Testing of Shipping Containers and Systems, including road, air and sea freight. Simulated shipping validation results are acceptable.

Product specification

The formulation and therefore all excipients and their concentrations used in 100 mg Dupixent are identical to those used in the authorised 300 mg Dupixent since both finished products are manufactured from 150 mg/mL dupilumab formulated active substance.

Resulting from the same concentration of the active ingredient (150 mg/mL dupilumab) and identical formulation, the specifications and acceptance criteria for 100 mg PFS-S are identical to the authorised specifications and acceptance criteria for the 300 mg PFS-S, except for expellable volume.

The specifications covers product solution properties, identity, strength, purity, potency and syringe with safety system performance properties. The specifications and acceptance criteria for 100 mg bulk PFS and 100 mg PFS-S are satisfactorily justified in CTD 3.2.P.5.6. Specifications for 100 mg bulk PFS are provided in the CTD section P.3.4.

The device-related functional performance specific specifications among 100 mg PFS-S and 300 mg PFS-S are the same irrespective of the different syringe size used.

The key elements described for the active substance specifications are also in many cases applicable for the finished product.

Analytical methods

Brief information on the analytical procedures applied for the 100 mg Dupixent has been provided. New method summary attachments for container closure integrity, and for sterility are provided. Container closure integrity (CCI) is introduced for 100 mg primary stability testing only. Descriptions of other analytical procedures applicable for 100 mg Dupixent have already been approved for either 300 mg or 200 mg Dupixent.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with ICH guidelines.

Batch analysis

Batch analysis data on three batches of the finished product were provided. The results are within the specifications and confirm consistency of the manufacturing process.

Stability of the product

A shelf life of 36 months is claimed for the 100 mg bulk PFS when stored at 2°C - 8°C.

The new strength 100 mg Dupixent uses the primary container closure system authorised for 200 mg Dupixent (175 mg/mL dupilumab in 1 mL syringe). Bulk PFS batches used in the stability studies were manufactured at two sites. The comparability of the syringes is appropriately addressed and a comparable stability profile has been confirmed.

The test parameters and test intervals for the primary stability lot long-term, accelerated, and stress stability studies are satisfactory.

Three lots of dupilumab 100 mg bulk PFS were selected as primary stability batches. These lots are considered representative of the intended commercial process and presentation with minor differences in the non-product contacting components.

A shelf life of 36 months is proposed for 100 mg bulk PFS when stored at 5 ± 3 °C based on 36 months of acceptable data for three representative primary stability 100 mg bulk PFS lots.

Stability data from bulk PFS lots manufactured at demonstrate stability over 24 months at 2-8°C. Additional bulk PFS batch demonstrates stability up to the 36-month time point.

Minimal dupilumab degradation and little change in any attribute was observed in primary and confirmatory stability batches during storage at the long-term condition of 5 ± 3°C up to the latest time points tested. No significant changes were observed in the primary stability lots during storage. No change was observed in expellable volume. No changes indicating loss of container closure integrity (sterility or endotoxin) were observed in any stability lots during storage at the long-term condition, to date. Out of specification (OOS) results for were observed which were adequately discussed in the Day 120 response document. The conclusions from the investigation can be accepted and the issue be considered as solved. The MAH confirmed that the discussion of the OOS will be implemented in *3.2.P.8.1 Stability Summary and Conclusions – Bulk PFS – 100 mg* with the submission of the completed stability data for the 100 mg bulk PFS. An OOS was observed for expellable volume for one batch which was back in specification at later time points. The potential root cause is the filling machine scale. The corrective action was implemented on the filling line. An additional commercially representative batch was manufactured to confirm the effectiveness of the corrective action.

Following storage under stress conditions, the expected degradation profile was observed. Little to no change was observed in tests related to performance after storage at the stress condition.

Stability studies under accelerated (6 months) and stress conditions (3 months) have been completed.

For 100 mg bulk PFS, the claimed shelf life of 36 months is acceptable based on satisfactory 36 months stability data of primary 100 mg bulk PFS batches and confirmatory 100 mg bulk PFS data.

For 100 mg PFS-S, a shelf life of 36 months from the date of fill is proposed when stored at 5 ± 3 °C and protected from light during storage.

Stability data are available through the 24-month time point for lots of 100 mg dupilumab in PFS-S after storage at the long-term condition at 5 ± 3°C. Dupilumab continued to meet the acceptance criteria for the monitored attributes after storage at 5 ± 3 °C up to the 24-month time point. Overall little degradation was observed to date in any of the batches following 24 months of storage at the long-term condition.

The proposed shelf life for 100 mg Dupixent PFS-S of 3 years from the date of fill when stored at 2°C - 8°C and protected from light during storage can be accepted based on 100 mg PFS-S stability batches demonstrating satisfactory stability at real-time conditions 2-8°C for 24 months and 100 mg bulk PFS batches demonstrating stability at 2-8°C for 36 months.

The MAH is recommended to provide an update of primary and confirmatory stability studies in sections P.8.1 and P.8.3 upon completion of the studies. (Recommendation)

Based on available stability data, the shelf life of 3 years when stored at 2°C - 8°C as stated in the SmPC are acceptable. If necessary, pre-filled syringes may be kept at room temperature up to 25°C for a maximum of 14 days. It should not be stored above 25°C. After removal from the refrigerator, Dupixent must be used within 14 days or discarded.

Adventitious agents

There is no change to the approved adventitious agents safety evaluation and the existing data adequately covers also the new strength.

Discussion on chemical, and pharmaceutical aspects

This line extension application includes the addition of a new dosage strength of 100 mg in pre-filled syringe with safety system (PFS-S). The same active substance and 150 mg/mL dupilumab formulated active substance is used to manufacture 100 mg Dupixent as is currently authorised for the manufacture of 300 mg Dupixent. Essentially, the 150 mg/mL dupilumab FDS is aseptically filled at a lower volume (0.67 mL) in a smaller primary container to yield the new 100 mg dose.

Finished product specifications for 100 mg Dupixent match those of 300 mg Dupixent except for the parameter expellable volume. The primary container used for 100 mg Dupixent PFS-S is the same 1-mL syringe as that authorised for 200 mg Dupixent PFS-S.

The manufacturing process steps of the 100 mg bulk PFS dose are the same as for the 300 mg dose (2.0 mL of dupilumab 150 mg/mL in a 2.25 mL syringe) except for batch size, filling (weight range) and stoppering recipe (plunger stopper position). The differences in manufacturing process conditions (CPPs, CIPCs, HTs and TOR) between the 100 mg dose and the 300 mg dose were adequately described and defined/verified following process validation.

The manufacturing process and process controls for the dupilumab 100 mg PFS-S assembly process is the same as for the authorised dupilumab 200 mg PFS-S. There is no change to the currently approved process parameters and in-process controls (IPC) of these manufacturing steps except for the Global Time Out of Refrigeration (TOR) validated for 100mg PFS-S during assembly process validation and applicable in routine manufacturing.

The clarification provided with the response on D120 LoQ on a new analytical procedure added for container closure integrity used in stability testing is acceptable.

Stability data have been updated for 100 mg bulk PFS and PFS-S as well as regarding the comparability of commercial and clinical finished product.

The proposed shelf life for 100 mg Dupixent PFS-S of 3 years from the date of fill when stored at 2°C - 8°C and protected from light during storage can be accepted based on 100 mg PFS-S stability batches demonstrating satisfactory stability at real-time conditions 2-8°C for 24 months and 100 mg bulk PFS batches demonstrating stability at 2-8°C for 36 months. The MAH committed to provide an update of primary and confirmatory stability studies in sections P.8.1 and P.8.3 upon completion of the studies. The letter of recommendation has been updated accordingly.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions as defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following point for investigation:

1. The MAH is recommended to provide an update of primary and confirmatory stability studies in sections P.8.1 and P.8.3 upon completion of the studies.

2.5. Non-clinical aspects

2.5.1. Introduction

No new non-clinical data have been submitted in this application, which is considered acceptable.

Non-clinical safety was assessed in a comprehensive program submitted as part of the original marketing application for atopic dermatitis (AD) indication.

Non-clinical studies in support of the asthma indication were submitted and approved with extension EMEA/H/C/004390/X/0004/G.

No new pre-clinical toxicology studies are included in this submission. However, an updated carcinogenicity risk assessment, based on a literature search, is provided in this application as part of module 4.

2.5.2. Toxicology

An amended carcinogenicity risk assessment (Amendment No. 6, dated 09 Nov. 2020) to that previously submitted to Health Authorities with the initial application for marketing approval of Dupixent for adult patients with moderate to severe atopic dermatitis is provided with this submission in CTD Module 4.2.3.7.7 (eCTD 0113):

The purpose of this amendment was to reflect an updated literature search cut-off date in support of subsequent marketing application for paediatric asthma (6 to <12 years old).

A literature search for any articles published between October 17 of 2019, and October 30 of 2020 was performed, and no new publications were identified that would change the conclusions of the original document.

No changes have been made to the original document.

2.5.3. Ecotoxicity/environmental risk assessment

Based on the updated data submitted in this application, the new/extended indication for paediatric asthma patients (6 to <12 yrs) does not lead to a significant increase in environmental exposure further to the use of dupilumab. Therefore, dupilumab is not expected to pose a risk to the environment.

2.5.4. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

Non-clinical safety was assessed in a comprehensive program submitted as part of the original

marketing application for atopic dermatitis (AD) indication.

Non-clinical studies in support of the asthma indication were submitted and approved with extension EMEA/H/C/004390/X/0004/G.

2.5.5. Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in this application.

A literature search for any articles published between October 17 of 2019 and October 30 of 2020 was performed, and no new publications were identified that would change the conclusions of the Non-clinical assessment performed during the original Marketing Authorization assessment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

The following efficacy studies supporting a new indication in asthma patients were provided:

Study number/ status at submission cut-off	Study objective	Treatment/ follow-up duration	Patients randomized/ treated[a]
Phase 3			
EFC14153 (VOYAGE) Completed (5.3.5.1 [Study EFC14153])	Efficacy and safety of dupilumab compared to placebo in children 6 to <12 years old with uncontrolled persistent asthma (Primary endpoint: Annualized rate of severe asthma exacerbation events during the 52-week placebo-controlled treatment period. Key secondary endpoint: Change from baseline in percent predicted pre-bronchodilator [BD] forced expiratory volume in 1 second [FEV_1] at Week 12)	52/12[c] weeks	Randomized/treated: 408/405 (dupilumab: 270[b], placebo: 135[b])
LTS14424 (EXCURSION) Open-label Ongoing (5.3.5.2 [Study LTS14424])	Long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (EFC14153) (Primary endpoint: incidence of treatment-emergent adverse events [TEAEs] defined as the number and percentage of patients experiencing any TEAE)	52/12 weeks Ongoing since 21 June 2018	Entered and treated: 365

FEV_1: Forced expiratory volume in 1 second; TEAE: Treatment-emergent adverse event.

a Including all data up to submission cut-off date (18 August 2020 for LTS14424).

b As treated.

c Patients subsequently enrolled in the long term extension study (LTS14424) did not participate in the post-treatment follow-up period.

Table 1: List of Phase 3 paediatric asthma studies evaluated in the summary of clinical efficacy and study status

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The package on clinical pharmacology regarding children aged ≥6 to <12 years with uncontrolled moderate-to-severe asthma comprises two phase-3 clinical studies with SC dupilumab in which PK and PD data have been collected. In the randomized, double-blind, placebo-controlled study EFC14153, patients were treated with either 100 mg dupilumab (body weight ≤30 kg) (n=91), 200 mg dupilumab (body weight >30 kg) (n=179) or placebo (n=135) q2w for a maximum of 52 weeks (in sum, 405 were treated, 270 with dupilumab and 135 with placebo). Eligible patients who completed the treatment period of this study (including patients of the placebo group) were offered the opportunity to participate in the ongoing 1-year long-term open-label extension study LTS14424 (n=365), during which dosing regimens of 100 mg q2w or 300 mg q4w for children with a body weight ≤30 kg (n=62) and 200 mg q2w for children with a body weight >30 kg (n=303) were assessed. Patients with body weight ≤30 kg were treated with 100 mg q2w prior to protocol amendment 03, dated 12 December 2019. After the amendment approval, children with body weight ≤30 kg with ≥8 weeks remaining before the planned end of treatment were switched to 300 mg q4w, based on data from the pivotal study R668-AD-1652 in children with AD.

Sparse sampling schemes were utilized in both of the studies, EFC14153 and LTS14424, with samples collected at weeks 0 (predose), 6 (study EFC14153 only), 12, 24, 52 (on-treatment) and 64 (follow-up).

Analytical methods

The method applied for detection of functional dupilumab was employed in previous dupilumab applications and has been accurately validated. Incurred sample reanalysis was conducted in asthma study EFC14153 and confirmed that the assay produced robust and reproducible results in the paediatric asthma population with an ISR passing rate of 98%.

In general, the methods applied for the detection of anti-dupilumab antibodies and neutralizing antibodies correspond to methods already utilized and described in previous applications.

For the detection of ADAs in paediatric asthma studies EFC14153 and LTS14424, updated assay method REGN668-AV-15153-VA-01V2 was employed. Assay updates were associated with the ADA assay cut point for the asthma population, selection of a lower level of low-quality control (LQC), and an assessment of sensitivity and drug tolerance level (DTL) using the screening asthma ADA cut point factor (CF).

Pop PK

A pop PK analysis was conducted using pooled data from the Phase 3 studies in children 6 to <12 years of age with asthma to characterize dupilumab PK, compare exposure between indication (Asthma vs AD) and across age groups, and assess the influence of extrinsic and intrinsic factors on dupilumab PK variability. In addition, this model was used to simulate dupilumab concentrations over time for the alternative regimen of 300 mg q4w in children 6 to <12 years of age with asthma.

The final pop PK dataset contained 1772 dupilumab concentrations from 377 children 6 to <12 years of age with asthma with a body weight range of 16.4 kg to 67.2 kg. In the final dataset, PK data following 300 mg q4w dose was very limited (N=2 patients in weight group of ≤30 kg, one from dupilumab treatment group and the other from placebo group of study EFC14153), which resulted in only two PK samples.

The pop PK model in the paediatric population with asthma used the same model structure as the previously developed global base model.

The PK of dupilumab in children 6 to <12 years of age with asthma was described by a 2-compartment model with first-order absorption kinetics, and parallel linear and nonlinear elimination parameterized in terms of a first-order Ke and Michaelis-Menten parameters.

Among the tested covariates, only body weight was identified to be a statistical significant covariate on dupilumab PK in children 6 to <12 years of age with asthma, and included as a time-varying covariate on V2, Ke, and Vmax.

Overall, model diagnostics indicate no major deviations or miss-specifications. Nevertheless, PK data is indicated to be highly variably.

ADME

Population PK model estimates for SC bioavailability and absorption rate constant were comparable between adults/adolescents and children 6 to < 12 years of age with asthma (SC bioavailability is 63% in children and 61% in adults/adolescents; Ka is 0.252/day in children and 0.263/day in adults/adolescents).

Dupilumab distributes primarily within the vascular compartment. Model-estimated volume of distribution at steady state (Vss) in children 6 to <12 years of age is 3.7 L.

The PK of dupilumab is characterized as nonlinear with parallel linear and nonlinear elimination pathways (target-mediated clearance).

Based on pop PK results, the derived linear clearance (CL), based on normalization by the median weight of the respective age group increases with age because of CL increase with body weight and body weight increase with age.

Dose proportionality and time dependency

Exposure in terms of AUC, Cmax and Ctrough_ss increased less than proportional with dose (100 mg q2w, 200 mg q2w) as indicated by Phase 3 data and exposure simulations.

In Study EFC14153, steady-state was achieved by Week 12 and was maintained up to 52 weeks during treatment with 100 mg q2w and 200 mg q2w in children 6 to <12 years of age with asthma. The observed steady-state trough concentrations were consistent between Study EFC14153 and Study LTS14424.

Based on the Pop PK model, the median time to steady-state was 14 weeks for 100 mg q2w and 200 mg q2w, and up to 18 weeks (300 mg q4w) in children 6 to <12 years of age with asthma as reflected in section 5.2. of the SmPC. As no loading dose was administered time to steady-state is prolonged compared to adults and adolescents with asthma (8 weeks) where a loading dose was used.

Intra- and inter-individual variability

The observed variability (total %CV) of Ctrough,ss after repeated SC doses of dupilumab 100 mg q2w or 200 mg q2w in the children 6 to <12 years of age with asthma was in the range of 47.9% to 52.8% (study EFC14153).

The magnitude of estimated IIV was modest for the central volume of distribution V2 (CV% = 25.4%) and elimination rate Ke (CV% = 16.1%).

While IIV on Ke was decreased by introducing time-varying weight effects, IIV on the central volume of distribution was increased (from 10.4 to 16.1 %CV).

Pharmacokinetics in target population

Mean (SD) predicted steady-state exposure in children 6 to <12 years of age with asthma

Following administration of 100 mg q2w and 200 mg q2w doses of dupilumab in children 6 to <12 years of age with a body weight ≤30 kg and >30 kg, dupilumab Ctrough,ss values (mean ± SD) were 58.4 ± 28.0 mg/L and 85.1 ± 44.9 mg/L, respectively.

Model-based simulations overall indicate dupilumab exposure at the doses tested in the Phase 3 study EFC14153 in children 6 to <12 years of age with asthma (100 mg q2w in children with body weight ≤ 30 kg and 200 mg q2w in children with body weight >30 kg) to be lower than the Cmax achieved in adults with asthma treated with 300 mg qw, and exceeded the exposure (Ctrough,ss) achieved with 200 mg q2w in adults with asthma.

Following 300 mg q4w, median Ctrough ss was estimated to 42.7 mg/L (30-60 kg) and 91.7 mg/L (15-30 kg), with percentiles to 14.6 mg/L (p5) and 96.4 mg/L (p95) and 41.9 mg/L (p5) and 177.2 (p95), respectively. The mean Ctrough,ss in children with body weight ≥30 kg to <60 kg receiving 300 mg q4w (48.0 mg/L) was similar to the observed Ctrough, ss in adolescent patients receiving 200 mg q2w (50.7 mg/L). The mean Cmax, ss in children with body weight ≥30 kg to <60 kg receiving 300 mg q4w (102 mg/L) was 40% lower than that observed in adult patients receiving 300 mg qw (171 mg/L). The mean Cmax,ss in children with body weight ≥15 kg to <30 kg receiving 300 mg q4w (170 mg/L) was similar to that observed in adult patients receiving 300 mg qw (171 mg/L).

Ctrough at steady state was within the range of the two regimens approved in adults and adolescents with asthma (200 mg q2w and 300 mg q2w).

Comparison of pop PK models reflects the fact the weight influence on Vmax (target-mediated CL) was needed and kept in the asthma pop PK model in contrast to AD. That might also be the source of variability in exposure in asthma vs AD. Simulations show that exposure in the asthma population is constantly slightly below the one in the corresponding AD weight category.

Overall, PK data and pop PK indicates similarity in PK across indication and age groups (after accounting for differences in body weight).

Mean (SD) trough concentration-time profiles in children 6 to <12 years of age, adults and adolescents with asthma

Special populations

Besides weight, all other tested covariates, were not found to have a statistically significant effect on dupilumab PK in children 6 to <12 years of age with asthma.

Prominent impact of weight on PK parameters (linear, non-linear clearance and volume of distribution) and consequently on exposure in each weight category (15-30 kg, 30-60 kg) was observed. This also led to the proposed weight tierd posology in children 6 to <12 years of age with asthma is:

• For children with body weight ≥15 kg to <30 kg: 100 mg q2w or 300 mg q4w

• For children with body weight ≥30 kg to <60 kg: 200 mg q2w or 300 mg q4w

• For children with body weight ≥60 kg: 200 mg q2w.

For 100 mg q2w dose regimen, dupilumab exposures increased with a decrease in body weight over the analysis range of 19.6 - 29.8 kg (median 26 kg). For a decrease in body weight from 26 kg to 19.6 kg (the 5th percentile weight of 100 mg q2w), the increase in $AUC_{T,ss}$ and Ctrough,ss was 41.7% and 45.8%, respectively. For an increase in body weight from 26 kg to 29.8 kg (the 95th percentile weight

of 100 mg q2w), the decrease in AUCτ,ss and Ctrough,ss was 14.8% and 16.0%, respectively. Similar trend was found for Cmax,ss.

For 200 mg q2w dose regimen, dupilumab exposures increased with a decrease in body weight over the analysis range of 31- 59.3 kg (median 38.6 kg). For a decrease in body weight from 38.6 kg to 31 kg (the 5th percentile weight of 200 mg q2w), the increase in AUCτ,ss and Ctrough,ss was 32.0% and 35.2%, respectively. For an increase in body weight from 38.6 kg to 59.3 kg (the 95th percentile weight of 200 mg q2w), the decrease in AUCτ,ss and Ctrough,ss was 42.6% and 45.9%, respectively. Similar trend was found for Cmax,ss.

For 300 mg q4w dose regimen in 15-<30 kg group, dupilumab exposures increased with a decrease in body weight over the analysis range of 19.6-29.8 kg (median 26 kg). The body weight effect translated to a 15.6% lower steady-state AUCτ,ss for a typical patient with a body weight of 29.8 kg (the 95th percentile of the weight range) and a 37.5% higher AUCτ,ss for a typical patient with a body weight of 19.6 kg (the 5th percentile), as compared with a typical patient with a body weight of 26.0 kg (the median weight). Similar trend was found for Ctrough,ss and Cmax,ss.

For 300 mg q4w dose regimen in 30-<60 kg group, dupilumab exposures increased with a decrease in body weight over the analysis range of 31-59.3 kg (median 38.6 kg). The body weight effect translated to a 45.1% lower steady-state AUCτ,ss for a typical patient with a body weight of 59.3 kg (the 95th percentile of the weight range) and a 33.4% higher AUCτ,ss for a typical patient with a body weight of 31.0 kg (the 5th percentile), as compared with a typical patient with a body weight of 38.6 kg (the median weight). Similar trend was found for Ctrough,ss and Cmax,ss.

With regards to disease, for the 100 mg q2w or 200 mg q2w dose regimens, the observed dupilumab Ctrough-values in children 6 to <12 years of age with asthma are similar to those with AD.

Pharmacokinetic interaction studies

Based on the comparison of Pop PK predicted post hoc estimates of individual steady-state exposure, the concomitant use of controller medications (LABA, and systemic corticosteroids) had no apparent effect on dupilumab PK.

The impact of methylxanthines and leukotriene receptor antagonist (LTRA) on dupilumab PK exposure could not be assessed due to limited data.

2.6.2.2. Pharmacodynamics

Mechanism of action

Biomarkers

Biomarkers of type 2 inflammation, including blood eosinophils, serum IgE, serum TARC, and the FeNO, were assessed in study EFC14153, and blood eosinophil and serum IgE measurement was continued in study LTS14424.

Dupilumab has been shown to consistently induce a rapid and sustained reduction in FeNO and TARC, as well as a progressive reduction of total IgE., while blood eosinophils was not a response PD biomarker for dupilumab treatment. In study LTS14424, mean total IgE in dupilumab-treated patients enrolled from study EFC14153 continued to decrease throughout the study treatment period. As expected, the mean total IgE in placebo-treated patients enrolled from Study EFC14153 decreased following dupilumab treatment in study LTS14424.

The treatment effect of dupilumab on type 2 inflammation biomarkers over time was similar in children 6 to <12 years of age to that observed in adults and adolescents with asthma.

Primary and Secondary pharmacology

Immunogenicity

Immunogenicity was analysed in both Phase 3 clinical studies children ≥6 to <12 years of age with asthma. The ADA response in children with asthma was low and consistent with that observed in children with AD of the same age group and at the same dupilumab dose. It was further consistent across age groups in patients with asthma.

PK/PD and exposure-response

Overall, PK/PD analyses indicated a clinically significant reduction in severe exacerbation rate and improvement in per cent predicted FEV1 change from baseline for both the 100 mg q2w and 200 mg q2w dose regimens in children 6 to <12 years of age with asthma. Treatment effect approaches near plateau of the E-R curve over the exposure range achieved at 100 mg q2w and 200 mg q2w. PK/PD relationships of key efficacy endpoints in children 6 to <12 years of age and in adult and adolescent patients with asthma are considered comparable in the exposure range at the therapeutic doses (dose regimens evaluated in the pivotal Phase 3 studies) across age groups in asthma populations.

As similarity in exposure-response relationships across age groups in asthma population is indicated, no meaningful difference between the proposed alternative dose regimen of 300 mg q4w and the 100 mg q2w/200 mg q2w evaluated in Study EFC14153 is expected.

No definite exposure-response relationship concerning safety was provided. Given the acceptable safety profile and exposure predicted to be lower than that at the highest dose tested (300 mg qw in adults), this is acceptable.

2.6.3. Discussion on clinical pharmacology

Clinical studies

Up to the updated data cut-off date of 26 May 2021, 18 patients with body weight ≤ 30kg were exposed to the 300 mg q4w schedule in study LTS14424. PK data of 17 patients out of 18 patients treated with the 300mg q4w dose regimen are now available.

All of the patients that were treated with the 300 mg q4w scheme switched from other regimes (100 mg q2w regimen in almost all cases, placebo regimen in one case) the timepoints of switching to the 300 mg q4w regime were disclosed. The closest time interval between the switch to the 300 g q4w regimen and first PK sampling after it was 4 weeks in 3 cases. All other patients switched 8 weeks (N=5) or longer prior to the next scheduled PK sampling. Thus, some of the samples are not collected under steady-state conditions. However, this was recognized by the applicant as the observed Ctrough,ss was calculated from samples in a steady-state only. Moreover, an external validation has been provided by the MAH and VPC plots indicate that all the observed concentrations were within in the prediction range [5th-95th] percentiles.

ADME

Population PK model estimates for SC bioavailability and absorption rate constant were comparable between adults/adolescents and children 6 to < 12 years of age with asthma.

The absorption rate constant in children (6-11 years) with AD was about 2-fold as high (0.641/day) than that in the same age group of children with asthma (0.252/day). The difference in absorption rate constant between both paediatric populations was discussed. The absorption rate constants were comparable between children and adolescents/adults with asthma, as it was described differently for the AD population that the estimated rate of absorption in children ≥6 to <12 years of age was higher

than in adults and that was consistent with the higher reported absorption rates in children (Robbie, 2012). It is agreed that the 2-fold difference in absorption rate between children 6 to <12 years of age with AD and asthma is expected to result in no clinically relevant impact on steady-state trough concentrations and in a small effect on steady-state maximum concentrations.

Dupilumab distributes primarily within the vascular compartment. Model-estimated volume of distribution at steady state (Vss) in children 6 to <12 years of age is 3.7 L.as reflected in the section 5.2 of the SmPC.

The measure of variability of V2, and of the derived PK Parameters CL (0.133 L/day), Q (0.209 L/day), V3 (1.39 L) and Vss (3.74 L) were provided.

The derived linear clearance (CL), based on normalization by the median weight of the respective age group (adults, adolescent, children with asthma 6 to <12 years) increases with age as the CL is correlated to body weight in the popPK analyses and body weight increases with the age.

PK in the target population

In contrast to all other age groups and indications, no loading dose has been foreseen. In consequence, time to steady-state is indicated to be prolonged for paediatric patients with asthma (6-12 years of age). A discussion of loading dose or, in other words time to steady state with respect to efficacy was considered to be needed given that treatment of "severe" status of disease is indicated. The MAH's reasoning for not considering a loading dose in EFC14153 can be followed and is supported. A rapid onset of action across several efficacy endpoints and in type 2 biomarkers are indicated when no load dose was given supporting that the differences that might be observed with or without loading dose are deemed not clinically relevant.

Pop PK analysis

The final pop PK dataset contained 1772 dupilumab concentrations from 377 children 6 to <12 years of age with asthma with a body weight range of 16.4 kg to 67.2 kg. In the final dataset, PK data following 300 mg q4w dose was very limited (N=2 patients in weight group of ≤30 kg, one from dupilumab treatment group and the other from placebo group of study EFC14153), which resulted in only two PK samples. The applicant provided an update using PK data following 300 mg q4w including external validation of the pop PK model. The updated data set comprises a total of 36 post-300 mg q4w treatment concentration data of dupilumab collected from 17 out of 18 patients 6 to <12 years of age exposed to dupilumab 300 mg q4w in Study LTS14424 by the PK data cut-off date of 26 May 2021. 7 post-dose samples that had dupilumab were classified below limit of quantification (BLQ). One patient was excluded from the Pop PK analysis, as dupilumab concentrations in all PK samples (collected at Week 52 and at Week 64) were BLQ. Thus the PK analysis dataset for 300 mg q4w regimen from Study LTS14424 contained 29 dupilumab concentrations from 16 children 6 to <12 years of age with asthma.

Observed trough concentrations following 300 mg q4w in LTS14424 showed that the 300 mg q4w (≤30 kg) dose regimen achieved dupilumab exposure similar to that for 200 mg q2w (≥30 kg) dose regimen in children 6 to <12 years of age with asthma. The requested external validation has been provided by the MAH. VPC plots indicate that all the observed concentrations were within in the prediction range [5th-95th] percentiles.

Overall, model diagnostics indicate no major deviations or miss-specifications.

All the fixed effect parameters and IIV terms estimated using final model estimates, were included in the 2.5th-97.5th interval calculated from the bootstrap. For the power coefficients of weight on Ke and V2, these intervals however are very broad. A sensitivity analysis, where the final Pop PK model was compared with a Pop PK model without considering weight effect on V2 and Ke. The results showed

that inclusion of weight effect on V2 and Ke resulted in a reduction in inter-individual variability, from 25.5% to 16.2% for V2 and from 34.6% to 25.4% for Ke. This is expected, as weight has been found as predictive covariate on PK for dupilumab and other mabs. However, as the pop PK model is used for exposure prediction regarding a paediatric subgroup, it is of importance to adequately include weight effects on PK.

The applicant was also asked to provide a comparison of pop PK modelling using a 2 compartment model, assuming non-linear clearance and a parameterization with CL and V instead of Ke. Model performance and diagnostics should be compared assuming fix allometry (0.75 for CL, 1 for V), estimated allometric exponents, as well as with the selected final pop PK model. To address the raised issue on pop PK model structure, the MAH provided a comparison of PK parameter estimates in different Pop PK models, including selected final asthma Pop PK model in children 6 to <12 years of age (Model 1), asthma Pop PK model using parameter CL instead of Ke (Model 3), and asthma Pop PK model using parameter CL and fixed allometry for CL and V2 (Model 4).

Weight effects on Ke, CL, respectively and volumes of distribution were compared. As weight effect on Vmax was fixed, and scaling of V3 and Q was not considered and or not provided in the Table of parameter estimates, the comparison is expected to be biased. Nevertheless, estimated influence of weight on V2 is comparable, regardless of the way of model parameterization, and a prominent influence of weight on Clearance (CL, Ke) is indicated in the data (1772 concentrations from 377 patients) used for building the model over a wide weight range (16.4-67.2 kg), as reflected in the estimated allometric exponents.

It is agreed, that the primary conclusions from the model would be similar, regardless of the way of model parameterization.

No significant bias in fit when examined across the predicted concentration range and the time after dose could be detected from GOF plots. Nevertheless, PK data is indicated to be highly variably.

The results of the VPC showed that a large majority of the observed concentrations were within in the prediction range [5th-95th percentiles] and a few concentration points outside of the percentile range appeared to distribute evenly on either side. The applicant was asked to provide VPC plots stratified by dosing regimens which were provided accordingly. A large majority of the observed concentrations were within the prediction range [5th-95th percentiles] for both dosing regimens.

BLQ data: The applicant was asked to state the number of <LLOQ data and respective % of total number of PK samples per dose. The exclusion of <LLOQ samples while using the pop PK model for the 300 mg Q4W regimen was acknowledged. An even greater range in exposure and potential increase in <LLOQ samples for paediatric patients at higher weight due to the extended dosing interval was expected. However, given the lack of influence of exclusion of BLQ values on PK parameter estimates and a similar percentage of BLQ values in children across dose regimens and across AD and asthma populations, no meaningful impact is expected on the predicted 300 mg q4w PK exposures with the final selected Pop PK model in children 6 to <12 years of age with asthma.

The number of BLQ values has been provided. There were 465 (267 pre-first dose and 198 post-first dose) out of 2250 concentrations (20.7%) in the dataset from the two clinical studies EFC14153 (completed) and LTS14424 (PK cut-off date of 18 August 2020) used for Pop PK model development in children 6 to <12 years of age with asthma. Out of these BLQ data, 120 and 345 records were from 100 mg q2w and 200 mg q2w regimens, respectively. For these data, M3 likelihood-based method was used to evaluate the influence of excluding BLQ observations on final Pop PK model performance and the results revealed that there were no appreciable changes in parameter estimates. The use of this method is supported.

For the 300 mg q4w regimen, the percentage of BLQ values was 21.1% (124/588 samples), which is deemed comparable with 22.0% (67/305 samples), 21.0% (60/286 samples), as observed for the dosing regimens 100 mg q2w (<30 kg) and 200 mg q2w (≥30 kg); as well as with the 6-<12 years of age population with asthma (% BLQ: 19.4% following 300 mg q4w, Study LTS14424).

Special populations

Prominent impact of weight on PK parameters (linear, non-linear clearance and volume of distribution) and consequently on exposure in each weight category (15-30 kg, 30-60 kg) was observed.

Weight effect on steady-state exposure was presented for 100 mg q2w and 200 mg q2w regimens considering median weight, and p5 and p95 weight percentiles. The applicant was asked to complement with expected exposure following 300 mg q4w for both weight categories, which has been provided accordingly.

Pharmacodynamics

Dupilumab has been shown to consistently induce a rapid and sustained reduction in FeNO and TARC, as well as a progressive reduction of total IgE.

Post-treatment biomarker data were limited to only a small number of patients of study EFC14153, as most participants switched to the LTS14424 study and were only reported for FeNO. A sustained effect on FeNO levels after dupilumab treatment discontinuation was not observed.

Immunogenicity

The ADA response in children with asthma was low and consistent with that observed in children with AD of the same age group and at the same dupilumab dose. It was further consistent across age groups in patients with asthma.

Moreover, immunogenicity data across all dosing regimens were in general similar.

PK/PD and exposure-response

The relationship between pre-bronchodilator FEV1pp (change from baseline at Week 12) and functional dupilumab Ctrough at Week 12, and the exposure-response relationships between severe exacerbation (annualized event rate) and average concentration (C average) over the event observation period, were best described by a log-linear model.

Results indicate the trend in lower predicted range in effect. Observed variability in results in terms of 95% CI is larger.

No definite exposure-response relationship with respect to safety was provided. Given the acceptable safety profile and exposure predicted to be lower than that at the highest dose tested (300 mg qw in adults), this is acceptable.

2.6.4. Conclusions on clinical pharmacology

Phase 3 PK data are deemed sufficient to characterize the pharmacokinetics following 100 mg q2w and 200 mg q2w of dupilumab in the proposed indication.

A pop PK analysis was conducted using pooled data from the Phase 3 studies in children 6 to <12 years of age with asthma to characterize dupilumab PK, compare exposure between indication (Asthma vs AD) and across age groups, and assess the influence of extrinsic and intrinsic factors on dupilumab PK variability. In addition, this model was used to simulate dupilumab concentrations over time for the

alternative regimen of 300 mg q4w in children 6 to <12 years of age with asthma, for which PK data were very few (N=2 subjects and PK samples in total).

Overall, model diagnostics indicate no mayor deviations or miss-specifications. Nevertheless, PK data is indicated to be highly variably.

With regard to pharmacodynamics, the treatment effect of dupilumab has been shown on type 2 inflammation biomarkers serum IgE, serum TARC, and the FeNO. This is supported by PK/PD and E-R analyses in terms of reduction in severe exacerbation rate and improvement in percent predicted FEV1 change from baseline for both the 100 mg q2w and 200 mg q2w dose regimens in children 6 to <12 years of age with asthma.

Off-treatment results for FeNO revealed no sustained effect of dupilumab on this type 2 biomarker.

With regard to immunogenicity, the ADA response in children with asthma was low and consistent with that observed in children with AD of the same age group and at the same dupilumab dose. It was further consistent across age groups in patients with asthma. Moreover, immunogenicity data across all dosing regimens were in general similar.

The clinical pharmacology properties are considered sufficiently characterised and reflected in section 5.2. of the SmPC.

2.6.5. Clinical efficacy

2.6.5.1. Main study

EFC14153 (VOYAGE)

- **Study design**

Study EFC14153 was a 52-week randomized, double-blind, placebo-controlled, parallel-group study in children 6 to <12 years of age with a physician diagnosis of persistent uncontrolled asthma for ≥12 months prior to screening, based on the GINA 2015 Guidelines.

- **Study Participants**

Main Inclusion criteria

1. Children 6 to <12 years of age, with a 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 second a controller medication (ie, LABA, LTRA, LAMA, or methylxanthines) or high-dose ICS alone or high-dose ICS with second controller, for at least 3 months with a stable dose ⩾1 month prior to Screening Visit 1

- Pre-bronchodilator forced expiratory volume in 1 second (FEV1) ⩽95% of predicted normal or pre-bronchodilator FEV1/forced vital capacity (FVC) ratio <0.85 at screening and baseline visits.

- 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 patient).

- Must have experienced, within 1 year prior to screening Visit 1, defined as any of the following events:

a) Treatment with a systemic corticosteroid (SCS, oral or parenteral) prescribed by a healthcare professional for worsening asthma at least once or,

b) 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:

c) Asthma Control Questionnaire 5-item version Interviewer Administered (ACQ-5-IA) score ⩾ 1.5 on at least one day of the screening period including Visit 2.

d) Use of reliever medication (ie, 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.

e) Sleep awakening due to asthma that required the use of reliever medication at least once during the screening period.

f) Asthma symptoms 3 or more days/week on at least one week during the screening period.

2. Willing and able to comply with clinic visits and study-related procedures.

3. With parent(s)/caregiver(s)/legal guardian(s) able to understand the study requirements.

4. Patients ⩾6 years of age (or above an age determined by the Institutional Review Board [IRB]/Independent Ethics Committee [IEC] and in accordance with the local regulations snd requirements) must provide written informed assent, and their parent(s)/caregiver(s)/legal guardian(s) must provide written informed consent.

Main exclusion criteria:

1. Patients <6 or ⩾12 years of age

2. Patients <16 kg body weight

3. Any other chronic lung disease (cystic fibrosis, bronchopulmonary dysplasia, etc) which may impair lung function.

4. A subject with any history of life-threatening asthma (eg, requiring intubation)

5. Co-morbid disease that might interfere with the evaluation of investigational medicinal product (IMP)

6. History of malignancy of any kind.

7. Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to Visit 1 or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease (eg, 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.

8. 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.

9. 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.

10. Diagnosed with active parasitic infection (helminths); suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

11. History of human immunodeficiency virus (HIV) infection or positive HIV serology at Visit 1.

- **Treatments**

-dupilumab 100 mg Q2W for children ≤30 kg or
-dupilumab 200 mg Q2W for children >30 kg
in combination with medium- or high-dose ICS and a second controller (ie, LABA, LTRA, LAMA, or methylxanthines) or with high-dose ICS alone
-matching placebo

- **Objectives**

Primary objectives
- To evaluate the efficacy of dupilumab in children 6 to <12 years of age with uncontrolled persistent asthma.

Secondary objectives
- To assess the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab in improving patient-reported outcomes (PROs) including health-related quality of life (HRQoL).
-To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies
-To evaluate the association between dupilumab treatment and paediatric immune responses to vaccines: any vaccination for tetanus, diphtheria, pertussis and/or seasonal trivalent/quadrivalent influenza vaccine.

- **Outcomes/endpoints**

The primary endpoint was the annualized rate of severe exacerbation events during the 52-week treatment period.
A severe exacerbation event was defined as a deterioration of asthma requiring:
-Use of SCS for ≥3 days; or,
-Hospitalization or emergency room visit because of asthma, requiring SCS.
Two events were considered as different if the interval between their start dates was ≥28 days.
The annualized rate of severe exacerbation events during the 52-week treatment period was defined as the number of severe exacerbation events with onset during the 52-week treatment period per patient-year.

The key secondary endpoint was the change from baseline in percent predicted pre-BD FEV1 at Week 12.

Other secondary endpoints were as follows:

• Change from baseline in percent predicted pre-BD FEV1 at Weeks 2, 4, 8, 24, 36, and 52 and other time points assessed.
• Time to first severe exacerbation event during 52-week treatment period.
• Time to first LOAC event during 52-week treatment period.
• Change from baseline in other lung function measurements (absolute and relative FEV1, AM/PM peak expiratory flow, FVC, forced expiratory flow (FEF) 25-75%, post-bronchodilator percent predicted FEV1) at Weeks 2, 4, 8, 12, 24, 36, 52, and other time points assessed.
• Effect of dupilumab on healthcare resource utilization (HCRU)
• Change from baseline at Weeks 2, 4, 8, 12, 24, 36, and 52 and other timepoints in:
- Morning/evening asthma symptom score (electronic diary)
- ACQ-7-IA and ACQ-5-IA
- Use of reliever medication and of SCS
- Number of nocturnal awakenings due to asthma symptoms requiring the use of reliever medication
• Change from baseline at Weeks 12, 24, 36, 52, 64 in:
- Paediatric Asthma Quality of Life Questionnaire with Standardized Activities Interviewer Administered (PAQLQ(S)-IA) score, for children ≥7 to <12 years old at randomization Visit 2.

- **Sample size**

Overall 402 patients were planned to be randomized in a 2:1 allocation to dupilumab versus placebo. The sample size is powered for the primary endpoint of annualized rate of severe exacerbations over 52 weeks for 3 populations of interest (patients with baseline blood eosinophils ≥0.3 Giga/L, patients with baseline blood eosinophils ≥0.15 Giga/L, and Type 2 inflammatory asthma phenotype populations) tested in a hierarchical testing approach. The power calculation bases on the assumption that the number of severe exacerbations follow a negative binomial distribution.

With a 2-sided 5% significance level, the study can fulfil the following power considerations:

- Patients with Type 2 inflammatory asthma phenotype: assuming a placebo annualized severe exacerbation rate of 0.7, and a dispersion parameter of 1.5, with approximately 345 patients randomized (230 for dupilumab and 115 for matching placebo group), the study had approximately 94% power to detect a 54% relative risk reduction (ie, annualized rate of 0.322 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05 among these patients.
- 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), the study had 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 patients.
- Patients with baseline blood eosinophils ≥0.15 Giga/L: Aassuming a placebo annualized severe exacerbation rate of 0.7, and a dispersion parameter of 1.5, with approximately 327 patients randomized (218 for dupilumab and 109 for matching placebo group), the study will have approximately 93% power to detect a 54% relative risk reduction (ie, annualized rate of 0.322 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05 among these patients.

The sample size calculation assumes a linear discontinuation rate (20% at 1 year), thus the average exposure duration for patients is 0.9 year. The assumed relative risk reductions are based on the results in the Phase 3 asthma study EFC13579 (QUEST).

To achieve target sample size for each of the populations stated above, at least a total of 402 patients in the overall population (268 for dupilumab and 134 for placebo) needed to be randomized assuming approximately 86% of the randomized patients had the Type 2 inflammatory

asthma phenotype baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb), approximately 81% of the randomized patients had the baseline blood eosinophils ≥0.15 Giga/L, and approximately 64% of the randomized patients had the baseline blood eosinophils ≥0.3 Giga/L.

- **Randomisation and Blinding (masking)**

Randomization

Patients were planned to be randomized in a 2:1 randomisation ratio for dupilumab and placebo, stratified by ICS dose level at screening (medium, high), eosinophil count at screening (<0.3/≥0.3 Giga/L), and regions (Latin America vs. Eastern Europe vs. Western Countries). Randomisation was conducted centrally via an Interactive Voice Response System/Interactive Web Response system (IVRS/IWRS). This was a double-blind study. Both investigator and patients were unblended to the dose level of dupilumab 200mg/matching placebo or dupilumab 100mg/matching placebo due to different volume (1.14 mL vs. 0.67 mL).

Blinding (masking)

In case of an AE, the code was only planned to be broken in circumstances when knowledge of the IMP is required for treating the patient. Only investigators (at site level) may break the blind in an emergency unblinding transaction, no one on the study level.

- **Statistical methods**

Analyses populations

The ITT population is defined as all randomised patients. Patients were analysed according to the treatment group to which they are randomised.

Type 2 inflammatory asthma phenotype population was defined as all randomised patients with baseline blood eosinophils ≥ 0.15 Giga/L or baseline FeNO ≥20 ppb.

The baseline blood eosinophils ≥ 0.3 Giga/L population, and the baseline blood eosinophils ≥ 0.15 Giga/L population is defined as all randomised patients with this characteristic at baseline.

The baseline FeNO≥20 ppb population is defined as all randomised patients with baseline FeNO≥20 ppb.

The safety population is defined as all patients who received at least one dose or part of one dose of the IMP, analysed according to the treatment patients actually received.

Results

- **Participant flow**

Patients disposition - Randomized population

The disposition for the 2 primary efficacy populations, the full intention-to-treat (ITT) population as well as the participant flow are presented in Table 2.

	Placebo (N=135)	Dupilumab (N=273)	All (N=408)
Randomized population	135 (100%)	273 (100%)	408 (100%)
Efficacy population			
Intent-to-Treat (ITT)	135 (100%)	273 (100%)	408 (100%)
Type 2 inflammatory asthma phenotype[a]	114 (84.4%)	236 (86.4%)	350 (85.8%)
Baseline blood eosinophils ≥0.3 Giga/L	84 (62.2%)	175 (64.1%)	259 (63.5%)
Baseline blood eosinophils ≥0.15 Giga/L	108 (80.0%)	223 (81.7%)	331 (81.1%)
Baseline FeNO ≥20 ppb	62 (45.9%)	141 (51.6%)	203 (49.8%)
Safety population	134	271	405
PK population	0	270	270
ADA population	133	269	402

Note: For the safety, PK and ADA population, patients are tabulated according to treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment
[a] Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.
PGM=PRODOPS/SAR231893/EFC14153/CSR/REPORT/PGM/dis_populations_i_t.sas OUT=REPORT/OUTPUT/dis_populations_i_t_i.rtf (26NOV2020 - 2:37)

Table 2: Analysis population – ITT population

- **Recruitment**

Study Initiation Date (first patient enrolled): 21 April 2017

Cut-off date for Clinical Study Report (EFC14153): 26 August 2020

Cut-off date for Clinical Study Report LTS14424: 18 August 2020 (interim analysis).

- **Baseline data**

Demographics and patient characteristics

Demographics and patient characteristics at baseline were balanced among the treatment groups and were similar across all 4 populations identified by baseline type 2 biomarkers, as well as the ITT population. In the population with type 2 inflammatory asthma phenotype, the mean (standard deviation [SD]) age of the patients was 8.9 (1.6) years, 65.7% were males, and the majority of patients (88.6%) were Caucasian/White. There were 32.0% of patients with weight ≤30 kg and 68.0% of patients with weight >30 kg at baseline.
In the population with baseline blood eosinophil ≥0.3 Giga/L, the mean (SD) age of the patients was 9.0 (1.6) years, 67.2% were males, and the majority of patients (87.3%) were Caucasian/White. There were 32.4% of patients with weight ≤30 kg and 67.6% of patients with weight >30 kg at baseline.

Disease characteristics at baseline

The disease characteristics for the other populations defined by type 2 inflammatory biomarkers as well as the ITT population (cf. CSR) were overall similar to the primary populations.

In the type 2 inflammatory asthma phenotype population, baseline disease characteristics were well balanced between treatment arms. The mean (SD) age at onset of asthma was 3.4 (2.6) years. At baseline, 43.4% of patients were on high dose ICS, 55.7% were on medium dose ICS (plus 1 additional controller), and 0.9% of patients were on low dose ICS (in violation of the protocol). The mean number of severe asthma exacerbations in the prior year was 2.47. The mean pre-BD FEV1 was 1.49 L and the mean percent predicted pre-BD FEV1 was 77.89%, with 50.0% of patients having a percent predicted pre-BD FEV1 <80%. The mean baseline FEV1 reversibility was 19.61% in the population overall and numerically greater in the dupilumab group compared to the placebo group (21.47% versus 15.81%). The enrolled population had evidence of uncontrolled asthma including a mean ACQ-7-IA total score of 2.14 . The majority of patients (94.0%) reported having an ongoing comorbid atopic disease, including 82.6% with allergic rhinitis and 38.9% with atopic dermatitis. The baseline disease characteristics were similar in the populations defined by baseline blood eosinophil ≥0.3 Giga/L.

Baseline biomarkers

In the population with the type 2 inflammatory asthma phenotype, the mean baseline level of biomarkers, including blood eosinophils, serum total IgE, serum thymus and activation-regulated chemokine (TARC), and FeNO, were balanced between treatment groups and were elevated. The mean eosinophil count at baseline was 0.57 Giga/L (median: 0.49 Giga/L), the mean FeNO was 30.71 ppb (median: 24 ppb), and the mean serum total IgE at baseline was 905.52 IU/mL (median: 483.00 IU/mL).
Overall, 259 (74.0%) patients had baseline eosinophil counts ≥0.3 Giga/L, 331 (94.6%) patients had baseline eosinophil counts ≥0.15 Giga/L, and 203 (58.0%) patients had baseline FeNO ≥20 ppb.

In the population with baseline blood eosinophils ≥0.3 Giga/L, the baseline type 2 inflammatory biomarkers were as expected numerically higher than the population with the type 2 inflammatory asthma phenotype. The mean eosinophil count at baseline was 0.71 Giga/L (median:0.62 Giga/L), the mean FeNO was 33.50 ppb (median: 27 ppb), and the mean serum total IgE at baseline was 1077.00 IU/mL (median: 586.00 IU/mL). Overall, 166 (64.1%) patients had baseline FeNO ≥20 ppb.

Background medication

All patients were receiving background asthma controller therapy at stable doses at study entry and continued with these medications throughout the study.
In the population with the type 2 inflammatory asthma phenotype, there were 43.4% of patients on high-dose ICS and 55.7% were on medium-dose ICS.
In the population with baseline blood eosinophils ⩾0.3 Giga/L, there were 44.4% of patients on high-dose ICS and 54.4% on medium-dose ICS. Most of the patients (84.9% and 83.8.% in the populations with the type 2 inflammatory asthma phenotype and with baseline blood eosinophils ⩾0.3 Giga/L, respectively) received ICS in combination with LABA, a small number of patients received high dose ICS alone (2.6% and 2.3%, respectively).

- **Numbers analysed**

The 2 primary efficacy populations consisted of the population with the type 2 inflammatory asthma phenotype, which was comprised of 350 patients and accounted for 85.8% of the ITT population, and the population with baseline blood eosinophils ≥0.3 Giga/L, which was comprised of 259 patients and accounted for 63.5% of the ITT population. The 2 other efficacy populations of interest consisted of the population with baseline blood eosinophils ≥0.15 Giga/L, which was comprised of 331 patients and accounted for 81.1% of the ITT population, and the population with baseline FeNO ≥20 ppb, which was comprised of 203 patients and accounted for 49.8% of the ITT population. In the population with baseline FeNO ≥20 ppb, the

majority of patients (184 [90.6%]) had baseline blood eosinophils ≥0.15 Giga/L and 19 (9.4%) had baseline blood eosinophils <0.15 Giga/L. The population with baseline blood eosinophils ≥0.3 Giga/L accounted for 74.0% of the type 2 inflammatory asthma phenotype population. The population with baseline blood eosinophils≥0.15 Giga/L accounted for the majority (94.6%) of the type 2 inflammatory asthma phenotype population, and the population with baseline FeNO ≥20 ppb constituted 58.0% of the type 2 inflammatory asthma phenotype population.

- **Outcomes and estimation**

Primary efficacy endpoint - Annualized rate of severe asthma exacerbation events

In the population with the type 2 inflammatory asthma phenotype, the adjusted annualized rate of severe asthma exacerbation events during the 52-week treatment period was lower in the dupilumab group compared with placebo group (0.305 and 0.748, respectively). The relative risk reduction versus placebo was 59.3% (p <0.0001). The percentage of patients who remained free of severe asthma exacerbation events during the 52-week treatment period was greater for patients in the dupilumab group in comparison with the placebo group (77.1% and 59.6%, respectively). Among the patients who had at least one severe asthma exacerbation, a lower percentage of patients in the dupilumab group had multiple exacerbations compared with the placebo group.

In the population with baseline blood eosinophils ≥0.3 Giga/L, the adjusted annualized rate of severe asthma exacerbation events during the 52-week treatment period was lower in the dupilumab group compared with placebo group (0.235 and 0.665, respectively). The relative risk reduction versus placebo was 64.7% (p <0.0001). The percentage of patients who remained free of severe asthma exacerbation events during the 52-week treatment period was greater for patients in the dupilumab group in comparison with the placebo group (78.9% and 58.3%, respectively). Among the patients who had at least one severe asthma exacerbation, a lower percentage of patients in the dupilumab group had multiple exacerbations compared with the placebo group.

This same pattern was observed in populations identified on the basis of individual markers of type 2 inflammation.

The relative risk in annualized rate of severe exacerbation events during the 52-week treatment is shown for all 5 efficacy populations in Figure 1.

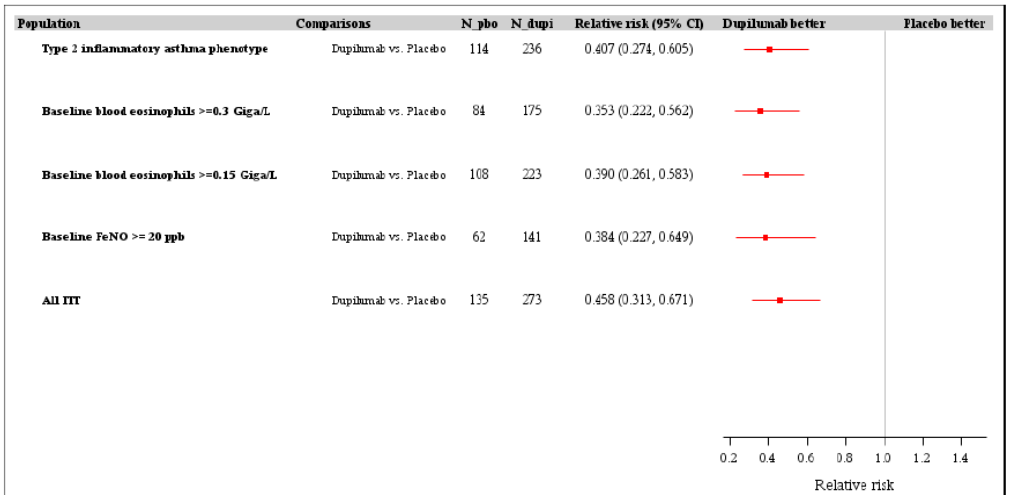


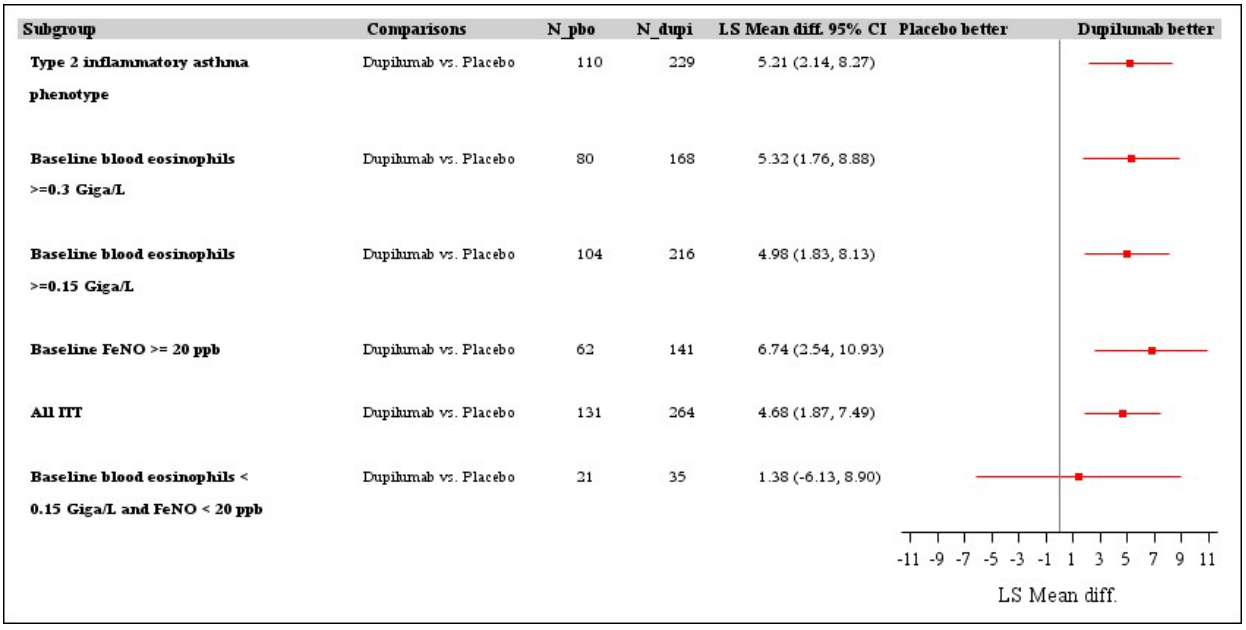
Figure 1: Forest plot of relative risk in annualized rate of severe exacerbation events during the 52-week treatment by different populations by biomarkers

Key secondary efficacy endpoint - Change from baseline in percent predicted pre-bronchodilator FEV1 at Week 12

In the population with the type 2 inflammatory asthma phenotype, the least square (LS) mean change from baseline in percent predicted pre-BD FEV1 at Week 12 was 10.53% in the dupilumab group versus 5.32% in the placebo group; the difference was statistically significant (5.21%, [95% CI:2.14, 8.27%], p=0.0009) (Figure 2). The least square (LS) mean change in percent predicted pre-BD FEV1 from baseline to Week 52 was 12.15% in the dupilumab group and 4.36% in the placebo group, resulting in an LS mean difference versus placebo of 7.79% (nominal p <0.0001).

In the population with baseline blood eosinophils ≥0.3 Giga/L, the LS mean change from baseline in percent predicted pre-BD FEV1 at Week 12 was 10.15% in the dupilumab group versus 4.83% in the placebo group; the difference was statistically significant (5.32%, [95% CI: 1.76, 8.88%], p=0.0036) (Figure 2). The LS mean change in percent predicted pre-BD FEV1 from baseline to Week 52 was 12.43% in the dupilumab group and 4.08% in the placebo group, resulting in an LS mean difference versus placebo of 8.35% (nominal p=0.0001).

In contrast, in the population with both baseline blood eosinophils <0.15 Giga/L and baseline FeNO <20 ppb, the LS mean difference between dupilumab versus placebo in percent predicted pre-BD FEV1 at Week 12 was not clinically meaningful (1.38% [95% CI: -6.13, 8.90]) (Figure 2).



Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.

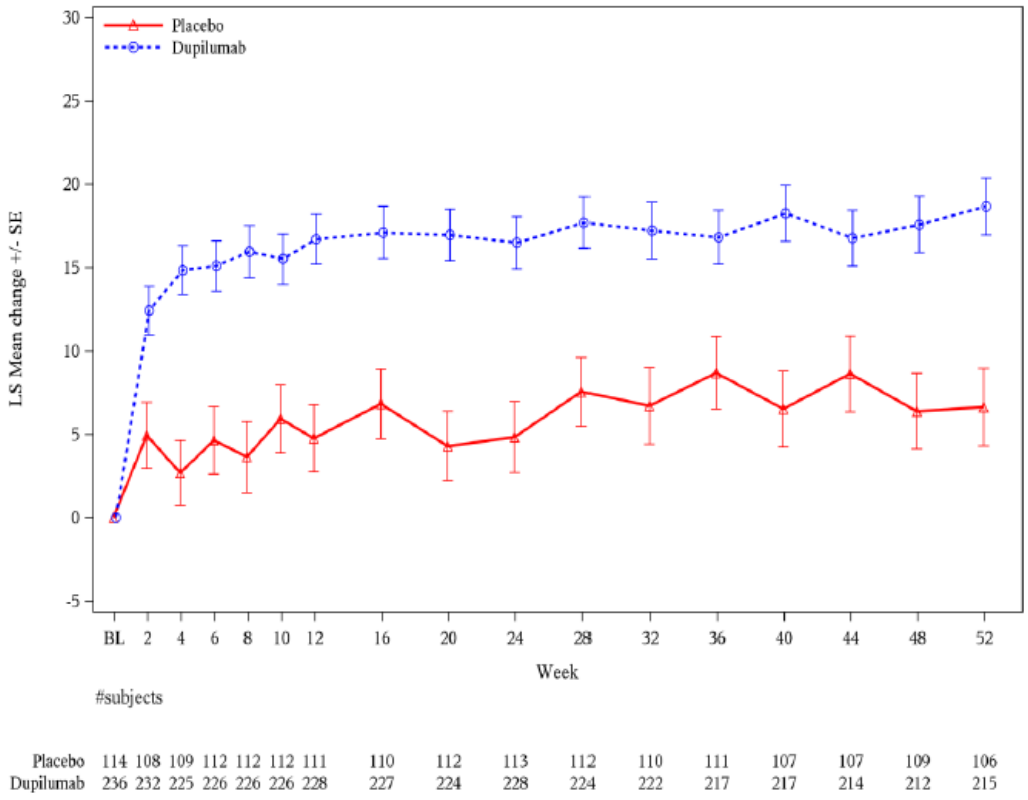
Figure 2 - Forest plot of summary of change from baseline in Pre-bronchodilator % predicted FEV1 at Week 12 different populations of EFC14153 study

Supportive analyses to key secondary endpoint: Other lung function measurements
Further parameters that were analysed regarding the treatment effect on lung function were the mean (SD) baseline absolute pre-BD FEV1 (L), percent predicted post-BD FEV1, in forced vital capacity (FVC); and in forced expiratory flow (FEF) 25-75%.

During treatment period, pre-BD FEV1 (L) of patients with type 2 inflammatory asthma phenotype improved with an LS mean change from baseline at Week 12 of 0.22 L in the dupilumab group and 0.12 L in the placebo group, and an LS mean difference versus placebo of 0.10 L ([95% CI: 0.04, 0.16], nominal p=0.0012). The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at Week 52 of 0.17 L ([95% CI: 0.09, 0.24], nominal <0.0001).

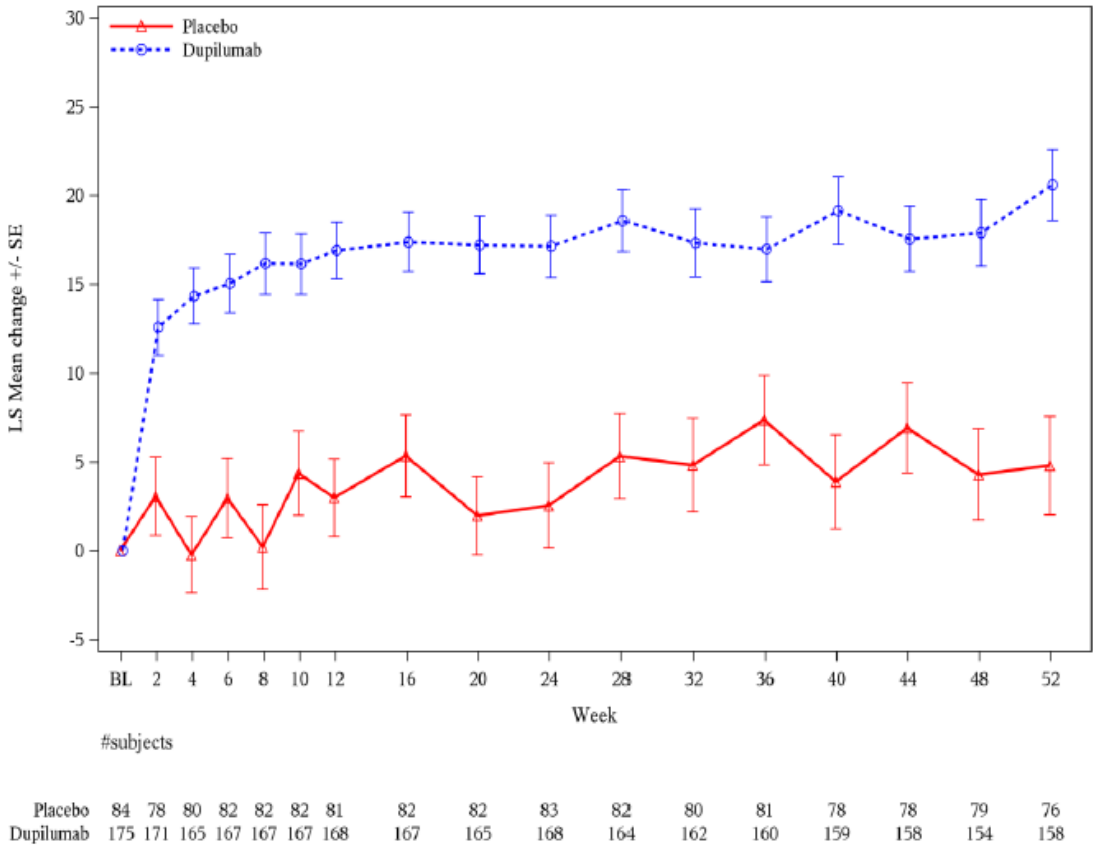
In the population with baseline blood eosinophils ≥0.3 Giga/L, the LS mean change from baseline at Week 12 was 0.22 L in the dupilumab group and 0.12 L in the placebo group, with an LS mean difference versus placebo of 0.10 L ([95% CI: 0.03, 0.17], nominal p=0.0042). The treatment effect was sustained over the 52-week treatment period, with an LS mean difference versus placebo at Week 52 of 0.17 L ([95% CI: 0.09, 0.26], nominal p=0.0001).

Improvements in predicted post-BD FEV1, forced vital capacity (FVC), and in forced expiratory flow (FEF) 25-75% (see. Fig. 4, 5) were observed in both primary efficacy populations.
There was no difference versus placebo for the endpoint of change from baseline in FVC across these populations, nor for morning or evening peak expiratory flow (PEF) over time.



BL=Baseline
Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.

Figure 3: Plot of LS mean change from baseline in % predicted FEF25-75% over time (MMRM including measurements up to week 52) – Type 2 inflammatory asthma phenotype population – Study EFC14153

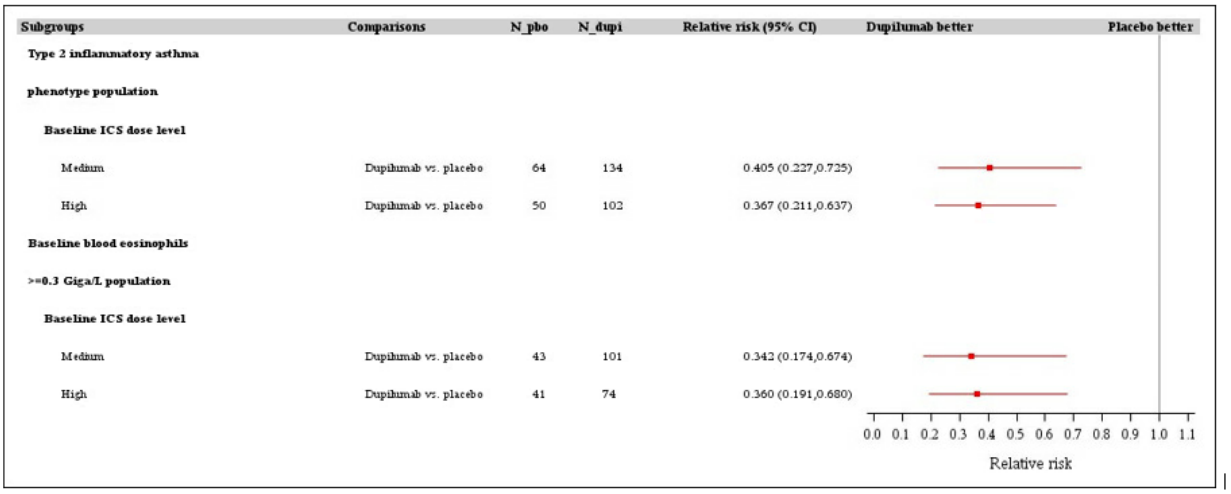


BL =Baseline

Figure 4: Plot of LS mean change from baseline in % predicted FEF25-75% over time (MMRM including measurements up to week 52) – Baseline blood eosinophils ≥0.3 G/L population - Study EFC14153

Efficacy within subgroups defined by baseline ICS dose

Among the patients treated with high-dose ICS at baseline, dupilumab led to a 63.3% (p=0.0004) and 64.0% (p=0.0019) reduction compared to placebo at Week 52 in the annualized rate of severe asthma exacerbation events for the population with type 2 inflammatory asthma phenotype and the population with baseline blood eosinophils ≥0.3 Giga/L, respectively (Figure 5). A similar magnitude of reduction in severe asthma exacerbations was observed for the populations with baseline blood eosinophils ≥0.15 Giga/L, the population with baseline FeNO ≥20 ppb, and the ITT population. Among the patients treated with medium-dose ICS at baseline, dupilumab led to a 59.5% (nominal p=0.0025) and 65.8% (nominal p=0.0021) reduction compared to placebo at Week 52 in the annualized rate of severe asthma exacerbation events for the population with type 2 inflammatory asthma phenotype and the population with baseline blood eosinophils ≥0.3 Giga/L, respectively (Figure 5).



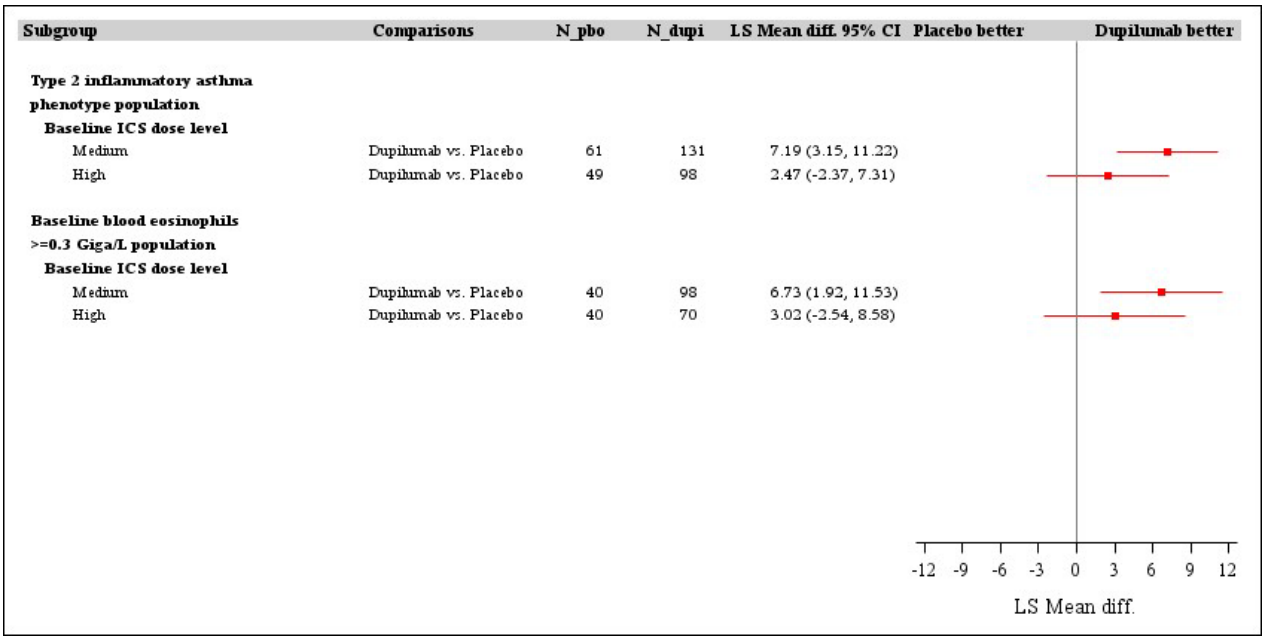
Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.

Figure 5 - Subgroup analysis: Forest plot of relative risk in annualized rate of severe exacerbation during the 52-week treatment period by baseline ICS dose level -Type 2 inflammatory asthma phenotype and baseline blood eosinophils >=0.3 Giga/L populations - Study EFC14153

Effect on percent predicted pre-bronchodilator FEV1 in patients on high- or medium-dose ICS at baseline

Among the high-dose ICS subgroups, the percent predicted pre-BD FEV1 in the dupilumab and placebo groups improved over time, and the dupilumab group had a numerically greater improvement in lung function, but this was not significantly different between the dupilumab group compared to the placebo group at Week 12. Among patients in the type 2 inflammatory asthma phenotype population on high-dose ICS at baseline, dupilumab led to an LS mean difference versus placebo of 2.47% (nominal p=0.3152) in the percent predicted pre-BD FEV1 at Week 12, and of 5.70% (nominal p=0.0180) at Week 52. In the population with baseline blood eosinophil ≥0.3 Giga/L dupilumab led to an LS mean difference versus placebo of 3.02% (nominal p=0.2843) in the percent predicted pre-BD FEV1 at Week 12, and of 6.48% (nominal p=0.0203) at Week 52.

In the medium-dose ICS subgroup, there was a nominally significant and clinically meaningful improvement in the percent predicted pre-BD FEV1 in the dupilumab groups compared to placebo. For the population with the type 2 inflammatory asthma phenotype, the LS mean difference in the percent predicted pre-BD FEV1 versus placebo at Week 12 was 7.19% (nominal p=0.0006). For the population with baseline blood eosinophil ≥0.3 Giga/L, the LS mean difference in the percent predicted pre-BD FEV1 versus placebo at Week 12 was 6.73% (nominal p=0.0064) (Figure 6).



Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils

Figure 6 - Subgroup Analysis: Forest plot of summary of change from baseline in pre-bronchodilator % predicted FEV1 at Week 12 by Baseline ICS dose level -Type 2 inflammatory asthma phenotype and Baseline eosinophils >=0.3 Giga/L populations - Study EFC14153

2.6.5.2. *Subgroup analyses based on markers of Type 2 inflammation*

In order to evaluate the independent role of either biomarker to appropriately select patients aged 6 to <12 years old that would respond to dupilumab, additional subgroup analyses were performed.

Biomarker subgroup analysis

To further support the ability of either blood eosinophils or FeNO to identify dupilumab responders in a reliable and independent manner, the following analyses were performed:
• Prespecified biomarker subgroup analyses, to evaluate the response within categories of baseline biomarker level
• Prespecified treatment-by-biomarker interaction testing, to evaluate the strength of the statistical evidence supporting the independent role of individual baseline biomarker level for the observed differences in treatment effect
• Prespecified quadrant analyses, to descriptively demonstrate that elevated biomarkers of type 2 inflammation as measured by either elevated blood eosinophils and/or FeNO predict efficacy
• Post-hoc penalized spline regression model analysis to explore the association between exacerbations or percent predicted pre-BD FEV1 and continuous baseline biomarker level in dupilumab and placebo arms
• Post-hoc evaluation of the correlation of blood eosinophils or FeNO over time in the placebo-exposed population to explore the stability of these biomarkers in a population with moderate-to-severe asthma

Treatment effect by baseline type 2 biomarkers

The effect of dupilumab on the annualized rate of severe exacerbation events and on the change from baseline in percent predicted pre-BD FEV1 at Week 12 was analyzed in the ITT population across subgroups defined by baseline type 2 biomarker level, including blood eosinophils (<0.15 Giga/L, ≥0.15-0.3 Giga/L, ≥0.3-0.5 Giga/L, and ≥0.5 Giga/L) and FeNO (<20 ppb and ≥20 ppb). Baseline

levels of blood eosinophils or FeNO independently predicted the magnitude of response to dupilumab for both exacerbation reduction and lung function improvement.
For exacerbation reduction, subgroup analyses by baseline blood eosinophils showed a clinically meaningful exacerbation reduction compared to placebo for all subgroups with baseline blood eosinophils ≥0.15 Giga/L and for both subgroups defined by baseline FeNO. The magnitude of response increased with increasing baseline blood eosinophil or FeNO level. There was no meaningful treatment effect in annualized rate of severe exacerbation events for the subgroup with baseline blood eosinophils <0.15 Giga/L. The efficacy observed in the population with baseline FeNO <20 ppb was likely driven by patients with baseline eosinophils ≥0.15 Giga/L, which, because of the recruitment cap on patients with blood eosinophils <0.15 Giga/L, accounted for 90.6% of patients in the FeNO <20 ppb subgroup.
For lung function improvement, dupilumab showed a consistent improvement in the percent predicted pre-BD FEV1 compared to placebo across all subgroups defined by baseline blood eosinophils, with the greatest magnitude of effect observed in patients with baseline blood eosinophils ≥0.5 Giga/L. There was a nominally significant improvement in lung function for the population with baseline FeNO ≥20 ppb, and no meaningful change observed in the population with baseline FeNO <20 ppb (see Figure 7 and Figure 8).

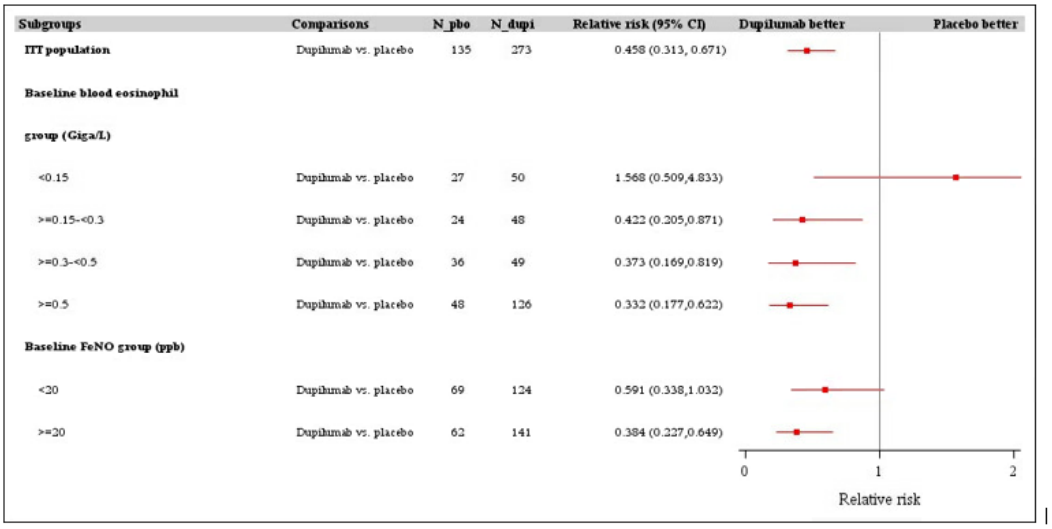


Figure 7: Subgroup analysis: Forest plot of relative risk in annualised event rate of severe exacerbation by baseline biomarker – ITT population – Study 14153

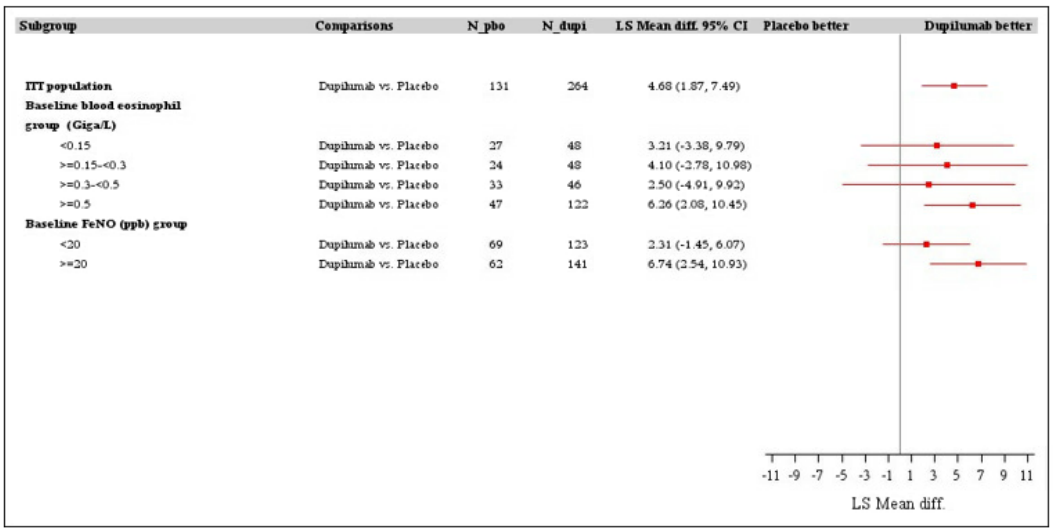


Figure 8: Subgroup analysis: Forest plot of change from baseline in pre-brochodilator % predicted FEV1 at week 12 by baseline biomarker – ITT population - Study 14153

Summary of efficacy by type 2 biomarkers

Taken together, this set of analyses support the role of blood eosinophils and FeNO as independent patient selection biomarkers. Subgroup analyses demonstrate a greater magnitude of response in subgroups defined by baseline biomarker, with no meaningful exacerbation reduction observed in the population with baseline blood eosinophils <0.15 Giga/L. Despite the fact that enrollment in the paediatric population limited the proportion of patients with baseline eosinophils <0.15 Giga/L, FeNO thresholds were still able to identify subgroups with greater response to dupilumab. Interaction testing supports the independence of these biomarkers, even adjusting for baseline biomarker and treatment-by-biomarker interactions, and the independent predictive ability of these biomarkers is further supported by quadrant analyses that show similar treatment effects across populations identified by either baseline blood eosinophils ⩾0.15 Giga/L or FeNO ⩾20 ppb or both, and minimal treatment effect in populations with baseline blood eosinophils <0.15 Giga/L and FeNO <20 ppb. This concept, further visualized by spline models, showed that baseline blood eosinophils and FeNO independently predict the response to treatment. Finally, blood eosinophils and FeNO are demonstrated to be stable biomarkers in this population, with potentially greater stability demonstrated for FeNO compared to blood eosinophils.
Taken together, these data support the findings from the primary analysis showing significant and clinically meaningful treatment effects in populations defined by either blood eosinophils ⩾0.15 Giga/L or FeNO ⩾20 ppb.

- **Ancillary analyses**

Analyses of any association between ADA and efficacy

The relationship between anti-drug antibodies (ADA) and clinical response (annualized rate of severe exacerbation events and change from baseline in pre-BD FEV_1) was investigated in patients with treatment-emergent ADA responses.
As exacerbations are a highly variable endpoint, evaluation of the association between ADA and the annualized rate of severe exacerbations did not yield meaningful results.
The evaluation of the association of a treatment-emergent ADA response with the change in percent predicted pre-BD FEV_1 at Week 12 is based on a small population (17 patients in the dupilumab group and 4 patients in the placebo group). As a result, there is limited data for comparison.
In the dupilumab group, mean changes from baseline in percent predicted pre-BD FEV_1 to Week 12 were 12.29% for the ADA-positive patients (N=17) and 10.09% for the ADA-negative patients (N=248). The individual profiles of percent predicted pre-BD FEV_1 in ADA-positive patients were generally within the range observed in ADA-negative patients.

Analysis of clinical information relevant to dosing recommendations

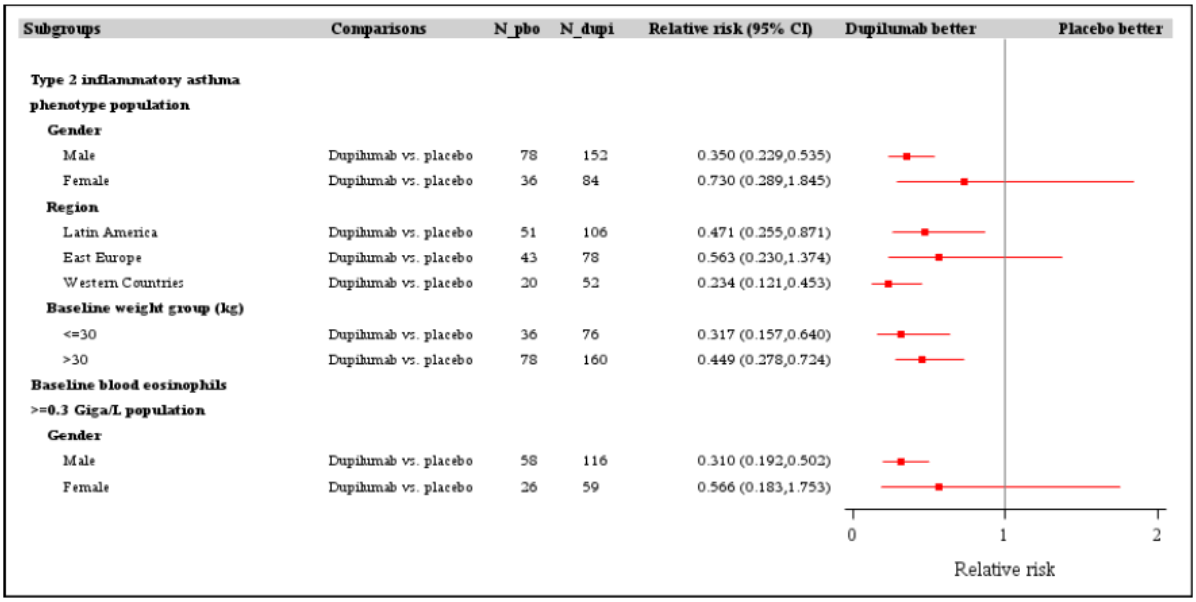
Supportive efficacy data include

The recommended dose for paediatric patients with asthma age 6 to <12 years old is:

- For patients with body weight ⩾15 to <30kg: 100 mg q2w or 300 mg q4w;
- For patients with body weight ⩾30kg to <60 kg: 200 mg q2w or 300 mg q4w;
- For patients with body weight ⩾60 kg: 200 mg q2w.

The results of the Phase 3 studies, along with supporting PK and exposure-response analyses, provide the basis for the proposed dosing regimens in children 6 to <12 years of age with

uncontrolled moderate-to-severe asthma. The 100 mg q2w and 200 mg q2w regimen is supported by observed clinical efficacy and safety. The 300 mg q4w dose is supported by population pharmacokinetic (Pop PK) and exposure-response analyses in children 6 to <12 years of age with asthma, and PK, PK/PD relationships, safety profile in adult and adolescent with asthma, as well as the acceptable safety profile for this dose regimen in children 6 to <12 years of age with AD. The 300 mg q4w dose regimen has been shown to have an acceptable safety and efficacy profile in the AD paediatric (6 to <12 year old) population and is included in the approved posology for AD.
The choice of dose options in a given weight category provides flexibility for the provider and patient, and includes an option that can reduce patient burden by reducing the frequency of injections while also providing improved consistency with AD dosing for same age/weight, which is desirable due to the high co-morbid occurrence of these conditions.
To support simplification of dosing across indications, the proposed weight threshold has been slightly adjusted from the threshold used in Study EFC14153, to be consistent with the approved posology for AD. The weight cut-offs of the proposed regimens differ from what was studied in the pivotal Study EFC14153. A minor change in the body weight cut-off (⩾15 kg to <30 kg instead of ⩾16 kg to ⩽30 kg) is proposed to be consistent with the approved posology for the AD paediatric population. This update is supported by PK simulations that show there are no meaningful differences in steady state trough concentration when using the updated threshold compared to the threshold used in the clinical trials. This minor change is not anticipated to have any impact on efficacy or safety.
Significant and clinically meaningful improvements were observed across multiple endpoints for both the 100 mg q2w dose regimen for children ⩽30 kg and the 200 mg q2w dose regimen for children >30 kg, and the magnitude of responses were similar between weight/dose groups (see Figure 9). In the population with the type 2 inflammatory asthma phenotype, the relative risk versus placebo for adjusted annualized severe exacerbation event rate in the ⩽30 kg subgroup and the >30 kg subgroup was 0.317 (95% CI: 0.157, 0.640) and 0.449 (95% CI: 0.278, 0.724), respectively. In the population with baseline blood eosinophils ⩾0.3 Giga/L, the relative risk versus placebo for adjusted annualized severe exacerbation event rate in the ⩽30 kg subgroup and the >30 kg subgroup was 0.344 (95% CI: 0.164 ,0.720) and 0.353 (95% CI: 0.196, 0.636), respectively. In the population with the type 2 inflammatory asthma phenotype, the percent predicted pre-BD FEV_1 LS mean difference from placebo in the change from baseline to Week 12 in the ⩽30 kg subgroup and the >30 kg subgroup was 6.52% (95% CI: 0.71, 12.33) and 4.47% (95% CI: 0.91, 8.03), respectively. In the population with baseline blood eosinophils ⩾0.3 Giga/L, the LS mean difference in the ⩽30 kg subgroup and the >30 kg subgroup was 7.94% (95% CI: 1.01, 14.87) and 3.94% (95% CI: -0.24, 8.12), respectively.
The introduction of the 300 mg q4w dose is supported by PK and PK/PD analyses and simulations in children 6 to <12 years of age and in adults and adolescents with asthma. Additional supportive data is provided by the descriptive efficacy of patients exposed to 300 mg q4w in Study LTS14424. This study included 14 patients aged 6 to <12 years with body weight ⩽30 kg who were exposed to 300 mg q4w for a total of 1.6 patient-years. Over the time period evaluated, these 14 patients experienced no severe asthma exacerbations and their lung function remained stable.
In summary, the results from the paediatric asthma studies together with the PK and exposure response analysis support the recommended weight tiered doses for children age 6 to <12 years with uncontrolled moderate-to-severe asthma and evidence of type 2 inflammation: for children with body weight 15 to <30 kg, 100 mg q2w or 300 mg q4w; for children with body weight 30 kg to <60 kg, 200 mg q2w or 300 mg q4w, and for children with body weight >60 kg, 200 mg q2w.



Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb
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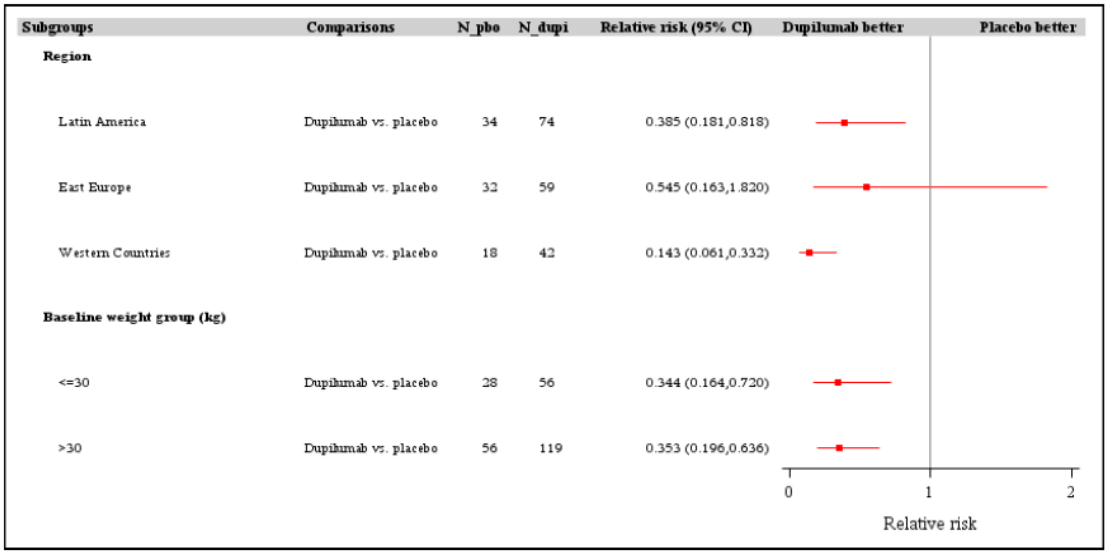
Figure 9: Subgroup analysis: Forest plot of relative risk in annualised rate of severe exacerbation events during the 52-week treatment period by demographics – Type 2 inflammatory asthma phenotype population and baseline eosinophils ≥0.3 G/L population _Study EFC14153



Type 2 inflammatory asthma phenotype population is defined as the randomized patients with baseline blood eosinophils >= 0.15 Giga/L or baseline FeNO >= 20 ppb.
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- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit-risk assessment (Table 3) (see later sections).

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 identifier	EFC14153		
Design	Multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		21 April 2017 (first patient enrolled) 26 Aug 2020 (last patient completed) not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Dupilumab		Dupilumab 100 mg q2w for children ⩽ 30 kg or Dupilumab 200 mg q2w fo children with >30 kg, 52 Weeks, 273
	Placebo		Placebo according to 100 mg or 200 mg, 52 Weeks, 135
Endpoints and definitions	Primary endpoint	Adjusted annualized rate of severe exacerbation events, Week 52	Adjusted annualized rate of severe exacerbation events during the 52 – week treatment period
	Key Secondary endpoint	Change from baseline in predicted pre-BD FEV_1 at week 12	Change from baseline in percentage predicted pre-bronchodilator (pre-BD) FEV1 at Week 12
	Secondary endpoint	ACQ-7-IA LS Mean change from baseline at week 24	Change from baseline in ACQ-7-IA Week 24

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Placebo	Dupilumab
	Patients with type 2 inflammatory asthma phenotype		
	Number of subject	114	236
	Adjusted annualized rate of severe exacerbation events	0.748	0.305
	95% CI	(0.542, 1.034)	(0.223, 0.416)
	Change from baseline in predicted pre-BD FEV1 at week 12, LS mean	5.32	10.53
	Standard error	1.36	1.01
	ACQ-7-IA LS Mean change from baseline at week 24, LS mean	-1.00	-1.33
	Standard error	0.07	0.05

	Patients with baseline blood eosinophils ⩾ 0.15 Giga/L		
	Number of subjects	108	223
	Adjusted annualized rate of severe exacerbation events	0.816	0.318
	95% CI	(0.588, 1.133)	(0.231, 0.438)
	Change from baseline in predicted pre-BD FEV1 at week 12, LS mean	5.65	10.63
	Standard error	1.42	1.05
	ACQ-7-IA LS Mean change from baseline at week 24, LS mean	-0.98	-1.33
	Standard error	0.08	0.06
	Patients with baseline blood eosinophils ⩾ 0.3 Giga/L		
	Number of subjects	84	175
	Adjusted annualized rate of severe exacerbation events	0.665	0.235
	95% CI	(0.467, 0.949)	(0.160, 0.345)
	Change from baseline in predicted pre-BD FEV1 at week 12, LS mean	4.83	10.15
	Standard error	1.54	1.12
	ACQ-7-IA LS Mean change from baseline at week 24, LS mean	-0.88	-1.34
	Standard error	0.09	0.06
	ITT population		
	Number of subject	135	273
	Adjusted annualized rate of severe exacerbation events	0.608	0.278
	95% CI	(0.447, 0.826)	(0.208, 0.372)
	Change from baseline in predicted pre-BD FEV1 at week 12, LS mean	5.17	9.85
	Standard error	1.22	0.91

Effect estimate per comparison		Comparison groups	Dupilumab vs Placebo
	Patients with type 2 inflammatory asthma phenotype		
	Adjusted annualized rate of severe exacerbation events	Relative risk	0.407
		95% CI	(0.274, 0.605)
		P-value (Order in Testing Hierarchy)	<0.0001 (1)
	Change from baseline in	LS Mean Diff	5.21

	predicted pre-BD FEV1 at week 12		
		95% CI	(2.14, 8.27)
		P-value (Order in Testing Hierarchy)	0.0009 (4)
	ACQ-7-IA LS Mean change from baseline at week 24	LS Mean Diff	-0.33
		95% CI	(-0.50, -0.16)
		P-value (Order in Testing Hierarchy)	0.0001 (7)
	Patients with baseline blood eosinophils ⩾ 0.15 Giga/L		
	Adjusted annualized rate of severe exacerbation events	Relative risk	0.390
		95% CI	(0.261, 0.583)
		P-value (Order in Testing Hierarchy)	<0.0001 (2)
	Change from baseline in predicted pre-BD FEV1 at week 12	LS Mean Diff	4.98
		95% CI	(1.83, 8.13)
		P-value (Order in Testing Hierarchy)	0.0020 (5)
	ACQ-7-IA LS Mean change from baseline at week 24	LS Mean Diff	-0.36
		95% CI	(-0.53, -0.18)
		P-value (Order in Testing Hierarchy)	<0.0001 (8)
	Patients with baseline blood eosinophils ⩾ 0.3 Giga/L		
	Adjusted annualized rate of severe exacerbation events	Relative risk	0.353
		95% CI	(0.222, 0.562)
		P-value (Order in Testing Hierarchy)	<0.0001 (3)
	Change from baseline in predicted pre-BD FEV1 at week 12	LS Mean Diff	5.32
		95% CI	(1.76, 8.88)
		P-value (Order in Testing Hierarchy)	0.0036 (6)
	ACQ-7-IA LS Mean change from baseline at week 24	LS Mean Diff	-0.46

		95% CI	(-0.67, -0.66)
		P-value (Order in Testing Hierarchy)	<0.0001 (9)
	ITT population		
	Adjusted annualized rate of severe exacerbation events	Relative risk	0.458
		95% CI	(0.313, 0.671)
		P-value (Order in Testing Hierarchy)	<0.0001 (13)
	Change from baseline in predicted pre-BD FEV1 at week 12	LS Mean Diff	4.68
		95% CI	(1.87, 7.49)
		P-value (Order in Testing Hierarchy)	0.0012 (14)
Notes	The Sponsor declares the analysis of primary and key secondary endpoints on populations with type 2 inflammatory asthma phenotype and with baseline blood eosinophil count ⩾ 0.3 Giga/L as primary efficacy analysis. However, in the hierarchical testing procedure the population of patients with baseline blood eosinophils ⩾ 0.15 Giga/L needed to be significant first in order to test the population of patients with baseline blood eosinophils ⩾ 0.3 Giga/L. In this Table all results up to order 9 plus those for the ITT population are shown. As multiplicity is controlled by hierarchical testing, all p-values can be compared with a 5 % significance level. All hypotheses tests show significant results.		

Table 3: Summary of efficacy results from the main studies

Efficacy analysis performed across trials

Study EFC13579 was a pivotal Phase 3 study that enrolled adults and adolescents with uncontrolled moderate-to-severe asthma without a minimum threshold for baseline blood eosinophil count or any other type 2 biomarkers. Efficacy was demonstrated in patients with moderate-to-severe asthma with type 2 inflammation, including patients with baseline blood eosinophils ⩾0.15 Giga/L as part of the testing hierarchy, or patients with baseline FeNO ⩾25 ppb in a prespecified analysis.

The paediatric Study EFC14153 was designed to provide confirmatory evidence that both eosinophils and FeNO can identify patients with type 2 inflammation that respond to dupilumab. The approach to using data across both studies to support FeNO in both populations comes from the understanding that type 2 inflammation is present across all age groups with asthma. This is demonstrated below by a descriptive comparison of the clinical features and magnitude of response to dupilumab between both the paediatric and adult/adolescent populations with the type 2 inflammatory asthma phenotype.
In addition to the primary efficacy evaluation, additional analyses were conducted to demonstrate the independent role and added value of FeNO as a patient selection biomarker, using the data from Study EFC14153. These analyses show 1) the primary efficacy results from Study EFC14153 confirm the observation in Study EFC13579, that in addition to blood eosinophil counts, FeNO is an appropriate predictive biomarker; and 2) the subgroup and interaction testing from Study EFC13579 strengthen the conclusion from the similar analyses for Study EFC14153: that FeNO is an independent predictive biomarker for dupilumab response that provides added value beyond eosinophils alone.

Treatment effect in the paediatric and adolescent/adult patient population

Dupilumab reduced exacerbations in both the adult/adolescent and paediatric (aged 6 to <12 years) populations with the type 2 inflammatory asthma phenotype across both studies. The magnitude of effect was similar across both populations. In the adult/adolescent study, the exacerbation reduction was 54.2% and 57.7% in the 200 mg q2w and 300 mg q2w groups, respectively and this was 59.3% for the paediatric population. Similar patterns were observed across populations selected by individual markers of type 2 inflammation including baseline eosinophils alone (eosinophils ≥0.15 Giga/L or eosinophils ≥0.3 Giga/L) or by baseline FeNO alone (≥20 ppb in children and ≥25 ppb in adolescents and adults).

Dupilumab improved lung function in both the adult/adolescent and paediatric (aged 6 to 12 years) populations with the type 2 inflammatory asthma phenotype across both studies. Despite the higher baseline mean percent predicted pre-BD FEV1 in the paediatric population, the magnitude of improvement was consistent across both populations. In the adult/adolescent study, the LS mean difference from placebo at Week 12 in percent predicted pre-BD FEV1 was 5.41% and 4.84% for the 200 mg q2w and 300 mg q2w groups, respectively and this was 5.21% for the paediatric population. Similar patterns were observed for patients identified by baseline eosinophils alone (eosinophils ≥0.15 Giga/L or eosinophils ≥0.3 Giga/L) or by baseline FeNO alone (≥20 ppb in children and ≥25 ppb in adolescents and adults).

Supportive study LTS14424 (Open-label extension study)

- **Study period**

Date first patient enrolled: 21 June 2018 (date of first signed informed consent)
Date last patient completed: Ongoing study; cutoff date for interim analysis: 18 August 2020

- **Study design**

Study LTS14424 is an ongoing open-label, single-arm, 1-year treatment study designed to evaluate the long-term safety and tolerability of dupilumab as well as its long term efficacy, pharmacokinetic (PK), and immunogenicity in paediatric patients 6 to <12 years of age in the parent Study EFC14153 with asthma who participated in a previous dupilumab asthma study(EFC14153). The study consisted of 3 periods with a total duration of up to 64 weeks for each patient: enrollment visit, randomized treatment (52 weeks), and post-treatment follow-up (12 weeks).
In Study LTS14424, patients were treated with dupilumab with dose level assigned based on body weight (100 mg q2w or 300 mg once every 4 weeks (q4w) after amended protocol 03 for children with weight ≤30 kg; 200 mg q2w for children with weight >30 kg), in combination with medium- or high-dose ICS with a second controller or high-dose ICS alone (5.3.5.2 Study Reports of Uncontrolled Clinical Studies, Study LTS14424 [Section 8.2.1] and [Section 8.4.1]). Amended protocol 03 (12 December 2019) introduced the dose of 300 mg q4w for children with body weight ≤30 kg, which replaced the 100 mg q2w dose for all patients with weight ≤30 kg with more than 8 weeks remaining in the study. This dose was introduced in order to be proposed as an alternative, convenient option, for less frequent dosing to decrease injection burden for children with moderate-to-severe asthma. Amendment 03 followed the results from the Atopic Dermatitis (AD) 6 to <12 years study (R668-AD-1652) which evaluated both the 100 mg q2w and 300 mg
q4w doses for patients with body weight ≥15 to <30 kg. Both doses demonstrated clinical efficacy with an acceptable tolerability and safety profile. Given that the PK of dupilumab is similar across the diseases for which dupilumab is indicated (AD, asthma, CRSwNP), it was predicted that 300 mg q4w for children with body weight ≤30kg with asthma would also be safe and effective.

- **Study participants**

Number of patients: Planned: 354, Enrolled: 365 (125 in placebo-dupilumab category, 240 in dupilumab-dupilumab category), Treated: 365
Evaluated: Efficacy/Safety: 365, Pharmacokinetics (PK): 32, ADA: 320
Diagnosis and criteria for inclusion: Paediatric patients with asthma who completed the treatment in EFC14153. Of note: patients who were not able to complete their treatment in Study EFC14153 due to the COVID-19 pandemic were allowed to enroll into Study LTS14424.

- **Treatments**

Investigational medicinal product (IMP): dupilumab

Formulation: Sterile dupilumab was supplied as a 150 mg/mL solution in pre-filled syringe to deliver a single 100 mg dose via a 0.67 mL injection or a 300 mg dose via a 2 mL injection, or as a 175 mg/mL solution in pre-filled syringe to deliver a single dose of 200 mg via a 1.14 mL injection.

Route of administration: Subcutaneous (SC)

Dose regimens: Patients with body weight ≤30 kg: 100 mg SC once every 2 weeks (q2w) (prior to protocol amendment 03, dated 12 December 2019) or 300 mg SC once every 4 weeks (q4w) (after protocol amendment 03). Patients with body weight >30 kg: 200 mg SC q2w. Of note: patients who started with or switched to 200 mg q2w continued the same dose regimen through the remaining treatment period irrespective of whether they remained >30 kg or not.

Duration of treatment: 52 weeks

Duration of observation: 64 weeks, including a 52-week treatment period and a 12-week follow-up period.

- **Objectives**

Primary objective:

- To evaluate the long-term safety and tolerability of dupilumab in paediatric patients with asthma who participated in a previous dupilumab asthma clinical study (EFC14153).

Secondary objectives:

- To evaluate the long-term efficacy of dupilumab in paediatric patients with asthma who participated in a dupilumab in paediatric patients with asthma clinical study,
- To evaluate dupilumab in paediatric patients with asthma who participated in a previous dupilumab asthma clinical study with regard to systemic exposure, anti-drug antibodies (ADAs), and biomarkers.

- **Outcome/endpoints**

Efficacy:

- Annualized rate of severe asthma exacerbation events during the treatment period.
- Change in mean percent (%) predicted pre-bronchodilator (pre-BD) forced expiratory volume in 1 second (FEV1) and other pre-BD lung function parameters (absolute FEV1, forced vital capacity [FVC], forced expiratory flow 25% to 75% [FEF25-75%]) from baseline at study time points assessed.

Safety: The primary endpoint for this study was the number (n) and percentage (%) of patients experiencing any treatment-emergent adverse events (TEAEs).

Pharmacokinetics: Serum dupilumab concentrations and ADAs

- **Statistical methods**

Analysis populations:
The primary analysis population was the safety population, which was defined as all patients exposed to at least 1 dose or part of a dose of dupilumab during the LTS14424 study regardless of the amount of treatment administered. Enrolled patients for whom it was unclear whether or not they took the IMP were included in the safety population. The efficacy population was the same as the safety population in this study.
The PK population consisted of all the patients in the safety population who had at least 1 non-missing and evaluable predose serum concentration value after the first dose of dupilumab in this study.
The ADA population consisted of all the patients in the safety population with at least 1 non-missing result in the ADA assay following the first dose of dupilumab in this study.
For each analysis population (safety, efficacy, PK, and ADA), the planned analyses were conducted in the following 2 analysis sets, respectively:
- Full analysis set: all data observed in the study. The analyses performed on the full analysis set were to evaluate the long term safety, efficacy, PK, immunogenicity, and PD of all the dose regimens that were investigated in the LTS14424 study, ie, dupilumab 100 mg q2w and 300 mg q4w for patients ≤30 kg and 200 mg q2w for patients >30 kg.
- Modified analysis set: 1) For patients never exposed to 300 mg q4w: all observed data were included, 2) For patients who switched from 100 mg q2w to 300 mg q4w in LTS14424: data were included up to the date of first dose of 300 mg q4w with censoring data observed on and after this date, 3) If any patients initiated the study on 300 mg q4w (ie, received 300 mg q4w at Week 0), no data were to be included in this analysis set. The analyses performed on the modified analysis set were to focus on the long-term safety, efficacy, PK, immunogenicity, and PD of the same regimens as the parent study, ie, dupilumab 100 mg q2w and 200 mg q2w.

Analyses:

For each analysis set, the planned analyses are presented by the treatment categories according to the actual treatment group in the parent study EFC14153.
Efficacy endpoints were all secondary endpoints in this study. All efficacy and safety analyses were descriptive and performed on the safety population for each analysis sets and presented by treatment category.

Results

Efficacy results:

The results of this study support the long-term sustained efficacy of dupilumab, when added on top of medium or high dose ICS plus another controller or ICS alone, in children 6 to <12 years with moderate to-severe uncontrolled asthma.
This report provides the results from the interim database lock for Study LTS14424, which includes data from 365 patients including 196 (53.7%) who had completed the 52-week treatment period. Patients treated with dupilumab for up to an additional year after the parent study demonstrated a low severe asthma exacerbation event rate and persistent improvement in lung function. These results were observed regardless of the treatment arm in the parent study. For those patients that rolled over from the placebo arm, there was a rapid onset of action, as demonstrated by the improvement in percent predicted FEV1 at Week 2.
Patients treated long-term with dupilumab demonstrated a low rate of severe asthma exacerbations with an unadjusted annualized event rate in the overall population of 0.134. Consistent with the low

exacerbation rate, the majority of patients did not experience any exacerbations during the study. Among the 365 patients, 336 (92.1%) had no asthma exacerbations over a mean exposure to dupilumab of 283.8 days. This low rate of severe exacerbations was observed regardless of the treatment arm in the parent study (dupilumab-dupilumab or placebo-dupilumab). The majority of exacerbations were treated with systemic
oral corticosteroids and only 1 patient required hospitalization or emergency room visit.
The low exacerbation rate was observed in the full analysis set, as well as across multiple subgroups identified by markers of type 2 inflammation, including the two primary populations from the parent study, the type 2 inflammatory asthma phenotype (0.146) and the patients with baseline blood eosinophils ≥0.3 Giga/L (0.144). The unadjusted severe exacerbation rate was similarly low across patients selected by baseline eosinophils ≥0.15 Giga/L and FeNO ≥20 ppb. The exacerbation rate was also low among subgroups defined by the use of either high dose (0.178) or medium dose (0.105) ICS at baseline of the parent study.

Dupilumab also demonstrated sustained improvement in lung function compared to the baseline of the parent study. There was a mean improvement in percent predicted FEV1 from baseline of +9.84% at Week 2 of this study, and this was maintained for the 52-week treatment period. The rapid onset in lung function improvement that was observed for dupilumab treated patients in the parent study was replicated for placebo-dupilumab patients in LTS14424. The mean change from baseline in this group was +3.64% at Week 0 and +7.89% at Week 2, and this was sustained over 52 weeks. The improvement in percent predicted FEV1 was observed in the full analysis set as well as across multiple subgroups identified by markers of type 2 inflammation, including the two primary populations from the parent study, the type 2 inflammatory
phenotype (+10.21% at Week 2) and the patients with baseline blood eosinophils ≥0.3 Giga/L (+10.77% at Week 2). There was a similar improvement across patients selected by baseline eosinophils ≥0.15 Giga/L and FeNO ≥20 ppb. The sustained improvement in percent predicted FEV1 was also observed among subgroups defined by the use of either high-dose ICS (+8.63% at Week 24) or medium-dose ICS (+10.16% at Week 24) at baseline of the parent study. There was also sustained improvement across other measures of lung function. The FEV1, FVC, and FEF25-75% continued to improve throughout the study.
There were 14 patients that were exposed to the 300 mg q4w dose for a limited cumulative exposure of 1.6 patient-years as of the cutoff date for this report. Among these patients, no severe exacerbations were reported and the lung functions remained stable.
As of the cut-off date of 25 June 2021, a total of 18 patients (8 in the placebo-dupilumab category and 10 in the dupilumab-dupilumab category) had been exposed to dupilumab 300 mg q4w for a cumulative exposure of 10.5 patient-years (mean [SD] duration of exposure: 213.9 [104.5] days). There were no severe asthma exacerbations among the 18 patients that were exposed to 300 mg q4w dose regimen. Overall, the percent predicted FEV1 remained stable for these individual patients over the timepoints evaluated after the switch to the dupilumab 300 mg q4w regimen in LTS14424.
In summary, this study supports the long-term sustained efficacy of dupilumab, both in the full analysis set as well as subgroups defined by markers of type 2 inflammation.

16.2.6 Efficacy response data

16.2.6.2 Percent predicted FEV1

16.2.6.2.1 Analysis of change from baseline in percent predicted FEV1 (%) over time - Exposed population - Full analysis set

Percent predicted FEV1 (%)	Placebo-Dupilumab (N=125)	Dupilumab-Dupilumab (N=240)	All (N=365)
Baseline of the parent study			
Value			
Number	125	240	365
Mean (SD)	79.33 (14.30)	76.83 (14.83)	77.68 (14.68)
Median	80.00	79.00	80.00
Q1 : Q3	72.00 : 89.00	67.00 : 88.00	70.00 : 88.00
Min : Max	39.0 : 110.0	24.0 : 111.0	24.0 : 111.0
Week 0			
Value			
Number	125	240	365
Mean (SD)	82.97 (16.13)	89.16 (15.60)	87.04 (16.03)
Median	85.00	90.00	87.00
Q1 : Q3	76.00 : 92.00	80.00 : 97.00	78.00 : 96.00
Min : Max	32.0 : 118.0	37.0 : 179.0	32.0 : 179.0
Change from baseline			
Number	101	182	283
Mean (SD)	7.87 (15.79)	10.55 (16.09)	9.59 (16.01)
Median	6.00	8.00	7.00
Q1 : Q3	-2.00 : 18.00	1.00 : 19.00	0.00 : 18.00
Min : Max	-32.0 : 46.0	-40.0 : 74.0	-40.0 : 74.0
Week 52			
Value			
Number	58	111	169
Mean (SD)	86.26 (15.24)	85.69 (13.35)	85.89 (13.98)
Median	85.50	87.00	86.00
Q1 : Q3	78.00 : 96.00	76.00 : 94.00	78.00 : 94.00
Min : Max	40.0 : 123.0	48.0 : 123.0	40.0 : 123.0
Change from baseline			
Number	58	111	169
Mean (SD)	8.41 (17.85)	8.93 (14.34)	8.75 (15.58)
Median	6.50	8.00	7.00
Q1 : Q3	-1.00 : 23.00	0.00 : 17.00	0.00 : 18.00
Min : Max	-27.0 : 43.0	-26.0 : 53.0	-27.0 : 53.0
Week 64			
Value			
Number	45	89	134
Mean (SD)	83.31 (16.04)	84.62 (15.23)	84.18 (15.46)
Median	83.00	85.00	85.00
Q1 : Q3	76.00 : 92.00	76.00 : 94.00	76.00 : 93.00
Min : Max	31.0 : 117.0	29.0 : 119.0	29.0 : 119.0

Table 4: Analysis of annualized event rate of severe exacerbation during the treatment – Exposed population – Full analysis set

Immunogenicity results:

The incidence of treatment-emergent positive ADA responses was low, reported in 3.8% of patients (7.3% in placebo-dupilumab category and 1.9% in dupilumab-dupilumab category) at the time of this report. Positive NAb responses were detected in 1.9% of patients. The majority of the positive ADA

responses had low to moderate ADA titers. Dupilumab exposure largely overlapped between patients with treatment-emergent positive ADA response and patients who were negative for ADA, except for 1 patient with high titer ADA response.

Among the limited number of patients with ADA positivity, no apparent associations between ADA positivity and PK, safety, or efficacy were observed.

2.6.6. Discussion on clinical efficacy

The main clinical trial conducted in support of this marketing authorisation application is the pivotal Phase 3 study EFC14153, 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 (EFC14153/LIBERTY ASTHMA VOYAGE). Dupilumab was tested against placebo as add-on therapy in combination with standard-of-care medication.

Supportive long-term safety and efficacy data comes from the ongoing open-label extension study LTS14424, a one-year study to evaluate the long-term safety and tolerability of dupilumab in paediatric patients with asthma who participated in a previous dupilumab asthma clinical study (LTS14424/LIBERTY ASTHMA EXCURSION).

Design and conduct of clinical studies

The pivotal study EFC14153 (VOYAGE) was adequately designed to investigate the efficacy of dupilumab in the defined target population based on the EMA Clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1).

The eligibility criteria appropriately defined the target population suffering from refractory asthma, requiring treatment step 4 or 5 according to GINA2015 Guideline. The required evidence of uncontrolled asthma adheres to the GINA guideline definitions based on aspects of asthma symptom control. The study objectives are reflected by the chosen endpoints; these are in line with the EMA Guideline on Clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1) and represent relevant factors for asthma symptom control. A broad range of secondary outcomes were analyzed which is standard for the evaluation of chronic asthma treatment.

Overall, there was a low number of major protocol deviations in the ITT population (DUP 2.6% vs. PLC 2.2%) mainly due to treatment incompliance, hampered assessments/procedures and violations of eligibility criteria. However, the patient numbers within the different categories were small and balanced between treatment groups and thus, a significant impact on efficacy and safety results seems unlikely. A sensitivity analysis to account for the use of SCS showed results similar to those of the primary efficacy analysis for both primary efficacy populations.

As to demographics and patient characteristics at baseline, patients included the combined pre-specified primary efficacy populations, i.e. the populations with type 2 inflammatory asthma phenotype defined by baseline blood eosinophils ≥0.15 Giga/L or FeNO ≥20 ppb and the population defined by baseline blood eosinophils ≥0.3 Giga/L (n=259) had a median age of 9.0 years. The majority of subjects enrolled to this study were white, two thirds were male and had a body weight >30 kg at baseline. Overall, demographics and patient characteristics are relatively similar between the treatment arms of all analysed populations apart from the sex. Boys have an increased prevalence of childhood asthma compared to girls which have led to the inclusion of lower female patient numbers. Regarding the different efficacy outcomes in male and female study participants, a more balanced gender ratio would have been beneficial as to interpretation of the results that are reflected below.

Regarding baseline disease characteristics for two primary efficacy populations, the median age at onset of asthma was 3.0 years and 5.7 years had elapsed between the first diagnosis of asthma and

study entry. The number of severe asthma exacerbations within the last year before study entry had been 2, one exacerbation thereof had required hospitalisation or urgent medical care, and 20.8% had experienced ≥4 exacerbations (median). Baseline pre-bronchodilator FEV1 percent was 79.0% with a reversibility of 16%, these values qualified for expiratory airflow limitation with a positive bronchodilator reversibility test. 44.4% of all patients had a high and 54.5% a medium ICS dose level at baseline. These facts mirror the disease severity in the included paediatric study population. As to disease characteristics at baseline, the applicant was asked to provide extra information on pre-existent asthma triggers such as seasonal and perennial allergens and their elimination before study entry, exposition to passive smoke, exacerbations based on viral infections, and adherence to inhaler technique before enrolment in order to evaluate the medical need for therapy escalation. Additionally, the optimal treatment duration was to be clarified. However, as this information was not collected during the studies, no specific information on these aspects could have been provided by the applicant.

As to baseline biomarkers, the median baseline eosinophil count was (mean) 0.57 G/l in the population with the type 2 inflammatory asthma phenotype, which is to be classified as mild peripheral eosinophilia in children aged 6-11years based on the literature. Mean FeNO values were elevated (mean 30.7 ppb, normal <20 ppb) and the majority (74.0%) had baseline eosinophil counts ≥0.3 Giga/L.
In the efficacy population defined as those with baseline blood eosinophils ≥0.3 Giga/L, mean eosinophil count at baseline was 0.71 Giga/L (hypereosinophilia >1.5 G/l). Dupilumab's effect seems to increase proportionally with increasing eosinophil counts similar to the effect observed in adults.

At baseline, the majority of patients in the population with the type 2 inflammatory asthma phenotype and with baseline blood eosinophils ≥0.3 Giga/L, respectively (96.9% in each population) were using 2 types of controller medications. Similar percentages used medium (54.4%) or high-dose (44.4%) ICS, most patients in combination with LABA (83.8%). Only 2 patients applied a third type of controller. Results were consistent with those of the ITT population. 6/259 (2.3%) were treated with ICS only at baseline and this is not representative for GINA Step 4 +5. The evaluated patient population is considered representative as regards patient and disease characteristics.

Efficacy data and additional analyses

The full intent-to-treat (ITT) efficacy population includes all randomized patients and consists of 408 patients, 273 of these were randomized to the dupilumab group and 135 to the placebo group (2:1). The majority had Type 2 inflammatory asthma phenotype (85.8%) and Baseline blood eosinophils ≥0.15 Giga/L (81.1%), 63.5% had Baseline blood eosinophils ≥0.3 Giga/L and Baseline FeNO ≥20 ppb. The percentage allocation of the different efficacy populations, identified by baseline type 2 biomarkers, was fairly balanced across treatment groups.

Overall, 248/273 (90.8%) of the ITT population completed the study treatment period after 52 weeks and slightly more patients assigned to the dupilumab group prematurely discontinued the study drug (DUP 8.1% vs. PLC 3.7%), however, no specific reason prevailed. 87.5% of all patients and slighty more patients of the placebo group continued dupilumab treatment in the open-label extension study LTS14424 study, which is still ongoing.

As mentioned above, 2 primary efficacy populations were defined, i.e. the population with the type 2 inflammatory asthma phenotype defined as the randomized patients with baseline blood eosinophils ≥0.15 Giga/L or baseline FeNO ≥20 ppb and the population with baseline blood eosinophils ≥0.3 Giga/L defined as the randomized patients with baseline blood eosinophils ≥0.3 Giga/L. The patients' disposition and the participant flow were very similar for the 2 primary efficacy populations and the full intention-to-treat (ITT) population. The primary analysis of both pre-specified populations is endorsed as these form the correct database with regard to the indication wording that is analogous to that for the adolescent/adult patient population. Thus, these results are further discussed here.

The mean compliance with administration of the IMP was high (around 99%). ICS and controller medication use were relatively steady (approximately 80% for all medications). Thus, reliable data are provided for assessment.

The primary endpoint for the EFC1415 study was the annualized rate of severe exacerbation events during the 52-week treatment period.

The annualized rate of severe exacerbation events during pivotal study EFC14153 was lower in both verum groups of the primary efficacy populations, i.e. the type 2 inflammatory asthma phenotype and the baseline blood eosinophils ≥0.3 Giga/L, respectively (DUP 0.305 vs. PLC 0.748 and DUP 0.235 vs. PLC 0.665). The overall relative risk reduction versus placebo was 59.3% and 64.7%, respectively. Meaningful differences as to gender were observed, i.e. 65% (p-value vs. placebo <0.0001) for male and 27 % for female (p-value vs. placebo <0.5) participants. The MAH reasoned this by the lower exacerbation rate and disease severity in the year prior to enrollment observed in the female subgroup of the placebo arm. This may have led to an unexpectedly low exacerbation rate in the placebo group and thus, to the smaller treatment effect in the female participants. Based on the literature (Bonini et al., 2020) it is concurred that the relative risk reduction in the annualized rate of severe exacerbations is still clinically meaningful.

A specific treatment effect was also observed within the other efficacy populations (cf. statistical methods of study EFC14153 above) including patients exhibiting baseline blood eosinophils ≥0.15 Giga/L (DUP 0.318 vs. PLC 0.816) or baseline FeNO ≥20 ppb (DUP 0.271 vs. PLC 0.705). All these results were statistically significant (p<0.0001). Over time (cf. correspondent plot), the cumulative mean number of severe exacerbations was lower in the verum groups in all four biomarker-based efficacy populations. Similarly, the relative risk in annualized rate of severe exacerbation events during the 52-week treatment period is lower for all 5 efficacy populations that received dupilumab. Consistent with these results, in dupilumab treated patients the time-to-first severe exacerbation event was prolonged in all analysed efficacy populations. The sensitivity analysis confirmed the robustness of the efficacy results indicating a clinically meaningful efficacy in the claimed indication.

Supportive information on efficacy data include subgroup analysis as to gender, region, race and body weight. Regarding the gender, the adjusted annualized severe exacerbation event rate was lower for males and females assigned to the dupilumab treatment groups of both primary efficacy populations compared to the placebo groups. Similarly, to the results concerning the primary endpoint, the effect for females was lower than for males (see above). This was also observed for other secondary endpoints including ACQ-7-IA and PAQLQ(S)-IA where no benefit (with a tendency to even negative effects) was observed in female subjects. Based on the additionally submitted data, it is concurred that these findings may be explained by the reasons mentioned for the divergent results of the primary endpoint, as eg. PAQLQ(S)-IA includes an item related to the symptom severity and thus, the endpoints are interdependent.

Study treatment was administered according to the body weight, i.e. for patients with body weight ⩾ 16 to <30kg: 100 mg q2w or 300 mg q4w; for patients with body weight ⩾30kg to <60 kg: 200 mg q2w or 300 mg q4w and for patients with body weight ⩾60 kg: 200 mg q2w.
The efficacy results were consistent and statistically significant in both primary efficacy populations with regard to baseline weight groups, i.e. ≤30 kg bw (type 2 inflammatory asthma phenotype: DUP 0.196 vs. PLC 0.618; baseline blood eosinophils ≥0.3 Giga/L: DUP 0.244 vs. PLC 0.710) and ≥30 kg bw (type 2 inflammatory asthma phenotype: DUP 0.344 vs. PLC 0.766; baseline blood eosinophils ≥0.3 Giga/L: DUP 0.209 vs. PLC 0.594).

The key secondary endpoint was defined as the change from baseline in percent predicted pre-bronchodilator FEV1 at Week 12.
In the efficacy population with the type 2 inflammatory asthma phenotype, the LS mean change from baseline in percent predicted pre-BD FEV1 at Week 12 was 10.53% (DUP) vs. 5.32% (PLC). Very similar results were observed in the population with baseline blood eosinophils ≥0.3 Giga/L, i.e.

10.15% (DUP) vs. 4.83% (PLC) as well as in the population with baseline blood eosinophils ≥0.15 Giga/L (DUP 10.36% vs. 5.65%) or baseline FeNO ≥ 20 ppb (DUP 11.36% vs. PLC 4.62%) indicating that the forced expiratory volume after 1 second hat improved after 12 weeks of dupilumab treatment. All results are statistically significant (p<0.005). In the combined efficacy population characterized by baseline FeNO ≤ 20 ppb and Baseline blood eosinophils ≤0.15 Giga/, no significant treatment effect could be detected, which is plausible considering the fact that no correlation with disease severity is to be expected in these patients. A sustained treatment effect was observable over time also reflected by the maintained LS mean change from baseline in PP FEV1 placebo after 52 weeks in all five efficacy populations.

Other secondary endpoints were effects on asthma control as measured by ACQ-7-IA including a ACQ-7-IA responder analysis, effects on PAQLQ(S)-IA, loss of asthma control (LOAC) events, type 2 airway inflammation, exposure to systemic corticosteroids and reliever medication, disease specific health-related quality of life (EQ-VAS), allergic rhinitis specific health-related quality of life in patients with comorbid allergic rhinitis.
More significant reductions from baseline in Asthma Control Questionnaire (ACQ-7-IA) scores at Week 24 were observed in all dupilumab-treated patients compared with placebo, mirrored by higher LS mean changes in all 5 pre-defined efficacy populations and higher responder percentages in the verum groups. A clinically relevant change was defined as the minimum clinically important difference of 0.5 based on 'The Global Strategy for Asthma Management and Prevention' (GINA2021) which is acceptable. All results were statistically significant or relevant. Another aspect of treatment benefit of dupilumab was also shown by reduction of the annualized rate of loss of asthma control events (LOAC) during the treatment period and by delay of the time to LOAC events during the treatment period and during the overall study period compared with placebo in both primary efficacy populations. The applicant was asked to submit the corresponding results of the remaining three efficacy populations taking into account the different dose groups; these confirmed a consistent efficacy.

Additionally, dupilumab's effect on airway inflammation was investigated by measuring the fractional concentration of exhaled nitric oxide (FeNO) levels, a marker that is increased in eosinophilic asthma and other atopic conditions. LS mean change from baseline in FeNO at Week 12 was higher in the verum groups, i.e. for the efficacy population with type 2 inflammatory asthma phenotype 18.94 ppb (DUP) compared to 0.98 ppb (PLC) and for patients included in the population with baseline blood eosinophil ⩾0.3 Giga/L -21.85 ppb (DUP) compared to 0.89 (PLC). Similar effects were observed in the other efficacy populations suggesting an adequate short- and long-term effect on airway inflammation. Patients assigned to the dupilumab groups of both primary efficacy populations had a lower intake of systemic corticosteroids compared with those of the placebo groups during the pivotal study as reflected by a slightly shorter annualized total SCS duration, for instance.

Dupilumab's effect on health-related quality of life was assessed by evaluating the LS mean change of Paediatric Asthma Quality of Life Questionnaire Scores with Standardized Activities (PAQLQ(S)-IA) at Weeks 12, 24, 36, and 52, for children ≥7 years. The questionnaire is considered to have a relatively good validity as regards the measurement of functional problems in daily life of children suffering from asthma. In both primary efficacy populations clinically important changes in scores were observed in favour of dupilumab treatment, however, results became nominally significant after 24 weeks (Baseline blood eosinophils >=0.3 Giga/L population) and after 36 weeks (Type 2 inflammatory asthma phenotype population). Hence, these results are considered clinically relevant after long-term therapy with dupilumab. This is also reflected by the PAQLQ(S)-IA responder analysis and an overall improvement in EQ-VAS in the 2 primary efficacy populations.

Several pre-specified subgroup analyses were performed. The biomarker subgroup analyses evaluated dupilumab's effect on the annualized rate of severe exacerbation events and on the change from baseline in percent predicted pre-BD FEV1 at Week 12 in the ITT population defined by baseline type 2 biomarker level, including blood eosinophils (<0.15 Giga/L, ≥0.15-0.3 Giga/L, ≥0.3-0.5 Giga/L, and ≥0.5 Giga/L) and FeNO (<20 ppb and ≥20 ppb). Results showed exacerbation reduction compared to placebo for all subgroups with baseline blood eosinophils ≥0.15 Giga/L and for both subgroups defined

by baseline FeNO. Again, no treatment benefit was observed for patients in the subgroup with baseline blood eosinophils <0.15 Giga/L or with baseline FeNO <20 ppb. Pre-specified treatment-by-biomarker interaction effects were detected in the ITT population for continuous baseline FeNO and blood eosinophils on the annualized severe exacerbation rate and LS mean change in percent predicted pre-BD FEV_1. Hence, both biomarkers serve independently for the identification of dupilumab responders. This is also supported by the quadrant analysis.
Thus, a treatment-by-subgroup interaction was observed in patients with elevated blood eosinophils and FeNO, meaning that the treatment effect differs depending on baseline biomarker values, i.e. decreases in patients with eosinophils < 0.15 Giga/L and FeNO < 20 ppb.

The applicant suggested a weight-based dosing for paediatric patients with asthma age 6 to <12 years as already existent for other indications, i.e. for patients with body weight ⩾15 to <30kg: 100 mg q2w or 300 mg q4w; for those ⩾30kg to <60 kg: 200 mg q2w or 300 mg q4w and for patients with body weight ⩾60 kg: 200 mg q2w and it was reflected as reflected in section 4.2. of the SmPc . Efficacy results related to the diverse dose regimes of the Phase 3 studies were consistent for all efficacy populations. Data on the 300 mg q4w dose regimen are uncontrolled and limited to 18 patients weighing <30 kg that were treated during OLE study LTS14424 (see below). Efficacy and safety results do not give rise to any objections against this dose regimen which is already authorized for AD patients with a body weight of 15-⩽60 kg following a split loading dose of 300 mg each on Day 1 and 15. Thus, this alternative dose regimen is acceptable.

The applicant's analysis on efficacy results across the adult/adolescent and paediatric population delivered similar results. The underlying disease characteristics in terms of severe asthma exacerbations frequencies before study entry, asthma control, comorbid atopic conditions and type 2 inflammatory biomarkers were relatively similar, if applicable.

The ongoing open-label extension study in children 6 to <12 years who participated in pivotal Phase 3 study EFC14153 evaluating the long-term safety, tolerability of dupilumab, long term efficacy, pharmacokinetic (PK), and immunogenicity provides supportive data up to 104 weeks of treatment with dupilumab. Analysed efficacy endpoints were the annualized rate of severe asthma exacerbation events and change in percent predicted FEV. Dose adjustments were performed at study entry, if needed. Long-term data is available from 189/365 (51.8%) patients that were treated for additional 52 weeks. The unadjusted annualized rate of severe asthma exacerbations during the treatment period in LTS14424 for all exposed patients was 0.134 and very similar for both pre- and newly exposed patients (cf. primary efficacy population of pivotal study adjusted annualized rate was 2.24-0.3). The majority had no severe asthma exacerbations throughout the study (336/365 patients (92.1%)). Regarding the 300 mg q4w dose regimen, no exacerbation was recorded, however, the duration of exposure was limited to 42.6 days (mean).

2.6.7. Conclusions on the clinical efficacy

The superiority of dupilumab over placebo is demonstrated for both dose regimens (100/200 mg q2w and 300 mg q4w) regarding the primary and key secondary endpoints.

Overall, dupilumab appears to be efficacious in paediatric patients with severe asthma with type 2 inflammation that is characterized by elevated blood eosinophils and /or raised FeNO.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Disposition of study subjects and extent of exposure

Study EFC14153

A total of 408 patients were randomized (273 patients in the dupilumab group and 135 patients in the placebo group). Among them, 405 were treated (3 patients, all in the dupilumab group, were randomized but not treated, 2 due to not meeting inclusion/exclusion criteria and 1 due to patient's decision). Among the 405 patients treated, 392 completed the study and 27 prematurely discontinued treatment. Early treatment discontinuation rate was higher in the dupilumab group compared to the placebo group (22 [8.1%] versus 5 [3.7%] patients, respectively). The main reasons for treatment discontinuation were AE (1.8 % in the dupilumab group and 1.5% in the placebo group) and vaccination prohibited by protocol (yellow fever vaccine or MMR) (6 patients in the dupilumab group).

Study duration was similar between placebo and dupilumab treatment groups, with a median of 365 days for each treatment group, and a mean of 364.93 in the placebo group and 361.75 in the dupilumab group.

Study LTS14424

Among the 405 patients randomized and treated in Study EFC14153, 365 rolled over to the OLE (Study LTS14424), all receiving open-label study treatment with dupilumab (at either 100 mg q2w, 200 mg q2w, or 300 mg q4w).

As of the study data cut-off date (18 August 2020), 196 patients completed the 52-week open-label study treatment period (70 in the placebo-dupilumab category and 126 in the dupilumab-dupilumab category), 155 were still ongoing (52 in the placebo-dupilumab category and 103 in the dupilumab-dupilumab category), and 14 patients prematurely discontinued treatment. Study duration was similar between placebo and dupilumab treatment groups, with a median of 375.0 days in the placebo-dupilumab category and 371.5 days in the dupilumab-dupilumab category, and a mean of 339.2 in the placebo-dupilumab category and 329.7 in the dupilumab-dupilumab category.

2.6.8.2. Disease characteristics

EFC14153: The patients' disease characteristics at baseline were consistent between dupilumab and placebo groups. Approximately 44.1% of patients were on high dose ICS at baseline, 55.1% were on medium dose ICS (plus 1 additional controller), and 0.7% (all in the dupilumab group) were on low dose ICS (in deviation of the protocol). The mean number of severe asthma exacerbation in the prior year was slightly higher in the dupilumab group as compared to placebo group (2.56 versus 2.19), however, median values were similar between treatment groups (2.0). Other asthma-specific baseline characteristics were similar between treatment groups and indicative of an enrolled population comprised of patients with moderate-to-severe uncontrolled disease.

The majority of patients (92.4%) reported having an ongoing atopic disease, allergic rhinitis being the most frequent (81.9%). Atopic dermatitis was reported in 36.3% of patients. All patients were receiving background asthma controller therapy at stable doses at study entry and continued with these medications throughout the study.

LTS14424: The disease characteristics at baseline of the parent study EFC14153 for the population enrolled in Study LTS14424 were similar between the two treatment categories.

Asthma-specific characteristics were similar between the two treatment groups at the baseline of the parent study, with an overall mean percent predicted pre-BD FEV1 of 77.68% (14.68). At Week 0 of the OLE study LTS14424, the mean percent predicted pre-BD FEV1 was higher in the dupilumab-dupilumab category (89.16%) than in the placebo-dupilumab category (82.97%), reflecting the differential treatment effects of dupilumab versus placebo in the parent study.

The profile of medical/surgical history was similar between the initial randomized population (Study EFC14153) and the population that rolled-over into Study LTS14424.

2.6.8.3. Adverse Events

Study EFC14153

The percentage of patients with any TEAE was similar in the dupilumab group compared with the placebo group (83.0% and 79.9%, respectively). There were no deaths reported during the study and the incidence of treatment-emergent SAEs was 4.8% in the dupilumab group versus 4.5% in the placebo group. The overall rate of treatment discontinuation due to TEAEs was 1.8% in the dupilumab group and 1.5% in the placebo groups (Table 5).

n(%)	Placebo (N=134)	Dupilumab (N=271)
Patients with any TEAE	107 (79.9%)	225 (83.0%)
Patients with any treatment emergent SAE	6 (4.5%)	13 (4.8%)
Patients with any TEAE leading to death	0	0
Patients with any TEAE leading to permanent treatment discontinuation	2 (1.5%)	5 (1.8%)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, n (%) = number and percentage of patients with at least one TEAE

Table 5: Overview of adverse event profile: Treatment-emergent adverse events in Study EFC14153 – Safety population

The number (%) of patients with at least 1 TEAE by primary SOC is presented in Table 6. The SOCs with the highest proportion of patients with TEAEs (≥10% of patients in either treatment group) were infections and infestations (65.3% in the dupilumab group versus 70.1% in the placebo group), General disorders and administration site conditions (22.5% versus 18.7%), Respiratory, thoracic and mediastinal disorders (17.7% versus 26.9%, respectively), Gastrointestinal disorders (14.8% versus 9.7%, respectively), Skin and subcutaneous tissue disorders (12.5% versus 10.4%, respectively), and Injury, poisoning and procedural complications (15.1% versus 14.2%, respectively).
The incidence of TEAEs at the SOC level was similar between the dupilumab and placebo groups, with the exception of the following SOCs for which a ≥5% difference between treatment groups was observed. The SOC with TEAEs more frequently reported in the dupilumab group compared to placebo were as follows:

- Blood and lymphatic system disorders (8.5% in the dupilumab group versus 3.0% in the placebo group), driven by eosinophilia PT (5.9% versus 0.7%).
- Gastrointestinal disorders (14.8% in the dupilumab group versus 9.7% in the placebo group), mainly driven by abdominal pain, nausea, and constipation. All events reported in the

gastrointestinal disorders SOC were mild to moderate in intensity, none were serious or led to permanent treatment discontinuation. All events were assessed by the Investigator as not related to the IMP except for 1 event of nausea.

Primary System Organ Class n(%)	Placebo (N=134)	Dupilumab (N=271)
Any class	107 (79.9%)	225 (83.0%)
Infections and infestations	94 (70.1%)	177 (65.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.4%)
Blood and lymphatic system disorders	4 (3.0%)	23 (8.5%)
Immune system disorders	5 (3.7%)	5 (1.8%)
Endocrine disorders	2 (1.5%)	0
Metabolism and nutrition disorders	3 (2.2%)	2 (0.7%)
Psychiatric disorders	0	3 (1.1%)
Nervous system disorders	11 (8.2%)	22 (8.1%)
Eye disorders	10 (7.5%)	9 (3.3%)
Ear and labyrinth disorders	2 (1.5%)	4 (1.5%)
Cardiac disorders	0	3 (1.1%)
Respiratory, thoracic and mediastinal disorders	36 (26.9%)	48 (17.7%)
Gastrointestinal disorders	13 (9.7%)	40 (14.8%)
Hepatobiliary disorders	1 (0.7%)	0
Skin and subcutaneous tissue disorders	14 (10.4%)	34 (12.5%)
Musculoskeletal and connective tissue disorders	5 (3.7%)	16 (5.9%)
General disorders and administration site conditions	25 (18.7%)	61 (22.5%)
Investigations	4 (3.0%)	6 (2.2%)
Injury, poisoning and procedural complications	19 (14.2%)	41 (15.1%)

TEAE: Treatment emergent adverse event, SOC: System organ class
MEDDRA 23.0
n (%) = number and percentage of patients with at least one TEAE

Table 6: Number (%) of patients with TEAE(s) by Primary SOC in Study EFC14153 – Safety population

The following TEAEs were reported more frequently in the dupilumab group when compared with the placebo group (≥5% in the dupilumab group and a difference of ≥1% versus the placebo group at the PT level, cf. Table 7):

- Viral upper respiratory tract infection (dupilumab: 12.2%, placebo: 9.7%); however, the incidence of TEAEs in the HLT of upper respiratory tract infections (40.2% in the dupilumab group versus 44.0% in the placebo group) and in the HLT of lower respiratory tract infections NEC (not elsewhere classified) (7.7% versus 11.2%, respectively) was comparable between treatment groups
- Eosinophilia (dupilumab: 5.9%, placebo: 0.7%)
- Injection site erythema (dupilumab: 12.9%, placebo: 9.7%)
- Injection site edema (dupilumab: 10.3%, placebo: 5.2%)
- Injection site nodule (dupilumab: 6.3%, placebo: 2.2%).

In contrast, the following TEAEs were reported less frequently in the dupilumab group compared with the placebo group (≥5% in the placebo group and a difference of ≥1% versus the dupilumab group at the PT level):

- Nasopharyngitis (dupilumab: 18.5%, placebo: 21.6%)
- Pharyngitis (dupilumab: 8.9%, placebo: 10.4%)
- Influenza (dupilumab: 7.4%, placebo: 9.0%)
- Bronchitis (dupilumab: 6.3%, placebo: 10.4%) • Rhinitis allergic (dupilumab: 5.9%, placebo: 11.9%)
- Cough (dupilumab: 5.5%, placebo: 6.7%).
- Sinusitis (dupilumab: 3.3%, placebo: 5.2%)
- Accidental overdose (dupilumab: 1.1%, placebo: 5.2%).

Primary System Organ Class Preferred Term n (%)	Placebo (N=134)	Dupilumab (N=271)
Infections and infestations		
Nasopharyngitis	29 (21.6%)	50 (18.5%)
Upper respiratory tract infection	18 (13.4%)	35 (12.9%)
Viral upper respiratory tract infection	13 (9.7%)	33 (12.2%)
Pharyngitis	14 (10.4%)	24 (8.9%)
Influenza	12 (9.0%)	20 (7.4%)
Bronchitis	14 (10.4%)	17 (6.3%)
Sinusitis	7 (5.2%)	9 (3.3%)
Blood and lymphatic system disorders		
Eosinophilia	1 (0.7%)	16 (5.9%)
Nervous system disorders		
Headache	10 (7.5%)	19 (7.0%)
Primary System Organ Class Preferred Term n (%)	**Placebo (N=134)**	**Dupilumab (N=271)**
Respiratory, thoracic and mediastinal disorders		
Rhinitis allergic	16 (11.9%)	16 (5.9%)
Cough	9 (6.7%)	15 (5.5%)
General disorders and administration site conditions		
Injection site erythema	13 (9.7%)	35 (12.9%)
Injection site oedema	7 (5.2%)	28 (10.3%)
Injection site nodule	3 (2.2%)	17 (6.3%)
Injury, poisoning and procedural complications		
Accidental overdose	7 (5.2%)	3 (1.1%)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 23.0
n (%) = number and percentage of patients with at least one TEAE
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab group
Only PT with at least one 5% in at least one group are presented

Table 7: Number (%) of patients with TEAE(s) that occurred with a frequency ≥5% in any treatment group by primary SOC and PT in Study EFC14153 – Safety population

An imbalance between treatment groups was observed for parasitic infections which was reported in 7 (2.6%) patients in the dupilumab group versus 1 (0.7%) patient in the placebo group (parasitic gastroenteritis erroneously not recorded as AESI). Among the events reported in the dupilumab group, there were 5 events of enterobiasis and all were assessed as not related to the IMP by the Investigator. However, a possible causal relationship between parasitic infection and dupilumab cannot be excluded. The PT of enterobiasis was designated as an adverse drug reaction (ADR) from Study EFC14153.

Most TEAEs were mild in intensity (38.7% in the dupilumab group and 38.1% in the placebo group) or moderate (41.3% and 37.3%, respectively). Severe TEAEs were reported for 8 (3.0%) patients in the dupilumab group and 6 (4.5%) patients in the placebo group.

Most TEAEs were considered by the Investigator to be unrelated to the IMP. The most frequently reported TEAEs (≥1% at PT level) that were considered by the Investigator to be related to the IMP were injection site erythema (12.9% in the dupilumab group versus 9.7% in the placebo group), injection site edema (10.3% versus 5.2%), injection site nodule (6.3% versus 2.2%), injection site pruritus (2.2% versus 2.2%), injection site pain (1.8% versus 1.5%), eosinophilia (1.8% versus 0), headache (1.5% versus 0.7%), injection site inflammation (1.5% versus 0), injection site urticaria (1.1% versus 1.5%), and accidental overdose (1.1% versus 0.7%).

No clinically meaningful differences were observed between subgroups based on body weight except for a higher incidence of injection site reactions observed in the subgroup of patients with baseline body weight >30 kg.

Study LTS14424

As of the data cut-off date of Study LTS14424, there were no death reported, and the incidence of both treatment-emergent SAE and TEAE leading to permanent treatment discontinuation was 1.4% and 0.5%, respectively. Overall, 201 (55.1%) patients experienced at least 1 TEAE during the study (Table 8). When adjusted by exposure, the incidence rate for patients with any TEAEs was higher in patients previously treated with placebo (153.1 patients per 100 PY) compared to those previously treated with dupilumab (102.0 patients per 100 PY) in the parent study.
The overall exposure-adjusted incidence for patients with at least 1 TEAE was lower in Study LTS14424 (117.4 per 100 PY) compared to the dupilumab group in Study EFC14153 (220.2 per 100 PY). The profile of TEAE by SOC was similar to the parent study (Study EFC14153), with Infections and infestations being the most frequently reported SOC (40.8%). At the SOC level, the incidence of TEAEs was similar between the dupilumab-dupilumab and placebo-dupilumab categories (Table 8).

n (%)	Placebo-Dupilumab (N=125, PY=114.9)	Dupilumab-Dupilumab (N=240, PY=215.4)	All (N=365, PY=330.3)
Patients with any TEAE	79 (63.2%)	122 (50.8%)	201 (55.1%)
Patients with any treatment emergent SAE	1 (0.8%)	4 (1.7%)	5 (1.4%)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	2 (0.8%)	2 (0.5%)

TEAE: Treatment emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE, PY = total patient-years in the corresponding

Table 8: Overview of adverse event profile: Treatment-emergent adverse events – Exposed population – Full analysis set

Primary System Organ Class n (%)	Placebo-Dupilumab (N=125, PY=114.9)	Dupilumab-Dupilumab (N=240, PY=215.4)	All (N=365, PY=330.3)
Any class	79 (63.2%)	122 (50.8%)	201 (55.1%)
Infections and infestations	57 (45.6%)	92 (38.3%)	149 (40.8%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (0.8%)	2 (0.5%)
Blood and lymphatic system disorders	7 (5.6%)	6 (2.5%)	13 (3.6%)
Immune system disorders	0	3 (1.3%)	3 (0.8%)
Metabolism and nutrition disorders	1 (0.8%)	0	1 (0.3%)
Psychiatric disorders	0	5 (2.1%)	5 (1.4%)
Nervous system disorders	5 (4.0%)	7 (2.9%)	12 (3.3%)
Eye disorders	2 (1.6%)	5 (2.1%)	7 (1.9%)
Ear and labyrinth disorders	2 (1.6%)	6 (2.5%)	8 (2.2%)
Cardiac disorders	0	1 (0.4%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	15 (12.0%)	26 (10.8%)	41 (11.2%)
Gastrointestinal disorders	14 (11.2%)	20 (8.3%)	34 (9.3%)
Hepatobiliary disorders	1 (0.8%)	0	1 (0.3%)
Skin and subcutaneous tissue disorders	11 (8.8%)	24 (10.0%)	35 (9.6%)
Musculoskeletal and connective tissue disorders	3 (2.4%)	5 (2.1%)	8 (2.2%)
Renal and urinary disorders	1 (0.8%)	1 (0.4%)	2 (0.5%)
Reproductive system and breast disorders	0	2 (0.8%)	2 (0.5%)
Congenital, familial and genetic disorders	0	1 (0.4%)	1 (0.3%)
General disorders and administration site conditions	15 (12.0%)	24 (10.0%)	39 (10.7%)
Investigations	4 (3.2%)	1 (0.4%)	5 (1.4%)
Injury, poisoning and procedural complications	13 (10.4%)	20 (8.3%)	33 (9.0%)

TEAE: Treatment emergent adverse event, SOC: System organ class
MedDRA 23.0
n (%) = number and percentage of patients with at least one TEAE, PY = total patient-years in the corresponding observational period

Table 9: Number (%) of patients with TEAE(s) by Primary SOC in Study LTS14424 – Exposed population – Full analysis set

The number (%) of patients with TEAEs that occurred with a frequency of ≥5% in any treatment group by primary SOC and PT is presented in Table 10. Most of the TEAEs were mild or moderate in intensity and 76.6% of patients had TEAEs that were considered as not related to the IMP by the Investigator. As for the parent study (Study EFC14153), the most frequently reported TEAEs (≥2% at PT level) that were assessed by the Investigator as related to the IMP were injection site reaction (4.4%) and injection site erythema (2.2%).

Primary System Organ Class Preferred Term n (%)	Placebo-Dupilumab (N=125, PY=114.9)	Dupilumab-Dupilumab (N=240, PY=215.4)	All (N=365, PY=330.3)
Infections and infestations			
Nasopharyngitis	11 (8.8%)	18 (7.5%)	29 (7.9%)
Pharyngitis	11 (8.8%)	12 (5.0%)	23 (6.3%)
Upper respiratory tract infection	4 (3.2%)	16 (6.7%)	20 (5.5%)
Influenza	6 (4.8%)	12 (5.0%)	18 (4.9%)
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic	7 (5.6%)	6 (2.5%)	13 (3.6%)
General disorders and administration site conditions			
Injection site reaction	9 (7.2%)	7 (2.9%)	16 (4.4%)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 23.0
n (%) = number and percentage of patients with at least one TEAE, PY = total patient-years in the corresponding observational period

Table 10: Number (%) of patients with TEAE(s) that occurred with a frequency ≥5% in any treatment category by Primary SOC and PT – Exposed population in Study LTS14424 – Full analysis set

Among the 14 patients who were exposed to 300 mg q4w, 4 patients experienced TEAEs during their exposure to 300 mg q4w:1 in the placebo-dupilumab category (skin laceration) and 3 in the dupilumab-dupilumab category (headache and abdominal pain, injection site reaction, and scratch [right leg]). Of these 4 patients, 1 patient had a similar TEAE (injection site reaction) before switching to 300 mg q4w. None of the TEAEs reported during the 300 mg q4w exposure were serious or led to permanent treatment discontinuation.

2.6.8.4. Serious adverse event/deaths/other significant events

Deaths

There were no deaths reported during Study EFC14153 and LTS14424 (up to the Study LTS14424 data cut-off date of 18 August 2020).

Serious Adverse Events

Study EFC14153

Most treatment-emergent SAEs occurred in 1 patient each, with the exception of asthma exacerbation (PT: asthma) that was reported by 4 (1.5%) patients in the dupilumab group (versus none in the placebo group) and eosinophilia that was reported by 2 (0.7%) patients in the dupilumab group (versus none in the placebo group). 4/271 patients (1.5%) in the dupilumab group and 0/134 patients in the placebo group experienced SAEs of asthma exacerbation requiring hospitalization. 3 out of 4 patients with SAEs of asthma reported at least 5 severe asthma exacerbations in the prior year, and in these 3 patients, the number of severe exacerbations observed during the course of the study significantly decreased compared to that observed in the prior year. When referring to severe

exacerbations leading to hospitalization or emergency room visit during the study in the intent to treat population, the overall rate was comparable between treatment groups (9 [3.3%] in the dupilumab group and 6 [4.4%] in the placebo group). As per protocol, only asthma exacerbations fulfilling seriousness criteria qualified for safety reporting, and as such, asthma exacerbations leading to an emergency room visit for less than 24 hours that was not considered as a medically important event by the Investigator were not reported as SAEs. Two patients, both in the dupilumab group, had treatment-emergent SAEs that were considered by the Investigator to be related to the IMP: pneumonia and eosinophilia with headache and blurred vision.

Study LTS14424

No patients experienced SAE of asthma exacerbation.

The other SAEs (complicated appendicitis, pneumonia, upper respiratory tract infection, and atelectasis) did not lead to treatment discontinuation, resolved with corrective treatment, and were assessed as not related to the IMP. There were no treatment-emergent SAE in the patients exposed to the 300 mg q4w regimen.

Adverse Events leading to permanent treatment discontinuation

Study EFC14153

The overall treatment discontinuation rate due to AEs was low and similar between treatment groups (1.8% in the dupilumab group versus 1.5% in the placebo group).

Most of the TEAEs that led to discontinuation occurred in only 1 patient each in any given treatment group, with the exception of:

- Injection site erythema and injection site edema PTs (2 patients in the dupilumab group versus none in the placebo group). Both cases were severe injection site reaction lasting for at least 24 hours and meeting AESI criteria.
- Neutropenia (dupilumab200 mg q2w).
- In addition, in the dupilumab group, 1 patient experienced erythema multiforme and 1 patient experienced eosinophilia, both leading to permanent treatment discontinuation.

Study LTS14424

The number of TEAE leading to treatment discontinuation was very low. Two (0.5%) patients, who both received dupilumab in the parent study (dupilumab-dupilumab category), experienced TEAEs leading to permanent treatment discontinuation (Pulmonary tuberculosis and Conjunctivitis allergic, both events assessed by the Investigator as related to the IMP. When adjusted by exposure, the incidence rate for patients with any TEAE leading to treatment discontinuation was 0.0 patients per 100 PY in patients previously treated with placebo and 0.9 patients per 100 PY in those previously treated with dupilumab in the parent study.

There were no TEAEs leading to treatment discontinuation reported in patients exposed to the 300 mg q4w regimen.

Adverse Events of Special Interest

Study EFC14153

There were no opportunistic infections, no malignancy, no pregnancy, and no symptomatic overdose to IMP or non-investigational medicinal product (NIMP) reported.

Study LTS14424

There were no AESI in the patients exposed to the 300 mg q4w regimen. As in the parent study, no malignancy, no pregnancy, and no symptomatic overdose to IMP or non-investigational medicinal product were reported.

Adverse drug reactions

The primary assessment for ADRs was conducted in the placebo-controlled Study EFC14153. Analysis was based on individual PTs and selected AE groupings (predefined SMQs/CMQs) in the Study EFC14153 safety population (N=405 patients).

The qualification of a TEAE PT as an ADR is based on the following quantitative and qualitative criteria:

• Quantitative Criteria: The PTs with incidence ≥1% in the dupilumab group and difference ≥1% versus placebo group and with lower bound of the 95% CI of relative risk >1 compared to placebo.

• Qualitative Criteria: Medical judgement was applied to confirm the PTs which met quantitative criteria as well as for qualifying the PTs, which did not meet the quantitative threshold, but deemed medically important to be made an ADR. The seriousness, severity, outcome of the TEAE and impact on IMP administered were also considered.

Despite not meeting the quantitative threshold for ADRs, enterobiasis is considered an ADR based on the numerical imbalance between treatment groups (1.8% in the dupilumab group versus 0% in the placebo group) and the theoretical mechanism that suppression of IL-4 and IL-13 may impair immune responses against helminthic infection. All events of enterobiasis recovered with anthelminthic treatment. The potential safety concern of helminthic infections is already included in the warning section of the current labeling. In addition, injection site reactions are considered as ADR despite not meeting the quantitative criteria based on the observed imbalance between treatment groups and because injection site reactions are considered as ADRs across indications for dupilumab. No additional ADRs were identified in the OLE study (Study LTS14424).

2.6.8.5. Laboratory findings

Mean blood eosinophil counts were elevated in both groups, with higher baseline values in the dupilumab versus placebo group (mean [SE]: 0.527 [0.410] Giga/L versus 0.446 [0.358] Giga/L, respectively). In the dupilumab group, a transient increase in the mean blood eosinophil count was observed at the first post-baseline assessment at Week 12; the mean eosinophil count returned to the baseline values by Week 36 (0.536 [0.584].

Overall, eosinophilia was considered as a TEAE in 18 patients in the dupilumab group and 1 patient in the placebo group, and were mainly self-limiting laboratory findings without any associated symptoms. Eosinophilia events with associated clinical symptoms were rarely reported, one case of serious eosinophilia led to permanent treatment discontinuation and was assessed as related to the IMP. Two cases of neutropenia led to treatment discontinuation (1 in the placebo and 1 in the dupilumab group).

During LTS14424, Changes in blood eosinophil mean or median from baseline were the same as the dupilumab group in the parent study.

As to clinical chemistry, dupilumab treatment did not result in changes in electrolytes or metabolic parameters in both studies. Moreover, Dupilumab treatment did not result in changes in liver or renal function tests over the course of both studies.

2.6.8.6. Immunological events

Immunogenicity

The ADA incidence in Study EFC14153 and Study LTS14424 is presented in Table 11.

Table 31 – ADA incidence in children 6 to <12 years of age with asthma (Studies EFC14153 and LTS14424)

Anti-dupilumab antibodies N (%)	Study EFC14153 (52-week TEAE period)				Study LTS14424[h]		
	Placebo	100 mg q2w (≤ 30 kg)	200 mg q2w (>30 kg)	100/200 mg q2w[g]	Placebo-Dupilumab	Dupilumab-Dupilumab	All
	(N=133)	(N=91)	(N=178)	(N=269)	(N=109)	(N=211)	(N=320)
Pre-existing ADA[a]	2 (1.5%)	1 (1.1%)	2 (1.1%)	3 (1.1%)	1 (0.9%)	2 (0.9%)	3 (0.9%)
Treatment-emergent response[b]	4 (3.0%)	4 (4.4%)	13 (7.3%)	17 (6.3%)	8 (7.3%)	4 (1.9%)	12 (3.8%)
Persistent response[c]	1 (0.8%)	3 (3.3%)	6 (3.4%)	9 (3.3%)	4 (3.7%)	3 (1.4%)	7 (2.2%)
Indeterminate response[d]	1 (0.8%)	0	3 (1.7%)	3 (1.1%)	1 (0.9%)	0	1 (0.3%)
Transient response[e]	2 (1.5%)	1 (1.1%)	4 (2.2%)	5 (1.9%)	3 (2.8%)	1 (0.5%)	4 (1.3%)
Peak post-baseline titer							
Low (<1,000)	3 (2.3%)	4 (4.4%)	12 (6.7%)	16 (5.9%)	3 (2.8%)	2 (0.9%)	5 (1.6%)
Moderate (1,000-10,000)	1 (0.8%)	0	1 (0.6%)	1 (0.4%)	4 (3.7%)	2 (0.9%)	6 (1.9%)
High (>10,000)	0	0	0	0	1 (0.9%)	0	1 (0.3%)
Treatment-boosted response[f]	0	0	0	0	1 (0.9%)	0	1 (0.3%)
Neutralizing antibodies	1 (0.8%)	2 (2.2%)	4 (2.2%)	6 (2.2%)	4 (3.7%)	2 (0.9%)	6 (1.9%)

ADA: anti-drug antibodies; N: number of patients; TEAE: treatment-emergent adverse event; q2w: every 2 weeks
a Either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline in the ADA assay with all post first dose ADA results less than 4-fold baseline titer levels.
b A positive response in the ADA assay post first dose when baseline results are negative or missing.
c Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points separated by greater than 12-week period (greater than 84 days), with no ADA negative samples in between.
d Treatment-emergent response with only the last collected sample positive in the ADA assay.
e Treatment-emergent ADA positive response that is not considered persistent or indeterminate.
f A positive response in the ADA assay post first dose that is greater than or equal to 4-fold over baseline titer levels, when baseline results are positive.
g 100 mg q2w and 200 mg q2w treatment pool
h Eligible patients from 5.3.5.1 Study EFC14153. Data collected up to the data cutoff of 18-Aug-2020 are included in this application.
Source: 5.3.5.1 Study EFC14153, Appendix 16.2.5 (16.2.5.4.1.2.2) and (16.2.5.4.1.2.6) and 5.3.5.1 Study LTS14424, Appendix 16.2.5 (16.2.5.4.1.2.3) and (16.2.5.4.1.2.6)

Table 11: ADA incidence in Study EFC14153 and Study LTS14424

In the dupilumab group, 14 out of the 17 (82.4%) ADA-positive patients and 210 out of the 252 (83.3%) ADA-negative patients experienced at least 1 TEAE during the study. There was no apparent pattern or increase in TEAE incidence in the ADA-positive patients compared with the ADA-negative patients. The TEAEs that occurred on or after the first postdose ADA positive response with a higher frequency in the dupilumab-treated ADA-positive subgroup compared to ADA-negative or placebo group (≥10% difference) were AEs that are not usually associated with ADA-positive response and consisted of pharyngitis, headache, and vomiting. However, due to small number of patients with an ADA positive response (N=17) versus ADA negative response (N=252), it is difficult to draw any definitive conclusion on the potential influence of treatment-emergent ADA response on the incidence of TEAEs. Among patients with a treatment-emergent ADA response, none had events that were considered SAEs and 1 patient had a TEAE that resulted in permanent treatment discontinuation. This patient was ADA negative around the time of the event and had a transient treatment-emergent ADA response with low titer (30) around 5 months later.
The frequency of TEAEs was examined in patients who were positive in the NAb assay. The number of patients with positive NAb status was low (6) and does not allow for any meaningful interpretation of the impact of NAb on TEAEs. In patient with positive NAb status, there were no anaphylactic reaction, hypersensitivity or injection sire reactions. Two patients with negative Nab status experienced injection site reactions of which 1 was severe and led to treatment discontinuation. There was also 1 patient who experienced moderate urticarial.
Of the 10 patients who had a persistent treatment-emergent positive ADA response, 7 out of 9 patients in the dupilumab group and 1 out of 1 patient in the placebo group experienced at least 1 TEAE. No particular pattern of AEs was observed.

In Study LTS14424, the treatment-emergent ADA incidence in the placebo-dupilumab category (8 [7.3%]) was similar to that observed in the dupilumab group from the parent study EFC14153 (17 [6.3%]). The treatment-emergent ADA incidence of 4 (1.9%) in the dupilumab-dupilumab category was lower than that observed in the dupilumab group from the parent study EFC14153 (17 [6.3%])

2.6.9. Discussion on clinical safety

The safety data base comprises a total of evaluable 770 patients that were included in pivotal study EFC14153, a randomized, double-blind placebo-controlled phase 3 study with 52 weeks treatment duration and in LTS14424, an ongoing, open-label extension study for patients previously enrolled in Study EFC14153.

In study EFC14153, 405 patients were treated (273 patients in the dupilumab group and 135 patients in the placebo group) and 96.8% (392/405) completed the study. Slightly more patients assigned to the dupilumab group prematurely discontinued the study treatment (8.1% vs. 3.7%). The study duration was balanced between both treatment groups.

90.1% (365/405) transitioned into the open-label extension study LTS14424 and 53.7% (196/365) patients thereof completed the 52-week treatment phase. 34.3% (93/271) of the dupilumab-treated patients rolling over from the parent study completed more than 52 weeks of treatment during the open-label extension study LTS14424. Thus, regulatory requirements as to long-term safety data are met. Demographics, patient and disease characteristics were fairly balanced between the treatment groups and categories, respectively, of both studies.

Patients were assigned to three different dose regimens receiving dupilumab at either 100 mg q2w $\leqslant$ 30 kg bw or 200 mg q2w $\geqslant$ 30 kg bw. As per protocol amendment 03 for study LTS14424, patients $\leqslant$ 30 kg bw received an additional treatment regimen, i.e. 300 mg q4w.

Overall, the percentage with any TEAE was slightly higher in the dupilumab treatment group, i.e. (DUP/PLC) 83.0% vs. 79.9%. Most TEAEs were reported in primary SOCs infections and infestations (65.3% vs. 70.1%), General disorders and administration site conditions (22.5% vs. 18.7%) and Respiratory, thoracic and mediastinal disorders (17.7% vs. 26.9%, respectively).
A higher TEAE frequency in the verum group was observed for SOCs Blood and lymphatic system disorders (8.5% vs. 3.0%) and Gastrointestinal disorders (14.8% vs. 9.7%). At PT level, eosinophilia and injection site reactions occurred more often in the dupilumab treatment group. Regarding viral or bacterial infections, no relevant imbalance was observed. However, more cases of parasitic infections such as enterobiasis were reported in the verum group (2.6% vs. 0.7%); despite a lacking causal relationship by medical judgement, the applicant suggests the designation of an ADR which is considered acceptable with regard to the numerical imbalance of this controlled data.

In children 6 to 11 years of age with moderate-to-severe asthma (VOYAGE), the additional adverse reaction of enterobiasis was reported in 1.8 % (5 patients) in the dupilumab groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with anti-helminth treatment without dupilumab treatment discontinuation as reflected in section 4.8 of the SmPC

Most TEAEs were mild-to-moderate and considered unrelated to the study drug. The most frequently reported TEAEs (≥1% at PT level) that were considered by the Investigator to be related to the IMP were: Injection site erythema (12.9% vs. 9.7%), injection site edema (10.3% vs. 5.2%), injection site nodule (6.3% versus 2.2%), injection site pain (1.8% versus 1.5%), eosinophilia (1.8% versus 0), headache (1.5% versus 0.7%). Single events of allergic conjunctivitis, nausea and skin disorders were assessed as related.
The overall TEAE frequency decreased over time, as reflected by the lower exposure-adjusted incidence rate for patients with at least 1 TEAE during study LTS14424 (117.4 per 100 PY) compared to the dupilumab group in Study EFC14153 (220 per 100 PY).

The results are consistent with the TEAE profiles that were analyzed during previous marketing authorization procedures.

In children 6 to 11 years of age with moderate-to-severe asthma, eosinophilia (blood eosinophils ≥ 3,000 cells/mcL or deemed by the investigator to be an adverse event) was reported in 6.6 % of the dupilumab groups and 0.7% in the placebo group. Most eosinophilia cases were mild to moderate and not associated with clinical symptoms. These cases were transient, decreased over time, and did not lead to dupilumab treatment discontinuation.

During study LTS14424, overall, 55.1% patients experienced at least 1 TEAE and 12.9% were assessed as possibly related to dupilumab.Generally, patients that had received dupilumab in the parent study reported TEAEs less frequently (50.8% vs. 63.2%). Single cases of ascariasis, enterobiasis, hordeolum, pulmonary tuberculosis, rash and headache were deemed related to the IMP. Most related TEAEs were reported for PTs Injection site reaction (4.4%), Injection site erythema (2.2%), Injection site nodule (1.4%), Accidental overdose (1.6%) and Eosinophilia (1.1%). These results are consistent with the known safety profile of Dupixent and corresponding ADRs are largely reflected in the PI.

During study EFC14153 the numbers of patients with treatment-emergent SAEs were generally low and comparable between both treatment groups (DUP 4.8% vs. PLC 4.5%). The individual cases were evenly distributed on the different SOCs and no specific pattern is evident. Two cases of pneumonia and eosinophilia with headache and blurred vision were assessed as possibly related to dupilumab. Another case of pulmonary tuberculosis was reported during LTS14424.

There were no deaths during Study EFC14153 and LTS14424 until the data cut-off.

Discontinuation rates were low in both studies and treatment groups. Individual TEAEs leading to permanent study drug discontinuation were attributed to different SOCs. No specific safety issue arises from these data.

Predefined Adverse events of special interest (AESI) based on the safety profile observed with dupilumab in adult patients were the following: Systemic or extensive hypersensitivity reactions including anaphylactic reactions, parasitic infections, symptomatic overdose and pregnancy.

Numerical differences of AESI were observed at PT levels 'Injection site reactions' (17.7% DUP vs. 13.4% PLC) and eosinophilia (6.6% DUP vs. 0.7% PLC). Regarding the subgroup analysis, more patients ≤30 kg bw experienced parasitic infections (5.5% vs. 1.1%) and eosinophilia (9.9% vs. 5.0%) than those ≥ 30 kg bw. Conversely, injection site reactions occurred more often within the higher weight class (20.0% vs. 13.2%). It is concurred that this phenomenon could be partially linked to the higher injection volume as a similar percentage difference is present between the placebo groups of both weight cohorts. The number of patients with treatment-emergent AESI were generally low in LTS14424 with qualitatively similar results.

Specific AESI were further analyzed. One dupilumab-related case of erythema multiforme was reported during study EFC14153 that recovered under OCS. Individual cases of dupilumab-related injection site reactions, opportunistic infections and conjunctivitis occurred. 18/271 patients (6.6%) experienced TEAE eosinophilia in the dupilumab group vs. 1/134 patients (0.7%) in the placebo group. 6 cases were assessed as treatment-related TEAE and one led to discontinuation. Most were mild-to-moderate, only 1 severe case was reported, all patients recovered without sequelae, 2 needed corrective treatment. In study LTS14424 similar results were obtained. As to eosinophilia, 13/365 (3.6%) were reported. All events were transient, without associated symptoms and decreased over time. The majority was mild to moderate. The results are consistent with those of the adolescent and adult CRSwNP and AD population and listed as common ADR in the SmPC. No cases of pregnancy, symptomatic overdose or malignancy were reported.

Slightly more patients assigned to the dupilumab 200 mg Q2W group (>30 kg) had treatment-emergent ADA response compared with the patients treated with 100 mg Q2W (≤30 kg), i.e. 7.3% vs. 4.4%. However, the former included twice as many patients making ADA detection more likely in this group. The persistent ADA responses were balanced across the dupilumab groups and ADA response gradually decreased during LTS14424. Around 2% had neutralizing antibodies during both studies. These results are in line with previous study results of different study populations and do not raise new safety concerns (cf. SmPC).
The safety profile cumulative exposure of 10.5 patient-years based on the data cut-off date of 25 June 2021 including 18 patients with body weight ≤30 kg exposed to 300 mg q4w in LTS14424, has not changed from the time of the initial paediatric asthma 6 to 11 years old application with cumulative exposure of 1.6 patient-years.

2.6.10. Conclusions on the clinical safety

The safety database of the pivotal placebo-controlled phase 3 study EFC14153 comprises 405 dupilumab-treated patients. Supportive long-term safety data of 196 patients that completed the 52-week treatment phase of OLE study 14424 are additionally provided. Based on the Guideline on the clinical investigation of medicinal products for the treatment of asthma (CHMP/EWP/2922/01 Rev.1.) the provided size of the data base is considered sufficient to assess the long-term safety of dupilumab in the claimed indication.

Based on the data available, the overall risk of systemic hypersensitivity reactions, opportunistic/severe/serious infections, suicidal behaviour and conjunctivitis as well as malignancy with dupilumab appears low. Currently, no negative consequences on immune defence are obvious. The overall safety results are consistent with the known safety profile of Dupixent, especially regarding the frequencies of Injection site reactions (ISR) and conjunctivitis under dupilumab treatment. It is concurred that ADRs enterobiasis and eosinophilia are included in the SmPC based on the provided data.

2.7. Risk Management Plan

The MAH submitted RMP versions 6.0 and 6.1 with this application. The proposed RMP changes in RMP v. 6.0 were:

Rationale for submitting an updated RMP	This updated EU-RMP ~~5~~6.0 is prepared as part of the application for the extension of ~~AD~~asthma indication in patients 6 to 11 years of age.
Summary of significant changes in this RMP	Significant changes to each module: • Module II SI: addition of epidemiological data for ~~AD~~asthma in patients 6 to 11 years of age; • Module II SIII: update of clinical trials exposure data for all indications; • Module II SIV: addition of data related to ~~AD~~asthma in patients 6 to 11 years of age; addition of a discussion on potential off-label use in paediatric patients not covered by the authorized indications; • Module II SV: update of post-authorization exposure data; • Module II SVII: missing information "conjunctivitis related events in AD patients" renamed "conjunctivitis and keratitis related events in AD patients" and reclassified as an important identified risk; update of risk tables with addition of ~~AD~~asthma data in patients 6 to 11 years of age and additional updates with RMP DLP; • Part III: ~~few editorial updates for studies R668-AD-1639, R668-AD-1760 and~~ removal of completed study LTS12551; • Part V: update for consistency with other modules; • Part VI: update for consistency with changes in other modules • ~~Annex 3 – part C: inclusion of amended protocols for studies R668-AD-1639 and R668-AD-1760.~~

AD: Atopic Dermatitis; DLP: Data Lock Point; EU: European Union; RMP: Risk Management Plan.

For RMP v.6.1, the following change was proposed:

- Part III: removal of completed study LTS12551; addition of LTS14424 in III.2 and III.3 tables; addition of due dates for R668-AD-1639 and R668-AD-1760.

2.7.1. Safety concerns

The applicant proposed the following changes to the safety specification (RMP table SVIII.1) in the RMP v. 6.0 and 6.1:

Important identified risks	Systemic hypersensitivity (including events associated with immunogenicity) Conjunctivitis and keratitis related events in AD patients
Important potential risk	None
Missing information	Use in pregnant and lactating women ~~Conjunctivitis related events in AD patients~~ Long-term safety

AD: Atopic Dermatitis.

Data lock-point for the current RMP version 6.1 is 28-Sep-2020.

Discussion of the safety specification

New safety concerns and reclassification with a submission of an updated RMP

The MAH concludes that *"With reference to the final assessment report of procedure EMEA/H/C/PSUSA/00010645/202003, an amendment of the RMP safety specification has been requested, specifically the missing information "Conjunctivitis related events in AD patients" should be replaced with "Conjunctivitis and keratitis related events in AD patients". Furthermore, in view of agreement from PRAC to include keratitis and ulcerative keratitis as ADRs in the EU SmPC sections 4.4 and 4.8 (see last approved SmPC), the MAH proposes to re-classify "Conjunctivitis and keratitis related events in AD patients" from missing information to an important identified risk."*

The MAH proposed the reclassification of *"Conjunctivitis and keratitis related events in AD patients"* from missing information to an important identified risk. As sufficient evidence has been accumulated to conclude that a causal relationship exists, and the events have been listed in the SmPC section 4.8, the proposed re-classification is justified. This safety concern will be further characterised in the ongoing additional PhV activity, namely in Ophthalmology substudy LTS14041 of R668-AD-1225, and therefore the safety concern should still remain in the RMP list of safety concerns. Therefore, MAH's justification and the proposed new RMP list of safety concerns are endorsed.

Conclusions on the safety specification

Having considered the data in the safety specification the CHMP agreed that the safety concerns listed by the applicant are appropriate.

2.7.2. Pharmacovigilance plan

2.7.2.1. Routine pharmacovigilance activities

MAH reports the following routine PhV activities beyond adverse reactions reporting and signal detection:

- Analysis of systemic hypersensitivity events in ongoing clinical studies: To detect any modifications in the risk characterization.
- Hypersensitivity questionnaire for systemic hypersensitivity (including events associated with immunogenicity) to collect data from healthcare professionals for serious hypersensitivity events received in post-marketing setting and detect any modifications in the risk characterization.
- Pregnancy questionnaire for post-marketing events: To monitor pregnancy and infant outcomes in women exposed to commercially supplied dupilumab.

2.7.2.2. Summary of additional PhV activities

Table Part III.3: On-going and planned additional pharmacovigilance activities by MAH (RMP v. 6.1)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1				
Not applicable				
Category 2				
Not applicable				
Category 3				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes in asthma and AD patients.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018) ~~Will also be submitted to other health authorities.~~
			Amended protocol (asthma cohorts)	Submitted for information with EU-RMP v5.0
			Final report	~~Will be submitted once available~~ Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease-matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease-matched cohort who were not exposed to these treatments during pregnancy.	Use in pregnant and lactating women	Protocol submission (amendment 1)	Submitted for information with EU-RMP v5.0
			Final report	~~Will be submitted once available~~Apr-2027
A single-arm extension study of dupilumab in patients with AD who participated in previous dupilumab clinical trials; including a sub study consisting of standardized ophthalmology assessments (Phase IV) (R668-AD-1225) (LTS14041) Ongoing	To assess the long-term safety, efficacy, PK, and immunogenicity of REGN668 in adult patients with moderate-to-severe AD.	Long-term safety (Ophthalmology sub study: additional information on conjunctivitis and keratitis related events in AD patients)	Final report	Q3 2023
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668-AD-1434) Ongoing	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in pediatric patients with AD	Final report	Q4 2024

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
An open-label study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study (Phase III) (LTS14424) Ongoing	To assess the long-term safety, tolerability and efficacy of dupilumab in pediatric patients with asthma	Long-term safety of dupilumab in pediatric patients with Asthma	Final report	Sep-2024

AD: Atopic Dermatitis; PK: Pharmacokinetics; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

2.7.2.3. Overall conclusions on the PhV Plan

The routine PhV activities beyond adverse reactions reporting and signal detection have been agreed in previous processes of dupilumab, and no new routine activities are proposed in the current procedure, no changes are necessary.

The CHMP, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The CHMP also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

2.7.2.4. Summary of Post authorisation efficacy development plan

MAH states that no imposed post-authorization efficacy studies as a condition of the MA or which are specific obligations in the context of conditional MA or MA under exceptional circumstances are planned or ongoing for dupilumab.

2.7.3. Risk minimisation measures

2.7.3.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimization measures by safety concern as presented by MAH (RMP v. 6.1).

Safety concern	Routine risk minimization activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk communication** SmPC section 4.8 PIL section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC section 4.3: contraindication in case of hypersensitivity to the active substance or to any of the excipients. SmPC section 4.4: recommendation to discontinue immediately DUPIXENT and to initiate appropriate therapy if a systemic reaction occurs. PIL section 2: how to detect signs and symptoms of allergic reactions, and recommendation to stop using DUPIXENT, tell the doctor or get medical help immediately if the patient notices any signs of an allergic reaction. **Other routine risk minimization measures beyond the Product Information** Prescription only medicine.
Conjunctivitis and keratitis related events in AD patients	**Routine risk communication** SmPC section 4.8 PIL sections 2 and 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC section 4.4: recommendation, for patients treated with DUPIXENT who develop conjunctivitis or signs and symptoms suggestive of keratitis that does not resolve following standard treatment, to undergo ophthalmological examination. **Other routine risk minimization measures beyond the Product Information** Prescription only medicine
Use in pregnant and lactating women	**Routine risk communication** SmPC sections 4.6 and 5.3 PIL section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk** SmPC section 4.6: recommendation that a decision must be made whether to discontinue breast-feeding or to discontinue DUPIXENT therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. PIL section 2: recommendation for the patient to ask doctor for advice before using DUPIXENT: if the patient is pregnant, thinks may be pregnant, or is planning to have a baby; and if breast-feeding or planning to breast-feed.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information Prescription only medicine
Long-term safety	**Routine risk communication** None **Routine risk minimization activities recommending specific clinical measures to address the risk** None **Other routine risk minimization measures beyond the Product Information** Prescription only medicine

AD: Atopic Dermatitis; PIL: Patient Information Leaflet; SmPC: Summary of Product Characteristics.

MAH's proposal of the description of routine risk minimisation measures by safety concern is endorsed. In addition, the MAH has proposed to the CHMP to update the SmPC in regard to enterobiasis and eosinophilia findings.

2.7.3.2. Summary of additional risk minimisation measures

MAH considers that routine risk minimization activities as described in RMP section V.1 are sufficient to manage the safety concerns of the medicinal product.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern as presented by MAH (RMP v6.1).

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** SmPC sections 4.3, 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None
Conjunctivitis and keratitis related events in AD patients	**Routine risk minimization measures:** SmPC sections 4.4 and 4.8 PIL sections 2 and 4 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Ophthalmology substudy in LTS14041 (R668-AD-1225)
Use in pregnant and lactating women	**Routine risk minimization measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** Pregnancy registry study (R668-AD-1639) in asthma and AD patients
		Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients
Long-term safety	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Studies LTS14041 (R668-AD-1225), LTS1434 (R668-AD-1434), and LTS14424

AD: Atopic Dermatitis; EU: European Union; PIL: Patient Information Leaflet; PK: Pharmacokinetic; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.7.3.3. Discussion on risk minimisation measures

Eosinophilia

As per MAH's protocol description, on-treatment eosinophil counts >3.0 Giga/L were to be reported as AEs, even if they were not associated with symptoms. An analysis on a selected grouping of "eosinophilia" TEAEs was performed, including the HLT "eosinophilic disorders" plus the PT "eosinophil count increased".

In EFC14153, the MAH reported that 6.6% (n=18) vs. 0.7% (n=1) experienced TEAE eosinophilia in the dupilumab group vs. placebo; 6 cases thereof in the dupilumab group were assessed as treatment-related TEAE. According to MAH, most TEAEs of eosinophilia (16 out of 18) were self-limiting laboratory findings without any associated symptoms. Two patients, both in the dupilumab group, required corrective treatment. All patients except one recovered (1 was recovering). MAH reports that all events were mild to moderate and did not require treatment discontinuation, except for one patient, for whom the event was considered serious, severe in intensity and led to treatment discontinuation. MAH considered two events of eosinophilia as SAEs, both in the dupilumab group: One of them was associated with clinical symptoms (headache and dizziness [reported as blurred vision]), was severe and led to permanent treatment discontinuation; In the other event, the patient was hospitalized to rule out suspected parasitic infection, the IMP was continued, and the patient recovered.

As per the MAH's PSUR list of safety concerns, the MAH has included *'eosinophilia associated with clinical symptoms in patients with asthma'* as an important potential risk; (not applicable to EU-RMP version 5.0 as per prior PRAC agreement). Therefore, the MAH has described, and is expected to

continue to do so, the up-to-date risk characterization of eosinophilia across all approved indications in the PSUR submissions. The MAH has not reported a change in the characterization of this risk.

As has been addressed in prior dupilumab MAA and extensions of indication in the adult AD and adult/adolescent asthma population, the transient increase in eosinophil counts during the first weeks of treatment is a known phenomenon caused by dupilumab treatment. Accordant and appropriate measures have been previously implemented in the RMP and SmPC in order to avert possible risks in patients with hyper-eosinophilic conditions.

The current SmPC section 4.4 gives a warning in regard to clinically significant eosinophilia (pneumonia, vasculitis, EGPA) in *adult* patients in previous clinical studies. In the current application, the MAH has proposed to the CHMP to include in section 4.8 a statement describing that eosinophilia (blood eosinophils ≥ 3,000 cells/mcL or deemed by the investigator to be an adverse event) was reported in 6.6 % of the dupilumab groups and 0.7% in the placebo group of paediatric patients. Furthermore, within the current process information regard the adverse event of eosinophilia was included in SmPC 4.8 in the paediatric population.

Parasitic infections (enterobiasis)

In EFC14153, more dupilumab-treated patients experienced parasitic infections (2.6% (n=7) vs. 0% (n=0)). The most frequently reported parasitic infection was enterobiasis (5/7 patients). None of the events were considered as treatment-emergent SAEs by MAH and none resulted in permanent treatment discontinuation or were assessed by the Investigator as related to the IMP. Despite a lacking causal relationship by medical judgement, MAH has suggested the designation of an ADR for the SmPC based on the numerical imbalance of this controlled data.

As per the MAH's PSUR list of safety concerns, the MAH has included *'Helminthic infections'* as missing information (not applicable to EU-RMP version 5.0 as per prior PRAC agreement). Therefore, the MAH has described, and is expected to continue to do so, the up-to-date risk characterization of helminthic infections across all approved indications in the PSUR submissions. The MAH considers that data are missing for populations who reside in endemic regions for helminth infections, including children between the ages of 5 and 15 years who experience the highest rates of specific helminthic (roundworm, hookworm, and whipworm) infections. The MAH reports in the recently submitted PSUR (PSUSA/00010645/202103) that a review of clinical trial and post-marketing data up to the DLP of 28-Mar-2021 identified no change in the characterization of this safety concern.

The current SmPC section 4.4 gives a warning in regard to helminthic infections, and that patients with pre-existing helminth infections should be treated before initiating dupilumab. Further, the SmPC instructs that "If patients become infected while receiving treatment with dupilumab and do not respond to anti-helminth treatment, treatment with dupilumab should be discontinued until the infection resolves". The MAH has now proposed to the CHMP addition of following information in section 4.4 "Cases of enterobiasis were reported in children 6 to 11 years old who participated in the paediatric asthma development program". Cross-reference is made to section 4.8. where the MAH has proposed addition of text "In children 6 to 11 years of age with moderate-to-severe asthma (VOYAGE), the additional adverse reactions of enterobiasis and eosinophilia were reported. Enterobiasis was reported in 1.8 % (5 patients) in the dupilumab groups and none in the placebo group. All enterobiasis cases were mild to moderate and patients recovered with anti-helminth treatment without dupilumab treatment discontinuation". Of note and to be taken into consideration, the dupilumab SmPC section 4.8 has recently been updated to replace ADR tables per indication with a consolidated table of ADRs across all approved indications (EMEA/H/C/004390/II/0039).

In light of current knowledge and results, the risks of eosinophilia and parasitic infections can be appropriately addressed by routine RMMs, i.e. SmPC sections 4.4 and 4.8, were updated according to

the consideration to reflect the current clinical trial findings. It is noted that the RMP no longer is a document describing the product and all the risks that may be associated with the product, but rather a planning tool for additional PhV activities and RMM. Neither additional PhV-activities nor additional RMMs have been considered necessary or have been planned for the topics of eosinophilia or parasitic infections in the past in the EU. The current results on the paediatric asthma patients do not for the time being change that consideration. Meanwhile, the MAH has been instructed in prior PSURs to continue to monitor these subjects by means of routine pharmacovigilance and report any concerns in future PSURs. No additional PhV activities or RMMs are deemed necessary in light of the present information.

2.7.3.4. Overall conclusions on risk minimisation measures

The CHMP had considered the data submitted and was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 6.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is the most common chronic disease of childhood affecting over 8% of children in the United-States (US), and over 9% of children in the European Union (EU), with a worldwide prevalence estimated at almost 12%. Over one-third of children with asthma in the US and Western Europe have a disease that can be characterized as moderate-to-severe, with around 19% of children having a disease characterized as moderate, and around 2% with severe disease.

Asthma is a complex, heterogeneous disease that can affect persons of all ages. Asthma is characterized by chronic airway inflammation and variable expiratory airflow limitation that is often reversible. Symptoms vary over time and in intensity and can include wheezing, shortness of breath, chest tightness, and cough. Children with uncontrolled moderate-to-severe asthma are at risk for future respiratory complications, including asthma exacerbations which can be life-threatening at times, and progressive lung function decline. These children are at increased risk for abnormal patterns of lung growth, including reductions in maximal lung function achieved or early decline in lung function. Progressive lung function decline can lead to fixed airflow obstruction or even the development of chronic obstructive pulmonary disease at a young age.

3.1.2. Available therapies and unmet medical need

The primary goal of asthma management in children is to achieve the control of symptoms, optimize lung function, and to decrease or eliminate asthma exacerbations while balancing the potential side effects of therapy. In addition, management of childhood asthma aims to reduce the chronic underlying inflammation process that if left uncontrolled may lead to non-reversible airflow limitation. The GINA guidelines for the management of asthma in children age 6 to <12 years old centre on a stepwise approach to therapy, with incremental adjustments in controller therapy for each step (1-5) reflecting the frequency and extent of underlying symptoms. Inhaled corticosteroids (ICS) are the primary controller medication, and additional controllers include long-acting β2 agonists (LABAs), leukotriene receptor antagonists (LTRAs), or long-acting muscarinic antagonists (LAMAs). Short-acting beta-2 agonists (SABA) are used as needed for rescue medication. Children meeting criteria for Step 4 and 5 therapy experience symptoms most days, and standard of care treatment as of the GINA 2020 includes medium-dose ICS plus a LABA, with other options including the combination of several controller therapies. For children uncontrolled with this approach, additional add-on therapy options at Step 5 include systemic corticosteroids (SCS), anti-IgE (omalizumab) for patients with moderate-to-severe persistent IgE-mediated asthma, or anti-IL-5 (mepolizumab) for patients with elevated blood eosinophil counts.

Inhaled corticosteroids and SCS carry known side effects, and therefore guidelines recommend using the minimum effective dose to maintain asthma control. While there is strong evidence that both ICS and SCS can prevent exacerbations and preserve lung function, there is little data to support added clinical benefit from increasing ICS above medium dose in children. In children, the long-term use of ICS can have negative impacts on growth, bone metabolism, and adrenal function. In addition to these adverse effects, short courses of SCS are additionally associated with acute mood changes and sleep disturbances.

For paediatric patients with uncontrolled asthma, add-on therapies beyond the standard of care therapies are currently still limited. Mentioned targeted biologic therapies for treating IgE-mediated and eosinophilic asthma are intended for specific patient populations, or clinical efficacy has yet to be demonstrated in randomized-controlled trials. Predictors of good asthma response to dupilumab are higher blood eosinophils and FeNo.

3.1.3. Main clinical studies

Table 12 List of Phase 3 asthma pediatric (6 to <12 years) studies evaluated in the Summary of Clinical Safety and study status

Study number/Status at submission cut-off	Summary of key study information	Planned study duration	Number of patients evaluated for safety
Patients with indication(s) of interest			
EFC14153/completed on 26-Aug-2020	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. Dose regimen: 100 mg q2w for patients ≤30 kg or 200 mg q2w for patients >30 kg	64 weeks after randomization (52 weeks of treatment + 12 weeks of follow-up only for patients who did not enter in Study LTS14424)	405
LTS14424/ongoing (cut-off on 18-Aug-2020)	One-year study to evaluate the long-term safety and tolerability of dupilumab in pediatric patients with asthma who participated in a previous dupilumab asthma clinical study Dose regimen: 100 mg q2w or 300 mg q4w for patients ≤30 kg or 200 mg q2w for patients >30 kg	64 weeks (52 weeks of treatment + 12 weeks of follow-up)	365

3.2. Favourable effects

Compared with placebo, the annualized rate of severe exacerbation events during pivotal study EFC14153 was significantly reduced in patients assigned to both the dupilumab 100 mg Q2W and 200 mg Q2W dupilumab groups of the pre-defined primary efficacy populations, i.e. 0.305 (dupilumab) vs. 0.748 (placebo) (type 2 inflammatory asthma phenotype) and 0.235 (dupilumab) vs. 0.665 (placebo) (baseline blood eosinophils ≥0.3 Giga/L phenotype). The relative risk reduction versus placebo was 59.3% and 64.7%, respectively.

These results were consistent across all efficacy populations, i.e. 0.318 vs. 0.816 (dupilumab/placebo) in patients exhibiting blood eosinophils ≥0.15 Giga/L at baseline and 0.271 vs. 0.705 (dupilumab/placebo) in those with baseline FeNO ≥20 ppb 0.271.

The long-term efficacy of dupilumab is substantiated by the fact that the cumulative mean number of severe exacerbations, as well as the relative risk in annualized rate of severe exacerbation, were lower

in the dupilumab-treated patients of all four biomarker-based efficacy populations compared to placebo over 52 treatment weeks.

Consistent with these results, in dupilumab-treated patients the time-to-first severe exacerbation event was prolonged in all analysed efficacy populations.

Efficacy was also demonstrated by a statistically significant and clinically relevant improvement (LS) mean change from baseline) in percent predicted pre-BD FEV1 at Week 12 in both primary efficacy populations, i.e. 10.53% (dupilumab) vs. 5.32% (placebo) (type 2 inflammatory asthma phenotype) and 10.15% (dupilumab) vs. 4.83% (placebo) (baseline blood eosinophils ≥0.3 Giga/L phenotype). These effects were maintained up to treatment week 52.

Dupilumab's clinical benefit is also reflected by significant change from baseline in Asthma Control Questionnaire (ACQ-7-IA) scores at Week 24 and in Paediatric Asthma Quality of Life Questionnaire Scores with Standardized Activities (PAQLQ(S)-IA) at Weeks 12, 24, 36, and 52, as well as reduction of the annualized rate of loss of asthma control events (LOAC).

3.3. Uncertainties and limitations about favourable effects

Regarding the gender, the adjusted annualized severe exacerbation event rate was lower for males and females assigned to the dupilumab treatment groups of both primary efficacy populations compared to the placebo groups. The effect for females was lower compared to males, most likely due to a lower exacerbation rate in the female placebo subgroup and sample size imbalances with regards to gender.

3.4. Unfavourable effects

Pivotal Phase 3 study EFC14153:

A higher TEAE frequency in the verum group was observed for SOCs 'Blood and lymphatic system disorders' (8.5% vs. 3.0%) and 'Gastrointestinal disorders' (14.8% vs. 9.7%). At PT level, 'eosinophilia' and 'injection site reactions' occurred more often in the dupilumab treatment group. More cases of parasitic infections such as enterobiasis were reported in the verum group (2.6% vs. 0.7%).

The following drug-related TEAEs occurred more often in the dupilumab group (PT level): 'Injection site erythema' (12.9% vs. 9.7%), 'injection site edema' (10.3% vs. 5.2%), 'injection site nodule' (6.3% versus 2.2%), 'injection site pain' (1.8% versus 1.5%), 'eosinophilia' (1.8% versus 0), and 'headache' (1.5% versus 0.7%). Single cases of ascariasis, enterobiasis, hordeolum, pulmonary tuberculosis, rash and headache were deemed related to the IMP.

Two SAEs of pneumonia and eosinophilia with headache and blurred vision were assessed as possibly related to dupilumab.

Numerical differences of AESI were observed at PT levels 'Injection site reactions' (17.7% DUP vs. 13.4% PLC) and 'eosinophilia' (6.6% DUP vs. 0.7% PLC). Regarding the subgroup analysis, more patients ≤30 kg bw experienced parasitic infections (5.5% vs. 1.1%) and eosinophilia (9.9% vs. 5.0%) than those ≥ 30 kg bw. Conversely, injection site reactions occurred more often within the higher weight class (20.0% vs. 13.2%).

Open-label extension study LTS14424:

During study LTS14424, overall, 55.1% patients experienced at least 1 TEAE and 12.9% were assessed as possibly related to dupilumab. Generally, patients that had received dupilumab in the parent study reported TEAEs less frequently (50.8% vs. 63.2%). Single cases of ascariasis,

enterobiasis, hordeolum, pulmonary tuberculosis, rash and headache were deemed related to the IMP. Most related TEAEs were reported for PTs 'Injection site reaction' (4.4%), 'Injection site erythema' (2.2%), 'Injection site nodule' (1.4%), 'Accidental overdose' (1.6%) and 'Eosinophilia' (1.1%).

3.5. Uncertainties and limitations about unfavourable effects

The safety profile of dupilumab is well-characterized, also in the targeted disease, and no new safety concerns were observed in the pivotal study.

Effects Table

Effect	Short description	Unit	DUP 100 / 200 mg q2w	PLC	Strength of evidence/ Uncertainties	References
Change in rate of exacerbation	Annualized event rate of severe exacerbation events during 52-week treatment period	n/52 weeks	0.196 (⩽ 30 kg) / 0.344 (⩾ 30 kg)	0.618 0.766	p<0.0016 p<0.0011	Type 2 inflammatory asthma phenotype population (EFC14153)
			0.244 (⩽ 30 kg) / 0.209 (⩾ 30 kg)	0.710 0.594	p<.00052 p<0.0006	Baseline blood eosinophils >=0.3 G/L population (EFC14153)
Change in lung function	LS Mean Percent Change in percent predicted pre-bronchodilator FEV_1 at week 12 from Baseline	%	10.53 10.15	5.32 4.83	p<0.0009 p<0.0001	Type 2 inflammatory asthma phenotype population (EFC14153) Baseline blood eosinophils >=0.3 G/L population (EFC14153)
Effects on asthma control	Reduction from Baseline in ACQ-7-IA score at Week 24	pts	-1.33 -1.34	-1.00 -0.88	p=0.0001 p=0.0001	Type 2 inflammatory asthma phenotype population (EFC14153) Baseline blood eosinophils >=0.3 G/L population (EFC14153)
Infections	Incidence of viral upper respiratory tract infection	%	12.2	9.7	Incidence of TEAEs in SOC Infections comparable between treatment groups	(1) Appendix 16.2.7 AE data
Injection site	Incidence of	%	12.9	9.7		(1)

Effect	Short description	Unit	DUP 100 / 200 mg q2w	PLC	Strength of evidence/ Uncertainties	References
reactions	injection site erythema, edema, nodule		10.3 6.3	5.2 2.2		Appendix 16.2.7 AE data
Eosinophilia	Incidence of eosinophilia	%	5.9	0.7		(1) Appendix 16.2.7 AE data
Enterobiasis	Incidence of enterobiasis	%	1.8	0	All were assessed as not related to the IMP by the Investigator	(2) Tab. 23 Clin. Safety Summary Listed as ADR as proposed by the applicant due to MoA
Immunogenicity	Treatment-emergent response[a]	%	6.3(1) 3.8(3)	3.0	Incidence decreasing over time	(1), (3) Tab. 31 Clin. Safety Summary

Abbreviations: ADA: Anti-drug antibodies, DUP: Dupilumab, ISR: Injection Site Reaction, LS: Least square, n: number, pts: Points, PLC: Placebo

Notes: (1) Study EFC14153- Safety population, (≥5% in the dupilumab group and a difference of ≥1% versus the placebo group at the PT level); (2) Summary of patients with treatment emergent parasitic infections in Study EFC14153 - Safety population; (3) ADA incidence in children 6 to <12 years of age with asthma study LTS14424; a: Positive response in the ADA assay post first dose when baseline results are negative or missing.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Results of the pivotal Phase 3 study EFC14153 show that dupilumab-treated paediatric patients aged 6-11 years with severe type 2 asthma had significantly lower rates of severe asthma exacerbations than those who received placebo and these results were substantiated by long-term data coming from study LTS14424.

Moreover, dupilumab improved lung function as measured by changes in pre-bronchodilator FEV1. The results were consistent in the primary pre-specified efficacy populations defined by type 2 biomarkers. The patient reported outcomes showed an improvement in quality of life of the patient population. Consistency of the results was demonstrated for the different dose groups (100/200 mg q2w and 300 mg q4w) regarding all efficacy endpoints and additional spirometric parameters that were added to the SmPC upon request. Note that efficacy and safety results were regarding the 300 mg q4w are based on uncontrolled data of 18 patients. This dose regimen, however, is already approved for AD patients ≥15 kg bw.

The most relevant safety concerns associated with dupilumab treatment identified during the development programs are related to immunogenicity and associated (systemic) hypersensitivity reactions, infections, eosinophilia and related conditions, eye disorders, injection site reactions, parasitic infection, risk of malignancy, as well as uncertainties about the impact of dupilumab on

pregnancies and their outcomes. These risks are commented below, mainly based on analyses of the Adverse Events of Special Interest (AESI):

During EFC14153 study, slightly more patients assigned to the dupilumab 200 mg Q2W group (>30 kg) had treatment-emergent ADA response compared with the patients treated with 100 mg Q2W (≤30 kg) and with placebo. Persistent ADA responses were balanced across the dupilumab groups and ADA response gradually decreased over time. There was no apparent pattern or increase in TEAE incidence in the ADA-positive patients compared with the ADA-negative patients; no anaphylactic reaction, hypersensitivity or injection sire reactions occurred in patients with neutralizing antibodies. Thus, the immunogenic risk associated with dupilumab remains low.

Events of hypersensitivity reactions occurred at a lower frequency in the dupilumab group of the pivotal study EFC14153 and only one event of moderate drug hypersensitivity in the dupilumab group was considered serious and led to treatment discontinuation. No anaphylactic reaction was observed in the verum group. Thus, the risk for developing hypersensitivity or anaphylactic events seems to be low under dupilumab treatment in the paediatric asthma population.

Similarly, dupilumab seems not to increase the risk for infections in general. The overall rate was lower in the dupilumab treated patients compared with the placebo group. Most TEAEs were mild-to-moderate and considered unrelated to the study drug. Results were similar in the open-label extension study.

As to injection site reactions (ISR), the following drug related TEAEs occurred more often in the dupilumab group during EFC141453 study. During study LTS14424, most related TEAEs were reported for PTs Injection site reaction, Injection site erythema and Injection site nodule, no severe or serious ISR occurred.

Eosinophilia was reported more frequently in the dupilumab group and again more frequently in children with baseline weight ≤30 kg. 2 events in the verum group were considered serious, one thereof was associated with headache and dizziness, assessed as related to dupilumab and lead to treatment discontinuation. The frequency decreased over time. Eosinophilia is a known ADR and listed in section 4.8 of the SmPC; no update of the frequency was considered necessary.

More dupilumab-treated patients experienced parasitic infections. The most frequently reported parasitic infection was enterobiasis. None of the events were considered as treatment-emergent SAEs and none resulted in permanent treatment discontinuation or were assessed by the Investigator as related to the IMP.

Eye disorders and especially conjunctivitis (narrow and broad) were reported less frequently in the dupilumab group when compared with the placebo group.

No event of malignancy was identified.

These results are consistent with the known safety profile of Dupixent and corresponding ADRs are reflected in the PI.

3.6.2. Balance of benefits and risks

For paediatric patients with uncontrolled asthma, add-on therapies beyond the standard of care therapies are currently still limited. Considering the efficacy and safety results, the CHMP is of the opinion that the favourable effects outweigh the unfavourable effects. The benefit-risk balance is positive and the same as the one observed in the adolescent and adult populations.

3.7. Conclusions

The overall benefit/risk balance of Dupixent is positive.

4. Recommendations

Outcome

POSITIVE OPINION

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Dupixent 100 mg solution for injection is favourable in the following indication:

Treatment of Asthma in children from 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO) who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Dupixent subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0404/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variations to the terms of the marketing authorisation concerning the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Adopted scope:

Extension application to add a new strength of 100 mg solution for injection in pre-filled syringe with safety system (PFS-S) grouped with a type II variation (C.I.6.a) to include the treatment of asthma in children from 6 to 11 years old as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with medium to high dose ICS plus another medicinal product for maintenance treatment.

As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated accordingly. Furthermore, the PI is brought in line with the latest QRD template version 10.2 Rev1.The RMP has been amended (version 6.1).