28 February 2019
EMA/188111/2019
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on extension of marketing authorisation and an extension of indication variation

Dupixent

International non-proprietary name: dupilumab

Procedure No. EMEA/H/C/004390/X/0004/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

ACQ: Asthma Control Questionnaire, diastolic blood pressure
AD: atopic dermatitis
ADA: anti-drug antibodies
AE: adverse event
ALT: alanine aminotransferase
AQLQ: Asthma Quality of Life Questionnaire, Standardized Version
AS: Active Substance
BLA: Biologics License Application
CHO: Chinese Hamster Ovary
CI: confidence interval
CMQ: Custom MedDRA Query
CPK: creatine phosphokinase
CRF(s): case report form(s)
CRSwNP: Chronic rhinosinusitis with nasal polyposis
CSR: clinical study report
CT: computerized tomography
CTD: Common Technical Document
DF: Direct Formulation
ECG: electrocardiogram
eCRF(s): electronic case report form(s)
EGPA: eosinophilic granulomatosis with polyangitiis
ER: emergency room
EU: European Union
FAS: Formulated Active Substance
FEV1: forced expiratory volume in 1 second
FP: Finished Product
GMP: Good Manufacturing Practice
HLGT: high-level group term
HLT: high-level term
ICH: International Conference on Harmonisation
ICS: inhaled corticosteroids
IgG4: immunoglobulin G4
IL-13: interleukin-13
IL-4: interleukin-4
IMP: investigational medicinal product
IPC: In Process Controls
ISS: Integrated Summary of Safety
K-M: Kaplan-Meier
LABA: long-acting beta agonist
LIVCA: Limit of In Vitro Cell Age
LLT: low-level term
LMW: low molecular weight
LTRA: leukotriene receptor antagonist
MAA: Marketing Authorisation Application
MACE: major adverse cardiovascular events
MedDRA: Medical Dictionary for Regulatory Activities
MRI: magnetic resonance
NAb: neutralizing antibody

NIMP: noninvestigational medicinal product
OCS: oral corticosteroid
OR: odds ratio
PA: Process area
PADER: periodic adverse drug experience report
PAR: Proven Acceptable Range
PCR: Polymerase Chain Reaction
PFP: Pre-Filled Pen
PFS: Prefilled Syringe
PFS-S: Prefilled Syringe with Safety System
Ph.Eur.: European Pharmacopoeia
PK: pharmacokinetic
PPQ: Process Performance Qualification
PT: preferred term
q2w: every 2 weeks
q4w: every 4 weeks
RBC: red blood cells
RS: Reference Standard
SA: Support Area
SAB: spontaneous abortion
SAE: serious adverse event(s)
SAP: statistical analysis plan
SBP: systolic blood pressure
SC: subcutaneous
SCS: Summary of Clinical Safety
SD: standard deviation
SI: standard international
SOC: system organ class
SPA: spontaneous abortion
SUSAR: suspected unexpected serious adverse reaction
TE: treatment-emergent
TEAE: treatment-emergent adverse event
TK: Toxicokinetics
TSE: Transmissible Spongiform Encephalopathies
ULN: upper limit of normal
US: United States
USP: United States Pharmacopeia
WBC: white blood cells

1. Background information on the procedure

1.1. Submission of the dossier

Sanofi-aventis groupe submitted on 6 March 2018 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

Extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP), grouped with a type II variation (C.I.6.a) to add the following indications:
- Add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older, who are inadequately controlled with medium-to-high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment, including those with or without an eosinophilic phenotype;
- Maintenance therapy to improve lung function;
- Maintenance therapy to reduce oral steroid use and improve lung function in steroid-dependent asthma patients;

based on the pivotal studies DRI12544, QUEST and VENTURE.

As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated accordingly.
The RMP (version 2.0) is updated accordingly.

In addition to the above changes in the approved 300 mg SmPC, a new SmPC for the 200 mg strength was submitted for the asthma population that would be eligible for this dose.
In addition, the MAH proposed to merge the SmPCs for the 200 mg and 300 mg strengths. This request was not approved by CHMP.

The legal basis for this application refers to:

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

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0021/2017 on the agreement of a paediatric investigation plan (PIP).

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

The PDCO issued an opinion on partial compliance for the PIP P/0021/2017.

Information relating to orphan market exclusivity

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.

Scientific Advice

The MAH received Scientific Advice from the CHMP on 24 April 2015 (EMEA/H/SA/2744/3/2015/II) pertaining to clinical aspects of the dossier, 5 June 2015 (EMEA/H/SA/2744/3/2015/II Clarification letter) pertaining to clinical aspects of the dossier and 14 September 2017 (EMEA/H/SA/2744/6/2017/I) pertaining to quality aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: Peter Kiely

The application was received by the EMA on	06 March 2018
The procedure started on	29 March 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 June 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	12 July 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 July 2018
The MAH submitted the responses to the CHMP consolidated List of Questions on	13 September 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 October 2018
The PRAC Rapporteur's Assessment Report was circulated to all PRAC members on	19 October 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	31 October 2018
The Rapporteurs circulated the Updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	08 November 2019

The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	15 November 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	31 December 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	16 January 2019
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	24 January 2019
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the MAH on	31 January 2019
The MAH submitted the responses to the CHMP List of Outstanding Issues on	06 February 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	14 February 2019
The outstanding issues were addressed by the MAH during an oral explanation during the meeting on	26 February 2019
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	28 February 2019

2. Scientific discussion

2.1. Problem statement

Asthma is a chronic inflammatory disease of the airways characterized by airway hyper responsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products.
The poor response of some patients with asthma to the standard regimen of controller and reliever therapies may reflect the number of cellular and molecular mechanisms operative in asthma. Recent therapeutic approaches in asthma have been focused on trying to control the Type 2/ T-helper cell-2 (Th2) response. Up-regulation of the Th2 cell-derived cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13) has been implicated as an important inflammatory component of asthma disease progression.

2.1.1. Epidemiology

Asthma is the most common chronic lung disease affecting approximately 334 million people world-wide.

Between 35% and 50% of asthma expenditures are consequences of exacerbations and hospitalizations, emergency department and unscheduled clinic visits comprise the majority of exacerbation-related treatment costs. Approximately 5 to 10% of the total asthma population has severe asthma. Nearly 25% of patients with severe asthma have had a near fatal asthma attack.

Recurrent exacerbations are thought to be associated with an increased risk of permanent damage to the lung tissue and lead to a progressive decline in lung function. Patients with asthma, especially those with more severe, persistent disease, are at risk of an excessive decline in lung function in adulthood.

2.1.2. Biologic features, Aetiology and pathogenesis

Complex inflammatory pathways in the airway underlie disease pathobiology of uncontrolled asthma. In the majority of cases this inflammatory process is driven by Type 2 inflammation characterized by the release of signature cytokines interleukin-4 (IL-4), interleukin-13 (IL-13) and interleukin-5 (IL-5) via both the innate and adaptive immune pathways. Typically, individuals with Type 2 high asthma present with airway eosinophilia (with or without blood eosinophilia), elevated levels of fractional exhaled nitric oxide (FeNO), increased numbers of airway mast cells, increased levels of serum periostin. It has been demonstrated that the elevations in Type 2 driven inflammation play a critical role in the pathogenesis of asthma exacerbations.

IL-4 is a central mediator of T lymphocyte cell differentiation; it induces the production of Type 2 associated cytokines and chemokines (IL-5, IL-9, IL-13, thymus and activation-regulated chemokine [TARC/CCL17] and eotaxins-3), isotype class switching of B cells to produce serum IgE, and the recruitment of eosinophils and other inflammatory cells (including tissue eosinophils). Although IL-13 displays some redundancies in these pro-inflammatory processes, it has additional roles in mediating goblet cell hyperplasia, mucus production, smooth muscle contractility, and airway hyper responsiveness. Together, IL-4 and IL-13 play critical roles in the induction and effector phases of asthma. Biomarkers of Type 2 inflammation include blood and sputum eosinophils, FeNO, serum IgE, serum periostin, TARC/CCL17, eosinophil cationic protein (ECP), eotaxin-3 and pulmonary and activation-regulated chemokine (PARC)/CCL18.

While IL-4 and IL-13 have overlapping pleotropic actions, IL-4 tends to predominate in modulating immune cell functions whereas IL-13 predominates in stimulation of tissues. IL-4 is a major mediator of the polarization of T helper cells toward the Th2 phenotype, ie, cells that secrete more exclusively IL-4, IL-5 and IL-13 and their proliferation. Th2 cytokines have a central role in stimulating secretion of chemotaxins that promote homing of Th2 cells, eosinophils and mast cells into the respiratory epithelium. Surface immunoglobulin E (IgE) receptors on mast cells and eosinophils facilitate release of stored pro-inflammatory mediators from these cells through both allergen-dependent and -independent mechanisms. Under conditions of asthmatic inflammation, IL-4 and IL-13 prime mast cells, enhancing their responsiveness, in part by up-regulating surface receptors for IgE, and inducing the production and storage of cytokines, including IL-4 and IL-13. Th2 asthma is often associated with elevation in serum IgE and allergen sensitization (ie, atopy). IL-4 is recognized as the principle promoter of IgE class switching in B cells and is thus central to elevation in IgE and the sensitization of cells expressing IgE receptors. The various mediators released by these sensitized cells during exposure to allergens are major contributors to airway hyper responsiveness and disease exacerbation.

2.1.3. Clinical presentation

Asthma is characterized by airway inflammation with edema, cellular infiltrations and mucus plugging, variable airway obstruction and bronchial hyper responsiveness 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 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 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 cause, especially in patients with reduced lung function. These findings underscore the importance of preserving normal lung function in the management of asthma.

2.1.4. Management

As defined by asthma treatment guidelines, the goals of therapy are twofold: reduction in impairment and reduction in risk. Reduction in impairment is defined by reduction in frequency and intensity of asthma symptoms, improvement in lung function, reduction in short acting beta agonist use. Reduction in risk includes prevention of acute recurrent exacerbations, prevention of loss of lung growth in children and loss of lung function in adults, and the optimization of pharmacotherapy to allow for minimal or limited adverse effects associated with treatment regimens. Although existing therapies are able to control symptoms and improve reversible airway obstruction in mild asthma, approximately 50% of patients with asthma have moderate-to-severe uncontrolled disease with 5% to 10% considered to have severe uncontrolled disease despite use of currently available therapies. These latter patients are at the highest risks of the morbidity and mortality associated with asthma. However, patients with moderate-to-severe disease have significant impairment to quality of life and contribute to the substantial healthcare costs for this disease.

As stated above, the long-term goals of asthma treatment are to achieve good symptom control, minimize future risk of exacerbations and to improve lung function, including preventing progression to a fixed airway obstruction while minimizing the risk of side effects associated with treatments (long-term, high dose ICS and chronic use of oral corticosteroids [OCS]).

There are three main categories of asthma medications:
• Reliever (rescue) medications: these provide as-needed immediate relief of symptoms related to bronchospasm which occurs in the setting of poorly controlled asthma or secondary to an allergen, microbe or pollutant. These are mostly short-acting β2-agonists (SABAs).
• Controller medications (inhaled corticosteroids, inhaled corticosteroids combined with a long acting β2-agonists (LABAs), and leukotrienes): these are used for regular maintenance treatment. They reduce airway inflammation, control symptoms and reduce future exacerbation risks.
• Add-on therapies: these are considered when symptoms persist despite treatment with inhaled controller medication. This category includes:
- Long-acting muscarinic antagonists (LAMAs) (eg, tiotropium), and methyl-xanthines (eg, theophylline)
- Chronic OCS therapy, used in the most severe patients who cannot achieve asthma control with standard-of-care
- Biologic treatments. These currently include 2 classes of drugs:
- anti-IgE (omalizumab)
- anti-IL-5 monoclonal antibodies (mAbs): mepolizumab, reslizumab, and anti-IL-5 receptor alpha mAb benralizumab.

Unmet medical need
For patients with moderate-to-severe uncontrolled asthma, combination inhalers delivering inhaled corticosteroids (ICS) and long-acting beta agonists (LABA) are the current standard of care recommended by asthma guidelines, and additional controller medications (leukotriene receptor antagonist [LTRA], theophylline, etc.) may be used. However, if patients remain uncontrolled on ICS, further dose increases provide little incremental benefit. Many severe patients with uncontrolled symptoms have significant Type 2 inflammation. Therapeutic options for these patients are limited and often require frequent or maintenance use of oral corticosteroids. Chronic use of oral corticosteroids leads to well-recognized and significant complications which may include increased risk of glaucoma, cataract, diabetes, osteoporosis, susceptibility to infections, obesity, avascular necrosis, stroke, hypertension, sleep disturbances, mood swings and weight gain. Long-term use of ICS treatment, especially high-dose, is also associated with adverse events: in adolescents, adrenal suppression and growth retardation has been observed; while in adults, increased incidence of glaucoma, cataract and bone density loss has been reported.
There is a recognized ceiling effect for what can be achieved with ICS/LABA combinations. It has been shown that if patients remain uncontrolled on medium doses of ICS, further dose increases provide little incremental benefit. For patients with uncontrolled asthma, ICSs often fail to normalize elevated Type 2 biomarkers in

blood, exhaled air and/or induced sputum, indicating persistence of significant residual Type 2 inflammation. The role of ICS in altering the airway remodeling and the natural course of asthma has not been well established; some studies demonstrated benefits with early intervention whereas others failed to show any benefit on lung function changes over time. Combination of ICS +LABA shows some improvement on FEV1 due to their bronchodilator effect. The add-on benefit of LABA to ICS, however, provides an additional reduction of exacerbations (on the order of a 20% to 25% reduction in severe exacerbations. Leukotriene receptor antagonists (LTRA) are less effective than ICS and may be appropriate for some patients who are unable or unwilling to use ICS or experience intolerable side-effects from ICS. LAMA add-on may have additional benefits on lung function and asthma control over LABA/ICS; however, effects in reducing the need for rescue oral steroids and benefits on quality of life are inconsistent and negligible.

About the product

Mode of Action (MoA)

Dupilumab (also referred to as SAR231893 and REGN668) is under development as a potential novel treatment for asthma. Dupilumab is a human monoclonal immunoglobulin G4 (IgG4) antibody that inhibits interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling by specifically binding to the IL-4Rα subunit shared by the IL-4 and IL-13 receptor complexes. Dupilumab inhibits IL-4 signaling via the Type I receptor and both IL-4 and IL-13 signaling through the Type II receptor. IL-4 is the central mediator of TH naive T cells differentiating into Type-2 cytokine-producing effectors cells, growth of B cells and initiation of isotype class switching (especially to IgE). Although IL-13 has some redundancy in these pro-inflammatory processes, IL-13 has additional roles in mediating goblet cell hyperplasia and smooth muscle contractility. IL-4 and IL-13 maintain immune polarization towards a Type-2 response. Blocking IL-4Rα with dupilumab inhibits IL-4 and IL-13 cytokine-induced responses, including the release of proinflammatory cytokines, chemokines and IgE. As a selective immunomodulator targeting Type 2 inflammation, dupilumab has been approved for the treatment of moderate-to-severe atopic dermatitis (AD) in the United States (US) and the European Union (EU).

Regulatory Histor

At time of submission, dupilumab is approved in the US, Canada and EU for the treatment of adult patients with moderate-to-severe atopic dermatitis (AD) and is under review by a number of other health authorities for the AD indication. Dupilumab has not been approved for the asthma indication by any regulatory agency to date.

Dupilumab is currently in development for the treatment of Nasal Polyposis (Phase 3) and Eosinophilic Esophagitis (Phase 2) in adults. Phase 3 pediatric studies in AD (from 6 to 11 years old, and from 12 to 17 years old) and asthma (from 6 to 11 years old) are also ongoing. The proposed dupilumab asthma program and the pooling strategy for the evaluation of efficacy and safety was discussed and agreed with regulatory authorities.

Type of Application and aspects on development

The application is submitted in accordance with Article 3(1) of Regulation (EC) No 726/2004.

The applicant is submitting, under the existing Dupixent MAA (EMA/H/C/004390), the following grouping according to article 7.2 (b) of the variation regulation (cases for grouping variations listed in Annex III to Commission Regulation (EC) No 1234/2008):

- New strength 200 mg: Extension of a marketing authorization under Annex I to Commission Regulation (EC) No 1234/2008 for dupilumab 175 mg/mL solution for injection to be used for the asthma indication.

- New asthma indication: Type II variation as defined in Article 2(3) of Commission Regulation (EC) No 1234/2008 for new therapeutic indication. The applicant is seeking the asthma indication in adults and

adolescents population under Article 8 of Paediatric Regulation 1901/2006.

2.2. Quality aspects

2.2.1. Introduction

The finished product (FP) is presented as a solution for injection containing 200 mg of dupilumab (INN) as active substance in 1.14 mL solution (175 mg/ mL). It is supplied as a clear to slightly opalescent, colourless to pale yellow solution for subcutaneous injection.

Other ingredients are: arginine hydrochloride; histidine; polysorbate 80; sodium acetate trihydrate; glacial acetic acid; sucrose and water for injections.

The product is available in a siliconised type-1 clear glass pre-filled syringe with needle shield (comprising a needle-safety system) (PFS-S) or pre-filled pen (PFP), with a fixed 27 gauge 12.7 mm (½ inch), thin wall stainless steel staked needle.

The active substance dupilumab is a fully human IgG4 monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cells. Dupixent is authorised in the EU for the treatment of atopic dermatitis with a dosage strength of 150 mg/mL dupilumab filled into a 2.25 mL single-use pre-filled syringe (PFS) to provide a deliverable volume of 2 mL (300 mg dose) and is available as 300 mg in a PFS and 300 mg PFS with safety system (PFS-S).

For the asthma indication an additional dosage of 200 mg is proposed which is the subject of this line extension application.

The 200 mg dose is delivered using a 1 mL glass syringe that contains a volume of 1.14 mL compared to the 300mg dose authorised product (2.25 mL). The reduced volume of administration of the 200 mg dose product (1.14 mL) compared to the 300mg dose authorised product (2.25 mL), will be manufactured from a proposed additional strength of 175 mg/mL which comprises - besides the higher dupilumab concentration - a slightly different formulation compared with the authorised strength of 150 mg/mL.

2.2.2. Active Substance

General information

Dupilumab is a recombinant human IgG4 monoclonal antibody that binds specifically to the IL-4R alpha sub-unit of the IL-4 and IL-13 receptor complex. Dupilumab has a predicted protein molecular weight of 146,897.0 Da and contains a single, conserved N-glycosylation site (Asn302) in the Fc region of each heavy chain subunit. Dupilumab heavy chains contain a serine to proline mutation at amino acid 233, which is located in the hinge region of the Fc domain.

Manufacture, characterisation and process controls

Manufacture of dupilumab active substance (AS) and formulated AS (FAS) is performed at Regeneron Pharmaceuticals, Inc., Columbia Turnpike, USA. Other sites for specified testing are described in the application. All sites are appropriately GMP-certified.

Description of manufacturing process and process controls

The new dosage/strength 200 mg (175 mg/mL x 1.14 mL) is made from the same active substance as the authorised dosage/strength 300 mg (150 mg/mL x 2 mL). Differences in the manufacturing processes that lead to the two different strengths start with formulation of AS into formulated AS (FAS). Besides the higher dupilumab concentration, the formulation of both strengths differs in arginine concentration.

No changes to the authorised strength have been made in the context of the present extension. The dupilumab AS is not affected by the additional strength. New or revised documentation regarding the “active substance” sections of the CTD dossier pertain to FAS only, except for some editorial changes.

The batch size is defined. FP derived from the commercial AS as well as from AS manufactured with an earlier process was used in pivotal clinical trials for both strengths- 150 and 175 mg/mL dupilumab. Regeneron currently maintains two manufacturing suites at the specified site. Both suites utilise equivalent or identical equipment. Commercial supply is planned to be manufactured in both process areas.

The manufacture of dupilumab AS represents a standard manufacturing process for the manufacture of monoclonal antibodies. It is achieved in three main parts, the upstream process, which produces the antibody, the downstream process, which purifies the antibody and the formulation of the AS.

Differences in the manufacturing processes of both strengths are specified and start with the formulation process from AS to FAS to obtain the higher concentration of the 175 mg/mL strength. The dupilumab formulation process for the 175 mg/mL allows for two slightly different processes at onset. To prepare 175 mg/mL FAS, the AS in the formulation bag is compounded to the desired concentration and formulation with the addition of a concentrated excipient buffer. While the dilution buffer composition is the same for both strengths, the excipient buffer composition for manufacture of 175 mg/mL FAS is different from that used for manufacture of 150 mg/mL FAS. Together with a different ratio of excipient buffer to adjust AS, this results in the commercial compositions of either 175 mg/mL or 150 mg/mL FAS differing in the concentration of active ingredient and arginine. This is then followed by filtration and mixing. The dupilumab FAS is then dispensed into specified bottles with caps and transferred to storage until shipment to FP filling site. Reprocessing is not claimed. There is no change to the AS and FAS container closure system with regard to the 175mg/mL strength.

Samples are collected throughout the process for endotoxin, bioburden and CHO host cell proteins (HCP) and DNA. In-process controls are adequately set to control the process. The applicant has provided a description of the composition and preparation of all buffers and solutions listed in this section as well as chromatography/filter conditions.

Control of materials

No changes were made to CTD section S.2.3 Control of materials. The control of materials as authorised for 150 mg/mL dupilumab also applies to 175 mg/mL dupilumab

The dupilumab manufacturing process does not use raw materials of direct animal origin, other than Chinese hamster ovary cells.

Control of critical steps and intermediates

All AS and FAS manufacturing processes steps include controls within the in process controls (IPC) program for assurance of operational and performance consistency, as well as adherence to product safety requirements for each step. The in process controls (IPCs) and action limits or acceptance criteria of most process steps for the 150 mg/mL and 175 mg/mL FAS are identical. The IPC action limits which are different

for 175 mg/mL have been defined in the dossier. All IPC action limits applicable for 175 mg/mL FAS are covered by process validation activities using 175 mg/mL batches.

Process validation

Process performance qualification (PPQ) studies, impurity clearance, hold times, limit of in vitro cell age (LIVCA), proven acceptable range (PAR) studies and resin life time validations of AS manufacturing remain applicable. The FAS manufacturing process has been successfully validated at the appropriate site for the 175 mg/mL strength. Earlier and current commercial processes were validated using an appropriate number of lots. Upper and lower limits of operational and performance parameters were evaluated and acceptance criteria of IPCs were based on the validated ranges. The capability of the process to operate consistently with extended processing times for each unit operation was assessed as part of the process validation and the shortest times were set as validated holding times.

The overall process validation confirmed that the formulation processes to manufacture the 175 mg/mL FAS are capable of operating in a consistent and robust manner. The validation and comparability activities demonstrated that the dupilumab formulation processes reproducibly produce 175 mg/mL FAS of consistent quality that meets the predetermined specifications.

Manufacturing process development

The commercial manufacturing process for the existing 150 and the new 175 mg/mL strength of dupilumab is identical to an earlier manufacturing process used to manufacture materials for the Phase 2b and pivotal Phase 3 clinical trials except for two specified changes: certain downstream purification steps.

a) Introduction of an additional chromatography step

b) Change to the virus-retentive filter.

Extended characterisation of manufacturing processes has been performed for authorised 150 mg/mL dupilumab and was confirmed for 175 mg/mL.

Comparability of 175 mg/mL dupilumab FAS produced from an earlier and the commercial A AS process was assessed by release, long term and accelerated stability testing and found acceptable during the authorisation of the existing formulation (150 mg/mL).

Comparability of 175 mg/mL dupilumab FAS produced from an earlier and the commercial FAS process was assessed by release, long term and accelerated stability testing and found acceptable during the authorisation of the existing formulation (150 mg/mL). Dupilumab 175 mg/mL FAS obtained with the slightly different processes were also studied and from the stability comparison it can be concluded that both 175 mg/mL FAS processes are comparable.

Characterisation

The characterisation of dupilumab structure and other characteristics as well as product- and process-related impurities has been demonstrated in an adequate and sufficient manner during MAA review of the authorised 150 mg/mL dupilumab strength and can also be applied to the proposed 175 mg/mL strength. It was clarified that worst-case impurity calculations were performed using the maximum 300 mg dose and are applicable to the 200 mg dose. All stated impurities and their levels have therefore been qualified by clinical studies and are present in the authorised product.

Specification

There is no change to the dupilumab AS release and end of shelf life specifications. The Duplimumab FAS specification includes appropriate physicochemical tests and tests for identity, potency and purity. Since the 150 mg/mL and 175 mg/mL formulations of dupilumab share the same AS but have minor differences in the formulation and concentration of excipients, the acceptance criteria for most quality attributes are the same between both strengths for the FAS, with specified exceptions.

The process used for setting and justification of specifications and acceptance criteria has been adequately described. In brief, clinically-qualified values were used where possible. The applicant also leveraged historical data from AS and FAS lots. Stability data were used to support end-of-shelf specifications.

Analytical methods

The same analytical procedures used for dupilumab release, stability, and IPC testing for AS and 150 mg/mL FAS are applicable to 175 mg/mL dupilumab.

The potency assay is performed as an AS, FAS and bulk PFS release test.

Validation data of analytical procedures were considered valid for 175 mg/mL dupilumab. Methods that required additional validation for 175 mg/mL dupilumab have been provided and are sufficiently described in the dossier.

Batch analysis

Dupilumab FAS include several formulations examined in clinical trials, as well as the commercial FAS composition.

The batch release results of an appropriate number of lots manufactured with the commercial 175 mg/mL formulation complied with the specifications. The batch release results demonstrate that the commercial manufacturing process is capable of consistently producing 175 mg/mL FAS.

Reference materials

There is no change to the dupilumab reference standard (RS) program with regard to the 175 mg/mL strength.

Stability

A shelf life is already approved for dupilumab AS.

A shelf life is proposed for the 175 mg/mL FAS.

Dupilumab 175 mg/mL FAS stability studies have been carried out according to ICH recommended long term conditions and accelerated storage conditions. Stress stability studies have been conducted. Test articles are packaged in representative packaging. Appropriate stability indicating parameters have been tested.

The representative real-time stability is based on an appropriate number of FAS batches produced with the commercial process. Supportive long-term stability studies of lots manufactured using the earlier AS process were also provided.

All results from primary studies met the acceptance criteria at all available time points and no meaningful changes were observed in any batches, regardless of manufacturing process.

The applicant committed to complete the stability studies of the primary and supporting dupilumab 175 mg/mL FAS batches at the long-term storage condition according to the stability protocols provided. Any confirmed out-of-specification result, or significant negative trend, will be reported to the Rapporteur and EMA.

Accelerated, forced degradation and photo- stability studies confirm the degradation pathways for 175 mg/mL dupilumab FAS as expected from 150 mg/mL dupilumab data.

The stability results indicate that the 175 mg/mL dupilumab FAS is sufficiently stable and justify the proposed shelf life in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The authorised 150 mg/mL dupilumab strength is supplied in PFS and PFS-S to deliver 2 mL resulting in a 300 mg dose. Dupixent 175 mg/mL is supplied in two presentations: prefilled syringe with safety system (PFS-S) and pre-filled pen (PFP), both containing the same deliverable volume of 1.14 mL (200 mg dose of AS). Both, the PFS-S presentation and the PFP presentation, are comprised of a primary container referred to as a “bulk prefilled syringe (bulk PFS)”.

Besides the different concentration and volume, there is a difference in the formulation regarding the 175mg/mL strength, as compared to the 150 mg/mL.

The composition of both 175 mg/mL presentations, PFS-S and PFP (200 mg dose) is the same.

Table 3: Nominal composition of 175 mg/mL FP

Component	Function	Reference to quality standard
Dupilumab	Active pharmaceutical ingredient	Custom specification
L-Histidine	Buffer	USP, Ph. Eur., JP
L-Histidine Monohydrochloride Monohydrate**Error! Reference source not found.**		Ph. Eur., JP
L-Arginine Monohydrochloride	Stabiliser	USP, Ph. Eur., JP
Sodium Acetate Trihydrate	Buffer	USP, Ph. Eur., JP
Glacial Acetic Acid		USP, Ph. Eur., JP
Sucrose	Stabiliser	NF, Ph. Eur., JP

Polysorbate 80	Stabiliser	NF, Ph. Eur., JP
Water for injection	Solvent	USP, Ph. Eur., JP

There are no novel excipients used in the FP formulation. Dupilumab FP contains no excipients of human or animal origin. All excipients used in the manufacture of dupilumab FAS/FP are purchased as compendial grade (Ph.Eur.) excipients. There are no overages included in the formula. An overfill is required for the pre-filled syringes to ensure there is adequate volume in the syringe to provide the required dose.

The primary container (bulk PFS) of both the PFS-S presentation and the PFP presentation consists of a siliconised glass syringe barrel with a staked, stainless steel 27 gauge, 1/2" needle, an elastomeric plunger stopper, and a needle shield. The PFS-S presentation is comprised of the bulk PFS, plunger rod, finger flange and a safety device for sharps injury prevention.

The PFP presentation is comprised of the bulk PFS which is assembled with the device subassemblies to form the finished dupilumab 1 mL PFP. It is a button-less, needle cover-triggered (“push-click”), single-dose drug/device combination product. The device possesses a passive needle-shielding safety mechanism to protect the patient from needle stick injuries after use of the device. The term PFP is considered to be synonymous to and may be used interchangeably with the term “auto-injector” (AI).

The medicinal product and the administration device for both, the PFS-S and PFP respectively, form a single integral unit. The device does not have a CE mark. The device components meet the relevant essential requirements of the Annex 1 of Regulation 2017/745/EC and Annex 1 of the medical device directive 93/42/EEC, respectively.

There were no process changes between clinical and commercial process except for batch size and the needle shield which are without impact on the product.

There is no difference in the formulations of phase 3 clinical and commercial presentations of 175 mg/mL dupilumab. However, phase 3 clinical trial material was manufactured from FAS derived either from the AS manufactured using the earlier or the commercial process. The change to the commercial process was already approved during the MAA for the existing strength.

Proven acceptable range studies demonstrate the robustness of the 175 mg/mL dupilumab formulation. Process parameters of the commercial 175 mg/mL manufacturing process were optimised and defined during development.

Extractable and leachable studies have been carried out on material which comes into contact with the FP during manufacture and storage. Data has been presented to show that the FP is compatible with the chosen container closure systems.

The process validation report for PFP assembly summarises the results of in-process control testing, quality control testing, and time-out-of-refrigeration (TOR) monitoring. All commercial specifications proposed for the bulk PFS and the PFP-related test items were met. The global TOR for PFP was validated. Successful process validation demonstrated that the PFP manufacturing process is capable of consistently producing a product that meets the pre-defined acceptance criteria.

PFP performance was evaluated according to ISO standards. The functionality of the PFP was discussed with regard to the strong discrepancy in the bioequivalence between PFS-S and PFP observed in clinical PK studies. This was questioned as part of a multidisciplinary major objection during the procedure (see discussion section for more details).

As part of the microbial attributes, sterility and endotoxin testing are monitored during batch release testing. The results of the container closure integrity tests demonstrate that the container closure system maintains the sterility of the product and that manufacturing operations and shipping do not impact the container closure integrity.

The results of the simulated shipping validation were satisfactory, with all acceptance criteria proposed for commercial product met. The packaging is able to protect the product from adverse conditions encountered during transport.

Manufacture of the product and process controls

No new GMP documentation is considered necessary for the 200 mg PFS-S. Appropriate GMP documentation for PFP was provided. AS, FAS and FP manufacturing sites are specified for the PFS-S and PFP.

The manufacturing process is relatively straightforward and involves thawing of FAS, pooling, mixing and sterile filtration, filling into syringes, which are then fitted with a stopper. The applicant clarified that syringes and plunger stoppers sterilisation cycles are Ph. Eur. compliant. The final PFS-S is assembled by inserting a plunger rod and attaching a finger flange and safety device for sharps injury prevention.

The manufacturing process of 200 mg DP is generally the same as for 300 mg DP. The in-process controls are, in general, the same.

The manufacturing processes and process controls described can be considered suitable for manufacturing of bulk PFS and PFS-S of sufficient quality as well as the process described for PFP manufacturing.

The batch size range is covered by the process validation batches.

Process validation of 175 mg/mL bulk PFS, PFS-S and PFP manufacturing were performed using an appropriate number of batches (from the commercial AS process). Overall the validated processes can generally be considered adequate to reproducibly produce FP within the defined process parameters. The manufacturing process simulation with media fill testing demonstrated the efficacy of the aseptic filling process. Simulated shipping validation demonstrated that product quality confirmed the absence of transport impact.

Product specification

FP specifications are provided. The acceptance criteria for most quality attributes are the same as currently authorised.

The release specifications for the PFS-S and PFP also contain a complete list of release tests and acceptance criteria covering product solution properties, identity, strength, purity, potency and functional performance properties specific for PFS-S and PFP, respectively.

In general the chosen release tests are sufficient to ensure the quality of the FP and are sufficiently in line with ICH Q6B and the Ph. Eur. monograph on monoclonal antibodies for human use.

The end-of-shelf-life specification for the dupilumab FP in PFS-S/PFP contains a complete list of stability tests and acceptance criteria covering product, strength, purity, potency and functional performance properties.

The product related impurities are the same for the FP as for the AS, i.e. high molecular weight species, low molecular weight species, charge variants and oxidised species. Appropriate specifications are in place for the FP to control these product-related impurities.

Analytical methods

The analytical methods are fully validated. Non-compendial methods have been validated in line with ICH guidance.

Batch analysis

Representative-scale batch data has been provided for several batches of bulk PFS and PFS-S. Furthermore, batch release data of a suitable number of PFP batches have been provided.

All batch analyses results of 175 mg/mL bulk PFS, PFS-S and PFP batches complied with the commercial release specifications.

Reference materials

The reference standard is the same as that used for AS.

Stability of the product

The proposed shelf life for bulk PFS, PFS-S and PFP is 18 months at 2 – 8°C.

Stability studies examining 175 mg/mL dupilumab bulk PFS, PFS-S and PFP have been executed according to ICH recommended long-term conditions (at 2-8°C for up to 36 months) and accelerated storage conditions (at 23-27°C for up to 6 months). Stress stability studies are conducted at 42-48°C (for up to 3 months).

Regarding the PFS bulk, the representative real-time stability is based on a suitable number of primary 175 mg/mL bulk PFS batches produced with the commercial process. Supportive 175 mg/mL bulk PFS data are available from confirmatory batches which were derived from AS manufactured by the earlier process.

The real-time stability bulk PFS commercial batches showed excellent dupilumab protein stability at the long-term storage condition, with little to no change in any attributes up to the latest time point tested.

Accelerated stability data are available for all lots. The trends observed were as expected from experience with 150 mg/mL dupilumab. The shelf life claim of 18-months for the 200 mg PFP based on available commercial bulk PFS stability data is acceptable.

Regarding 175 mg/mL PFS-S and PFP, real-time stability results were provided for an appropriate number of batches (from the commercial process). PFS-S and PFP specific parameters tested beyond those of bulk PFS parameters perform satisfactorily up to the latest time-point tested so far. In accordance with EU GMP guidelines[1], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

Data have been provided supporting the SmPC statement "*If necessary, pre-filled syringes or pre-filled pens may be kept at room temperature up to 25°C for a maximum of 14 days. Do not store above 25°C. If the carton needs to be removed permanently from refrigerator, the date of removal may be recorded on the outer carton. After removal from the refrigerator, Dupixent must be used within 14 days or discarded*."

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

Overall the proposed shelf life of 18 months is acceptable. Based on the stability results, the proposed concurrent shelf life of 18 months when stored at 5 ± 3°C for dupilumab PFS-S and PFP are also accepted as the assembly process does not affect stability

Adventitious agents

The same AS is used for the manufacture of the proposed new strengths 175 mg/mL as has been used for the authorised strengths 150 mg/mL and the FP does not introduce any new risks with respect to adventitious agents. Dupilumab is expressed in CHO cells manufactured without the direct use of animal-derived raw materials (ADM). The indirect use of animal-derived raw materials is limited and confined to usage of ADMs during cell line development which have been clearly documented. The company has in place a suitable strategy to minimise risk from potential adventitious agents which involves:

The controlled sourcing and safety of the raw materials (including the cell banks) used during cell line development and in the manufacturing process (safety of raw materials)

The suitability of the approaches used to test and eliminate potential risks during the manufacturing process (in-process adventitious agent testing)

The effectiveness and robustness of the viral inactivation and removal during the product purification process (viral clearance).

The adventitious agents documentation is identical to that approved for the currently authorised Dupixent 300 mg strength.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Manufacture

The new strength 175 mg/mL is made from the same AS as the authorised strength 150 mg/mL. Differences in the manufacturing processes that lead to the two different strengths start with formulation of AS into formulated AS (FAS). Besides the higher dupilumab concentration, the formulation of both strengths differs in arginine concentration. In general, the manufacturing processes of FAS and FP were adequately described. All IPC action limits applicable for 175 mg/mL FAS are covered by process validation activities using 175 mg/mL batches.

Pharmaceutical development and process validation of PFP

A significant discrepancy in the bioequivalence between PFS-S and PFP was observed in clinical PK studies and was raised as part of a multidisciplinary major objection during the procedure. In this regard the functionality of the PFP was extensively discussed.

In relationship to this, further questions were raised during the procedure to establish whether the functionality of the PFP could be responsible for the discrepancy in the bioequivalence between PFS-S and PFP observed in clinical PK studies. Data were provided to show that the PFP assembly process can be regarded as successfully validated. All commercial specifications proposed for the bulk PFS and the PFP-related test items were met.

PFP device performance was evaluated according to ISO standards. The dose accuracy requirements of ISO 11608-1 were met by dupilumab 1 mL PFP for all investigated test conditions. Dupilumab 1 mL PFP complied with performance parameter testing and the pre-defined acceptance criteria which correspond to those of the respective functional PFP release specifications. Accelerated ageing of the device-constituent parts of the PFP did not have an influence on the functionality of the PFP.

The primary container closure system (bulk PFS) that comes into direct contact with the FP is the same for PFS-S and PFP. Particularly, there is no difference in the needle of the bulk PFS. Factors that might lead to differences in the application of the dose, e.g. the injection depth with PFS-S vs. PFP and the instructions for use of PFS-S (45° injection) and PFP (90° injection) were discussed by the MAH. The results of a study demonstrated that the volume delivered from all 200 mg dupilumab FP is equivalent as measured in the respective release tests.

It is stated that there was no expected usability-related issue in the pre-clinical human factors validation studies and in the clinical trial (R668-AD-1607) that could lead to a difference in dupilumab exposure. A sample of PFPs were returned for evaluation after use in the bridging study. All PFPs were found to have functioned as intended and in accordance with their design. A visual assessment of plunger stopper position at the needle end of the syringe demonstrated that the syringe was emptied completely and the full dose was delivered.

The differences in the usability and performance of PFS/PFS-S on the one hand and PFP on the other hand were compared. Needle length and injection angle was investigated. PFP users are instructed to place the PFP on the skin at a 90° angle so that the needle cover touches the injection site. A slight underfill was observed in batch release of the clinical/PK PFP batch. A summary of the investigations related to the observer OOS result was provided. The investigation concluded that both filling and 100% visual inspection processes demonstrated the ability to reject syringes filled with less than the required amount. No drift in the manufacturing process was identified. It is agreed that considering the insignificance of the under-dose, this would not be the cause of the difference seen in PK in the clinical study.

Following the human factors studies additional information was added to the instructions for use in the package leaflet (e.g. “In adolescents 12 years and older, it is recommended that Dupixent be administered by or under supervision of an adult”, “Do not give yourself a second dose without speaking to your healthcare provider”).

In conclusion, the information related to the device performance and the underfill addressed the possibility that the difference in bioequivalence that had been observed was attributable to the device/quality aspects of the product. Therefore, the major objection was satisfactorily addressed from the quality perspective.

2.2.5. 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 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.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. The applicant submitted some non clinical data supporting the asthma indication as outlined below. No new pharmacokinetic and toxicology data were submitted in this application as they were submitted with the original atopic dermatitis application . . Pharmacology

A summary of previously assessed data relevant to this application is provided below.

Primary pharmacodynamic studies

Primary pharmacology *in vitro*

The initial characterising experiments demonstrated that dupilumab had a high affinity for human IL-4Rα, with a KD of 12 pM to the dimeric form of the receptor. However, subsequent surface plasma resonance experiments using the Biacore system suggested a much diminished ability to bind IL-4Rα of mouse or monkey origin. Therefore, surrogate antibodies were generated, REGN1103 and REGN646, which bind to IL-4Rα of mouse and monkey origin respectively. These surrogate antibodies were shown to have affinities in a similar range as that of dupilumab.

Further *in vitro* characterisation of dupilumab and the surrogate antibodies was performed. Dupilumab was shown to bind to CD20 positive lymphocytes which was blocked by pre-incubation with excess IL-4. Using STAT6 mediated luciferase expression as a readout of activity of either IL-4 or IL-13 signalling, dupilumab demonstrated a similar IC50 of 25 or 27 pM for IL-4 or IL-13 mediated STAT6 signalling respectively. Increased cell surface expression of CD23 was also inhibited by dupilumab in human PBMCs and in the Ramos lymphoma cell line. Inhibition of secretion of TARC, a type 2 chemokine whose secretion is mediated by IL-4 or IL-13, was also inhibited by dupilumab in PBMCs isolated from donors.

Given that dupilumab is a human IgG4 molecule, Fc-effector function is not expected. In accordance, using cell lines expressing IL-4Rα, no ADCC or CDC activity of dupilumab against target cells could be detected.

Functional characterisation studies with the surrogate antibodies were also performed. REGN1103, the mouse surrogate antibody, inhibited IL-4- and IL-13-dependent proliferation of cell lines at IC50's of 1.9 nM and 11 pM respectively. Similar experiments to those performed with dupilumab were also performed for REGN646, the monkey surrogate antibody. REGN646 inhibited IL-4 and IL-13-mediated signalling as measured by STAT6 mediated luciferase expression or TARC secretion. Flow cytometry analysis showed a comparable staining pattern of human and monkey lymphocytes by dupilumab and REGN646, respectively.

Primary pharmacology *in vivo*

Due to the lack of an *in vivo* model of atopic dermatitis the proof of principle experiments have been performed using classical models of type 2 immune response which have been shown to be mediated at least in part through signalling via IL-4 and IL-13. To this end, a genetically engineered transgenic mouse was established which expresses human IL-4 and IL-4Rα and was validated as a system in human to evaluate the efficacy of dupilumab *in vivo*. Using this transgenic mouse, efficacy of dupilumab was demonstrated in a model of IL-25 induced Type-2-driven inflammation. Maximum pharmacodynamic response was evident at 25

mg/kg of dupilumab as shown by examining goblet cell metaplasia, total serum IgE levels as well as lung histopathology score. In a model of house dust mite (HDM) allergen lung inflammation efficacy was seen with sub-cutaneous administration of 25 mg/kg of dupilumab twice weekly for a period of 4 weeks. Dupilumab treatment reduced the total levels of IgE in HDM treated mice to that of control untreated animals, as well as inhibiting the activation of eosinophils and goblet cell metaplasia.

Additional *in vivo* studies in wild-type mice were conducted with REGN1103, a surrogate monoclonal antibody specific for murine IL-4Rα. Efficacy of REGN1103 in mice was studied in HDM-induced lung inflammation. When given in parallel to allergen exposition over four weeks, REGN1103 achieved the expected pharmacologic effect. Treatment was associated with reduced pulmonary eosinophil infiltration, reduced in goblet cell metaplasia and less total IgE and HDM-specific IgG1 in serum. The study provides a proof-of-concept for the inhibition of IL-4Rα in hyperactive type 2 immune responses.

In order to support the therapeutic effect of dupilumab in allergic asthma, an additional study with humanized mice was conducted. Herein, mice were challenged with HDM three times per week for four weeks. Dupilumab blocked HDM-induced eosinophil infiltration into the lungs and reduced the number of activated CD23+ B cells and ST2+ CD4+ T cells in both blood and lung tissue. As blockage of eosinophil lung infiltration by dupilumab was associated with an increase in blood eosinophils compared to controls, this suggests that dupilumab does not impact the eosinophil generation but rather prevents infiltration into the lung tissue. Dupilumab also prevented HDM-induced impairment in lung function and prevented expression of chemoattractant chemokines and type 2 cytokines. In summary, the data support a beneficial role of dupilumab in allergic asthma.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed because no test article-related adverse primary pharmacodynamics or changes to safety pharmacology parameters were observed in nonclinical pharmacology and toxicology studies, indicating absence of off-target effect.

Safety pharmacology programme

In line with ICH S6(R1) safety pharmacology endpoints were evaluated as part of the repeat-dose toxicity studies in cynomolgus monkeys. No dupilumab-related effects were observed on cardiovascular, respiratory or CNS function.

2.3.3. Pharmacokinetics

No new PK studies were submitted for the asthma indication , However a summary of the available data from the initial marketing authorisation in atopic dermatitis is provided below.

The pharmacokinetics of dupilumab were evaluated in single-dose PK studies in rats and cynomolgus monkeys after IV and SC administration to provide PK information in the absence of target-mediated clearance. PK/TK of REGN646 were evaluated were evaluated after single and repeated IV or SC administration in cynomolgus monkeys; TK of REGN1103 was evaluated after SC administration in mice. The SC route is the proposed clinical route of administration.

A qualified ELISA was used for detection of dupilumab in rat and cynomolgus serum. Validated ELISAs were used for detection of REGN1103 in mouse serum and REGN646 in cynomolgus serum. For detection of anti-REGN646 antibodies in cynomolgus a bridging ECL assay was developed and validated.

PK characteristics of dupilumab after single IV and SC administration in rats and cynomolgus were typical for a monoclonal antibody and consistent with a lack of target binding. In both species, the concentration-time profile of dupilumab was characterized by an initial distribution or absorption phase following IV or SC administration, respectively, followed by a single elimination phase. The mean half-life of dupilumab ranged from 4.8 – 7 days in rats and 11.7 to 20.5 days in cynomolgus and was comparable following IV or SC administration. The bioavailability following SC dosing was high (84.2 % in rats, > 92% in cynomolgus).

PK of REGN646 in cynomolgus was characterized by non-linear kinetics, which is consistent with target-mediated disposition. After single IV administration (ranging from 1 – 15 mg/kg), Cmax increased approximately dose-proportionally while AUCinf increased in a greater than dose-proportional manner. Elimination of REGN646 was biphasic, with a long β elimination phase and a more rapid terminal target elimination phase. Consistently, the mean beta elimination half-life of REGN646 at serum concentrations above the target-saturation ranged from 7.2 to 9.1 days while the mean terminal elimination half-life was 1.5 – 2.1 at concentrations where target-mediated elimination is the primary clearance process. The absolute bioavailability of REGN646 following SC administration was approx. 70.0%. After repeated once weekly doses of 25 and 100 mg/kg/week, accumulation of REGN646 was observed, ranging from 2.2 to 4.6-fold.

REGN1103 showed non-linear kinetics in mice; increases in exposure were greater than dose-proportional at lower doses and approximately dose-proportional at doses ≥ 25 mg/kg/week.

In accordance with ICH S6 (R1), studies on distribution, metabolism and excretion were not conducted.

Since dupilumab and the surrogate antibodies, REGN1103 and REGN646, are large proteins that are above the glomerular filtration cut-off threshold, they are primarily eliminated by proteolytic catabolism that results in smaller peptides and amino acids that can be reused for new protein synthesis. The clearance of therapeutic monoclonal antibodies typically does not involve cytochrome P450 (CYP450)-mediated metabolism or interaction with cell membrane transporters, therefore pharmacokinetic interactions with small molecule drugs are limited. However, published literature suggests IL-4 plays a role in the regulation of CYP1E2, a highly conserved protein that is involved in paracetamol and alcohol metabolism. The clinical significance of this is unclear, and the applicants have currently ongoing a drug-drug interaction study (R668-AD-1433) designed to examine the effects of dupilumab on the PK of selected CYP450 substrates in adult patients with moderate-to-severe AD.

2.3.4. Toxicology

No new toxicology studies were submitted for the asthma indication, however a summary of the available data from the initial marketing authorisation in atopic dermatitis is provided below.

Dupilumab is specific for human IL-4Rα and does not adequately interact with IL-4Rα from non-clinical species. Therefore the toxicity of IL-4Rα blockade was evaluated using surrogate antibodies specific for cynomolgus or mouse IL-4Rα. The pharmacologic activity of these surrogate antibodies was adequately characterized and is considered comparable to that of dupilumab.

Single dose toxicity

No data were provided in this application however single dose toxicity studies were performed for the initial approval for Atopic Dermatitis, this is acceptable by CHMP.

Repeat dose toxicity

Repeated dose studies of up to 26 weeks duration were conducted with REGN646 in cynomolgus monkeys. In these studies, once weekly IV or SC treatment with REGN646 at doses up to 100 mg/kg was well tolerated. No REGN646-related adverse effects were noted. Lymphocytic infiltrates were observed at the SC injection sites. These are considered a reaction to injection of high concentration of human protein.

Of note, no immunological effects of REGN646 were observed in the repeat-dose toxicity studies. There were no test-article-related changes in peripheral blood lymphocyte subpopulations. In addition, there were no treatment-related changes in serum IgM, IgG and IgE, with the exception of the 13-week study. In this study, lower IgE serum levels were observed in individual monkeys who had received saturating doses of REGN646. However, this finding is considered a pharmacologic effect of IL-4Rα blockade. Furthermore, REGN646 treatment did not affect the development of an antibody response to immunization with KLH. The primary and secondary IgM and IgG response against KLH in REGN646-treated cynomolgus was comparable to that of control animals.

In summary, no adverse effects were observed in the repeat-dose studies. In all studies, the NOAEL was the highest dose administered and was associated with a Ctrough of 4150 µg/ml and an AUC0-168h of 791,000 µg*h/ml at 100 mg/kg SC in the chronic toxicity study. Given that the toxicity studies were conducted with a surrogate antibody a direct comparison of exposure multiples in the toxicity studies with exposure of dupilumab in humans is not considered meaningful. However, the Ctrough at the end of treatment in the chronic toxicity study corresponds to 52x of IC90 determined for REGN646-mediated inhibition of IL-4-stimulated TARC section in vitro. This indicates that a sufficiently high exposure to REGN646 was maintained throughout the study.

Genotoxicity

Genotoxicity studies have not been conducted, in accordance with ICH S6(R1). This is acceptable.

Carcinogenicity

No carcinogenicity studies were conducted for this asthma submission. However, an updated assessment of the carcinogenic potential of dupilumab was made based on literature data on the role of the IL-4/IL-13 pathway in tumour development and on non-clinical data for both REGN646 and REGN1103.

The majority of literature data indicate that IL-4 and IL-13 mediate pro-tumorigenic effects either by directly promoting tumour cell proliferation or indirectly via the activation of immunomodulatory cells. Such effects would be inhibited by anti-IL-4Rα treatment. In addition, results from the repeated-dose toxicity studies in mice and cynomolgus do not indicate a carcinogenic risk. The applied weight of evidence approach is in accordance with ICH S6 (R1). It can be agreed that chronic treatment with dupilumab is not associated with an increased risk of cancer. In contrast, blockade of IL-4Rα signalling may contribute to inhibition of tumour growth.

For this submission, no publications were identified that would change the conclusions of the original document.

Reproduction toxicity

The effect of IL-4Rα inhibition on fertility and early embryonic development was evaluated in mice treated with the surrogate mAb. Subcutaneous administration of REGN1103 to adult male and female mice at 25, 75, or 200 mg/kg/week did not result in any compound-related mortality. There were no REGN1103-related clinical signs, effects on body weight or food consumption, macroscopic observations or microscopic findings. In addition, there were no compound-related effects on mating, fertility, oestrous cycling, embryo survival or any of the male reproductive assessments (organ weights). Therefore, dupilumab is not expected to have an effect on fertility.

In the cynomolgus enhanced pre-/post-natal development study, there were no REGN646-related maternal effects. The incidence of embryo-foetal loss was higher in REGN646-treated groups (32.4% combined 25 and 100 mg/kg groups) than in the control group (25%) but was within the range of historical control data reported at the test facility (6.7 – 38.9%). In the surviving offspring, there were no REGN646-related findings. According to the agreed PIP, juvenile animal toxicity studies have not been conducted.

2.3.5. Ecotoxicity / environmental risk assessment

Dupilumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, dupilumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The pharmacology studies have demonstrated that dupilumab has a high affinity for the human IL-4Rα receptor and a much lower affinity for IL-4Rα of mouse and monkey origin necessitating the generation of surrogate antibodies. The surrogate antibodies, REGN1103 and REGN646 demonstrated affinities to mouse and monkey IL-4Rα respectively in a comparable, albeit lower, range to that of dupilumab to hIL-4Rα. The staining pattern of human and monkey lymphocytes by dupilumab and REGN646, respectively was comparable. *In vitro* functionality of these antibodies was demonstrated in cells of the respective species with inhibition of IL-4 or IL-13 dependent signalling. Although no preclinical models of atopic dermatitis were available a transgenic mouse expressing hIL-4 and hIL-4Rα was generated and used for proof of efficacy studies with dupilumab in models of type 2 immune responses. An additional mouse study was conducted to support the efficacy of dupilumab in allergic asthma and submitted in this application. Herein, the data support a beneficial role of dupilumab. Similar *in vivo* experiments were performed demonstrating efficacy with the mouse surrogate REGN1103 antibody. Taken together the studies provide a comprehensive basis for the potential mechanism of action of dupilumab in atopic dermatitis and lung inflammation as well as establishing the appropriateness of the surrogate antibodies for the toxicity studies.

Carcinogenicity studies have not been conducted with dupilumab. An evaluation of the available evidence (literature data) related to IL-4Rα inhibition and animal toxicology data with surrogate antibodies does not suggest an increased carcinogenic potential for dupilumab.

In rats and monkeys dupilumab exhibited linear kinetics as expected in species that do not bind dupilumab with high affinity. No target-mediated clearance was observed and total dupilumab exposure was approximately dose proportional. In monkeys REGN646, the monkey surrogate anti-IL-4Rα antibody, displayed non-linear kinetics. The concentration-time profiles of REGN646 are characterized by an initial distribution phase following IV administration, or an absorption phase following SC administration, followed by a target-saturating beta elimination phase and a terminal target-mediated elimination phase. The target-

mediated elimination is most notable at the lower concentrations. Low volumes of distribution are seen along with long elimination half-life, which are typical pharmacokinetic characteristics of monoclonal Abs. The presence of ADA in animals in the REGN646 monkey study clearly impacted the rate of drug clearance observed in the study especially at lower concentrations, and there was no evidence of adverse toxicity associated with the occurrence of ADA.

To support the safety of dupilumab, a toxicology programme was conducted in accordance with current guidance and considered adequate. Given the lack of cross-reactivity of dupilumab with IL-4Rα from non-clinical species, surrogate mAbs were used, which is acceptable. By and large the repeated-dose toxicity studies IL-4Rα blockade did not reveal any adverse effects.

The effect of IL-4Rα blockade on reproductive and developmental toxicity was evaluated in a fertility study in mice which and in an ePPND study in cynomolgus monkeys. No adverse effects on fertility were noted.

In the present submission, a new strength (from 150 mg/mL to 175 mg/mL) and formulation was introduced. As the excipients remain the same and the formulation is only slightly different, no new local tolerance studies are warranted.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies are sufficient to support the asthma indication and new dosage form of dupilumab.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

Studies included in this application

Drug product presentations comparability (Phase 1b)					
PK comparability in actual-use study	R668-AD-1607	Part A: 200 mg SC q2w/12 weeks; loading dose of 400 mg	Adolescents ≥12 years and adults with AD	42 (PFP), 43 (PFS)	Dense sampling
Intrinsic factors (Phase 2a)					
Age (6 -17 years)	AD-1412	2 mg/kg and 4 mg/kg, single dose phase and qw/4 weeks for repeat-dose phase	AD, pediatrics of 6 to 17 years	20/cohort	Semi-dense sampling

Pharmacokinetic and pharmacodynamic assessment in asthma efficacy/safety studies					
Repeated SC dose, Proof of concept study	ACT11457	300 mg qw/12 weeks	Adults with asthma	52	Sparse sampling
Repeated SC dose, Pivotal Dose ranging study (add-on to ICS/LABA)	DRI12544	200 mg q2w (400 mg loading dose), 300 mg q2w (600 mg loading dose), 200 mg q4w (400 mg loading dose), 300 mg q4w (600 mg loading dose)/24 weeks	Adults with asthma	200 mg q4w: 150, 300 mg q4w: 157, 200 mg q2w: 148, 300 mg q2w: 156	Sparse sampling
Repeated SC dose, Pivotal Phase 3 study (add-on to ICS with one or two controllers)	EFC13579[a] (QUEST)	200 mg q2w (400 mg loading dose), 300 mg q2w (600 mg loading dose)/52 weeks	Adolescents and adults with asthma	200 mg q2w: 629, 300 mg q2w: 632	Sparse sampling
Repeated SC dose, Phase 3 study (OCS-sparing)	EFC13691 (VENTURE)	300 mg q2w (600 mg loading dose)/24 weeks	Adolescents and adults with asthma	103	Sparse sampling
Repeated SC dose, open-label extension study	LTS12551[b] (TRAVERSE)	300 mg q2w (600 mg loading dose)/48 to 96 weeks	Adolescents and adults with asthma	DRI12544: placebo-dupilumab: 421, dupilumab-dupilumab: 111, EF13579: placebo-dupilumab: 439, dupilumab-dupilumab: 873, EFC13691: placebo-dupilumab: 70, dupilumab-dupilumab: 67	Sparse sampling
Asthma population pharmacokinetic analysis, pooled Phase 1 to 3 data					
Population pharmacokinetics in patients with asthma	POH0530[c]	Pooled data from Phase 1 (AS-0907, TDU12265,HV-1108, PKM12350, PKM14161 and PKM14271), Phase 2 (ACT11457 and DRI12544) and Phase 3 (EFC13579) clinical studies	Pooled healthy and asthma, adults and adolescents	202 healthy subjects and 1912 patients with asthma (including 68 adolescents)	–

2.4.2. Pharmacokinetics

The to-be marketed dupilumab drug product (DP) for the asthma indication is a liquid formulation at a concentration of either 150 mg/mL or 175 mg/mL, supplied as PFS or PFP, to deliver a dose of 300 mg or 200 mg for SC Q2W. The intended posology of Dupixent for patients with asthma is 200 mg SC Q2W after an initial loading dose of 400 mg. In patients with oral corticosteroids-dependent asthma or with co-morbid moderate-to-severe atopic dermatitis for which Dupixent is indicated, the intended posology is 300 mg SC Q2W after an initial dose of 600 mg.

The clinical pharmacology program for the asthma indication consisted of two Phase 2 studies (Studies ACT11457, DRI12544) and three Phase 3 studies (Studies EFC13579, EFC13691, LTS12551) in which dupilumab was administered SC QW, Q2W, or Q4W for treatment periods ranging from 12 weeks to 96 weeks. In these studies, only sparse PK sampling was conducted. In addition, Study R668-AD-1607 was an actual-use study in adult and adolescent patients with AD and provided data on the comparison of PFS with PFP. In this study, dense PK sampling was performed.

Analytical methods

The PK assay methods for determination of dupilumab concentrations in the studies contributing to clinical pharmacology data in this extension of indication application were identical to those used for the AD program (REGN668-AV-09095-VA-01V2 and REGN668-AV-13074-VA-01V1). Functional dupilumab concentration in serum samples was analysed using a validated enzyme-linked immunosorbent assay (ELISA).

The anti-drug antibody (ADA) assay method (REGN668-AV-13089-VA-01V3) and the neutralizing antibody (NAb) assay method (REGN668-AV-13112-VA-01V2) were updated as compared to the assay methods used in the AD program (ADA assay methods: REGN668-AV-09106-VA-01V2 and REGN668-AV-13089-VA-01V2; neutralizing ADA assay method: REGN668-AV-13112-VA-01V1). In addition, a new ADA method (REGN668-AV-15153-VA-01V1) was developed and validated. In general, the ADA method is based on a non-quantitative, titer-based, electrochemiluminescent bridging immunoassay which involves acid dissociation. The standard three-tier approach is applied (screening, confirmation and titer/NAb analysis).

Population PK Analysis

A population PK (Pop PK) analysis of dupilumab PK samples was conducted using data from healthy subjects and adolescent and adult asthma patients. Although only sparse data have been recruited in asthma patients, the overall data package on clinical pharmacology is sufficient. Parameter estimates of the final asthma Pop PK model for dupilumab described the observed dupilumab PK acceptably well. A two-compartment model with parallel linear and nonlinear elimination with first order absorption was selected.

Table – Parameter estimates of asthma Pop PK model for dupilumab

Parameter	Estimate	% RSE	[95%CI]
Typical value of K_e (θ_1, 1/day)	0.0418	2.77%	[0.0395 ; 0.0442]
Typical value of V_2 (θ_2, L)	2.76	2.43%	[2.63 ; 2.90]
Typical value of K_{23} (θ_3, 1/day)	0.0952	6.97%	[0.0819 ; 0.108]
Typical value of K_{32} (θ_4, 1/day)	0.163	4.36%	[0.148 ; 0.177]
Typical value of V_{max} (θ_5, mg/L/day)	1.39	3.80%	[1.28 ; 1.49]
Typical value of K_m (θ_6, mg/L)	2.08	13.6%	[1.52; 2.65]
Typical value of K_a (θ_7, 1/day)	0.263	3.80%	[0.243 ; 0.283]
Typical value of F_{sc} (θ_8, 1/day)	0.609	3.27%	[0.569 ; 0.649]
Power coefficient of weight on K_e[a]	0.222	22.5%	[0.122 ; 0.321]
Proportional coefficient of positive ADA on K_e[a]	0.191	13.6%	[0.139 ; 0.243]
Power coefficient of creatinine clearance on K_e[a]	0.217	12.1%	[0.164 ; 0.269]
Power coefficient of weight on V_2[a]	0.667	3.89%	[0.615 ; 0.719]
Power coefficient of albumin on V_2[a]	-0.484	12.3%	[-0.604 ; -0.365]
Power coefficient of weight on V_{max}[a]	0.224	24.0%	[0.117 ; 0.332]
Inter-individual variability (CV%)			
Parameter	**Estimate**	**% RSE**	**[95%CI] (Shrinkage %)**
K_e	0.0385 (19.6%)	10.6%	[0.0303 ; 0.0466] (47.3%)
V_2	0.00834 (9.13%)	18.2%	[0.00530 ; 0.0114] (57.7%)
V_{max}	0.0589 (24.3%)	7.69%	[0.0499 ; 0.0680] (44.2%)
K_a	0.243 (49.2%)	7.68%	[0.205 ; 0.280] (57.6%)
F_{sc}	0.132 (36.3%)	11.9%	[0.100 ; 0.163] (36.3%)
Residual variability			
Proportional term (CV %)	0.0388 (19.7%)	0.880%	[0.0381 ; 0.0395]
Additive term (mg/L) (SD)	2.98 (1.73)	2.86%	[2.81; 3.16]
Derived Parameters			
CL (L/day)[b]	0.115	NA	NA
Q (L/day)[b]	0.263	NA	NA
V_3 (L)[b]	1.61	NA	NA

Abbreviation : K_e : linear elimination rate constant ; V_2 : volume of central compartment; K_{23}, K_{32} : inter-compartment distribution rate constants; V_{max} : maximum target-mediated rate of elimination; K_m : Michaelis-Menten constant; K_a : absorption rate constant; F_{sc} :bioavailability; CL: linear clearance; Q: inter-compartment distribution clearance; V_3 : volume of peripheral compartment; RSE: relative standard error;. CI: confidence interval; θ and ω are the Pop PK parameters (θ) and the variance of their associated inter-individual variability (ω); CV: coefficient of variation; SD: standard deviation.

a $V_2 = 2.76 \times (WT/78)^{0.667} \times (ALB/44)^{-0.484}$; $K_e = (0.0418 + 0.0418 \times 0.191 \times ADA) \times (WT/78)^{0.222} \times (CLCRN/111)^{0.217}$; $V_{max} = 1.39 \times (WT/78)^{0.224}$
The median values of weight (WT), albumin (ALB), and creatinine clearance normalized by body surface area (CLCRN) in the dataset were 78 kg, 44 g/L, 111 mL/min/1.73 m2, respectively. ADA is 0 for patients with negative ADA and 1 for patients with positive ADA at any time

b Derived parameters calcualted as CL=V2*Ke; Q=K23*V2; V3=V2*K23/K32

Absorption / distribution / metabolism / elimination

In patients with asthma, dupilumab is well-absorbed: Model-estimated SC bioavailability was 61% and absorption rate constant was 0.260/day. Following SC administration, the concentration-time profile of dupilumab was characterized by an SC absorption phase (median tmax of 3 to 7 days).

- *Relative Bioavailability*

Study R668-AD-1607 was an open-label, randomized, actual use study of dupilumab in adult and adolescent patients with AD. In Part A of this study, patients with moderate to severe AD received dupilumab 200 mg q2w via PFP device or PFS, with a loading dose of 400 mg on Day 1. The study was not formally powered to show PK comparability/bioequivalence between PFS and PFP. The comparison of systemic dupilumab exposure (AUC, Cmax, Ctrough) between PFS and PFP was included as secondary objective in the study (Table 7).

Table 7 - Estimates of Geometric Mean Ratios (AI/PFS) for functional dupilumab exposure following 200 mg q2w administration (Study R668-AD-1607)

Study Day	PK Parameter	Geometric Mean Ratio	90% CI
Day 1	AUC_{0-14}	0.723	0.635 – 0.823
	C_{max}	0.741	0.655 – 0.839
	C_{trough}	0.757	0.638 – 0.897
Day 85	AUC_{0-14}	0.903	0.767 – 1.063
	C_{max}	0.890	0.779 – 1.017
	C_{trough}	0.872	0.722 – 1.053

AI = Auto-injector; PFS = Prefilled syringe

Notes: AUC_{0-14} is the area under the concentration-time curve from time zero to 14 days, relative to the day listed in the study day column. C_{trough} is the concentration observed at nominal 14 days following dose.

At both time points the 90% confidence interval of the geometric mean ratios for AUC(0-14), Cmax and Ctrough were not contained within the acceptance interval of 0.8 – 1.25 interval.

Distribution primarily took place within the vascular compartment (model-estimated volume of distribution at 4.37 L).

For a monoclonal antibody, the elimination of dupilumab is expected to be limited to proteolytic catabolism to small peptides and individual amino acids, and therefore, no specific metabolism or excretion studies were conducted.
Dupilumab exhibits nonlinear PK with target-mediated disposition. At higher concentrations, elimination is predominantly through the linear, non-saturable proteolytic pathway; at lower concentrations, the nonlinear saturable target-mediated elimination pathway predominates.

Linear clearance has been derived to 0.115 L/day.

Dose proportionality and time dependencies

At steady-state concentrations for 200 mg q2w and 300 mg q2w regimens, dupilumab PK exhibited a more than dose-proportional increases in exposure.

In Study DRI12544, 4 dose regimens have been examined. A 1.5-fold dose increase from 200 mg and 300 mg resulted in a steady-state trough concentration increase (Week 16) by 2.06-fold (29.2 to 60.3 mg/L) for q2w regimens and 3.46-fold (3.61 to 12.5 mg/L) for q4w regimens, respectively. A similar observation was noted in Study EFC13579, where a 1.86-fold increase from 36.5 mg/L to 67.8 mg/L in the mean Ctrough at Week 16 for a 1.5 fold dose increase from 200 mg q2w to 300 mg q2w has been observed. This is deemed acceptable for a monoclonal antibody that is characterized by non-linear target-mediated kinetics.

After the last SC dose at steady state, the model-predicted median time for dupilumab concentration to decline from PK steady-state to below the LLOQ (0.078 mg/L) level was 9 weeks for the 200 mg q2w regimen and 11 weeks for the 300 mg q2w regimen in patients with asthma.

Based on the asthma Pop PK model, the median time to steady-state was 6 weeks for 200 mg q2w with 400 mg loading dose and 8 weeks for 300 mg q2w with 600 mg loading dose in a typical individual. Longterm data showed that Ctrough, ss achieved by Week 16 were maintained up to two years during treatment in patients with asthma, indicating the lack of time-dependent changes in dupilumab PK.

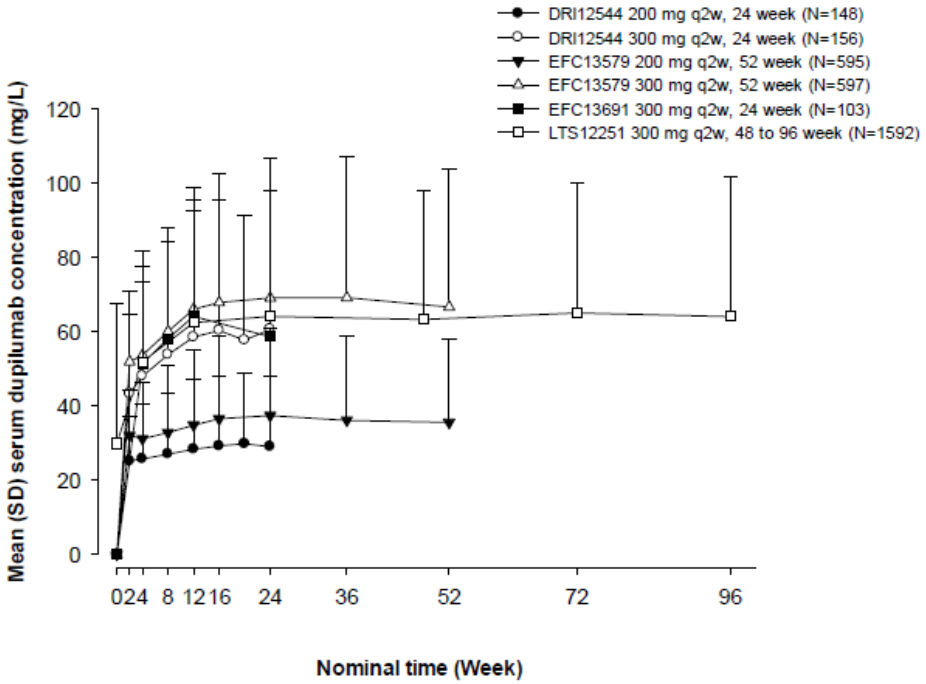
Loading doses: administration of the loading dose does not result in systemic exposure that may exceed the steady-state levels at 200 mg or 300 mg q2w regimens but helps in reaching the steady state more rapidly. The difference in exposure with and without loading dose is thus mainly limited to the first 12 weeks before reaching the same steady-state levels, which is deemed plausible and acceptable. This is supported by a fast response of PD biomarker time profiles.

Intra- and interindividual variability

The asthma Pop PK analysis showed moderate inter-individual variability in PK parameters Fsc, Ke, V2 and Vm (36.3%, 19.6%, 9.13%, and 24.3%, respectively), as derived by population PK analysis. The inclusion of covariates into the base population PK model did not serve to explain the inter-individual variability observed among the patients.

PK in the target population

Figure 4 - Comparison of mean trough concentration-time profiles between asthma and AD adult populations at 300 mg q2w (with a 600 mg loading dose)



Note: the mean concentration-time profiles to the end of treatment following SC administration of dupilumab for 200 mg q2w (with 400 mg loading dose) or 300 mg q2w (with 600 mg loading dose) regimens. Shown for Study LTS12551 is the mean concentration-time profile for patients rolled over from 5.3.5.1 Studies DRI12544 and EFC13579. Patients rolled over from Study EFC13691 are not included as most patients only had limited concentration data up to Week 24.

Sources: Studies EFC13579 and EFC13691 PK appendices, see 5.3.5.1 Study EFC13579, 16.2.5 Compliance and drug concentration data [16.2.5.4.1.1] and Study EFC13691, 16.2.5 Compliance and drug concentration data [16.2.5.4.1.1] ; Study LTS12551 PK appendix, 5.3.5.2 Study LTS12551, 16.2.5 Compliance and drug concentration data [16.2.5.4.1.1]; and Study DRI12544 PK appendix, see in original marketing application for AD, 5.3.5.1 Study DRI1254416.2.5 Compliance and drug concentration data (16.2.5.4.1.1)

Based on the Pop PK analysis, there is no significant difference in dupilumab PK between healthy subjects and patients with asthma. Within the overall asthma population, both the descriptive comparison and the Pop PK demonstated that dupilumab PK profile in severe OCS-dependent asthma patients (Study EFC13691) is

comparable to those with uncontrolled moderate-to-severe asthma. Dupilumab PK is also comparable between asthma and AD populations.

Special populations

From the tested intrinsic and extrinsic factors the following covariates have been selected by stepwise covariate modelling (SCM) and included in the final asthma population PK model.

Central volume of distribution V2 was significantly related to body weight and albumin, with larger V2 in patients with higher body weight and lower albumin level. Vmax was significantly related to body weight, with greater Vmax in patients with higher body weight. Ke was significantly related to ADA status, CLCRN, and body weight, with higher Ke in patients with higher body weight, higher CLCRN and positive ADA status (positive at any time).

Body weight remained the primary source responsible for dupilumab PK variability in the asthma population, reducing inter-individual variability for V2 from 14.8% to 9.5%, while inclusion of other covariates only led to a modest reduction of inter-individual variabilities. In contrast, none of the other tested covariates had a significant effect on dupilumab PK in asthma population.

Covariate analysis indicated that body weight accounts for most of inter-patient variability in exposure compared to other statistically significant covariates, including ADA status, CLCRN and albumin causing less than 20% change in exposure estimated at 5th or 95th percentile of the covariate range relative to the reference individual. The influence of body weight, that was investigated over the range of 32 – 186 kg, could be detected on the volume of distribution and on elimination of dupilumab. This translates to a respective decrease of 48.0% or 40.7% in the steady state $AUC_{\tau,ss}$ for a typical patient weighing 116 kg (the 95th percentile) and a respective increase of 68.8% or 56.7% for a typical patient weighing 52.9 kg (the 5th percentile), as compared with a typical patient of 78 kg (median weight) after 200 mg or 300 mg q2w doses, respectively. This effect was slightly more pronounced regarding the change in Cmin_ss. Despite body weight, a high variability in the data remained unexplained.

As only a very flat exposure-response and dose-response relation regarding efficacy could be observed, no need for dose adjustment by weight is indicated.

Higher exposure (about 1.5 – 2 fold) is observed in adolescent patients compared to adults in both dosing groups. However, for the higher dosing, this trend was more pronounced and still present when comparing the exposure of adolescent and adults patients stratified by weight groups. To some degree, it is likely that exposure differences between adolescent and adult asthma patients are correlated with body weight effect.

The PK in severe oral corticosteroid dependent asthma patients (EFC13691) and in non-OCS dependent asthma patients (DRI12544 and EFC13579) was highly comparable as the final asthma population PK model was able to predict the patient exposures from study EFC13691 acceptably well.

Interactions

Dupilumab, as a monoclonal antibody, directed against IL-4Rα, is not expected to have a direct or indirect effect on cytochrome P450 (CYP) enzyme-mediated metabolism. This was confirmed in the drug interaction Study R668-AD-1433 in patients with atopic dermatitis, where there was no clinically relevant effect of dupilumab on the activities of CYP isoforms including CYP1A2, 2C9, 2C19, 2D6 and 3A. The results indicate that IL-4/IL-13 has no meaningful impact on CYP enzymes in vivo.

The impact of concomitant medications (defined as any treatments received concomitantly to dupilumab from the first dupilumab administration of to the end of post-treatment period) on dupilumab PK were assessed in the Pop PK analysis. The comparison of the post hoc estimates of exposure showed no apparent effect of concomitant use of common asthma controllers (LTRA, LABA, systemic corticosteroids, methylxanthines) on dupilumab exposure. Further, patients from Study EFC13691 with regular treatment of maintenance OCS showed similar PK exposure to those not on OCS (Study EFC13579).

2.4.3. Pharmacodynamics

Mechanism of action

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

PD Biomarker

Mean percent change in FeNO over time following 24 to 52 weeks of treatments of both envisaged SC dupilumab dosing regimens in patients with asthma (Studies DRI12544 and EFC13579) was equally strong and reached before steady state after about 2 weeks.

The time course of PD biomarkers does not allow for a distinction between both SC dupilumab dosing regimen, as they showed highly comparable PD effect and variability throughout the studies, study duration and doses. Substantial reduction of PD markers FeNO, TARC, periostin, eotaxin-3 with dupilumab treatment with maximum effect achieved rapidly and sustained over the treatment period both regimens.

Immunogenicity

Dupilumab immunogenicity was evaluated in all dupilumab clinical studies. Study EFC13579 provides long-term data on ADA responses in patients with asthma and has sufficient duration (52 weeks) to enable the evaluation of persistent ADA responses.

A summary of ADA incidence for asthma patients in Studies DRI12544, EFC13579, and EFC13691 is provided below (Table 17).

Table 17 – ADA incidence in Studies DRI12544, EFC13579, and EFC13691

Anti-dupilumab antibodies N (%)	Study DRI12544 (24-week duration)			Study EFC13579 (52-week duration)			Study EFC13691 (24-week duration)	
	Placebo (N=158)	200 mg q2w (N=148)	300 mg q2w (N=155)	Combined placebo[g] (N=630)	200 mg q2w (N=625)	300 mg q2w (N=626)	Placebo (N=107)	300 mg q2w (N=101)
Pre-existing ADA[a]	2 (1.3%)	3 (2.0%)	3 (1.9%)	7 (1.1%)	7 (1.1%)	9 (1.4%)	1 (0.9%)	3 (3.0%)
Treatment-emergent response[b]	11 (7.0%)	37 (25.0%)	28 (18.1%)	22 (3.5%)	58 (9.3%)	32 (5.1%)	5 (4.7%)	5 (5.0%)
Persistent response[c]	3 (1.9%)	16 (10.8%)	7 (4.5%)	7 (1.1%)	26 (4.2%)	13 (2.1%)	1 (0.9%)	0
Indeterminate response[d]	4 (2.5%)	8 (5.4%)	4 (2.6%)	13 (2.1%)	11 (1.8%)	9 (1.4%)	3 (2.8%)	2 (2.0%)
Transient response[e]	4 (2.5%)	13 (8.8%)	17 (11.0%)	2 (0.3%)	21 (3.4%)	10 (1.6%)	1 (0.9%)	3 (3.0%)
Peak post-baseline titer								
Low (<1,000)	10 (6.3%)	31 (20.9%)	24 (15.5%)	19 (3.0%)	48 (7.7%)	28 (4.5%)	5 (4.7%)	2 (2.0%)
Moderate (1,000-10,000)	1 (0.6%)	5 (3.4%)	3 (1.9%)	2 (0.3%)	5 (0.8%)	1 (0.2%)	0	0
High (>10,000)	0	1 (0.7%)	1 (0.6%)	1 (0.2%)	5 (0.8%)	3 (0.5%)	0	3 (3.0%)
Treatment-boosted response[f]	0	1 (0.7%)	0	3 (0.5%)	0	1 (0.2%)	1 (0.9%)	0
Neutralizing antibodies	--[h]	--[h]	--[h]	10 (1.6%)	27 (4.3%)	14 (2.2%)	1 (0.9%)	3 (3.0%)

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 Combined ADA data from placebo 1.14 mL and placebo 2 mL treatments in Study EFC13579.
h Analysis for neutralizing antibodies conducted in Phase 3 studies only

PK/PD

Descriptive and model-based analyses were used to investigate the exposure-response relationship for the key clinical efficacy endpoints in the uncontrolled moderate-to-severe asthma population and severe OCS-dependent asthma population.

Semi-mechanistic population PK/PD analysis: The time course for FEV1 following SC administration of dupilumab was best described by a direct response model relating dupilumab concentrations with FEV1 response. The model was based on the combined data from adult and adolescent moderate-to-severe asthma patients (non-OCS dependent) in pivotal studies (DRI12544 and EFC13579). The model was parameterized with the maximum drug effect (Emax) and the drug concentration to produce 50% of Emax (EC50). The placebo effect was included in the model described by an empirical model where Pmax is the maximum placebo effect and kplb is the rate constant for placebo effect development.

Population estimates of dupilumab treatment effect were 0.104 L for Emax and 0.713 mg/L for EC50. The inter-individual variability for EC50 was very large, with estimated CV% at 193% and large for Emax (84.3%). Shrinkage was high for EC50 (80.3%) and Emax (52.2%), respectively. In general, the precision of the parameter estimates was acceptable (%RSE < 21%). The IIV estimates for Emax and baseline FEV1 were decreased by 20.7% and 8.8%, respectively, compared to the base model by including covariates. Covariate analysis indicated that baseline eosinophil count and FeNO significantly influence the Emax level. A larger treatment effect on FEV1 in patients with higher baseline eosinophils and FeNO levels could be detected.

However a high inter-individual variability that remained unexplained by investigated covariates and high shrinkage values regarding Emax and EC50 could be detected. Thus, the small simulated increase (6.25%) in FEV1 response for dose 300 mg compared to the 200 mg treatment is not considered a clinically relevant finding and does not allow differentiation between the doses.

Empirical PK/PD modelling (FEV1 response and severe exacerbation): Overall, both the semi-mechanistic and the empirical PK/PD analyses identified a similar exposure-response relationship for FEV1 in uncontrolled moderate-to-severe asthma patients. The response showed a rapid increase in response with increasing dupilumab concentration approaching a response plateau at concentrations reached in both Phase III q2w dosing regimens using an Emax-Model.

Modelling and data indicate a clinically significant improvement in FEV1 for both the 200 and 300 mg q2w dosing regimens. Regarding variability, both models identified Type 2 inflammation markers (FeNO and eosinophils for the semi-mechanistic model, and FeNO and periostin for the empirical model) as significant covariates of the treatment effect on FEV1. Response was higher in patients with elevated biomarker levels. In this line, no significant effect of covariate age, body weight, or ADA status could be detected.

For severe exacerbation event empirical PK/PD modelling, the model estimated EC50 was 8.54 mg/L for Study EFC13579 and 17.36 for the DRI1254 Study. Emax was calculated to be -1.525 (severe exacerbation events). Baseline EOS, baseline FeNO and asthma age onset were identified as influential factors to the treatment efficacy.

Given the large confidence intervals around these ratios and the estimates of EC50 and Emax, no definite benefit of one dosing regimen regarding efficacy can be concluded based on clinical data and PK/PD modelling.

Overall, both the semi-mechanistic and the empirical PK/PD analyses identified a similar exposure-response relationship for efficacy in uncontrolled moderate-to-severe asthma patients. The response showed a rapid increase in response with increasing dupilumab concentration approaching a response plateau at concentrations reached in both Phase III q2w dosing regimens.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Analytical methods

The methods applied for detection of functional dupilumab correspond to the methods used in the initial marketing authorisation application for AD and these have been accurately validated. Incurred sample reanalysis was conducted in asthma studies ACT11457 and DRI12544 and confirmed that the assay produced robust and reproducible results in the asthma population.

Anti-dupilumab antibodies were detected in serum samples using a validated electrochemi-luminescence bridging immunoassay. The applied assay method used in the AD clinical study program was updated (REGN668-AV-13089-VA-01V3) with additional long-term stability testing, cut points determined for the asthma population and drug tolerance level at 120 ng/mL of monoclonal antibody control for the asthma population cut point. In addition, due to the observation of a higher background signal in baseline serum samples in study DRI12544 the REGN668-AV-13089-VA-01V2 method was modified and validated and an updated report (REGN668-AV-15153-VA-01V1) was generated. As stated by the applicant, this method uses a modified version of the dupilumab drug as one of the bridging components to mitigate the non-dupilumab

specific background responses and was used to reanalyse samples of patients who had a positive assay response at baseline in the screening assay of the original assay method REGN668-AV-13089-VA-01V2 (2-assay approach). In this respect, the appropriateness of the original assay method REGN668-AV-13089-VA-01V2 was questioned and the applicant was asked for a justification for not testing all samples with the modified assay method REGN668-AV-15153-VA-01V1 given the obviously higher selectivity of the assay. Additionally, the applicant was requested to provide the method validation report of the modified assay REGN668-AV-15153-VA-01V1. The validation report for the modified ADA assay REGN668-AV-15153-VA-01V1 was submitted as part of the response package. Validation results reveal that the assay method used was appropriate to adequately analyse the ADA response to dupilumab. The applicant further adequately justified that only those samples with pre-existing reactivity were re-analysed with the modified assay.

The previous method for NAb detection was updated (REGN668-AV-13112-VA-01V2) to add the analysis of the validation data using the 19% inhibition cut point (1% false positive rate) and to add an additional recovery experiment investigating hemoglobin interference.

Relative Bioavailability (Study R668-AD-1607)

Study R668-AD-1607 investigated the systemic exposure of 200 mg dupilumab (Part A) administered SC using PFP device versus PFS. The study was not formally powered to show bioequivalence between PFS and PFP. The geometric mean ratio for AUC(0-14) was 0.723 (90% CI: 0.635-0.823) at study day 1 and 0.903 (90% CI: 0.767-1.063) at study day 85 (steady state). The geometric mean ratio for Cmax was 0.741 (90% CI: 0.655-0.839) at study day 1 and 0.890 (90% CI: 0.779-1.017) at study day 85 (steady state).

Based on the presented data, it has to be assumed that the two presentations are not bioequivalent since the bioequivalence margin (0.8-1.25) for the 90% confidence intervals of the geometric mean ratio was not met in any of the investigated exposure parameters (AUC, Cmax, Ctrough) Of note, the study was not powered to allow for definitive statements with regards to bioequivalence. The applicant was however requested to thoroughly elucidate possible reasons for this unexpected difference in dupilumab exposure. In response, the applicant provided a thorough discussion and additional supportive data so that it might now be concluded that the performance of both the 1 mL PFP and 1 mL PFS can be considered similar and the potentially present differences are not clinically meaningful.

Population PK Analysis

A population PK (Pop PK) analysis of dupilumab PK samples was conducted using data from healthy subjects and adolescent and adult asthma patients. Although only sparse data have been recruited in asthma patients, the overall data package on clinical pharmacology is sufficient. Parameter estimates of the final asthma Pop PK model for dupilumab described the observed dupilumab PK acceptably well. A two-compartment model with parallel linear and nonlinear elimination with first order absorption was selected. In response to the list of questions, the applicant adequately elaborated on the influence of shrinkage on the covariate selection procedure and the relevance of this regarding the PK/PD models for investigating the exposure-efficacy relationship.

Higher exposure (about 1.5 – 2 fold) is observed in adolescent patients compared to adults in both dosing groups. However, for the higher dosing, this trend was more pronounced and still present when comparing the exposure of adolescent and adults patients stratified by weight groups. To some degree, it is likely that exposure differences between adolescent and adult asthma patients are correlated with body weight effect.

ADME

In patients with asthma, dupilumab is absorbed with an estimated SC bioavailability at 61%. PK is characterized by a limited volume of distribution estimated to 4.37 L and by non-linear target-mediated elimination. Linear clearance has been derived to 0.115 L/day. This value was derived using the estimated Ke value.

The asthma Pop PK analysis showed moderate inter-individual variability in PK parameters Fsc, Ke, V2 and Vm (36.3%, 19.6%, 9.13%, and 24.3%, respectively as derived by population PK analysis). In response to the list of questions, the applicant further provided the estimate for IIV on linear clearance, which was 26.7% (%CV) in the base model and was reduced to 20.5% after inclusion of weight effects.

Pharmacodynamics

PK/PD

Both the semi-mechanistic and the empirical PK/PD analyses identified a similar exposure-response relationship for FEV1 response and severe exacerbation event in uncontrolled moderate-to-severe asthma patients. The predicted response showed a rapid increase in response with increasing dupilumab concentration approaching a response plateau at concentrations reached in both Phase III q2w dosing regimens using different PK metrics.

An analysis investigating the exposure-safety and dose-safety relationship has been provided in response to the d120 LoQ in order to better decipher and assess the risk-benefit profile regarding the envisaged dosing regimen for all patients and for adolescent patients in particular. There was no apparent dose relationship for any particular treatment-emergent adverse event (TEAE) except for injection site reactions, which occurred at a higher incidence with the 300 mg q2w dose.

Immunogenicity

Throughout the entire Phase 2 and Phase 3 studies, the analysis of anti-dupilumab antibodies revealed a consistent trend towards decreased incidence of ADA with higher dupilumab doses.

The development of ADA was associated with lower dupilumab concentrations (positive ADA predicted to result in less than 20% lower steady state AUC_T), which did not have an impact on efficacy and/or safety in case of low to moderate ADA titers. A meaningful reduction of dupilumab exposure was observed in patients with high titers (>10 000). However, the incidence of high titer ADA responses was low (<1%) and this issue is therefore not further pursued.

The incidence of ADA was comparable between asthma and AD studies. Referring to Study EFC13579, there was no difference in ADA incidence or character in the adolescent population as compared to the adult population.

In Study DRI12544, higher rates of treatment-emergent and persistent ADA as compared to the Phase 3 studies have been observed. The applicant elaborated that differences in ADA incidence between studies DRI12544 and EFC13579 were mainly associated with the low titer category. This finding might have resulted by chance due to the smaller sample size in study DRI12544 or due to minor differences in background immunoreactivity between both studies, which might have led to samples being considered (“borderline”) ADA positive more frequently. Taking into account that differences in immunogenicity rates did not have an impact on exposure, efficacy and safety of dupilumab, the issue is now considered resolved.

2.4.5. Conclusions on clinical pharmacology

Analytical methods mainly corresponded to the methods applied in the initial MAA for AD. Only the ADA analysis method was modified and validated.

Remaining uncertainties with regard to the bioequivalence of the newly to-be-marketed PFP compared to the PFS were sufficiently addressed by the applicant and it was concluded that the performance of both the 1 mL PFP and 1 mL PFS can be considered similar and the differences are not clinically meaningful.

Overall, the immunogenicity of dupilumab in the asthma population was low and comparable to the AD population. In study DRI12544 the incidence of ADA was unusually high compared to other studies, which adequately discussed by the applicant. This issue is now considered resolved mainly taking into account that differences in ADA status did not have an impact on exposure, efficacy and safety of dupilumab.

The data package on clinical pharmacology was deemed sufficient to characterize the PK of dupilumab in the target population.

From PK/PD modelling and data, no dose-efficacy and exposure-efficacy relationship can be concluded. Both doses showed equal efficacy compared to placebo. An analysis investigating the exposure-safety and dose-safety relationship has been provided by the applicant upon CHMP request. There was no apparent dose relationship for any particular treatment-emergent adverse event (TEAE) except for injection site reactions, which occurred at a higher incidence with the 300 mg q2w dose.

2.5. Clinical efficacy

As of the last data cut date for this submission dossier (30 September 2017), the dupilumab asthma clinical program consisted of 7 studies, of which 5 are included in the submission.

Two completed Phase 2 studies, of which one is a **pivotal** study:

- ACT11457 was a 12-week randomized, double-blind, placebo-controlled, proof of concept (POC) study in patients with persistent moderate-to-severe asthma with eosinophilic phenotype.
- **DRI12544** was a pivotal 24-week randomized, double-blind, placebo-controlled, dose ranging, Phase 2b study in patients with moderate-to-severe uncontrolled asthma. The CSR and a partial dataset have been submitted previously with the original marketing application for AD.

Two Phase 3 **pivotal** studies:

- **EFC13579 (QUEST)** was a pivotal 52-week randomized, double blind, placebo-controlled study in patients with persistent (moderate-to-severe uncontrolled) asthma. It was a confirmatory efficacy and safety study with the primary analysis completed (data cutoff of 29 July 2017).
- **EFC13691 (VENTURE)** was a pivotal 24-week, double-blind, placebo-controlled study in patients with severe steroid-dependent asthma; the end-of-treatment (EOT) analyses were completed (data cutoff of 20 September 2017)

One ongoing Phase 3 open-label extension (OLE) study:

- LTS12551 (TRAVERSE) is a long-term safety and tolerability study in patients who previously participated in another asthma study; an interim CSR was prepared for patients who rolled over from Studies DRI12544, EFC13579 and EFC13691 (data cutoff of 29 July 2017). Data for patients who rolled over from Study EFC13691 remained blinded with respect to dose regimen in the parent study

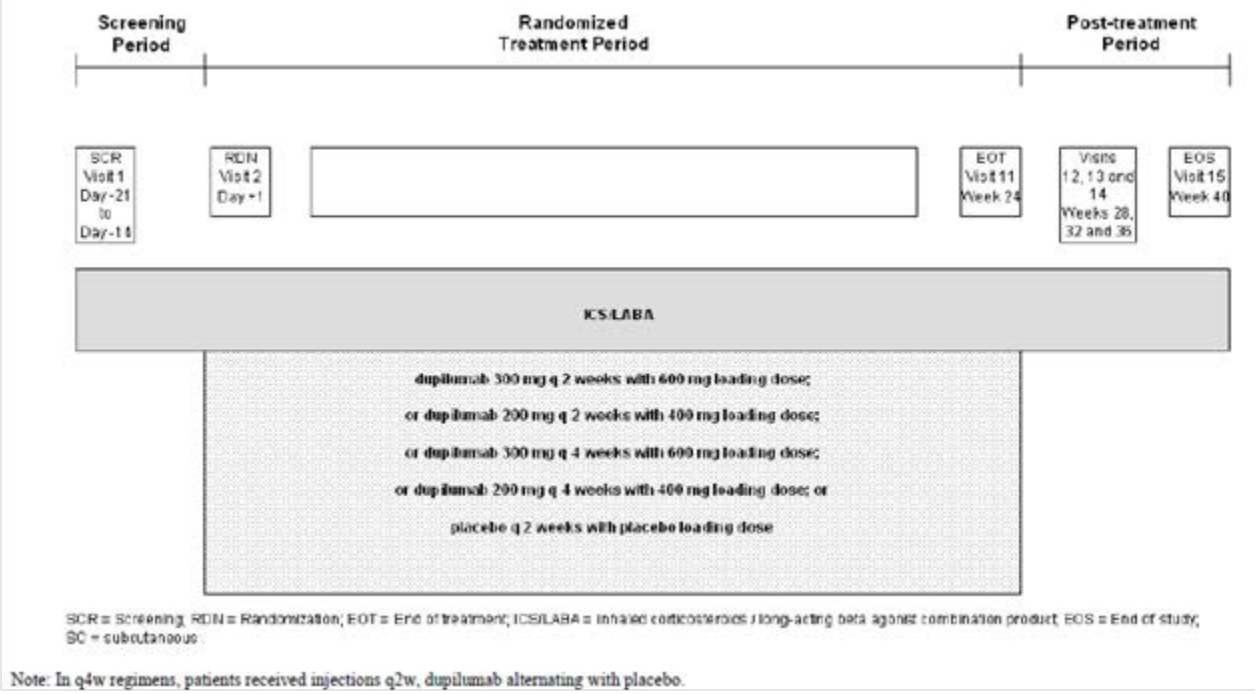
until the parent study database was locked on 16 October 2017. A previous interim CSR was submitted with the original marketing application for AD and had a data cutoff of 31 January 2016.

2.5.1. Dose response study

Study DRI12544

Methods

Study DRI12544 was a pivotal 24-week randomized, double-blind, placebo-controlled, dose ranging, Phase 2b study in patients with moderate-to-severe uncontrolled asthma.



The study consisted of 3 periods, a screening period (14 to 21 days) to determine whether patients met eligibility criteria and to establish level of asthma control before the randomized treatment period, a randomized treatment period (24 weeks) and a post-treatment period (16 weeks) to monitor patients after treatment with a total duration of approximately 43 weeks.

Methods

Study Participants

Main Inclusion criteria

Adults with a physician diagnosis of moderate-to-severe, uncontrolled asthma for ≥12 months, based on the GINA 2009 Guidelines and following criteria were eligible: Existing treatment with moderate- or high-dose ICS/LABA, FEV1 40 to 80% predicted normal at visit 1 and 2, ACQ-5 score ≥1.5, Reversibility of at least 12% and 200 mL in FEV1 after 200 µg to 400 µg of salbutamol/albuterol at Visit 1 and experienced treatment with ≥1 systemic (oral or parenteral) steroid bursts or hospitalization or an emergency/urgent medical care visit for worsening asthma. Excluded were patients with other lung diseases which could have impaired pulmonary

function tests, current smokers, history of HIV, HBV or HCV as well as diagnosed active parasitic or chronic infections.

Main Exclusion criteria

- Patients <18 years of age.
- Chronic obstructive pulmonary disease or other lung diseases (eg, emphysema, idiopathic pulmonary fibrosis, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis) which impaired pulmonary function tests.
- Current smoker or cessation of smoking within 6 months prior to Visit 1.
- Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to Visit 1; biologic therapy within 6 months of Visit 1.
- Treatment with systemic (oral or injectable) corticosteroids (>10 mg per day of oral prednisone or equivalent) within 28 days of the screening visit and at any time during the screening period.
- Diagnosed active parasitic infection; suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments had ruled out active infection before randomization.
- History of human immunodeficiency virus (HIV) infection or positive HIV screen (anti-HIV-1 and HIV-2 antibodies) at Visit 1.
- Patients who had positive or indeterminate hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), or hepatitis C antibody at Visit 1.
- Evidence of acute or chronic infection that required treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1; significant viral infections within 4 weeks before Visit 1 that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).
- Live, attenuated vaccinations within 12 weeks prior to Visit 1 or planned live, attenuated vaccinations during the study

Treatments

Dupilumab was used as an add-on therapy to inhaled corticosteroid / long-acting beta agonist combination therapy (ICS/LABA). Prior to screening, patients were to have been on a stable dose of moderate- or high-dose ICS/LABA (≥fluticasone propionate 250 μg twice daily or equipotent ICS dosage) for ≥1 month prior to Visit 1. During the randomized treatment period as well as upon completion of the randomized treatment period, patients continued the stable dose of ICS/LABA of equivalent dosage used during the screening period. In addition, patients were allowed to administer salbutamol/albuterol hydrofluoroalkane pressurized metered dose inhaler (MDI) or levosalbutamol/levalbuterol hydrofluoroalkane pressurized MDI as reliever medication as needed.

Objectives

The **primary** objective of the study was:

- To evaluate the efficacy of different doses and regimens of dupilumab in patients with moderate-to-severe, uncontrolled asthma

The **secondary** objectives of the study were:

- To evaluate different doses and regimens of dupilumab in patients with moderate-to-severe, uncontrolled asthma, with regards to:

  - Safety and tolerability

  - Dupilumab systemic exposure and anti-drug antibodies (ADA)

  - Patient-reported outcomes (PROs)

- To evaluate baseline biomarkers for their potential value to predict treatment response
- To evaluate on-treatment biomarkers for their potential value to associate with treatment response
- To evaluate genetic profiles for their potential value to predict treatment response

Outcomes/endpoints

The **primary endpoint** was the change from baseline at Week 12 in FEV1.

The **secondary efficacy endpoints** assessed included:

- Relative change (%) from baseline at Week 12 in FEV1
- Annualized rate of loss of asthma control events (LOAC) during the treatment period
- Annualized rate of severe exacerbation events during the treatment period
- Time to LOAC events during the treatment period and during the overall study period
- Time to severe exacerbation events during the treatment period and during the overall study period
- Change from baseline at Week 12 in forced vital capacity (FVC)
- Relative change (%) from baseline at Week 12 in FVC
- Change from baseline at Week 12 in FEV1/FVC ratio
- Change from baseline at Week 12 in forced expiratory flow at 25-75% of FVC (FEF25-75)
- Change from baseline at Week 12 in forced expiratory flow at 25-75% of FVC (FEF25-75)

<u>Two types of asthma exacerbation events were predefined in the protocol:</u>

A **LOAC** (Loss of Asthma Control) event during the study was defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with baseline) on 2 consecutive days; or
- Increase in ICS ≥4 times the dose at Visit 2; or

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

A **severe exacerbation event** during the study was defined as a deterioration of asthma requiring:

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

A severe exacerbation event was counted as a LOAC event.

Sample size

Sample size calculation was based on the following assumptions:

- A 0.2 L mean difference between the highest dupilumab dose and placebo in change from baseline in FEV1
- A common (SD) of 0.35 (from study ACT11457)
- t-test at a 2-sided 5% significant level with 83% power
- Expected early discontinuation rate of 10%

Based on these assumptions it was calculated that 300 HEos patients (60 per group) would provide 94% power to detect a mean difference of 0.24 L as observed from the ACT11457 study. Anticipating a 40% recruitment rate for the HEos category, approximately 750 patients were to be randomized in order to achieve 300 HEos patients.

Randomisation

Subjects were randomized in an 1:1:1:1:1 ratio to receive dupilumab 300 mg q2w, dupilumab 200 mg q2w, dupilumab 300 mg q4w, dupilumab 200 mg q4w, or placebo. Randomization was stratified by Visit 1 central laboratory blood eosinophils (HEos ≥0.3 G/L, eosinophils = 0.2 to 0.299 G/L, and eosinophils <0.2 G/L) and country.

Blinding (masking)

Dupilumab and placebo were provided in identically matched vials.

Statistical methods

Efficacy analyses were performed on both the overall ITT population (all randomized subjects) and the HEos ITT population (all randomized subjects with baseline blood eosinophils ≥0.3 G/L). The primary analysis was for the ITT population (based on EMA scientific advice).

The primary efficacy variable (change from baseline in FEV1 at week 12) was analyzed using a mixed-effect model with repeated measures (MMRM) approach with factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries / regions, visit, treatment-by-visit interaction, FEV1 baseline value, and baseline-by-visit interaction. An unstructured correlation matrix was used to model the within-patient errors. Parameters were estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Differences in least squares (LS) means, corresponding 95% confidence intervals (CI), and p-values were

provided for comparison for each dose-regimen against placebo. The FEV1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date + 30 days for each exacerbation episode were excluded from the primary analysis in order to reduce the confounding effect of systemic corticosteroids.

Sensitivity analyses were performed to assess the impact of systemic corticosteroid use and / or missing values:

- Repeating the main analysis, but including all FEV1 measurements (even following systematic corticosteroid use),
- Repeating the main analysis, but excluding all FEV1 measurements collected on and after first day of systemic corticosteroid use.
- Pattern mixture model-multiple imputation (PMM-MI)
- Control based PMM-MI
- Tipping point analysis to search for tipping points that reverse the study conclusion.

To assess the consistency of treatment effects, pre-specified subgroup analyses were performed for the primary efficacy variable.

A negative binomial regression model was used to assess treatment differences in annualized rate of LOAC and severe exacerbation events. The model included treatment group, baseline eosinophil strata, pooled countries / regions, and number of asthma events prior to the study (number of asthma exacerbation during 1 year prior to visit 1) as covariates and the log-transformed observation duration as offset. Each active dose group was tested separately versus placebo and 2-sided 95% CIs of the rate ratio are provided for each treatment group.

Time to event data was analyzed applying Kaplan-Meier methods. Cox regression was used to assess treatment differences. Treatment, baseline eosinophil strata, number of asthma events prior to the study, and pooled countries/regions were used as covariates in the Cox regression. Hazard ratio (HR) was estimated for pairwise comparison between each dose of dupilumab and placebo.

After database lock a hierarchical testing procedure to assess the efficacy of dupilumab 300 mg q2w and dupilumab 200 mg q2w was defined, ie, each hypothesis was formally tested only if the preceding one was significant at the 2-sided 5% level:

1) annualized severe exacerbation rate for 300 mg q2w versus placebo,
2) absolute change from baseline in FEV1 at week 12 for 300 mg q2w versus placebo,
3) annualized severe exacerbation rate for 200 mg q2w versus placebo,
4) absolute change from baseline in FEV1 at week 12 for 200 mg q2w versus placebo.

If both dupilumab doses were significant for both primary endpoints further tests were to be performed following a hierarchical testing procedure at a 2-sided 5% significant level.

Results

Participant flow

A total of 776 patients were randomized to 1 of the 4 dupilumab dose groups (200 mg q4w: 154, 300 mg q4w: 157, 200 mg q2w: 150, and 300 mg q2w: 157) or placebo (158). Of them, 325 patients (40.3% to

43.3% of the overall population in the different treatment groups) had elevated (≥0.3 G/L) blood eosinophils at baseline and constituted the HEos population. Overall, 732 (94.3%) patients completed the 12-week primary efficacy endpoint treatment period and 709 (91.4%) patients completed the entire treatment period (24 weeks).

Numbers analysed

Analysis population – Randomized population

		Dupilumab				
	Placebo	200 mg q4w	300 mg q4w	200 mg q2w	300 mg q2w	All
Randomized population	158 (100%)	154 (100%)	157 (100%)	150 (100%)	157 (100%)	776 (100%)
Efficacy population						
Intent-to-Treat (ITT)	158 (100%)	154 (100%)	157 (100%)	150 (100%)	157 (100%)	776 (100%)
HEos ITT	68 (43.0%)	62 (40.3%)	66 (42.0%)	65 (43.3%)	64 (40.8%)	325 (41.9%)
Safety population	158	150	157	148	156	769
HEos Safety	68	59	66	64	64	321
PK Population	158	150	157	148	156	769
ADA Population	158	148	157	148	155	766

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
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Baseline characteristics

The demographic and baseline characteristics were generally similar between treatment groups in the overall randomized population. The mean age was 48.6 years with a range of 18 to 87 years. 63.1% of the patients were females and 78.2% of the patients were white. Asthma-specific baseline characteristics were similar between treatment groups, including the mean FEV1 percent predicted (dupilumab: 60.3% to 61.2%; placebo: 61.0%), mean ACQ-5 score (dupilumab: 2.70 to 2.80; placebo: 2.69), and global AQLQ (dupilumab: 3.91 to 4.03; placebo: 4.12). 77.3% of the patients had a history of atopic disease, allergic rhinitis being the most frequent one (64.7%).

The primary efficacy analysis population as pre-specified in the SAP was the HEos ITT population. After the interim analysis, conducted in the HEos population, had been performed, the Sponsor received feedback from both the EMA and FDA, that the primary analysis should be based on the overall ITT population.

Primary endpoint: In the overall ITT population, the LS mean changes in FEV1 from baseline to Week 12 were +0.12 L in the placebo group and ranged from +0.21 L (200 mg q4w dose) to +0.31 L (200 mg q2w dose) in the 4 dupilumab treatment groups. When compared with placebo, the LS mean differences were significant for dupilumab 200 mg q4w (+0.10 L, p=0.0304), 300 mg q4w (+0.12 L; p=0.0048), 200 mg q2w (+0.20 L; p<0.0001), and 300 mg q2w (+0.16 L; p=0.0002).

Change from baseline in FEV1 (L) at week 12 - ITT population

FEV1 (L)	Placebo (N=158)	Dupilumab 200 mg q4w (N=154)	Dupilumab 300 mg q4w (N=157)	Dupilumab 200 mg q2w (N=150)	Dupilumab 300 mg q2w (N=157)
Baseline					
Number	158	154	157	150	157
Mean (SD)	1.82 (0.55)	1.88 (0.54)	1.86 (0.57)	1.79 (0.52)	1.85 (0.53)
Median	1.74	1.80	1.74	1.72	1.75
Q1 : Q3	1.44 : 2.16	1.49 : 2.19	1.45 : 2.15	1.42 : 2.04	1.46 : 2.18
Min : Max	0.9 : 3.6	0.9 : 3.9	0.8 : 4.2	0.8 : 3.4	0.8 : 3.8
Week 12					
Number	129	134	134	136	146
Mean (SD)	2.01 (0.69)	2.07 (0.63)	2.14 (0.69)	2.12 (0.68)	2.12 (0.59)
Median	1.84	1.99	2.09	1.99	2.10
Q1 : Q3	1.52 : 2.39	1.62 : 2.41	1.66 : 2.56	1.57 : 2.48	1.72 : 2.55
Min : Max	0.9 : 4.0	0.8 : 4.0	0.9 : 4.2	1.0 : 4.6	0.8 : 4.4
Change from baseline					
Number	129	134	134	136	146
Mean (SD)	0.13 (0.37)	0.20 (0.41)	0.24 (0.40)	0.32 (0.38)	0.26 (0.39)
Median	0.09	0.18	0.18	0.24	0.21
Q1 : Q3	-0.10 : 0.29	-0.03 : 0.40	-0.03 : 0.42	0.08 : 0.53	0.00 : 0.46
Min : Max	-0.7 : 1.5	-1.5 : 1.3	-0.7 : 1.4	-0.4 : 1.8	-0.5 : 1.6
LS Mean (SE) [a]	0.12 (0.03)	0.21 (0.03)	0.24 (0.03)	0.31 (0.03)	0.28 (0.03)
LS Mean Diff, 95% CI [a]		0.10 (0.01, 0.18)	0.12 (0.04, 0.21)	0.20 (0.11, 0.28)	0.16 (0.08, 0.25)
P-value vs placebo [a]		0.0304	0.0048	<.0001	0.0002

[a] Derived from MMRM model with change in FEV1 (L) from baseline up to week 12 as dependent variables, factors (fixed effects) for treatment, baseline eosinophil strata, pooled countries / regions, visit, treatment-by-visit interaction, FEV1 (L) baseline value and baseline-by-visit interaction as covariates, unstructured correlation matrix.

FEV1 (L) collected from systemic corticosteroid start date to systemic corticosteroid end date + 30 days for each severe exacerbation episode are excluded in order to reduce the confounding effect of systemic corticosteroids.

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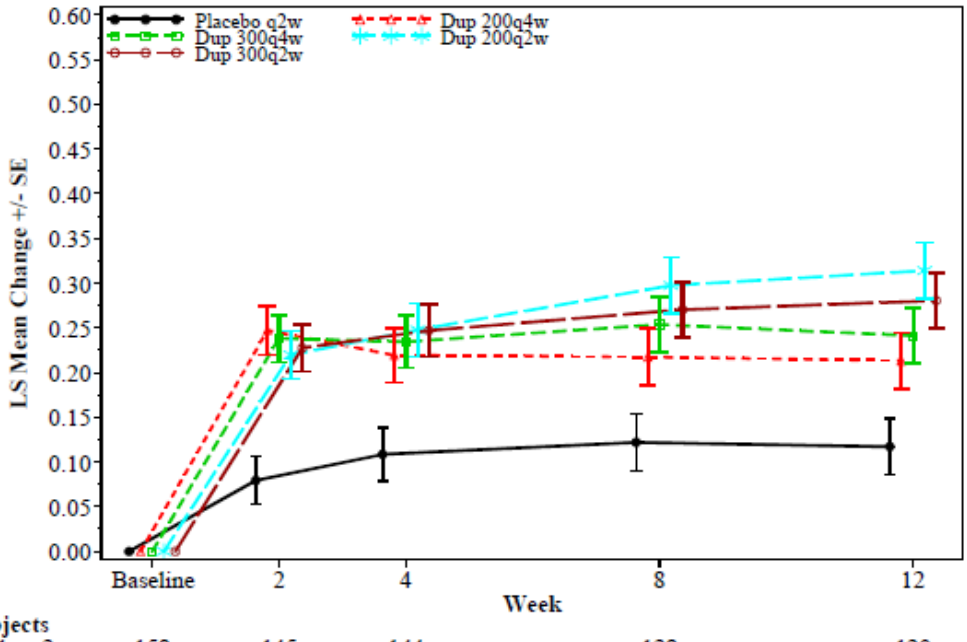
1. *LS mean change from baseline in FEV1 (L) over time (MMRM including measurements up to Week 12) - ITT population*



# subjects					
Placebo q2w	158	145	144	128	129
Dup 200q4w	154	145	142	134	134
Dup 300q4w	157	152	146	140	134
Dup 200q2w	150	148	146	137	136
Dup 300q2w	157	152	147	139	146

FEV1 (L) collected from systemic corticosteroid start date to systemic corticosteroid end date + 30 days for each severe exacerbation episode are excluded in order to reduce the confounding effect of systemic corticosteroids.
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In the **subgroup of patients with baseline eosinophils <0.3 G/L**, dupilumab demonstrated an improvement in the changes in FEV1 from baseline to Week 12 at the doses of 200 mg q2w (LS mean difference = +0.15 L) and 300 mg q2w (+0.12 L) as compared to placebo, with nominal p-values <0.05, while the treatment effect of q4w dose regimens were smaller with nominal p-values >0.05.

Secondary endpoints:

In the overall ITT population, improvement in FEV1 induced by all 4 doses dupilumab over placebo was observed at Week 12 was and maintained up to Week 24. All 4 doses of dupilumab showed statistically significant increases in FEV1 from baseline to Week 24.

The relative risks for a severe asthma exacerbation, based on the adjusted annualized rate of severe exacerbation over the treatment period compared to placebo were 0.463 (200 mg q4w), 0.668 (300 mg q4w), 0.300 (200 mg q2w), and 0.295 (300 mg q2w). Statistical significance was demonstrated for dupilumab 200 mg q2w and 300 mg q2w regimens.

Analysis of annualized event rate of severe exacerbation- treatment period - ITT population

	Placebo (N=158)	Dupilumab 200 mg q4w (N=154)	Dupilumab 300 mg q4w (N=157)	Dupilumab 200 mg q2w (N=150)	Dupilumab 300 mg q2w (N=157)
Number of patients with >=1 severe exacerbation event					
Number	158	150	157	148	156
No	117 (74.1%)	127 (84.7%)	128 (81.5%)	135 (91.2%)	139 (89.1%)
Yes	41 (25.9%)	23 (15.3%)	29 (18.5%)	13 (8.8%)	17 (10.9%)
Number of severe exacerbation events					
0	117 (74.1%)	127 (84.7%)	128 (81.5%)	135 (91.2%)	139 (89.1%)
1	21 (13.3%)	17 (11.3%)	17 (10.8%)	9 (6.1%)	12 (7.7%)
2	11 (7.0%)	5 (3.3%)	7 (4.5%)	3 (2.0%)	4 (2.6%)
3	7 (4.4%)	1 (0.7%)	4 (2.5%)	0	1 (0.6%)
>=4	2 (1.3%)	0	1 (0.6%)	1 (0.7%)	0
Total number of severe exacerbation events	75	30	47	20	23
Total patient-years followed	69.9	65.9	68.4	65.5	69.2
Unadjusted annualized severe exacerbation event rate [a]	1.073	0.455	0.687	0.305	0.332
Adjusted annualized severe exacerbation event rate [b]					
Estimate (95% CI)	0.897 (0.619, 1.300)	0.415 (0.260, 0.664)	0.599 (0.396, 0.907)	0.269 (0.157, 0.461)	0.265 (0.157, 0.445)
Relative risk (95% CI)		0.463 (0.259, 0.827)	0.668 (0.392, 1.138)	0.300 (0.159, 0.565)	0.295 (0.159, 0.546)
P-value		0.0093	0.1380	0.0002	0.0001
Individual patient annualized severe exacerbation events rate [c]					
Number	158	150	157	148	156
Mean (SD)	1.07 (2.26)	0.47 (1.20)	0.66 (1.60)	0.30 (1.19)	0.32 (1.02)
Median	0.00	0.00	0.00	0.00	0.00
Min : Max	0.0 : 15.2	0.0 : 6.5	0.0 : 8.7	0.0 : 10.9	0.0 : 6.6

[a] The total number of event that occurred during the treatment period divided by the total number of patient-years followed in the treatment period.
[b] Derived using negative binomial model with the total number of events onset between first dose date and last dose date + 14 days as the response variable, treatment, baseline eosinophil strata, pooled countries/regions and number of asthma event prior to the study as covariates, and log-transformed standardized treatment duration as an offset variable.
[c] The number of severe exacerbation events for each patient divided by the number of years followed in the treatment period for that patient.
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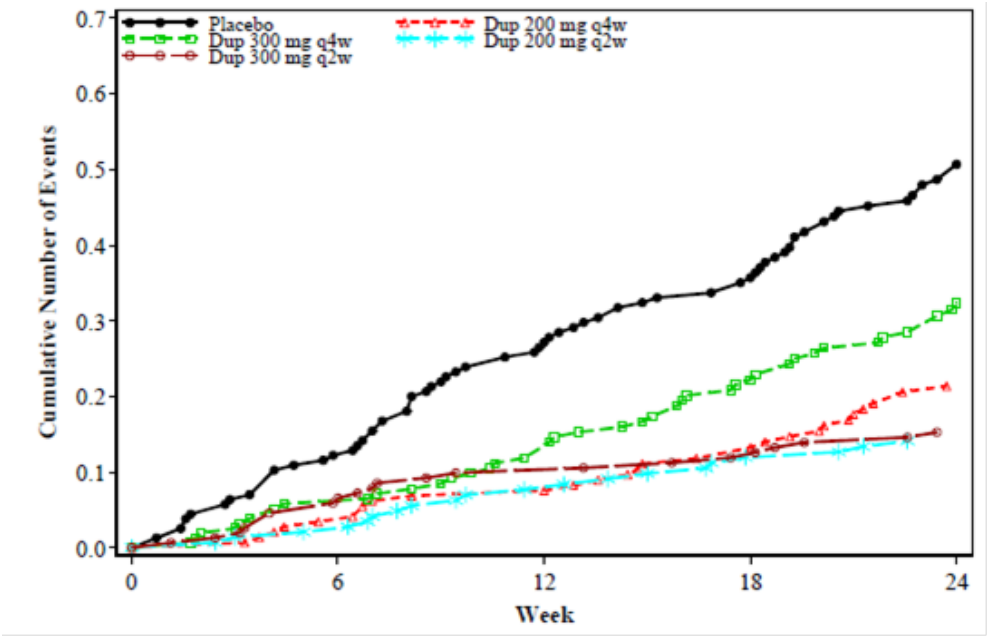
Cumulative mean function for the number of severe exacerbation events – treatment period - ITT population



The other endpoints showed similar efficacy of the two dupilumab doses compared to placebo.

Results of ACQ-5 and AQLQ questionnaires also supported the efficacy of both the 200 mg q2w and 300 mg q2w dose regimens of dupilumab while no significant differences were observed between the two q4w dose regimens and placebo.

A significant improvement in morning and evening asthma symptom scores was observed for all doses of dupilumab as compared to placebo in the overall population.

The two q2w doses also showed a statistically significant improvement in HADS total score in the HEos population while in the overall population, only the 200 mg q2w dosing regimen showed a significant effect.

2.5.2. Main studies

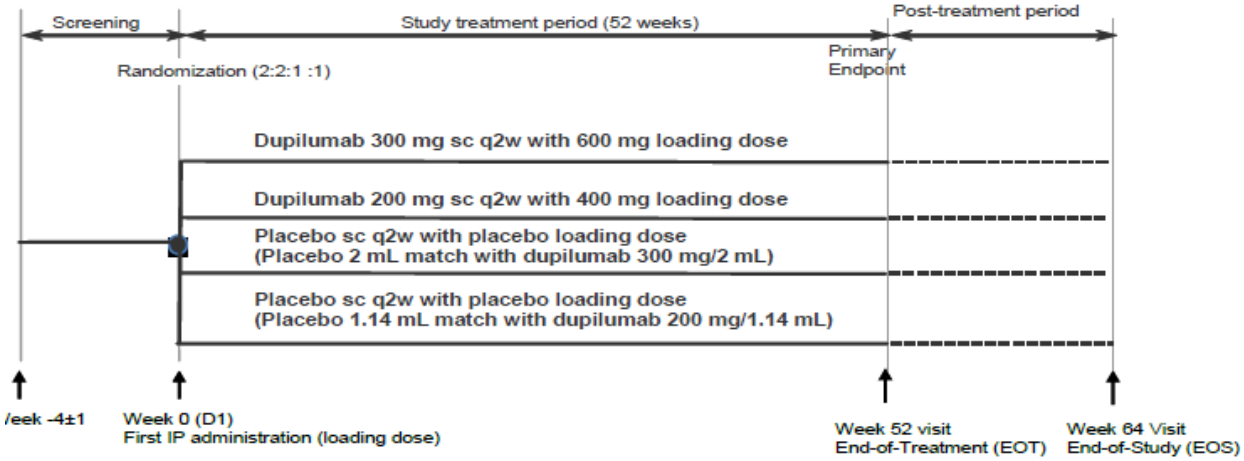
2.5.2.1. EFC13579 (QUEST)

Title of study

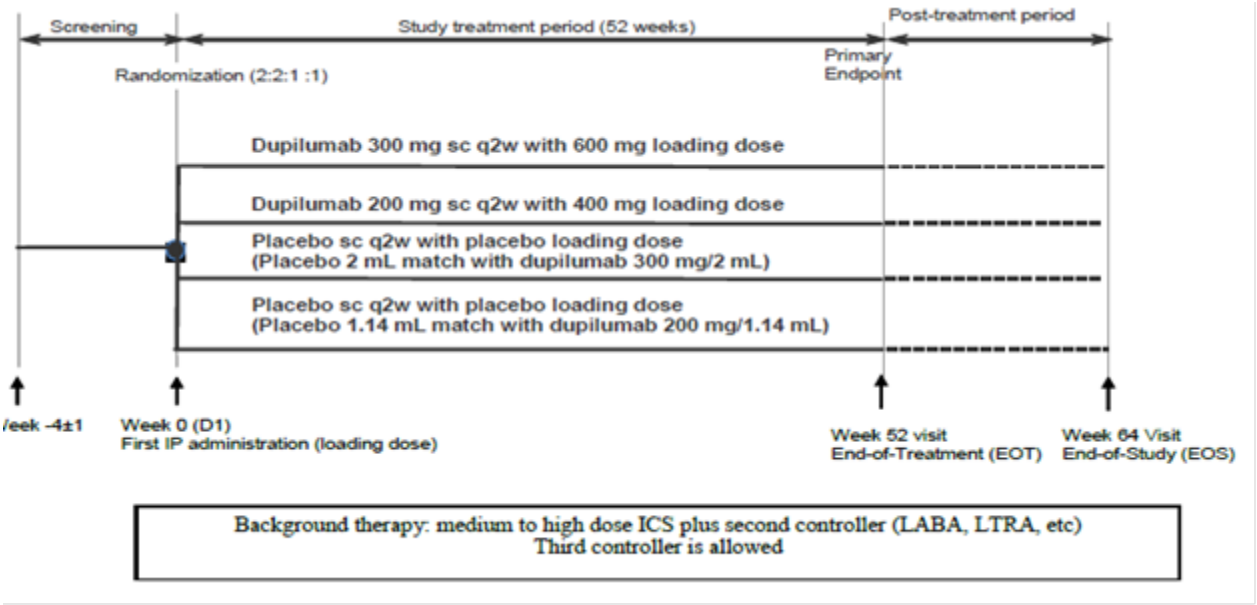
EFC13579 (QUEST)

Methods

Study EFC13579 was a pivotal 52-week randomized, double blind, placebo-controlled study in patients with persistent (moderate-to-severe uncontrolled) asthma using dupilumab or placebo as add-on therapy to ICS in combination with one or two other controller medicines (eg, LABA, long-acting muscarinic antagonists [LAMAs], LTRA, methylxanthines).



Background therapy: medium to high dose ICS plus second controller (LABA, LTRA, etc)
Third controller is allowed



The study consisted of 3 periods with a total duration of 67 to 69 weeks for each patient: screening period (4±1 weeks), randomized treatment period (52 weeks), and post-treatment follow-up period (12 weeks). Prior to and during the screening period, patients were required to be on a stable dose of medium to high dose ICS in combination with a second controller medication (e.g., LABA, LAMA, LTRA, methylxanthines). During the randomized treatment period patients continued taking their background controller medication(s) at the stable dose used during the screening period. Patients needing a third controller were also eligible for this study.

Randomization was stratified by age (<18 years, ≥18 years), central laboratory blood eosinophil count (<0.3 Giga/L, ≥0.3 Giga/L), ICS dose (medium, high), and country at screening.

Study participants

At least 1638 patients were planned to be randomized to dupilumab or placebo with at least 690 patients with a baseline blood eosinophil count ≥0.3 Giga/L and with approximately 84 adolescent patients. A protocol amendment limited the recruitment of patients on medium dose of ICS to approximately 819 to ensure at least 50% patients on a high dose of ICS.

Main Inclusion criteria

Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months (based on the GINA 2014 Guidelines) were eligible if they met the following criteria:

- Physician diagnosis of uncontrolled asthma for ≥12 months, based on the GINA 2014 Guidelines
- Medium to high dose ICS in combination with a second controller (eg, LABA, LTRA, methylxanthines) for at least 3 months with a stable dose ≥1 month prior to screening; patients requiring a third controller were also eligible
- Pre-bronchodilator FEV1 ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents prior to randomization

- Reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol
- ACQ-5- Total Score ≥1.5 at screening and baseline
- Must have experienced treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once; OR hospitalization or emergency medical care visit for worsening asthma.

Main Exclusion criteria

- Weight <30 kg
- COPD or other lung disease which may impair pulmonary function; chest X-ray within 12 months of screening visit with clinically significant findings of lung disease(s) other than asthma.
- Severe asthma exacerbation at any time from 1 month prior to the screening up to and including the Baseline Visit
- Prior and concomitant medications: Non-selective beta-1 adrenergic receptor, or initiation or change in dose of a selective beta-1 adrenergic receptor blocker within 1 month prior to screening
- Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to Visit 1 or any other biologic therapy/ immunosuppressant within 2 months or 5 half-lives • Initiation of allergen immunotherapy within 3 months prior to screening • Bronchial thermoplasty within 3 years prior to screening.
- Current smoker or cessation of smoking within 6 months prior to Visit 1; previous smoker with a smoking history >10 pack-years.

Treatments

Dupilumab/ Placebo

All dupilumab doses were administered by SC injection once every 2 weeks. Patients were randomized to 1 of the following treatment groups:

- Dupilumab 200mg q2w (1.14 mL) after a 400 mg loading dose
- Dupilumab 300 mg q2w (2 mL) after a 600 mg loading dose
- Placebo matched to dupilumab 200 mg (1.14 mL) q2w after a loading dose (2 x 1.14 mL)
- Placebo matched to dupilumab 300 mg (2.0 mL) q2w after a loading dose (2 x 2.0 mL)

Two injections of dupilumab (or placebo) were administered on Day 1 at Visit 2 as a loading dose. Subsequently, one injection was to be given every 14 ± 3 days (q2w).

Dose-ranging study DRI12544 randomized patients to 1 of 4 dupilumab regimens: 200 mg q4w, 300 mg q4w, 200 mg q2w, 300 mg q2w, or placebo. The results showed that treatment with dupilumab 300 mg q2w and dupilumab 200 mg q2w resulted highest improvements in FEV1 of all tested doses at Week 12 and a reduction by approximately 70% in the annualized rate of severe exacerbations compared to placebo. Both doses provided generally comparable efficacy.

Background treatment

The permitted asthma controllers for the study included the following 5 classes: ICS, LABA, LAMA, anti-leukotrienes and methylxanthines. Controller medication was not dispensed or supplied by the Sponsor.

Randomized treatment period:

Patients were required to continue their controller medication(s) at the same dose and regimen as used during the screening period. A transient increase in dose of ICS in addition to reliever/rescue medication was allowed to treat acute symptoms of asthma as per Investigator's guidance. The rescue medication was used as needed for symptom control. All use of controller and rescue medications was to be documented by the patient in an electronic diary.

Post-treatment period:

All patients continued treatment with the controller medication regimen and dose used during the randomized treatment period, which was adjusted as needed, based on the medical judgment of the Investigator.

Reliever / rescue medication

Patients were allowed to administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study except during the 6 hour period prior to spirometry measurements.

Objectives

Primary objective:

- To evaluate the efficacy of dupilumab in patients with persistent asthma.

Secondary objectives:

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab on improving patient-reported outcomes (PROs) including health-related quality of life (HRQoL)
- To evaluate dupilumab systemic exposure and incidence of ADA

Outcomes / endpoints

Primary Endpoint

- Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12

Secondary Endpoint

Key secondary endpoint:

- Percent change from baseline in pre-bronchodilator FEV1 at week 12

Other secondary endpoints:

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25- 75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period
- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score (for adults) and ACQ-7 (for adolescents) at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:

  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)

  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 4, 8, 12, 24, 36, and 52
- Change from baseline in PROs at Week 12, 24, 36, and 52:

  - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)

  - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)

  - Hospital Anxiety and Depression Scale (HADS)

- 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis

- Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis.

Sample size

Assuming the number of severe asthma exacerbations follows a negative binomial distribution with a dispersion parameter of 2, the placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study would have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) at α=0.05 (2-sided).

Assuming a common SD of 0.5 L, 1638 patients would provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at week 12 for the overall population.

A further 220 patients were randomized in order to have additional patients treated with the drug product manufactured using the intended commercial process.

Randomisation

Patients were randomized 2:2:1:1 to receive dupilumab 200 mg (in 1.14 mL) every 2 weeks (Q2W) with a 400 mg loading dose, dupilumab 300 mg (in 2 mL) Q2W with a 600 mg loading dose, placebo Q2W in 1.14 mL, or placebo Q2W in 2 mL. Due to the different volumes administered two matching placebos were required for this study. The permitted asthma controllers for the study included the following 5 classes: ICS, LABA, LAMA, anti-leukotrienes and methylxanthines. Patients were allowed to administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study except during the 6 hour period prior to spirometry measurements.

Blinding (masking)

Patients and investigators were blinded to the study treatment (dupilumab or placebo), but not to the dose/volume of the injection (200 mg/1.14 mL; 300 mg/2.0 mL).

Statistical methods

The ITT population (all randomized patients) was the primary efficacy analysis population.

The 1st primary parameter, annualized rate of severe exacerbation events was analysed by means of a negative binomial regression model with treatment, age, region (pooled country), baseline eosinophil stratum, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates and log-transformed duration of observation as offset variable. In this analysis, off-treatment measurements of patients who prematurely discontinued treatment were included in the analysis, including all severe exacerbation events up to visit 18 (week 52), regardless of whether the patient was on treatment or not, and the observation duration was defined as from randomization to visit 18. Estimates for treatment effects, corresponding 95% confidence intervals (CI), and p-values were derived by comparing each dupilumab group vs. its matching placebo group separately.

Supportive and sensitivity analyses

- An analysis to assess the efficacy of dupilumab in patients who adhered to the treatment as directed was conducted.
- Analyses to examine whether the loading dose has any confounding effect over the entire treatment period included analyses of severe asthma exacerbation events excluding the first 4 week and also the first 12 weeks of randomization. Additionally, only on-treatment events (ie, those that occurred before or on the last dose date + 14 days) were included to avoid possible confounding effect due to off-treatment data.

The 2nd primary parameter, absolute change from baseline in FEV1 at week 12 was analysed using a MMRM approach including treatment, age, sex, baseline height, region (pooled country), baseline eosinophil stratum, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-bronchodilator FEV1 value, and baseline-by-visit interaction as covariates. Within-patient errors were modelled via an unstructured correlation matrix. For patients who discontinued IMP before week 12, additional off-study treatment pre-bronchodilator FEV1 values measured up to week 12 were included in the primary analysis. Differences in the least squares (LS) mean change from baseline with the corresponding 95% CI and p-value with Kenward-Roger adjustment were provided for comparison of each dupilumab group with its matching placebo.

Supportive and sensitivity analyses:

- To assess the treatment effect when patients adhere to the study treatment as directed, on treatment prebronchodilator FEV1 measurements were analyzed using an MMRM model similar to the primary analyses. A prebronchodilator FEV1 value was considered as on-treatment if measured before or on the last dose date + 14 days.
- Concomitant use of systemic corticosteroids was prohibited by protocol, except for treatment of asthma exacerbation. Two sensitivity analyses were performed with different methods of handling pre-bronchodilator FEV1 measurements confounded by systemic corticosteroid use. The 2 censoring methods were applied to both the primary and on-treatment analyses.

For both primary parameter, the number of patients with missing data, reasons for and timing of patient withdrawals was summarized and examined for patterns across treatment groups. Sensitivity analyses including pattern mixture modeling-multiple imputation (PMM-MI), control-based PMM-MI, and tipping point analyses were conducted to assess the robustness of the conclusion of the main model.

For both primary efficacy parameters pre-specified subgroup analyses were conducted in order to assess the consistency of treatment effects.

The same method as for absolute change from baseline in pre-bronchodilator FEV1 at week 12 was applied to analyse the key secondary endpoints, percent change from baseline in pre-bronchodilator FEV1 at week 12, and PEF, FEF25-75%, FVC, and post-bronchodilator FEV1.

Change from baseline in ACQ-5 and AQLQ at week 24 were analyzed using an MMRM approach. In addition a responder analysis was performed for ACQ-5, ACQ-7, and AQLQ global scores at weeks 12, 24, 36 and 52, using logistic regression models.

The rate of post-bronchodilator change in FEV1 over time (termed as FEV1 slope) was compared between each dupilumab dose against its matching placebo using a linear mixed-effects model.

Annualized rate of LOAC events and annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period were analyzed in a manner similar to the analysis for the annualized rate of severe exacerbation events.

A Cox regression model was used to assess treatment differences in time to event variables. The model included treatment, age, region (pooled country), baseline eosinophil stratum, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates.

To strongly control the type-I error rate for the primary family of hypotheses (two primary endpoints and two doses), a hierarchical testing procedure was defined, i.e., each hypothesis was formally tested only if the preceding one is significant at the 2-sided 5% level:

1) annualized severe exacerbation rate for 300 mg q2w versus placebo,
2) absolute change from baseline in FEV1 at week 12 for 300 mg q2w versus placebo,
3) annualized severe exacerbation rate for 200 mg q2w versus placebo,
4) absolute change from baseline in FEV1 at week 12 for 200 mg q2w versus placebo.

Results

Participant flow

1897 randomized and treated patients as of the **cut-off date (29 July 2017)**, 1434 patients completed the treatment, 235 patients had treatment ongoing, and 228 patients discontinued treatment. Each of the 235 patients with ongoing treatment had completed at least 47 weeks of the 52-week treatment period at the time of the data cut-off date. Among the 1434 patients who completed the study treatment as of the cut-off date, most (1317 [91.8%] patients) continued into the open-label extension study LTS12551 (873 patients in the combined dupilumab group and 444 patients in the combined placebo group). Of the 107 randomized and treated adolescent patients as of the cut-off date, 72 adolescents completed treatment, 22 adolescents had treatment ongoing, and 13 adolescents discontinued treatment.

Recruitment

Study Initiation Date (first patient enrolled): 27 April 2015

Cut-off date for Clinical Study Report: 29 July 2017

Conduct of the study

Amendments

Eight local and global amendments were made to the study protocol, most occurring after the first patient entered the study. The amendments are adequate and it is unlikely that they have impacted the results of the study.

Most deviations were balanced across the treatment groups. It is unlikely that they have impacted the overall outcome of the study.

Baseline data

Overall, the baseline characteristics were generally similar between treatment groups in the randomized population. The mean age of the randomized population was 47.9 years with a range of 12 to 84 years, while the mean age of the adolescent population was 14.2 years with a range of 12 to 17 years. 62.9% were females, 5.6% were adolescents and 82.9% were White, with Asian and Black representing 11.7% and 4.2%, respectively. The mean age at onset of asthma was 27.0 years, with 37.0% having asthma onset prior to age 18 years. In the adolescent population the mean age at onset of asthma in this population was 5.0 years.

51.5% were on high dose ICS at baseline, 47.7% were on medium dose ICS (plus 1 or 2 additional controllers), and 0.8% of patients were on low dose ICS (in violation of the protocol). In adolescents 75.7% were on medium dose and 24,3% were on high dose ICS at baseline. The majority of patients (82.3%, adolescents 96,3%) had an ongoing atopic medical condition.

Disease characteristics at baseline - Randomized population

	1.14mL/200mg q2w		2mL/300mg q2w		Combined		
	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)	Placebo (N=638)	Dupilumab (N=1264)	All (N=1902)
ICS dose level at baseline							
Number	317	631	321	633	638	1264	1902
High	172 (54.3%)	317 (50.2%)	167 (52.0%)	323 (51.0%)	339 (53.1%)	640 (50.6%)	979 (51.5%)
Medium	144 (45.4%)	310 (49.1%)	151 (47.0%)	303 (47.9%)	295 (46.2%)	613 (48.5%)	908 (47.7%)
Low	1 (0.3%)	4 (0.6%)	3 (0.9%)	7 (1.1%)	4 (0.6%)	11 (0.9%)	15 (0.8%)
Age at onset of asthma (years)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	27.2 (19.1)	27.1 (19.2)	27.4 (18.6)	26.6 (19.4)	27.3 (18.9)	26.8 (19.3)	27.0 (19.1)
Median	29.0	26.0	28.0	26.0	28.0	26.0	27.0
Min : Max	0 : 69	0 : 77	0 : 71	0 : 78	0 : 71	0 : 78	0 : 78
<18	113 (35.6%)	237 (37.6%)	116 (36.1%)	238 (37.6%)	229 (35.9%)	475 (37.6%)	704 (37.0%)
18 - 40	110 (34.7%)	216 (34.2%)	111 (34.6%)	228 (36.0%)	221 (34.6%)	444 (35.1%)	665 (35.0%)
>40	94 (29.7%)	178 (28.2%)	94 (29.3%)	167 (26.4%)	188 (29.5%)	345 (27.3%)	533 (28.0%)
Time since first diagnosis of asthma (years)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	21.01 (15.25)	20.85 (15.54)	20.74 (15.48)	21.10 (15.19)	20.87 (15.35)	20.97 (15.36)	20.94 (15.36)
Median	17.83	17.33	16.42	16.50	17.13	17.00	17.04
Min : Max	1.4 : 76.4	1.2 : 71.5	1.2 : 70.4	1.1 : 70.3	1.2 : 76.4	1.1 : 71.5	1.1 : 76.4
With ongoing atopic medical condition[a] [n (%)]							
Number	317	631	321	633	638	1264	1902
Yes	266 (83.9%)	509 (80.7%)	266 (82.9%)	524 (82.8%)	532 (83.4%)	1033 (81.7%)	1565 (82.3%)
Smoking history							
Number	317	631	321	633	638	1264	1902
Former	59 (18.6%)	126 (20.0%)	67 (20.9%)	116 (18.3%)	126 (19.7%)	242 (19.1%)	368 (19.3%)
Never	258 (81.4%)	505 (80.0%)	254 (79.1%)	517 (81.7%)	512 (80.3%)	1022 (80.9%)	1534 (80.7%)
Time since cessation (years)							
Number	59	126	67	116	126	242	368
Mean (SD)	15.86 (12.82)	17.88 (13.30)	16.10 (12.21)	18.18 (12.39)	15.99 (12.45)	18.03 (12.85)	17.33 (12.73)
Median	12.83	15.79	12.25	15.75	12.54	15.75	15.17
Min : Max	0.6 : 48.6	0.7 : 52.4	0.8 : 48.4	0.6 : 49.6	0.6 : 48.6	0.6 : 52.4	0.6 : 52.4
Pack-year							
Number	59	126	67	116	126	242	368
Mean (SD)	3.96 (2.81)	3.89 (2.69)	4.07 (3.12)	4.15 (3.04)	4.02 (2.97)	4.01 (2.86)	4.02 (2.89)
Median	3.50	3.25	2.85	3.75	3.50	3.50	3.50
Min : Max	0.0 : 10.0	0.0 : 10.0	0.1 : 10.0	0.1 : 10.0	0.0 : 10.0	0.0 : 10.0	0.0 : 10.0
Time since last severe asthma exacerbation[b] (months)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	5.59 (3.06)	5.53 (2.97)	5.58 (2.83)	5.67 (2.91)	5.58 (2.94)	5.60 (2.94)	5.60 (2.94)
Median	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Min : Max	2.0 : 15.0	1.0 : 14.0	1.0 : 13.0	1.0 : 13.0	1.0 : 15.0	1.0 : 14.0	1.0 : 15.0

Number of severe asthma exacerbations[b] experienced in the past year							
Number	317	631	321	633	638	1264	1902
Mean (SD)	2.07 (1.58)	2.07 (2.66)	2.31 (2.07)	2.02 (1.86)	2.19 (1.84)	2.04 (2.29)	2.09 (2.15)
Median	2.00	1.00	2.00	1.00	2.00	1.00	1.00
Min : Max	1.0 : 12.0	1.0 : 50.0	1.0 : 12.0	1.0 : 24.0	1.0 : 12.0	1.0 : 50.0	1.0 : 50.0
1	150 (47.3%)	340 (53.9%)	144 (44.9%)	330 (52.1%)	294 (46.1%)	670 (53.0%)	964 (50.7%)
2	91 (28.7%)	163 (25.8%)	93 (29.0%)	158 (25.0%)	184 (28.8%)	321 (25.4%)	505 (26.6%)
3	39 (12.3%)	64 (10.1%)	36 (11.2%)	80 (12.6%)	75 (11.8%)	144 (11.4%)	219 (11.5%)
≥4	37 (11.7%)	64 (10.1%)	48 (15.0%)	65 (10.3%)	85 (13.3%)	129 (10.2%)	214 (11.3%)
Number of severe asthma exacerbations[b] requiring hospitalization or urgent medical care experienced in the past year							
Number	316	631	321	633	637	1264	1901
Mean (SD)	0.62 (1.15)	0.69 (1.41)	0.82 (1.59)	0.66 (1.21)	0.72 (1.39)	0.67 (1.31)	0.69 (1.34)
Median	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Min : Max	0.0 : 8.0	0.0 : 15.0	0.0 : 12.0	0.0 : 10.0	0.0 : 12.0	0.0 : 15.0	0.0 : 15.0
0	205 (64.9%)	393 (62.3%)	190 (59.2%)	385 (60.8%)	395 (62.0%)	778 (61.6%)	1173 (61.7%)
1	64 (20.3%)	155 (24.6%)	80 (24.9%)	170 (26.9%)	144 (22.6%)	325 (25.7%)	469 (24.7%)
2	31 (9.8%)	45 (7.1%)	27 (8.4%)	35 (5.5%)	58 (9.1%)	80 (6.3%)	138 (7.3%)
3	7 (2.2%)	16 (2.5%)	7 (2.2%)	25 (3.9%)	14 (2.2%)	41 (3.2%)	55 (2.9%)
≥4	9 (2.8%)	22 (3.5%)	17 (5.3%)	18 (2.8%)	26 (4.1%)	40 (3.2%)	66 (3.5%)
Baseline pre-bronchodilator FEV1 (L)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.76 (0.59)	1.78 (0.61)	1.78 (0.60)
Median	1.70	1.72	1.69	1.75	1.70	1.73	1.72
Min : Max	0.5 : 3.5	0.4 : 4.2	0.5 : 3.7	0.4 : 3.8	0.5 : 3.7	0.4 : 4.2	0.4 : 4.2
Baseline pre-bronchodilator FEV1 percent predicted (%)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	58.43 (13.22)	58.38 (13.52)	58.35 (13.87)	58.51 (13.52)	58.39 (13.54)	58.44 (13.51)	58.43 (13.52)
Median	60.00	60.00	60.00	60.00	60.00	60.00	60.00
Min : Max	19.0 : 90.0	20.0 : 99.0	13.0 : 88.0	17.0 : 89.0	13.0 : 90.0	17.0 : 99.0	13.0 : 99.0
Baseline post-bronchodilator FEV1 (L)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	2.16 (0.71)	2.16 (0.74)	2.14 (0.69)	2.17 (0.72)	2.15 (0.70)	2.17 (0.73)	2.16 (0.72)
Median	2.06	2.04	2.07	2.10	2.07	2.07	2.07
Min : Max	0.6 : 4.7	0.7 : 5.0	0.6 : 4.2	0.4 : 4.5	0.6 : 4.7	0.4 : 5.0	0.4 : 5.0
Baseline FEV1 reversibility (%)							
Number	317	631	321	633	638	1264	1902
Mean (SD)	25.06 (18.76)	27.39 (22.79)	26.45 (17.65)	25.73 (23.79)	25.76 (18.21)	26.56 (23.30)	26.29 (21.73)
Median	20.26	22.39	22.16	19.33	21.62	20.64	20.89
Min : Max	-23.7 : 167.7	-37.3 : 147.2	-5.9 : 114.3	-15.3 : 268.9	-23.7 : 167.7	-37.3 : 268.9	-37.3 : 268.9

Baseline AM PEF (L/min)							
Number	317	627	321	633	638	1260	1898
Mean (SD)	286.84 (111.72)	281.37 (112.13)	281.27 (107.57)	294.55 (115.93)	284.04 (109.60)	287.99 (114.20)	286.66 (112.66)
Median	277.20	271.14	272.43	282.33	274.36	275.85	275.14
Min : Max	73.4 : 658.7	65.6 : 674.0	72.0 : 616.2	61.9 : 702.0	72.0 : 658.7	61.9 : 702.0	61.9 : 702.0
Baseline PM PEF (L/min)							
Number	317	626	321	632	638	1258	1896
Mean (SD)	298.31 (110.59)	293.55 (115.34)	294.75 (109.17)	306.93 (116.37)	296.52 (109.80)	300.27 (116.00)	299.01 (113.94)
Median	286.00	284.88	282.50	296.21	283.58	289.13	287.00
Min : Max	69.5 : 659.8	66.8 : 747.3	64.3 : 613.8	60.8 : 695.3	64.3 : 659.8	60.8 : 747.3	60.8 : 747.3
Baseline AM symptom score							
Number	317	631	321	633	638	1264	1902
Mean (SD)	1.16 (0.81)	1.14 (0.85)	1.12 (0.84)	1.12 (0.87)	1.14 (0.82)	1.13 (0.86)	1.14 (0.85)
Median	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Min : Max	0.0 : 3.1	0.0 : 4.0	0.0 : 4.0	0.0 : 3.9	0.0 : 4.0	0.0 : 4.0	0.0 : 4.0
Baseline PM symptom score							
Number	317	631	321	633	638	1264	1902
Mean (SD)	1.27 (0.82)	1.26 (0.85)	1.23 (0.82)	1.27 (0.84)	1.25 (0.82)	1.26 (0.85)	1.26 (0.84)
Median	1.20	1.17	1.14	1.29	1.14	1.17	1.17
Min : Max	0.0 : 3.3	0.0 : 4.0	0.0 : 4.0	0.0 : 3.7	0.0 : 4.0	0.0 : 4.0	0.0 : 4.0
Baseline number of nocturnal awakenings/night							
Number	317	631	321	633	638	1264	1902
Mean (SD)	0.52 (0.81)	0.56 (0.94)	0.50 (0.81)	0.54 (0.87)	0.51 (0.81)	0.55 (0.90)	0.53 (0.87)
Median	0.14	0.14	0.14	0.14	0.14	0.14	0.14
Min : Max	0.0 : 5.6	0.0 : 7.0	0.0 : 5.4	0.0 : 5.9	0.0 : 5.6	0.0 : 7.0	0.0 : 7.0
Baseline ACQ-5 score							
Number	317	631	321	633	638	1264	1902
Mean (SD)	2.71 (0.73)	2.76 (0.80)	2.77 (0.77)	2.77 (0.76)	2.74 (0.75)	2.76 (0.78)	2.76 (0.77)
Median	2.60	2.60	2.60	2.60	2.60	2.60	2.60
Min : Max	0.6 : 5.6	1.2 : 6.0	0.6 : 5.8	0.0 : 5.6	0.6 : 5.8	0.0 : 6.0	0.0 : 6.0
Baseline ACQ-7 score							
Number	317	631	321	633	638	1264	1902
Mean (SD)	2.84 (0.65)	2.86 (0.71)	2.86 (0.69)	2.87 (0.69)	2.85 (0.67)	2.87 (0.70)	2.86 (0.69)
Median	2.71	2.71	2.71	2.71	2.71	2.71	2.71
Min : Max	1.1 : 5.4	1.6 : 6.0	1.4 : 5.7	0.4 : 5.3	1.1 : 5.7	0.4 : 6.0	0.4 : 6.0
Baseline AQLQ global score							
Number	299	591	314	603	613	1194	1807
Mean (SD)	4.26 (1.02)	4.31 (1.08)	4.30 (1.03)	4.28 (1.05)	4.28 (1.02)	4.29 (1.06)	4.29 (1.05)
Median	4.22	4.28	4.30	4.31	4.25	4.28	4.28
Min : Max	1.2 : 6.8	1.0 : 6.8	1.4 : 6.8	1.6 : 7.0	1.2 : 6.8	1.0 : 7.0	1.0 : 7.0

Baseline number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol /24 hours							
Number	317	631	321	633	638	1264	1902
Mean (SD)	3.15 (3.55)	3.45 (4.23)	3.13 (4.04)	3.14 (3.48)	3.14 (3.80)	3.30 (3.87)	3.24 (3.85)
Median	2.29	2.17	2.00	2.33	2.14	2.29	2.20
Min : Max	0.0 : 30.0	0.0 : 32.6	0.0 : 28.8	0.0 : 29.7	0.0 : 30.0	0.0 : 32.6	0.0 : 32.6
With hypersensitivity to aspirin or other NSAID [n (%)]							
Number	317	631	321	633	638	1264	1902
Yes	24 (7.6%)	53 (8.4%)	25 (7.8%)	69 (10.9%)	49 (7.7%)	122 (9.7%)	171 (9.0%)
Ongoing condition	23 (7.3%)	52 (8.2%)	24 (7.5%)	66 (10.4%)	47 (7.4%)	118 (9.3%)	165 (8.7%)

[a] A patient is considered to have ongoing atopic medical condition if he/she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE >=100 IU/mL and at least one aeroantigen specific IgE is positive (>=0.35 IU/mL) at baseline.
[b] Severe asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma
ICS: inhaled corticosteroid
PGM=PRODOPS/SAR231893/EFC13579/CSR/REPORT/PGM/dem_basdisease_r_t.sas OUT=REPORT/OUTPUT/dem_basdisease_r_t_i.rtf (17SEP2017 - 15:52)

Baseline biomarkers

Baseline biomarkers associated with Type 2 inflammation including blood eosinophils, serum total IgE, serum ECP, serum periostin, serum TARC, and FeNO were generally similar across treatment groups.

Consistent with the assumption used in the sample size calculation, overall 831 (43.7%) patients across all treatment groups had baseline blood eosinophil counts ≥0.3 Giga/L. Mean eosinophil count at baseline was 0.36 Giga/L, with a median of 0.26, and was balanced across treatment groups. Mean FeNO was 34.97 ppb, and median FeNO was 25.0 ppb, which was elevated relative to the median FeNO for healthy subjects (16 ppb) (38). Mean total IgE at baseline was 432.40 IU/mL, with a median of 167.0 IU/mL, and was balanced across treatment groups.

Numbers analysed

The randomized population and the ITT population were comprised of 1902 patients (1264 patients in the combined dupilumab group and 638 patients in the combined placebo group). Five patients were randomized but did not receive treatment (3 in the dupilumab and 2 in the placebo groups). In addition, 2 patients randomized to the 1.14 mL placebo group received single doses of dupilumab 200 mg q2w and dupilumab 300 mg q2w, and were accordingly included in the respective dupilumab treatment arms of the safety population and 1 patient randomized to the dupilumab 300 mg q2w group received a single dose of 200 mg q2w and was accordingly included in the 200 mg q2w treatment arm of the safety population.

Thereby, a total of 1897 patients made up the safety population (1263 patients in the combined dupilumab group and 634 patients in the combined placebo group).

The PK population was comprised of 1262 patients from the safety population (1260 patients in the combined dupilumab group and 2 patients in the combined placebo group) with at least 1 non-missing result for functional dupilumab concentration in serum.

The ADA population was comprised of 1881 patients from the safety population (1251 patients in the combined dupilumab group and 630 patients in the combined placebo group) who had at least 1 non-missing ADA result (either 'ADA negative' or 'ADA positive') after the first dose of IMP.

Outcomes and estimation

Primary endpoints

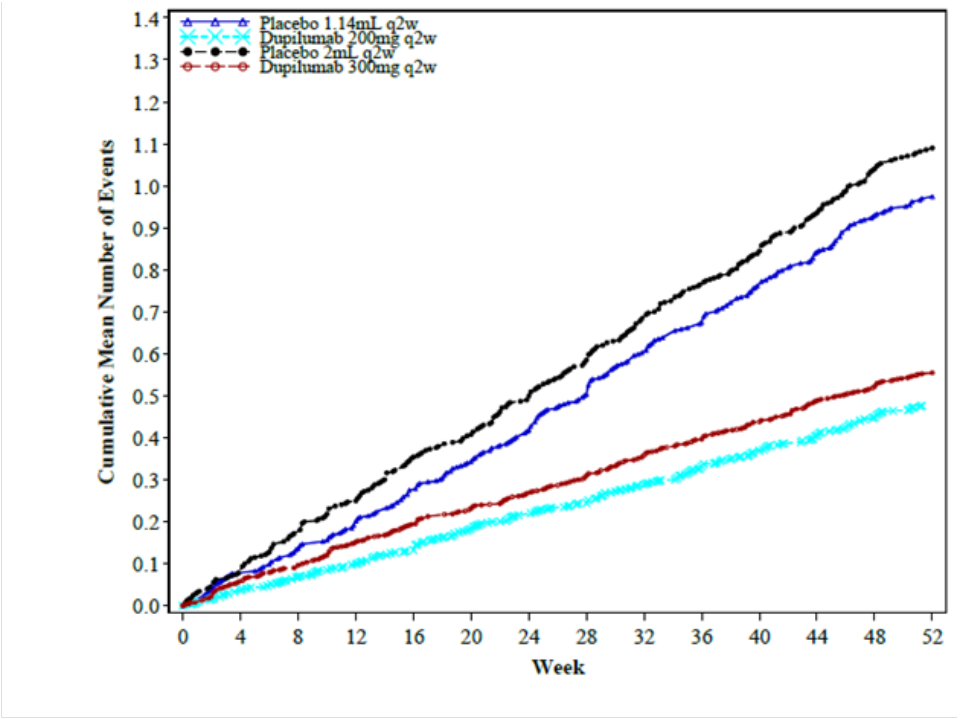
- The adjusted annualized event rate of severe exacerbation in the ITT population during the 52-week treatment period was lower in the 2 dupilumab dose groups compared with their respective placebo groups (0.456 and 0.524 for the dupilumab 200 mg q2w and 300 mg q2w groups compared with 0.871 and 0.970 for the matching placebo groups). The dupilumab versus placebo relative risk in both dose groups was statistically significant (p<0.0001), indicating a 47.7% and 46.0% reduced risk of severe exacerbation events with 200 mg q2w and 300 mg q2w dupilumab treatment, respectively, compared with matching placebo.

Primary analysis: Annualized event rate of severe exacerbation during 52-week treatment period - ITT population

	1.14mL/200mg q2w		2mL/300mg q2w	
	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)
Patients with >=1 severe exacerbation events [n(%)]				
Number	317	631	321	633
No	183 (57.7%)	447 (70.8%)	182 (56.7%)	431 (68.1%)
Yes	134 (42.3%)	184 (29.2%)	139 (43.3%)	202 (31.9%)
Number of severe exacerbation events				
0	183 (57.7%)	447 (70.8%)	182 (56.7%)	431 (68.1%)
1	62 (19.6%)	111 (17.6%)	54 (16.8%)	121 (19.1%)
2	31 (9.8%)	44 (7.0%)	34 (10.6%)	43 (6.8%)
3	19 (6.0%)	23 (3.6%)	26 (8.1%)	24 (3.8%)
>=4	22 (6.9%)	6 (1.0%)	25 (7.8%)	14 (2.2%)
Total number of severe exacerbation events	298	295	342	343
Total patient-years followed	303.9	613.7	313.2	612.5
Unadjusted annualized rate of severe exacerbation events [a]	0.980	0.481	1.092	0.560
Adjusted annualized rate of severe exacerbation events				
Estimate [b] (95% CI)	0.871 (0.724, 1.048)	0.456 (0.389, 0.534)	0.970 (0.810, 1.160)	0.524 (0.450, 0.611)
Relative risk [b] vs. matching placebo (95% CI)		0.523 (0.413, 0.662)		0.540 (0.430, 0.680)
P-value [b] vs. matching placebo		<.0001		<.0001
Risk difference [c] vs. matching placebo (95% CI)		-0.416 (-0.588, -0.243)		-0.446 (-0.633, -0.258)

All severe exacerbation events occurred during the 52-week treatment period are included, regardless if the patient is on-treatment or not
[a] The total number of event that occurred during the 52-week treatment period divided by the total number of patient-years followed in the 52-week treatment period.
[b] Derived using negative binomial model with the total number of events onset from randomization up to Visit 18 or last contact date (whichever comes earlier) as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.
[c] Derived using delta method
PGM=PRODOPS/SAR231893/EFC13579/CSR/REPORT/PGM/eff_event_summary.sas OUT=REPORT/OUTPUT/eff_event_summary_ea_wk52_i_t_i.rtf (18OCT2017 - 6:50)

Cumulative mean functions for the number of severe exacerbation events during 52-week treatment period - ITT population



- An increase in pre-bronchodilator FEV1 from baseline to Week 12 for the ITT population was observed in the 200 mg q2w group (LS mean 0.32 L) and 300 mg q2w group (LS mean 0.34 L) compared with the matching placebo groups (0.18 L and 0.21 L, respectively). The LS mean difference in absolute change from baseline to Week 12 in pre-bronchodilator FEV1 in the dupilumab dose groups versus placebo was statistically significant for both the 200 mg q2w (0.14 L, p<0.0001) and 300 mg q2w (0.13 L, p<0.0001) treatment groups.

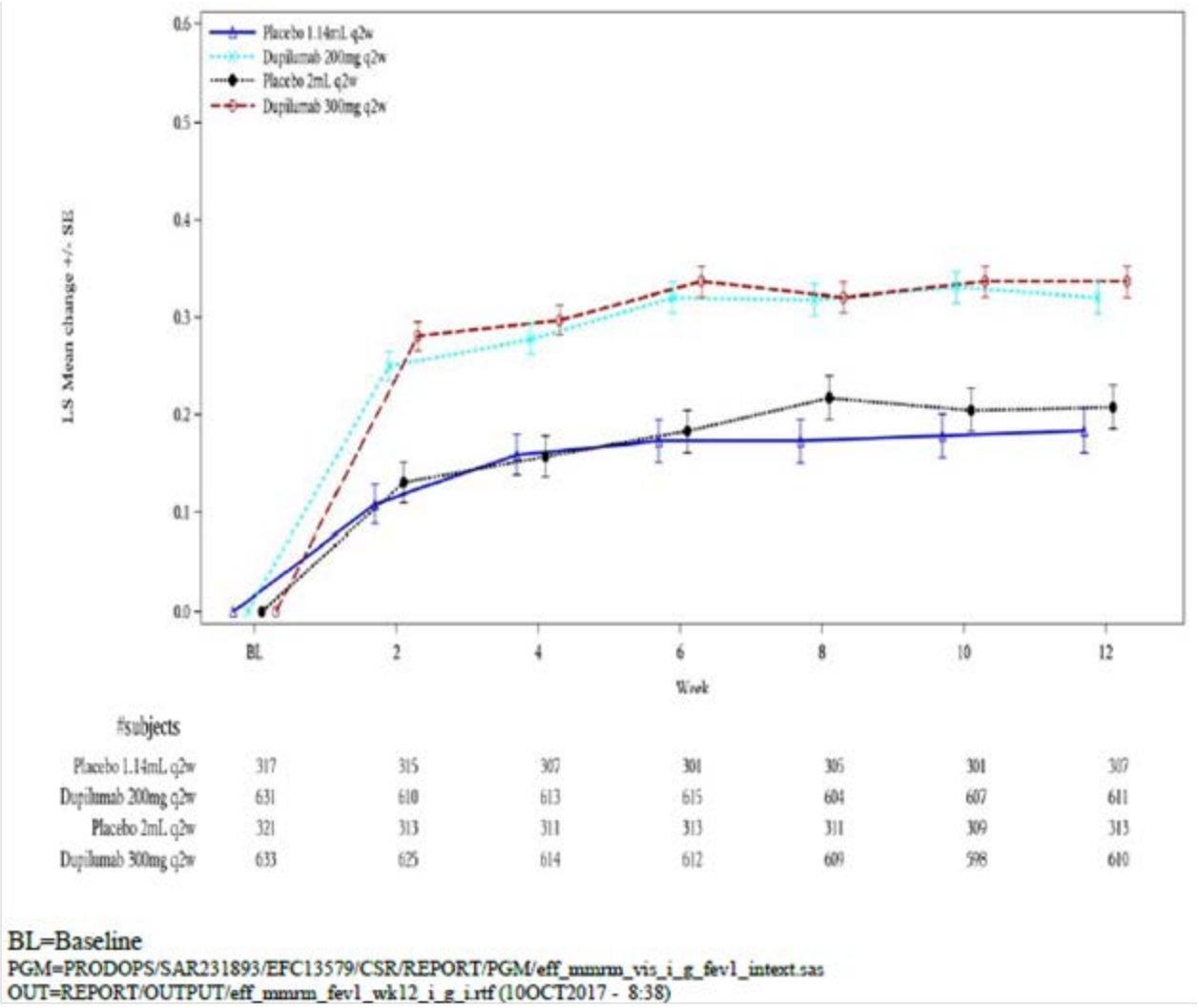
Primary analysis: Change from baseline in pre-bronchodilator FEV1 (L) at Week 12 – ITT population

	1.14mL/200mg q2w		2mL/300mg q2w	
	Placebo	Dupilumab	Placebo	Dupilumab
Pre-bronchodilator FEV1 (L)	(N=317)	(N=631)	(N=321)	(N=633)
Baseline				
Value				
Number	317	631	321	633
Mean (SD)	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)
Median	1.70	1.72	1.69	1.75
Q1 : Q3	1.30 : 2.14	1.33 : 2.18	1.37 : 2.11	1.34 : 2.18
Min : Max	0.5 : 3.5	0.4 : 4.2	0.5 : 3.7	0.4 : 3.8
Week 12				
Value				
Number	307	611	313	610
Mean (SD)	1.92 (0.70)	2.07 (0.76)	1.93 (0.68)	2.09 (0.70)
Median	1.86	1.96	1.87	2.07
Q1 : Q3	1.39 : 2.34	1.51 : 2.53	1.47 : 2.36	1.55 : 2.52
Min : Max	0.4 : 4.2	0.5 : 5.1	0.4 : 4.2	0.5 : 4.7

Change from baseline				
Number	307	611	313	610
Mean (SD)	0.15 (0.36)	0.28 (0.45)	0.18 (0.39)	0.31 (0.43)
Median	0.10	0.21	0.10	0.21
Q1 : Q3	-0.07 : 0.33	-0.01 : 0.52	-0.05 : 0.37	0.01 : 0.51
Min : Max	-1.6 : 1.6	-1.0 : 2.7	-0.7 : 1.5	-0.8 : 2.5
LS Mean (SE) [a]	0.18 (0.02)	0.32 (0.02)	0.21 (0.02)	0.34 (0.02)
LS Mean Diff vs. matching placebo (95% CI) [a]		0.14 (0.08, 0.19)		0.13 (0.08, 0.18)
P-value vs. matching placebo [a]		<.0001		<.0001

[a] Derived from MMRM model with change from baseline in pre-bronchodilator FEV1 values up to Week 12 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-bronchodilator FEV1 value and baseline-by-visit interaction as covariates.
PGM=PRODOPS/SAR231893/EFC13579/CSR/REPORT/PGM/eff_mmrm_wk_i_t_intext.sas
OUT=REPORT/OUTPUT/eff_mmrm_fev1_chg_wk12_i_t_i.rtf (17SEP2017 - 16:49)

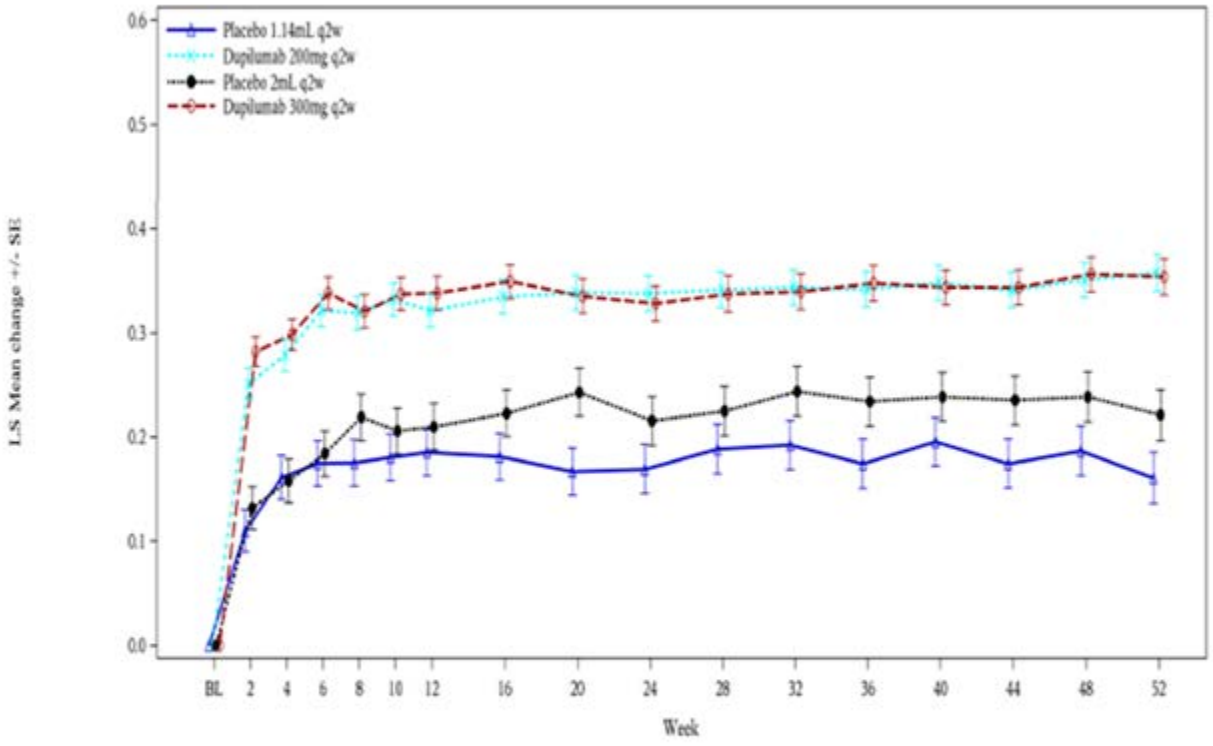
LS mean change from baseline in pre-bronchodilator FEV1 (L) over time (MMRM including measurements up to Week 12) - ITT population



Secondary endpoints

The Key secondary endpoint showed consistent results with the primary endpoint, dupilumab at 200 mg q2w or 300 mg q2w significantly increased the percent change from baseline pre-bronchodilator FEV1 at Week 12 compared with matching placebo treatment, with no meaningful difference observed between the 2 dupilumab dose groups. The LS mean percent change from baseline in pre-bronchodilator FEV1 at Week 12 for the ITT population was 21.34% for dupilumab 200 mg q2w, 23.08% for dupilumab 300 mg q2w, and 12.11% and 13.67% for matching placebo, respectively. When compared with matching placebo, the LS mean difference was 9.23% for dupilumab 200 mg q2w and 9.41% for dupilumab 300 mg q2w. The difference was statistically significant for dupilumab 300 mg q2w ($p<0.0001$). Due to the hierarchy break, the treatment effect for the 200 mg q2w dose was highly, but only nominally significant (nominal $p<0.0001$). The improvement in pre-bronchodilator FEV1 was rapid (onset of a difference was observed as early as Week 2) and sustained over 12 weeks.

EFC13579 - LS mean change from baseline in pre-bronchodilator FEV1 (L) over time (MMRM including measurements up to Week 52) - ITT population



#subjects

Placebo 1.14mL q2w	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240
Dupilumab 200mg q2w	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo 2mL q2w	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Dupilumab 300mg q2w	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488

In the population of patients with **baseline blood eosinophils ≥0.3 Giga/L** an increase in pre-bronchodilator FEV1 from baseline to Week 12 was observed in the 200 mg q2w (LS mean 0.43 L) and 300 mg q2w groups (LS mean 0.47 L) compared with the matching placebo groups (0.21 L and 0.22 L, respectively). Statistical significance was demonstrated for the comparison of the 300 mg q2w group to the matching placebo group (LS mean difference versus placebo: 0.24 L, $p<0.0001$) with nominal significance demonstrated for the comparison of the 200 mg q2w group to the matching placebo group (0.21 L, nominal $p<0.0001$). The adjusted annualized event rate of severe exacerbation during the 52-week treatment period was lower in the 2 dupilumab dose groups compared with their respective placebo groups (0.370 and 0.403 for the dupilumab 200 mg q2w and 300 mg q2w groups compared with 1.081 and 1.236 for the matching placebo groups). The risk reduction was 65.8% and 67.4% for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with the matching placebo groups. Statistical significance was demonstrated for the 300 mg q2w group ($p<0.0001$) with nominal significance demonstrated for the 200 mg q2w group (nominal $p<0.0001$). There was no meaningful difference in the treatment effect on severe exacerbation between the 200 mg q2w and 300 mg q2w dose groups.

In the population of patients with **baseline blood eosinophils ≥0.15 Giga/L** an increase in pre-bronchodilator FEV1 from baseline to Week 12 was observed in the 200 mg q2w (LS mean 0.36 L) and 300 mg q2w groups (LS mean 0.37 L) compared with the matching placebo groups (0.18 L and 0.22 L,

respectively). Statistical significance was demonstrated for the comparison of the 300 mg q2w group to the matching placebo group (LS mean difference versus placebo: 0.15 L, p<0.0001). The adjusted annualized event rate of severe exacerbation during the 52-week treatment period was lower in the 2 dupilumab dose groups compared with their respective placebo groups (0.445 and 0.434 for the dupilumab 200 mg q2w and 300 mg q2w groups compared with 1.007 and 1.081 for the matching placebo groups). The risk reduction was 55.8% and 59.8% for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with the matching placebo groups.

In the population with **baseline blood eosinophils <0.3 Giga/L** an increase in pre-bronchodilator FEV1 from baseline to Week 12 was observed in the 200 mg q2w (LS mean 0.23 L) and 300 mg q2w groups (LS mean 0.22 L) compared with the matching placebo groups (0.15 L and 0.18 L, respectively). Nominal significance was demonstrated for the comparison of the 200 mg q2w group to the matching placebo group (LS mean difference versus placebo: 0.08 L, nominal p=0.0242) with a smaller difference observed for the comparison of the 300 mg q2w group to the matching placebo group (0.04 L, nominal p=0.2511). A statistically significant difference was not observed in the adjusted annualized event rate of severe exacerbation during the 52-week treatment period between the 2 dupilumab dose groups compared with their respective placebo groups (0.512 and 0.610 for the dupilumab 200 mg q2w and 300 mg q2w groups compared with 0.675 and 0.732 for the matching placebo groups). The risk reduction was 24.1% and 16.6% for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with the matching placebo groups.

An alternative analysis of the annualized rate of severe exacerbation events in patients by baseline blood eosinophil level was conducted using the following baseline blood eosinophil counts: <0.15 Giga/L, ≥0.15 to <0.3 Giga/L, ≥0.3 to <0.5 Giga/L, ≥0.5 Giga/L. The magnitude of the treatment effect at both dose levels increased with higher baseline blood eosinophil counts. Of note, the rate of severe exacerbation events in the population of patients with baseline blood eosinophils <0.15 Giga/L was low across all treatment groups (0.472 and 0.737 for the 200 mg q2w and 300 mg q2w groups and 0.511 and 0.642 for the matching placebo groups).

Response by baseline FeNO level:
In a prespecified analysis from Study EFC13579, patients with baseline FeNO levels 25-50 ppb and ≥50 ppb had a significantly better clinical response by exacerbation reduction and FEV1 improvement compared to placebo regardless of baseline blood eosinophils (Figure 3 and Figure 4).

Figure 3 - Rate ratio of severe asthma exacerbations by baseline FeNO subgroup (QUEST study)

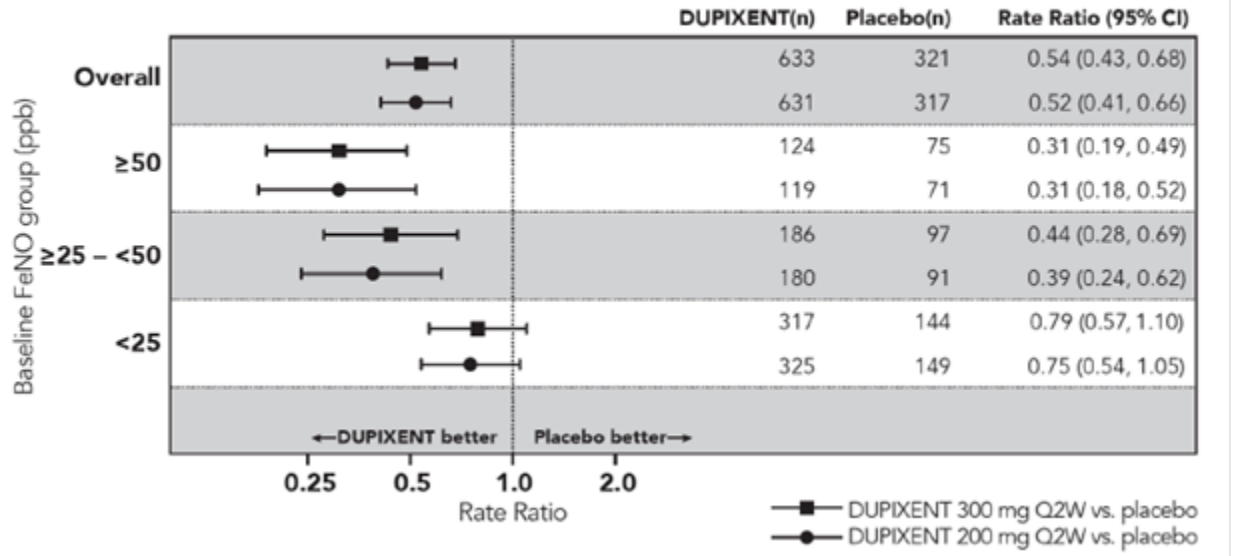
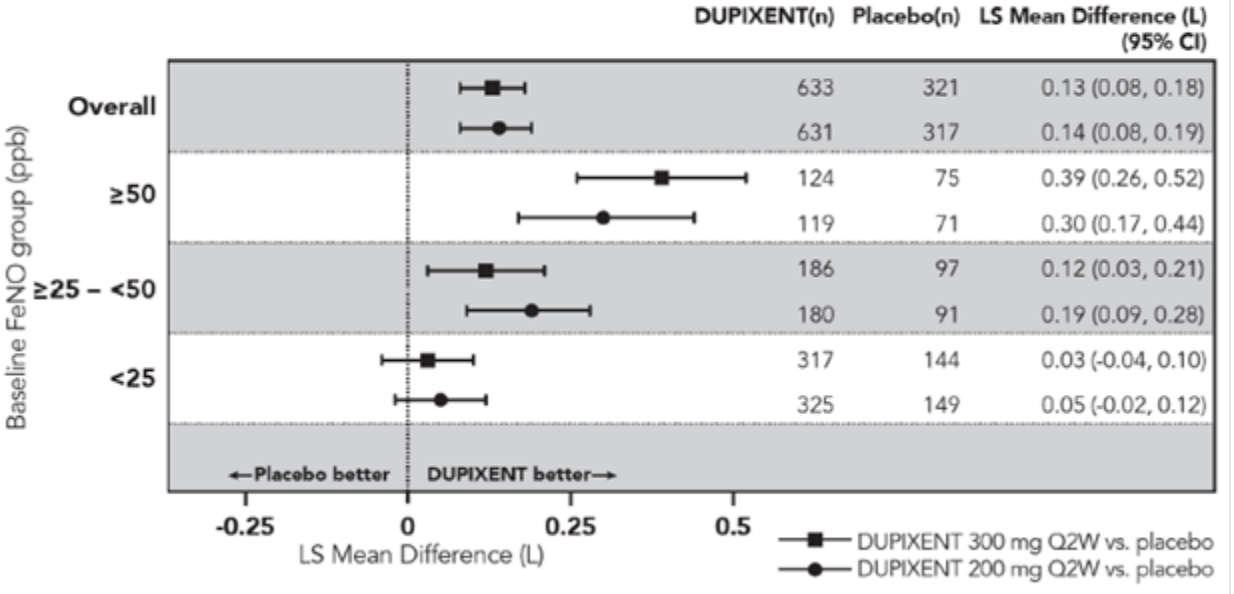


Figure 4 - Mean difference in change from baseline in FEV1 at Week 12 by baseline FeNO subgroup (QUEST study)

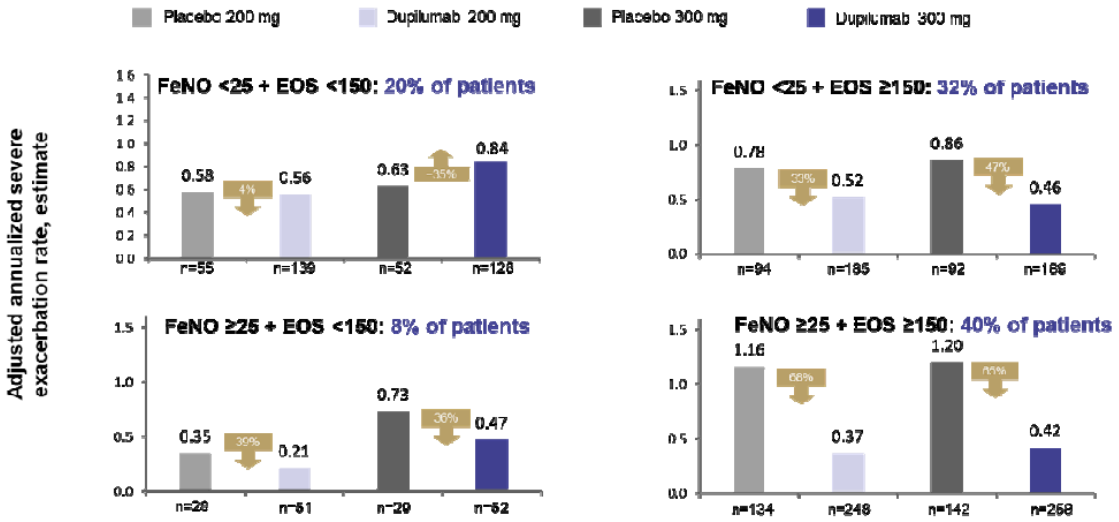


The magnitude of response increased for subgroups with increasing baseline FeNO levels.

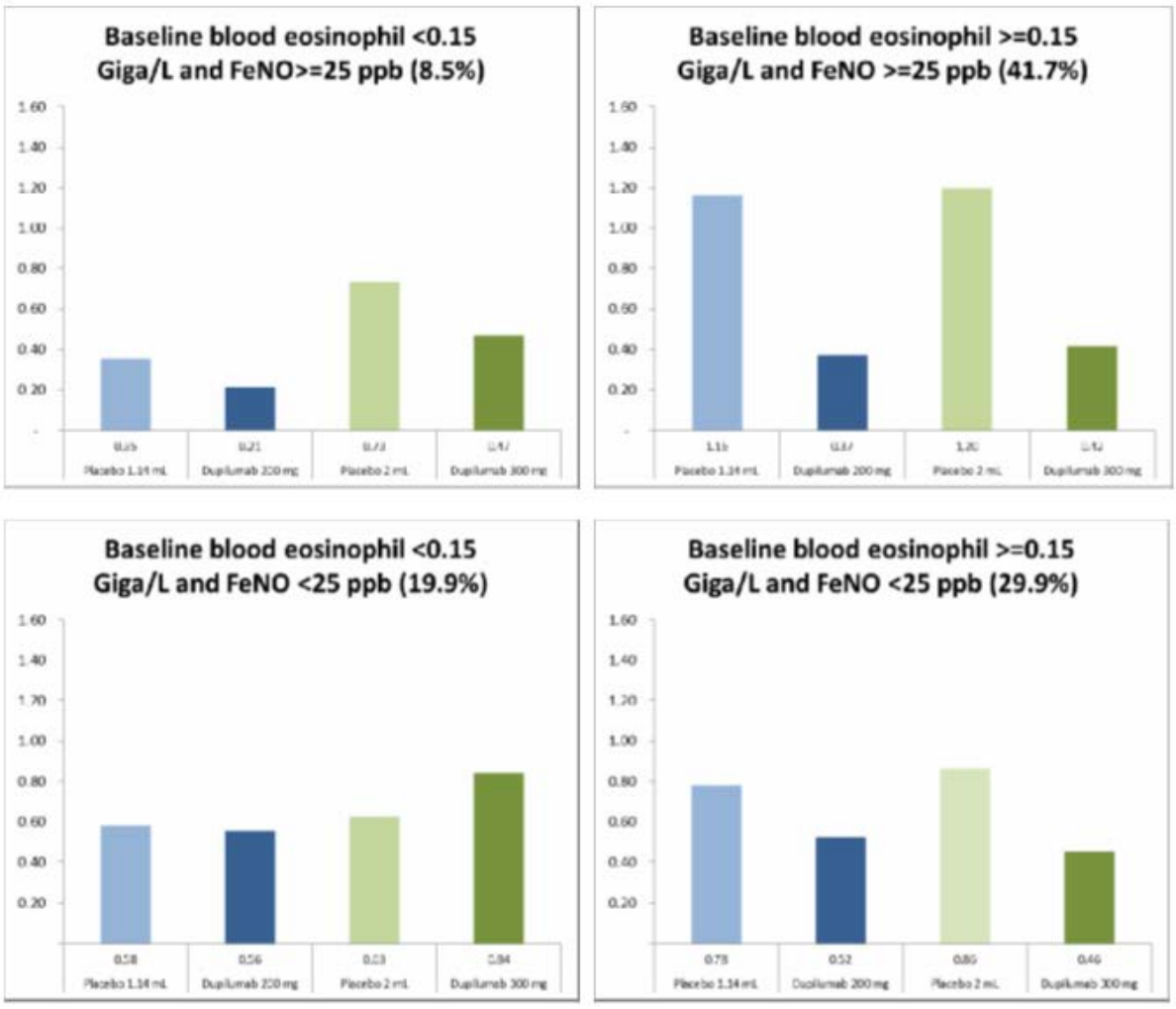
Quadrant analysis:

A post hoc analysis was conducted to examine the interaction between these baseline biomarkers, evaluating subgroups of patients with elevations in either one of these biomarkers compared with those who did not have an elevation in either biomarker and those who had elevations in both.

Quadrant analysis: Reduction in severe exacerbation by Eos and FeNO



Summary of relative risk in annualized event rate of severe exacerbation by subgroups defined by baseline blood eosinophil (<0.15 and ≥0.15 Giga/L) and FeNO (ppb) – ITT population



Note: The percentage shown in the parentheses is the proportion of patients in each of the 4 subgroups out of all patients in the ITT population who had both a blood eosinophil count and FeNO value at baseline.

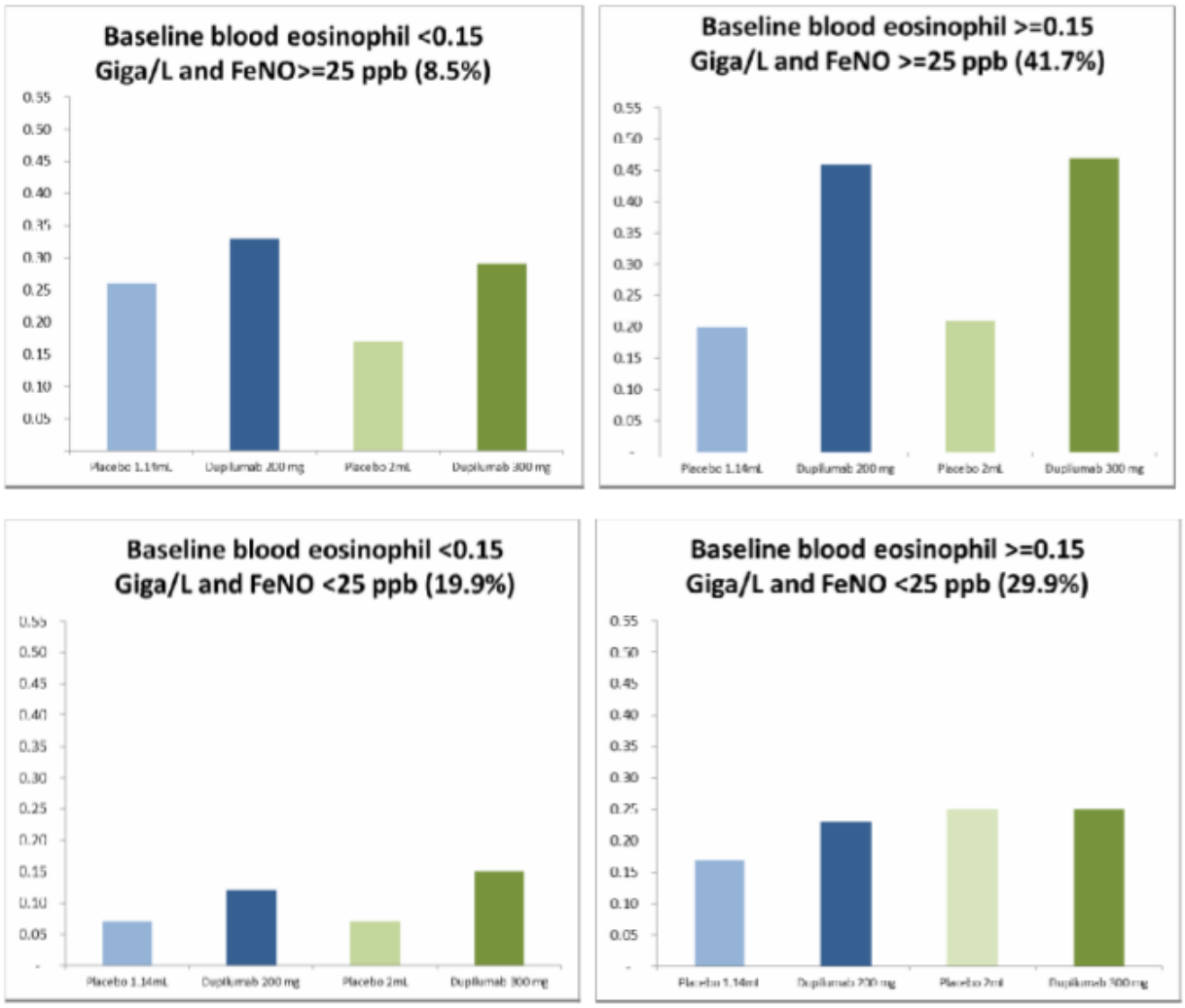
The greatest effect of dupilumab on annualized severe exacerbation event rate was observed among the patients with baseline eosinophils ≥0.15 Giga/L and FeNO ≥25 ppb. These patients (41.7% of the ITT population) showed a risk reduction of 68.2% for the dupilumab 200 mg q2w and 65.3% for the 300 mg q2w group compared with placebo.

Patients with baseline eosinophils <0.15 Giga/L and FeNO <25 ppb, (19.9% of the ITT population) had very low rates of exacerbation in this study and showed no reduction in the rate of severe exacerbation with dupilumab compared to placebo (4.2% and -34.6% risk reduction for the dupilumab 200 mg q2w and 300 mg q2w groups compared with the matching placebo groups).

Patients who had an elevation in either one or the other of these biomarkers at baseline showed a clinically meaningful reduction in the rate of severe exacerbation compared with the placebo. Patients with baseline eosinophils <0.15 Giga/L and FeNO ≥25 ppb (8.5% of the ITT population) showed a risk reduction of 39.2% for the dupilumab 200 mg q2w and 36.3% for the 300 mg q2w group compared with placebo.

Patients with baseline eosinophil ≥0.15 Giga/L and FeNO <25 ppb (29.9% of the ITT population) showed a risk reduction of 33.0% and 47.2% for the dupilumab 200 mg q2w and 300 mg q2w groups compared with the matching placebo groups.

Summary of treatment effect on change from baseline in pre-bronchodilator FEV1 (L) at Week 12 by subgroups defined by baseline blood eosinophil (<0.15 and ≥0.15 Giga/L) and FeNO (ppb) – ITT population



Note: The percentage shown in the parentheses is the proportion of patients in each of the 4 subgroups out of all patients in the ITT population who had both a blood eosinophil count and FeNO value at baseline.

The greatest effect of dupilumab on change from baseline to Week 12 in pre-bronchodilator FEV1 was observed among the patients with baseline blood eosinophils ≥0.15 Giga/L and FeNO ≥25 ppb. This population of patients (41.7% of the ITT population) showed an LS mean difference of 0.26 L for the dupilumab 200 mg q2w and 0.26 L for the 300 mg q2w groups compared with placebo.

In comparison, patients with baseline eosinophils <0.15 Giga/L and FeNO <25 ppb, (19.9% of the ITT population) showed a smaller change from baseline to Week 12 in pre-bronchodilator FEV1 (LS mean

difference of 0.04 L and 0.08 L for the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with the matching placebo groups).

Patients with baseline blood eosinophils <0.15 Giga/L and FeNO ≥25 ppb (8.5% of the ITT population) showed an LS mean difference in change from baseline of 0.07 L and 0.12 L for the dupilumab 200 mg q2w and 300 mg q2w groups compared with the matching placebo groups. Patients with baseline blood eosinophil ≥0.15 Giga/L and FeNO <25 ppb (29.9% of the ITT population) showed an LS mean difference in change from baseline of 0.06 L and 0.01 L for the dupilumab 200 mg q2w and 300 mg q2w groups compared with the matching placebo groups.

AQLQ and ACQ-5 ITT population:

In the dupilumab 200 mg q2w and 300 mg q2w groups AQLQ global scores at Week 24 were higher (indicating better health-related quality of life) compared with the matching placebo groups. LS mean differences versus placebo for the change from baseline in the dupilumab 200 mg q2w and 300 mg q2w groups were 0.20 (nominal p=0.0039) and 0.15 (nominal p=0.0298), respectively.

A decrease in ACQ-5 score was observed in the dupilumab dose groups (The LS mean change from baseline at Week 24 for the ITT population was -1.44 for dupilumab 200 mg q2w, -1.40 for dupilumab 300 mg q2w, and -1.10 and -1.21 for matching placebo, respectively). When compared with matching placebo, ACQ-5 scores at Week 24 showed a greater reduction in the dupilumab 200 mg q2w and 300 mg q2w groups compared with the matching placebo groups.

The absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, 52 showed that improvement in pre-bronchodilator FEV1 was rapid (onset of a difference was observed as early as Week 2) and sustained through Week 52. The LS mean change in pre-bronchodilator FEV1 from baseline to Week 52 was 0.36 L and 0.35 L in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with 0.16 L and 0.22 L in the matching placebo groups, resulting in an LS mean difference versus matching placebo of 0.20 L (p<0.0001) and 0.13 L (p<0.0001).

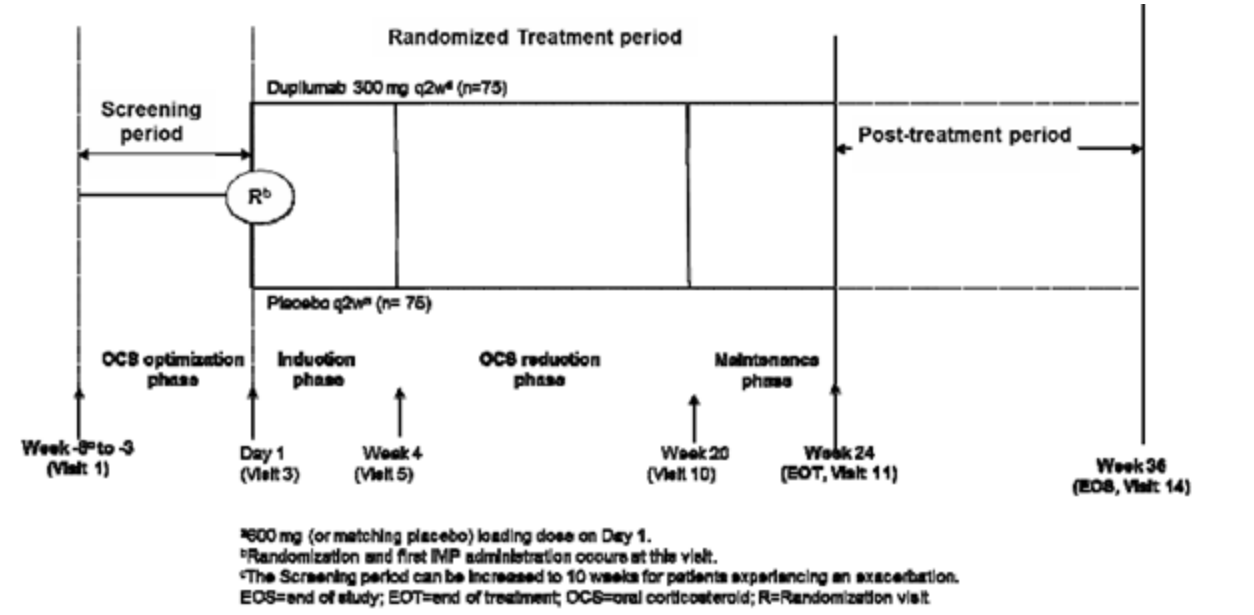
Absolute mean change from baseline in pre-bronchodilator FEV1 in adolescents:

A greater increase in pre-bronchodilator FEV1 from baseline to Week 12 for the adolescent population was observed in the 200 mg q2w group (LS mean 0.40 L) and 300 mg q2w group (LS mean 0.46 L) compared with the matching placebo groups (0.03 L and 0.18 L, respectively).

2.5.2.2. EFC13691 (VENTURE)

Objective / Methods

Study EFC13691 (Venture) was a randomized, double-blind, placebo-controlled study assessing the effect of dupilumab administered subcutaneously (SC) for a maximum of 24 weeks in patients with severe steroid-dependent asthma. The study assessed the corticosteroid sparing effect of dupilumab in patients with severe steroid-dependent asthma receiving daily OCS, regardless of baseline blood eosinophil count.



Prior to the screening and throughout the Screening, Treatment, and Post-treatment periods, patients were to be on a stable dose of high dose ICS with a second or third controller medication (LABA, LTRA, theophylline, etc). During the study patients could administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed.

Patients were treated on an outpatient basis and were stratified by optimized OCS dose at Week 0 (≤10 mg/day, >10 mg/day) and country.

The total duration of the study (per patient) was expected to be up to 44 weeks (or up to 46 weeks to allow for 2 weeks of stabilization prior to randomization in patients who experience an asthma exacerbation during the OCS optimization phase that required a change in OCS dose) and consisted of 3 periods:

The **screening period** was the **OCS optimization** period up to 10 weeks. Prednisone or prednisolone were the only OCS to be used in this study. During the Screening visit, patients currently using other OCS medications were switched to either of these corticosteroids at a dose clinically comparable to their current stable OCS dose. To optimize the OCS dose during this phase, investigators were instructed to adjust the OCS dose weekly according to a pre-specified titration schedule, based on changes in patient's asthma control, and their clinical judgment. The lowest effective OCS dose was defined during this phase as the lowest dose a patient can tolerate without experiencing an increase in ACQ-5 of at least 0.5, a severe asthma exacerbation or a clinically significant event that required treatment by an OCS dose adjustment.

Randomisation

At the beginning of the 24 week **treatment period** patients were randomized in a **1:1 ratio** to receive **dupilumab as a 600 mg loading dose followed by 300 mg once every 2 weeks (q2w) or matching placebo**. This period consisted of 3 Phases, a 4 week induction phase with stable (optimized) OCS dose, followed by a 16 week reduction phase with down-titration of OCS following a predetermined schedule and only if the patient did not meet any of the predefined criteria that would prohibit dose reduction, followed by a maintenance phase of 4 weeks in which patients were to be maintained on the same OCS dose established at Week 20. This period was followed by the **post-treatment period** of 12 weeks.

Study participants

Approximately 180 patients were planned to be randomized to either dupilumab 300 mg q2w or placebo in a 1:1 ratio. Enrolment of patients with blood eosinophils (count of <0.15 Giga/L) was limited to approximately 25% of total sample size to obtain a study population that would be representative of the target population. In addition, patients whose optimized OCS dose was 5 mg/day at randomization were limited to approximately 30% of the study population.

Main Inclusion criteria

- Adult and adolescents patients with a physician diagnosis of severe asthma for ≥12 months, based on the GINA 2014 Guidelines
- Well-documented, regular prescribed treatment of maintenance systemic corticosteroids (prednisone or equivalent of 5 to 35 mg) in the 6 months prior to Screening Visit and using a stable OCS dose (ie, no change of OCS dose) for 4 weeks prior to Screening Visit.
- Existing treatment with high dose ICS in combination with a second controller (ie, LABA, LTRA) for at least 3 months with a stable dose of ICS for ≥1 month prior to screening Visit; patients requiring a third controller were also eligible.
- Pre-bronchodilator FEV1 ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents prior to randomization
- Reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 µg (2 to 4 puffs of salbutamol) before randomization or documented in the 12 months prior to Visit 1 OR
- Airway hyper responsiveness (methacholine: provocative concentration that causes a positive reaction [PC20] of <8 mg/mL) documented in the 12 months prior to Screening Visit.

Exclusion criteria

A patient who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at least twice their current dose for at least 3 days) within 4 weeks before Visit 1.210 patients were enrolled (103 patients in the dupilumab group and 107 patients in the placebo group). The demographic and baseline characteristics were generally similar between treatment groups with a mean age of 51.3 years and 60.5% were female patients. Although adolescent patients were eligible according to the inclusion/exclusion criteria only 2 patients <18 years were enrolled. The patients' disease characteristics at baseline were also generally similar between dupilumab and placebo groups. All patients received background asthma controller therapy at stable doses at study entry in addition to a stable dose of OCS. No relevant differences are seen in the use of the non-ICS controllers at randomization between treatment groups. For most of the days (85.64% days in the dupilumab group and 87.47% days in the placebo group) patients were compliant with the prescribed OCS dosing and the compliance with administration of the IMP was high (>98%).

Treatments

Investigational treatment:

Patients were to receive q2w SC injections of 300 mg dupilumab following a loading dose of 600 mg on Day 1, or placebo during the 24-week Treatment period.

Dupilumab or placebo was supplied as one glass pre-filled syringe packed in a patient kit box. Both the glass pre-filled syringe and box were packaged in accordance with the administration schedule. The content of the labelling was in accordance with local regulatory specifications and requirements.

Oral corticosteroids

Screening period/OCS optimization phase: At the Screening visit, patients currently using other forms of maintenance OCS were switched to either prednisone or prednisolone at a dose clinically comparable to their current stable OCS maintenance dose.

The lowest effective or optimized OCS dose was defined during this phase as the lowest dose a patient could tolerate without experiencing any of the following OCS optimization phase interruption criteria:

- An increase in ACQ-5 of ≥0.5 from the last ACQ-5 score
- A severe asthma exacerbation
- A clinically significant event, based on investigator judgment that required treatment by OCS dose adjustment

No change in OCS dose was to be made at the Screening visit (Visit 1). One week later at Visit 2 and weekly throughout the optimization phase, patient stability was to be assessed by the above OCS optimization phase interruption criteria. If at each visit, the patient's asthma status remained controlled (ie, none of the above criteria were met), the Investigator was to down titrate the patient's OCS dose. If they remained stable without meeting any of the OCS optimization phase interruption criteria, they were eligible for randomization.

Induction phase: During the 4-week induction phase patients remained on their optimized dose of OCS along with their baseline asthma medications.

Oral corticosteroid reduction phase: The OCS dose was to be down-titrated following a predetermined schedule. Dose reductions were to occur every 4 weeks to minimize carryover effects from the previous dose and minimize the risk for clinically significant events. The last possible dose reduction could occur at Week 20.

Maintenance phase: The OCS dose established at Week 20 was not to be further reduced during the last 4 weeks of the randomized treatment period. However, if any of the OCS reduction phase interruption criteria were met, the Investigator was to decide whether to maintain or increase the current OCS dose by 1 step.

Eligible patients completing the treatment period were offered the opportunity to roll over into a long-term open-label extension study.

Inhaled corticosteroid with a second or third controller

Prior to and during the Screening period, patients were to be on a stable dose of high dose ICS with a second controller medication (LABA, LTRA, theophylline, etc.). Patients requiring a third controller for their asthma were considered eligible for this study, also to be used for at least 3 months with a stable dose ≥1 month prior to Screening. During the Randomized Treatment period and Post-treatment period (for those patients not rolling over into a long term study), patients were to continue taking their controller medication(s).

Reliever medication

Patients could administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed during the study. Nebulizer solutions could be used as an alternative delivery method.

Objectives

Primary:

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

Secondary:

Secondary objectives of the study included:

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab in improving patient-reported outcomes (PROs)
- To evaluate dupilumab systemic exposure and the incidence of treatment-emergent anti-drug antibodies (ADA).

Endpoints/outcomes

The primary endpoint was the percentage reduction of OCS dose at Week 24 compared with the baseline dose, while maintaining asthma control. Key secondary endpoint was the proportion of patients achieving a reduction of 50% or greater in their OCS dose compared with baseline at Week 24, while maintaining asthma control. Other secondary endpoints were e.g. absolute reduction of OCS dose at Week 24 compared with the baseline dose while maintaining asthma control and proportion of patients achieving a reduction of OCS dose to <5 mg at Week 24 while maintaining asthma control.

Sample size

While initially 150 patients (75 per group) were to be included into the trial this was changed with amendment 4 (dated 30-Jan-2017) to include 180 patients (90 per group). It was calculated that for the primary endpoint (percentage reduction of OCS dose at week 24 compared with the baseline dose), assuming a common SD of 50%, with 90 patients per group, the study had 94% power to detect a treatment difference of 27% at the 2-tailed significance level of α=0.05.

Randomisation

Subjects were randomized in a 1:1 ratio to receive either dupilumab 300 mg q2w or placebo q2w. Randomization was stratified by the optimized OCS dose (≤10 mg/day and >10 mg/day) at the randomization visit and by country.

Blinding (masking)

Dupilumab and placebo were provided in matching glass syringes.

Statistical methods

The primary estimand is the treatment difference between dupilumab and control in the mean percentage reduction of OCS dose at week 24 while maintaining asthma control of all patients in the ITT population of all randomized patients no matter whether the patients discontinue treatment before week 24 or not.

Change from baseline in FEV_1 was analysed using an analysis of covariance (ANCOVA) model with covariates treatment, optimized OCS dose at baseline, regions (pooled countries), and baseline eosinophil level subgroups (<0.15 Giga/L, ≥0.15 Giga/L). The treatment difference was tested at α=0.05 (2-sided), treatment effects were described by LS means including their 95%-CI. Patients who permanently discontinued the study medication were encouraged to return to the clinic for all remaining study visits, and the Investigator was to continue OCS dose adjustment after treatment discontinuation, as guided by their medical judgment. These data collected after treatment discontinuation was included in the primary analysis. For patients who discontinued the study the primary missing data handling approach was pattern mixture model by multiple imputation (PMM-MI).

To assess the robustness of this analysis several sensitivity and supportive analyses were performed:

- Sensitivity analyses including control-based PMM-MI, worse of the last two observations carried forward, and tipping point analyses were conducted to assess the robustness of the conclusion of the main model.
- If the normality assumption was not met, rank ANCOVA with the extended Mantel-Haenszel (MH) statistics was used for nonparametric comparisons between treatment groups. The same covariates in the main ANCOVA model were adjusted for in this method.
- The percentage reduction of OCS dose at week 24 was classified into five ordinal categories: ≥90%, 75-<90%, 50-<75%, >0-<50%, no reduction or any increase in OCS dose or dropped out from study. The model used the endpoint category as the response variable, and adjusted for the same covariates in the main ANCOVA model.
- For patients who permanently discontinued treatment but continued in the study for remaining visits, data collected after treatment discontinuation were excluded from the on treatment analysis. The main statistical model was used. Then the primary missing data handling approach, PMM-MI, was applied to impute missing data and estimate the LS means by the treatment groups and difference in the LS means.
- The consistency of treatment effects across pre-specified subgroups was assessed for the primary efficacy endpoint.

The key secondary endpoints, the proportion of patients achieving a reduction of 50% or greater in their OCS dose at week 24 compared with baseline and the proportion of patients achieving a reduction of OCS dose to <5 mg/day at week 24 were analysed using a logistic regression model adjusted for the same covariates as the main ANCOVA model was used.

For the 2 key secondary efficacy endpoints, the primary missing data handling approach used the imputed datasets from the primary missing data handling approach for the primary efficacy endpoint, and the binary response status of each patient with missing endpoint was determined from the imputed percent reduction at week 24.

The absolute reduction of OCS dose at week 24 was analysed using an ANCOVA model in the same manner as for the primary endpoint. The imputed datasets generated from the primary missing data handling approach for the primary efficacy endpoint were used.

Multiplicity control

If the primary endpoint met the significance level (5%, 2-sided), the following secondary endpoints were tested at a 2-sided 5% significance level in the following order (in case of a non-significant result the procedure had to stop):

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

Results

Participant flow

A total of 390 adult and adolescent patients signed the written informed consent and were screened for study eligibility, and 210 adult and adolescent patients were enrolled, for a screen failure rate of 46.2%. The leading reasons for screen failure were active hepatitis or patients with positive hepatitis B or positive hepatitis C (Exclusion E33), enrolment/randomization stopped at the study level (Exclusion E37) and FEV1 <80% of predicted normal for adults and ≤90% of predicted normal for adolescents during the Screening period, prior to randomization (Inclusion I01C).

Recruitment

Study Initiation Date (first patient enrolled): 15 October 2015

Cut-off date for Clinical Study Report: 20 September 2017.

Baseline data

The mean age of the overall population was 51.3 years with a range of 15 to 77 years. Approximately 60.5% of the patients were female and 93.8% White, with Asian and Black representing 1.0% and 2.4%, respectively. One patient in the dupilumab group and 2 patients in the placebo group were under 18 years of age.

Disease characteristics at baseline

The mean age of onset of asthma was 31.4 years, with 76.2% having asthma onset after 18 years of age. 71.9% had an ongoing atopic medical condition and 80.5% did not have a history of smoking. The mean number of severe asthma exacerbations in the prior year was 2.09 events with 1.02 of them requiring hospitalization or urgent medical care. Mean pre-bronchodilator FEV1 percent predicted was 51.50%. The median daily OCS dose at Visit 1 (ie, pre-optimization) was 10.0 mg/day, and the median optimized daily OCS dose at baseline was 10.0 mg/day. Consistent with the protocol, <30% of the population were receiving ≤5 mg/day OCS at baseline. Asthma-specific baseline characteristics were similar between treatment groups, with an overall mean pre-BD FEV1 1.58 L, mean % predicted pre-BD FEV1 of 52.18%, mean ACQ-5 score of 2.50, and mean AQLQ global score of 4.35.

Disease characteristics at baseline - Randomized population

	Placebo (N=107)	Dupilumab 300mg q2w (N=103)	All (N=210)
Age at onset of asthma (years)			
Number	107	103	210
Mean (SD)	31.6 (16.4)	31.2 (18.9)	31.4 (17.6)
Median	30.0	34.0	32.0
Min : Max	0 : 65	0 : 65	0 : 65
<18	24 (22.4%)	26 (25.2%)	50 (23.8%)
18 - 40	51 (47.7%)	43 (41.7%)	94 (44.8%)
>40	32 (29.9%)	34 (33.0%)	66 (31.4%)
Time since first diagnosis of asthma (years)			
Number	107	103	210
Mean (SD)	19.17 (12.97)	20.76 (14.81)	19.95 (13.90)
Median	17.92	19.08	18.13
Min : Max	1.2 : 56.8	1.8 : 63.8	1.2 : 63.8
With ongoing atopic medical condition[a] [n (%)]			
Number	107	103	210
Yes	77 (72.0%)	74 (71.8%)	151 (71.9%)
Time since last severe asthma exacerbation[b] before entering the study (months)			
Number	104	99	203
Mean (SD)	9.12 (9.18)	10.77 (12.35)	9.92 (10.85)
Median	7.00	6.00	7.00
Min : Max	2.0 : 58.0	1.0 : 83.0	1.0 : 83.0
Number of severe asthma exacerbations[b] experienced in the past year			
Number	107	103	210
Mean (SD)	2.17 (2.24)	2.01 (2.08)	2.09 (2.16)
Median	2.00	2.00	2.00
Min : Max	0.0 : 12.0	0.0 : 12.0	0.0 : 12.0
0	18 (16.8%)	21 (20.4%)	39 (18.6%)
1	31 (29.0%)	29 (28.2%)	60 (28.6%)
2	27 (25.2%)	24 (23.3%)	51 (24.3%)
3	17 (15.9%)	12 (11.7%)	29 (13.8%)
≥4	14 (13.1%)	17 (16.5%)	31 (14.8%)

Number of severe asthma exacerbations[b] requiring hospitalization or urgent medical care experienced in the past year			
Number	107	103	210
Mean (SD)	1.00 (1.40)	1.04 (1.83)	1.02 (1.62)
Median	1.00	0.00	0.00
Min : Max	0.0 : 6.0	0.0 : 12.0	0.0 : 12.0
0	52 (48.6%)	55 (53.4%)	107 (51.0%)
1	29 (27.1%)	26 (25.2%)	55 (26.2%)
2	14 (13.1%)	10 (9.7%)	24 (11.4%)
3	6 (5.6%)	4 (3.9%)	10 (4.8%)
≥4	6 (5.6%)	8 (7.8%)	14 (6.7%)
Smoking history			
Number	107	103	210
Former	17 (15.9%)	24 (23.3%)	41 (19.5%)
Never	90 (84.1%)	79 (76.7%)	169 (80.5%)
Time since cessation (years)			
Number	17	24	41
Mean (SD)	16.98 (11.01)	13.99 (10.96)	15.23 (10.94)
Median	17.08	12.38	13.83
Min : Max	2.3 : 42.1	1.3 : 45.7	1.3 : 45.7
Pack-year			
Number	17	24	41
Mean (SD)	4.17 (2.77)	4.83 (2.60)	4.55 (2.66)
Median	3.50	5.00	4.75
Min : Max	0.4 : 8.0	1.5 : 10.0	0.4 : 10.0
Daily OCS dose at Visit 1 (ie, pre-optimization) (mg/day)			
Number	107	103	210
Mean (SD)	11.83 (6.02)	11.79 (6.40)	11.81 (6.20)
Median	10.00	10.00	10.00
Min : Max	5.0 : 35.0	5.0 : 35.0	5.0 : 35.0
5	20 (18.7%)	20 (19.4%)	40 (19.0%)
>5 -≤10	53 (49.5%)	49 (47.6%)	102 (48.6%)
>10-≤15	15 (14.0%)	15 (14.6%)	30 (14.3%)
>15-≤25	18 (16.8%)	15 (14.6%)	33 (15.7%)
>25	1 (0.9%)	4 (3.9%)	5 (2.4%)

Optimized daily OCS dose at baseline (mg/day)			
Number	107	103	210
Mean (SD)	11.75 (6.31)	10.75 (5.90)	11.26 (6.12)
Median	10.00	10.00	10.00
Min : Max	2.5 : 35.0	5.0 : 30.0	2.5 : 35.0
≤5	18 (16.8%)	25 (24.3%)	43 (20.5%)
>5 -≤10	48 (44.9%)	44 (42.7%)	92 (43.8%)
>10-≤15	24 (22.4%)	19 (18.4%)	43 (20.5%)
>15-≤25	14 (13.1%)	13 (12.6%)	27 (12.9%)
>25	3 (2.8%)	2 (1.9%)	5 (2.4%)
Baseline number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol /24 hours			
Number	107	103	210
Mean (SD)	4.94 (6.65)	4.29 (4.33)	4.62 (5.63)
Median	3.67	3.43	3.43
Min : Max	0.0 : 42.0	0.0 : 23.2	0.0 : 42.0
Baseline pre-bronchodilator FEV1 (L)			
Number	107	103	210
Mean (SD)	1.63 (0.61)	1.53 (0.53)	1.58 (0.57)
Median	1.54	1.49	1.49
Min : Max	0.6 : 3.6	0.7 : 3.1	0.6 : 3.6
Baseline pre-bronchodilator FEV1 percent predicted (%)			
Number	107	103	210
Mean (SD)	52.69 (15.14)	51.64 (15.28)	52.18 (15.18)
Median	54.00	51.00	51.50
Min : Max	21.0 : 81.0	18.0 : 96.0	18.0 : 96.0
Baseline post-bronchodilator FEV1 (L)			
Number	105	102	207
Mean (SD)	1.89 (0.73)	1.83 (0.60)	1.86 (0.67)
Median	1.76	1.80	1.78
Min : Max	0.7 : 4.2	0.8 : 3.3	0.7 : 4.2

Baseline FEV1 reversibility (L)			
Number	105	102	207
Mean (SD)	0.28 (0.32)	0.29 (0.31)	0.28 (0.31)
Median	0.22	0.22	0.22
Min : Max	-0.4 : 2.2	-0.6 : 1.5	-0.6 : 2.2
Baseline FEV1 reversibility (%)			
Number	105	102	207
Mean (SD)	18.39 (22.97)	20.58 (23.59)	19.47 (23.25)
Median	15.00	14.00	14.00
Min : Max	-16.0 : 181.0	-24.0 : 132.0	-24.0 : 181.0
Baseline AM PEF (L/min)			
Number	106	103	209
Mean (SD)	240.60 (115.50)	236.57 (100.21)	238.62 (108.00)
Median	221.64	226.00	226.00
Min : Max	72.3 : 592.4	65.6 : 492.0	65.6 : 592.4
Baseline PM PEF (L/min)			
Number	106	103	209
Mean (SD)	256.12 (117.92)	251.79 (109.15)	253.99 (113.43)
Median	244.57	246.86	246.17
Min : Max	62.5 : 604.4	61.3 : 536.0	61.3 : 604.4
Baseline AM symptom score			
Number	107	103	210
Mean (SD)	1.37 (0.92)	1.37 (0.93)	1.37 (0.92)
Median	1.29	1.29	1.29
Min : Max	0.0 : 3.1	0.0 : 3.0	0.0 : 3.1
Baseline PM symptom score			
Number	107	103	210
Mean (SD)	1.52 (0.93)	1.50 (0.97)	1.51 (0.95)
Median	1.71	1.57	1.71
Min : Max	0.0 : 3.1	0.0 : 3.1	0.0 : 3.1

Baseline number of nocturnal awakenings/24 hours			
Number	107	103	210
Mean (SD)	0.75 (1.07)	0.89 (1.41)	0.82 (1.25)
Median	0.29	0.29	0.29
Min : Max	0.0 : 6.6	0.0 : 11.0	0.0 : 11.0
Baseline ACQ-5 score			
Number	107	102	209
Mean (SD)	2.58 (1.09)	2.42 (1.24)	2.50 (1.16)
Median	3.00	2.60	2.80
Min : Max	0.0 : 4.6	0.0 : 5.4	0.0 : 5.4
≤2	30 (28.0%)	39 (38.2%)	69 (33.0%)
>2	77 (72.0%)	63 (61.8%)	140 (67.0%)
Baseline ACQ-7 score			
Number	94	92	186
Mean (SD)	2.81 (1.00)	2.70 (0.98)	2.75 (0.99)
Median	3.14	2.86	3.00
Min : Max	0.6 : 5.0	0.4 : 4.3	0.4 : 5.0
Baseline AQLQ global score			
Number	107	103	210
Mean (SD)	4.31 (1.12)	4.38 (1.24)	4.35 (1.17)
Median	4.22	4.28	4.25
Min : Max	1.6 : 6.6	1.4 : 7.0	1.4 : 7.0
With hypersensitivity to aspirin or other NSAID [n (%)]			
Number	107	103	210
Yes	9 (8.4%)	15 (14.6%)	24 (11.4%)
Ongoing condition	9 (8.4%)	15 (14.6%)	24 (11.4%)

[a] A patient is considered to have atopic medical condition if he/she has any of the following: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥ 100 IU/mL or at least one aeroantigen specific IgE ≥ 0.35 kU/L at baseline

[b] Severe asthma exacerbation prior to the study is defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at least twice their current dose for at least 3 days.

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Baseline biomarkers

Mean blood eosinophil count at baseline was 0.35 Giga/L and approximately 42.4% of patients had blood eosinophil count ≥0.3 Giga/L. Mean FeNO at baseline was 37.61 ppb and overall 112 patients (53.3%) had baseline FeNO ≥25 ppb.

Baseline biomarkers - Randomized population

	Placebo (N=107)	Dupilumab 300mg q2w (N=103)	All (N=210)
Baseline Blood Eosinophil (GIGA/L)			
Number	107	103	210
Mean (SD)	0.33 (0.30)	0.37 (0.32)	0.35 (0.31)
Median	0.24	0.28	0.26
Q1 : Q3	0.12 : 0.45	0.16 : 0.52	0.14 : 0.48
Min : Max	0.0 : 1.5	0.0 : 1.8	0.0 : 1.8
Baseline Blood Eosinophil Group (GIGA/L)			
< 0.15	38 (35.5%)	22 (21.4%)	60 (28.6%)
≥0.15 - < 0.3	28 (26.2%)	33 (32.0%)	61 (29.0%)
≥0.3	41 (38.3%)	48 (46.6%)	89 (42.4%)
Baseline Total IgE (IU/ML)			
Number	106	103	209
Mean (SD)	426.62 (881.22)	434.65 (654.54)	430.58 (775.96)
Median	143.00	183.00	164.00
Q1 : Q3	38.00 : 360.00	90.00 : 498.00	64.00 : 460.00
Min : Max	1.0 : 5000.0	2.0 : 3805.0	1.0 : 5000.0
Baseline Eotaxin-3 (PG/ML)			
Number	107	103	210
Mean (SD)	50.62 (40.75)	47.86 (52.18)	49.27 (46.61)
Median	42.40	37.20	38.55
Q1 : Q3	25.20 : 69.80	25.20 : 58.20	25.20 : 62.90
Min : Max	2.0 : 234.0	2.0 : 463.0	2.0 : 463.0
Baseline TARC (PG/ML)			
Number	106	103	209
Mean (SD)	428.03 (663.07)	369.81 (298.11)	399.34 (516.11)
Median	284.50	268.00	272.00
Q1 : Q3	170.00 : 475.00	197.00 : 472.00	175.00 : 472.00
Min : Max	33.5 : 5690.0	45.1 : 1790.0	33.5 : 5690.0
Baseline FeNO (ppb)			
Number	103	101	204
Mean (SD)	39.62 (34.12)	35.55 (28.34)	37.61 (31.38)
Median	29.00	28.00	28.50
Q1 : Q3	17.00 : 56.00	14.00 : 48.00	16.00 : 51.00
Min : Max	2.0 : 195.0	6.0 : 199.0	2.0 : 199.0

PGM=PRODOPS/SAR231893/EFC13691/CSR/REPORT/PGM/dem_basbiomarker_r_t.sas
OUT=REPORT/OUTPUT/dem_basbiomarker_r_t_i.rtf (19NOV2017 - 17:03)

Medical / surgical history

A patient was considered to have an ongoing atopic medical condition if he/she self-reported any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, hives; or had baseline total IgE ≥100 IU/mL and at least one positive aero-antigen specific IgE (≥0.35 IU/mL) at baseline. The percentages of patients with an ongoing atopic medical condition at baseline were well balanced between treatment groups. 71.9% reported having an ongoing atopic disease, with allergic rhinitis being the most frequent (55.7%). 50 patients (23.8%) had ongoing chronic rhinosinusitis and 44 patients (21.0%) had ongoing nasal polyposis.

Prior and / or concomitant medication

In addition to a stable dose of OCS, all patients were receiving background asthma controller therapy at stable doses at study entry and continued with these medications throughout the study.

Controller medication other than OCS at randomization by type - Randomized population

	Placebo (N=106)	Dupilumab 300mg q2w (N=103)	All (N=209)
Total daily ICS dose (mcg)[a]			
Mean (SD)	982.12 (473.94)	1084.32 (572.08)	1032.24 (525.59)
Median	1000.00	1000.00	1000.00
Non-ICS controller medication [n (%)]	106 (100%)	102 (99.0%)	208 (99.5%)
LABA [n (%)]	106 (100%)	102 (99.0%)	208 (99.5%)
LAMA [n (%)]	20 (18.9%)	27 (26.2%)	47 (22.5%)
Anti-leukotrienes [n (%)]	24 (22.6%)	28 (27.2%)	52 (24.9%)
Methylxanthines [n (%)]	13 (12.3%)	6 (5.8%)	19 (9.1%)

Two controller medications [n (%)]	49 (46.2%)	43 (41.7%)	92 (44.0%)
ICS/LABA [n (%)]	49 (46.2%)	43 (41.7%)	92 (44.0%)
Other [n (%)]	0	0	0
Three controller medications [n (%)]	56 (52.8%)	56 (54.4%)	112 (53.6%)
ICS/LABA/LAMA [n (%)]	19 (17.9%)	24 (23.3%)	43 (20.6%)
ICS/LABA/ Anti-leukotrienes [n (%)]	23 (21.7%)	25 (24.3%)	48 (23.0%)
Other [n (%)]	14 (13.2%)	7 (6.8%)	21 (10.0%)

Patient 528001301 in the Placebo group is excluded from the summary because the patient has a reported dose of fluticasone propionate of 125mg (125000mcg), which is confirmed a data entry error post database lock.
[a] The ICS dose is established on the comparability to fluticasone propionate. The ICS dose of different products is standardized according to equivalent dose specified in SAP Table 6.
Note: Only those medications in the list of commonly used controller medications (SAP appendix A) are summarized in this table
PGM=PRODOPS/SAR231893/EFC13691/CSR/REPORT/PGM/dem_conmed_controller_intxt_r_t.sas
OUT=REPORT/OUTPUT/dem_conmed_controller_intxt_r_t_i.rtf (29NOV2017 - 8:27)

Numbers analysed

The randomized population and the ITT population were comprised of 210 adult and adolescent patients (103 patients in the dupilumab group and 107 patients in the placebo group). All patients who were randomized received treatment, and all treated patients were randomized, resulting in a safety population that was equivalent to the randomized population (103 patients in the dupilumab group and 107 patients in the placebo group). The PK population was comprised of all 103 patients treated with dupilumab from the safety population, and the ADA population was comprised of 208 patients from the safety population who had at least one reportable ADA result after first dose of the study treatment.

Summary of analysis populations - Randomized population

	Placebo (N=107)	Dupilumab 300mg q2w (N=103)	All (N=210)
Randomized population	107 (100%)	103 (100%)	210 (100%)
Efficacy population			
Intent-to-Treat (ITT)	107 (100%)	103 (100%)	210 (100%)
Safety population	107	103	210
PK population	0	103	103
ADA population	107	101	208

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
PGM=PRODOPS/SAR231893/EFC13691/CSR/REPORT/PGM/dis_populations_r_t.sas OUT=REPORT/OUTPUT/dis_populations_r_t_i.rtf (19NOV2017 - 17:15)

The **primary endpoint** was percentage reduction from baseline in OCS dose at Week 24. The mean percent reduction in OCS dose at Week 24 was greater in the dupilumab group (LS mean 70.09) compared with the placebo group (LS mean 41.85). The dupilumab group showed an increasing reduction in OCS dose at each time point through Week 20, at which time no further dose adjustments were permitted.

Outcomes and estimation

Summary of the primary and secondary endpoints in the hierarchical testing procedure - ITT population

OCS (mg/day)	Placebo	Dupilumab 300mg q2w	Difference vs. Placebo (p-value)[a]
Primary endpoints			
LS Mean percent reduction of OCS dose at Week 24	41.85	70.09	28.24 (<.0001)
Key secondary endpoints			
Adjusted probability of patients achieving a reduction of 50% or greater in their OCS dose at Week 24	0.50	0.80	3.98 (<.0001)
Adjusted probability of patients achieving a reduction of OCS dose to <5 mg/day at Week 24	0.33	0.69	4.48 (<.0001)
Other secondary endpoints			
Adjusted probability of patients achieving their maximum possible reduction of OCS dose per protocol at Week 24	0.26	0.48	2.57 (0.0024)
Adjusted probability of patients no longer requiring OCS at Week 24[b]	0.25	0.48	2.74 (0.0015)

[a] For the primary endpoint, the difference is expressed as LS Mean difference. For all other outcomes, the differences are expressed as odds ratio.

[b] Only the patients whose baseline OCS dose is less than or equal to 30mg/day are included in the analysis of the endpoint.

PGM=PRODOPS/SAR231893/EFC13691/CSR/REPORT/PGM/eff_ocs_hier_test_i_t.sas OUT=REPORT/OUTPUT/eff_ocs_hier_test_i_t_i.rtf (19NOV2017 - 20:02)

Primary analysis: percentage reduction of OCS dose (mg/day) at Week 24 – ITT population

OCS (mg/day)	Placebo (N=107)	Dupilumab 300mg q2w (N=103)
Baseline		
Number	107	103
Mean (SD)	11.75 (6.31)	10.75 (5.90)
Median	10.00	10.00
Q1 : Q3	7.50 : 15.00	7.50 : 12.50
Min : Max	2.5 : 35.0	5.0 : 30.0
Week 24		
Number	106	101
Mean (SD)	6.32 (6.75)	3.13 (5.44)
Median	5.00	0.00
Q1 : Q3	0.00 : 10.00	0.00 : 5.00
Min : Max	0.0 : 30.0	0.0 : 30.0
Percentage reduction from baseline		
Number	106	101
Mean (SD) [a]	45.28 (50.73)	73.85 (39.78)
Median [a]	50.00	100.00
Q1 : Q3 [a]	0.00 : 100.00	62.50 : 100.00
Min : Max [a]	-100.0 : 100.0	-100.0 : 100.0
LS Mean (SE) [b]	41.85 (4.57)	70.09 (4.90)
LS Mean Diff vs. placebo (95% CI) [b]		28.24 (15.81, 40.67)
P-value vs. placebo [b]		<.0001

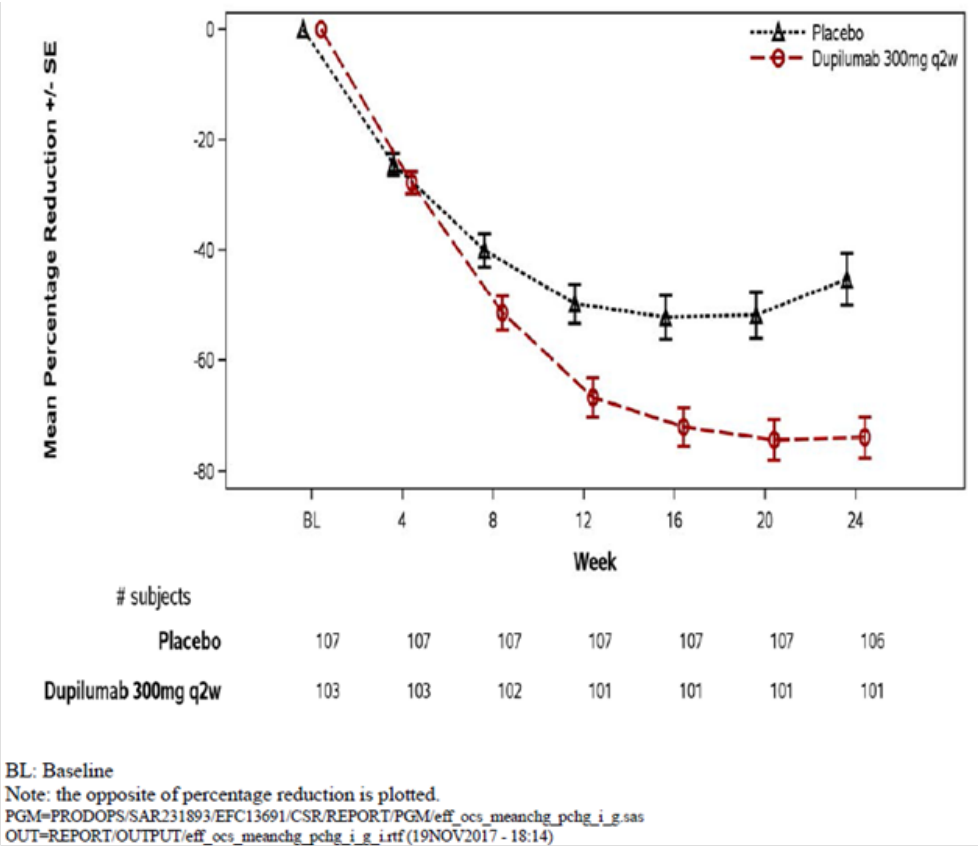
[a] Calculated from observed data only

[b] Derived from combining results from analyzing multiple imputed data using an ANCOVA model by Rubin's rule. The model includes the percentage reduction of OCS dose at Week 24 as the response variable, and the treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups (<0.15, ≥0.15 Giga/L) as covariates. Missing data is imputed using the primary approach - pattern mixture model by multiple imputation (seed = 13691).

PGM=PRODOPS/SAR231893/EFC13691/CSR/REPORT/PGM/eff_ocs_ancov_i_t.sas OUT=REPORT/OUTPUT/eff_ocs_ancov_i_t_i.rtf (21NOV2017 - 2:34)

The mean percent reduction in OCS dose at Week 24 was greater in the dupilumab group (LS mean 70.09) compared with the placebo group (LS mean 41.85). The LS mean difference in the percent reduction from baseline to Week 24 was statistically significant (+28.24, p<0.0001). The median percent reduction in OCS dose from baseline to Week 24 was 100.0% in patients who received dupilumab as compared with a reduction of 50.0% in the patients who received placebo.

Mean percentage reduction from baseline of OCS dose (mg/day) over time – ITT population



BL: Baseline
Note: the opposite of percentage reduction is plotted.
PGM=PRODOPS/SAR231893/EFC13691/CSR/REPORT/PGM/eff_ocs_meanchg_pchg_i_g.sas
OUT=REPORT/OUTPUT/eff_ocs_meanchg_pchg_i_g_i.rtf (19NOV2017 - 18:14)

The results of sensitivity analyses performed were similar to the results of the primary analysis.

Secondary endpoints

The Key secondary endpoint was the proportion of patients with ≥50% reduction in OCS dose compared with baseline at Week 24, which was greater in the dupilumab group (80%) than in the placebo group (50%). The odds of a ≥50% reduction in the OCS dose was 3.98 times (95% CI, 2.06 to 7.67) as high with dupilumab as compared to placebo (p<0.0001).

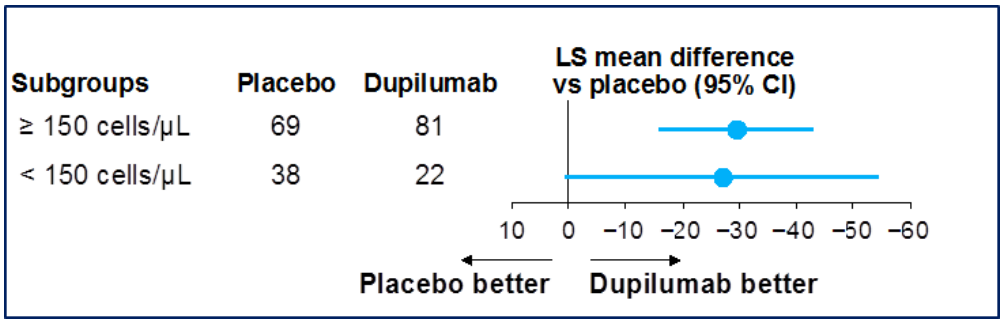
Of clinical relevance was also the secondary endpoint of the proportion of patients with a reduction in OCS dose to <5 mg/day at week 24, which was significantly greater in the dupilumab group (69%) than in the placebo group (33%). The odds of a reduction in OCS dose to <5 mg/day was 4.48 times (95% CI, 2.39 to 8.39) as high with dupilumab as compared to placebo (p<0.0001).

The mean absolute reduction in OCS dose at Week 24 was greater in the dupilumab group (LS mean 7.58) compared with the placebo group (LS mean 4.77). The LS mean difference in the percent reduction from baseline to Week 24 was statistically significant and clinically relevant (+2.81, p=0.0002).

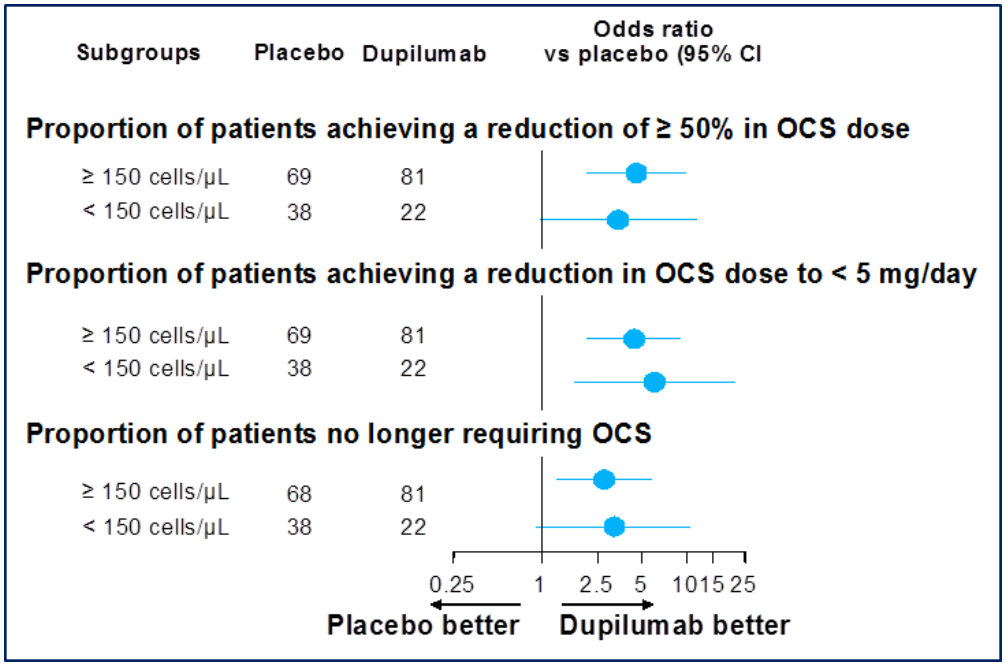
The proportion of patients with ≥50% reduction in OCS dose compared with baseline was greater in the dupilumab group than in the placebo group across all categories of baseline blood eosinophils. The proportion of patients with ≥50% reduction in OCS dose compared with baseline was greater in the dupilumab group than in the placebo group across all categories of baseline FeNO. Although, higher efficacy was seen with higher baseline values of FeNO (e.g. <25ppb with 70.5% to >50ppb with 95.6%) and blood eosinophils (e.g. <0.15 with 72.5 % to >0.3 with 86.5%) the results across all subgroups are clinically meaningful.

Subgroup analyses

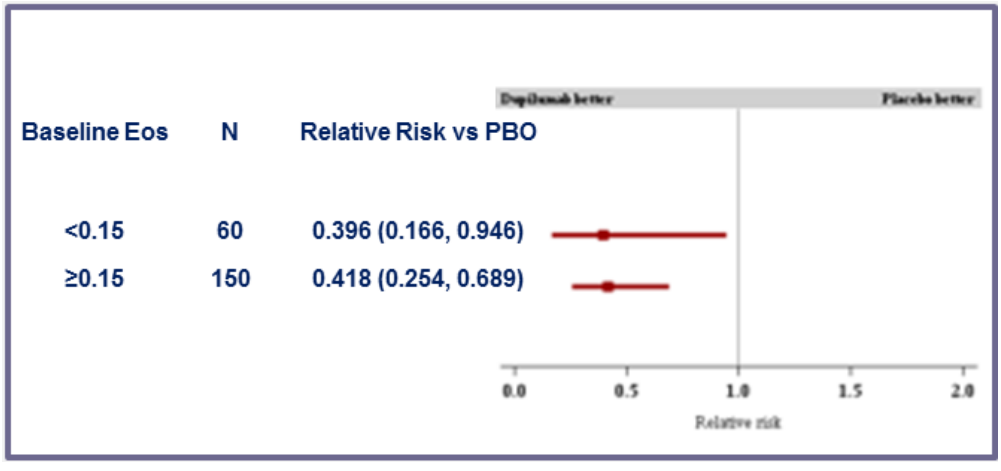
Percent reduction in OCS dose, according to blood eosinophil subgroup



Secondary OCS reduction endpoints, according to eosinophil subgroup

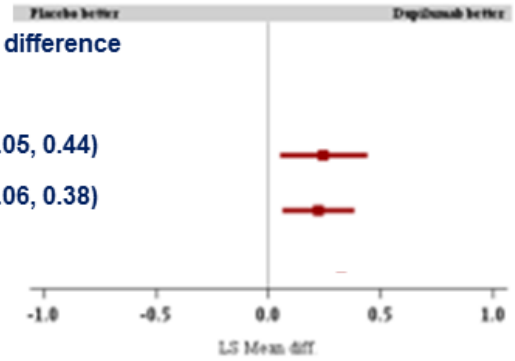


Exacerbation reduction by blood eos



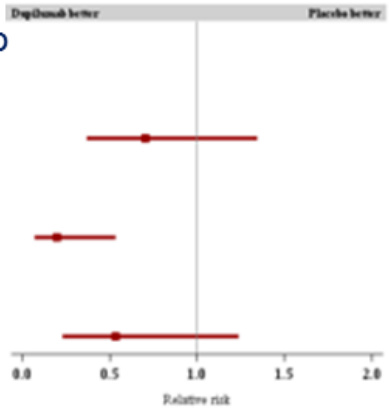
LS mean difference FEV1 by blood eos

Baseline Eos	N	LS mean difference
<0.15	59	0.24 (0.05, 0.44)
≥0.15	142	0.22 (0.06, 0.38)



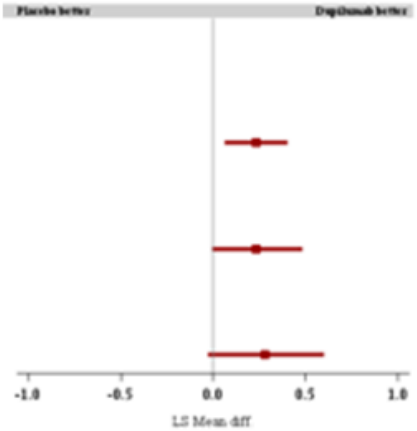
Exacerbation reduction by FeNO

Baseline FeNO	N	Relative Risk vs PBO
<0.25	90	0.704 (0.369, 1.346)
≥25-<50	61	0.195 (0.072, 0.531)
≥50	53	0.532 (0.228,1.239)



LS mean difference FEV1 by FeNO

Baseline FeNO	N	LS mean difference
<0.25	86	0.23 (0.06, 0.40)
≥25-<50	59	0.23 (-0.01,0.48)
≥50	50	0.28 (-0.03,0.60)



In line with the results of the efficacy endpoints were the results of the Patient Reported Outcomes. The dupilumab group showed a reduction in ACQ-5 (i.e. indicating improvement in asthma control) from baseline to Week that was nominally greater than that observed in the placebo group. The analysis of the change from baseline in Asthma Quality Of Life Questionnaire (AQLQ) showed an increase from baseline to week 24 that was greater in the dupilumab group than in the placebo group.

Summary of main studies

The following tables summarise the efficacy results from the two 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 (see later sections).

Table 1: Summary of efficacy for trial EFC13579

<table>
<tr><td colspan="6"><u>Title:</u> A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma</td></tr>
<tr><td>Study identifier</td><td colspan="5">EFC13579</td></tr>
<tr><td rowspan="4">Design</td><td colspan="5">Randomized, double-blind, parallel-group study vs. Placebo treatment</td></tr>
<tr><td colspan="2">Duration of main phase:</td><td colspan="3">52 weeks</td></tr>
<tr><td colspan="2">Duration of Run-in phase:</td><td colspan="3">not applicable</td></tr>
<tr><td colspan="2">Duration of Extension phase:</td><td colspan="3">not applicable</td></tr>
<tr><td>Hypothesis</td><td colspan="5">Superiority</td></tr>
<tr><td rowspan="4">Treatments groups</td><td colspan="2">Dup200</td><td colspan="3">Dupilumab 200 mg q2w with 400 mg loading dose
n = 631</td></tr>
<tr><td colspan="2">Dup300</td><td colspan="3">Dupilumab 300 mg q2w with 600 mg loading dose
n = 633</td></tr>
<tr><td colspan="2">Plac200</td><td colspan="3">Placebo to Dup200
n = 317</td></tr>
<tr><td colspan="2">Plac300</td><td colspan="3">Placebo to Dup300
n = 321</td></tr>
<tr><td rowspan="3">Endpoints and definitions</td><td>Co-Primary</td><td>ARR severe</td><td colspan="3">Annualized rate of severe exacerbation events during the 52-week placebo controlled treatment period</td></tr>
<tr><td>Co-Primary</td><td>FEV_1</td><td colspan="3">Absolute change from baseline in pre-bronchodilator FEV_1 at week 12</td></tr>
<tr><td>Key-secondary</td><td>%FEV_1</td><td colspan="3">Percent change from baseline in pre-bronchodilator FEV_1 at week 12</td></tr>
<tr><td>Database lock</td><td colspan="5">Date not provided</td></tr>
<tr><td colspan="6"><u>Results and Analysis</u></td></tr>
<tr><td>Analysis description</td><td colspan="5">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="5">Intent to treat (data cutoff date: 29-Jul-2017)</td></tr>
<tr><td rowspan="3">Descriptive statistics and estimate variability</td><td rowspan="2">Treatment group</td><td colspan="2">200 mg</td><td colspan="2">300 mg</td></tr>
<tr><td>Plac200</td><td>Dup200</td><td>Plac300</td><td>Dup300</td></tr>
<tr><td>Number of subject</td><td>317</td><td>631</td><td>321</td><td>633</td></tr>
</table>

	ARR severe	0.871	0.456	0.970	0.524
	95%-CI	(0.724, 1.048)	(0.389, 0.534)	(0.810, 1.160)	(0.450, 0.611)
	Number of subject	307	611	313	610
	FEV_1 (LS Mean)	0.18	0.32	0.21	0.34
	SE	0.02	0.02	0.02	0.02

Effect estimate per comparison	ARR severe	Comparison groups	DUP300 vs. Plac300
		Relative risk	0.540
		95%-CI	(0.430, 0.680)
		P-value	< 0.0001
		Comparison groups	Dup200 vs. Plac200
		Relative risk	0.523
		95%-CI	(0.413, 0.662)
		P-value	< 0.0001
	FEV_1	Comparison groups	DUP300 vs. Plac300
		Difference	0.13
		95%-CI	(0.08,0.18)
		P-value	< 0.0001
		Comparison groups	Dup200 vs. Plac200
		Difference	0.14
		95%-CI	(0.08, 0.19)
		P-value	< 0.0001

Notes	Both doses of dupilumab were superior to placebo with regard to both co-primary endpoints. This was also true in the subgroup of patients with baseline blood eosinophil ≥ 0.3 Giga/L				
Analysis description	Key secondary analysis				
Analysis population and time point description	Intent to treat				
Descriptive statistics and estimate variability	Treatment group	200 mg		300 mg	
		Plac200	Dup200	Plac300	Dup300
	Number of subject	307	611	313	610
	$\%FEV_1$ (LS Mean)	12.11	21.34	13.67	23.08
	SE	1.56	1.13	1.56	1.13

Effect estimate per comparison	$\%FEV_1$	Comparison groups	DUP300 vs. Plac300
		Difference	9.41
		95%-CI	(5.74, 13.07)
		P-value	< 0.0001
		Comparison groups	Dup200 vs. Plac200
		Difference	9.23
		95%-CI	(5.54, 12.92)
		P-value	< 0.0001

Table: Summary of efficacy for trial EFC13691 (venture)

Title: A randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab in patients with severe steroid dependent asthma			
Study identifier	EFC13691		
Design	Randomized, double-blind, parallel-group study vs. placebo treatment		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Dup300		Dupilumab 300 mg q2w n = 103
	Placebo		Placebo n = 107
Endpoints and definitions	Primary	OCS reduction	percentage reduction of investigator prescribed OCS dose at week 24 compared with the baseline dose, while maintaining asthma control
	Key-secondary	OCS 50% response	probability of achieving a reduction of 50% or greater in their OCS dose at week 24 compared with baseline while maintaining asthma control.
	Key-secondary	OCS 5 response	probability of achieving a reduction of OCS dose to <5 mg/day at week 24 while maintaining asthma control.
	Secondary	OCS max	probability of achieving the individual maximum possible reduction of OCS dose per protocol at week 24 while maintaining asthma control.
	Secondary	OCS free	proportion of no longer requiring OCS at week 24 while maintaining asthma control.
Database lock	Date not provided		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (data cutoff date: 20 Sep 2017)		

Descriptive statistics and estimate variability	Treatment group	Placebo	Dup300	
	Number of subject	107	103	
	OCS reduction (LS means)	41.85	70.09	
	SE	4.57	4.90	

Effect estimate per comparison	Mean OCS reduction	Comparison groups	Dup300 - Placebo
		Difference	28.24
		95%-CI	(15.81, 40.67)
		P-value (1-sided)	< 0.0001

Median % reduction in daily OCS dose from baseline	Treatment group	placebo	Dup300
		50	100

Notes	Regarding the primary parameter, the efficacy of dupilumab was statistically proven. The results of the pre-planned sensitivity and subgroup analyses (not shown here) do also support the primary analysis results.
Analysis description	**Key secondary analyses**
Analysis population and time point description	Intent to treat

Descriptive statistics and estimate variability	Treatment group	Placebo	Dup300	
	Number of subject	107	103	
	OCS 50% response (%)	50%	80%	
	95%-CI	(40%, 61%)	(70%, 87%)	
	OCS 5 response (%)	33%	69%	
	95%-CI	(24%, 44%)	(58%, 79%)	

Effect estimate per comparison	OCS 50% response	Comparison groups	Dup300 vs. Placebo
		Odds ratio	3.98
		95%-CI	(2.06, 7.67)
		P-value	< 0.0001
	OC 5 response	Odds ratio	4.48
		95%-CI	(2.39, 8.39)
		P-value	< 0.0001

Notes	

Analysis description	**Secondary analyses**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Placebo	Dup300	
	Number of subject	107	103	
	OCS max (%)	26%	48%	
	95%-CI	(18%, 36%)	(36%, 59%)	
	OCS free (%)	25%	48%	
	95%-CI	(17%, 35%)	(36%, 59%)	

Effect estimate per comparison	OCS max	Comparison groups	DUP300 vs. Placebo
		Odds ratio	2.57
		95%-CI	(1.40, 4.73)
		P-value	< 0.0024
	OCS free	Odds ratio	2.74
		95%-CI	(1.47, 5.10)
		P-value	0.0015

Analysis performed across trials (pooled analyses and meta-analysis)

Clinical studies in special populations

Adolescents:

In study EFC1579 and EFC13691 adolescent patients over 12 years of age with a physician diagnosis of asthma for ≥12 months (based on the GINA 2014 Guidelines) were eligible.

107 adolescents were randomized in study EFC13579. The mean age of the adolescent population was 14.2 years with a range of 12 to 17 years. Approximately one-third of the patients (35.5%) were females, and the majority of the patients (90.7%) were White. The majority of adolescent patients (96.3%) had an ongoing atopic medical condition.

The adjusted annualized event rate of severe exacerbation in the 107 adolescent patients during the 52-week treatment period was lower in the dupilumab 200 mg q2w group compared with the matching placebo groups (0.191 for the dupilumab 200 mg q2w compared with 0.356 for the matching placebo group), indicating a 46.4% reduced risk of severe exacerbation events. A difference between the dupilumab 300 mg q2w group and matching placebo group was not observed. A greater increase in pre-bronchodilator FEV1 from baseline to Week 12 for the adolescent population was observed in the 200 mg q2w group (LS mean 0.40 L) and 300 mg q2w group (LS mean 0.46 L) compared with the matching placebo groups (0.03 L and 0.18 L, respectively).

In study EFC13691 only 3 adolescent patients were enrolled (one in the dupilumab and 2 in the placebo group). This number is considered too low to draw any conclusions.

Analysis performed across trials

The applicant performed different analyses across Studies DRI12544 and EFC13579. To demonstrate consistency of results of Study EFC13691 were presented side-by-side. Due to differences in endpoints/populations it was not possible to pool all pivotal studies.

In all studies higher efficacy was seen in patients demonstrating evidence of Type 2 inflammation, such as higher blood eosinophil counts at baseline or elevated baseline FeNO levels. For the subgroup of patients with baseline eosinophil count <0.3 Giga/L, in Study DRI12544 and EFC13691 dupilumab demonstrated reductions in the risk of severe asthma exacerbations in comparison to placebo, while in Study EFC13579 the rate of exacerbations for the dupilumab treated patients did not show a significant reduction. For FEV1, the treatment response was more consistent across the 3 studies with higher effect in patients with higher baseline eosinophil counts, and also showing improvement among patients with baseline eosinophil counts of either <0.3 or <0.15 Giga/L.

Pivotal studies - Summary of efficacy on asthma exacerbation and FEV1 in overall ITT population

	DRI12544			EFC13579				EFC13691	
	Dupilumab/2mL			1.14 mL/200 mg q2w		2 mL/300 mg q2w		Dupilumab/2mL	
	Placebo/2mL (N=158)	200 mg q2w (N=150)	300 mg q2w (N=157)	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)	Placebo (N=107)	Dupilumab (N=103)
Annualized rate of severe exacerbation events during placebo-controlled treatment period - ITT population[a]									
Estimate (95% CI)	0.897 (0.619, 1.300)	0.269 (0.157, 0.461)	0.265 (0.157, 0.445)	0.871 (0.724, 1.048)	0.456 (0.389, 0.534)	0.970 (0.810, 1.160)	0.524 (0.450, 0.611)	1.597 (1.248, 2.043)	0.649 (0.442, 0.955)
Relative risk vs. placebo (95% CI)		0.300 (0.159, 0.565)	0.295 (0.159, 0.546)		0.523 (0.413, 0.662)		0.540 (0.430, 0.680)		0.407 (0.263, 0.630)
P-value vs. placebo		0.0002	0.0001		<.0001		<.0001		<.0001
Risk difference vs. placebo (95% CI)		-0.629 (-0.983, -0.274)	-0.633 (-0.984, -0.282)		-0.416 (-0.588, -0.243)		-0.446 (-0.633, -0.258)		-0.947 (-1.393, -0.501)
Change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population[b]									
LS Mean (SE)	0.12 (0.03)	0.31 (0.03)	0.28 (0.03)	0.18 (0.02)	0.32 (0.02)	0.21 (0.02)	0.34 (0.02)	0.01 (0.05)	0.22 (0.05)
LS Mean Diff vs. placebo (95% CI)		0.20 (0.11, 0.28)	0.16 (0.08, 0.25)		0.14 (0.08, 0.19)		0.13 (0.08, 0.18)		0.22 (0.09, 0.34)
P-value vs. placebo		<.0001	0.0002		<.0001		<.0001		0.0007
Percent change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population[b]									
LS Mean (SE)	6.06 (1.89)	18.00 (1.89)	17.75 (1.84)	12.11 (1.56)	21.34 (1.13)	13.67 (1.56)	23.08 (1.13)	4.77 (3.30)	19.90 (3.48)
LS Mean Diff vs. placebo (95% CI)		11.94 (6.77, 17.11)	11.69 (6.59, 16.80)		9.23 (5.54, 12.92)		9.41 (5.74, 13.07)		15.13 (6.12, 24.15)
P-value vs. placebo		<.0001	<.0001		<.0001		<.0001		0.0011

CI=confidence interval; FEV1= forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error

Pivotal studies - Summary of efficacy on asthma exacerbation and FEV1 in ITT population with baseline blood eosinophils ≥0.15 Giga/L

	DRI12544			EFC13579				EFC13691	
	Dupilumab/2mL			1.14 mL/200 mg q2w		2 mL/300 mg q2w		Dupilumab/2mL	
	Placebo/2mL (N=127)	200 mg q2w (N=120)	300 mg q2w (N=129)	Placebo (N=232)	Dupilumab (N=437)	Placebo (N=237)	Dupilumab (N=452)	Placebo (N=69)	Dupilumab (N=81)
Annualized rate of severe exacerbation events during placebo-controlled treatment period - ITT population with baseline eosinophil ≥ 0.15 Giga/L[a]									
Estimate (95% CI)	1.052 (0.693, 1.598)	0.290 (0.159, 0.529)	0.280 (0.158, 0.496)	1.007 (0.814, 1.245)	0.445 (0.368, 0.538)	1.081 (0.879, 1.329)	0.434 (0.359, 0.525)	1.536 (1.139, 2.071)	0.642 (0.425, 0.971)
Relative risk vs. placebo (95% CI)		0.276 (0.138, 0.552)	0.266 (0.136, 0.521)		0.442 (0.337,0.581)		0.402 (0.307, 0.526)		0.418 (0.254, 0.689)
P-value vs. placebo		0.0003	0.0001		<.0001		<.0001		0.0007
Risk difference vs. placebo (95% CI)		-0.762 (-1.218, -0.306)	-0.772 (-1.226, -0.319)		-0.561 (-0.785, -0.338)		-0.647 (-0.879, -0.415)		-0.894 (-1.414, -0.374)
Change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population with baseline eosinophil ≥ 0.15 Giga/L[b]									
LS Mean (SE)	0.09 (0.04)	0.32 (0.04)	0.26 (0.03)	0.18 (0.03)	0.36 (0.02)	0.22 (0.03)	0.37 (0.02)	0.09 (0.06)	0.32 (0.06)
LS Mean Diff vs. placebo (95% CI)		0.23 (0.13, 0.33)	0.18 (0.08, 0.27)		0.17 (0.11, 0.23)		0.15 (0.09, 0.21)		0.22 (0.06, 0.38)
P-value vs. placebo		<.0001	0.0004		<.0001		<.0001		0.0062
Percent change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population with baseline eosinophil ≥0.15 Giga/L[b]									
LS Mean (SE)	4.36 (2.19)	18.25 (2.18)	17.11 (2.10)	12.35 (1.84)	23.56 (1.36)	14.17 (1.84)	25.34 (1.35)	9.09 (4.50)	25.98 (4.12)
LS Mean Diff vs. placebo (95% CI)		13.89 (7.98, 19.80)	12.75 (6.94, 18.56)		11.21 (6.85, 15.57)		11.16 (6.85, 15.47)		16.89 (5.37, 28.41)
P-value vs. placebo		<.0001	<.0001		<.0001		<.0001		0.0043

CI=confidence interval; FEV1= forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error

a For the results of DRI12544, only on-treatment (from first dose date to last dose date + 14 days) severe exacerbation events were included in the primary analysis. For the results of EFC13579 and EFC13691, all severe exacerbation events occurred during the placebo-controlled treatment period (from randomization up to study planned end of treatment visit/time or last contact date, whichever comes earlier, were included in the primary analysis, regardless if patient is on-treatment or not.

b For the results of DRI12544, the values collected from systemic corticosteroid start date to systemic corticosteroid end date + 30 days for each exacerbation episode were excluded and only on-treatment values up to Week 12 or Week 24 were included in the primary analysis. For the results of EFC13579 and EFC13691, all values measured up to Week 12 or week 24 were included in the primary analysis, regardless if the patient is on-treatment or not.

*: For Study EFC13691, change from baseline in pre-bronchodilator FEV1 at Week 24 was reported to allow time for OCS reduction to reach optimization.

Pivotal studies - Summary of efficacy on asthma exacerbation and FEV1 in ITT population with baseline blood eosinophils ≥0.3 Giga/L

	DRI12544			EFC13579				EFC13691	
	Dupilumab/2mL			1.14 mL/200 mg q2w		2 mL/300 mg q2w		Dupilumab/2mL	
	Placebo/2mL (N=68)	200 mg q2w (N=65)	300 mg q2w (N=64)	Placebo (N=148)	Dupilumab (N=264)	Placebo (N=142)	Dupilumab (N=277)	Placebo (N=41)	Dupilumab (N=48)
Annualized rate of severe exacerbation events during placebo-controlled treatment period - ITT population with baseline eosinophil ≥ 0.3 Giga/L[a]									
Estimate (95% CI)	1.044 (0.572, 1.904)	0.300 (0.133, 0.678)	0.201 (0.078, 0.517)	1.081 (0.846, 1.382)	0.370 (0.289, 0.475)	1.236 (0.972, 1.571)	0.403 (0.317, 0.512)	1.742 (1.202, 2.525)	0.504 (0.260, 0.975)
Relative risk vs. placebo (95% CI)		0.288 (0.109, 0.757)	0.193 (0.067, 0.559)		0.342 (0.244,0.480)		0.326 (0.234, 0.454)		0.289 (0.139, 0.601)
P-value vs. placebo		0.0116	0.0024		<.0001		<.0001		0.0011
Risk difference vs. placebo (95% CI)		-0.743 (-1.399, -0.088)	-0.842 (-1.482, -0.203)		-0.711 (-0.987, -0.436)		-0.833 (-1.140, -0.525)		-1.238 (-1.942, -0.534)
Change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population with baseline eosinophil ≥0.3 Giga/L[b]									
LS Mean (SE)	0.18 (0.05)	0.43 (0.05)	0.39 (0.05)	0.21 (0.03)	0.43 (0.03)	0.22 (0.03)	0.47 (0.02)	0.12 (0.09)	0.44 (0.09)
LS Mean Diff vs. placebo (95% CI)		0.26 (0.11, 0.40)	0.21 (0.06, 0.36)		0.21 (0.13, 0.29)		0.24 (0.16, 0.32)		0.32 (0.10, 0.54)
P-value vs. placebo		0.0008	0.0063		<.0001		<.0001		0.0049
Percent change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population with baseline eosinophil ≥0.3 Giga/L[b]									
LS Mean (SE)	10.17 (3.32)	25.91 (3.32)	25.80 (3.35)	15.55 (2.40)	28.97 (1.83)	14.35 (2.47)	32.52 (1.79)	10.52 (6.77)	35.09 (6.50)
LS Mean Diff vs. placebo (95% CI)		15.74 (6.61, 24.87)	15.63 (6.47, 24.80)		13.42 (7.60, 19.23)		18.16 (12.34, 23.99)		24.57 (7.32, 41.82)
P-value vs. placebo		0.0008	0.0009		<.0001		<.0001		0.0058

Pivotal studies - Summary of efficacy on asthma exacerbation and FEV1 in ITT population with baseline blood eosinophils <0.3 Giga/L

	DRI12544			EFC13579				EFC13691	
	Dupilumab/2mL			1.14 mL/200 mg q2w		2 mL/300 mg q2w		Dupilumab/2mL	
	Placebo/2mL (N=90)	200 mg q2w (N=85)	300 mg q2w (N=93)	Placebo (N=169)	Dupilumab (N=366)	Placebo (N=178)	Dupilumab (N=356)	Placebo (N=66)	Dupilumab (N=55)
Annualized rate of severe exacerbation events during placebo-controlled treatment period - ITT population with baseline eosinophil <0.3 Giga/L[a]									
Estimate (95% CI)	0.779 (0.493, 1.231)	0.253 (0.124, 0.516)	0.313 (0.170, 0.576)	0.675 (0.515, 0.884)	0.512 (0.418, 0.628)	0.732 (0.562, 0.954)	0.610 (0.502, 0.742)	1.440 (1.045, 1.984)	0.784 (0.502, 1.226)
Relative risk vs. placebo (95% CI)		0.324 (0.141, 0.746)	0.401 (0.192, 0.839)		0.759 (0.548,1.052)		0.834 (0.608, 1.144)		0.545 (0.315, 0.940)
P-value vs. placebo		0.0081	0.0152		0.0975		0.2599		0.0295
Risk difference vs. placebo (95% CI)		-0.526 (-0.921, -0.132)	-0.466 (-0.860, -0.072)		-0.163 (-0.366, 0.041)		-0.122 (-0.341, 0.098)		-0.656 (-1.231, -0.080)
Change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population with baseline eosinophil <0.3 Giga/L[b]									
LS Mean (SE)	0.10 (0.04)	0.25 (0.04)	0.22 (0.04)	0.15 (0.03)	0.23 (0.02)	0.18 (0.03)	0.22 (0.02)	0.00 (0.05)	0.13 (0.05)
LS Mean Diff vs. placebo (95% CI)		0.15 (0.04, 0.25)	0.12 (0.01, 0.22)		0.08 (0.01, 0.15)		0.04 (-0.03, 0.11)		0.13 (-0.02, 0.28)
P-value vs. placebo		0.0057	0.0262		0.0242		0.2511		0.0864

Percent change from baseline in pre-bronchodilator FEV1 at Week 12* - ITT population with baseline eosinophil <0.3 Giga/L[b]									
LS Mean (SE)	4.82 (2.16)	13.63 (2.14)	12.56 (2.06)	8.66 (2.01)	14.87 (1.38)	11.95 (1.95)	14.46 (1.39)	5.44 (3.42)	13.31 (3.67)
LS Mean Diff vs. placebo (95% CI)		8.81 (2.93, 14.69)	7.74 (1.98, 13.50)		6.21 (1.58, 10.83)		2.51 (-2.04, 7.06)		7.87 (-2.12, 17.85)
P-value vs. placebo		0.0034	0.0086		0.0086		0.2792		0.1213

CI=confidence interval; FEV1= forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error

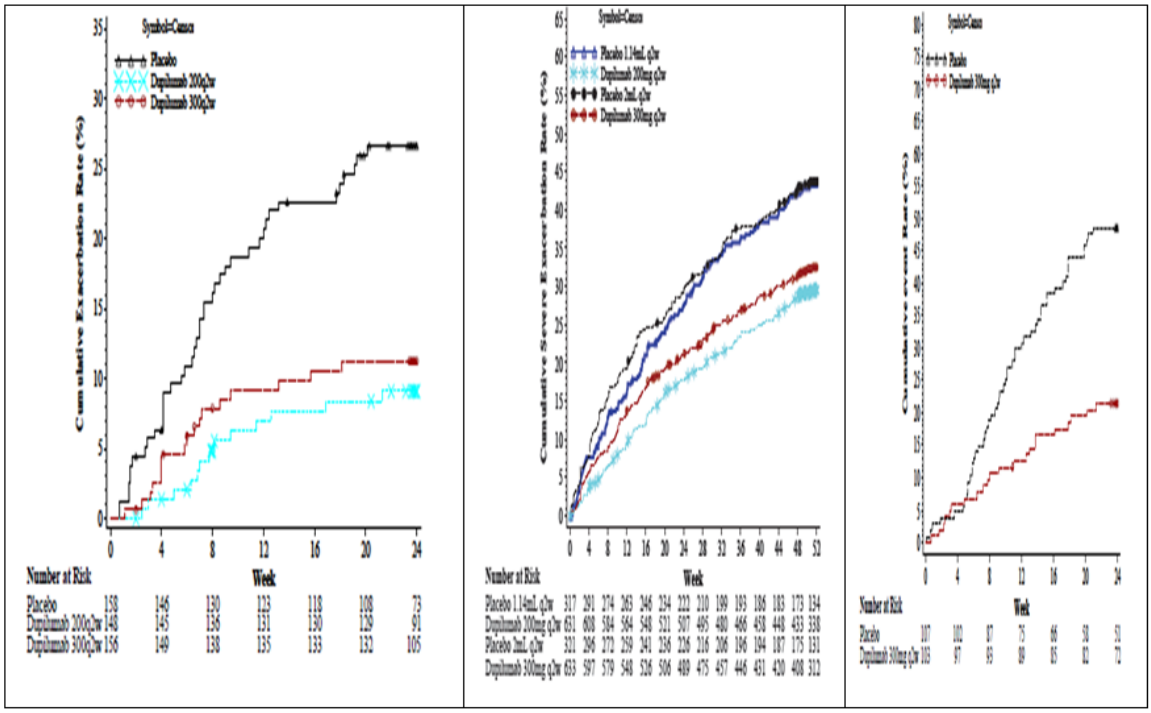
a For the results of DRI12544, only on-treatment (from first dose date to last dose date + 14 days) severe exacerbation events were included in the primary analysis. For the results of EFC13579 and EFC13691, all severe exacerbation events occurred during the placebo-controlled treatment period (from randomization up to study planned end of treatment visit/time or last contact date, whichever comes earlier, were included in the primary analysis, regardless if patient is on-treatment or not.

b For the results of DRI12544, the values collected from systemic corticosteroid start date to systemic corticosteroid end date + 30 days for each exacerbation episode were excluded and only on-treatment values up to Week 12 or Week 24 were included in the primary analysis. For the results of EFC13579 and EFC13691, all values measured up to Week 12 or week 24 were included in the primary analysis, regardless if the patient is on-treatment or not.

*: For Study EFC13691, change from baseline in pre-bronchodilator FEV1 at Week 24 was reported to allow time for OCS reduction to reach optimization.

Kaplan-Meier plot of time to first severe exacerbation event – treatment period- ITT population

DRI12544 **EFC13579** **EFC13691**



Change from baseline in ACQ-5 at Week 24 - ITT population

	DRI12544			EFC13579			
		Dupilumab/2mL		1.14mL/200mg q2w		2mL/300mg q2w	
ACQ-5	Placebo /2mL (N=158)	200 mg q2w (N=150)	300 mg q2w (N=157)	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)
Baseline							
Number	158	150	157	317	631	321	633
Mean (SD)	2.69 (0.80)	2.73 (0.82)	2.80 (0.83)	2.71 (0.73)	2.76 (0.80)	2.77 (0.77)	2.77 (0.76)
Change from baseline in ACQ-5 score at Week 24							
Number	127	134	145	296	590	297	585
Mean (SD)	-1.13 (1.01)	-1.50 (1.00)	-1.51 (1.18)	-1.06 (1.01)	-1.43 (1.05)	-1.19 (1.10)	-1.38 (1.10)
LS Mean (SE) [a]	-1.14 (0.08)	-1.49 (0.08)	-1.45 (0.08)	-1.10 (0.06)	-1.44 (0.04)	-1.21 (0.06)	-1.40 (0.04)
LS Mean Diff vs. placebo (95% CI) [a]		-0.35 (-0.57, -0.14)	-0.31 (-0.52, -0.09)		-0.35 (-0.48, -0.21)		-0.19 (-0.32, -0.05)
P-value vs. placebo [a]		0.0015	0.0049		<.0001		0.0069

Summary of treatment effect on change from baseline in ACQ-5 at Week 24 by baseline blood eosinophil subgroups - ITT population

	DRI12544			EFC13579			
		Dupilumab/2mL		1.14mL/200mg q2w		2mL/300mg q2w	
Change from baseline in ACQ-5 score at week 24	Placebo /2mL (N=158)	200 mg q2w (N=150)	300 mg q2w (N=157)	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)
Baseline blood eosinophil >= 0.15 Giga/L							
Number	100	108	118	214	412	215	417
Mean (SD)	-1.09 (1.05)	-1.53 (1.02)	-1.59 (1.21)	-1.09 (1.00)	-1.52 (1.08)	-1.18 (1.11)	-1.42 (1.11)
LS Mean (SE)[3]	-1.07 (0.09)	-1.55 (0.09)	-1.51 (0.09)	-1.09 (0.07)	-1.51 (0.05)	-1.17 (0.07)	-1.43 (0.05)
LS Mean Diff vs. placebo (95% CI)[4]		-0.48 (-0.72, -0.23)	-0.44 (-0.68, -0.20)		-0.42 (-0.58, -0.26)		-0.27 (-0.43, -0.11)
P-value vs. placebo[4]		0.0001	0.0004		<.0001		0.0011
Baseline blood eosinophil >= 0.3 Giga/L							
Number	52	59	58	140	249	129	253
Mean (SD)	-1.17 (0.97)	-1.52 (1.04)	-1.84 (1.23)	-1.10 (0.97)	-1.72 (1.05)	-1.20 (1.15)	-1.56 (1.11)
LS Mean (SE)[3]	-1.17 (0.13)	-1.59 (0.12)	-1.72 (0.13)	-1.12 (0.08)	-1.70 (0.06)	-1.19 (0.09)	-1.60 (0.06)
LS Mean Diff vs. placebo (95% CI)[4]		-0.42 (-0.76, -0.07)	-0.55 (-0.90, -0.20)		-0.58 (-0.78, -0.38)		-0.41 (-0.62, -0.21)
P-value vs. placebo[4]		0.0171	0.0021		<.0001		<.0001
Baseline blood eosinophil < 0.3 Giga/L							
Number	75	75	87	156	340	167	332
Mean (SD)	-1.10 (1.04)	-1.49 (0.98)	-1.29 (1.10)	-1.02 (1.04)	-1.22 (1.01)	-1.18 (1.07)	-1.24 (1.07)
LS Mean (SE)[3]	-1.13 (0.10)	-1.46 (0.10)	-1.29 (0.10)	-1.07 (0.08)	-1.23 (0.05)	-1.20 (0.08)	-1.22 (0.05)
LS Mean Diff vs. placebo (95% CI)[4]		-0.33 (-0.61, -0.05)	-0.17 (-0.44, 0.10)		-0.16 (-0.34, 0.02)		-0.02 (-0.20, 0.16)
P-value vs. placebo[4]		0.0201	0.2259		0.0897		0.8446

DRI12544 and EFC13579 – Summary of treatment effect on change from baseline in AQLQ global score at Week 24 by baseline blood eosinophil subgroups - ITT population

	DRI12544			EFC13579			
		Dupilumab/2mL		1.14mL/200mg q2w		2mL/300mg q2w	
Change from baseline in AQLQ global score at week 24	Placebo /2mL (N=158)	200 mg q2w (N=150)	300 mg q2w (N=157)	Placebo (N=317)	Dupilumab (N=631)	Placebo (N=321)	Dupilumab (N=633)
Baseline blood eosinophil >= 0.15 Giga/L							
Number	100	106	115	202	394	215	406
Mean (SD)	0.80 (1.06)	1.31 (1.13)	1.46 (1.28)	0.99 (1.04)	1.20 (1.16)	1.02 (1.18)	1.19 (1.12)
LS Mean (SE)[3]	0.78 (0.10)	1.27 (0.10)	1.33 (0.09)	0.94 (0.07)	1.19 (0.05)	0.95 (0.07)	1.16 (0.05)
LS Mean Diff vs. placebo (95% CI)[3]		0.49 (0.24, 0.75)	0.56 (0.30, 0.81)		0.26 (0.09, 0.42)		0.21 (0.05, 0.37)
P-value vs. placebo[3]		0.0002	<.0001		0.0022		0.0111
Baseline blood eosinophil >= 0.3 Giga/L							
Number	53	58	56	129	241	130	244
Mean (SD)	0.78 (0.99)	1.45 (1.17)	1.68 (1.30)	0.97 (1.01)	1.39 (1.15)	1.02 (1.25)	1.30 (1.15)
LS Mean (SE)[3]	0.79 (0.13)	1.46 (0.13)	1.57 (0.13)	0.96 (0.09)	1.37 (0.06)	0.98 (0.09)	1.32 (0.06)
LS Mean Diff vs. placebo (95% CI)[3]		0.67 (0.31, 1.03)	0.78 (0.42, 1.15)		0.41 (0.20, 0.62)		0.34 (0.13, 0.54)
P-value vs. placebo[3]		0.0003	<.0001		0.0001		0.0013
Baseline blood eosinophil < 0.3 Giga/L							
Number	74	74	85	152	319	164	325
Mean (SD)	0.98 (1.16)	1.09 (1.22)	1.14 (1.13)	0.94 (1.05)	0.94 (1.09)	1.01 (0.96)	1.06 (1.07)
LS Mean (SE)[3]	1.01 (0.11)	1.06 (0.11)	1.07 (0.11)	0.90 (0.08)	0.93 (0.05)	0.98 (0.07)	1.00 (0.05)
LS Mean Diff vs. placebo (95% CI)[3]		0.05 (-0.26, 0.36)	0.06 (-0.24, 0.36)		0.03 (-0.15, 0.21)		0.02 (-0.15, 0.20)
P-value vs. placebo[3]		0.7400	0.6899		0.7628		0.8131

2.5.3. Supportive studies

2.5.3.1. Study ACT11457

Study ACT11457 was a randomized, double-blind, placebo-controlled, parallel group phase 2a study comparing 300 mg SAR231893/REGN668 to placebo administered (SC) once weekly for 12 weeks in patients with persistent moderate to severe eosinophilic asthma.

A relative reduction of 87% in the primary endpoint of the proportion of patients with asthma exacerbations was observed during treatment SAR231893 (5.8%) compared with placebo (44.2%). The odds ratio was 0.077 ($p<0.0001$). The efficacy of SAR231893 in reducing the incidence of asthma exacerbations was independent of the specific subgroups examined, i.e. no significant interactions between treatment and subgroups were observed. Statistically significant differences favouring the dupilumab treatment group versus placebo were also observed for lung function parameters as measured by FEV1 and morning PEF, as well as ACQ-5 symptom scores and albuterol use. Positive trends were observed for nocturnal awakenings and a statistically significant improvement was also observed for the SNOT-22 score. Within the dupilumab group, a sustained improvement versus baseline was observed during the course of the study for all parameters, despite LABA and ICS withdrawal.

2.5.3.2. Study LTS12551

Study LTS12551 (TRAVERSE) is single-arm open-label extension (OLE) study evaluating dupilumab in patients with asthma who participated in a previous dupilumab asthma clinical study up to 96-week duration. Although the primary objective of the study is safety, the assessment of long-term efficacy is a secondary objective. The dupilumab dose tested in this study is 300 mg q2w. The approximate sample size (based on the size of the parent studies) is 2206 patients. At the time of the data cut-off date for this interim analysis, only patients from the DRI12554 study were rolled over to this study. The interim clinical study report is being written to support the safety database (see safety part of this report).

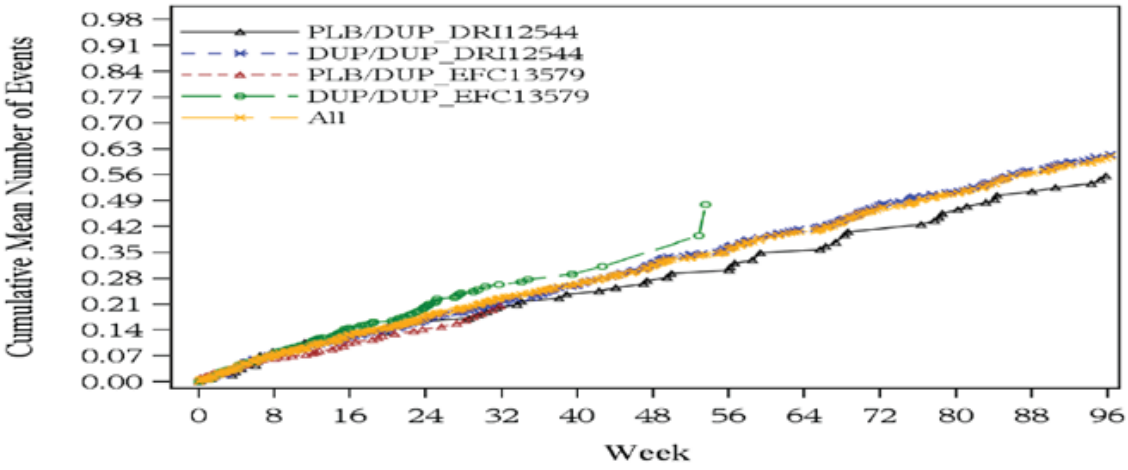
The effect of dupilumab on contributing to a low event rate of severe asthma exacerbation was sustained over the treatment period in the OLE study.

Overall, 1538 (83.4%) patients who participated from these 2 studies had no asthma exacerbation over a mean exposure to dupilumab of 634 days for patients enrolled from Study DRI12544 and 140 days for patients enrolled from Study EFC13579. The unadjusted annualized event rate was low in both the continuously treated or previously treated groups (dupilumab/dupilumab) and the newly treated group (placebo/dupilumab) in both Study DRI12544 (0.332 and 0.302, respectively) and Study EFC13579 (0.425 and 0.311, respectively). These results confirm the sustained effect of dupilumab over time.

For comparison with results in the OLE study, the unadjusted annualized events rates in the parent study EFC13691 were 1.568 for placebo and 0.646 for dupilumab 300 mg q2w.

Overall, 122 (89.1%) patients enrolled from Study EFC13691 in the OLE study had no asthma exacerbation over a mean exposure to dupilumab of 141 days. The unadjusted annualized severe exacerbation event rate of severe asthma continued to stay low (0.313) throughout the extension study. The unadjusted annualized event rate was low in both the continuously treated group (dupilumab/dupilumab) and the newly treated group (placebo/dupilumab) (0.304 and 0.319, respectively).

LTS12551 – Cumulative mean functions for the number of severe exacerbation events during the treatment period - Exposed population - Patients rolled over from DRI12544 and EFC13579 studies



FEV1 for up to 96 weeks

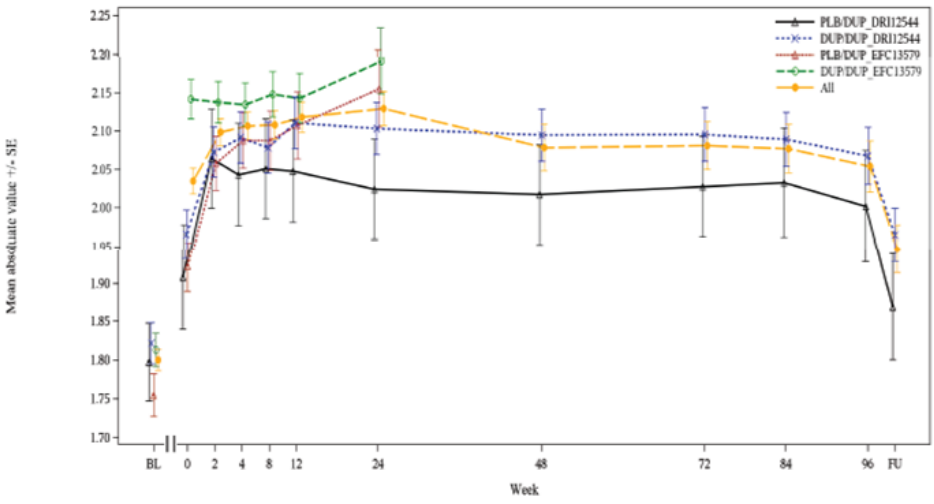
For patients enrolled from Study DRI12544, patients previously on placebo during the parent study (newly treated group) and those previously treated with dupilumab but who had a treatment interruption for at least 16 weeks (re-treated group), had similar FEV1 values at baseline of the

OLE study Week 0 (1.91 L and 1.96 L, respectively).

For patients enrolled from Study EFC13579, patients previously on placebo during the parent study (newly treated group) showed a marked improvement in FEV1 at Week 2 (2.06 L) as compared to baseline of the OLE study (1.92 L).

In the population rolled over from Study EFC13691, a sustained improvement in lung function was also demonstrated.

LTS12551 – Mean absolute FEV1 (L) over time - Exposed population - Patients rolled over from DRI12544 and EFC13579 studies

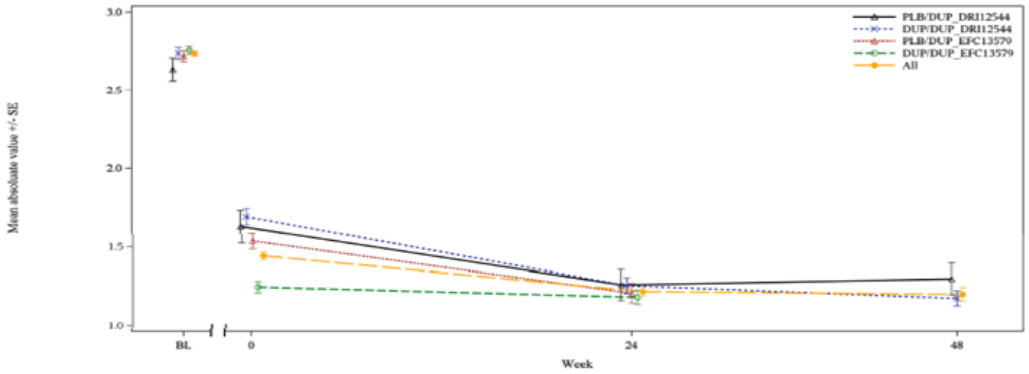


#subjects												
PLB/DUP_DRI12544	111	111	108	111	111	110	109	105	104	102	92	90
DUP/DUP_DRI12544	421	421	412	417	410	415	409	396	385	377	349	367
PLB/DUP_EFC13579	439	438	395	376	311	270	152					
DUP/DUP_EFC13579	873	871	785	726	630	547	296					
All	1844	1841	1700	1630	1462	1342	966	501	489	479	441	457

ACQ-5 over time in Study LTS12251

In patients enrolling from all 3 studies, an improvement was demonstrated in both ACQ-5 and AQLQ at Week 0 of the OLE study, compared to the baseline of the original study

LTS12551 – Mean absolute ACQ-5 over time - Exposed population - Patients rolled over from DRI12544 and EFC13579 studies



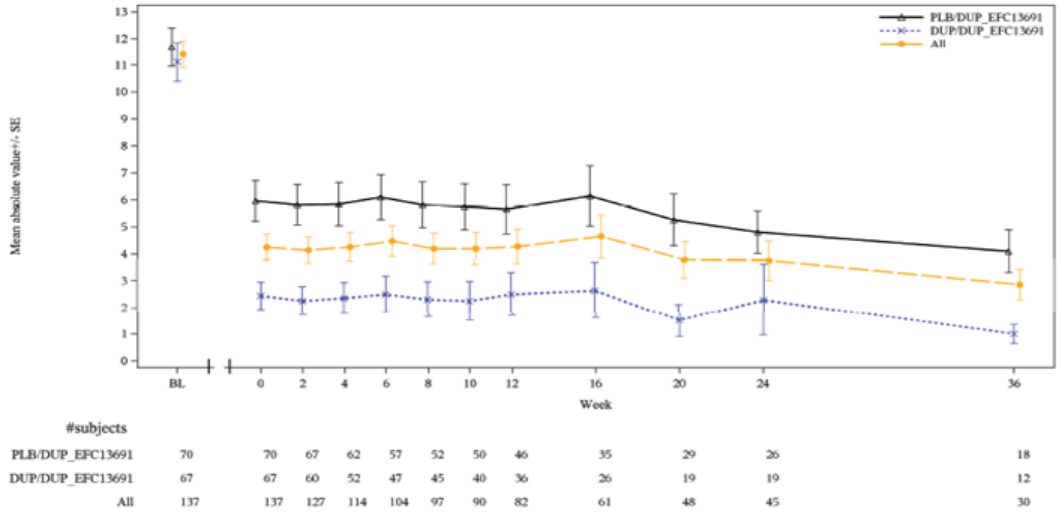
#subjects				
PLB/DUP_DRI12544	111	111	110	105
DUP/DUP_DRI12544	421	421	421	400
PLB/DUP_EFC13579	439	430	250	
DUP/DUP_EFC13579	873	841	496	
All	1844	1803	1277	505

REDUCTION IN OCS USE FOR SEVERE STEROID-DEPENDENT PATIENTS

In patients who entered the OLE study from Study EFC13691, mean reductions in OCS dose from baseline of the parent study at Week 0 were 48.8% in patients previously treated with placebo and

77.1% in patients previously treated with dupilumab. A further reduction in OCS dose was observed over time with mean reductions of 58.9% in the placebo/dupilumab group and 87.7% in the dupilumab/dupilumab group at Week 36. Mean reductions in OCS dose were sustained over time.

LTS12251 - Mean absolute OCS dose over time - Exposed population - Patients rolled over from study EFC13691



#subjects											
PLB/DUP_EFC13691	70	70	67	62	57	52	50	46	35	29	26	18
DUP/DUP_EFC13691	67	67	60	52	47	45	40	36	26	19	19	12
All	137	137	127	114	104	97	90	82	61	48	45	30

2.5.4. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development program for dupilumab in patients with asthma included three placebo-controlled Phase 2/3 pivotal studies (DRI12544, EFC13579 and EFC13691) with a total of 2888 patients and the long-term extension Study LTS12251.

Study DRI12544 was a pivotal 24-week randomized double-blind, placebo-controlled, dose ranging, Phase 2b study in patients with moderate-to-severe uncontrolled asthma to evaluate the efficacy of 4 different doses of dupilumab (200mg Q2W and Q4W and 300 mg Q2W and Q4W). The study consisted of 3 periods (Screening-, Randomized treatment and Post-treatment period) with a total duration of approximately 43 weeks. Dupilumab was used as an add-on therapy to inhaled corticosteroid / long-acting beta agonist combination therapy (ICS/LABA). Prior to screening, patients were to have been on a stable dose of moderate- or high-dose ICS/LABA for ≥1 month prior to Visit 1. Patients continued the stable dose of ICS/LABA combination product during the randomized treatment period as well as upon completion of the randomized treatment period. In addition, patients were allowed to administer salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication as needed.

Study EFC13579 (QUEST) was a randomized, double blind, placebo-controlled, parallel group study, using dupilumab or placebo as add-on therapy to ICS in combination with one or two other controller medicines (e.g., LABA, long-acting muscarinic antagonists [LAMAs], LTRA, methylxanthines). Patients were required to be on a stable dose of medium to high dose ICS in combination with a second controller medication during the study. These treatments were in line with guidelines suggested medications for GINA steps 4 asthma. Patients were allowed to use albuterol/salbutamol or levalbuterol/levosalbutamol as reliever medication as needed. Patients were to receive dupilumab 200 mg Q2W with a 400 mg loading dose, dupilumab 300 mg Q2W with a 600 mg loading dose or placebo Q2W. Due to the different volumes (1.14 ml and 2.0 ml)

administered two matching placebos were required for this study. Randomization was stratified by age (<18 years, ≥18 years), blood eosinophil count (<0.3 Giga/L, ≥0.3 Giga/L), ICS dose level (medium, high) and country at screening. The study consisted of 3 periods with a total duration of 67 to 69 weeks for each patient: screening (4±1 weeks), randomized treatment (52 weeks) and post-treatment follow-up (12 weeks) or the open-label extension study LTS12551.

Study EFC13691(Venture) was a randomized, double-blind, placebo-controlled study assessing the effect of dupilumab administered subcutaneously (SC) for a maximum of 24 weeks in patients with severe steroid-dependent asthma. Prior to the screening and throughout the Screening, Treatment, and Post-treatment periods, patients were to be on a stable dose of high dose ICS with a second or third controller medication (LABA, LTRA, theophylline, etc.). The total duration of the study (per patient) was expected to be up to 44 weeks and consisted of a Screening period/OCS Optimization phase, where investigators were instructed to adjust the OCS dose weekly according to a pre-specified titration schedule, a treatment period (24 weeks), where patients who met the eligibility criteria were randomized in a 1:1 ratio to receive dupilumab as a 600 mg loading dose followed by 300 mg Q2W or matching placebo. The treatment period consisted of an induction phase (4 weeks), a reduction phase (16 weeks) and a maintenance phase (4 weeks). In the post-treatment period (12 weeks, for patients not rolling over into a long-term open-label extension study) patients continued treatment with their stable dose of OCS and controller medication that could be modified based on their level of asthma control, as determined by the Investigator.

The patient population consisted of adults (all pivotal studies) and adolescents (EFC13579 and EFC13691) with moderate-to-severe, uncontrolled asthma despite receiving maximal standard of care treatment. All patients in these trials were on either medium or high dose inhaled steroids in combination with up to two additional controllers which typically included a long acting bronchodilator and in Study EFC13691 patients required chronic oral corticosteroids and high dose ICS.

At baseline patients had significantly impaired lung function, poor asthma control and a high risk for exacerbations. Patients enrolled in Study EFC13691 had more significant airflow limitation despite treatment with daily OCS along with high dose ICS plus additional controller medication, had a mean of 2.1 severe asthma exacerbations in the previous year. Patients were enrolled without the requirement for a specific minimum threshold for biomarker (i.e. eosinophil count and FeNO).

The pivotal studies were adequate in design, sample size and overall balanced in baseline characteristics to provide sufficient efficacy data for the planned indication of patients with moderate –to-severe asthma and patients with OCS dependent asthma. The numbers of (adult) patients providing long-term data is also sufficient.

Efficacy data and additional analyses

Dose-Response-Study DRI12544 demonstrated a statistically significant improvement in FEV1 at week 12 (primary efficacy endpoint) of the 3 highest doses of dupilumab compared to placebo.

The results were provided as an overall ITT population, and by subgroup baseline eosinophil counts >0.3 Giga/L or < 0.3 Giga/L. In the HEos ITT population, the LS mean changes in FEV1 from baseline at Week 12 were +0.18 L in the placebo group and ranged from +0.26 L (200 mg q4w dose) to +0.43 L (200 mg q2w dose) in the 4 dupilumab treatment groups. When compared with placebo, the LS mean differences were significant for dupilumab 300 mg q4w (+0.17 L; p=0.0212), 200 mg q2w (+0.26 L; p=0.0008), and 300 mg q2w (+0.21 L; p=0.0063). For later time point at 24 weeks the LS mean changes in FEV1 from baseline at Week 24 were +0.22 L in the placebo group and ranged from +0.28 L (200 mg q4w dose) to +0.38 L (200

mg q2w dose and 300mg Q2W). In the other subgroup blood eosinophil <0.3 Giga/L the LS mean changes in FEV1 from baseline at 12 weeks ranged from +0.10 L placebo to 0.18 L (300mg Q4W) to +0.25L (200mg Q2W). At week 24, LS mean changes in FEV1 from baseline ranged from 0.09 in placebo and ranged from 0.20 L (300mg Q4W) to 0.23L (both 200mg Q2w and 300mg Q2W). Compared to placebo the LS mean differences ranged from 0.10 L (300mg Q4W) to 0.14L for both 200mg q2w (p 0.0104) and 300mg Q2W (p 0.0109). Efficacy tended to be better in subgroups of patients with atopy and elevations in Th2 biomarkers at baseline. Both the 200 mg q2w and 300 mg Q2W dose regimens of dupilumab demonstrated, as compared to placebo, a significant reduction in the annualized rate of severe asthma exacerbations and a delayed time to first severe asthma exacerbation event, during the treatment period, in all 3 populations. The majority of patients did not experience a severe exacerbation during treatment. In the HEos ITT population the total number of severe exacerbation was lowest for the 200mg Q2W arm (29) and had the lowest relative risk 0.567 (difference from placebo was 28). In the subgroup with low eosinophils counts (<0.3 Giga/L) overall there was a lower rate of severe exacerbations as the events in the placebo arm in this group was 38 compared to 57 in the HEos ITT population the number of severe events was lower for all treatment groups and ranged from 10 (200mg Q2W) to 23 (300mg Q4W). The difference from placebo ranges from 18 to 28 respectively with relative risk 0.324 to 0.401 respectively. However the event rate was annualised as the duration of the study was only 24 weeks.

Overall the study supported further investigation of the 200mg and 300mg Q2W regimens.

Study EFC13579 had two primary endpoints: annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and absolute change from baseline in pre-bronchodilator FEV1 at Week 12.
Severe exacerbations were defined as per the CHMP guidelines (need for systemic CS, emergency room visit or hospitalisation due to asthma). It is agreed that this is the most important outcome in this patient population because they constitute the greatest risk to patients. The second primary endpoint was the assessment of absolute change from baseline in pre-bronchodilator FEV1 at Week 12. The key secondary efficacy endpoint was the percent change from baseline in pre-bronchodilator FEV1 at Week 12. In addition a broad range of other secondary outcomes was used, which are standard for the evaluation of chronic asthma treatment including the assessment of pulmonary function, patient-reported outcomes (including Asthma Quality of Life Questionnaire (AQLQ(S) at week 24) and the assessment of asthma control through the Asthma Control Questionnaire (ACQ-5) at week 24. The primary endpoints and secondary endpoints were analysed in subgroups of patients with normal or increased baseline eosinophil level e.g. in subgroups of patients with baseline eosinophil counts ≥0.3 Giga/L, ≥0.15 Giga/L, <0.3 Giga/L and in subgroups of patients with normal or elevated FeNO level e.g. subgroups of patients with baseline FeNO < 25ppb, < 50ppb and >50 ppb.
Overall 831 (43.7%) patients across all treatment groups had baseline blood eosinophil counts ≥0.3 Giga/L. Mean eosinophil count at baseline was 0.36 Giga/L, with a median of 0.26, and was balanced across treatment groups. Early treatment discontinuation was balanced across treatment groups, with frequencies between 10.9% and 13.4%. The treatment withdrawals and their reasons were balanced between arms. The main reason was a patient decision.

The primary endpoints were the reduction in the annualized rate of severe asthma exacerbations over 52 weeks and the change from baseline in pre-bronchodilator FEV1 at Week 12. Dupilumab at 200 mg q2w or 300 mg q2w reduced the rate of severe asthma exacerbations compared with matching placebo treatment. The adjusted annualized event rate of severe exacerbation in the ITT population during the 52-week treatment period was lower in the two dupilumab dose groups compared with their respective placebo

groups. While statistically significant, the treatment effect in relative terms (relative risk reduction approximately 46%-47% for both regimens) and absolute terms (reduction from 0.871 and 0.970 exacerbation per year observed in the placebo group to 0.456 and 0.524 exacerbation per year in the treatment groups) is considered moderate from a clinical perspective. The treatment effect in the subgroup of patients with baseline blood eosinophils ≥0.15 Giga/L and ≥0.3 Giga/L, was greater than that observed in the overall ITT. In those patients with baseline blood eosinophils ≥0.3 Giga/L, the relative reduction in annualized exacerbation rate versus placebo was 65.8% and 67.4% for the 200mg Q2W and 300mg Q2W doses, respectively. For the subpopulation with baseline eosinophil levels <0.15 Giga/L and <0.3 Giga/Lthe reduction in the annualized rate of severe exacerbations did not reach statistical significance for either dose. The percent risk reduction of severe exacerbation events with 200 mg q2w and 300 mg q2w dupilumab treatment, respectively, compared with matching placebo for each of the baseline FeNO levels were as follows: 24.8% and 20.8% for the <25 ppb subgroup, 61.4% and 55.8% for the ≥25 to <50 ppb subgroup, and 69.2% and 69.5% for the ≥50 ppb subgroup.

A significant increase in pre-bronchodilator FEV1 from baseline to Week 12 was observed in both dupilumab groups as compared to the placebo groups. The LS mean difference in absolute change from baseline to Week 12 in pre-bronchodilator FEV1 in the dupilumab dose groups versus placebo was statistically significant for both the 200 mg q2w (0.14 L, p<0.0001) and 300 mg q2w (0.13 L, p<0.0001) treatment groups.

The minimal clinically important difference in FEV1 has not been rigorously established for asthma but it is likely that change of 100-200 ml in FEV1 can be perceived by patients as clinically important. Therefore the observed difference in pre-bronchodilator FEV1 at Week 12 observed for the 200 mg Q2W group (0.14 L) and for the 300 mg Q2W group (0.13 L) in the overall ITT population over the matching placebo groups (p<0.0001) is likely to be clinically significant.

Results observed in the population of patients with baseline blood eosinophils ≥0.15 Giga/L were consistent with those observed in the ITT population whereas the treatment effect in the subpopulation of patients with baseline blood eosinophils ≥0.3 Giga/L was greater than that observed in the overall ITT population. On the other hand the effect observed in patients with baseline blood eosinophils <0.15 Giga/L and < 0.3 Giga/L was lower and not statistically significant. Patients with baseline FeNO levels 25-50 ppb and ≥50 ppb had a significantly better clinical response by exacerbation reduction and FEV1 improvement compared to placebo regardless of baseline blood eosinophils.

Consistent with the results observed for the primary endpoint, dupilumab at 200 mg q2w or 300 mg q2w increased the percent change from baseline pre-bronchodilator FEV1, at Week 12 compared with matching placebo treatment (although the difference for 200 mg dose was only nominally significant).

The improvement in pre-bronchodilator FEV1 was sustained through Week 52. The LS mean change in pre-bronchodilator FEV1 from baseline to Week 52 was 0.36 L and 0.35 L in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, compared with 0.16 L and 0.22 L in the matching placebo groups, resulting in an LS mean difference versus matching placebo of 0.20 L (p<0.0001) and 0.13 L (p<0.0001).

A post hoc analysis was conducted to examine the interaction between the baseline biomarkers of Type 2 inflammation, evaluating subgroups of patients with elevations in either one of these biomarkers compared with those who did not have an elevation in either biomarker and those who had elevations in both.

The greatest effect of dupilumab on annualized severe exacerbation event rate was observed among the patients with baseline eosinophils ≥0.15 Giga/L and FeNO ≥25 ppb, while patients with baseline eosinophils <0.15 Giga/L and FeNO <25 ppb, had very low rates of exacerbation in this study and showed no reduction in the rate of severe exacerbation in either group compared to placebo.

The greatest effect of dupilumab on change from baseline to Week 12 in pre-bronchodilator FEV1 was similar to the exacerbation rate observed among the patients with baseline blood eosinophils ≥0.15 Giga/L and FeNO ≥25 ppb. For this endpoint it was also demonstrated that the efficacy of dupilumab in patients with baseline eosinophils <0.15 Giga/L and FeNO <25 ppb was low.

The results of other secondary endpoints support some level of improvement in pulmonary functions on the dupilumab treated patients compared to placebo with no obvious differences between two dosing regimens.

Dupilumab reduced FeNO in the population of patients with an eosinophilic phenotype to concentrations considered normal indicating an -effect on airway inflammation. A higher decrease in ACQ-5 scores was observed in the dupilumab treatment groups as comparing to the placebo groups. Although the observed mean difference between groups e.g -0.35 for dupilumab/placebo 200 mg q2w and dupilumab/placebo 300 mg q2w was nominally significant, the clinical relevance of the observed differences is not clear.

In general some level of improvements of asthma symptoms such as morning/evening asthma symptom score and nocturnal awakenings were observed between treatment groups.

A difference between the dupilumab groups and matching placebo groups was not consistently apparent in relation to the use of daily puffs of rescue medications, in particular for the comparison between the 300 mg q2w group and the placebo group. In line with the ATS/ERS guidelines minimal important difference in relation to the use of rescue medication was established as 0.81 puffs/day. Such difference was never observed in the study.

In Study EFC13691 all endpoints were met. The primary endpoint was percentage reduction from baseline in OCS dose at Week 24. The mean percent reduction in OCS dose at Week 24 was greater in the dupilumab group (LS mean 70.09) compared with the placebo group (LS mean 41.85), while the median percent reduction was 100 % in the dupilumab group as compared with a reduction of 50.0% in the patients who received placebo. The LS mean difference in the percent reduction from baseline to Week 24 was statistically significant (+28.24, p<0.0001). It has to be noted that following the 4-week Induction Phase, the dupilumab group showed increasing reduction in OCS dose at each time point though week 20 in contrast to placebo where the reduction plateaued after week 16. After week 20 no further dose adjustments were permitted. The results of sensitivity analyses performed were similar to the results of the primary analysis. The results of the secondary endpoints support the results of the primary endpoint and showed, that at Week 24, the proportion of patients with ≥50% reduction in OCS dose compared with baseline was significantly greater in the dupilumab group (80%) than in the placebo group (50%).

Of clinical relevance was also the proportion of patients with a reduction in OCS dose to <5 mg/day at week 24, which was significantly greater in the dupilumab group (69%) than in the placebo group (33%). Similar were the results regarding the absolute reduction in OCS dose at Week 24. The median absolute reduction in OCS dose from baseline to Week 24 was 7.5 mg/day in patients who received dupilumab as compared with a reduction of 5.0 mg/day in the patients who received placebo. No treatment-by-subgroup interaction was observed ~~for~~ based on baseline blood eosinophil level. A difference which is likely to favour dupilumab was the imbalance in the percentage of patients with baseline ACQ-5 score >2. 72% of such patients were randomized to the placebo group and 61% to the dupilumab group.

In all pivotal studies a loading dose, which is a one-time doubling of the maintenance dose, was administered at Day 1. In Study EFC13579, a sensitivity analysis was performed to examine the influence of the loading dose on maintenance of the dupilumab treatment effect. The analyses showed that the dupilumab effects on

reducing the risk of exacerbations observed early in the study (in the first 4 or 12 weeks) were well maintained in the later part and showed a rapid improvement in FEV1 by 2-4 weeks. Therefore, the administration of a loading dose to achieve more rapid target saturation is also adequate for the asthma indication.

The LTS12551 (TRAVERSE) study was designed as a single-arm open-label extension (OLE) study to evaluate the long-term safety and tolerability of dupilumab in adult and adolescent patients with asthma who participated in a previous dupilumab asthma study. The study is still ongoing. The overall mean duration of patient participation in the study was of 310.3 days and the overall cumulative study duration of 1566.6 patient-years. All patients were treated with 300mg Q2W regardless of their previous doses. A critical GCP issue which was identified by the MAH evidence suggested that Investigational Medicinal Products kits had been tampered with after the discrepancy was identified. Of 10 patients recruited by the site, 4 were screen failures and 6 were randomized in EFC13579. The primary objective was safety however secondary objectives analysed severe exacerbations, FEV1, Asthma control and quality of life. The unadjusted annualized event rate of severe asthma exacerbation was 0.347. Most of patients who had asthma exacerbation experienced single episodes during the observation period. Among the 306 patients who experienced at least one event of severe asthma exacerbation, 29 (1.6% of the overall population) had severe asthma exacerbations that required hospitalization or emergency room visit; the unadjusted annualized event rate of severe exacerbations requiring hospitalization or emergency room visit was 0.021. A low annualized event rate of severe asthma in all patients irrespective of the ICS dose at baseline was seen. The observed annualized event rate of severe asthma exacerbations was lower in the subgroup of patients receiving medium ICS dose as compared to those receiving high ICS dose (0.254 and 0.427 in the 2 subgroups, respectively).

Overall, 122 (89.1%) patients enrolled from Study EFC13691 and who participated in the OLE study had no asthma exacerbation over a mean exposure to dupilumab of 141 days. The unadjusted annualized event rate of severe asthma exacerbation was 0.313. Subgroup analysis based on baseline blood eosinophil counts of the parent studies showed a consistent low annualized event rate of severe asthma in all patients irrespective of the baseline counts (0.224 and 0.381 in patients with blood eosinophil levels ≥0.3 Giga/L and <0.3 Giga/L, respectively).

In the overall population, a mean (SD) increase in FEV1 of +0.23 L (0.45) from baseline of the parent study was observed at Week 0 of the OLE study. A further improvement in FEV1 was observed at Week 2, with a mean (SD) increase of +0.30 L (0.44) versus baseline of the parent study. Improvement in FEV1 was sustained throughout the study duration.

Subgroup analysis based on baseline blood eosinophil counts of the parent studies showed a consistent FEV1 improvement in all patients irrespective of the baseline counts; the effect was larger in those patients with baseline blood eosinophil counts ≥0.3 Giga/L (mean changes of +0.42 L and +0.18 L from baseline of the parent study at Week 24 in patients with blood eosinophil levels ≥0.3 Giga/L and <0.3 Giga/L, respectively).

Subgroup analysis based on baseline blood eosinophil counts of the parent studies showed a consistent FEV1 improvement with the larger effect in those patients with baseline blood eosinophil counts ≥0.3 Giga/L (mean changes of +0.59 L versus +0.14 L from baseline at Week 24: in patients with blood eosinophil levels ≥0.3 Giga/L and <0.3 Giga/L, respectively). Even if more significant results are demonstrated in the subpopulation with high blood eosinophils > 0.3 Giga/L, some efficacy is also observed in patients with low blood eosinophil level. In conclusion, the efficacy is considered demonstrated in eosinophilic patients with high blood eosinophils > 0.3 Giga/L.

2.5.5. Conclusions on clinical efficacy

Both, the 200 mg Q2W and 300 mg Q2W doses of dupilumab, when added to standard of care to patients with persistent, uncontrolled, moderate-to-severe asthma, demonstrated clinically meaningful and significant effects on primary endpoints and most other secondary endpoints including patient reported outcomes. Subgroup analyses showed higher treatment effects in patients with eosinophilic asthma or in patients without elevated eosinophils at baseline but with other baseline markers for a Type 2 phenotype, in particular FeNO. Efficacy was noted across the other analysed subgroups, including adolescents and patients with different levels of severity at baseline. No reduction was seen for the rate of severe exacerbations in the subgroup of patients with blood eosinophil count <0.15 Giga/L in study EFC13579, only a small benefit with regards to lung function was observed.

Subgroup analyses demonstrated that the greatest effect of dupilumab on the rate of exacerbations and on the change in pre-bronchodilator FEV1 were seen in patients with baseline blood eosinophils ≥0.15 Giga/L and FeNO ≥25 ppb, patients with elevations in either one of these biomarkers still showed clinically meaningful effects while patients with <0.15 Giga/L and FeNO <25 ppb showed no reduction on the rate of exacerbations and only small changes in pre-bronchodilator FEV1.

These results demonstrate that dupilumab is most effective in patients with type 2 inflammation asthma characterised by raised eosinophils and/or raised FeNO to reduce the rate of annualized severe exacerbations and to improve the pre-bronchodilator FEV1. The results of the patients reported outcomes were in line the primary endpoints and showed improvement in asthma control and quality of life. Furthermore, dupilumab treatment resulted in a greater reduction in the need for oral corticoid-steroids in OCS dependent asthma patients compared to placebo.

The applicant has conducted two trials that included subpopulations of difficult to treat asthma as characterized by the persistence of symptoms. The majority of patients in both trials had signs of a type 2 inflammatory asthma when using eosinophilia and/or FeNO as biomarkers. In trial EFC13579 efficacy appeared to be driven by the subpopulation of patients with type 2 inflammatory asthma (defined by eosinophilia and FeNO) and no efficacy was observed in patients without these inflammatory characteristics.

Patients on medium and high dose ICS were included in the asthma development program. However, as stated in current treatment guidelines for severe asthma a maximally optimized treatment is mandatory for the patient population with severe asthma, which cannot be agreed for patients with medium dose ICS. The applicant mentioned that there is a ceiling effect expected with ICS and other controller medications. However, some patients may well respond to a high dose as recommended in the asthma guidelines for at least 3 to 6 months, which is the next step to optimize the treatment in patients with medium dose ICS before escalating to systemic treatment or biologics. It has also to be noted that the studies conducted (DRI12544 and EFC13579) as acknowledged by the applicant did not cover the full range of medium ICS. Therefore, the indication wording including a population on medium ICS dose was not acceptable. The indication was revised accordingly to only patients with high dose ICS.

The trial EFC13691 included patients on oral corticosteroid treatment and the majority of patients also presented with eosinophilia. Even though the interaction test was not positive for the biomarkers (eosinophilia and FeNO), the mechanism of action strongly suggests that this population is composed of patients with type 2 inflammation in this relatively small trial which is already covered in the above indication. The justification presented by the applicant for a separate part of the indication for patients on OCS treatment without biomarker is not sufficient to date. The applicant states in his responses that patients were enrolled regardless of baseline type 2 biomarkers. This cannot be fully agreed as according to the study

report submitted, enrolment of patients in study EFC13691 with blood eosinophils (count of <0.15 Giga/L) was limited to approximately 25% of total sample size to obtain a study population that would be representative of the target population. Overall, the numbers of patients receiving dupilumab with blood eosinophil level <0.15 G/L were small. From the results provided it can be seen that 102 patients were treated with dupilumab although positive effect statistically and clinically relevant effect is seen, the majority of patients had Eosinophil level greater than ≥ 0,15 G/L, only 22 patients had Eos < 0,15., therefore the evidence for non-biomarkers is considered too uncertain. Thus a separate statement in the indication for the inclusion of a population only characterized by oral glucocorticoid use is not acceptable.

2.6. Clinical safety

Patient exposure

Exposure to dupilumab in all completed/unblinded Phase 2/3 asthma studies is provided in table 3. Overall a total of 2649 patients were exposed to dupilumab of which 2136, 1553, 834, and 531 patients were exposed for ≥6 months (24 weeks), ≥1 year, ≥1.5 years, and ≥2 years (96 weeks), respectively.

Table 2: Exposure to dupilumab in completed/unblinded Phase 2/3 asthma studies

		Exposed				
Study	Dupilumab	All	>=6 months	>=1 year	>=1.5 years	>=2 years
EFC13579	200 mg q2w	631	591	510	0	0
	300 mg q2w	632	576	487	0	0
	Total	1263	1167	997	0	0
DRI12544	200 mg q4w	150	129	0	0	0
	300 mg q4w	157	140	0	0	0
	200 mg q2w	148	135	0	0	0
	300 mg q2w	156	149	0	0	0
	Total	611	553	0	0	0
EFC13691	300 mg q2w	103	100	0	0	0
ACT11457	300 mg qw	52	0	0	0	0
LTS12551	300 mg q2w[a]	1981	1067	524	488	437

		Exposed				
Study	Dupilumab	All	>=6 months	>=1 year	>=1.5 years	>=2 years
Total	200 mg q4w	150	129	0	0	0
	300 mg q4w	157	140	0	0	0
	200 mg q2w	779	726	510	0	0
	300 mg q2w[b]	2267	1592	1035	662	473
	300 mg qw	52	0	0	0	0
	Any[c]	2649	2136	1553	834	531

qw=every week, q2w=every 2 weeks, q4w=every 4 weeks

Note: To account for the visit window, >=6 month duration includes patients with exposure of at least 164 days [ie, (24*7)-4] and >=1 year duration includes patients with exposure of at least 361 days (ie, 365-4). For the purposes of this summary, 2 years is considered to be 96 weeks, ie, the original maximum planned treatment duration in the LTS12551 long-term extension study; to account for the visit window, >= 2 years duration includes patient with exposure of at least 665 days [ie, (96*7)-7]. In case a patient dies on treatment, the end of exposure is taken as the death date if it is earlier than the last dose + 14 days

a Exposure is for 300 mg q2w in the LTS12551 study only, ie, first dose of IMP in LTS12551 to last dose in LTS12551 + 14 days. Does not include exposure for patients entering LTS12551 from the ongoing, blinded PDY14192 study.

b For patients switching to 300 mg q2w in LTS12551, exposure is from first dose of IMP in LTS12551 to last dose in LTS12551 + 14 days. For patients continuing 300 mg q2w in LTS12551, exposure is from first dose of IMP in the placebo-controlled parent study to last dose in LTS12551 + 14 days, except for patients entering from DRI12544 where exposure is the sum of DRI12544 exposure plus LTS12551 exposure given the protocol defined 16 week follow-up period required before entering the extension . Patients in LTS12551 previously treated with 300 mg q2w are only counted once. Does not include exposure from patients entering LTS12551 from the ongoing, blinded PDY14192 study.

c Patients are only counted once for total dupilumab exposure duration regardless of dose/regimen. For patients coming from DRI12544, with a protocol defined 16 week follow-up period required before entering LTS12551, exposure is the sum of exposure durations from the two studies (DRI12544 and LTS12551) separately. Does not include exposure from patients entering LTS12551 from the ongoing, blinded PDY14192 study

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Safety pool (studies DRI12544 and EFC13579)

Exposure in PY in the individual safety pool studies (EFC13579 and DRI12544) and the safety pool overall is provided in Table 4. The treatment period was 24 weeks in Study DRI12544 and 52 weeks in Study EFC13579, thus exposure is greater in Study EFC13579 due to a longer treatment period and a larger number of patients in the study.

For the pooled safety population (DRI12544 and EFC13579) exposure was similar across the 3 treatment groups: 653.6 PY (dupilumab 200 mg q2w), 646.0 PY (dupilumab 300 mg q2w), and 661.7 PY (placebo).

Table 3: Patient-years exposure to investigational medicinal product by study – pooled safety population

Studies	Placebo	Dupilumab		
		200 mg q2w	300 mg q2w	Combined
EFC13579				
N=exposed	634	631	632	1263
Patient-years	591.7	588.1	576.8	1164.9
DRI12544[a]				
N=exposed	158	148	156	304
Patient-years	69.9	65.5	69.2	134.8
All				
N=exposed	792	779	788	1567
Patient-years	661.7	653.6	646.0	1299.6

a Phase 3 selected doses only, ie, 200 mg q2w and 300 mg q2w

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The median duration of treatment exposure was the same across all treatment groups, 363 days (Table 5). Given that the majority of patients were 18 to 64 years of age, were Caucasian/White, and females, exposure to study drug treatments was highest in those categories: 18 to 64 year old age category (ranging from 530.8 PY in the dupilumab 300 mg q2w group to 545.6 PY in the placebo group); Caucasian/White patients (ranging from 524.2 PY in the dupilumab 200 mg q2w group to 551.1 PY in the placebo group) and female patients (ranging from 401.8 PY in the dupilumab 300 mg q2w group to 429.4 PY in the placebo group). In patients <18 years of age, exposure to study drug was 32.1 PY for both the dupilumab 200 mg q2w and 300 mg q2w treatment groups compared with 36.5 PY for placebo.

Adolescents 12 to 17

Exposure in North America ranged from 149.3 PY in the dupilumab 300 mg q2w group to 157.0 PY in the dupilumab 200 mg q2w group, and in the European Union exposure ranged from 81.3 PY in the dupilumab 300 mg q2w group to 90.2 PY in the placebo group). Exposure for rest of world ranged from 409.0 PY in the dupilumab 200 mg q2w group to 415.7 PY in the placebo group; rest of world includes Australia, Argentina, Brazil, Colombia, Chile, Japan, Mexico, New Zealand, Russia, South Africa, South Korea, Taiwan, Turkey, and Ukraine.

Adverse events

MedDRA Terms	Adolescents (12-18 years)		Age 18-65 years number (percentage)	
	200 mg q2w	300 mg q2w	200 mg q2w	300 mg q2w
Total AEs	70.6	76.5	80.5	80.7
Serious AEs – Total	8.8	2.9	8.0	9.0
- Treatment-emergent	8.8	2.9	7.6	8.6
- Cardiac disorders	0	2.9	0.5	1.3
- Respiratory, thoracic and - mediastinal disorders	11.8	11.8	2.7	1.6

MedDRA Terms	Adolescents (12-18 years)		Age 18-65 years number (percentage)	
- Neoplasms benign, malignant and - unspecified (incl cysts and polyps)	0	0	0.9	0.6
- Infections and infestations	58.8	55.9	57.7	59.2
- Fatal (any TEAE)	0	0	0.1	0.5
- Permanent discontinuation	2.9	5.9	3.2	6.1
Infections/Infestations	0	5.6	56.6	58.6
- Herpes zoster	0	5.6	-	-
- Viral upper respiratory tract infection	5.9	29.4	17.2	16.1
- Bronchitis	11,8	5.9	10.8	11.4
- Sinusitis	2.9	0	5.1	4.1
General disorders and Administration site conditions				
- Injection site erythema	5.9	11.8	12.5	16.8
- Injection site oedema	5.9	11.8	3.5	6.1
- Injection site pruritus	2.9	2.9	4.0	5.5
- Injection site pain	8.8	2.9	3.3	3.8
Immune system disorders				
- Hypersensitivity	5.9	0	3.0	4.3
Blood and lymphatic system disorders	2.9	0	4.2	4.7
Psychiatric disorders				
Nervous system disorders			12.6	12.3
- Headache	0	0	8.1	7.2
- Dizziness	0	0	1.0	1.5

Table 1: Number (%) of patients with common TEAE(s), PT >= 2% in any treatment group, by primary SOC and PT - pooled safety population

Safety pool (Studies DRI12544 and EFC13579)

The proportion of patients who experienced any TEAE or SAE during the entire treatment period was similar in all treatment groups. The proportion of patients with TEAEs that resulted in permanent discontinuation of study drug was generally low, and was similar in the dupilumab 200 mg q2w and placebo groups (3.2% and 4.3%, respectively) and numerically higher in the dupilumab 300 mg q2w group (6.1%), mainly due to Injection site reactions. In the safety pool, a total of 5 patients had TEAEs leading to death reported in the dupilumab treatment groups (1 patient in the 200 mg q2w group and 4 patients in the 300 mg q2w group); 3 patients had TEAEs leading to death in the placebo group. None of the deaths were considered related to IMP.

n(%)	Placebo (N=792)	Dupilumab 200 mg q2w (N=779)	Dupilumab 300 mg q2w (N=788)	Dupilumab Combined (N=1567)
Patients with any TEAE	645 (81.4%)	627 (80.5%)	636 (80.7%)	1263 (80.6%)
Patients with any SAE (regardless of treatment emergent status)	64 (8.1%)	62 (8.0%)	71 (9.0%)	133 (8.5%)
Patients with any treatment emergent SAE	62 (7.8%)	59 (7.6%)	68 (8.6%)	127 (8.1%)
Patients with any treatment emergent severe AE	55 (6.9%)	53 (6.8%)	74 (9.4%)	127 (8.1%)
Patients with any TEAE leading to death	3 (0.4%)	1 (0.1%)	4 (0.5%)	5 (0.3%)
Patients with any TEAE leading to permanent treatment discontinuation	34 (4.3%)	25 (3.2%)	48 (6.1%)	73 (4.7%)

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

Safety pool (studies DRI12544 and EFC13579)

The number (%) of patients with common TEAEs (defined as TEAEs with PTs ≥2% in any treatment group) is provided in Table 9 When viewed at the SOC level, there were a few imbalances noted, some with a higher incidence of TEAEs in the dupilumab groups and others with a higher incidence in the placebo group.

The Infections and infestations SOC had the highest proportion of patients with TEAEs. The proportion of patients with infections was lower in the dupilumab 200 mg q2w and 300 mg q2w groups (56.6% and 58.6%, respectively; 57.6% for the combined group) compared with the placebo group (63.4%). The General disorders and administration site conditions SOC had the second highest proportion of patients with TEAEs (mainly due to injection site reactions). The proportion of patients with TEAEs in this SOC was higher in the dupilumab 300 mg q2w group (25.1%) compared with the dupilumab 200 mg q2w group (19.9%) and the placebo group (14.4%). Numeric differences in the TEAEs in the hepatobiliary disorders SOC among the treatment groups in the pooled safety population were driven by events in Study EFC13579: 12 (1.5%) and 18 (2.3%) patients in the dupilumab 200 mg q2w and 300 mg q2w treatment groups, respectively, and 4 (0.5%) in the placebo-treated group.

Seven cases were SAEs, 2 in the dupilumab 200 mg q2w and 5 in the dupilumab 300 mg q2w group. Of the 30 patients, none experienced liver injury and 22 patients experienced events related to gallbladder disorders (eg, Cholelithiasis, Cholecystitis, acute Cholecystitis, Cholecystitis chronic, Bile duct stone, Hyperplastic cholecystopathy, Biliary colic). Of these, 18 were females, 12 were >40 years old, 6 reported high cholesterol or other dyslipidemia, and 14 had BMI >28 kg/m2. Past medical history of cholelithiasis was reported in 2 female patients. AST/ALT were normal at the time of the event in 12 patients; >2.5 ULN in 5 patients, and not provided in 5 patients.

Alkaline phosphatase was elevated up to 2.99 x ULN in 5 patients. Serum bilirubin was normal in 15 patients; 1.3 x ULN in 1 patient, and not available in 6 patients. Six patients received no corrective treatment, 10 received medical treatment and 6 received surgical procedures. One patient discontinued treatment due to acute cholecystitis. In the other two Phase 3 studies (ie, EFC13691 and LTS12551), TEAEs in the Hepatobiliary SOC were reported in 0 and 2 patients in Studies EFC13691 and LTS12551, respectively. There were no deaths in the hepatobiliary SOC. With longer duration of exposure to dupilumab treatment in the open-label extension study (LTS12551) there was no increase in TEAEs of hepatobiliary disorders over time. A similar imbalance between dupilumab and placebo for cholelithiasis related events was not observed in the AD studies. There were no observed trends in PCSAs in the relevant laboratory values.

The most frequently reported TEAEs with an incidence ≥5% at the PT level in any of the treatment groups are provided below. The PTs listed are respective to the 3 treatment groups (dupilumab 200 mg q2w, dupilumab 300 mg q2w, and placebo).

- Injection site erythema (12.5%, 16.8%, and 5.9%)
- Viral upper respiratory tract infection (17.2%, 16.1%, and 18.1%)
- Upper respiratory tract infection (11.7%, 12.3%, and 14.4%)
- Bronchitis (10.8%, 11.4%, and 13.3%)
- Headache (8.1%, 7.2%, and 9.0%)
- Injection site oedema (3.5%, 6.1%, and 1.0%)
- Influenza (5.4%, 6.0%, and 7.1%)
- Injection site pruritus (4.0%, 5.5%, and 1.1%)
- Sinusitis (5.1%, 4.1%, and 8.3%)

Consistent with any large safety database where the overall incidence of TEAEs is similar between drug and placebo, numeric imbalances occur in both directions. As shown, TEAEs with higher frequencies in the dupilumab groups compared with placebo were Injection site erythema, Injection site oedema, and Injection site pruritus. Upper respiratory infections, Bronchitis, Headache, and Influenza were more frequently reported by patients in the placebo groups.

Table 4: Number (%) of patients with common TEAE(s), PT >= 2% in any treatment group, by primary SOC and PT - pooled safety population

Primary System Organ Class Preferred Term n(%)	Placebo (N=792)	Dupilumab 200 mg q2w (N=779)	Dupilumab 300 mg q2w (N=788)	Dupilumab Combined (N=1567)
Any class	645 (81.4%)	627 (80.5%)	636 (80.7%)	1263 (80.6%)
Infections and infestations	502 (63.4%)	441 (56.6%)	462 (58.6%)	903 (57.6%)
Viral upper respiratory tract infection	143 (18.1%)	134 (17.2%)	127 (16.1%)	261 (16.7%)
Upper respiratory tract infection	114 (14.4%)	91 (11.7%)	97 (12.3%)	188 (12.0%)
Bronchitis	105 (13.3%)	84 (10.8%)	90 (11.4%)	174 (11.1%)
Influenza	56 (7.1%)	42 (5.4%)	47 (6.0%)	89 (5.7%)
Gastroenteritis	25 (3.2%)	19 (2.4%)	32 (4.1%)	51 (3.3%)
Sinusitis	66 (8.3%)	40 (5.1%)	32 (4.1%)	72 (4.6%)
Pharyngitis	37 (4.7%)	32 (4.1%)	29 (3.7%)	61 (3.9%)
Urinary tract infection	33 (4.2%)	20 (2.6%)	23 (2.9%)	43 (2.7%)
Nasopharyngitis	13 (1.6%)	15 (1.9%)	19 (2.4%)	34 (2.2%)
Respiratory tract infection	18 (2.3%)	18 (2.3%)	17 (2.2%)	35 (2.2%)
Rhinitis	13 (1.6%)	12 (1.5%)	17 (2.2%)	29 (1.9%)
Acute sinusitis	27 (3.4%)	19 (2.4%)	11 (1.4%)	30 (1.9%)
Blood and lymphatic system disorders	17 (2.1%)	33 (4.2%)	37 (4.7%)	70 (4.5%)
Eosinophilia[a]	2 (0.3%)	21 (2.7%)	18 (2.3%)	39 (2.5%)
Nervous system disorders	118 (14.9%)	98 (12.6%)	97 (12.3%)	195 (12.4%)
Headache	71 (9.0%)	63 (8.1%)	57 (7.2%)	120 (7.7%)
Dizziness	17 (2.1%)	8 (1.0%)	12 (1.5%)	20 (1.3%)
Vascular disorders	26 (3.3%)	27 (3.5%)	23 (2.9%)	50 (3.2%)
Hypertension	12 (1.5%)	18 (2.3%)	10 (1.3%)	28 (1.8%)
Respiratory, thoracic and mediastinal disorders	129 (16.3%)	125 (16.0%)	123 (15.6%)	248 (15.8%)
Cough	24 (3.0%)	22 (2.8%)	24 (3.0%)	46 (2.9%)
Oropharyngeal pain	13 (1.6%)	25 (3.2%)	24 (3.0%)	49 (3.1%)
Rhinitis allergic	36 (4.5%)	24 (3.1%)	23 (2.9%)	47 (3.0%)
Asthma	18 (2.3%)	19 (2.4%)	7 (0.9%)	26 (1.7%)
Gastrointestinal disorders	117 (14.8%)	116 (14.9%)	115 (14.6%)	231 (14.7%)
Diarrhoea	21 (2.7%)	25 (3.2%)	21 (2.7%)	46 (2.9%)
Nausea	18 (2.3%)	7 (0.9%)	14 (1.8%)	21 (1.3%)
Musculoskeletal and connective tissue disorders	124 (15.7%)	114 (14.6%)	131 (16.6%)	245 (15.6%)
Back pain	29 (3.7%)	38 (4.9%)	37 (4.7%)	75 (4.8%)
Arthralgia	30 (3.8%)	18 (2.3%)	22 (2.8%)	40 (2.6%)
Myalgia	11 (1.4%)	9 (1.2%)	16 (2.0%)	25 (1.6%)
General disorders and administration site conditions	114 (14.4%)	155 (19.9%)	198 (25.1%)	353 (22.5%)
Injection site erythema	47 (5.9%)	97 (12.5%)	132 (16.8%)	229 (14.6%)
Injection site oedema	8 (1.0%)	27 (3.5%)	48 (6.1%)	75 (4.8%)
Injection site pruritus	9 (1.1%)	31 (4.0%)	43 (5.5%)	74 (4.7%)
Injection site pain	19 (2.4%)	27 (3.5%)	32 (4.1%)	59 (3.8%)
Injection site inflammation	1 (0.1%)	10 (1.3%)	17 (2.2%)	27 (1.7%)
Pyrexia	10 (1.3%)	8 (1.0%)	16 (2.0%)	24 (1.5%)
Injury, poisoning and procedural complications	107 (13.5%)	111 (14.2%)	125 (15.9%)	236 (15.1%)
Accidental overdose	36 (4.5%)	37 (4.7%)	36 (4.6%)	73 (4.7%)
Contusion	16 (2.0%)	17 (2.2%)	22 (2.8%)	39 (2.5%)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 20.0
n (%) = number and percentage of patients with at least one TEAE
a As per protocol, on treatment eosinophil counts >3.0 Giga/L were to be reported as AEs, even if they were not associated with symptoms.
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group.
Only PTs at least 2% in at least one group are presented.
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No differences other than those noted above were observed based on exposure adjusted data.

Treatment-emergent adverse event incidence in the dupilumab combined group was higher (≥1%) than the placebo group for the following PTs: Injection site erythema (14.6% versus 5.9%), Injection site oedema (4.8% versus 1.0%), Back pain (4.8% versus 3.7%), Injection site pruritus (4.7% versus 1.1%), Injection site pain (3.8% versus 2.4%), Oropharyngeal pain (3.1% versus 1.6%), Eosinophilia (2.5% versus 0.3%), and Injection site inflammation (1.7% versus 0.1%). Treatment-emergent AE incidence in the placebo group was higher (≥1%) than the dupilumab combined group for the following PTs: Viral upper respiratory tract infection (18.1% versus 16.7%), Upper respiratory tract infection (14.4% versus 12.0%), Bronchitis (13.3% versus 11.1%), Headache (9.0% versus 7.7%), Sinusitis (8.3% versus 4.6%), Influenza (7.1% versus 5.7%), Rhinitis allergic (4.5% versus 3.0%), Urinary tract infection (4.2% versus 2.7%), Arthralgia (3.8% versus 2.6%), Acute sinusitis (3.4% versus 1.9%), and Nausea (2.3% versus 1.3%).

Of the TEAEs listed above, an analysis of relative risk (dupilumab combined group versus placebo) based on 95% confidence intervals showed that dupilumab treatment was associated with a higher relative risk of experiencing TEAEs of Injection site erythema (RR=2.46; 95% CI 1.82-3.33), Injection site oedema (RR=4.74; 95% CI 2.30-9.77), Injection site pruritus (RR=4.16; 95% CI 2.09-8.26), Injection site inflammation (RR=13.65; 95% CI 1.86-100.24), Eosinophilia (RR=9.86; 95% CI 2.39-40.71), and Oropharyngeal pain (RR=1.91; 95% CI 1.04-3.49). Dupilumab treatment was associated with a lower relative risk of experiencing TEAEs of Sinusitis (RR=0.55; 95% CI 0.40-0.76) and acute sinusitis (RR=0.56; 95% CI 0.34-0.94), and also a lower risk of Asthma in the dupilumab 300 mg q2w group compared with placebo (RR: 0.39 (95% CI 0.16-0.93). Further information on injection site reactions and eosinophilia is provided below (AESIs and other select AE grouping events). Forest plots of the risk ratios (95% CI) of all common TEAEs (PT ≥2%) with ≥1% higher incidence in one of the groups compared to any other group for the dupilumab 200 mg q2w and 300 mg q2w treatment groups versus placebo are presented in Figure 2 and Figure 3, respectively.

Figure 2 - Forest plot of relative risk ratio of all common TEAEs (PT >= 2%) with >= 1% higher incidence in one of the groups compared to any other - dupilumab 200 mg q2w versus placebo - pooled safety population

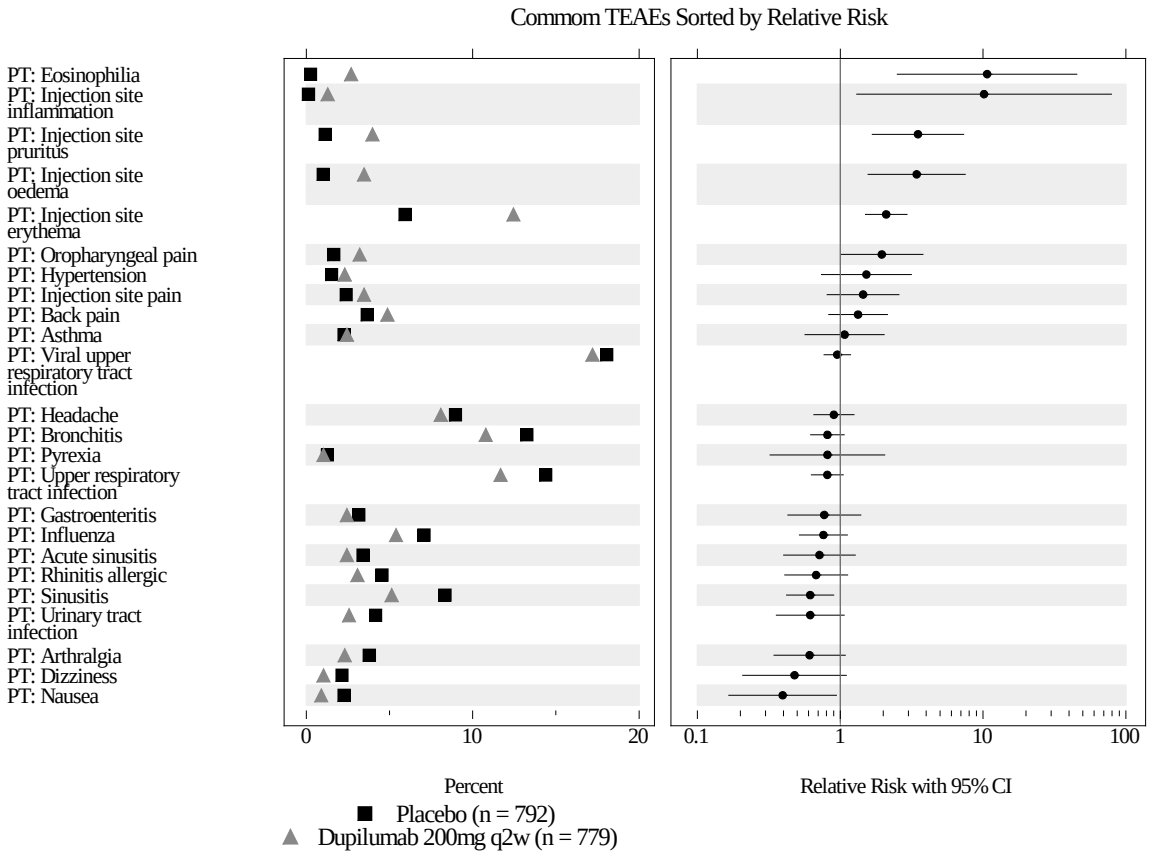

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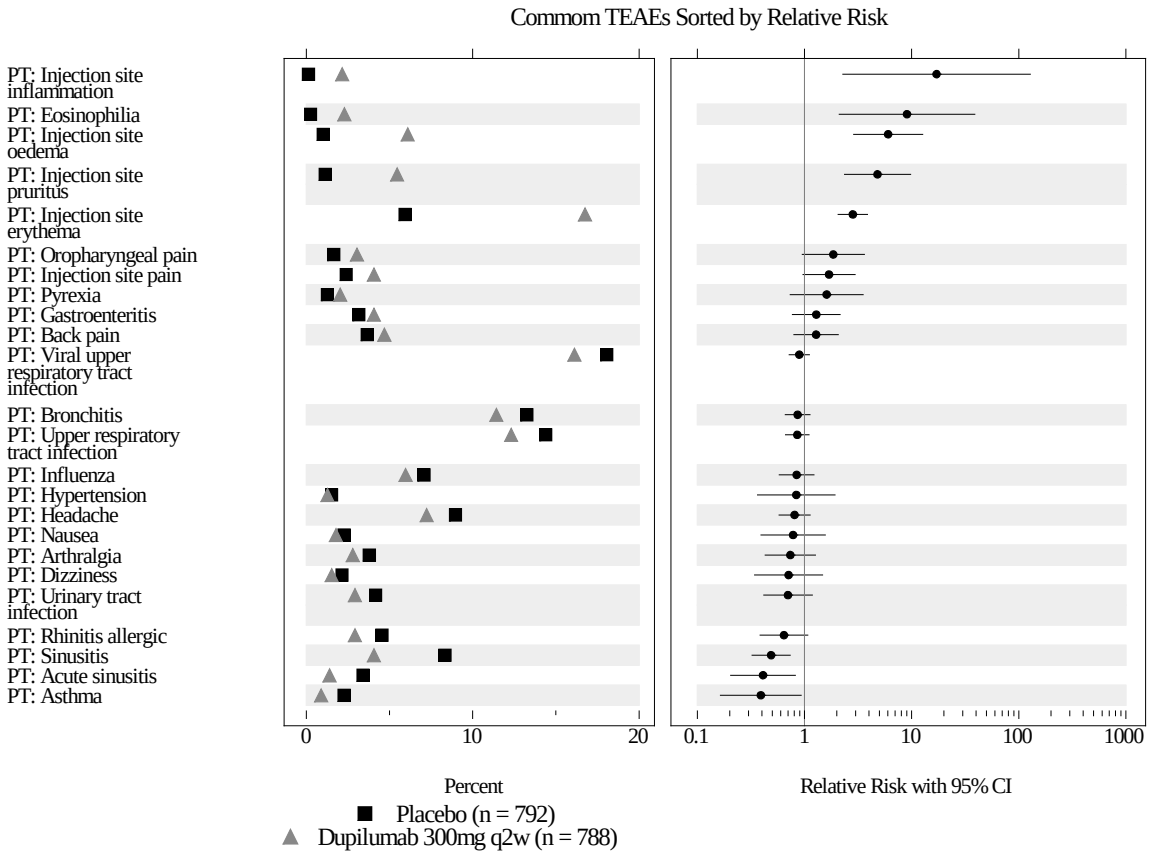
Figure 1 - Forest plot of relative risk ratio of all common TEAEs (PT >= 2%) with >= 1% higher incidence in one of the groups compared to any other - dupilumab 300 mg q2w versus placebo - pooled safety population



24 week period in the safety pool

The incidence and type of common TEAEs observed during the 24-week treatment period were consistent with those observed during the whole TEAE period. No additional safety signals were identified during the first 24 week treatment-emergent period of each study.

Summary of TEAE findings

• The proportion of patients who experienced any TEAEs during the entire treatment period (24 weeks in Study DRI12544 and 52 weeks in Study EFC13579) was similar in all treatment groups (range: 80.5% to 81.4%).

• The proportion of patients with infections was lower in the dupilumab 200 mg q2w and 300 mg q2w groups (56.6% and 58.6%, respectively) compared with the placebo group (63.4%), thus suggesting that dupilumab treatment did not increase the overall occurrence of infections.

• Based on an analysis of relative risk, dupilumab treatment (combined group) was associated with a higher risk of experiencing TEAEs of injection site reactions (erythema, edema, pruritus, and inflammation), eosinophilia, and oropharyngeal pain. Dupilumab treatment (combined group) was associated with a lower risk of experiencing TEAEs of sinusitis and acute sinusitis, and also a lower risk of Asthma in the dupilumab 300 mg q2w group.

2) Treatment-emergent adverse events by Investigator causality

Safety pool (studies DRI12544 and EFC13579)

The proportion of patients with treatment-related TEAEs (relatedness assessed by the Investigator) in the dupilumab 200 mg q2w (21.7% [169/779]) and dupilumab 300 mg q2w (24.4% [192/788]) groups was higher than for patients in the placebo group (14.0% [111/792]).
The General disorders and administration site conditions SOC had the highest proportion of patients with treatment-related TEAEs. A higher proportion of patients in the dupilumab 200 mg q2w (15.9% [124/779]) and dupilumab 300 mg q2w (19.7% [155/788]) groups reported TEAEs from this SOC compared to patients in the placebo group (9.0% [71/792]). The most frequently reported treatment-related TEAEs with an incidence ≥1% in any of the treatment groups are provided below. The PTs listed are respective to the 3 treatment groups (dupilumab 200 mg q2w, dupilumab 300 mg q2w, and placebo).

- injection site erythema (12.2%, 16.1%, and 5.8%)
- injection site edema (3.5%, 5.6%, and 1.0%)
- injection site pruritus (4.0%, 5.3%, and 1.1%)
- injection site pain (3.3%, 3.8%, and 2.3%)
- injection site inflammation (1.3%, 2.2%, and 0.1%)
- headache (0.8%, 1.4%, and 0.4%)
- eosinophilia (0.8%, 1.1%, and 0.3%)
- injection site urticaria (0.5%, 1.1%, and 0.1%)

In summary, treatment-related TEAEs (≥1%) that occurred with a higher frequency in the dupilumab treatment groups than in the placebo group were mainly injection site reactions (as listed above). None of the treatment-related TEAEs in the placebo group occurred with an incidence ≥1% with the exception of PTs of injection site reactions listed in the bullets above.

Study EFC13691
Most TEAEs were considered by the Investigator to be unrelated to the IMP. The most frequently reported TEAEs that were considered by the Investigator to be related to the IMP included injection site pain (3.9% in the dupilumab group and 0.9% of patients in the placebo group), eosinophilia (2.9% of patients in the dupilumab group and 0 patients in the placebo group), injection site erythema (1.9% of patients in both groups), injection site edema (1.9% of patients in the dupilumab group and 0.9% of patients in the placebo group), headaches and nausea (each in 0.9% of patients in the dupilumab group and 1.9% of patients in the placebo group), pruritus and injection site bruising (each in 1.9% of patients in the dupilumab group and 0% of patients in the placebo group). All other related TEAEs were reported in 1 patient only.

Study LTS12551
Patients rolled over from DRI12544 and EFC13579 studies Most TEAEs were considered by the Investigator to be unrelated to the IMP. The most frequently reported TEAEs (≥2% at PT level) that were considered by the Investigator to be related to the IMP included injection site erythema (6.8%), injection site pain (2.3%), and injection site pruritus (2.0%). Patients rolled over from EFC13691 study Most TEAEs were considered by the Investigator to be unrelated to the IMP. The following TEAEs were considered by the Investigator to be related to dupilumab and were reported by a single patient each: fibroadenoma of breast, eosinophilia, hypersensitivity, thyroiditis, headache, tendinitis, accidental overdose, and intentional overdose; and injection site erythema in 2 patients.

3) Overall summary of treatment-emergent adverse events in adolescents
In Study EFC13579, the percentage of adolescent patients with at least 1 TEAE was 70.6% and 76.5% in the dupilumab groups (200 mg q2w and 300 mg q2w, respectively) versus 76.2% and 88.9% in the matching placebo groups, with no apparent difference between dupilumab dose groups (Table 10). The most frequent TEAEs were in the SOC of infections and infestations (58.8% and 55.9% in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively versus 71.4% and 83.3% in the matching placebo groups), mainly due to viral upper respiratory tract infections (5.9% and 29.4% in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively versus 28.6% and 38.9% in the matching placebo groups).

The incidence of treatment-emergent SAEs in the adolescent population was low in all treatment groups (3 [8.8%] and 1 [2.9%] patients in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively versus 0 and 2 [11.1%] patients in the matching placebo groups). PTs in the dupilumab 200 mg q2w group were hypertension, asthma, non-infective bronchitis, and abdominal pain. PTs in the dupilumab 300 mg q2w group was gastroenteritis. PTs in the placebo for dupilumab 300 mg q2w were asthma, concussion, and road accident. No adolescent patients died during the study.

The overall treatment discontinuation rate due to TEAEs was low in all treatment groups (1 [2.9%]: neutropenia and 2 [5.9%]: Epstein Barr virus infection and neutrophil count decreased, patients in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively versus 0 and 1 [5.6%]: herpes zoster patient in the matching placebo groups). Injection site reactions were the most frequently reported AESIs (3 patients [8.8%] and 4 patients [11.8%] in the dupilumab 200 mg q2w and dupilumab 300 mg q2w groups, respectively versus 0 and 1 patient [5.6%] in the matching placebo groups).

Overall, the AE profile of dupilumab in adolescent patients with asthma was similar to the AE profile seen in adults. There were 3 adolescents randomized in EFC13691. Of these, 2 were assigned to placebo. The single adolescent who received dupilumab did not experience any AEs.

Table 5: Overview of AE profile: TEAE – Adolescents in the safety population

	1.14mL/200mg q2w		2mL/300mg q2w		Combined	
n(%)	Placebo (N=21)	Dupilumab (N=34)	Placebo (N=18)	Dupilumab (N=34)	Placebo (N=39)	Dupilumab (N=68)
Patients with any TEAE	16 (76.2%)	24 (70.6%)	16 (88.9%)	26 (76.5%)	32 (82.1%)	50 (73.5%)
Patients with any treatment emergent SAE	0	3 (8.8%)	2 (11.1%)	1 (2.9%)	2 (5.1%)	4 (5.9%)
Patients with any TEAE leading to death	0	0	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	0	1 (2.9%)	1 (5.6%)	2 (5.9%)	1 (2.6%)	3 (4.4%)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event
n (%) = number and percentage of patients with at least one TEAE
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Study R668-AD-1412 (supportive safety data)

Study Design

Study R668-AD-1412 was a Phase 2a, multicenter, open-label, ascending dose, sequential cohort study investigating the safety, tolerability, PK, immunogenicity, and efficacy of single dose and repeat doses of subcutaneous dupilumab in pediatric patients with moderate-to-severe AD (for adolescents ≥12 to <18 years of age) or severe AD (for children ≥6 to <12 years of age) that was not adequately controlled by topical treatments. The primary objective of this first pediatric study of dupilumab was to obtain safety and PK data in pediatric patients with AD. Patients received a single dose of dupilumab in Part A followed by 8 weeks of no treatment and then 4 weekly doses of dupilumab in Part B.

Disposition

A total of 40 adolescent patients (aged ≥12 to <18 years), were enrolled into the study and randomized to the 2 treatment groups (20 patients in the 2 mg/kg group and 20 patients in the 4 mg/kg group). Among adolescent patients, most (38/40 [95.0%] patients) completed treatment in both Part A and Part B. Two (5.0%) patients aged ≥12 to <18 years old were withdrawn from treatment.

Exposure and Overall Safety Findings

In adolescents, with the exception of two patients (1 in the 2 mg/kg subgroup, and 1 in the 4 mg/kg subgroup) all patients received all 5 scheduled doses of study drug. As shown in Table 11, the number of

patients experiencing at least 1 TEAE during the entire study was higher in the 4 mg/kg dose cohort than in the 2 mg/kg cohort in adolescents (16 [80.0%] versus 11 [55.0%]).

Table 6: Summary of treatment-emergent adverse events during Study R668-AD-1412 - adolescent >=12 to <18 years of age (safety analysis set)

	2 mg/kg SC (N=20)	4 mg/kg SC (N=20)	Total (N=40)
Adolescents ≥12 to <18 years of age			
Patients with at least one TEAE	11 (55.0%)	16 (80.0%)	27 (67.5%)
Patients with serious TEAEs	1 (5.0%)	1 (5.0%)	2 (5.0%)
Patients with TEAEs resulting in permanent discontinuation of study drug	0	0	0
Patients with TEAEs leading to death	0	0	0

SAF=safety analysis set, 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 observational period
The safety analysis set included all patients who received any study drug.
Source: 5.3.3.2 Study R668-AD-1412 [Table 35] and [Table 36]

Overall, dupilumab administered as single and repeated weekly doses of 2 mg/kg and 4 mg/kg for 4 weeks was generally well tolerated in both pediatric age groups included in this study. There was a higher incidence of TEAEs after administration of a single dose of 4 mg/kg in both age groups. Similarly, there was a higher incidence of TEAEs after administration of repeated weekly doses of 4 mg/kg in both age-groups. However, most of the AEs were mild in intensity, transient in nature and not related to study drug. There were no new safety signals detected with dupilumab in this pediatric population. The most common AEs reported after both single doses and repeated weekly doses were Nasopharyngitis and exacerbation of AD. Nasopharyngitis has been reported previously as one of the most common AEs in adult trials with dupilumab. The episodes of exacerbation of AD could have resulted from the study design in which patients had an 8 week gap in treatment between single dose administration during Part A and start of Part B. There were very few AEs of conjunctivitis reported in both age groups in this study.

Severe and serious adverse events and deaths

1) Severe TEAE

Safety pool (studies DRI12544 and EFC13579)

Most of the TEAEs in all treatment groups were mild to moderate in intensity. A higher proportion of patients in the dupilumab 300 mg q2w group (9.4% [74/788]) experienced severe TEAEs compared with patients in the dupilumab 200 mg q2w and placebo groups (6.8% [53/779] and 6.9% [55/792], respectively); incidence in the dupilumab combined group was 8.1%).

Overall, the most frequently reported severe TEAE was Asthma with 25 patients reporting the event: 10 patients (1.3%) in both the dupilumab 200 mg q2w group and the placebo group, and 5 patients (0.6%) in the dupilumab 300 mg q2w group.
The most frequently reported severe TEAEs in dupilumab-treated patients were mainly injection site reactions and they occurred in the dupilumab 300 mg q2w treatment group (injection site erythema (10 patients [1.3%]), injection site pruritus (6 patients [0.8%]), injection site pain (6 patients [0.8%]), injection site oedema (5 patients [0.6%]), and injection site inflammation (4 patients [0.5%]).
Severe TEAE PTs in the dupilumab 200 mg q2w group reported in 2 patients were eosinophilia and pregnancy. No PTs were reported in more than 2 patients with the exception of worsening of Asthma (10 patients), as provided above. Severe TEAE PTs in the placebo group reported in 2 patients or more were Asthma (10 patients) headache (4 patients), road traffic accident (3 patients), syncope (2 patients), breast cancer (2 patients), and pneumonia (2 patients).

Study EFC13691

Most TEAEs were mild or moderate in intensity. Severe TEAEs were reported for 9.7% in the dupilumab group versus 4.7% in the placebo group. TEAEs of severe intensity reported in at least 2 patients in any treatment group included worsening of Asthma (2.9% in the dupilumab group versus 1.9% in the placebo group) and cough (1.9% in the dupilumab group versus 0% in the placebo group).

Study LTS12551

Patients rolled over from DRI12544 and EFC13579 studies.
Most patients had TEAEs that were mild or moderate in intensity. Severe TEAEs were reported for 77 (4.2%) patients overall. The only severe TEAE that occurred with an incidence of ≥0.5% of patients overall was Asthma (0.5%)
Patients rolled over from EFC13691 study Most patients had TEAEs that were mild or moderate in intensity. Severe TEAEs were reported for 5 (3.6%) patients.

2) Deaths

Overall, in the dupilumab asthma studies, a total of 15 deaths were reported of which 13 deaths occurred during the treatment period, one of these cases had the AE onset during the treatment emergent period and died approximately 77 days after the last dose of IMP. One death occurred during the post-treatment period, and 1 death occurred during the screening period (prior to receiving IMP). The deaths are presented below.

Pooled Safety Population

The proportion of deaths was balanced between the combined dupilumab group (0.3% [n=5]) and the placebo group (0.4% [n=3]).
In the pooled safety population treatment groups, 8 patients experienced one or more TEAEs leading to death: 1 (0.1%) patient in the dupilumab 200 mg q2w group, 4 (0.5%) patients in the dupilumab 300 mg q2w group, and 3 (0.4%) patients in the placebo group. One of these cases had the AE onset during the treatment emergent period and died approximately 77 days after the last dose of IMP.

Dupilumab 200 mg q2w treatment group

• A 76-year-old female patient experienced **pulmonary embolism** on Day 311 that resulted in death on Day 354. Investigator's assessment of causality for the pulmonary embolism was not related to the IMP.

Dupilumab 300 mg q2w treatment group

• A 61-year-old female experienced a fatal cardio-respiratory arrest on Day 124. No acute asthma exacerbation was noted in the days preceding death. No autopsy was performed. The Investigator's assessment of causality for the cardio-respiratory arrest was not related to the IMP.

• A 70-year-old male experienced respiratory depression and cardio-respiratory arrest on Day 125, which required hospitalization and resulted in death on Day 145. The cardio-respiratory arrest was considered as a consequence of a severe hypoxic condition secondary to the respiratory depression. No autopsy was performed. The Investigator's assessment of causality of this event was not related to the IMP.

• A 59-year-old male patient from the US with a BMI of 41.81 kg/m2 experienced cardiac failure congestive on Day 88, ventricular tachycardia on Day 159, and multiple organ dysfunction syndrome on Day 162, which required hospitalization and resulted in death on Day 165. The Investigator's assessment of causality for these events was not related to the IMP.

• A 64-year-old female experienced hemorrhagic necrotic pancreatitis and abdominal sepsis approximately 6 months after IMP discontinuation that resulted in death on Day 350 (7 months after the last IMP administration). The Investigator's assessment of causality for these events was not related to the IMP.

Study DRI12544
2 patients in the dupilumab 300 mg q4w treatment group experienced TEAEs leading to death. Please note that these 2 deaths are not included in the pooled safety population because the patients were in the dupilumab 300 mg q4w treatment group.

• A 43-year-old male patient died due to an SAE of severe acute cardiovascular failure. The event of cardiac failure acute was considered as not related to the IMP by the Investigator.

• A 45-year-old male patient died on 10 October 2014 due to severe metastatic gastric cancer, severe bilateral subtotal organizing pneumonia, and severe acute cor pulmonale. These events were considered as not related to the IMP by the Investigator.

Study LTS12551
In Study LTS12551 – 3 patients in the dupilumab 300 mg q2w group, all of them rolled over from DRI12544 and previously treated with dupilumab in the parent study, experienced TEAEs leading to death.

• Lung cancer metastatic - this 64-year-old male former smoker patient the patient was diagnosed with lung cancer with brain metastases leading to death less than 3 months later. Final clinical diagnosis was peripheral right upper lobe lung cancer without histological confirmation.

• Adenocarcinoma gastric - this non-smoker 62-year-old male patient, previously in Study DRI12544 (dupilumab 200 mg q2w), with a past medical history of chronic gastritis, was diagnosed with adenocarcinoma of the stomach with liver metastases 1 year and 5 months after the first dose of dupilumab, and leading to death 4 months later.

• Craniocerebral injury - this 72-year-old male patient, previously in Study DRI12544 (dupilumab 200 mg q2w) was struck by motor vehicle and suffered fatal craniocerebral injury after he had completed study participation.

The cases of lung cancer metastatic and adenocarcinoma gastric were assessed by the Investigator as related to the IMP.

•Screening period: A patient, who was randomized to Study EFC13579 but did not receive IMP, died suddenly during the screening period. The causes of death were Ventricular fibrillation, Hypoxemic respiratory failure with no pulse, and Hypokalemia (not related to IMP).

• Additionally, 1 patient in the dupilumab 300 mg q2w group had an adverse event leading to death (suicide) that occurred in the post treatment period (not related to IMP).

3) Other serious adverse events

Safety pool (Studies DRI12544 and EFC13579)
The proportion of patients with treatment-emergent SAEs was comparable across the treatment groups (7.6% and 8.6% of patients in the dupilumab 200 mg q2w and dupilumab 300 mg q2w groups and 7.8% in the placebo group).

The most frequently reported treatment-emergent SAE was worsening of asthma with similar incidences in the dupilumab 200 mg q2w and placebo groups (2.1% [16 patients] and 2.3% [18 patients], respectively) and a lower incidence in the dupilumab 300 mg q2w group (0.9% [7 patients]).
After the SAE of Asthma, the next most frequently reported events were Pneumonia (5 patients in the dupilumab 300 mg q2w group and 2 patients in the placebo group), Gastroenteritis (3 patients in the dupilumab 300 mg q2w group and 1 patient in the placebo group), and Pregnancy (3 patients in the dupilumab 300 mg q2w group). Apart from asthma, the most commonly reported SAEs in the placebo group were Road traffic accident and Osteoarthritis (3 patients for each PT).
Incidence of treatment-related SAEs, as determined by the Investigator, was low in all treatment groups: 0.1% (1 patient, dupilumab 200 mg q2w), 0.8% (6 patients, dupilumab 300 mg q2w), 0.4% (7 patients, dupilumab combined), and 0.1% (1 patient, placebo). In the dupilumab 300 mg q2w group the treatment-related SAE PTs were eosinophilia (n=2), Eosinophilic pneumonia chronic (n=1), Anaphylactic reaction (n=1), Eczema (n=1), Injection site erythema (n=1), Injection site inflammation (n=1), and Injection site oedema (n=1).

Table 7: Number (%) of patients with treatment-emergent SAE(s), >=0.5% in Primary SOC in any treatment group - pooled safety population

		Dupilumab		
Primary System Organ Class	Placebo (N=792)	200 mg q2w (N=779)	300 mg q2w (N=788)	Combined (N=1567)
Any class, n (%)	62 (7.8%)	59 (7.6%)	68 (8.6%)	127 (8.1%)
Respiratory, thoracic and mediastinal disorders	20 (2.5%)	21 (2.7%)	13 (1.6%)	34 (2.2%)
Infections and infestations	11 (1.4%)	6 (0.8%)	18 (2.3%)	24 (1.5%)
Cardiac disorders	0	4 (0.5%)	10 (1.3%)	14 (0.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (0.9%)	7 (0.9%)	5 (0.6%)	12 (0.8%)
Gastrointestinal disorders	3 (0.4%)	4 (0.5%)	7 (0.9%)	11 (0.7%)
Injury, poisoning and procedural complications	9 (1.1%)	4 (0.5%)	6 (0.8%)	10 (0.6%)
Hepatobiliary disorders	1 (0.1%)	2 (0.3%)	5 (0.6%)	7 (0.4%)
Musculoskeletal and connective tissue disorders	5 (0.6%)	3 (0.4%)	3 (0.4%)	6 (0.4%)
Nervous system disorders	4 (0.5%)	3 (0.4%)	2 (0.3%)	5 (0.3%)

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term
MEDDRA 20.0
n (%) = number and percentage of patients with at least one treatment emergent SAE
Source; 5.3.5.3 ISS Appendices, Appendix 1.4.2.1

An apparent treatment group difference was noted for the cardiac disorders primary SOC, with 10 (1.3%) patients in the 300 mg q2w dupilumab group, 4 (0.5%) patients in the 200 mg q2w dupilumab group, and 0 patients in the placebo group experiencing a serious event. An apparent treatment difference for SAEs identified by the cardiac was only observed in the EFC13579 study and prompted a database search followed by an external adjudication of potential cardiovascular events.

24 Week period in the safety pool

The proportion of patients with treatment-emergent SAEs during the entire TEAE period was more than or almost double of what was observed during the 24-week treatment period in the treatment groups (7.6% versus 3.6% in the dupilumab 200 mg q2w group, 8.6% versus 4.4% in the dupilumab 300 mg q2w group, and 7.8% versus 4.4% in the placebo group) due to longer exposure period. But the incidence and type of

SAEs observed during the 24-week treatment period were consistent with those observed during the entire TEAE period. No additional safety signals were identified during the first 24 week treatment-emergent period.

Study EFC13691

Overall, 9 (8.7%) patients in the dupilumab group versus 6 (5.6%) patients in the placebo group reported at least 1 treatment-emergent SAE. With few exceptions, treatment-emergent SAEs by PT were reported by single patients only, with no pattern of distribution or imbalance among treatment groups. The most frequent SAE was asthma, reported in 6 patients (3 patients each in the dupilumab and placebo groups); each of these events was a severe asthma exacerbation requiring hospitalization. Two patients in the dupilumab group had eosinophilia compared to none in the placebo group. All other SAEs were reported in 1 patient and no apparent differences were observed between groups. No SAEs in the cardiac disorders SOC were reported during the study.

Study LTS12551

Patients rolled over from DRI12544 and EFC13579 studies. Overall, 94 (5.1%) patients reported at least 1 treatment-emergent SAE. In general, individual PTs were reported at a low frequency with no marked trend. The most frequently reported treatment emergent SAEs (PT) that occurred in ≥0.5% of patients in the overall group were asthma and pneumonia (0.6% of patients for each PT). Asthma events consisted of severe asthma exacerbation requiring hospitalization or prolongation of hospitalization, except one event that did not require hospitalization but was considered by the Investigator as medically important

In patients enrolled from Study DRI12544, 14 (12.6%) patients in the placebo/dupilumab group and 42 (10.0%) patients in the dupilumab/dupilumab group experienced at least 1 SAE during the study. A trend towards a higher incidence of asthma in patients previously treated with placebo as compared to those previously treated with dupilumab was observed in patients enrolled from Study DRI12544 (3.6% versus 0.5%).

In patients enrolled from Study EFC13579, 9 (2.1%) patients in the placebo/dupilumab group and 29 (3.3%) patients in the dupilumab/dupilumab group experienced at least 1 SAE during the study. No apparent differences were observed between groups. The incidence of serious cardiac events was low. Three patients had SAEs of atrial fibrillation. Patients rolled over from EFC13691 study Overall, 8 (5.8%) patients reported at least 1 treatment-emergent SAE; the incidence was similar between the placebo/dupilumab and dupilumab/dupilumab groups (6.0% and 5.7%, respectively). Treatment emergent SAEs by PT were reported by single patients only. No SAEs in the cardiac disorders SOC were reported during the study.

4) Adverse events of special interest (AESI)

Safety pool (Studies DRI12544 and EFC13579)

An overview of the number (%) of patients who experienced AESIs or other selected AE grouping events (by category) in the safety pool is provided in Table 13. The injection site reaction group had the highest incidence of treatment-emergent AE in all treatment groups, with higher incidences in the dupilumab 200 mg q2w and 300 mg q2w groups (16.0% [125/779] and 20.1% [158/788], respectively) compared with placebo (9.0% [71/792]). Further information on each AESI category and other AE grouping categories along with all PTs in those categories is provided in the sub-sections below, starting with Anaphylactic Reactions.

Table 8: Number (%) of patients with treatment-emergent AESIs and other selected AE grouping events by category – pooled safety population

Category	Placebo	Dupilumab		
		200 mg q2w	300 mg q2w	Combined
Preferred Term n(%)	(N=792)	(N=779)	(N=788)	(N=1567)
Any TE AESI	56 (7.1%)	52 (6.7%)	78 (9.9%)	130 (8.3%)
Anaphylactic reactions	0	2 (0.3%)	3 (0.4%)	5 (0.3%)
Hypersensitivity (medically reviewed)	20 (2.5%)	23 (3.0%)	34 (4.3%)	57 (3.6%)
Injection site reaction (serious/severe)	0	2 (0.3%)	11 (1.4%)	13 (0.8%)
Infection (serious/severe)	13 (1.6%)	8 (1.0%)	24 (3.0%)	32 (2.0%)
Parasitic infection	1 (0.1%)	0	1 (0.1%)	1 (<0.1%)
Opportunistic infection	6 (0.8%)	1 (0.1%)	3 (0.4%)	4 (0.3%)
Potentially drug-related hepatic disorder	14 (1.8%)	14 (1.8%)	12 (1.5%)	26 (1.7%)
Pregnancy	4 (0.5%)	4 (0.5%)	6 (0.8%)	10 (0.6%)
Symptomatic overdose	0	0	0	0
Any TE Other AE grouping event	103 (13.0%)	160 (20.5%)	201 (25.5%)	361 (23.0%)
Injection site reaction	71 (9.0%)	125 (16.0%)	158 (20.1%)	283 (18.1%)
Malignancy	7 (0.9%)	5 (0.6%)	5 (0.6%)	10 (0.6%)
Suicidal behavior	1 (0.1%)	0	0	0
Partner pregnancy	1 (0.1%)	1 (0.1%)	0	1 (<0.1%)
Conjunctivitis (narrow)	17 (2.1%)	10 (1.3%)	14 (1.8%)	24 (1.5%)
Conjunctivitis (broad)	24 (3.0%)	12 (1.5%)	21 (2.7%)	33 (2.1%)
Eosinophilia[a]	4 (0.5%)	28 (3.6%)	25 (3.2%)	53 (3.4%)

TE: Treatment emergent, AESI: Adverse event of special interest
MEDDRA 20.0
a As per protocol, on treatment eosinophil counts >3.0 Giga/L were to be reported as AEs, even if they were not associated with symptoms.
n (%) = number and percentage of patients with at least one TE AESI/other AE grouping event
Note: Table sorted by AESI/other AE grouping category and decreasing percentage of PT in dupilumab 300 mg q2w group within category.
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Source: 2.7.4 [Table 27].

24 Week period in the safety pool

Incidences for all AESI and events in other AE grouping categories were lower in the 24-week treatment period compared with the whole treatment period.

For the AESI category of “injection site reactions (serious/severe)” and for the other AE group of “injection site reactions”, incidences were the same or similar in the 24-week treatment period and the whole TEAE period (ie, 52 weeks). This indicates that most injection site reactions occurred during the first 24 weeks of treatment. The data below are respective to dupilumab 200 mg q2w, dupilumab 300 mg q2w, and placebo groups.

• Injection site reactions (serious/severe)
- 24-week (0.3% [2/779], 1.4% [11/788], and 0% [0/792])
- 52-week (0.3% [2/779], 1.4% [11/788], and 0% [0/792])

• Injection site reactions (other AE group)
- 24-week (15.1% [118/779], 19.3% [152/788], and 7.6% [60/792])
- 52-week (16.0% [125/779], 20.1% [158/788], and 9.0% [71/792])

Study EFC13691

An overview summary of the number (%) of patients with treatment-emergent AESIs or other selected AE grouping events by category and PT is provided in Table 14. Overall, the number (%) of patients with any

treatment-emergent AESIs was low and comparable between the dupilumab group (5 [4.9%]) and the placebo group (6 [5.6%]). More patients in dupilumab group (n=21 [20.4%]) experienced any treatment-emergent selected AE grouping events compared to placebo (n=8 [7.5%]); difference predominantly driven by "Eosinophilia TEAEs", which occurred at a higher frequency in the dupilumab group compared with the placebo group: 14 (13.6%) patients in the dupilumab group versus 1 (0.9%) in the placebo group. These events and others are further detailed by category in the sub-sections below.

Table 9: Number (%) of patients with treatment emergent AESIs and other selected AE grouping events by category in Study EFC13691- Safety population

Category n(%)	Placebo (N=107)	Dupilumab 300mg q2w (N=103)
Any TE AESI	6 (5.6%)	5 (4.9%)
Anaphylactic reaction	0	0
Hypersensitivity (medically reviewed)	1 (0.9%)	2 (1.9%)
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	0	0
Severe or serious infection	1 (0.9%)	2 (1.9%)
Parasitic infection	0	0
Opportunistic infection	0	0
Pregnancy	0	0
Potentially drug-related hepatic disorder	4 (3.7%)	1 (1.0%)
Symptomatic overdose with IMP	0	0
Symptomatic overdose with NIMP	0	0
Any TE Other AE grouping event	8 (7.5%)	21 (20.4%)
Injection site reaction	4 (3.7%)	9 (8.7%)
Malignancy	1 (0.9%)	0
Suicidal behavior	0	0
Partner pregnancy	0	0
Conjunctivitis (narrow)	1 (0.9%)	1 (1.0%)
Conjunctivitis (broad)	2 (1.9%)	1 (1.0%)
Eosinophilia[a]	1 (0.9%)	14 (13.6%)

TE: Treatment emergent, AESI: Adverse event of special interest, IMP: Investigational medicinal product, NIMP: Noninvestigational medicinal product
MEDDRA 20.0

a As per protocol, on treatment eosinophil counts >3.0 Giga/L were to be reported as AEs, even if they were not associated with symptoms.

n (%) = number and percentage of patients with at least one TE AESI/other AE grouping event
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Study LTS12551 (Patients rolled over from DRI12544 and EFC13579 studies)

An overview summary of the number (%) of patients with treatment-emergent AESIs or other selected AE grouping events by category and PT is provided in Table 15. As shown, more patients who were on placebo in the parent study reported other selected AE grouping events by category compared to patients who were on dupilumab in the parent study with difference not surprisingly driven predominantly by injection site reactions.

Patients rolled over from EFC13691 study

An overview summary of the number (%) of patients with treatment-emergent AESIs or other selected AE grouping events by category and PT is provided in Table 15. As shown, few patients reported AESIs or other

selected AE grouping events, with most events being reported by patients who were on placebo in the parent study.

Analyses of different AESI

Safety pool (studies DRI12544 and EFC13579)

Anaphylactic reaction

In the safety pool, there was a single anaphylactic reaction related to IMP, for which the causal relationship to dupilumab could not be ruled out. In total, there were 3 reports of anaphylactic reactions and 1 report of anaphylactic shock, all were SAEs.

Systemic hypersensitivity

Systemic hypersensitivity (medically reviewed) was reported for 23 (3.0%) patients in the dupilumab 200 mg q2w group, 34 (4.3%) patients in the 300 mg q2w, and 20 (2.5%) in the placebo group (Table 32). The most frequently reported events were Urticaria with similar incidences in the dupilumab 200 mg q2w and placebo groups (0.5% [4/779] and 0.6% [5/792],respectively), and a higher incidence in the dupilumab 300 mg q2w group (1.3% [10/788]); and Rash with similar incidences in the dupilumab 200 mg q2w and 300 mg q2w groups (0.6% [5/779] and 0.5% [4/788], respectively) and a lower incidence in placebo (0.1% [1/792]). Most cases of hypersensitivity were mild or moderate in severity and did not result in discontinuation of the IMP. 3 patients each, in the dupilumab dose groups, experienced TEAE of Erythema nodosum and Angioedema. None of these TEAE of Erythema nodosum and Angioedema were serious, did not lead to treatment discontinuation, resolved completely and were not related to dupilumab.

Table 32 - Summary of treatment-emergent hypersensitivity (medically reviewed) AESI - pooled safety population

		Dupilumab		
Hypersensitivity (medically reviewed)	**Placebo (N=792)**	**200 mg q2w (N=779)**	**300 mg q2w (N=788)**	**Combined (N=1567)**
Patients with any TEAE	20 (2.5%)	23 (3.0%)	34 (4.3%)	57 (3.6%)
Patients with any SAE	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Patients with any treatment-emergent SAE	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Patients with any AE leading to death	0	0	0	0
Patients with any TEAE leading to death	0	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	2 (0.3%)	2 (0.3%)	3 (0.4%)	5 (0.3%)
Patients with any TEAE related to IMP reported by investigator	2 (0.3%)	4 (0.5%)	7 (0.9%)	11 (0.7%)
Number of TEAE (Number of TEAE per 100 patient-years)	23 (3.1)	26 (3.6)	39 (5.4)	65 (4.5)
Number of patients with at least one TEAE (Number of patients with at least one TEAE per 100 patient-years)	20 (2.7)	23 (3.2)	34 (4.7)	57 (4.0)
Primary System Organ Class/ Preferred Term n(%)				
Immune system disorders				
Anaphylactic reaction	0	1 (0.1%)	2 (0.3%)	3 (0.2%)
Hypersensitivity	3 (0.4%)	0	2 (0.3%)	2 (0.1%)
Drug hypersensitivity	2 (0.3%)	1 (0.1%)	1 (0.1%)	2 (0.1%)
Anaphylactic shock	0	1 (0.1%)	0	1 (<0.1%)
Contrast media reaction	0	1 (0.1%)	0	1 (<0.1%)
Eye disorders				
Eyelid oedema	0	0	1 (0.1%)	1 (<0.1%)
Conjunctivitis allergic	0	1 (0.1%)	0	1 (<0.1%)

Hypersensitivity (medically reviewed)	Placebo (N=792)	Dupilumab 200 mg q2w (N=779)	Dupilumab 300 mg q2w (N=788)	Dupilumab Combined (N=1567)
Respiratory, thoracic and mediastinal disorders				
Allergic pharyngitis	1 (0.1%)	0	0	0
Bronchospasm	1 (0.1%)	0	0	0
Skin and subcutaneous tissue disorders				
Urticaria	5 (0.6%)	4 (0.5%)	10 (1.3%)	14 (0.9%)
Rash	1 (0.1%)	5 (0.6%)	4 (0.5%)	9 (0.6%)
Rash pruritic	3 (0.4%)	3 (0.4%)	4 (0.5%)	7 (0.4%)
Erythema nodosum	0	0	3 (0.4%)	3 (0.2%)
Dermatitis	1 (0.1%)	0	2 (0.3%)	2 (0.1%)
Dermatitis allergic	0	2 (0.3%)	2 (0.3%)	4 (0.3%)
Angioedema	0	2 (0.3%)	1 (0.1%)	3 (0.2%)
Dermatitis atopic	0	0	1 (0.1%)	1 (<0.1%)
Pruritus allergic	0	0	1 (0.1%)	1 (<0.1%)
Rash maculo-papular	0	1 (0.1%)	1 (0.1%)	2 (0.1%)
Drug eruption	1 (0.1%)	0	0	0
Idiopathic urticaria	1 (0.1%)	1 (0.1%)	0	1 (<0.1%)
Rash generalised	0	1 (0.1%)	0	1 (<0.1%)
Urticaria chronic	0	1 (0.1%)	0	1 (<0.1%)
General disorders and administration site conditions				
Face oedema	1 (0.1%)	1 (0.1%)	0	1 (<0.1%)
Investigations				
Skin test positive	0	0	1 (0.1%)	1 (<0.1%)

TE: Treatment emergent, TEAE: Treatment emergent adverse event, SAE: Serious adverse event, AE: adverse event, AESI: Adverse event of special interest, IMP: Investigational medicinal product
MEDDRA 20.0
n (%) = number and percentage of patients with at least one TEAE
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Study EFC13691
Anaphylactic reaction No cases.

Systemic hypersensitivity
Hypersensitivity (rash) was reported for 2 patients (1.9%) in the dupilumab group and 1 patient (1.0%) in the placebo group (Patient No. 013691-804-001-303). None of these events were considered SAEs. All cases of hypersensitivity were mild or moderate in severity, and all patients with hypersensitivity recovered. All 3 patients were ADA negative at all time points.

Study LTS12551 (Patients rolled over from DRI12544 and EFC13579 studies)
Anaphylactic reaction
Events identified by anaphylactic reaction SMQ algorithmic approach were reported by 3 patients overall, 1 patient was previously treated with dupilumab in Study DRI12544 and 2 were previously treated with placebo in Study EFC13579. None of the cases of anaphylactic reaction was considered to be related to dupilumab. Two cases of anaphylactic reaction were related to known triggers other than dupilumab and had negative re-challenges with IMP; the third one occurred 90 days after last IMP administration. None of the cases led to permanent discontinuation of dupilumab. All 3 patients recovered from these events.

Systemic hypersensitivity
The number of patients with hypersensitivity TEAEs was similar in the placebo/dupilumab and dupilumab/dupilumab groups for patients enrolled from Study DRI12544 (4.5% and 5.2%, respectively) and

was also similar in the placebo/dupilumab and dupilumab/dupilumab groups for patients enrolled from Study EFC13579 (0.7% and 1.0%, respectively. Most cases of hypersensitivity were mild or moderate in intensity, with only 3 cases reported as severe. Most patients with hypersensitivity recovered or were recovering, with only 2 cases reported as not recovered at the data cut-off date.

Patients rolled over from EFC13691 study

Anaphylactic reaction

No cases.

Systemic hypersensitivity

Hypersensitivity was reported by 1 (0.7%) patient that led to permanent treatment discontinuation; the patient recovered. The patient had high IgE levels (302 IU/mL at baseline of the parent study and 197 IU/mL at Visit 17). The AE was considered by the Investigator as related to the IMP. The patient was negative for ADA.

Injection site reactions

Injection site reactions (high level term)

Dupilumab is administered as a subcutaneous (SC) injection and like all biologics administered SC would be expected to cause injection site reactions (ISRs) in some patients. Data on the incidence of ISRs were collected as part of the safety program and serious or severe ISRs lasting longer than 24 hours were handled as adverse events of special interest (AESI) in the dupilumab program.

Safety pool (Studies DRI12544 and EFC13579)

Injection site reactions, identified by HLT, were reported for more patients in the combined dupilumab group (283 patients [18.1%]) than the placebo group (71 patients [9.0%]). ISRs were reported more frequently in dupilumab 300 mg q2w treated patients than 200 mg q2w treated patients (158 patients [20.1%]) and 125 patients [16.0%]. Among patients who experienced ISRs, most of the ISRs were mild (85.9%, 80.8%, and 74.7%) or moderate (12.7%, 17.6%, and 18.4%) in the placebo, dupilumab 200 mg q2w, and dupilumab 300 mg q2w group respectively and resolved spontaneously. Severe or serious ISRs were infrequent. Injection site reactions leading to discontinuation was uncommon. None of placebo patients, 5 (0.6%) patients in the dupilumab 200 mg q2w group, and 13 (1.6%) patients in the dupilumab 300 mg q2w discontinued the IMP due to an ISR. The proportion of patients experiencing ISRs (ie, HLT of injection site reactions) was highest at Week 0 (after loading dose injection) and then diminished over time. There was no discernible difference in the proportion between the two dose groups by Week 8 (5.5% versus 5.0%, respectively).

Study EFC13691

Injection site reactions were reported for 9 patients (8.7%) in the dupilumab group and 4 patients (3.7%) in the placebo group. The majority of patients (77.8% [7/9]) in the dupilumab group who experienced a local injection site reaction had a single episode while 2 patients (22.2% [2/9]) had 2 episodes; 1 (25.0% [1/4]) patient in the placebo group had at least 4 episodes. Injection site reactions occurred at every injection week and there was no apparent distribution pattern.

Study LTS12551 (Patients rolled over from DRI12544 and EFC13579 studies)

Overall, injection site reactions were reported by 165 (8.9%) patients. In patients enrolled from Study DRI12544, patients previously treated with placebo and newly treated with dupilumab in this study had a higher incidence of injection site reaction TEAEs than patients previously treated with dupilumab (29.7% versus 15.7%). In patients enrolled from Study EFC13579, patients previously treated with placebo and newly treated with dupilumab in this study had a higher incidence of injection site reaction TEAEs than patients previously treated with dupilumab (6.6% versus 4.2%). Most injection site reactions occurred before

24 weeks of treatment. No case of injection site reaction was considered as serious. Injection site reaction led to permanent discontinuation of dupilumab in only 2 patients.

5) OTHER EVENTS OF INTEREST:

Eosinophilia

Across all dupilumab studies for the treatment of asthma as well as most studies in atopic dermatitis, dupilumab-treated subjects had a greater mean initial increase from baseline in blood eosinophils compared to subjects treated with placebo. Eosinophil counts declined to near baseline levels by the end of the studies. This transient rise in blood eosinophils seen across these studies is consistent with the current understanding of the mechanism of action of dupilumab. In the atopic dermatitis clinical development program, approximately 1% of patients treated with dupilumab developed a transient blood eosinophilia of greater than 5 Giga/L. In the clinical development program for atopic dermatitis there were no serious adverse events associated with this level of elevated blood eosinophils.

In the asthma pooled safety population a greater proportion of patients in the combined dupilumab treatment group experienced transient blood eosinophilia to greater than 5 Giga/L (1.1%) compared with placebo-treated patients (0.4%). In the oral steroid withdrawal study, EFC13691, in which patients on dupilumab had greater oral corticosteroid reductions than patients on placebo, 2.9% of dupilumab and 0.9% for placebo had blood eosinophilia counts >5 Giga/L; whilst 0.15% of dupilumab treated patients in long-term safety study LTS12551 had this level of eosinophil increase at any time during the course of the study.

This increase in blood eosinophils was typically transient and generally not associated with clinically relevant adverse events and, in fact, was associated with greater efficacy on FEV1 and exacerbations when compared with the treatment group as a whole. Unlike the clinical program for AD, in the asthma program, there were rare cases of patients treated with dupilumab who experienced blood eosinophilia associated with clinical symptoms such as eosinophilic granulomatosis with polyangitiis (2 patients with EGPA, otherwise known as Churg Strauss) and 2 with eosinophilic pneumonia.

In the Phase 3 studies (EFC13579, EFC13691 and LTS12551) patients with baseline eosinophil counts >1.5 Giga/L were excluded. The effects of further increases in blood eosinophils in these patients with moderate to severe asthma were uncertain at the time these studies were initiated. In addition, investigators were instructed to report elevations of eosinophil counts ≥3.0 Giga/L as a TEAE, in order to enhance identification of these cases for close observation during study conduct.

In the pooled safety population, a total of 57 patients experienced “Eosinophilia TEAEs”, which occurred at a higher frequency in the dupilumab group compared with the placebo group:

53 (3.4%) dupilumab combined group dupilumab group versus 4 (0.5% in the placebo group. In the oral steroid withdrawal study (EFC13691), a total of 15 patients experienced “Eosinophilia TEAEs”, which occurred at a higher frequency in the dupilumab group compared with the placebo group: 14 (13.6%) patients in the dupilumab group versus 1 (0.9%) in the placebo group. The higher frequency of increase in eosinophils reported in this study, compared to other dupilumab asthma studies, is likely due to the fact that steroid tapering is a known trigger for eosinophilia and patients on dupilumab had a more extensive taper than those on placebo. In the study LTS12551 “Eosinophilia TEAEs” were reported by 28 (1.4%) patients overall.

Laboratory findings

- **HEMATOLOGY**

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for hematology parameters (hemoglobin, hematocrit, red blood cells, and platelets) over time in any of the treatment groups in the safety pool.

Study EFC13691

No relevant mean changes from baseline were observed in the dupilumab and placebo treatment groups for hematology parameters (hemoglobin, hematocrit, red blood cells, and platelets). The number of patients with PCSAs for hemoglobin, hematocrit, RBCs and platelets was generally well balanced across the dupilumab and placebo groups. No patients had a TEAE related to hematological RBC or platelet abnormalities that was considered serious or that led to permanent treatment discontinuation.

Study LTS12551

Patients rolled over from DRI12544 and EFC13579 studies:

No meaningful changes from baseline were observed for the RBC and platelets parameters over time (5.3.5.2 Study LTS12551. The overall number of patients with PCSAs for RBC and platelets was overall low and without clinically meaningful differences across the treatment groups from both studies. The most frequently reported PCSA was for hemoglobin decrease from baseline ≥2 g/dL (6.5%). No patients had PCSAs related to RBC or platelets that were considered SAEs or were TEAEs that led to treatment discontinuation.

Patients rolled over from EFC13691 study:

No meaningful changes from baseline were observed for the RBC and platelets parameters over Time. The overall number of patients with PCSAs for RBC and platelets was overall low and without clinically meaningful differences between the treatment groups. The most frequently reported PCSA was for hemoglobin decrease from baseline ≥2 g/dL (6.5%). No patients had PCSAs related to RBC or platelets that were considered SAEs or were TEAEs that led to treatment discontinuation.

Table 10: Red blood cell and platelet count: number (%) of patients with abnormalities (PCSA) during the entire TEAE period - pooled safety population

		Dupilumab		
Laboratory parameter	**Placebo**	**200 mg q2w**	**300 mg q2w**	**Combined**
PCSA criteria n/N1 (%)	**(N=792)**	**(N=779)**	**(N=788)**	**(N=1567)**
Hemoglobin				
≤ 115 g/L (Male); ≤ 95 g/L (Female) (< 100 g/L Adolescents)	15/790 (1.9%)	19/775 (2.5%)	23/784 (2.9%)	42/1559 (2.7%)
≥ 185 g/L (Male); ≥ 165 g/L (Female) (≥ 200 g/L Adolescents)	9/790 (1.1%)	7/775 (0.9%)	5/784 (0.6%)	12/1559 (0.8%)
Decrease from baseline ≥ 20 g/L	58/789 (7.4%)	73/774 (9.4%)	92/784 (11.7%)	165/1558 (10.6%)
Hematocrit				
≤ 0.37 v/v (Male); ≤ 0.32 v/v (Female) (< 0.32 v/v)	33/790 (4.2%)	38/775 (4.9%)	34/783 (4.3%)	72/1558 (4.6%)
≥ 0.55 v/v (Male); ≥ 0.5 v/v (Female) (> 0.47 v/v)	50/790 (6.3%)	39/775 (5.0%)	36/783 (4.6%)	75/1558 (4.8%)
RBC				
≥ 6 Tera/L	16/789 (2.0%)	26/775 (3.4%)	15/784 (1.9%)	41/1559 (2.6%)
Platelets				
< 100 Giga/L	6/788 (0.8%)	2/774 (0.3%)	9/784 (1.1%)	11/1558 (0.7%)
≥ 700 Giga/L	4/788 (0.5%)	1/774 (0.1%)	1/784 (0.1%)	2/1558 (0.1%)

PCSA: Potentially clinically significant abnormalities
Note: The adolescent criteria are provided in parentheses.
The number (n) represents the subset of the total number of patients who met the criterion at least once during treatment. The denominator (/N1) for each parameter within an age and treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period.
A patient who experienced one PCSA in several categories is counted only in the worst category.
For PCSA based on change from baseline, the denominator is restricted to patients having (non missing) baseline and a post-baseline value during the TEAE period.
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- **White blood cells**

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for white blood cell parameters (WBC count, neutrophils, lymphocytes, monocytes, and basophils) over time in any of the treatment groups in the safety pool. A transient increase in eosinophils was observed in the dupilumab groups compared with placebo, which was apparent from Week 4 to Week 24.

Study EFC13691

No meaningful changes from baseline were observed for most WBC parameters, with the exception of eosinophils.

Study LTS12551

Patients rolled over from DRI12544 and EFC13579 studies:

No meaningful changes from baseline were observed for the WBC parameters over time with the exception of eosinophil counts. No patients had PCSAs related to WBC that were considered SAEs. Five patients had PCSAs related to WBCs that were reported as non-serious TEAEs leading to treatment discontinuation: eosinophilia, eosinophilic granulomatosis with polyangiitis, and neutropenia.

Patients rolled over from EFC13691 study:

No meaningful changes from baseline were observed for the WBC parameters over time with the exception of eosinophil counts. No patients had PCSAs related to WBC that were considered SAEs. One patient (dupilumab 300 mg q2w) reported a non-serious TEAE of eosinophilia leading to treatment discontinuation.

Table 11: White blood cell count: number (%) of patients with abnormalities (PCSA) during the entire TEAE period - pooled safety population

Laboratory parameter PCSA criteria n/N1 (%)	Placebo (N=792)	Dupilumab 200 mg q2w (N=779)	Dupilumab 300 mg q2w (N=788)	Dupilumab Combined (N=1567)
WBC				
< 3.0 Giga/L (Non-Black); < 2.0 Giga/L (Black) (< 4.5 Giga/L)	23/790 (2.9%)	18/775 (2.3%)	29/784 (3.7%)	47/1559 (3.0%)
≥ 16.0 (> 13.5) Giga/L	20/790 (2.5%)	20/775 (2.6%)	20/784 (2.6%)	40/1559 (2.6%)
Neutrophils				
< 1.5 Giga/L (Non-Black); < 1.0 Giga/L (Black) (< 1.2 Giga/L)	64/788 (8.1%)	57/775 (7.4%)	73/784 (9.3%)	130/1559 (8.3%)
> 1 ULN (Adolescents only)	7/39 (17.9%)	7/34 (20.6%)	8/34 (23.5%)	15/68 (22.1%)
Lymphocytes				
< 0.6 Giga/L (Adolescents only)	1/39 (2.6%)	0/34	0/34	0/68
> 4.0 (> 6.0) Giga/L	99/788 (12.6%)	75/775 (9.7%)	65/784 (8.3%)	140/1559 (9.0%)
Monocytes				
> 0.7 Giga/L	209/788 (26.5%)	174/775 (22.5%)	180/784 (23.0%)	354/1559 (22.7%)
Basophils				
> 0.1 Giga/L (Adults only)	127/749 (17.0%)	130/741 (17.5%)	128/750 (17.1%)	258/1491 (17.3%)
Eosinophils				
> 0.5 Giga/L or > ULN (if ULN ≥ 0.5 Giga/L)	219/789 (27.8%)	268/775 (34.6%)	257/784 (32.8%)	525/1559 (33.7%)

PCSA: Potentially clinically significant abnormalities
Note: The adolescent criteria are provided in parentheses.
The number (n) represents the subset of the total number of patients who met the criterion at least once during treatment. The denominator (/N1) for each parameter within an age and treatment group is the number of patients who had that parameter assessed post-baseline (not missing) during the TEAE period.
A patient who experienced one PCSA in several categories is counted only in the worst category.
For PCSA based on change from baseline, the denominator is restricted to patients having (non missing) baseline and a post-baseline value during the TEAE period.
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- **CLINICAL CHEMISTRY**

Metabolic parameters

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for metabolic parameters (glucose, total cholesterol, total protein, albumin, and CPK) over time in any of the treatment groups in the safety pool.

Table 12: Metabolism: number (%) of patients with abnormalities (PCSA) during the entire TEAE period - pooled safety population

Laboratory parameter PCSA criteria n/N1 (%)	Placebo (N=792)	Dupilumab 200 mg q2w (N=779)	Dupilumab 300 mg q2w (N=788)	Dupilumab Combined (N=1567)
Glucose				
≤ 3.9 mmol/L and < LLN (< 2.7 mmol/L)	49/788 (6.2%)	40/775 (5.2%)	32/785 (4.1%)	72/1560 (4.6%)
≥ 11.1 (≥ 10) mmol/L (unfasted); ≥ 7 mmol/L (fasted)	131/788 (16.6%)	136/775 (17.5%)	141/785 (18.0%)	277/1560 (17.8%)
Glucose (US unit)				
≤ 70 mg/dL and < LLN (< 50 mg/dL)	49/788 (6.2%)	40/775 (5.2%)	32/785 (4.1%)	72/1560 (4.6%)
≥ 200 (≥ 180) mg/dL (unfasted); ≥ 126 mg/dL (fasted)	131/788 (16.6%)	136/775 (17.5%)	141/785 (18.0%)	277/1560 (17.8%)
Total cholesterol				
≥ 7.74 (≥ 6.2) mmol/L	44/788 (5.6%)	30/775 (3.9%)	48/785 (6.1%)	78/1560 (5.0%)
Total cholesterol (US unit)				
≥ 300 (≥ 240) mg/dL	44/788 (5.6%)	30/775 (3.9%)	48/785 (6.1%)	78/1560 (5.0%)
Creatine Kinase				
> 3 ULN	69/788 (8.8%)	61/775 (7.9%)	79/785 (10.1%)	140/1560 (9.0%)
> 10 ULN	11/788 (1.4%)	10/775 (1.3%)	16/785 (2.0%)	26/1560 (1.7%)
Total protein[a]				
<LLN	32/788 (4.1%)	24/775 (3.1%)	31/785 (3.9%)	55/1560 (3.5%)
>ULN	51/788 (6.5%)	61/775 (7.9%)	54/785 (6.9%)	115/1560 (7.4%)

Electrolytes

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for electrolytes (sodium, potassium, chloride, bicarbonate) over time in any of the treatment groups in the safety pool.

Renal function parameters

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for renal function parameters (creatinine, estimated creatinine clearance, uric acid, and blood urea nitrogen [BUN]) over time in any of the treatment groups in the safety pool.

Liver function parameters

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for liver function parameters (ALT, AST, ALP, and total bilirubin) over time in any of the treatment groups in the safety pool.

- **VITAL SIGNS**

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed over time in any of the treatment groups in the safety pool for vital sign parameters (SBP, DBP, HR, respiratory rate, weight, and body temperature). Mean decreases from baseline in sitting SBP and DBP over the 52 week treatment period were less than 2 mmHg for all treatment groups; no mean increases in either BP parameter were observed. Mean decreases in heart rate were less than 2.5 bpm for all treatment groups; no mean increases from baseline in heart rate were observed.

- **ELECTROCARDIOGRAM**

Safety pool (Studies DRI12544 and EFC13579)

Descriptive statistics

No relevant mean changes from baseline were observed for ECG parameters (HR, PR interval, QRS complex, QTcF, and QT interval) over time in any of the treatment groups in the safety pool.

Safety in special populations

The effect of patient baseline characteristics on the incidence of patients with any TEAE, any TEAE by primary SOC, any treatment emergent SAE, any TEAE leading to treatment discontinuation, and any AESI/other selected AE grouping by category were assessed according to pre-defined intrinsic factors (age, sex, race, weight, BMI, baseline blood eosinophil level, baseline ACQ-5, and number of prior severe asthma exacerbations). The incidence of patients for each treatment group and the relative risk (95% CI) for each dupilumab dose versus placebo was summarized for each subgroup category of intrinsic factor (eg, age categories of <18 years, 18 to 64 years, and ≥65 years).

Dupilumab treatment was not associated with an increase in the proportion of patients with TEAEs for each subgroup category as the 95% CIs of the relative risk ratios for each dupilumab treatment group (200 q2w and 300 mg q2w) versus placebo included the value of 1.0.

In summary, there was no suggestion of increased risk for TEAEs with dupilumab treatment compared with placebo in any of the intrinsic factor subgroups examined (ie, age, sex, race, weight, BMI, baseline blood eosinophil level, baseline ACQ-5 scores, and the number of prior severe asthma exacerbations at baseline).

Table 13: Incidence of patients with a TEAE and relative risk ratio (95% CI) for each dupilumab group versus placebo within each level of demographic subgroup factors - pooled safety population

		Dupilumab			Relative risk ratio (95% CI)		
Subgroups	Placebo (N=792)	200 mg q2w (N=779)	300 mg q2w (N=788)	Combined (N=1567)	dupilumab 200 mg q2w versus placebo	dupilumab 300 mg q2w versus placebo	Combined dupilumab versus placebo
Age (years)							
< 18	32/39 (82.1%)	24/34 (70.6%)	26/34 (76.5%)	50/68 (73.5%)	0.86 (0.66 , 1.12)	0.93 (0.74 , 1.18)	0.90 (0.73 , 1.10)
18-64	534/658 (81.2%)	519/640 (81.1%)	533/660 (80.8%)	1052/1300 (80.9%)	1.00 (0.95 , 1.05)	1.00 (0.94 , 1.05)	1.00 (0.95 , 1.04)
≥ 65	79/95 (83.2%)	84/105 (80.0%)	77/94 (81.9%)	161/199 (80.9%)	0.96 (0.84 , 1.10)	0.99 (0.86 , 1.12)	0.97 (0.87 , 1.09)
Age (years)							
< 18	32/39 (82.1%)	24/34 (70.6%)	26/34 (76.5%)	50/68 (73.5%)	0.86 (0.66 , 1.12)	0.93 (0.74 , 1.18)	0.90 (0.73 , 1.10)
≥ 18	613/753 (81.4%)	603/745 (80.9%)	610/754 (80.9%)	1213/1499 (80.9%)	0.99 (0.95 , 1.04)	0.99 (0.95 , 1.04)	0.99 (0.95 , 1.04)
Sex							
Male	217/274 (79.2%)	230/298 (77.2%)	219/292 (75.0%)	449/590 (76.1%)	0.97 (0.89 , 1.06)	0.95 (0.87 , 1.04)	0.96 (0.89 , 1.04)
Female	428/518 (82.6%)	397/481 (82.5%)	417/496 (84.1%)	814/977 (83.3%)	1.00 (0.94 , 1.06)	1.02 (0.96 , 1.08)	1.01 (0.96 , 1.06)

EXTRINSIC FACTORS

The incidence of any TEAE, any TEAE by primary SOC, any treatment emergent SAE, any TEAE leading to treatment discontinuation, and any AESI/other selected AE grouping by category was assessed according to the following extrinsic factors using the same methodology as described for intrinsic factors:

- Region (Asia, Latin America, Eastern Europe, Western Countries)
- Territory (North America, European Union, Rest of World)
- Territory (Japan, non-Japan)

For subgroups of region and territories, dupilumab treatment was not associated with an increase in the proportion of patients with TEAEs as the 95% CIs of the relative risk ratios for each dupilumab treatment group (200 q2w and 300 mg q2w) versus placebo included the value of 1.0.

USE IN PREGNANCY AND LACTATION

A total of 23 pregnancies were reported in asthma studies DRI12544, EFC13579, and LTS12551. No pregnancies were reported in studies EFC13691 and ACT11457. Of the 23 pregnancies, 4 pregnancies occurred in placebo patients in Study EFC13579. Of these 4, 2 pregnancies resulted in live births of normal infants, 1 pregnancy ended in ectopic pregnancy and 1 pregnancy is ongoing at the time of this report. Among the 19 pregnancies in dupilumab treated patients, 6 occurred in Study DRI12544, 10 occurred in Study EFC13579 and 3 occurred in Study LTS12551. Spontaneous abortions (SABs) occurred in 3 of 6 dupilumab treated patients in Study DRI12544 and 2 of 3 in long-term, open-label Study LTS12551. There were no SABs
reported in Study EFC13579. To date, one women in study EFC13579 delivered a baby with congenital anomaly of Turner's syndrome associated with bicuspid aortic valve (Table 22).

Table 14: Summary of pregnancy outcomes in asthma studies DRI12544, EFC13579, and LTS12551

Table 64 - Summary of pregnancy outcomes in asthma studies DRI12544, EFC13579, and LTS12551

Pregnancy outcome through 29 July 2017	DRI12544		EFC13579		LTS12551	Combined studies	
	Placebo	Dupilumab	Placebo	Dupilumab	Dupilumab	Placebo	Dupilumab
No. of pregnancies in randomized subjects	0	6	4	10	3	4	19
No. of subjects with unknown pregnancy outcome due to loss to follow up	0	0	0	0	0	0	0
No. of subjects available for pregnancy outcome	0	6	4	10	3	4	19
Elective/Induced abortion	0	1	0	2	0	0	3
Spontaneous abortion	0	3	0	0	2	0	5
Still birth (2nd trimester)	0	0	0	0	0	0	0
Still birth (3rd trimester)	0	0	0	0	0	0	0
Ectopic pregnancy	0	0	1	0	0	1	0
Ongoing pregnancy with no known malformation	0	0	1	3	0	1	3
Ongoing pregnancy with known malformation	0	0	0	0	0	0	0
Delivery - Healthy	0	2 (1 set of twins)	2	4	1	2	7 (1 set of twins)
Delivery - Unhealthy	0	0	0	1*	0	0	1
Proportion of subjects with spontaneous abortion	0%	50%	0	0%	67%	0	26.3%

* Turner's Syndrome infant

No pregnancies were reported in Study EFC13691 or in Study ACT11457.

Review of past medical history and obstetrical history in those patients who experienced SAB revealed etiologies for this event that were not related to dupilumab in 3 of 5 patients. Alternate explanations for these 3 SABs included genetic mutations associated with hypercoagulable state, which are known risk factors for pregnancy loss, prior use of infertility treatments, advanced maternal age, and twin pregnancy.

Immunological events

Incidence and characterization of Anti-dupilumab Antibodies

Anti dupilumab antibody status was determined at baseline (Day 1) and at pre-specified time points. ADA population consisted of all patients in the safety population who received any study drug and who had at least one non-missing reportable ADA result post first dose. An inverse relationship between ADA incidence and cumulative monthly dose was observed, where lower ADA incidence was associated with a higher dose. Majority of ADA responses in the dupilumab dosed groups were low titer. The frequency of high titer ADA responses, treatment boosted responses, persistent ADA responses were generally similar in the dupilumab dosed groups compared to the placebo group. The pooled ADA analysis with Studies DRI12544, EFC13579 and EFC13691 was consistent with ADA results observed in the safety pool.

Analyses for neutralizing antibodies were performed for Phase 3 studies only. In Study EFC13579 approximately 2% of all subjects at 300 mg q2w and 4.3% of all subjects at 200 mg q2w were classified as neutralizing antibody (NAb) positive, compared to 1.6% in the placebo group. Among the NAb positive patients, only 8 patients had high ADA titers (>10 000), of which 5 were in the 200 mg q2w dose group and 3 were in the 300 mg q2w dose group. In Study EFC13691 the treatment emergent positive ADA response in the OCS-sparing study (Study EFC13691) was similar to Study EFC13579 in the 300 mg q2w group (5.0%) and placebo group (4.7%), with majority being low titer responses. NAb incidence was also low with 3.0% of patients with dupilumab treatment positive for NAb.

ASSOCIATION OF ADA TO ADVERSE EVENTS

For the discussion of ADAs and adverse events, patients with treatment-emergent or treatment-boosted ADA responses were defined as ADA-positive, and patients who were ADA negative at all times or had pre-existing immunoreactivity were defined as ADA-negative (neither treatmentemergent nor treatment-boosted). Analyses of TEAEs by MedDRA primary SOC and PT were performed for subgroups of patients based on ADA response status. More focused analyses evaluated association of anaphylaxis, hypersensitivity, and serious or severe (lasting more than 24 hours) injection site reactions by ADA response status. In addition, the occurrence of these TEAEs was evaluated in patients with a high titer (>10 000) response.

The limited numbers of patients with Nab responses in Studies EFC13579 and EFC13691 do not allow for any statistical approach to assess the impact of NAb on TEAEs. However, manual review of cases did not identify any meaningful associations.

Overview of TEAEs in the Safety pool (studies DRI12544 and EFC13579)

Overall, comparison of the frequencies of TEAEs by primary SOC and ADA status did not show meaningful differences between the ADA positive and ADA negative group, except for a numerical difference between the incidence of ISRs. The incidences of experiencing at least 1 TEAE were similar between treatment groups and ADA response status. Of all the TEAEs listed in the table, only injection site erythema and injection site pruritis showed a numerical difference greater than ≥10 % between ADA positive and ADA negative group. However, the number of patients with treatment emergent ADA who experienced at least 1 TEAE in all treatment groups was small and is even smaller at the individual TEAE level.

In the dupilumab 300 mg q2w group, incidence of severe TEAEs was higher in ADA positive patients than in ADA negative patients: 16.4% (10/61) versus 8.6% (62/720) this was driven primarily by severe injection site reactions. Severe TEAEs were similar in proportion in the ADA positive 7.3% (7/96)) versus the ADA negative 6.6% (45/677) population in the dupilumab 200 mg q2w group. Overall these TEAE rates were similar to those observed in the placebo group. Incidence of SAEs in the dupilumab 300 mg q2w group was numerically higher in ADA positive patients than in ADA negative patients (14.8% (9/61) versus 7.9% (57/720]), and was not driven by any particular PT. However, the number of patients who experienced an SAE and exhibited ADA positive response was very small and therefore no clear association can be established. A higher percentage of ADA positive patients 13.1% (8/61) discontinued treatment compared to ADA negative patients 5.1% (37/720) in the dupilumab 300 mg q2w group. In the ADA positive group 4 out of 8 patients discontinued treatment due to injection site reactions. Incidence of treatment-emergent AEs

leading to permanent discontinuation of treatment was low and similar between ADA positive and ADA negative patients in the dupilumab 200 mg q2w group (5.2% [5/96] and 3.0% [20/677]).

Study EFC13691

Analysis of the potential association between treatment-emergent ADA response and the incidence of TEAEs was limited by the small number of ADA-positive patients (N=5) in the dupilumab group in this study. Only 3 of these 5 patients exhibited high titers (>10 000). Of these 5 ADA positive patients, only 3 had TEAEs of which none were hypersensitivity reactions and none of these led to treatment discontinuation. Two patients with an AESI of hypersensitivity and 13 other patients who experienced ISRs were all ADA negative. The review of the results of the subgroup analyses based on ADA response status and AEs showed that presence of ADA response did not appear to be associated with any safety findings in this study.

Study LTS12551

Patients rolled over from DRI12544 and EFC13579 studies:

Overall, 69 of the 90 (76.7%) treatment-emergent ADA-positive patients and 832 of the 1195 (69.5%) ADA-negative patients had at least 1 TEAE during the study. The most frequently affected SOCs in the ADA-positive population were similar to that observed in the overall safety population and no differences in the type of TEAEs was noted between ADA-positive and ADA-negative patients.

No particular pattern of TEAEs was found among the 5 patients with high (>10 000) ADA titer. Four of the 5 patients experienced TEAEs; none of which were serious or led to permanent treatment discontinuation. Four of the 90 (4.4%) patients with treatment-emergent ADA responses versus 32 of 1195 (2.7%) ADA-negative patients experienced hypersensitivity. No association was observed between persistent ADA response and hypersensitivity reactions. Three other patients experienced anaphylactic reactions. One of these patients was ADA negative at time of the AE onset, however, later developed a low titer transient ADA response. The other 2 patients were ADA negative. None of the patients who exhibited persistent ADA response or high titers (>10 000) experienced any anaphylactic reaction.

Overall, 10 of 90 (11.1%) of the treatment-emergent ADA positive patients and 136 of 1195 (11.4%) of the ADA negative patients had injection site reactions. Of the 10 ADA-positive patients who had injection site reactions, 6 exhibited persistent ADA response, however, none of these events were considered serious or resulted in permanent treatment discontinuation.

Patients rolled over from EFC13691 study:

There were a total of 4 treatment-emergent ADA-positive patients. Three of these 4 treatment-emergent ADA-positive patients and 37 of the 69 ADA-negative patients had at least 1 TEAE during the study. None of the 4 treatment-emergent ADA-positive patients experienced hypersensitivity or injection site reactions. Neutralizing antibody responses do not appear to have any association with hypersensitivity or injection site reactions, as the only patient who was NAb positive did not experience hypersensitivity reaction or injection site reactions. This patient experienced some TEAEs and also exhibited high (>10 000) ADA titer. However, all of these TEAEs were non-serious and did not lead to permanent treatment discontinuation.

Overall, the incidence of treatment emergent ADA was generally low in all dupilumab treated groups. High titer responses were uncommon (<1%) in the safety pool. Of the patients with treatment emergent high ADA titer, none reported serious TEAEs. Comparison of TEAEs in patients by ADA status in safety pool showed that the clinically relevant events observed at a higher frequency in ADA positive versus ADA negative subgroup, were injection site reactions (injection site erythema and injection site pruritus). Only in the dupilumab 300 mg q2w treated group, some ADA positive patients discontinued treatment due to ISRs, compared to ADA negative patients. Overall, hypersensitivity reactions did not show a clear temporal association with presence of ADA responses. There was one anaphylactic reaction considered to be drug related and this case was not associated with a treatment emergent ADA response.

Safety related to drug-drug interactions and other interactions

No data available.

Discontinuation due to AES

Adverse events leading to permanent treatment discontinuation

Safety pool (Studies DRI12544 and EFC13579)

The proportion of patients who had at least 1 TEAE leading to permanent study drug discontinuation was low (3.2% and 6.1% in the dupilumab 200 mg q2w and 300 mg q2w groups, respectively, and 4.3% in the placebo group).

Based on 100 patient-year data, the number of patients who permanently discontinued treatment due to one or more TEAEs was: 3.5 (dupilumab 200 mg q2w), 6.8 (dupilumab 300 mg q2w) and 4.7 (placebo).

The most frequently reported TEAEs that led to study discontinuation in the dupilumab 200 mg q2w and dupilumab 300 mg q2w treatment groups were injection site erythema (0.5% [4 patients] and 1.5% [12 patients]), injection site oedema (0.1% [1 patient] and 0.9% [7 patients]), injection site pruritus (0.3% [2 patients] and 0.9% [7 patients]), injection site inflammation (0.0% and 0.6% [5 patients]), and injection site pain (0.1% [1 patient] and 0.6% [5 patients]); no placebo-treated patients reported discontinuations due to these PTs. In the placebo treatment group, the most frequently reported TEAEs leading to discontinuation in 2 patients or more and with a frequency greater than in the dupilumab groups were herpes zoster (0.4% [3 patients] versus 0.0% in the both dupilumab groups), breast cancer (0.3% [2 patients] versus 0.0% in the both dupilumab groups), and rash pruritic (0.3% [2 patients] versus 0.1% [1 patient] in the dupilumab 200 mg q2w group]).

The majority of patients in the dupilumab treatment groups who permanently discontinued treatment due to a TEAE did so within the first 13 weeks of treatment: 60% (15 of 25 patients) for the dupilumab 200 mg q2w group and 54.2% (26 of 48 patients) in the dupilumab 300 mg q2w group, compared with 35.3% (12 of 34 patients) in the placebo group.

24 Week period in the safety pool

As described above (discontinuation rates by exposure interval in the pooled safety population), the majority of the dupilumab-treated patients who permanently discontinued treatment due to a TEAE did so within the first 13 weeks of the study. The most frequently reported TEAEs that led to study discontinuation in the dupilumab treatment groups were the same TEAEs and with the identical frequency as in the 52 week data.

Study EFC13691

The overall discontinuation rate due to TEAEs was low: 1 (1.0%) patient in the dupilumab group versus 4 (3.7%) patients in the placebo group. All TEAEs leading to permanent treatment discontinuation at PT level were reported by 1 patient each: arthralgia in the dupilumab group; gastrointestinal stromal tumour, eosinophilia, adrenal insufficiency, and asthmatic crisis in the placebo group.

Study LTS12551

Patients rolled over from DRI12544 and EFC13579 studies:

The overall rate of treatment discontinuation due to TEAEs was low (2.1%). Most of TEAEs leading to permanent treatment discontinuation at PT level were reported by 1 patient each. The following TEAEs leading to treatment discontinuation were reported by 2 patients each: eosinophilia, neutropenia, urticaria, injection site erythema, and injection site pain.

Patients rolled over from EFC13691 study:

The overall rate of treatment discontinuation due to AE was low (2.2%). Three patients previously treated with dupilumab, versus none receiving placebo in the parent study, experienced AEs leading to permanent treatment discontinuation. The PTs were eosinophilia, hypersensitivity, and tendinitis.

WITHDRAWAL AND REBOUND

Post-treatment AE incidence was low in all treatment groups: 2.7% (dupilumab 200 mg q2w) 3.6% dupilumab 300 mg q2w), and 2.1% (placebo). No PT had an incidence ≥1%. The most frequently reported post-treatment AEs (all with low incidences) were viral upper respiratory tract infection (0.3%, 0.9%, and 0.4%, respectively), bronchitis (0.4% for all treatment groups), and upper respiratory tract infection (0.6%, 0.4%, and 0.0%, respectively). Based on a review of post-treatment AEs in the pooled safety population and the supportive safety studies, no TEAEs were observed that are suggestive of rebound associated with cessation of dupilumab treatment and in particular, no rebound of asthma symptoms or lung dysfunction to above baseline levels.

2.6.1. Discussion on clinical safety

To date, a total of 2649 patients were exposed to dupilumab during all conducted phase 2/3 asthma studies. The safety pool derived from the two pivotal studies (*QUEST and DRI12544*) comprises 2359 patients of which 1567 received dupilumab and 792 were placebo-treated.

The clinical development program for patients with moderate to severe persistent asthma comprises 7 studies; of these, data from 5 Phase 2/3 studies were submitted for safety assessment (ACT11457, DRI12544, EFC13579, EFC13691 and LTS12551, *TRAVERSE*).

The pivotal studies DRI12544 (final CSR) and EFC13579 (*QUEST*, completed primary analysis) were pooled for safety analyses; pivotal study EFC13691 (*VENTURE*, completed primary analysis) was analysed separately since it comprises steroid-dependent patients. The treatment duration of both pooled studies varies between 24 and 52 weeks, however, the two pooled studies were similar as to administered dose regimens (200 or 300 mg q2w) and included target population so that the pooling of the correspondent safety data is endorsed. The MAH presents separate analyses that explicitly refer to a 24 week treatment period of the whole safety pool which is acceptable. The presented supportive safety data (LTS12551, ACT11457, and R668-AD-1412) provide additional information on long-term safety over a treatment period of almost three years (Aug 14-Jul 17) and paediatric patients (EFC14153 and AD-study R668-AD-1412 for PK and safety data).

There is one ongoing OLE study (LTS12551, cut-off 29 July 2017) in asthma that provides further data on long-term safety regarding a dose of 300 mg q2w. 1844 patients were enrolled and treated since study initiation in Aug 2014. The available long-term data is rather extensive and the applicant sufficiently set out the ongoing and planned long - term safety considerations of the dupilumab development program concerning the paediatric population.

The total exposure of patients in the safety pool was balanced across the different treatment groups as well as within the paediatric treatment population. Adolescent's total exposure was significantly lower compared to that of the treated adults (150 vs. 530 PY) due to the lower patient number (107 adolescents (*QUEST*) vs. 1567 adults (*DRI+QUEST*). Administered doses during the phase 2/3 studies ranged from 200 mg q2w up to maximal 300 mg qw. The highest cumulative dose received patients participating in the LTS12551 study (N=437, treatment duration ≥2 years). The ICH E1 safety exposure requirements are met.

The overall proportion of patients experiencing any TEAE was balanced across the different treatment groups. The asthma population showed a greater percentage of overall TEAE than the AD population in the primary safety pool (PSP) (ca. 80 % vs. 69%); the latter had a shorter treatment period though (24 vs. 16 weeks). Within the safety pool the major share of TEAE is attributable to the infections and infestations SOC. Here, the sub-items of infections were balanced and only minimally higher in the placebo group.

Differences were observed regarding the 'General disorders and administration site conditions' whereof the injection site reactions (erythema/oedema and pruritus) prevailed compared to the placebo group, as already observed in the AD studies and during the administration of other subcutaneously administered monoclonal antibodies. Back pain and eosinophilia were observed more often in the dupilumab treatment groups.

Interestingly to note is that conjunctivitis, as seen in the dupilumab-treated AD population, did not predominate within the dupilumab treatment groups of the asthma patients (1.5% vs. ca. 8% in the AD programme). This observation supports the hypothesis that the conjunctivitis was rather associated with the underlying clinical condition of AD.

All other SOCs showed nearly balanced and showed no special pattern of TEAE.

TEAE type and incidence were consistent independent of the treatment duration. As to treatment-related AE (TRAE) a similar pattern was existent in both the asthma population compared to the AD population regarding the pivotal studies as well as the steroid-dependent study population (*VENTURE*).

The SAE rates were low in general for both the safety pool and the more severely affected *VENTURE* population. A greater proportion of patients treated with the higher dupilumab dose experienced SAEs. Asthma was the most common SAE and exacerbations occurred more frequently in the dupilumab 200 mg and placebo group than in the 300 mg group. The incidences of the other most common SAEs (those with a frequency of >2 patients in any group) were low and similar across treatment arms. Besides, the SAE pattern did not significantly differ from the above presented TEAE pattern in the safety pool and again, it was similar to patients included in the *VENTURE* and OLE LTS12551 studies.

15 deaths were reported in total in the asthma program: 8 cases (5 of the dupilumab treatment group/3 of placebo group) of the pooled safety population died following a SAE. Most were associated to comorbidities/risk factors, thus none of these were assessed to be related to IMP.

2 deaths occurred during DRI12544 study in the 300 mg q4w group, which were not related to the study drug. Of the 3 deaths recorded during the OLE study LTS12551, 2 were assessed to be study-drug related:

A case of lung cancer metastatic (this case was already presented during the initial MAA in the AD indication) and one case of gastric adenocarcinoma. Malignancy is listed as an Important Potential Risk in the current RMP of dupilumab and long-term data concerning this aspect are being collected during the ongoing OLE study R-668-AD-1225 which has been prolonged from 3 up to 5 years.

The remaining 2 cases were reported during screening and post-treatment phase without causal relationship to dupilumab.

The most frequently reported treatment-emergent SAE was worsening of asthma with similar incidences across placebo and treatment group, however, patients receiving the higher dupilumab dose showed the lowest incidence.

The observed treatment differences of the SOC 'Cardiac disorders' during the *QUEST* study lead the MAH to a deeper investigation regarding the relatedness of the cardiac events to the IMP; a database search combined with a blinded adjudication analysis did not reveal a causal relationship. Hitherto, the available data show no striking evidence that the risk of cardiovascular events may be increased by dupilumab. The time of 1st dose of dupilumab to the onset of cardiac SAE ranged between 1 and 10 months, so no clear temporal link between dupilumab dosing and SAE could be established. All recorded cases of the TRAVERSE study were considered to be unrelated to the study drug. Neither safety results of the conducted AD studies nor the analysis of the cumulative post-marketing experience via global safety database search seem to support the initial suspicion of a potential connection between cardiac SAE and dupilumab treatment so far. Certainly the interpretation of post-marketing data is hampered by the missing availability of precise case reports but no safety signals were triggered so far. On the basis of currently available data from ongoing clinical studies and post-marketing experience no new safety concerns with regard to MACE/MACE+ especially in patients with long-term use (LTS12551) were revealed. The further strategy is endorsed and thus, the issue solved.

Injection site reactions (ISR) clearly constitute the largest category of AESI; the incidence remained stable over time under dupilumab administration. Severe ISR (lasting longer than 24 hours) are considered to be an important potential risk and they belonged to the predefined AESI of the initial MAA in AD. Here, they were rare (1.4% in the 300 mg q2w group) in general and 0.6-1.6% discontinued the IMP due to an ISR. However, during the AD program only one patient included in the OLE study (R668-AD-1225 OLE study) was presented to have experienced a severe ISR; with regard to the similar dose and treatment duration (300 mg q2w, 52-week data) only 14.5% showed ISR whereas 20% of the 300 mg q2w treatment group of the asthma program had ISR.

The applicant highlighted that the higher discontinuation rate noted in patients treated with 300 mg versus 200 mg dosage is likely to be related to an increase in the incidence of ISRs. This possibly results from the higher volume of Dupixent administered with the 300 mg dose (2 ml versus 1.14 ml).

The treatment-emergent AESI of eosinophilia up to greater 5 G/l due to a greater mean initial increase from baseline in blood eosinophils were observed to be numerically higher in all dupilumab treatment groups compared to the placebo groups. This phenomenon is known to be associated with dupilumab treatment and was already discussed during the initial MA, it is therefore reflected as common ADR for AD in the RMP and SmPC. The proportion of patients experiencing a treatment-related eosinophilia observed in the pooled safety population was consistent to that one observed in the AD program (~1%).

In the *VENTURE* study, the increase of eosinophils was considerably higher in patients with higher baseline levels (>0.5 G/l) and in patients with a higher disease burden. Thus, the effect and clinical consequences of a possible eosinophilia in patients with peripheral blood eosinophilia and with hypereosinophilic diseases has not been investigated to date. In addition, 8 patients showing a rise in blood eosinophils associated with clinically relevant moderate to severe adverse events and 4 cases experiencing eosinophilic pneumonia and EGPA (Churg-Strauss-Syndrome) were recorded. This has been adequately reflected in the SmPC section 4.4.

Systemic dupilumab-related hypersensitivity occurred in 1 adolescent patient during the OLE study (enrolled from *VENTURE*), that led to treatment discontinuation. 1 case of dupilumab-related anaphylactic reaction was noted in the pooled safety population. In total, 10 cases of systemic hypersensitivity led to treatment discontinuation, 3 were severe and 3 serious. Hence, systemic hypersensitivity reactions occurred rarely and seemed to be manageable. This AESI is listed under section 4.8 of the SmPC and as an ADR which is endorsed.

Opportunistic infections were rare in general and patients of the dupilumab treatment groups showed similar incidences as the placebo groups. Concerning the severe infections similar results were obtained.

Furthermore, there was no evidence of an elevated risk for malignancies or endoparasitosis.

Basically, red blood cell and platelet counts seem to remain stable under dupilumab treatment apart from an observed decrease in hemoglobin which was more pronounced in the in the dupilumab groups and most significant in the 300 mg q2w treatment group. According to the provided analysis, a decrease of hemoglobin >20 g/l occurred more often in patients with higher baseline haemoglobin levels independent of the assigned treatment. An anemia resulted in the same proportion of patients of both the dupilumab 300 mg q2w and placebo group. This effect was ascertainable during the AD development program, too. These data do not suggest a harmful effect of dupilumab on haemoglobin levels resulting in anemia.

White blood cells counts did not change significantly from baseline under dupilumab treatment. Changes were higher in the dupilumab groups concerning the eosinophil and neutrophil counts. One case of neutropenia did not result in a higher susceptibility for infections. It is acknowledged that there were little significant differences between dupilumab and placebo groups concerning the differential blood counts.According to the MAH, the different percentages between the asthma and AD clinical development program result from a different analysis method (PCSA criteria) of abnormal blood cell counts used for the asthma population compared to the AD indication.

The renal function in adolescents treated with dupixent due to divergent renal parameters (more patients of the verum group showing ≥ 30% change from baseline in creatinine compared to the placebo group) in Study EFC13579 and LTS12551 was questioned. As the change from baseline serum creatinine was not associated with renal adverse events or elevated creatinine levels (UNL) per se, no safety issue is currently discernible and no change to the SmPC was necessary.

Three cases of drug-related CPK increase were reported whereof 2 led to treatment discontinuation; all patients recovered without additional intervention. Overall, there were no striking differences between placebo and dupilumab treatment groups regarding the clinical chemistry parameters.

No IMP-related alterations of vital signs and ECG were apparent during the studies.

Overall, approximately 6% of study subjects receiving dupilumab 300 mg q2w and 5% of those in the placebo groups developed ADA. Treatment-emergent ADA response was slightly higher in the dupilumab treatment groups than in the placebo groups regarding the pooled ADA population. Concerning the TEAE no distinct pattern was discernible in ADA-positive study subjects apart from ISR which were in general higher in the dupilumab treatment groups. Overall, few patients developed ADA and persistent titers were similar between placebo and dupilumab groups. 2-4% treated with Dupixent developed neutralizing antibody responses, which were not generally associated with loss of efficacy. No clear relationship was observed between anaphylactic or hypersensitivity reactions and ADA status.

The spontaneous abortion rate registered during the dupilumab studies does not seem to exceed the general rate and was consistent with that observed in the AD program. However, dedicated studies analysing the effect of dupilumab on pregnancies and their outcomes are hitherto missing and the number of pregnancies is too small to deduce a specific risk of adverse pregnancy effects of dupilumab. So far, no adverse effects on pregnancy or on the baby could be determined. The same applies to breastfeeding. This is adequately reflected in the SmPC. A pregnancy registry was set up in the course of the initial MA.

Assessment of paediatric data on clinical safety

No increased risk was apparent for TEAEs with dupilumab treatment compared with placebo in any of the intrinsic factor subgroups examined (i.e., age, sex, race, weight, BMI, baseline blood eosinophil level, baseline ACQ-5 scores, and the number of prior severe asthma exacerbations at baseline). The same applies to subgroups of regions and territories.

The TEAE incidence in adolescents seems to be slightly lower than in adults and fewer TEAE were recorded in the dupilumab treatment groups compared to the placebo groups. No special TEAE pattern was identifiable so far. The same applied to SAE frequency and quality. Supportive data coming from AD study 1412 that included adolescents receiving two different weight-based doses did not reveal any special safety concerns.

In the paediatric population, the treatment-related treatment-emergent AE (TEAE) were most frequently noted in the General disorders and administration site conditions SOC triggered by injection site reactions (injection site erythema (8.8%) injection site oedema (8.8%), and injection site pain (5.9%) in patients receiving dupilumab.

The individual reasons for treatment discontinuation in the paediatric population didn't reveal any special AE pattern and no significant percentage difference were recorded between the placebo and verum group. .

Regarding the AESI only the injection site reactions prevailed in the dupilumab group which is consistent with the already presented safety results obtained from the treated paediatric patients.

Supportive blinded paediatric safety data of study EFC14153 were provided on request. As far as could be observed, no divergent AE pattern became apparent during study EFC14153. The 4 SAEs were considered as unrelated to the IMP (placebo or verum) as well as the majority of the remaining TEAE and AESI.

Available paediatric data of *TRAVERSE* study LTS12551 showed similar safety data, therefore the observed safety profile seem comparable to that seen in adults at present.

Furthermore, adolescents showed a more pronounced decrease in neutrophil counts than adults which was questioned. After correction additional 15 adolescent patients were included in the whole analysis with regard to changes of the neutrophil blood counts. Seven of the nine adolescent patients showing a decreased neutrophil count had associated infections which were probably the cause for the neutropenia, two had no associated clinical signs. One additional patient had a transient moderate neutropenia without clinical signs. Abnormalities of the neutrophil counts were slightly higher in the adolescent asthma population compared to the adult one but these TEAE were balanced between the treatment groups. Hence, no safety issue is suspected concerning this matter.

2.6.2. Conclusions on clinical safety

Overall, dupilumab treatment appears to be well tolerated, including the dose and method of administration (200 and 300 mg q2w SC) proposed for licensing. The size of the safety database for dupilumab to support the indication in adolescent and adult patients with moderate to severe asthma is considered sufficient. An ongoing open label extension study is being conducted that will provide further data on long-term safety in the post marketing setting.

Treatment with dupilumab in the adult asthma placebo-controlled studies, during the open-label extension study and the supportive paediatric study was generally well tolerated and exhibited a relatively low immunogenic potential. Long-term safety considerations for dupilumab have been adequately addressed in this population and the SmPC is considered acceptable.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	• Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risks	• Malignancy
Missing information	• Use in pediatric AD patients <18 years of age and asthma patients <12 years of age • Use in pregnant and lactating women • Conjunctivitis related events in AD patients • Long-term safety

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Pregnancy registry (R668-AD-1639) Planned	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 Will also be submitted to other health

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
				authorities.
			Amended protocol (asthma cohorts) Final report	Will be submitted once available Will be submitted once available
Pregnancy Outcomes Database Study (R668-AD-1760) Planned	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 Final report	Will be submitted once available Will be submitted once available
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 related events in AD patients)	Final report	Will be submitted once available
A randomized, double blind, placebo controlled study to investigate the efficacy and safety of dupilumab in patients 12 to <18 years of age, with moderate-to-severe AD (Phase III) (EFC1526) (R668-AD-1526) Ongoing	To demonstrate the efficacy of dupilumab in patients ≥12 years to <18 years of age with moderate-to-severe AD.	Safety of dupilumab in patients 12 to <18 years of age, with moderate-to-severe AD	Final report	3Q 2019
A phase 2/3 randomized double-blind study investigating the pharmacokinetics, safety, and efficacy of dupilumab in patients aged ≥6 months to <6 years with severe atopic dermatitis (R668-AD-1539) Ongoing	To characterize the safety and PK of dupilumab administered as a single dose in pediatric patients, 6 months to less than 6 years of age; demonstrate the efficacy of multiple doses of dupilumab over 16 weeks of treatment when administered concomitantly with TCS.	Safety in children <6 years of age with severe AD	Final report	1Q 2023
A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of dupilumab administered concomitantly with topical corticosteroids in patients,	To demonstrate the safety and efficacy of dupilumab administered concomitantly with TCS in patients, ≥6 years to <12 years of age, with severe AD.	Safety in children ≥6 years to <12 years of age, with severe AD	Final report	2Q 2020

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
≥6 years to <12 years of age, with severe AD (Phase III) (R668-AD-1652) Planned				
An single-arm 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	4Q 2024
Prospective cohort study of Dupixent® (dupilumab) safety in long-term use in adult atopic dermatitis patients in Europe (OBS15906) Planned	To monitor for long-term adverse events, in particular malignancy, with a targeted follow-up of 5 years	Long-term safety Malignancy	Protocol submission Final report	2Q 2018 Will be submitted 10 years after study start
Pediatric asthma study in children 6 to <12 years of age who have uncontrolled persistent asthma (EFC14153). Ongoing	To assess the efficacy of dupilumab in children 6 to leass than12 years old with uncontrolled persistent asthma	Safety and tolerability of dupilumab in children 6 to <12 years with uncontrolled asthma	Final report	4Q 2021
Pediatric asthma study in children 6 months to <6 years of age with recurrent severe asthmatic wheezing uncontrolled by ICS (EFC14771). Planned	To assess the efficacy and safety of dupilumab in children 6 months to less than 6 years old with recurrent asthmatic wheezing uncontrolled by ICS	Safety of dupilumab in children 6 months to <6 years with recurrent asthmatic wheezing	Final report	2Q 2026
Long term safety and tolerability study of dupilumab in children who participated in previous dupilumab asthma clinical studies (LTS14424). Planned	To evaluate the long-term safety and tolerability of dupilumab in children 6 months to less than 12 years patients who participated in previous dupilumab asthma clinical studies.	Long-term safety in children with asthma	Final report	4Q 2026

AD: Atopic Dermatitis; ICS: Inhaled Corticosteroid; PK: Pharmacokinetics; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; TCS: Topical Corticosteroid.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risk		
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
Important potential risks		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Malignancy	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: Study OBS15906: Prospective cohort study of Dupixent® (dupilumab) safety in long-term use in adult AD patients in Europe, with a targeted follow-up of 5 years
Missing information		
Use in pediatric AD patients <18 years of age and asthma patients <12 years of age	Routine risk minimization measures: SmPC sections 4.2 and 5.2 PIL section 2 Prescription only medicine Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: Pediatric PK studies R668-AD-1434, R668-AD-1526 (adolescent confirmatory trial), R668-AD-1539 and R668-AD-1652, EFC14153, EFC14771, LTS14424
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: None Additional pharmacovigilance activities: Pregnancy registry study (R668-AD-1639) in asthma and AD patients Pregnancy Outcomes Database Study (R668-AD-1760) in AD patients
Conjunctivitis 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 R668-AD-1225
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: Study OBS15906: Prospective cohort study of Dupixent® (dupilumab)

Safety concern	Risk minimization measures	Pharmacovigilance activities
		safety in long-term use in adult AD patients in Europe, with a targeted follow-up of 5 years

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

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.1 is acceptable.

2.8. Pharmacovigilance

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.

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

As agreed with EMA the applicant circulated the results of the user testing and bridging reports as part of the responses to LoQ at D 121. The approach was as follows: a bridging UT report for the 200 mg PFS-S package leaflet and IFU using the tested 300 mg PFS-S leaflet as parent leaflet. Furthermore, a bridging for the 200 mg PFP package leaflet using the already tested 300 mg PFS-S leaflet and a full user test for the 200 mg PFP.

With regard to the extension " new asthma indication with new strength and additional presentation as pre-filled pen" the applicant Sanofi-Aventis Groupe submitted a full user test for the package leaflet including the IFU section for the medicinal product Dupixent 200 mg solution for injection in PFP. A previous readability test was carried out in 2016 for Dupixent 300 mg solution for injection in a PFS. The contractor used the same methodology as before.

Unfortunately the full user testing failed due to the results related to several questions. The company selected various participants which were regularly involved (13 to 15 times previously) but the inclusion of well-trained persons should be avoided as much as possible. With regard to question 2 and in particular to question 7 the time aspects exceeded the limit of 120 seconds considerably: Participant number 20 (P20) = 263 and P11 = 259 seconds, this means more than 4 minutes, P2 = 227, P18= 211, and P3= 200 seconds, this means more than 3 minutes and P20 = 172, P1=154, P4=153, P6=146, P=8=136, etc -> more than 2 minutes. Therefore the testing failed regrettably.

The readability guideline is clear as well as the QRD checklist. However, a satisfactory test outcome could not

be demonstrated: when the information requested within the package leaflet can be found by 90% of the test participants, of whom 90% can show that they understand it. That means to have 16 out of 20 participants able to find the information and answer each question correctly and act appropriately. The success criteria will need to be achieved with each question and the results cannot be aggregated.

Therefore, the company is requested to carry out a consultation with target patient groups which reflect all issues sufficiently. The main focus of the readability testing is to achieve a legible, clear and easy to use package leaflet in order to avoid medication errors and that the suggestions made by the volunteers will be taken into consideration or otherwise adequately justified.

In conclusion, the MAH will submit the results of a new user consultation with target patient groups on the package leaflet that 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* as soon as possible and no later than Q3 2019.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Dupixent (dupilumab) is included in the additional monitoring list as it is a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products.
The poor response of some patients with asthma to the standard regimen of controller and reliever therapies may reflect the number of cellular and molecular mechanisms operative in asthma. Type 2 inflammation is characterized by the release of signature cytokines interleukin 4 (IL-4), interleukin 13 (IL-13) and interleukin 5 (IL-5). While IL-5 primarily functions to increase release of eosinophils from bone marrow, IL-4 and IL-13 have effects on multiple cellular pathways, working via both the innate and adaptive immune pathways, leading to mast cell activation, IgE production, eosinophil recruitment into tissues via increasing levels of chemokines such as eotaxin, and increased smooth muscle hyperresponsiveness and remodeling. Type 2 inflammation asthma is associated with elevated levels in related biomarkers (e.g. Eosinophil count in blood or sputum, FeNO, TARC, periostin, eotaxin-3). Current asthma treatment guidelines support using Eosinophil count and FeNO as patient response biomarker that can identify patients with Type 2 inflammation.

3.1.1. Available therapies and unmet medical need

There is a recognized ceiling effect for what can be achieved with ICS/LABA combinations. It has been shown that if patients remain uncontrolled on high doses of ICS, further dose increases provide little incremental benefit.

For patients with uncontrolled asthma, ICSs often fail to normalize elevated Type 2 biomarkers in blood, exhaled air and/or induced sputum, indicating persistence of significant residual Type 2 inflammation. Combination of ICS +LABA show some improvement on FEV1 due to their bronchodilator effect. LAMA add-on may have additional benefits on lung function and asthma control over LABA/ICS; however, their effects in reducing the need for rescue oral steroids and benefits on quality of life are inconsistent and negligible. Thirty percent of severe asthmatics currently require oral steroids to control their asthma symptoms. Though moderately effective in the majority of cases to control airway disease, the broad spectrum anti-inflammatory activity of OCS has a well-known toxicity profile across multiple organ systems. There remains a significant need to develop therapies that can be used earlier, after ICS +/- LABA, for those moderate-to-severe patients who currently are not severe enough to warrant OCS use, and to prevent the need for oral corticosteroid use in the most severe asthmatics who would otherwise have no choice but accept the risks of OCS use. Biologics targeting specific inflammatory mediators of asthma are used as add-on treatments and are currently limited to subgroups of patients. Omalizumab, which inhibits the binding of IgE to its receptor, is indicated in the EU as add-on therapy to improve asthma control in patients (adult and children aged ≥6 years) with severe persistent allergic asthma who have a positive skin test or in vitro reactivity to a perennial aeroallergen. More recently approved biologics include the IL-5 inhibitors mepolizumab, reslizumab, and benralizumab. These IL-5 inhibitor therapies are indicated only for patients with elevated blood eosinophils. The results of these clinical studies demonstrate an ability to reduce exacerbations in a targeted group of asthmatics but also highlight their inability to treat a broader range of asthmatics whose disease is driven by a more complex network of cellular inflammation.

3.1.2. Main clinical studies

Three pivotal studies are included in the submission. DRI12544 a 24-week Phase 2b, placebo-controlled dose ranging in patients with moderate-to-severe uncontrolled asthma, EFC13579 (QUEST) a 52-week Phase 3, placebo-controlled study in patients with persistent (moderate-to-severe uncontrolled) asthma. It was a confirmatory efficacy and safety study with the primary analysis completed (data cutoff of 29 July 2017) and EFC13691 (VENTURE) was a 24-week Phase 3, placebo-controlled study in patients with severe steroid-dependent asthma. The end-of-treatment (EOT) analyses were completed (data cutoff of 20 September 2017).

A total of 2649 patients were exposed to dupilumab of which 2136, 1553, 834, and 531 patients were exposed for ≥6 months (24 weeks), ≥1 year, ≥1.5 years, and ≥2 years (96 weeks), respectively. A total of 110 (5.2%) adolescents (12 to <18 years, in Studies EFC13579 and EFC13691) and 353 (12.2%) elderly (≥65 years) patients were randomized and treated.

3.2. Favourable effects

Dupilumab treatment reduced severe asthma exacerbations and improved lung function in all 3 pivotal studies for the overall population in both 200mg and 300mg Q2W regimens.

In study DRI12544 and EFC13579 both 200 mg q2w and 300 mg q2w doses of dupilumab, when added to standard of care to patients with persistent, uncontrolled, moderate-to-severe asthma, demonstrated clinically meaningful effects on primary endpoints and most other secondary endpoints including patient reported outcomes.

Dose-Response-Study DRI12544 demonstrated a clinically relevant improvement in FEV1 at week 12 (primary efficacy endpoint) of the 2 highest doses of dupilumab compared to placebo. Furthermore both the 200 mg q2w and 300 mg q2w dose regimens of dupilumab demonstrated, as compared to placebo, a significant reduction in the annualized rate of severe asthma exacerbations and a delayed time to first severe asthma exacerbation event, during the treatment period. The LS mean changes in FEV1 from baseline to Week 12 were +0.12 L in the placebo group, +0.31 L (200 mg Q2W dose) and +0.28 L (300mg Q2W dose).

When compared with placebo, the LS mean differences were significant for dupilumab 200 mg Q2W (+0.20 L; p<0.0001), and 300 mg Q2W (+0.16 L; p=0.0002). The number of patients with severe exacerbation over the treatment period 25.9% in the placebo group, 8.8% in the 200 mg Q2W and 10.9% in the 300mg Q2W group.

In Study EFC13579 the reduction in the annualized rate of severe asthma exacerbations was 47.7% and 46.0%, for the 200 mg q2w and 300 mg q2w groups, respectively, compared with the matching placebo groups (p<0.0001 for both dose groups). The improvement in in pre-bronchodilator FEV1 at Week 12 was observed for the 200 mg q2w group (0.14 L) and for the 300 mg q2w group (0.13 L) in the overall ITT population over the matching placebo groups (p<0.0001). Higher efficacy was demonstrated in patients with higher blood eosinophil and FeNO values at baseline. . A post hoc analysis to examine the interaction between these baseline biomarkers demonstrated that the greatest effect of dupilumab on annualized severe exacerbation event rate and on change from baseline to Week 12 in pre-bronchodilator FEV1 was observed among the patients with baseline eosinophils ≥0.15 Giga/L and FeNO ≥25 ppb. This population of patients (41.7% of the entire ITT population) showed a risk reduction of 68.2% and 65.3% and an LS mean difference of 0.26 L and 0.26 L in pre-bronchodilator FEV1 for the dupilumab 200 mg q2w and 300 mg q2w groups compared with the matching placebo groups, while those with blood eosinophils <0.15 Giga/L and FeNO < 25 ppb do not demonstrate a clinically meaningful improvement in exacerbation rate or lung function.

In study EFC13691 dupilumab was administered to patients with OCS dependent asthma. The primary endpoint was percentage reduction from baseline in OCS dose at Week 24. The mean percent reduction in OCS dose at Week 24 was greater in the dupilumab group (LS mean 70.09) compared with the placebo group (LS mean 41.85). The results of the secondary endpoints support the results of the primary endpoint and showed, that at Week 24, the proportion of patients with ≥50% reduction in OCS dose compared with baseline was significantly greater in the dupilumab group (80%) than in the placebo group (50%).

In study EFC13579 and EFC13691 adolescent patients over 12 years of age with a physician diagnosis of asthma for ≥12 months (based on the GINA 2014 Guidelines) were eligible. The adjusted annualized event rate of severe exacerbation in the 107 adolescent patients during the 52-week treatment period of Study EFC13579 was lower in the dupilumab 200 mg q2w group compared with the matching placebo groups (0.191 for the dupilumab 200 mg q2w compared with 0.356 for the matching placebo group), indicating a 46.4% reduced risk of severe exacerbation events.

3.3. Uncertainties and limitations about favourable effects

In study DRI12544 and EFC13579 the 200 mg Q2W and 300 mg Q2W showed similar efficacy in reducing the annual rate of exacerbations and improving the pre-bronchodilator FEV1 in patients with type 2 inflammation asthma treated with ICS plus another inhaler controller for maintenance treatment. In Study EFC13579 the reduction in the annualized rate of severe asthma exacerbations was 47.7% and 46.0%, for the 200 mg q2w and 300 mg q2w groups, respectively, compared with the matching placebo groups (p<0.0001 for both dose groups). The improvement in pre-bronchodilator FEV1 at Week 12 was 0.14 L for the 200 mg q2w group and 0.13 L for the 300 mg q2w group in the overall ITT population over the matching placebo groups (p<0.0001). No additional benefit for patients with the higher dose of 300 mg Q2W has been identified in these studies. Due to this fact and together with a slightly better safety profile the benefit/risk ratio is in favour of the 200 mg dose in these patientsDue to this fact and together with a slightly better safety profile the benefit/risk ratio is in favour of the 200 mg dose in these patients.

Higher efficacy has been demonstrated in the subpopulation with higher baseline eosinophils and FeNO values. In study EFC13579 patients with both eosinophil levels <0.15 Giga/L and FeNO <25 ppb, dupilumab did not demonstrate any relevant effect in reducing the risk of exacerbations. A statistically significant difference was not observed in the adjusted annualized event rate of severe exacerbation during the 52-week treatment period between the 2 dupilumab dose groups compared with their respective placebo groups (0.512 and 0.610 for the dupilumab 200 mg q2w and 300 mg q2w groups compared with 0.675 and 0.732 for the matching placebo groups). The recruited patients had moderate to severe asthma both with high and low eosinophil baseline counts and it would appear that the efficacy favours patients with uncontrolled asthma with elevated levels of eosinophils and frequent (≥ 2) severe exacerbations. The main Phase 3 study EFC13579 the subgroup with eosinophil < 0.3 Giga /L did not show a clinically significant reduction in exacerbations compared to placebo whereas this was demonstrated in the high eosinophil group > 0.3 Giga/L and therefore drives the overall ITT result.

Exacerbation events leading to hospitalisation or emergency room visit were very low the relative risk reduction of dupilumab versus placebo was 25.5% and 46.9% for the 200 mg q2w and 300 mg q2w doses, respectively. In OCS-dependent patients (Study EFC13691) treated with 300 mg q2w dupilumab, the relative risk reduction versus placebo was 42.3% although the reduction did not reach statistical significance (nominal p =0.397) due to a small number of events. While the effects of Dupilumab in patients taking oral steroids in study EFC13691 were encouraging and meaningful the study was relatively small (106 patients) and was of short duration (26 weeks) therefore a maintenance of effect was not demonstrated sufficiently for a specific claim in the indication (section 4.1). However it is agreed that the effects should be conveyed to physicians and this information has been incorporated into section 5.1.

In study EFC13691 dupilumab treatment significantly reduced the need for oral corticosteroids in OCS dependent patients. However, due to the small sample size it was unclear whether this effect was independent from type 2 inflammation biomarkers (i.e. blood eosinophils and FeNO) since only 22 patients had low eosinophils count (<0.15 G/L) at baseline.

Use in elderly patients > 65 years of age is limited. Also the trials limited recruitment in relation to smokers as current smoker or cessation of smoking within 6 months were excluded.
The applicant only conducted this study using the higher dose of 300mg Q2W and it is not known whether similar results could have been achieved with 200mg Q2W. Also there were limited number of patients in both subgroups and 50% of placebo treated patients achieved a ≥50% reduction in OCS dose compared with baseline which questions whether some of the patients were over treated on enrolment.

Finally it is not clear what the duration of effect is following withdrawal of treatment and whether any rebound effect would occur if patients needed to be taken off therapy for duration of time.

3.4. Unfavourable effects

3 deaths occurred during the OLE study LTS12551 whereof 2 were assessed to be related to dupilumab: one case of lung cancer and one case of gastric adenocarcinoma. The impact of Dupilumab on malignancy cannot be assessed conclusively to date because long-term safety data are not yet available. Malignancy is therefore covered in the current RMP as Important Potential Risk and is subject of further investigations (OLE study R-668-AD-1225 which is set up for 5 years).

8% of patients independent of the study treatment experienced Serious AEs. Asthma was the most common SAE, ranging between 0.9 in the 300 mg q2w group, 2.1% in the 200 m q2w group and 2.3% in the placebo group. Severe TEAE were almost balanced between the treatment groups, asthma exacerbations occurred more frequently in the dupilumab 200 mg and placebo group than in the 300 mg group (1.3% vs. 0.6%). The

SAE pattern was similar to the general TEAE pattern in the safety pool and it did not differ from that observed in patients included in the VENTURE and OLE studies.

The observed treatment differences of AE of the SOC 'Cardiac disorders' during the *QUEST* study were subject to a closer analysis regarding the relatedness of the cardiac events to the IMP. According to the presented data no striking evidence of any relatedness to dupilumab could be determined.
Injection site reactions (ISR) were the most common AESI. Their incidence remained stable over time under dupilumab administration. Severe ISR were rare (1.4% in the 300 mg q2w group) and 0.6-1.6% discontinued the IMP due to an ISR. However, a rise in ISR incidence can be observed compared to the AD program referred to similar dosage and treatment duration (14.5% vs. 20% of the 300 mg q2w treatment group of the asthma program) that might be related to the different drug formulation.

Eosinophilia up to or greater 5 G/l due to a greater mean initial increase from baseline in blood eosinophils that were observed to be numerically higher in all dupilumab treatment groups compared to the placebo groups. This phenomenon is known to be associated with dupilumab treatment. The increase of eosinophils was considerably higher in patients with higher baseline levels (>0.5 G/l) and in patients with a higher disease burden (*VENTUR*E study). Patients with eosinophil counts >1.5 G/l were excluded from participation in the pivotal Phase III studies *QUEST* and *VENTURE*; thus, the effect and clinical consequences of a possible eosinophilia in patients with peripheral blood eosinophilia and with hypereosinophilic diseases has not been investigated. This safety concern is mirrored in the SmPC in section 4.4, 4.8 and 5.1 and in the RMP as an important potential risk.

Red blood cell and platelet counts seem to remain stable under dupilumab treatment apart from an observed decrease in hemoglobin which was more pronounced in the in the dupilumab groups and most significant in the 300 mg q2w treatment group. Further explanation was requested to clarify if the decrease of > 20 g/l in almost 11% of the pooled safety population led to anemia or clinical signs.
According to the provided analysis, a decrease of hemoglobin >20 g/l occurred more often in patients with higher baseline haemoglobin levels independent of the assigned treatment. An anemia resulted in the same proportion of patients of both the dupilumab 300 mg q2w and placebo group. This effect was ascertainable during the AD development program, too. These data do not suggest a harmful effect of dupilumab on haemoglobin levels resulting in anemia.

Changes in WCB counts were higher in the dupilumab groups concerning the eosinophil and neutrophil counts. Percentages are significantly higher than in the AD program. According to the MAH, the different percentages concerning the recorded abnormal blood cell counts between the asthma and AD clinical development program result from a different analysis method (PCSA criteria) of abnormal blood cell counts used for the asthma population compared to the AD indication. Furthermore, adolescents showed a more pronounced decrease in neutrophil counts than adults; these were not accompanied or followed by clinical issues.

Overall, approximately 6% of study subjects receiving dupilumab 300 mg q2w and 5% of those in the placebo groups developed ADA. Treatment-emergent ADA response was slightly higher in the dupilumab treatment groups than in the placebo groups regarding the pooled ADA population. Concerning the TEAE no distinct pattern was discernible in ADA-positive study subjects apart from ISR which were in general higher in the dupilumab treatment groups (see assessment above). Overall, few patients developed ADA and persistent titers were similar between placebo and dupilumab groups. 2-4% treated with Dupixent developed neutralizing antibody responses. No clear relationship was observed between anaphylactic or hypersensitivity reactions and ADA status.

The spontaneous abortion rate registered during the dupilumab studies does not seem to exceed the general rate and was consistent with that observed in the AD program. The number of pregnancies is too small to

deduce a specific risk of adverse pregnancy effects of dupilumab. So far, no adverse effects on pregnancy or on the baby could be determined. This is adequately reflected in the SmPC.

Uncertainties and limitations about unfavourable effects

Paediatric data is limited to 107 patients.

Based on the currently available data there was no significantly increased risk detectable for dupilumab regarding malignancy, all types of infections or systemic hypersensitivity reactions. The immunogenic potential of dupilumab seems to be low. However, the safety profile has to be refined over the next years with more data coming from the ongoing open label extension trials in asthma and AD as outlined in the RMP.

Currently there is a limited amount of safety data for the elderly (>64 years) and other special populations such as pregnant women, children under 12 years of age and patients with organ impairment. Further data are generated in the post-marketing setting with the ongoing trial.

Effects of dupilumab on patients with hypereosinophilic conditions have not been investigated as stated in the SmPC.

Animal studies do not indicate reproductive toxicity. However, data from use of dupilumab is too limited to draw any conclusions on potential embryo-foetal harms. This is reflected in the SmPC.

3.5. Effects Table

Table 15: Effects Table for dupilumab in asthma (data cut-off: 29 July 2017).

Effect	Short description	Unit	DUP 200 mg q2w	DUP 300 mg q2w	PLAC (200 mg q2w; 300 mg q2w)	Uncertainties / Strength of evidence	
		Favourable Effects					
Change in rate of exacerbation	Annualized event rate of severe exacerbation during 52-week treatment period		0.456	0.524	0.871 0.970	Reduced risk of severe exacerbation events with 47.7% (200 mg q2w) and 46.0% (300 mg q2w dupilumab) compared with matching placebo No statistically significant	Study EFC13579

Effect	Short description	Unit	DUP 200 mg q2w	DUP 300 mg q2w	PLAC (200 mg q2w; 300 mg q2w)	Uncertainties / Strength of evidence	
						effect in subgroup with baseline eosinophil levels ⩽0.15 Giga/L and FeNO ≤25ppb	
Change FEV1	LS mean Change in Pre-bronchodilator FEV1 From Baseline at WEEK 12	L	0.32 0.31	 0.34 0.28	0.18 0.21 0.12	Increase across all subgroups	Study EFC13579 Study DRI12544
Reduction OCS	Percentage reduction from baseline in OCS dose at Week 24	%	N/A	70.09	41.85	Relative high reduction in placebo despite dose optimization phase; Similar effect across all subgroups	EFC13691
⩾50% reduction OCS dose	Proportion of patients with ⩾50% reduction OCS dose compared with baseline at Week 24	%	N/A	81.0%	53.3%	Relative high reduction in placebo despite dose optimization phase; Similar effect across all subgroups	EFC13691
Unfavourable Effects							
HYS	Incidence of	%	2.5	3.0	4.3	ADA were balanced (6%DUP,	

Effect	Short description	Unit	DUP 200 mg q2w	DUP 300 mg q2w	PLAC (200 mg q2w; 300 mg q2w)	Uncertainties / Strength of evidence
	hypersensitivity reactions					5% PLAC) and were not associated with special TEAE. Higher doses associated with lower ADA incidence. Most adverse drug reactions were mild. Similar incidence irrespective of age category (12-64) Exclusion of patients with Eos>1.5G/l from Ph III studies QUEST and VENTURE. 8 cases with moderate-severe AE due to Eosinophilia, thereof 4 cases with EGPA and eos. Pneumonia.
ISR	Incidence of injection site reactions	%	15.9	19.7	9.0	
EOS	Incidence of eosinophilia	%	0.5	3.6	3.2	
HEAD	Incidence of Headache	%	0.8	1.4	0.4	

Abbreviations: DUP= Dupilumab, PLAC=Placebo, ISR=Injection Site Reaction, ADA= Anti-drug antibodies, PSP=Pooled Safety Population (QUEST+DRI12544)

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Dupilumab is a first-in-class drug with a new mechanism of action and can provide an alternative treatment option for patients.

Dupilumab treatment reduced severe asthma exacerbations and improved lung function in all 3 pivotal studies for the overall population in both 200mg and 300mg Q2W regimens. Improvement in lung function and the reduction of exacerbations are the clinically relevant aims of the asthma treatment. Additionally the reduction of systemic corticosteroid dose in patients with systemic corticosteroid dependent diseases is clinically important, due to the possible side effects of higher dose chronic systemic corticosteroid use.

The overall population is rather heterogeneous and it appears that the effects on both exacerbation and lung function are most favourable for patients with blood eosinophils > 0.3 Giga/L as they achieved significant results. In the pivotal study the difference from placebo in annualised rate of severe exacerbations was in the region of -0.43 for overall population however in the subpopulation baseline blood eosinophils ≥ 0.3 Giga/L the difference was 0.77 whereas for the baseline blood eosinophils < 0.3 Giga/L it was 0.14. In the subpopulation with eosinophils ≥ 0.15 Giga/L the difference was 0.60 whereas for baseline blood eosinophils <0.15 Giga/L, it was 0.03. However, similar effects were seen in patients receiving moderate and high ICS therapy. In the OCS sparing study EFC13691 the difference from placebo was -1.24 and -0.66 in the baseline

blood eosinophils ≥ 0.3 Giga/L and <0.3 Giga/L respectively. Although it could be considered clinically meaningful in the <0.3 Giga/L group, it has to be considered with caution as there were a limited number of patients and the duration was only for 24 weeks.

For effects on lung function change from baseline in pre bronchodilator FEV1 at Week 12, the overall ITT population form the main pivotal study showed an improvement of between 130 to 140 ml compared to placebo. In relation to the subgroups the effects demonstrated were more favourable for patients with baseline blood eosinophils ≥0.3 Giga/L as they achieved results between 210 to 240 mls compared to placebo whereas the population with <0.3 Giga/L only achieved differences of 4 to 8mls. Patients with baseline blood eosinophils ≥0.15 Giga/L achieved results between 150 to 170 mls compared to placebo whereas the population with <0.15 Giga/L only achieved differences of 6 to 9 mls.

The effects on lung function appear to improve rapidly 2-4 weeks and appear to be sustained over time to 52 weeks. Outcomes of total asthma symptom score and ACQ-5 score, significantly greater responder rate compared to placebo was observed for both dupilumab doses, based on the responder definition as improvement of ACQ-5 by 0.5, which is considered MCID. Although clinically meaningful effects were seen in patients with and without an eosinophilic phenotype, greater treatment effects in the subgroup of patients with baseline blood eosinophil ≥0.3 Giga/L compared to the overall ITT population were reported in all 3 pivotal studies.

The patient reported outcomes showed an improvement in Quality of life of the patient population similar to the efficacy endpoints.

The most relevant safety concerns identified during the asthma program are related to injection site reactions, potential risk of malignancy, limited long term data in paediatric and elderly adult patients, and uncertainties about the impact of dupilumab on pregnancies and their outcomes.

In terms of infections the overall rate was lower in the dupilumab treated patients compared with the placebo group. These were generally mild to moderate and common viral infections prevailed. No increased risk for helminth or opportunistic infections was identified. No treatment group differences were observed in the incidence of conjunctivitis concerning the asthma population.

Dupilumab use was not associated with a higher risk of experiencing TEAEs of hypersensitivity. Systemic hypersensitivity rates in the dupilumab treatment groups were low and similar to placebo. A single case of treatment-related anaphylaxis occurred. This suggests a low immunogenic potential of dupilumab in the asthma population and were mainly locally restricted. The proposed SmPC contraindicates use in patient with known hypersensitivity and incudes a warning in section 4.4 which is reasonable and endorsed by the CHMP.

The overall rates of malignancy were very low and comparable across treatment groups. However, there is insufficient long term exposure data to characterise the risk of developing malignancy particularly at the dose proposed. This issue has been discussed during the initial MA for AD and is part of the RMP and subject to investigation in the OLE studies.

The toxicity of dupilumab seems to be low with only minor ADRs identified. Despite its immunogenicity, hypersensitivity reactions were mainly locally restricted.

Long-term exposure at the intended dose of dupilumab 300mg Q2W is limited to date, especially for elderly and the paediatric population. The paediatric data show a similar safety profile compared with that seen in the adult population. The applicant should ensured that long term safety considerations for dupilumab are adequately addressed in this population.

3.6.2. Balance of benefits and risks

Based on the data provided on efficacy and safety, and considering the uncertainties in relation to safety and efficacy, the therapeutic need of dupilumab in the asthma population is acknowledged. The CHMP considers that the favourable effects of the 200 mg Q2W in the overall ITT population and 300 mg Q2W in the population with severe asthma type II patients who are treated with oral systemic corticosteroids and with concomitant moderate-to-severe atopic dermatitis outweigh the unfavourable effects. Hence, the benefit/risk balance is deemed positive in this population.

3.7. Conclusions

The overall B/R of Dupixent is positive *in adults and adolescents 12 years and older patients as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment."*.

4. Recommendations

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 of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP) and new indication is favourable in: *"adults and adolescents 12 years and older patients as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

Risk Management Plan (RMP)

The 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;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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 0021/2017 the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommend the variation(s) to the terms of the marketing authorisation, concerning the following change(s):

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

Extension application to add a new strength of 200 mg solution for injection in pre-filled syringe with safety system (PFS-S) and pre-filled pen (PFP), grouped with a type II variation (C.I.6.a) to add the following indication in severe asthma patients based on the pivotal studies DRI12544, QUEST and VENTURE:
Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

Therefore, the above indication is approved for the new strength (200 mg) and the existing strength (300 mg) where the SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 have been updated accordingly. The Package Leaflet and RMP (version 2.0) were updated accordingly.