30 May 2024
EMA/291386/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dupixent

International non-proprietary name: Dupilumab

Procedure No. EMEA/H/C/004390/II/0079

Note

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

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List of abbreviations

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AECOPD	acute exacerbation(s) of chronic obstructive pulmonary disease
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BODE	body mass index, airflow obstruction, dyspnea, and exercise capacity
$C_{average}$	average concentration over the event observation period
CAT	COPD Assessment Test
CI	confidence interval
CMQ	customized MedDRA query
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CSR	clinical study report
C_{trough}	trough concentration
CV:	cardiovascular
DBP	diastolic blood pressure
ECG	electrocardiogram
EMA	European Medicines Agency
E-R	exposure-response
E-RS: COPD	Evaluating Respiratory Symptoms in COPD
E-RS	Evaluating Respiratory Symptoms
EXACT	Exacerbations of Chronic Pulmonary Disease Tool
$FEF_{25-75\%}$	forced expiratory flow at 25% to 75% of forced vital capacity
FeNO	fraction of exhaled nitric acid
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HLGT	high level group term
HLT	high level term
HRQoL	health-related quality of life
ICS	inhaled corticosteroids
IgE	immunoglobulin E
IL	interleukin
IMP	investigational medicinal product
ITT	intention-to-treat
IV	intravenous
KM	Kaplan-Meier
LABA	long-acting beta agonist
LAMA	long-acting muscarinic antagonist
LLOQ	lower limit of quantification
LS	least square
MACE	major cardiovascular adverse events
MedDRA	medical dictionary for regulatory activities
mMRC	modified Medical Research Council
NAb	neutralizing antibody
NSAID	nonsteroidal anti-inflammatory drug
OCS	oral corticosteroid
PCSA	potentially clinically significant abnormality
PDE	phosphodiesterase
PK	pharmacokinetics
post-BD	post-bronchodilator
pre-BD	pre-bronchodilator
PRO	patient-reported outcome
PT	preferred term
PY	participant-year
Q2W	every 2 weeks
SABA	short-acting beta agonist
SAP	statistical analysis plan

SC	subcutaneous(ly)
SCS	systemic corticosteroid(s)
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WBC	white blood cell

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the European Medicines Agency on 9 October 2023 an application for a variation.

The following variation was requested:

Variation 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 and IIIB

Extension of indication for DUPIXENT to include treatment of adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) with type 2 inflammation on triple therapy or double therapy if inhaled corticosteroids (ICS) are contraindicated, based on final results from study EFC15804 (BOREAS); this is a phase 3, randomized, double blind, placebo-controlled, multi-center, parallel group, 52-week study to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with type 2 inflammation. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 10.0 of the RMP has also been submitted.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (CW/0001/2015) on the granting of a class waiver.

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 31 January 2019 (EMEA/H/SA/2744/8/2018/II). The Scientific Advice pertained to clinical aspects.

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: Finbarr Leacy

Timetable	Actual dates
Submission date	9 October 2023
Start of procedure:	28 October 2023
CHMP Rapporteur Assessment Report	21 December 2023
PRAC Rapporteur Assessment Report	28 December 2023
CHMP Co-Rapporteur Assessment	10 January 2024
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	7 May 2024
PRAC Rapporteur Assessment Report	3 May 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	16 May 2024
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	23 May 2024
Opinion	30 May 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

COPD is a complex heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, and sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. The disease results from gene-environment interactions and occurs in response to chronic exposure to noxious stimuli including tobacco smoke, pollutants, biomass, and gases. Periods of acute worsening of respiratory symptoms, called exacerbations can occur that lead to further disease progression.

An evidence-based strategy document for COPD diagnosis, management, and prevention is available by the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD 2023). Main aspects are summarized in the following paragraphs.

State the claimed therapeutic indication

"Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) with type 2 inflammation on triple therapy or double therapy if inhaled corticosteroids (ICS) are contraindicated (see Section 5.1)."

Posology as proposed by the MAH

The recommended dose of dupilumab for adult patients is 300 mg given every other week.

Epidemiology and risk factors

Existing COPD prevalence data vary widely due to differences in survey methods. Recent reports indicate that COPD is highly prevalent and it is estimated that 391.9 million patients had COPD in 2019, with an estimated worldwide COPD mean prevalence of 13.1% (95% CI: 10.2–15.6%), with similar distributions in Europe (12.4%; 95% CI: 8.8–16.0%), America, (13.2%; 95% CI: 10.5–15.9%) and Asia (13.5%; 95 % CI: 10.0–16.0%) (Blanco et al., 2019).

COPD results from gene-environment interactions occurring over the lifetime of the individual that can damage the lungs and/or alter their normal development/aging processes. One of the main environmental exposures leading to COPD are tobacco smoking and other environmental exposures such as inhalation of toxic particles and gases from household and outdoor air pollution. Host factors (including abnormal lung development and accelerated lung aging) can also contribute. Exacerbations are often triggered by respiratory viral infections although bacterial infections and environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events. When associated with viral infections, exacerbations are often more severe, last longer and precipitate more hospitalizations, as seen during the winter season.

Pathogenesis

Markers of type 2 inflammation, including sputum IL-4 and IL-5, have been identified in subgroups of patients with COPD and are linked to elevated peripheral eosinophil counts. Moreover, elevated levels of IL-4 and IL-13 have been observed in patients with COPD during acute exacerbations.

A higher peripheral blood eosinophil count has been reported to identify a subgroup of up to 40% of patients with COPD associated with distinct clinical features such as frequent respiratory exacerbations and more severe airflow limitation and thus increased risk of mortality. Blood eosinophil count has been shown to correlate with sputum eosinophil count. Blood eosinophil count has been identified as an independent biomarker of response to ICS in patients with COPD, with higher blood eosinophil counts demonstrating higher benefit.

Clinical presentation, diagnosis

Patients with COPD typically complain of dyspnea, activity limitation and/or cough. Chronic dyspnea is the most characteristic symptom of COPD. Cough with sputum production is present in up to 30% of patients. Patients with severe COPD often experience acute respiratory events (called exacerbations) characterized by increased respiratory symptoms.

COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course. These comorbid conditions can mimic and/or aggravate an acute exacerbation. Cardiovascular diseases are common and important comorbidities in COPD. Lung cancer is frequently seen in people with COPD and is a major cause of death.

As per recent GOLD 2023 guidelines, a combined assessment of presence of COPD symptoms (mMRC dyspnea scale or CAT) and exacerbation history and is used to determine disease severity and to guide pharmacological therapy. Four grades (GOLD grades 1-4) based on severity of airflow limitation are defined with GOLD grade 1 (mild, FEV1 ≥80% predicted), GOLD grade 2 (moderate, FEV1 ≥50% and <80% predicted), GOLD grade 3 (severe, FEV1 ⩾30% and <50% predicted), or GOLD grade 4 (very severe, FEV1 <30% predicted). These disease grades are part of a combined assessment strategy of symptoms and risk for exacerbations. The GOLD groups A and B are comprised of patients without a history of frequent or severe exacerbations with low or high symptom burden, respectively. As per GOLD 2023, patients with a history of ≥2 moderate exacerbations or ⩾1 exacerbation leading to hospitalization in the previous year) are included in the GOLD Group E group.

An assessment of the degree of reversibility (eg, change in FEV1 after administration of bronchodilator) may be of clinical interest in obstructive lung disease. However, current guidelines no longer recommend assessment of the degree of reversibility in COPD to inform treatment decisions as the degree of reversibility is variable over time and has not been shown to reliably differentiate the diagnosis of asthma from COPD nor to reliably predict response to therapies.

Management

The management strategy of stable COPD is predominantly based on the assessment of symptoms and the history of exacerbations with the main treatment goal of reduction of symptoms and future risk of exacerbation.

Smoking cessation has the greatest capacity to influence the natural history of COPD. Still, a significant proportion of people with COPD continue to smoke despite knowing they have the disease (approximately 40% of COPD patients are current smokers).

As per current GOLD 2023 guidelines, in addition to smoking cessation, the standard of care for patients at high risk of COPD exacerbation (GOLD group E) includes inhaled bronchodilators (LABA+LAMA); the addition of ICS to comprise 'triple therapy' (ie, ICS+LABA+LAMA) is strongly recommended for those with blood eosinophils ≥0.3 Giga/L. The recommendation for standard-of-care inhaled therapy does not differ for patients by phenotype (eg, chronic bronchitis and/or emphysema).

In case of an acute exacerbations, short-acting inhaled beta2-agonists (SABA), with or without short-acting anticholinergics, are recommended. In patients with severe exacerbations, systemic corticosteroids and antibiotics can improve lung function (FEV1), oxygenation and shorten recovery time including hospitalization duration.

Unmet medical need

COPD is a progressive condition characterized by irreversible airflow limitation with frequent exacerbations potentially accelerating disease progression and mortality. Though treatment recommendations for the management of severe COPD exist, no currently approved therapy is able to prevent the decline in lung function. While inhaled corticosteroids have a consistent effect in reducing the risk of moderate COPD exacerbations there is no consistent benefit on severe exacerbations.

Among severe COPD patients with high exacerbation risk on maximal standard-of-care triple therapy (ICS+LABA+LAMA) patients with an eosinophilic COPD phenotype may continue to experience exacerbations and disease progression providing important unmet need for new treatment options in this patient population.

2.1.2. About the product

Dupilumab is a human monoclonal IgG4 antibody that inhibits IL-4 and IL-13 signalling by specifically binding to the IL4Rα subunit shared by the IL-4 and IL-13 receptor complexes. The IL4Rα receptor is present on multiple cell types known to be involved in the type 2 inflammatory process. Both IL-4 and IL-13 signaling pathways are thought to play key roles in the pathophysiology of type 2 inflammatory diseases.

Dupilumab is currently approved for the following indications: atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, prurigo nodularis, eosinophilic esophagitis.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program of dupilumab in COPD is comprised of 2 pivotal Phase 3 studies with similar design and objectives: EFC15804 (BOREAS) and EFC15805 (NOTUS).

Scientific Advice from the CHMP was given on 31 January 2019 (EMEA/H/SA/2744/8/2018/II). CHMP noted that there is a lack of consensus on the appropriate blood eosinophil thresholds used to define eosinophilic COPD and advised the MAH to explore the effect of dupilumab in patients with lower blood eosinophil counts. The proposed indication wording with the broad term of "type 2 inflammation" was questioned given that this term is not being described/used in the context of COPD. The respective CHMP recommendations were not completely followed.

2.2. Quality

No new quality data have been submitted in this application, which is considered acceptable.

The MAH provided in section 3.2.R the Justification for no need of Notified Body Opinion - MDR Article 117. The MAH sufficiently outlined that there are no changes to the design or intended purpose of the device (300mg PFS and PFP presentations), nor is there a new medical device being introduced. The justification for not providing the notified body opinion is acceptable.

2.3. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

Dupilumab is a monoclonal antibody consisting of linked naturally occurring amino acids. As per the ERA Guideline, vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempt from ERA study requirements because by their nature they are unlikely to result in significant risk to the environment.

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.

Clinical efficacy and safety were evaluated in the pivotal phase 3 study (EFC15804; BOREAS). This study was designed as multinational, randomized, double-blind, placebo-controlled, parallel group study to assess the efficacy and safety of a 52-week treatment period with dupilumab 300 mg q2w in participants with uncontrolled COPD despite receiving maximized standard-of-care background therapy of with blood eosinophils ≥0.3 Giga/L during the screening period. Efficacy and safety data (interim results) from the second phase 3 study in COPD (EFC15805; NOTUS) with similar design were provided during the procedure.

- Tabular overview of clinical studies

Table 1 - Phase 3 COPD studies as part of the submitted dossier

Study number/ Status at study data cut-off date	Primary study objective	Treatment/ follow-up duration	Participants randomized/ treated
Phase 3 EFC15804 (BOREAS) Primary analysis completed (52-week intervention period completed) *Last participant last visit occurred on 02 May 2023* (5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication [Study EFC15804])	Primary objective: to evaluate the efficacy of dupilumab 300 mg q2w in participants with moderate-to-severe COPD as measured by AECOPD. Primary endpoint: annualized rate of moderate[b] or severe[c] COPD exacerbations over the 52-week treatment period compared to placebo. For both moderate and severe events to be counted as separate events, they had to be separated by at least 14 days. Key secondary objectives : to evaluate the effect of dupilumab 300 mg q2w on: • Pre-BD FEV_1 over 12 weeks compared to placebo. • Pre-BD FEV_1 over 52 weeks compared to placebo. • Health-related quality of life, assessed by the change from baseline to Week 52 in SGRQ.	52/12 weeks	Randomized: 939 (placebo: 471, dupilumab 300 mg q2w: 468) Treated: 939 (placebo: 470; dupilumab 300 mg q2w: 469)[d]
Phase 3 EFC15805 (NOTUS) Primary analysis based on interim analysis when the information fraction was ≥0.92 based on follow-up time of the ITT population (N=935) for the primary endpoint of annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period (data cut-off date: 29 September 2023, database lock date: 01 November 2023)	Primary objective: to evaluate the efficacy of dupilumab 300 mg q2w in participants with moderate-to-severe COPD as measured by AECOPD. Primary endpoint: annualized rate of moderate[b] or severe[c] COPD exacerbations over the 52-week treatment period compared to placebo. For both moderate and severe events to be counted as separate events, they had to be separated by at least 14 days. Key secondary objectives : to evaluate the effect of dupilumab 300 mg q2w on: • Pre-BD FEV_1 over 12 weeks compared to placebo. • Pre-BD FEV_1 over 52 weeks compared to placebo. • Health-related quality of life, assessed by the change from baseline to Week 52 in SGRQ.	52/12 weeks	Randomized: 935 (placebo : 465, dupilumab 300 mq q2w : 470) Treated: At time of interim analysis cut-off date, the first 721 participants randomized (placebo: 359, dupilumab: 362) had reached Week 52

a Including all data up to the data cut-off date of 08 February 2023.

b Moderate exacerbations were recorded by the Investigator and defined as AECOPD requiring either systemic corticosteroids (such as intramuscular, intravenous, or oral) and/or antibiotics.

c Severe exacerbations were recorded by the Investigator and defined as AECOPD requiring hospitalization, or observation for >24 hours in an emergency department/urgent care facility or resulting in death.

d One participant randomized to the placebo group received 1 dose of dupilumab and was considered as part of the dupilumab group for safety analyses.

The PK and PD profiles of dupilumab in COPD were assessed in participants in study EFC15804. The study also includes an assessment of immunogenicity.

Table 2 - Dupilumab pharmacokinetic and pharmacodynamic assessments in clinical studies and analyses

Study type	Study code	Dose or dose range Duration of intervention	Number of study participants randomized	Dupilumab PK sampling
Pharmacokinetic and pharmacodynamic assessments in efficacy/safety study in participants with COPD[a]				
Repeated SC dose, pivotal Phase 3 study (52 weeks)	EFC15804	SC injections of 300 mg or matching placebo q2w for 52 weeks	468 dupilumab[b] 471 placebo[c]	Sparse sampling[d]
Population pharmacokinetic analysis, Phase 3 data in participants with COPD[a]				
Pop PK	POH0858	Data from Phase 3 (EFC15804) study	466[e]	
Pharmacokinetic-pharmacodynamic analysis, Phase 3 data in participants with COPD[a]				
PK/PD	CTS0124	Data from Phase 3 (EFC15804) study	466 dupilumab 471 placebo	

Abbreviations: PD: pharmacodynamic; PK: pharmacokinetic; COPD: chronic obstructive pulmonary disease; Pop PK: population PK; q2w: every 2 weeks; SC: subcutaneous.

a Data up to the data cut-off date of 08 February 2023 for Study EFC15804 with PK/ADA data cut-off date of 19 January 2023.

b All participants in the dupilumab group were randomized and exposed to study intervention.

c 1 participant in the placebo group was randomized to placebo but was exposed once to dupilumab.

d Samples collected at predose (Week 0), during treatment (Weeks 2, 4, 8, 12, 16, 24, 36, 52), and follow-up period (Weeks 56, 60 and 64).

e In Study POH0858, the final dataset included 466 participants at the cut-off date of 19 January 2023.

Out of the 468 participants, 466 participants received at least 1 dose of dupilumab with available PK post-dose data.

Choice of dosing regimen

The dosing regimen for Study EFC15804 was dupilumab 300 mg q2w SC. This dose has proven to be effective and to have an acceptable safety profile in multiple type 2 inflammatory diseases. The 300 mg q2w dose (with or without loading dose) is the approved dosing regimen for AD, CRSwNP, PN, and is an approved dosing regimen for patients with asthma. Efficacy results from the completed pivotal studies in patients with moderate-to-severe asthma demonstrated that the 300 mg q2w dose had a clinically meaningful and statistically significant effect in reducing exacerbations, improving lung function, asthma control and quality of life with a satisfactory safety profile.

Doses of 200 mg q2w and 300 mg q2w demonstrated comparable efficacy and safety in reducing exacerbations and improving pre-BD FEV1 in patients with moderate-to-severe asthma who were not prescribed chronic concomitant OCS. Moreover, analysis of the E-R relationships using descriptive exposure quartile and model-based analyses for these 2 efficacy endpoints showed that increasing dupilumab exposure resulted in a greater effect for both efficacy endpoints in patients with uncontrolled moderate-to-severe asthma. The lung function improvement and severe exacerbation rate reduction approached a maximum at the exposure of 200 mg and 300 mg q2w, with a 5 to 9% greater reduction in exacerbations for 300 mg q2w. Pre-BD FEV1 response was also predicted to be better maintained over the dosing interval for 300 mg q2w.

There is a flat E-R relationship for safety in most populations studied (except in AD where there is an inverse relationship between exposure and conjunctivitis adverse events).

Considering that the COPD population enrolled in the study has the potential for significant risk for morbidity and mortality associated with impairment of their lung function, as seen with the patients in the

OCS-sparing Phase 3 asthma study (Study EFC13691), the 300 mg q2w dose regimen was expected to achieve the optimal benefit/risk ratio in this difficult-to-treat COPD patient population.

Bioanalytical methods

Serum samples for quantitation of functional dupilumab (ie, dupilumab with 1 or both binding sites available for target IL4Rα binding) in human serum were analyzed using validated enzyme linked immunosorbent assays with a LLOQ of functional dupilumab of 0.078 mg/L in undiluted human serum (validation studies REGN668-AV-13074 and REGN668-AV-09095).

The type 2 inflammation biomarkers (FeNO, eosinophils, eotaxin 3, PARC, and total IgE) were assessed at baseline and during treatment as markers for type 2 disease activity/severity. FeNO was analyzed using a nitric-oxide instrument or similar analyzer. Blood eosinophil count was measured by hematology autoanalyzer. Eotaxin 3 was measured in heparinized plasma with a qualified enzyme immunoassay. Serum PARC was assayed with a qualified enzyme immunoassay. Concentrations of total IgE in serum were measured using a validated quantitative method: a fluoroenzyme immunoassay (Phadia™, ImmunoCAP™), globally, and a comparable electrochemiluminescence immunoassay in China (Roche Elecsys® IgE II, COBAS®). Fibrinogen was assessed at baseline and over treatment as severity and prognostic marker of AECOPD. Fibrinogen was measured with a validated enzyme immunoassay.

ADAs were assessed in serum samples from Study EFC15804, using a validated, non-quantitative, titer-based, electrochemiluminescence bridging immunoassay (validation studies REGN668-AV-15153 and REGN668-AV-13089). NAb activity was assessed in samples that were confirmed positive in the ADA assay using a validated competitive ligand binding assay (validation study REGN668-AV-13112).

2.4.2. Pharmacokinetics

The PK of dupilumab has been well characterized and the effect of intrinsic and extrinsic factors in various disease populations has been detailed in previous submissions. Dupilumab exhibits similar PK across different disease populations (AD, asthma, CRSwNP, EoE, and PN) after accounting for body weight. Therefore, PK in participants with COPD was evaluated with a maximum a posteriori (MAP) Bayesian approach (Study POH0858: Section 1.2.1.3) using an established Pop PK model (Study POH0668; previously submitted in the application supporting the CRSwNP indication).

Dupilumab concentrations in serum were measured in Study EFC15804 using sparse sampling (initially, samples collected at predose, during treatment at Weeks 2, 4, 8, 12, 16, 24, 36, 52, and at the end of the follow-up period at Weeks 56, 60 and 64. However, after protocol amendment 8, samples collected at predose, during treatment at Weeks 2, 4, 8, 12, 24, 36, 52, and at the end of the follow-up period at Week 64) up to the PK/ADA data cut-off date of 19 January 2023. Descriptive statistics were used to summarize the concentration data over time in participants with COPD in Study EFC15804. Dupilumab concentrations from the COPD population were compared to the dupilumab concentrations in serum from AD, asthma, CRSwNP, EoE, and PN populations as well as healthy subjects, using both a descriptive analysis from the observed data and a model-based approach.

A Pop PK analysis was conducted, using a MAP Bayesian approach (Study POH0858), based on a previously established global Pop PK base model (Study POH0668) from the CRSwNP submission (see Section 5.3.4). Data from Study EFC15804 were not included in the global Pop PK model development, but were evaluated using the MAP Bayesian approach, which allows the incorporation of prior information into the analysis for the PK data in participants with COPD. The adequacy of the Bayesian approach based on the global model to describe the PK data in participants with COPD was first confirmed by standard diagnostic criteria (external validation). The post-hoc exposure estimates from the model were then used to assess the effect of intrinsic and extrinsic factors on dupilumab PK in the COPD population.

Pharmacokinetic parameters in patients with COPD

The observed Ctrough and Pop PK model-based post-hoc estimates of dupilumab exposure at steady state (Cmax, Ctrough, and AUC) are shown below. The Pop PK model estimates were consistent with the observed values for Ctrough, demonstrating a robust performance of the model developed previously (without inclusion of data from participants with COPD) in describing dupilumab PK in the COPD population. The observed concentration at different time points in the study is shown in Table 4.

Table 3 - Mean (SD) steady-state exposure of dupilumab in participants with COPD (Study EFC15804)

Study identifier	Dose		$AUC_{\tau,ss}$[a] (mg•day/L)	$C_{max,ss}$ (mg/L)	$C_{trough,ss}$ (mg/L)[b]		
		N[c]	Predicted[d]	Predicted[d]	Predicted[d]	N	Observed
EFC15804	300 mg q2w	445	1070 (462)	85.2 (34.3)	62.1 (30.7)	423	61.8 (34.3)

Abbreviations: N: number of participants; $AUC_{\tau,ss}$: area under the concentration time curve over the dosing interval (τ) at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: trough concentration at steady state; q2w: every 2 weeks; SD: standard deviation.

a $AUC_{\tau,ss}$ = $AUC_{[Week\ 22 – Week\ 24]}$ for 300 mg q2w.

b $C_{trough,ss}$ represents the mean trough concentration at Week 24.

c In Study EFC15804, 40 out of 466 participants were not included in the post-hoc PK exposure summary due to dose discontinuation for those participants with last dose earlier than Week 22.

d Predicted: summary statistics of post-hoc estimates of exposure parameters in Study POH0858.

Sources: Study POH0858 COPD Pop PK analysis report, see 5.3.3.5 Study POH0858 ; PK appendices of Study EFC15804, see 5.3.5.1 Study EFC15804, Appendix 16.2.5 (16.2.5.4).

Table 4 - Summary of observed concentrations of dupilumab in serum in participants with COPD (Study EFC15804)

Study identifier	Dupilumab dose (N)	Mean (SD) C_{trough} (mg/L)											
		Week 0	Week 2	Week 4	Week 8	Week 12	Week 16	Week 24	Week 36	Week 52	Week 50	Week 56	Week 64
EFC15804	300 mg q2w SC (466)	BLQ (NC)	20.5 (9.80)	32.8 (16.5)	46.8 (24.4)	53.8 (30.4)	59.8 (34.1)	61.8 (34.3)	61.1 (35.7)	60.0 (36.2)	17.7 (19.7)	4.10 (11.0)	0.815 (4.36)[a]

a Represents the concentration at follow-up visits where the last dose was at Week 50.

Abbreviations: C_{trough}: trough concentration; N: number of participants; q2w: every 2 weeks; BLQ: below the LLOQ (0.078 mg/L); LLOQ: lower limit of quantification; NC: not calculated; SD: standard deviation.

Absorption, distribution, and elimination

The parameters of dupilumab disposition in participants with COPD was similar with those reported for dupilumab in the AD, asthma, CRSwNP, EoE, and PN populations based on observed data as well as Pop PK analysis utilizing the global Pop PK model. Dupilumab has previously been shown to be well absorbed (global Pop PK base model-estimated SC bioavailability of 62.8%), distributes primarily within the vascular compartment (global Pop PK base model-estimated volume of distribution of 4.46 L), and exhibits saturable target-mediated elimination in participants with COPD. In Study EFC15804, following discontinuation of study treatment at Week 52, median dupilumab concentration decreased to below the LLOQ at Week 64 follow-up visit. Consistent with the observed data, 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) was 12 weeks for a typical adult patient with COPD.

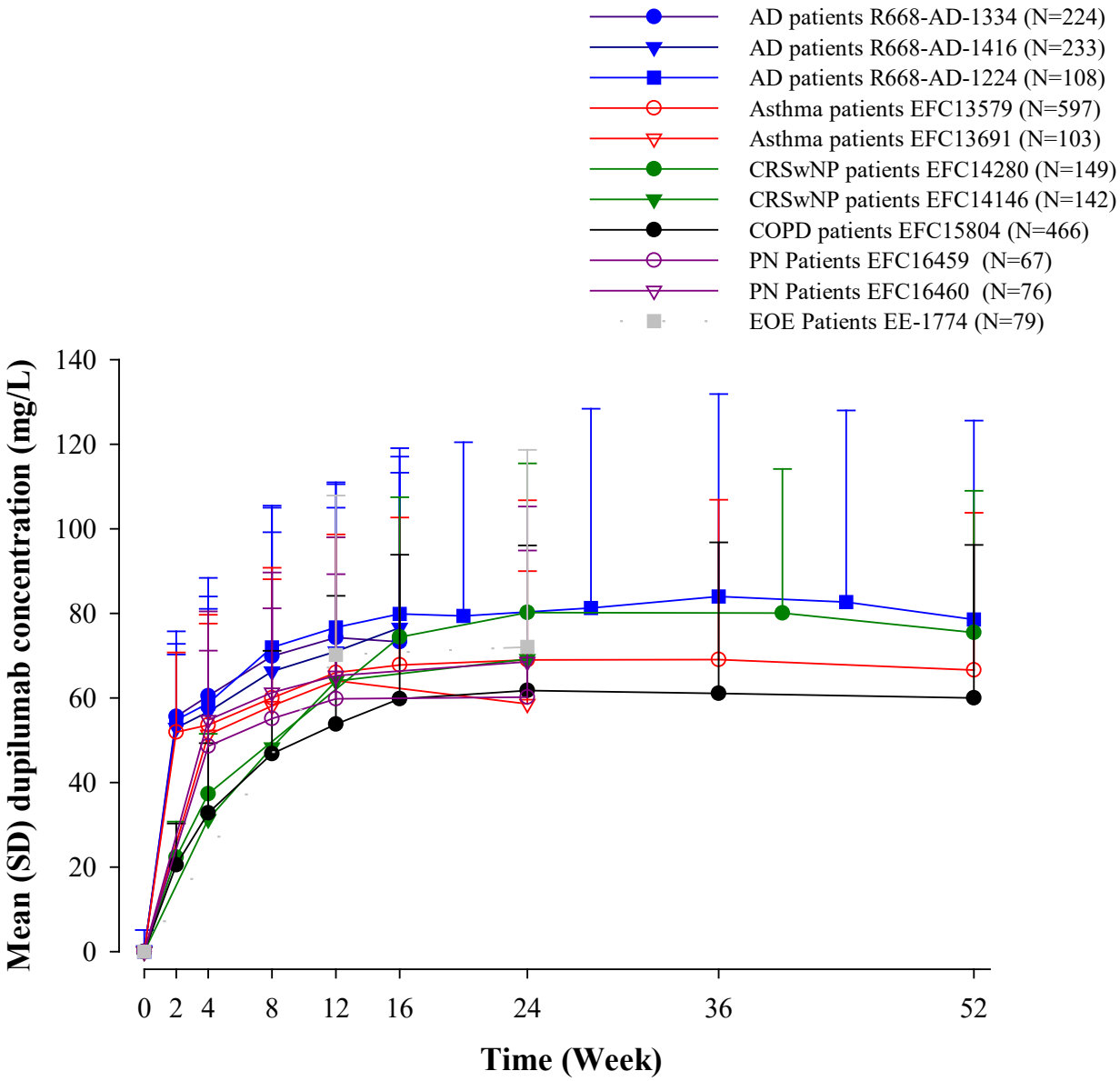
Comparison between adult COPD population and other adult disease populations

As shown in the Figure 1 below the observed dupilumab concentration-time profiles in participants with COPD are similar to those observed in the AD, asthma, CRSwNP, EoE, and PN populations at 300 mg q2w

with various treatment durations, except for the difference in time to reach steady state in participants with COPD/CRSwNP/EoE due to the absence of a loading dose in these populations. The observed dupilumab steady-state exposure (Ctrough) at 300 mg q2w was similar across COPD, AD, asthma, CRSwNP, EoE, and PN populations.

In participants with COPD, steady state was achieved by Week 16 for the 300 mg q2w regimen. The mean steady-state trough concentrations from Week 16 to Week 52 (end of treatment) were consistent and ranged between 59.8 and 61.8 mg/L.

Figure 1 - Mean (SD) trough concentration-time profiles of dupilumab in serum at 300 mg q2w in patients with COPD, AD, asthma CRSwNP, EoE and PN



Sources:

- Study EFC15804 (without a loading dose), PK appendices: 5.3.5.1 Study EFC15804, Appendix 16.2.5 (16.2.5.4.2.1);
- Prior marketing application for CRSwNP for studies EFC14146 and EFC14280 (without a loading dose of 600 mg), PK appendices: 5.3.5.1 Studies EFC14146 and EFC14280, Appendix 16.2.5 (16.2.5.4.1.1);
- Prior marketing application for asthma for studies EFC13579 and EFC13691 (with a loading dose of 600 mg), PK appendices: 5.3.5.1 Studies EFC13579 and EFC13691, Appendix 16.2.5 (16.2.5.4.1.1);
- For PN for studies EFC16459 and EFC16460 (with a loading dose of 600 mg), PK appendices: 5.3.5.1 Studies EFC16459 and EFC16460, Appendix 16.2.5 (16.2.5.4.2.1);

- For EoE for Study R668-EE-1774_CP_03V1 (without a loading dose); 300 mg q2w was studied in the Phase 3 Study R668-EE-1774 Part B; the approved dose in patients with EoE is 300 mg qw;
- Original marketing application for AD, Section 5.3.5.4 Other Study Reports: clinical pharmacology reports R668-AD-1416-CP-01V1, R668-AD-1334-CP-01V1, and R668-AD-1224-CP-01V1 (with a loading dose of 600 mg).

Table 5 - Mean (SD) observed steady-state exposure of dupilumab in adults with COPD, AD, asthma, CRSwNP, EoE and PN

Population	Study identifier	Dose[a]	$C_{trough,ss}$ (SD) (mg/L)	
			N	Observed[b]
COPD	EFC15804	300 mg q2w without loading dose	423	61.8 (34.3)
AD	R668-AD-1334	300 mg q2w	219	73.3 (40.0)
	R668-AD-1416		219	76.6 (40.5)
	R668-AD-1224		101	79.9 (39.2)
Asthma	EFC13579	300 mg q2w	544	69.0 (37.8)
	EFC13691		99	58.8 (31.4)
CRSwNP	EFC14146	300 mg q2w	136	69.2 (36.9)
	EFC14280	without loading dose	142	80.2 (35.3)
EoE	R668-EE-1774 Part B	300 mg q2w without loading dose[c]	46	69.8 (35.9)
PN	EFC16459	300 mg q2w	65	60.2 (34.7)
	EFC16460		67	68.6 (36.7)

Abbreviations: AD: atopic dermatitis; COPD: chronic obstructive pulmonary disease; CRSwNP: chronic rhinosinusitis with nasal polyposis; $C_{trough,ss}$: trough concentration at steady state; EoE: eosinophilic esophagitis ; N: number of patients; PN: prurigo nodularis; q2w: every 2 weeks; SD: standard deviation

a Dose regimen of 300 mg q2w with a loading dose of 600 mg, respectively, in AD, asthma, and PN population. No loading dose in COPD, CRSwNP or EoE populations.

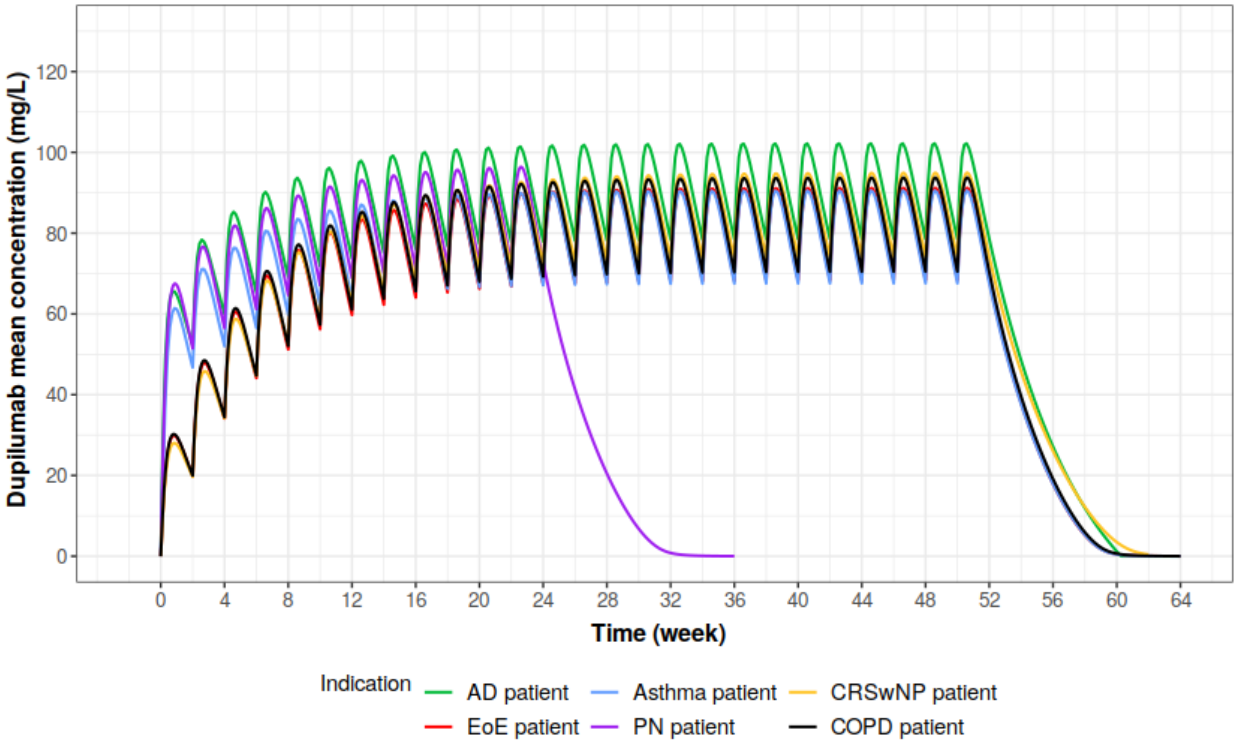
b The observed $C_{trough,ss}$ at Week 24 in COPD and asthma population, at Week 16 in AD population.

c 300 mg q2w was studied in the Phase 3 Study R668-EE-1774 Part B. The approved dose in adults with EoE is 300 mg qw.

Sources:
- 5.3.5.1 Study EFC15804, Appendix 16.2.5 (16.2.5.4.2.1) of the current submission;
- 5.3.5.1 Studies R668-AD-1334, R668-AD-1416, R668-AD-1224, previously submitted in the marketing application for adults with AD;
- 5.3.5.1 Study R668-AD-1526, previously submitted in the marketing application for adolescents with AD;
- 5.3.5.1 Studies EFC13579 and EFC13691, previously submitted in the marketing application for adults and adolescents with asthma;
- 5.3.5.1 Studies EFC14146 and EFC14280, previously submitted in the marketing application for adults and adolescents with CRSwNP;
- 5.3.5.1 Stud EFC15804, previously submitted in the marketing application for adults with PN;
- 5.3.5.1 Study R668-EE-1774 Part B, previously submitted in the marketing application for adults and adolescents with EoE.

The similarity in the PK of dupilumab between COPD, AD, asthma, CRSwNP, EoE, and PN populations was further supported by the results of the Pop PK analysis conducted for the COPD population (Study POH0858). The main sources of variability in dupilumab PK identified in these populations and the magnitude of the covariate effects indicate that body weight is the most influential factor. Consistent with this, the global Pop PK base model, built with data from healthy subjects and patients with AD and asthma (Study POH0668) and including only one covariate (body weight).

Figure 2 - Typical concentration-time profiles of dupilumab at 300 mg q2w in adult patients with COPD, AD, asthma, CRSwNP, EoE, and PN as predicted by population pharmacokinetic models



Abbreviations: AD: atopic dermatitis; COPD: chronic obstructive pulmonary disease; CRSwNP: chronic rhinosinusitis with nasal polyposis; EoE: eosinophilic esophagitis; PN: prurigo nodularis.
Note: The typical profile simulation was conducted at 300 mg q2w using Pop PK models of COPD, CRSwNP and EoE (without a loading dose; 300 mg q2w was studied in the Phase 3 Study R668-EE-1774 Part B; the approved dose in patients with EoE is 300 mg qw), asthma, AD and PN (with a loading dose) for a typical Caucasian adult with COPD, CRSwNP, asthma, AD, PN or EoE, respectively with demographics described as follows: weight of 75 kg (78 kg for asthma, 73 for PN, 79 kg for CRSwNP), albumin of 45 g/L, body mass index (BMI) of 25.1 kg/m^2, creatinine clearance normalized to body surface area (CLCRN) of 111 mL/min/1.73 m^2, and eczema area severity index (EASI) of 29.5 (AD only) and negative ADA (median values of the covariates for the respective populations). 300 mg q2w was studied in the Phase 3 Study R668-EE-1774 Part B. The approved dose in adults with EoE is 300 mg qw.
Sources: Studies POH0858, POH0779, POH0611, POH0530, REGN668-MX-16103-CP-01V1, R668-PK-21229-SR-01V1.

Sources of pharmacokinetic variability

Table 6 - Mean (SD) for post-hoc estimates of steady-state exposure of dupilumab in participants with COPD from Study EFC15804 by covariates tested in population pharmacokinetic analysis (POH0858)

Potential covariates		N[a] (mean weight)	$AUC_{T,ss}$[b] (mg.day/L)	$C_{max,ss}$[b] (mg/L)	$C_{trough,ss}$[b] (mg/L)
All (300 mg q2w)		445 (76.9 kg)	1070 (462)	85.2 (34.3)	62.1 (30.7)
Age (year)	< 65	185 (78.8 kg)	980 (430)	78.7 (32.0)	56.1 (28.3)
	65 - < 75	203 (75.9 kg)	1100 (457)	87.5 (34.0)	64.2 (30.3)
	≥ 75	57 (74.4 kg)	1240 (520)	97.9 (38.4)	74.0 (34.9)
Weight (kg)[c]	< 60	76 (53.3 kg)	1530 (549)	120 (39.9)	91.0 (37.5)
	≥ 60	369 (81.8 kg)	974 (379)	77.9 (28.0)	56.2 (25.3)
Stationary ADA	Negative ADA	396 (76.2 kg)	1100 (462)	87.2 (34.3)	63.9 (30.7)
	Positive ADA	49 (82.5 kg)	848 (400)	68.8 (29.8)	47.2 (26.3)
Sex	Male	287 (80.5 kg)	997 (406)	79.9 (30.4)	57.4 (26.8)
	Female	158 (70.3 kg)	1200 (526)	94.8 (38.7)	70.7 (35.2)

Potential covariates		N[a] (mean weight)	$AUC_{\tau,ss}$[b] (mg.day/L)	$C_{max,ss}$[b] (mg/L)	$C_{trough,ss}$[b] (mg/L)
Race	White	374 (79.0 kg)	1030 (454)	82.1 (33.7)	59.7 (30.1)
	Black	3 (96.3 kg)	782 (211)	64.3 (16.9)	42.1 (12.6)
	Asian	63 (64.2 kg)	1310 (445)	103 (32.9)	76.6 (30.1)
	Other	5 (70.5 kg)	1220 (522)	96.0 (38.2)	72.0 (35.5)
Ethnicity	Japanese	9 (63.7 kg)	1500 (801)	117 (58.5)	90.6 (54.5)
	Non-Japanese	436 (77.2 kg)	1060 (450)	84.5 (33.4)	61.5 (29.8)
	Chinese	52 (64.0 kg)	1280 (360)	101. (27.0)	74.5 (24.3)
	Non-Chinese	393 (78.6 kg)	1040 (467)	83.0 (34.6)	60.5 (31.1)
Albumin (g/L)	30 -< 40	19 (79.6 kg)	859 (429)	69.6 (32.7)	48.0 (27.5)
	40 -<50	395 (76.6 kg)	1090 (472)	86.5 (35.0)	63.3 (31.4)
	≥ 50	31 (79.8 kg)	971 (281)	77.9 (21.2)	55.4 (18.1)
CLCR (mL/min)	< 30	1 (70.0 kg)	1830 (NA)	139 (NA)	116 (NA)
	30 - <60	43 (62.1 kg)	1460 (688)	114 (50.9)	87.8 (46.1)
	60 - <90	138 (68.1 kg)	1190 (383)	94.6 (28.7)	69.7 (25.5)
	≥ 90	263 (84.0 kg)	937 (395)	75.3 (29.2)	53.7 (26.3)
CLCRN (mL/min/1.73 m^2)	< 30	2 (54.3 kg)	2590 (1080)	197 (81.1)	165 (69.7)
	30 - <60	55 (59.1 kg)	1430 (585)	112 (43.2)	84.7 (39.6)
	60 - <90	108 (65.7 kg)	1270 (374)	100. (27.8)	74.7 (25.1)
	≥ 90	280 (84.9 kg)	911 (365)	73.3 (27.)	52.1 (24.4)
FeNO[d] (ppb)	< 20	260 (76.5 kg)	1080 (445)	86.2 (33.)	62.9 (29.5)
	≥ 20	185 (77.6 kg)	1050 (485)	83.7 (36.1)	61.1 (32.3)
FEV_1 reversibility (%)	< 12	306 (77.8 kg)	1030 (441)	82.3 (32.9)	59.7 (29.2)
	≥ 12	139 (75.1 kg)	1150 (497)	91.4 (36.6)	67.4 (33.2)
Pre-bronchodilator FEV_1	< 1.2	215 (71.2 kg)	1200 (519)	94.8 (38.3)	70.3 (34.8)
	≥ 1.2	230 (82.2 kg)	948 (362)	76.1 (27.2)	54.4 (23.8)
Eotaxin-3[d] (pg/mL)	< 146	218 (75.3 kg)	1090 (484)	87.0 (35.8)	63.7 (32.2)
	≥146	227 (78.4 kg)	1050 (440)	83.4 (32.8)	60.6 (29.1)
IgE[d] (ng/mL)	< 120	206 (77.2 kg)	1100 (477)	87.1 (35.2)	63.9 (31.8)
	≥ 120	239 (76.6 kg)	1050 (449)	83.5 (33.5)	60.5 (29.6)
PARC[d] (ng/mL)	< 72.3	217 (75.4 kg)	1140 (504)	90.5 (37.3)	67.0 (33.7)
	≥ 72.3	228 (78.3 kg)	1000 (407)	80.1 (30.4)	57.5 (26.7)
Fibrinogen[d] (mg/dL)	< 350	81 (74.2 kg)	1140 (550)	91.2 (40.9)	66.7 (36.5)
	≥ 350	364 (77.5 kg)	1050 (439)	83.8 (32.6)	61.1 (29.2)
MEOS (Giga/L)	0.3 - < 0.5	297 (78.5 kg)	1070 (469)	85.0 (34.7)	62.1 (31.2)
	≥ 0.5	148 (73.7 kg)	1070 (449)	85.6 (33.6)	62.2 (29.7)
Number of moderate and severe exacerbations[e]	< 4	96 (77.1 kg)	1120 (428)	89.3 (31.8)	65.3 (28.4)
	≥ 4	349 (76.9 kg)	1050 (471)	84. (34.9)	61.2 (31.2)

Abbreviations: ADA: anti-drug antibody; $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; CLCR: creatinine clearance; CLCRN: creatinine clearance normalized by body surface area; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in first second; MEOS: max eosinophils counts during screening eosinophil; IgE: total Immunoglobulin; N: subject number; PARC: pulmonary and activation-regulated chemokine; q2w: every two weeks; SD: standard deviation.

a. In Study EFC15804, 21 out of 466 participates (ie, PK population) were not included in the post-hoc PK exposure summary due to dose discontinuation for those paritcipants with last dose earlier than Week 22.

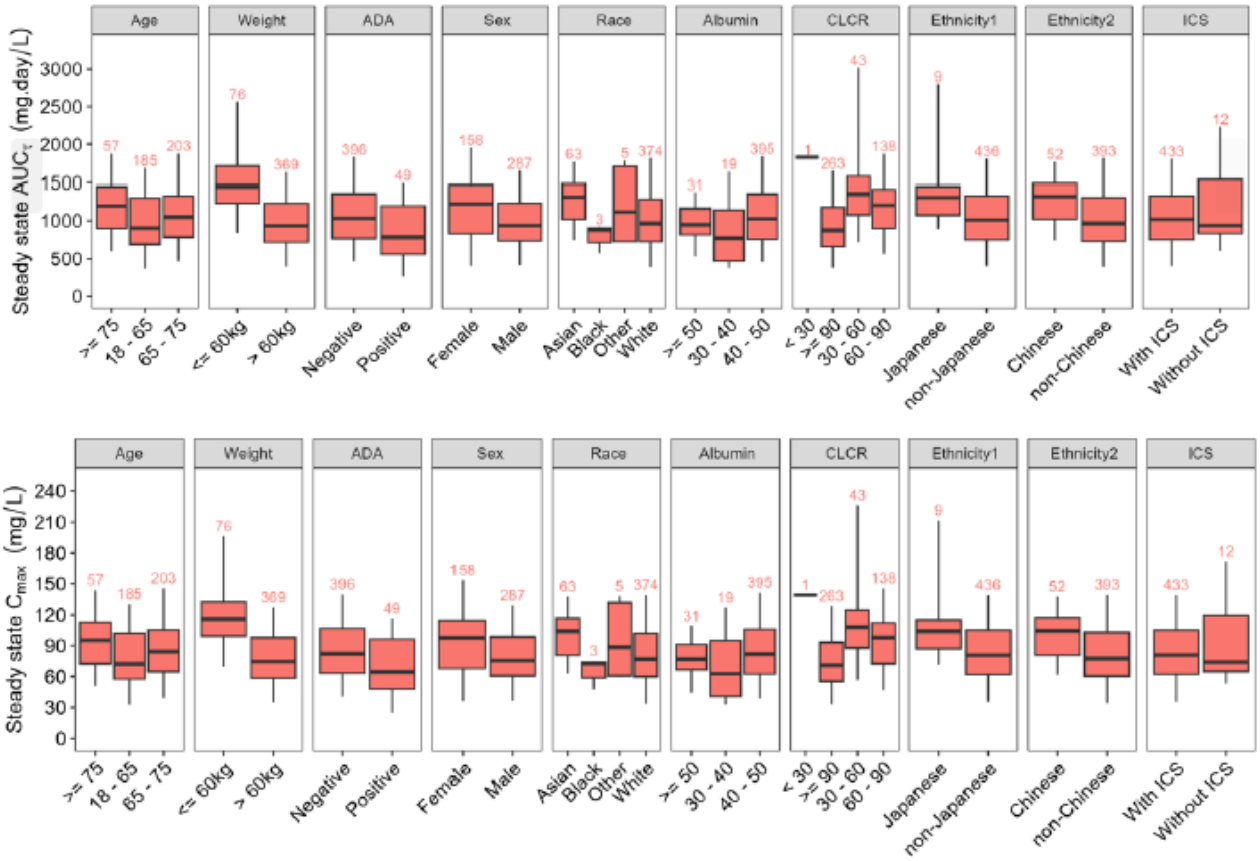
b. Predicted $AUC_{\tau,ss} = AUC_{[Week\ 22 - Week\ 24]}$ for 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24.

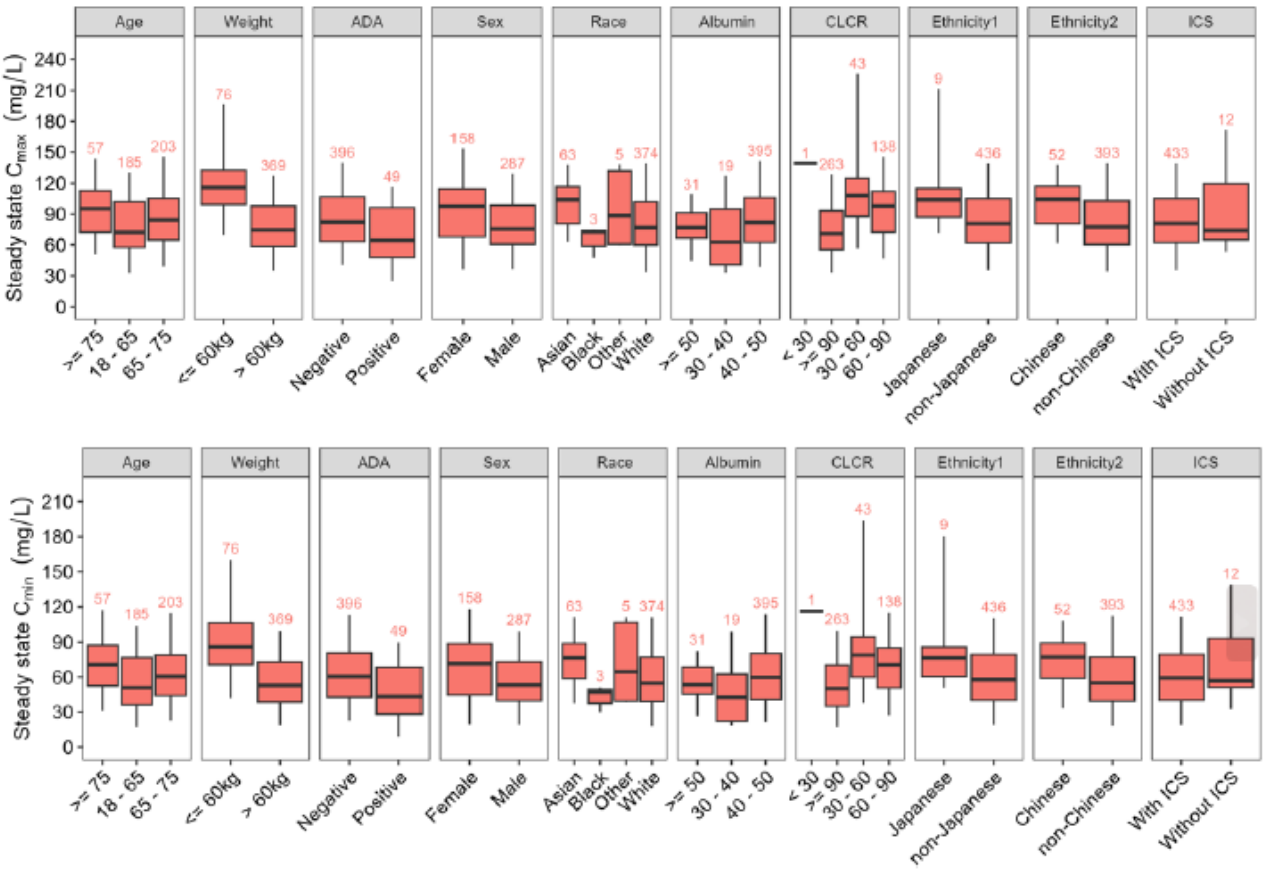
c. The mean weight for Non-Asian (N=95) is 78.8 kg. The mean (SD) $AUC_{t,ss}$, $C_{max,ss}$ and $C_{min,ss}$ for Non-Asian are 1080 (529) mg·day/L, 85.7 (39.3) mg/L and 62.9 (35.1) mg/L, respectively.

d. In this summary, the missing values for baseline FeNO (N=33), eotaxin-3 (N=7), IgE (N=25), PARC (N=11) and fibrinogen (N=4) were imputed using the population median in Study EFC15804.

e. Number of moderate and severe exacerbations prior to the study (1 year prior).

Figure 3 - Boxplot of dupilumab predicted $AUC_{t,ss}$, $Cmax_{,ss}$ and $Ctrough_{,ss}$ in patients with COPD as a function of intrinsic/extrinsic factors





Abbreviation: ADA: anti-drug antibody; AUC_{τ}: $AUC_{\tau,ss}$, area under the concentration-time curve from 0 to τ at steady state; C_{max}: $C_{max,ss}$, maximum concentration at steady state ; C_{mm}: $C_{trough,ss}$, minimum concentration at steady state; CLCR: creatinine clearance; RI: renal impairment.

Note: Lower and upper end of whisker indicated 5th and 95th percentile of $AUC_{\tau,ss}$, $C_{max,ss}$ and $C_{trough,ss}$ (Week 22 to Week 24). Number inside plot panel indicate patient numbers in each bin of covariate; Weight (kg), Age (year), Negative ADA = negative ADA at all the time, Positive ADA = positive ADA at any time, Sex, Race, Albumin (g/L), CLCR (mL/min),Ethnicity and ICS = inhaled corticosteroid used as concomitant medication.

Intrincis factors

Body weight

Consistent with previous findings in different disease and age populations, body weight is the primary factor explaining between-subject variability of dupilumab PK in participants with COPD with a body weight range of 39 to 130 kg. The linear elimination rate constant (K_e), volume of the central compartment (V_2), and maximum target-mediated rate of elimination (V_{max}) decreased with a decrease in body weight. Hence, exposure increased with a decrease in body weight in participants with COPD (Study POH0858).

Dupilumab exposures for participants with COPD in Study EFC15804 by 3 body weight groups (<60 kg, 60 to <90 kg, and ≥ 90 kg) are provided in Table 7. Similar to results of 2 weight groups (≤60 kg and >60 kg, Study POH0858), body weight is the primary factor explaining between- subject variability of dupilumab PK in participants with COPD. Dupilumab exposure increased with a decrease in body weight in participants with COPD. The results of dupilumab exposures in participants with COPD by body weight groups are consistent with observed dupilumab exposures by body weight groups in other indications (AD, asthma, CRSwNP, EoE, and PN).

Table 7 – Mean (SD) predicted steady – state exposures of dupilumab in participants with COPD at 300 mg q2w by body weight groups (N=445)

Weight Group (kg)	N[a] (mean weight)	$AUC_{\tau,ss}$[b] (mg.day/L)	$C_{max,ss}$[b] (mg/L)	$C_{trough,ss}$[b] (mg/L)
< 60	72 (53.0 kg)	1530 (561)	120 (40.8)	90.7 (38.4)
60 to < 90	282 (74.8 kg)	1070 (366)	85.4 (27.0)	62.5 (24.7)
≥ 90	91 (102 kg)	693 (276)	56.6 (20.2)	38.3 (18.5)
≤ 60[c]	76 (53.3 kg)	1530 (549)	120 (39.9)	91.0 (37.5)
> 60[c]	369 (81.8 kg)	974 (379)	77.9 (28.0)	56.2 (25.3)

Abbreviation: $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; N: subject number; q2w: every two weeks; SD: standard deviation.

a. In study EFC15804, 21 out of 466 participants (i.e., PK population) were not included in the post hoc PK exposure summary due to dose discontinuation for those paritcipants with last dose earlier than Week 22.
b. Predicted $AUC_{\tau,ss}$ = AUC[Week 22 – Week 24] for 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24.
c. Revised results of two weight groups in Table 6 of POH0858 report: two weight groups category should be ≤ 60 kg and > 60 kg.

Age

In participants with COPD ranging from 40 to 80 years, majority were elderly participants: N=275 participants ≥65 years of age and N=60 participants ≥75 years, respectively; representing 59.0% and 12.9% of total participants in the Pop PK dataset. Dupilumab PK parameters were comparable across different age groups, consistent with previous findings for different disease populations. Due to the lack of age effect on PK in adults and as there are no clinically significant differences in efficacy and safety (see 5.4 and 5.5.) across age subgroups, no dose adjustment based on age is recommended in participants with COPD.

Gender

There are no differences in the dupilumab concentrations between female and male participants with COPD in Study EFC15804. The post-hoc assessment (Study POH0858) of data from 169 (36.3%) female and 297 (63.7%) male participants confirmed that gender had no impact on dupilumab PK, similar to previous findings in patients with AD, asthma, CRSwNP, EoE, and PN. Due to the lack of an effect of gender on PK and, as there are no clinically significant differences in efficacy and safety across gender subgroups, no dose adjustment is recommended based on gender.

Race/ethnicity

Post-hoc assessments (Study POH0858) of the data from participants with COPD in Study EFC15804 consisting of White (N=391, 83.9%), Asian (N=67, 14.4%), Black (N=3, 0.6%), and other races (N=5, 1.1%) were conducted.

The number of Black participants enrolled in Study EFC15804 was low. The lower mean exposure in the Black population versus other races is mainly the result of differences in body weight (mean weight of 96.3 kg in Blacks versus 64.2-79.0 kg in other races). The clinical efficacy and safety in Black/of African descent participants are discussed section 5.4 and 5.5.

The higher mean exposure (observed C_{trough} and post-hoc estimate of steady-state exposure in Asians versus non-Asians could be attributed mainly to the differences in body weight (mean weight of 64.2 kg in Asians versus 79.0 kg in White). Similarly, when data from subsets of participants with COPD from Japan and China are considered, the higher mean exposure in this subset of Japanese participants and

Chinese participants versus the rest of the non-Japanese participants and non-Chinese participants, respectively, is mainly the result of differences in body weight.

As there are no clinically significant differences in efficacy and safety across race groups or ethnic groups, no dose adjustment is recommended based on race or ethnicity.

Table 8 - Mean (SD) for post-hoc estimates of steady-state exposure of dupilumab by race in population pharmacokinetic analyses in participants with COPD, asthma, CRSwNP, or PN

Population (Study)	Pop PK Analysis	Race	N[a] (mean/median weight)	$AUC_{\tau,ss}$[b] (mg.day/L)	$C_{max,ss}$[b] (mg/L)	$C_{trough,ss}$[b] (mg/L)
COPD (EFC15804)	POH0858	White	374 (79.0 kg)	1030 (454)	82.1 (33.7)	59.7 (30.1)
		Black	3 (96.3 kg)	782 (211)	64.3 (16.9)	42.1 (12.6)
		Asian	63 (64.2 kg)	1310 (445)	103 (32.9)	76.6 (30.1)
		Other	5 (70.5 kg)	1220 (522)	96. (38.2)	72.0 (35.5)
Asthma (DRI12544 and EFC13579)	POH0530	White	652 (79 kg)	1028 (558)	82.1 (42.1)	65.3 (38.5)
		Black	27 (89 kg)	890 (464)	71.2 (36.3)	54.2 (29.3)
		Asian	101 (64 kg)	1399 (654)	110 (48.9)	89.1 (45.3)
		Other	4 (81 kg)	661 (133)	58.2 (10.9)	39.4 (16.2)
CRSwNP (EFC14146 and EFC14280)	POH0611	White	366 (79.9 kg)	1179 (447)	92.3 (33.1)	71.0 (29.7)
		Black	5 (105.4 kg)	878 (438)	69.6 (33.0)	51.4 (28.3)
		Asian	36 (64.3 kg)	1489 (452)	115 (33.4)	91.3 (30.0)
		Other	11 (85.3 kg)	1196 (487)	93.1 (35.9)	72.3 (32.3)
PN (EFC16459 and EFC16460)	POH0779	White	79 (76.8 kg)	1120 (513)	89.2 (38.0)	66.0 (34.1)
		Black	11 (94.3 kg)	645 (278)	53.0 (20.7)	34.4 (18.4)
		Asian	44 (67.1 kg)	1220 (402)	97.0 (30.0)	71.7 (26.5)
		Other	5 (75.2 kg)	1300 (799)	103 (59.0)	76.8 (53.5)

Abbreviations: $AUC_{\tau,ss}$: area under the concentration time curve from time 0 to 14 days at steady state; $C_{max,ss}$: maximum concentration at steady state; $C_{trough,ss}$: minimum concentration at steady state; N: participant number; NA: not applicable; ICS: inhaled corticosteroid; LABA: long-acting beta agonist; LAMA: long acting muscarinic antagonist; q2w: every two weeks; SD: standard deviation.

a Mean weight for COPD and PN populations, median weight for CRSwNP and asthma populations.

b Predicted $AUC_{\tau,ss} = AUC_{[Week\ 22 - Week\ 24]}$ for 300 mg q2w. $C_{max,ss}$ and $C_{trough,ss}$ were calculated over Week 22 and Week 24.

Other laboratory parameters

The comparison of Pop PK model-predicted post-hoc estimates (Study POH0858) confirmed that albumin had no clinical meaningful impact on dupilumab PK in participants with COPD, similar to previous findings in patients with AD, asthma, CRSwNP, EoE, and PN.

Baseline biomarkers and disease markers

The influence of baseline covariates on the PK of dupilumab was assessed based on a comparison by Pop PK model-predicted post-hoc estimates (Study POH0858), baseline type 2 inflammation biomarkers (FeNO, eosinophils, eotaxin-3, PARC, and total IgE) and baseline disease characteristics (number of moderate or severe exacerbations prior to the study, baseline pre-BD FEV_1, and baseline FEV_1 reversibility). None of these baseline characteristics significantly affected the PK of dupilumab in participants with COPD.

Disease populations

The observed dupilumab steady-state C_{trough} in participants with COPD are similar to those with AD, asthma, CRSwNP, EoE, and PN and confirmed by Pop PK analysis via MAP Bayesian approach.

Extrinsic factors

Concomitant medications

Based on a comparison by Pop PK post-hoc assessment of individual steady-state exposure concomitant medications (LABA, LAMA, and ICS) had no effect on dupilumab PK in participants with COPD (Study POH0858).

2.4.3. Pharmacodynamics

Mechanism of action

The type 2/Th2 cytokines such as IL 4, IL 5, and IL 13 act in concert to induce the production of chemokines, including PARC and eotaxin 3, which are known potent chemoattractants for Th2 cells and eosinophils. IL-4 and IL-13 also mediate the regulation of B-cell immunoglobulin class switching and induce the production of total IgE. Since activation of IL 4 and IL 13 signaling precedes the release of pro-inflammatory mediators, antagonism of these cytokines signaling by dupilumab reduces the pro-allergic and other type 2 responses, resulting in subsequent therapeutic benefit. As upregulation of nitric oxide synthase during airway inflammation is reflected by elevation in exhaled nitric oxide, FeNO is considered as a marker for airway inflammation with reports suggesting that high FeNo may also be indicative of eosinophilic airway inflammation in patients with COPD.

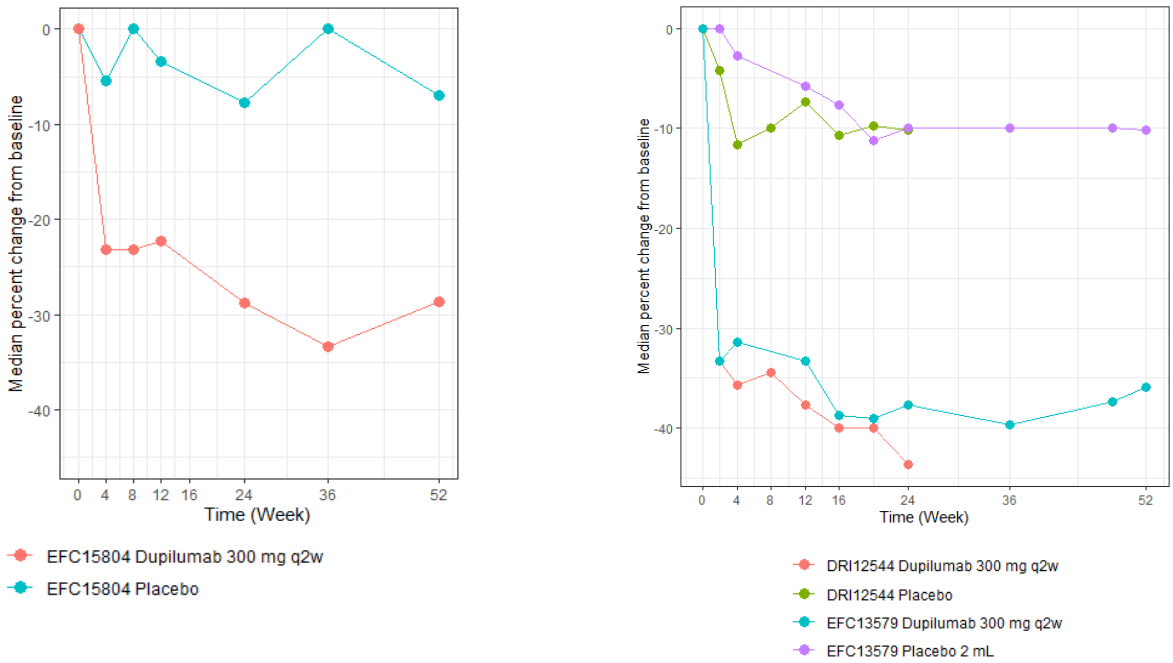
Primary and secondary pharmacology

Fractional exhaled nitric oxide

A marked decrease in FeNO was observed in the dupilumab group by Week 4, with a median percent change from baseline of -23.1% as compared to -5.4% in the placebo group. The effect was maintained through the 52-week intervention period. At Week 52, the median percent change from baseline was -28.6% in the dupilumab group as compared to -6.9% in the placebo group. The percent change from baseline profiles of FeNO showed a similar median magnitude of effect over time in asthma and COPD patient populations.

Figure 4 - Median percent change in FeNO over 52 weeks of treatment with dupilumab or placebo in patients with COPD or asthma

Adults with COPD (EFC15804)[a]	Adults and adolescents with asthma (Studies DRI12544[c] and EFC13579[b])



Abbreviations: EOS: end of study; EOT: end of treatment.
Note: N was as follows:
a Study EFC15804 dupilumab 300 mg q2w N = 434, placebo N = 441. EOT = 52 weeks; EOS = 64 weeks;
b Study EFC13579 300 mg q2w N = 632, placebo 2 mL (matching placebo for 300 mg q2w) N = 321. EOT = 52 weeks; EOS = 64 weeks;
c Study DRI12544 300 mg q2w N = 156, placebo N = 158. EOT = 24 weeks; EOS = 40 weeks.
Sources:
- 5.3.5.1 Study EFC15804 of the current submission;
- 5.3.5.1 Studies DRI12544 and EFC13579, previously submitted in the marketing application for adults and adolescents with asthma.

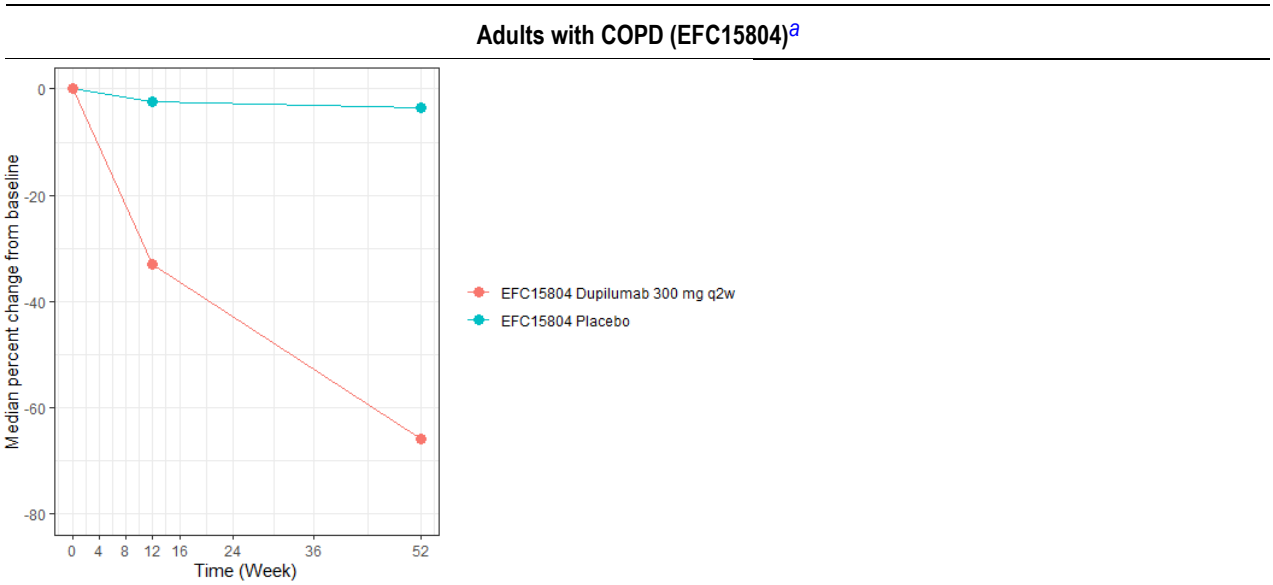
Eotaxin-3 in plasma

At baseline, median eotaxin-3 levels were similar between treatment groups: 146 pg/mL in the dupilumab group and 154 pg/mL in the placebo group. A marked decrease in eotaxin-3 was observed by Week 4 and was maintained throughout the 52-week intervention period in the dupilumab group, while no notable changes were observed in the placebo group. At Week 4, the median percent change from baseline in eotaxin-3 was -30.64% in the dupilumab group versus 3.13% in the placebo group. At Week 52, the median percent change from baseline in eotaxin-3 was -35.53% in the dupilumab group versus -1.85% in the placebo group. The percent change from baseline profiles of eotaxin-3 showed a similar magnitude of effect over time in COPD, asthma, CRSwNP, and EoE populations.

Total IgE in serum

Concentrations of total IgE in serum showed a continuous decline throughout the dupilumab-treatment period. Median total IgE concentrations at baseline were 121 IU/mL for the dupilumab group and 116 IU/mL for the placebo group. The median percent reduction from baseline in total IgE concentrations with dupilumab treatment was -76% at Week 52. The decline in total IgE, a marker specific for type 2 immunity, is consistent with effective IL-4 and IL-13 signaling blockade. The IgE profiles showed a similar median magnitude of effect over time in COPD, AD, CRSwNP, PN, asthma, and EoE populations.

Figure 5 - Median percent change in total IgE in serum over time during dupilumab or placebo treatment in adults with COPD



Abbreviations: EOS: end of study; EOT: end of treatment.

a Study EFC15804 dupilumab 300 mg q2w N = 443, placebo N = 443. EOT = 52 weeks; EOS = 64 weeks.

Sources:

- 5.3.5.1 Study EFC15804 of the current submission;

Immunogenicity Data

In study EFC15804, the treatment-emergent ADA incidence during the on-treatment period (up to Week 52) was 6.5% in the dupilumab group compared to 1.5% in the placebo group.

Table 9- ADA incidence in Phase 3 study in participants with COPD (EFC15804) during the on-treatment period

Anti-dupilumab antibodies N (%)	EFC15804	
	Placebo (N=453)	Dupilumab 300 mg q2w (N=462)
Pre-existing ADA[a]	6 (1.3%)	5 (1.1%)
Treatment-emergent response[b]	7 (1.5%)	30 (6.5%)
Persistent response[c]	1 (0.2%)	10 (2.2%)
Indeterminate response[d]	1 (0.2%)	4 (0.9%)
Transient response[e]	5 (1.1%)	16 (3.5%)
Peak post-baseline titer		
Low (<1,000)	7 (1.5%)	27 (5.8%)
Moderate (1,000-10,000)	0 (0%)	1 (0.2%)
High (>10,000)	0 (0%)	2 (0.4%)
Treatment-boosted response[f]	0 (0%)	0 (0%)
Neutralizing antibodies	5 (1.1%)	5 (1.1%)

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.

The incidence of treatment-emergent ADAs through Week 64 was 10.0% in the dupilumab group compared to 2.4% in the placebo group. The proportion of participants with a treatment-emergent ADA-positive response to dupilumab during the 52-week treatment period was similar from Week 12 to Week 52 (4.3% to 6.7%) and was 9.8% at Week 64 in the post treatment period.

The ADA incidence was generally similar across the AD, asthma, CRSwNP, EoE, PN, and COPD populations in the on-treatment period with respect to treatment emergent positive ADA response (2.6-6.6%), persistent ADA response (0-2.2%), and NAb response (1.0-3.4%) after 24 or 52 weeks of treatment with dupilumab 300 mg q2w with or without a loading dose.

2.4.4. PK/PD modelling

PK in participants with COPD was evaluated with a maximum a posteriori (MAP) Bayesian approach (Study POH0858) using an established Pop PK model (Study POH0668; previously submitted in the application supporting the CRSwNP indication). The E-R or PK/PD relationship for key efficacy endpoints in the COPD population was assessed using a descriptive E-R analysis by exposure quartiles as well as an empirical model-based PK/PD analysis (Study CTS0124) with data from Study EFC15804.

Table 10 - Summary of clinical studies included in the population pharmacokinetic (Study POH0668) and empirical pharmacokinetic/pharmacodynamic (Study CTS0124) analyses

Phase	Study	Dupilumab Dose Regimens	Duration of Treatment	Population	PK Sampling	N[a]
3	EFC15804	300 mg q2w SC	52 weeks	Adult participants with COPD	Sparse sampling[b]	466[c]

Abbreviations: COPD: chronic obstructive pulmonary disease; q2w: every two weeks; SC: subcutaneously.

a. N is the number of PK population, which was defined as patients who received at least 1 dose of dupilumab and with at least one post-dose dupilumab concentration in serum.

b. Samples collected at predose (Week 0), during treatment (Weeks 2, 4, 8, 12, 16, 24, 36, 52), and follow-up period (Weeks 56, 60 and 64).

c. Total number of participants in EFC15804 was 939. There were 471 placebo participants and 468 participants who were randomly assigned to be exposed to dupilumab. Out of these 468 participants, 466 participants received at least 1 dose of dupilumab with available PK post-dose data.

Study type	Study code	Dose or dose range Duration of intervention	Number of study participants randomized	Dupilumab PK sampling
Pharmacokinetic-pharmacodynamic analysis, Phase 3 data in participants with COPD[a]				
PK/PD	CTS0124	Data from Phase 3 (EFC15804) study	466 dupilumab 471 placebo	

Abbreviations: PD: pharmacodynamic; PK: pharmacokinetic; COPD: chronic obstructive pulmonary disease; Pop PK: population PK; q2w: every 2 weeks; SC: subcutaneous.

a Data up to the data cut-off date of 08 February 2023 for Study EFC15804 with PK/ADA data cut-off date of 19 January 2023.

Study POH0858

Population Pharmacokinetic Analysis of Dupilumab Using Data from a Phase 3 Study EFC15804 in Participants with Chronic Obstructive Pulmonary Disease

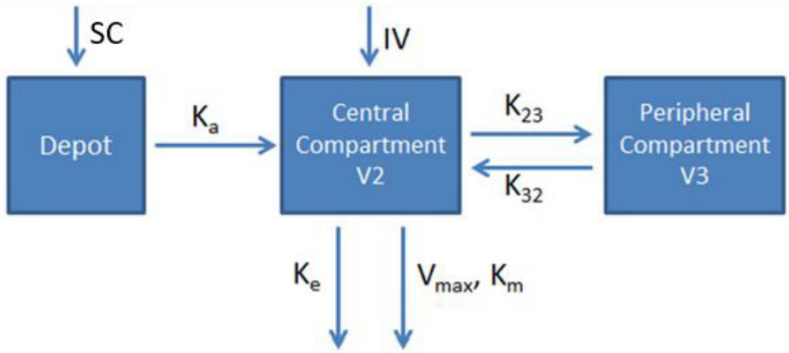
Objectives and methods: The main objectives of this analysis were to apply dupilumab global Pop PK base model to characterize dupilumab PK in participants with COPD and to generate individual dupilumab post

hoc exposures and assess the influence of intrinsic and extrinsic factors on dupilumab PK in participants with COPD.

Concentrations of functional dupilumab in serum and associated dose records in participants with COPD from a Phase 3 study after subcutaneous (SC) administration of dupilumab were included in the analysis as shown in Table 10. At the Pop PK cut-off date of 19 January 2023 (prior to clinical database lock), PK data were available for 80% of participants (N=372) at Week 52 and 70% of participants (N=325) at Week 64. The final dataset included 466 participants with COPD with a total of 3564 dupilumab concentrations.

Given the similarity in the observed dupilumab PK profiles across different populations, the previously developed global Pop PK base model based on pooled data from HV and patients with AD and asthma was utilized in the analysis in participants with COPD from study EFC15804. This global Pop PK base model was developed based on pooled data from 6 studies in HV, 10 studies in AD adult patients and 4 studies in asthma adult and adolescent patients and was a two-compartment model with a first order absorption and parallel linear and nonlinear elimination, with body weight as a covariate (POH0668). This global Pop PK base model was applied to the sparse PK data from participants with COPD in Phase 3 study EFC15804 by fixing all the population parameter estimates to generate individual PK parameters and exposure estimates for participants with COPD with maximum a posteriori (MAP) Bayesian approach. The adequacy of the global Pop PK base model was confirmed by the examination of the goodness of fit plots, visual predicted checks (VPC) and the estimates of quality criteria. Given the well characterized body weight effect on dupilumab PK, the covariate effect of weight on Ke, V2 and Vmax was included in the global Pop PK base model structure.

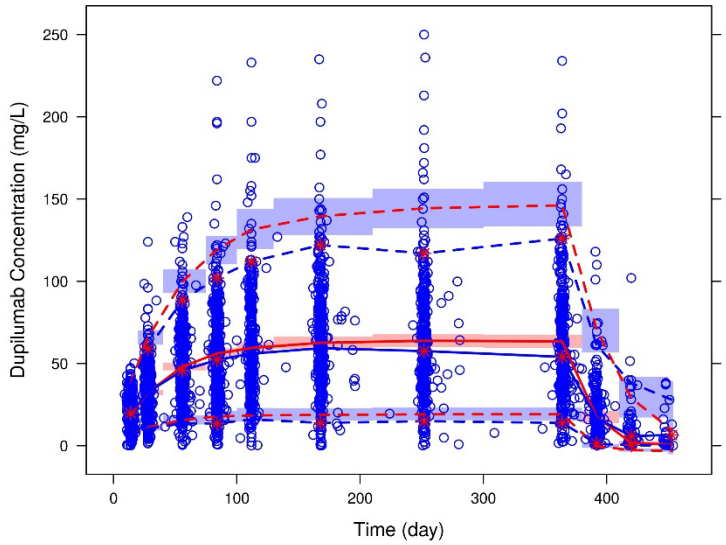
Figure 6 - Schematic structure of dupilumab global PK base model



Abbreviations: IV: intravenous; K_a : absorption rate constant; V_2 : central compartment volume; V_3 : peripheral compartment volume; K_{23}, K_{32} : inter-compartmental rate constants; K_e : elimination rate constant; SC: subcutaneous; V_{max} : maximum target-mediated rate of elimination; K_m : Michaelis constant.

Results: Goodness-of-fit plots and visual predictive checks (Figure 6) all demonstrated a reasonable model performance. These results indicated the adequate predictive performance of the global Pop PK base model in participants with COPD.

Figure 7 - Visual predictive check for global Pop PK base model in participants with COPD from Study EFC15804 (POH0858)



Legend: blue dots: observations; blue solid and dashed lines: the median and bounds (5th and 95th percentiles) of observed concentrations at each time bin; red solid and dashed lines: the median and bounds (5th and 95th percentiles) of predicted concentrations at each time bin; pink and light blue areas: confidence intervals of median and percentiles of predicted concentrations at each time bin.

The predicted dupilumab typical concentration-time profile at 300 mg q2w in adult patients with COPD is very similar to the observed trough concentration-time profiles in study EFC15804 and also comparable to the other dupilumab indications (see Section 2.4.2).

Individual post hoc exposure estimates were used to assess the effect of selected intrinsic and extrinsic factors including demographics (gender, age, and race), baseline laboratory parameters and baseline disease characteristics. As described in Section 2.4.2, no relevant effect on the dupilumab PK is apparent considering intrinsic and extrinsic factors and no dose adjustment is recommended for PN with respect to PK covariates which is endorsed.

Study CTS0124

Empirical exposure-response modeling for dupilumab in participants with moderate-to-severe chronic obstructive pulmonary disease with type 2 inflammation

Objectives and methods: The objectives of empirical PK/PD analyses in this study were to understand dupilumab E-R relationships in participants with COPD with regard to the primary efficacy endpoints and to identify covariates influencing E-R relationships. Efficacy endpoints assessed were the annualized rate of moderate or severe exacerbation events and the absolute change from baseline at Week 12 in pre-BD FEV_1. The PK/PD analysis included data from the pivotal Study EFC15804.

For the model-based analysis, three base models of the E-R relationship, linear, log linear, and maximum drug-induced effect (E_{max}), with appropriate covariates, were compared to select the best model by a goodness of fit criterion (Akaike information criterion with sample size correction). The exposure metric used was the predicted average concentration of dupilumab over the event observation period ($C_{average}$) or observed steady-state trough concentration (C_{trough}).

The descriptive E-R analyses for the annualized rate of moderate or severe exacerbation events and pre-BD FEV_1 are presented in the following. The exposure metrics used were predicted $C_{average}$ and observed C_{trough}. Any missing observed C_{trough} at Week 12 was imputed using observed C_{trough} at Week 8.

Results: The exposure-response relationships between moderate or severe exacerbation (annualized event rate) and $C_{average}$ were best described by a log-linear model. Two interaction covariates were identified, including baseline blood eosinophil count (screening eosinophils <0.5 Giga/L), and territory (European Union). Participants with baseline eosinophils <0.5 Giga/L and from European Union were predicted to have lower efficacy consistent with subgroup analysis of AECOPD by baseline eosinophil and by territory. Subgroup analysis showed overall a consistent trend of reduction in the rate of moderate or severe AECOPD events with dupilumab versus placebo by territory subgroups. As shown in Table 11, the model predicted responses for moderate or severe exacerbation reduction are in good agreement with the observed data.

Table 11 - Observed and pharmacokinetic/pharmacodynamic model-predicted moderate or severe exacerbation event: relative risk of active versus placebo (Study CTS0124)

Comparison versus placebo	Observed adjusted RR (95% CI)[a]	Model-predicted RR (95% CI)[b]	Median $C_{average}$ at Week 24[c] (mg/L)
Dupilumab	0.71 (0.58, 0.86)	0.68 (0.42, 0.95)	63.6

Abbreviations: CI: confidence interval; $C_{average}$: average concentration (=the estimated AUC Pop PK model during the event observation period and standardized by observation days); PD: pharmacodynamic(s); PK: pharmacokinetic(s) RR: relative risk of active versus placebo.

a Observed relative risk of active versus placebo (95% CI) from PD model in the PK/PD population.

b Predicted relative risk (95% CI) of active versus placebo at median $C_{average}$ from PK/PD model at the median of baseline covariates and estimated.

c $C_{average}$ (average concentration) is the Pop PK model estimated cumulative AUC during the event observation period and standardized by observation days.

Source: 5.3.3.5 Study CTS0124.

The exposure-response relationship between FEV_1 (absolute change from baseline at Week 12) and dupilumab C_{trough} at Week 12 was best described by a log-linear model. The significant covariate was baseline eosinophils, while other identified covariates (baseline FeNO, fibrinogen, pre-BD FEV_1, post-BD FEV_1, region [Asian], and height) contributed to a lesser extent to the variability in the FEV_1 response. Participants with higher baseline blood eosinophils counts were predicted to have greater efficacy.

Table 12 - Observed and pharmacokinetic/pharmacodynamic model-predicted pre-bronchodilator FEV_1 change from baseline versus trough concentration at Week 12 (Study CTS0124)

Comparison versus placebo	Observed LS mean difference (95% CI)[a] (L)	Model-predicted mean difference (95% CI)[b] (L)	Median C_{trough} at Week 24 (mg/L)
Dupilumab	0.085 (0.042, 0.127)	0.072 (0.026, 0.117)	50.6

Abbreviations: CI: confidence interval; C_{trough}: trough concentration; LS: least square; PD: pharmacodynamic(s); PK: pharmacokinetic(s)
Observed effects were based on PD analysis of observed FEV_1 change from baseline at Week 12 as response and the treatment arm, age, sex, height, region (Asia, East Europe, Latin America and Western Countries), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (former or current smokers), and pre-BD FEV_1 at baseline as covariates.

a Observed LS mean (95% CI) treatment differences of active versus placebo in EFC15804 from analysis of covariance (ANCOVA model).

b Predicted mean (95% CI) treatment differences of active versus placebo at median C_{trough} and median screening eosinophil from PK/PD model.

Source: 5.3.3.5 Study CTS0124.

Overall, E-R relationships were established for efficacy endpoints of pre-BD FEV_1 at Week 12 and moderate or severe exacerbation rate in participants with COPD. Higher baseline eosinophil counts, a marker of type 2 inflammation, correlated with a greater efficacy.

Descriptive quartile analysis for annualized rate of moderate or severe exacerbation events

The annualized rate of moderate or severe exacerbation events response over the exposure quartiles appeared to show a generally flat relationship within the range of dupilumab concentrations at 300 mg q2w dose regimen. Except for small numerical difference of baseline FeNO in the Q1 compared with other quartiles, in general the baseline values of type 2 inflammation markers (eosinophils and FeNO), and the number of moderate or severe exacerbations prior to the study, were balanced in each exposure quartile. Additionally, baseline body weight was generally higher in the patients in the lowest exposure quartile, which is expected, since body weight is the main source of PK variability.

Table 13 - Annualized rate of moderate or severe exacerbation events by quartiles of observed average dupilumab concentration over 52 weeks in participants with COPD in Study EFC15804 (Study CTS0124)

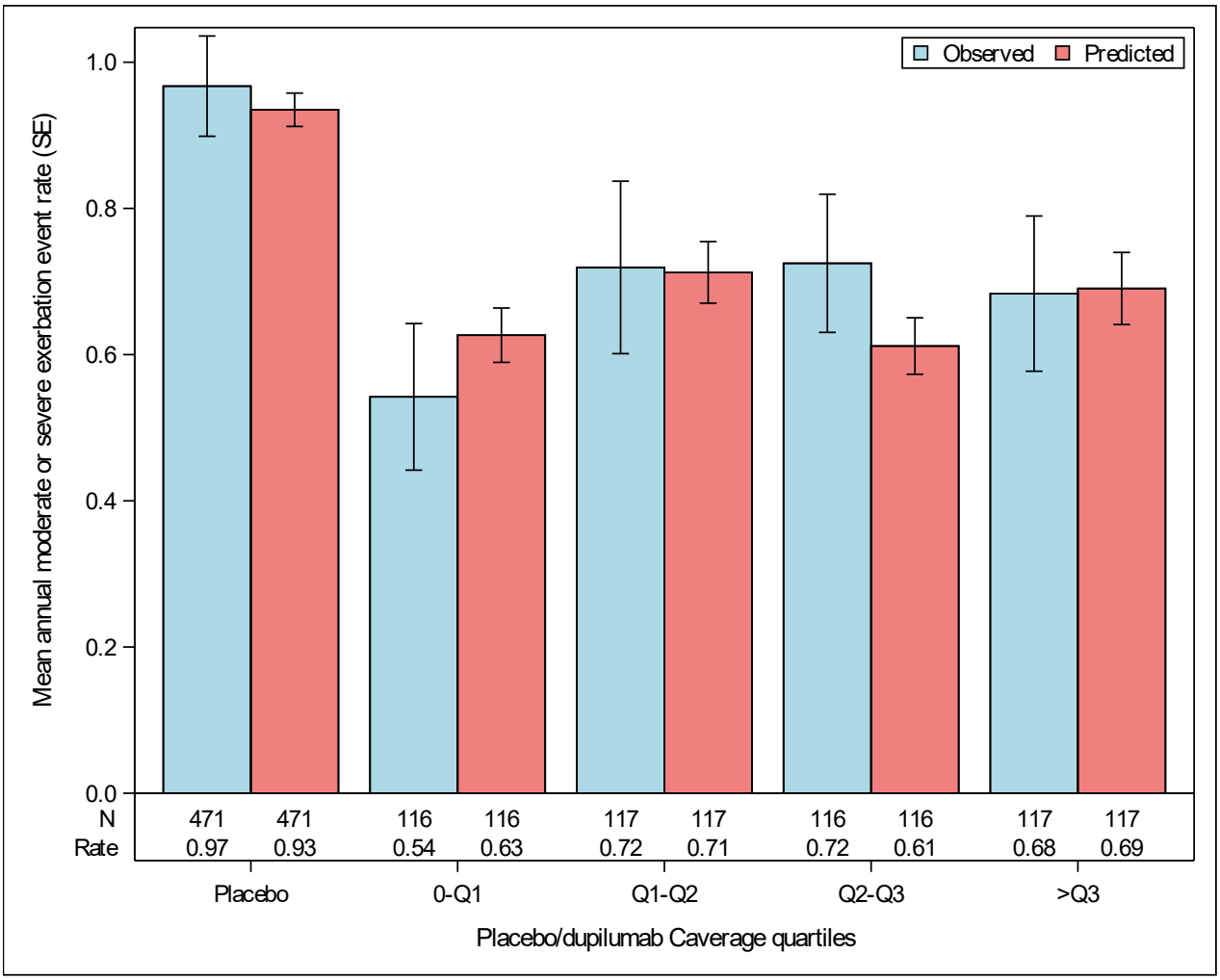
$C_{average}$ quartile	N	Annualized exacerbation event rate RR mean (SE)	$C_{average}$ mean (SE) (mg/L)	Number of moderate or severe exacerbations prior to the study	EOS screening mean (Giga/L)	EOS BL mean (Giga/L)	FeNO BL mean (ppb)	BL weight (kg)
1	116	0.54 (0.10)	32.9 (1.1)	2.09	0.51	0.38	27.8	88.8
2	117	0.72 (0.12)	55.8 (0.4)	2.34	0.50	0.39	23.0	80.5
3	116	0.72 (0.09)	74.3 (0.6)	2.12	0.50	0.40	23.8	73.7
4	117	0.68 (0.11)	106.4 (2.3)	2.41	0.52	0.42	25.1	63.4

Abbreviations: BL: baseline; $C_{average}$: average concentration; EOS: eosinophils; FeNO: fractional exhaled nitric oxide; RR relative risk of active versus placebo; SE: standard error.
Quartile values: Q1=48.68; Q2=63.64; Q3=85.26 mg/L for dupilumab N=116-117 per quartile.
Source: 5.3.3.5 Study CTS0124.

Empirical model for annualized rate of moderate or severe exacerbation events

The model-predicted relative risk of dupilumab versus placebo for the annualized rate of moderate or severe exacerbation events is consistent with the clinical observation in Study EFC15804. In addition, the annualized rate of moderate or severe exacerbation events was predicted using the E-R model and compared with observed data in the placebo group and each quartile in the dupilumab group. Baseline blood eosinophils (screening eosinophils <0.5 Giga/L) and territory (European Union), were found to have a significant interaction effect with exposure. Participants with baseline eosinophils <0.5 Giga/L and from European Union were predicted to have lower efficacy, as also observed in the subgroup analysis of AECOPD by baseline eosinophil and by territory (see efficacy assessment; section 5.4). In addition, baseline FeNO was found to have a significant interaction effect with exposure at the step of screening for interaction. However, it was not significant after the E-R model including the interaction effect of baseline blood eosinophils.

Figure 8 - Observed and predicted annualized rate moderate or severe exacerbation events (relative risk of active versus placebo) based on PK/PD model in participants with COPD in Study EFC15804 (Study CTS0124)



Observed effects were based on PD analysis of observed data in the PK/PD population.

Table 14 – Annualized moderate or severe exacerbation event: Covariates selected for final PK/PD model building step with forward method

Covariate	Model inclusion type	Main Effect /Interaction P-value	AIC_C	# Observations used
Screening eosinophils: <0.5 Giga/L	Interaction	0.0115	2173.46	937
Screening eosinophils	Interaction	0.0132	2180.43	937
Baseline FEV1 Reversibility (LOG)	Main effect only	0.0294	2180.89	937
Territory: European Union vs Rest of World	Interaction	0.0303	2182.10	937
Baseline FEV1 Reversibility: <median	Main effect only	0.0464	2181.89	937
Baseline FENO	Interaction	0.0465	2025.85	873

Descriptive quartile analysis for pre-bronchodilator FEV1 at Week 12

The FEV1 response over the exposure quartiles appeared to show a generally flat relationship within the range of dupilumab concentrations at 300 mg q2w dose regimen. In general, the baseline values of type 2 inflammation markers (eosinophils and FeNO) and baseline FEV1 were balanced in each exposure quartile. Additionally, baseline body weight was higher in the patients in the lowest exposure quartile, which is expected since body weight is the main source of PK variability.

Table 15 - Pre-bronchodilator FEV_1 at Week 12 by quartiles of observed trough dupilumab concentration in participants with COPD treated with dupilumab in Study EFC15804 (Study CTS0124)

C_{trough} quartile	N	FEV_1 change mean (SE) (L)	C_{trough} mean (SE) (mg/L)	FEV_1 BL mean	EOS screening mean (Giga/L)	EOS BL mean (Giga/L)	FeNO BL mean (ppb)	Weight BL mean (kg)
1	112	0.16 (0.04)	18.6 (1.0)	1.45	0.53	0.40	29.4	88.2
2	113	0.09 (0.03)	42.3 (0.5)	1.40	0.50	0.38	24.6	80.8
3	109	0.18 (0.03)	60.4 (0.6)	1.24	0.48	0.39	22.2	74.5
4	111	0.16 (0.04)	93.1 (2.3)	1.07	0.52	0.41	25.3	63.3

Abbreviations: BL: baseline; C_{trough}: trough concentration; EOS: eosinophils; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in first second; SE: standard error.
Quartile values: Q1=33.0; Q2=50.6; Q3=71.7 mg/L for dupilumab N=109-112 per quartile.
Source: 5.3.3.5 Study CTS0124.

Empirical model for pre-bronchodilator FEV1

Model-based analysis for Study EFC15804 showed a greater increase in FEV1 with increasing dupilumab Ctrough at Week 12 and appeared to plateau at the exposure of the first quartile Q1 (mean Ctrough of 18.6 mg/L). The model-predicted FEV1 responses are consistent with the clinical observation in Study EFC15804. Baseline blood eosinophils were found to have a significant interaction effect with exposure. Participants with higher baseline blood eosinophils counts were predicted to have greater efficacy.

2.4.5. Discussion on clinical pharmacology

The PK and PD profiles of dupilumab were evaluated in study EFC15804 (BOREAS). Efficacy and the main safety data for this application were also derived from this study. Dupilumab was administered for 52 weeks with the same dose regimen (300mg, Q2W; without a loading dose) as for other approved indications. The choice of the dose regimen in COPD is endorsed.

Bioanalytical methods for the PK and PD analysis include assays for quantitation of functional dupilumab, quantitative and functional assays for anti-drug antibodies, and assays for type 2 inflammation biomarkers (FeNO, eosinophils, eotaxin 3, PARC, and total IgE).

In study EFC15804, the mean Ctrough of functional dupilumab reached steady state by Week 16, and remained on this level until the end of the treatment period (Week 52). At Week 52, the mean (SD) trough concentration of dupilumab was 60 (36.2) mg/L. After discontinuation, dupilumab concentrations declined to 0.815 (4.36) mg/L within the 12-Week follow-up period.

Comparing the observed dupilumab concentrations in COPD across other indications for which dupilumab is already approved overall similar PK profiles are apparent. The mean observed steady state exposure of dupilumab are comparable to what has been observed in adult patients with asthma. However, slightly

lower through concentrations are observed. The time profile of observed through concentrations appears similar as compared to the other approved adult indications.

A previously developed dupilumab global Pop PK base model (study POH0668) that has been assessed in the CRSwNP application (EMEA/H/C/004390/II/17) was utilized in the current Pop PK analysis for patients with COPD. This global Pop PK base model is based on pooled data from 6 studies in healthy subjects, 10 studies in adult AD and 4 studies in asthma with adult and adolescent patients and was a two-compartment model with a first order absorption and parallel linear and nonlinear elimination, with body weight as covariate. Data from the COPD study EFC15804 were not included in the global Pop PK model development but were evaluated using the MAP Bayesian approach. The predicted dupilumab typical concentration-time profile at 300 mg q2w in adult patients with COPD is very similar to the observed trough concentration-time profiles in study EFC15804 and also comparable to the other dupilumab indications.

As within the other indications, body weight was identified as the primary factor responsible for dupilumab PK variability, but this is considered to have no impact on the posology. Steady-state exposures by body weight within more categories (i.e. <60kg, 60-<90kg, and ≥90kg) were provided and were similar to what have been already observed in the other adult dupilumab indications.

A base PK/PD model was used to evaluate the exposure/response form within linear, log-linear and Emax models. The results indicated that increasing dupilumab exposure results in a greater effect when the exposure was lower than the median value of first quartile. The treatment effect is predicted to approach a plateau of the E-R curve by the first quartile of dupilumab exposure. Blood eosinophils at baseline were found to be significant covariates for the treatment response. A greater treatment effect was observed in patients with elevated eosinophil counts, in line with the targeted COPD subpopulation assumed to be more responsive to dupilumab. Of note, territory was found to be a significant covariate for exacerbations (but not for FEV1). Participants from European Union were predicted to have lower efficacy which is a relevant observation that is further discussed in the efficacy assessment. However, treatment-by-subgroup interactions data have shown that the treatment effect on the annualized rate of moderate or severe COPD exacerbations was similar between Europe and North America (see section 2.5.2 in clinical efficacy).

At Week 52, the median percent change for FeNO from baseline was -28.6% in the dupilumab group as compared to -6.9% in the placebo group. Reductions seen for FeNO are similar to what has been observed in the asthma population. Treatment with dupilumab led to a pronounced reduction (median percent reduction from baseline: 76%) of total IgE at the end of the treatment period at Week 52. This is reflected in section 5.1 of the SmPC. The extent and the kinetics of IgE and FeNO reductions are comparable to what has been already observed in the other indications such as asthma.

In study EFC15804, the incidence of treatment emergent during the treatment period ADAs was 1.5% (n=7) and 6.5% (n=30) for the placebo and dupilumab group, respectively, which is comparable to the incidences observed in other dupilumab indications. Most ADAs were low titer. NAbs were observed in 5 participants in the dupilumab group. Pooled ADA information from study EFC15804 and EFC15805 were provided during the procedure. During the 52-week treatment period, the incidence of treatment-emergent ADA responses was 1.8% (n=16) and 8.4% (n=77) for the placebo and dupilumab group, respectively. A total of 0.4% (placebo) and 2.6% (dupilumab) of participants had persisting ADA responses. Neutralizing antibodies were observed in 1.1% and 3.0% of participants in the placebo and dupilumab group, respectively.

Overall, the PK profile of dupilumab 300mg Q2W in patients with COPD is similar to the observed PK profiles in other adult population for which dupilumab is already approved.

2.4.6. Conclusions on clinical pharmacology

The PK profile of dupilumab in COPD is similar to adult patients with AD, asthma and CRSwNP, PN, and EoE with regard to absorption, distribution and elimination, steady state exposures and pharmacokinetic variability.

Descriptive and model-based analysis showed no relevant relationship with individual dupilumab exposure ranges. The ADA response in COPD patients is low and consistent with ADAs observed for other dupilumab indications. As within other indications, treatment with dupilumab led to a pronounced reduction in the type 2 inflammation biomarkers IgE and also FeNO.

Overall, the proposed dose regimen for dupilumab 300 mg Q2W in adults with COPD is endorsed.

2.5. Clinical efficacy

2.5.1. Dose response study

No dose response study was performed.

2.5.2. Main studies

Data for clinical efficacy is based on the pivotal phase 3 study EFC15804 (BOREAS), a randomized, double blind, placebo controlled, parallel group studies to assess the efficacy and safety of a 52-week intervention period with dupilumab 300 mg q2w in participants aged 40 to 80 years (EFC15804) with uncontrolled COPD despite receiving maximized standard-of-care background therapy and elevated blood eosinophils ≥0.3 Giga/L during the screening period). Study EFC15804 was ongoing at the time of the worldwide COVID-19 pandemic. Data from the additional phase 3 replicate study EFC15805 (NOTUS) with similar design and objectives were also submitted.

2.5.2.1. Study EFC15804 (BOREAS)

Study EFC15804 was a multinational, randomized, double-blind, placebo-controlled, parallel-group (2 groups), 52-week, pivotal Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in participants with uncontrolled COPD (ie, ≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2), moderate-to-severe airflow obstruction (ie, post-BD FEV1 >30% to ≤70% of predicted), and evidence of type 2 inflammation, on top of an established background therapy of LABA, LAMA, and ICS (unless ICS was contraindicated).

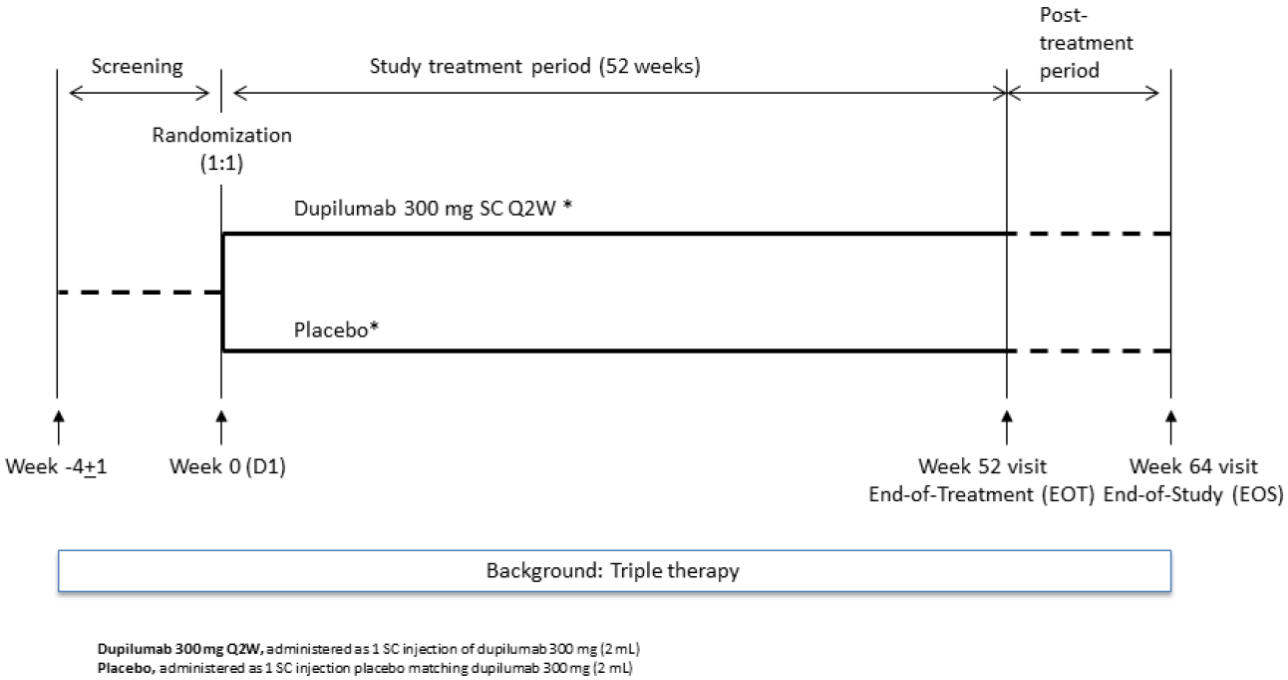
The study population consisted of participants 40 to 80 years of age who were current or former smokers with a smoking history of at least 10 pack-years and who did not have either a history of or current diagnosis of asthma.

Methods

The study consisted of the following 3 periods:

- Screening period (4 weeks)
- Randomized study intervention period (52 weeks)
- Post-intervention follow-up period (12 weeks)

Figure 9 - Overview on the study design for study EFC15804 (BOREAS)



Study participants

Key inclusion criteria were:

- Participants had to be ≥40 to ≤80 years of age, at the time of signing the informed consent
- Current or former smokers with a smoking history of ≥10 pack-years.
- Moderate-to-severe COPD (post-BD FEV1/FVC ratio <0.70 and post BD FEV1 % predicted >30% and ≤70%)
- Medical Research Council (MRC) Dyspnea Scale grade ≥2
- Patient-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough.
- Documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate* or ≥1 severe** within the year prior to inclusion.

  At least 1 exacerbation should have occurred while the participant was taking ICS+LAMA+LABA (or LAMA+LABA if ICS was contradicted).
- Background triple therapy (ICS+LABA+LAMA) for 3 months prior to randomization with a stable dose of medication for ≥1 month prior to Visit 1 (double therapy: LABA+LAMA allowed if ICS was contraindicated).
- Participants with blood eosinophils ≥0.3 Giga/L at Visit 1 (screening).

*Moderate exacerbations were recorded by the Investigator and defined as AECOPD requiring either SCS (intramuscular, IV, or oral) and/or antibiotics. One of the 2 required moderate exacerbations must have been treated with SCS.

**Severe exacerbations were recorded by the Investigator and defined as AECOPD requiring hospitalization or observation >24 hours in emergency department/urgent care facility.

Key exclusion criteria were:

- COPD diagnosis for less than 12 months prior to randomization.
- Current diagnosis of asthma or history of asthma.
- Significant pulmonary disease other than COPD (eg, lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, bronchiectasis, Churg-Strauss Syndrome, etc) or another diagnosed pulmonary or systemic disease associated with elevated peripheral eosinophil counts.
- Cor pulmonale, evidence of right cardiac failure.
- Treatment with oxygen for more than 12 hours per day.
- Hypercapnia requiring BiPAP.
- AECOPD within 4 weeks prior to screening, or during the screening period.
- Respiratory tract infection within 4 weeks prior to screening, or during the screening period.
- History of, or planned pneumonectomy or lung volume reduction surgery. Participants who were participating in the acute phase of a pulmonary rehabilitation program, ie, who started rehabilitation <4 weeks prior to screening (Note: participants in the maintenance phase of a rehabilitation program could be included).
- Diagnosis of α-1 anti-trypsin deficiency.
- History of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory (other than COPD), gastrointestinal, cerebrovascular disease/condition, substance and/or alcohol abuse disorder, active or prior history of malignancy or active malignancy, including lymphoproliferative diseases (except successfully-treated carcinoma in-situ of the cervix, non-metastatic squamous cell or basal cell carcinoma of the skin) within 5 years prior to baseline, or history of or current other significant medical illness or disorder which, in the judgment of the Investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples included but were not limited to poorly controlled insulin-dependent diabetes, uncontrolled hypertension.
- Active autoimmune disease or use of immunosuppressive therapy for autoimmune disease (eg, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc).

Treatments

Dupilumab

Dupilumab 300 mg Q2W administered as 1 SC injection.

Placebo

Placebo administered as 1 SC injection of placebo matching dupilumab 300 mg (2 mL).

Background Medication

Participants had to be on a triple background therapy with LABA+LAMA+ICS (unless ICS was contraindicated) for 3 months prior to randomization and at a stable dose of medications for at least 1 month prior to the screening visit. Throughout the study, participants were required to continue their established background therapy at the same dose and regimen. Use of PDE-4 inhibitors and

methylxanthines was allowed during the study if the dose was stable >6 months prior to the screening visit.

For participants who experienced AECOPD requiring treatment (eg, SCS and/or antibiotics), after successful treatment of exacerbations, they should resume the initial background treatment regimen if considered medically acceptable by the Investigator. After 1 severe or 2 moderate exacerbations of COPD, dose adjustment of background therapy was permitted for symptom control and as needed for the rest of the study.

Reliever medication

Participants were allowed to use reliever medications including albuterol/salbutamol, levalbuterol/levosalbutamol, ipratropium, ipratropium/SABA combinations, or terbutaline as needed during the study.

Objectives

Primary objective:

- To evaluate the efficacy of dupilumab 300 mg q2w in patients with moderate or severe COPD as measured by the annualized rate of acute moderate or severe COPD exacerbation

Key secondary objectives

- To evaluate the effect of dupilumab 300 mg q2w on
  - Pre-bronchodilator forced expiratory volume in 1 second (FEV1) over 12 weeks compared to placebo
  - Health related quality of life, assessed by the change from baseline to Week 52 in the St. George's Respiratory Questionnaire (SGRQ)
  - Pre-bronchodilator FEV1 over 52 weeks compared to placebo

Other secondary objectives

- Evaluate the effects of dupilumab 300 mg q2w on lung function assessments
- Evaluate the effect of dupilumab on moderate and severe COPD exacerbations
- To evaluate safety and tolerability
- To evaluate dupilumab systemic exposure and incidence of antidrug antibodies (ADA)

Tertiary/exploratory

- To evaluate the drug concentration of dupilumab in serum over time
- To explore the association of biomarkers with treatment response
- To evaluate the effects of dupilumab compared with placebo on FEV1 and FVC
- To evaluate the effects of dupilumab compared to placebo on annualized rate of moderate to severe COPD exacerbation utilizing the Exacerbations of Chronic Pulmonary Disease Tool (EXACT)
- To evaluate the effects of dupilumab compared to placebo on treatment failure requiring background medication change

Outcomes/endpoints

Primary and secondary endpoints as defined in the latest study protocol version are presented below. Of note, the annualized rate of moderate or severe COPD exacerbation events and change from baseline in FEV1 at Week 12 and Week 52 in participants with baseline FeNO ≥20 ppb were later added as key secondary endpoints in the SAP prior to database lock and unblinding (see also Statistical methods).

Primary endpoint:

- Annualized rate of moderate or severe COPD exacerbations* over the 52-week treatment period compared to placebo

*A moderate exacerbation was defined as an AECOPD event that required either systemic corticosteroids (such as intramuscular, intravenous, or oral) and/or antibiotics. A severe exacerbation was defined as an AECOPD event requiring hospitalization or observation for >24 hours in an emergency department/urgent care facility or resulting in death. Two AECOPD events were considered as different if they were separated by at least 14 days. Any AECOPD event recorded in the eCRF was reviewed by a confirmatory adjudication committee. Only AECOPD events confirmed by the adjudication committee were included in the analysis.

Key secondary endpoints:

- Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo
- Change from baseline to Week 52 in SGRQ total score compared to placebo
- Proportion of patients with SGRQ improvement ≥4 points at Week 52
- Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo

Other secondary endpoints:

- Change in pre-bronchodilator FEV1 from baseline to weeks other than 12 and 52 (ie, Weeks 2, 4, 8, 24, 36, and 44) compared to placebo
- Change in post-bronchodilator FEV1 from baseline to Week 2, 4, 8, 12, 24, 36 and 52 compared to placebo
- Change in forced expiratory flow (FEF) 25-75% from baseline to Weeks 2, 4, 8, 12, 24, 36, 44, and 52
- Annualized rate of severe COPD exacerbations compared to placebo over the 52-week treatment period
- Time to first moderate or severe COPD exacerbation compared with placebo during the 52-week treatment period
- Adverse events (AEs)/treatment-emergent adverse events (TEAEs)
- Potentially clinically significant laboratory abnormalities in hematology, biochemistry and urinalysis
- ADA against dupilumab

Tertiary/exploratory endpoints (summary):

- Pharmacodynamic response of selected biomarkers: Pulmonary and activation-regulated chemokine (PARC), Eotaxin-3, Fractional exhaled nitric oxide (FeNO; postbronchodilator), total IgE
- Predictive effects of selected biomarkers (e.g. fibrinogen, sputum RNA) on treatment response

- Annualized loss of lung function as assessed by a FEV1 slope analysis
- Change from baseline in FVC (% predicted and absolute values in mL) from baseline to Week 12, Week 24 and Week 52
- Evaluation of clinical respiratory symptoms of COPD using the Evaluating Respiratory Symptoms in COPD (E-RS: COPD) comprised in the EXACT tool
- Annualized rate of COPD exacerbations assessed by the EXACT over 52 week
- Increase in number of controller medication after exacerbation
- Increase in patient total daily dose of controller medication after exacerbation

Of note, the annualized rate of moderate or severe COPD exacerbation events and change from baseline in FEV1 at Week 12 and Week 52 in the ITT population with baseline FeNO ≥20 ppb were added as key secondary endpoints in the SAP prior to database lock and unblinding.

Overall, the proposed endpoints are acceptable considering the recommendations in the COPD guideline (EMA/CHMP/700491/2012).

Sample size

Overall, 924 patients were planned to be randomized in a 1:1 allocation to dupilumab versus placebo. The sample size was powered for the primary endpoint of annualized rate of moderate or severe exacerbations over 52 weeks. The power calculation bases on the assumption that the number of severe exacerbations follow a negative binomial distribution with a dispersion parameter of 1.

With a 2-sided significance level of α=0.049 (an administrative penalty of 0.001 was taken from the significance level used at final analysis due to a planned interim analysis) the study has 90% power to detect a 25% relative risk reduction assuming a placebo annualized rate of moderate or severe exacerbations being 1.5 (i.e., annualized rate of 1.125 for the dupilumab group) and an average treatment duration of 0.95 year (to account for an average of 5% of the planned treatment period with missing data).

Given the assumptions, the sample size calculations are comprehensible. Significance level and anticipated power are acceptable. A total of 939 participants were randomized to study intervention: 468 in the dupilumab group and 471 in the placebo group. Thus, the number of planned patients correspond to the number of enrolled patients (924 vs 939).

Randomisation

After a run-in period of 4 weeks ±1 week, patients were centrally randomized using a permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 1:1 randomization ratio for dupilumab 300 mg q2w and a matching placebo q2w for sc administration. Randomization was stratified by country and by ICS dose (high dose ICS [yes/no]) at baseline. Enrollment was capped at 30% current smokers (as defined by smoking status at screening visit).

Blinding (masking)

Dupilumab and placebo were provided in identically matched 2 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) glass pre-filled syringes was prepared such that

the treatments (dupilumab and its matching placebo) are identical and indistinguishable and were labeled with a treatment kit number.

In accordance with the double-blind design, study patients, Investigators, and study site personnel remained blinded to study treatment and had no access to the randomization arm or to the IMP content (dupilumab or placebo) except under circumstances described as follows.

In case of an AE, the randomization code had only to be broken in circumstances when knowledge of the IMP was required for treating the patient. Code breaking could be performed at any time by using the proper module of the IVRS/IWRS and/or by calling a phone number provided by the Sponsor for that purpose. If the blind was broken, the Investigator had to document the date, time of day, and reason for code breaking. Patient withdrawal only occurred when the code break call was made at the site level, not the study level. This means that if the Emergency Unblinding transaction was performed by the Investigator (ie, at the site level), then the patient would be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the patient will not be withdrawn from treatment. Patients who were withdrawn from treatment were encouraged to remain in the study and the Investigator should discuss with them the key visits to attend.

The blind was broken for regulatory purposes (ie, safety reporting of SUSARs by the Sponsor) for 3 participants in the dupilumab group due to SAEs of pneumonia, rhabdomyolysis and cardiac failure and 2 participants in the placebo group due to SAEs of pneumonia and COVID-19. The blind was broken by the Investigator at the clinical site for 1 participant in the dupilumab group due to a SAE of cerebral hemorrhage with a fatal outcome which was considered not related to IMP by the Investigator. After death, the participant's family requested information about the actual IMP received. These unblindings are not seen critically.

Statistical methods

Analysis Populations/Sets

The intent-to-treat (ITT) population was defined as the randomized population analyzed according to the treatment group allocated by randomization.

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

Primary Estimand / Primary Analysis strategy

The primary efficacy variable was annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.

The following null hypothesis and alternative were tested for dupilumab arm against placebo:

H0: No treatment difference between the dupilumab dose regimen and placebo in annualized rate of COPD exacerbation.

H1: There is a treatment difference between the dupilumab dose regimen and placebo in annualized rate of COPD exacerbation.

The primary analysis of the annualized rate of moderate or severe exacerbation events during the 52-week placebo-controlled treatment period was to assess the efficacy of dupilumab in an intention-to-treat setting. Adjudicated COPD exacerbation events data were used.

The primary estimand is described in the following table:

Endpoint Category	Estimands			
	Endpoint(s)	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Primary objective: The primary objective of this study is to evaluate the efficacy of dupilumab 300 mg every 2 weeks compared to placebo in reducing annualized rate of acute moderate or severe COPD exacerbation (AECOPD) over the 52-week treatment period in patients with moderate or severe COPD.				
Primary endpoint – Event	Annualized rate of AECOPD exacerbation events over the 52-week treatment period.	ITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment before Week 52: Off-study treatment data up to Week 52 will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up before Week 52: Analyses will be censored at the time of study discontinuation.	Negative binomial regression model using the total number of events occurred during the 52-week planned treatment period as the response variable, with the treatment group, region (pooled country), ICS dose at baseline, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates. Log-transformed observation duration will be used as offset variable.

If a patient withdrew from study prior to the end of 52-week treatment period, all observed moderate or severe exacerbation events up to the last contact date or the end date of the planned 52-week treatment period (whichever is earlier) were included in the analysis, and the observation duration is defined as from randomization to the last contact date or the end date of the planned 52-week treatment period, whichever was earlier. No imputation was performed for the unobserved events that may have happened after study discontinuation and up to Week 52.

The annualized rate of moderate or severe COPD exacerbation events was analyzed using a negative binomial regression model. The negative binomial regression model includes the total number of events occurred during the 52-week planned treatment period as the response variable, with the treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study ($\leq$2, 3, or $\geq$4) as covariates. Log-transformed observation duration was used as offset variable. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals were derived. The event rate ratio of the dupilumab group against placebo, its two-sided 95% confidence interval and p-value are provided.

The rate difference between dupilumab and placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

Supplementary Analysis for Primary Endpoint

If patients withdrew from the study before Visit 16 (Week 52), moderate or severe exacerbation events that may have occurred after study discontinuation were not observed. These patients are considered as patients with missing data on moderate or severe exacerbation. Number of patients with missing data, reasons and timing for patient withdrawals were summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics are provided for patients with missing data and patients with complete data separately. In addition, the following sensitivity analyses were conducted to assess the robustness of the conclusion based on the primary analysis.

Pattern mixture model - multiple imputation (PMM-MI): For each patient with missing data of moderate or severe exacerbation events, individual bi-weekly event probability was estimated using observed data with adjustment for the same variables as in primary analysis model. The total number of AECOPD moderate or severe events (on bi-weekly basis) was calculated based on data imputed using multiple imputation.

Control-based PMM-MI: For each patient with missing data of moderate or severe exacerbation events, individual bi-weekly event probability was estimated using observation in the placebo arms only, with adjustment for the same variables as in primary analysis model except treatment group. The total number of AECOPD moderate or severe events (on bi-weekly basis) was calculated based on data imputed using multiple imputation.

Tipping point analysis: For each patient with missing data of moderate or severe exacerbation events, the bi-weekly event was imputed in a similar fashion as PMM-MI based on various odds values. If the patient is on dupilumab, the predicted odds were increased; if the patient is on Placebo, the predicted odds value were decreased. The adjusted rate then was used to impute the number of events that would occur during the missing observation period. A sequence of increasing/decreasing ratio was used to generate different imputed datasets.

For each of the above methods, a negative binomial model was fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the same covariates as in the primary analysis model. Log transformed observation duration was the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks was the offset variable for patients who discontinue the study before Visit 16 (Week 52). SAS MIANALYZE procedure was used to generate statistical inferences by combining results from the analysis with each dataset using Rubin’s formula.

Secondary Estimand(s)/ Secondary Analysis strategy

The analysis of secondary endpoints was based on the ITT population.

The secondary estimands are described in the following table:

Endpoint Category	Estimands			
	Endpoint(s) [a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary objective: To demonstrate the efficacy of dupilumab on spirometry and health related quality of life endpoints, separately, at various time points or population				
Secondary endpoint – Continuous	Change from baseline in FEV1 at Week 12 Change from baseline in FEV1 at Week 52 Change from baseline in SGRQ at Week 52 Change from baseline in E-RS at Week 52	ITT (For FEV1 endpoints, also patients with baseline FeNO ≥ 20 ppb)	The intercurrent events will be handled as follows: • Discontinuing the study intervention prior to Week 12 or Week 52: all data collected after discontinuation will be used in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: • Missing data will be imputed latently by MMRM based on missing at random assumption	MMRM model using change from baseline in corresponding endpoint values up to corresponding weeks as response variables, and factors for treatment group, age, sex, height (age, sex and height are only included for spirometry endpoints analyses), region (pooled country), ICS dose at baseline, smoking status at screening, visit, treatment-by-visit interaction, baseline value of the endpoint, and baseline-by-visit interaction as covariates.
Secondary endpoint – Proportion	Proportion of SGRQ improvement (≥4 points) at Week 52	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention prior to Week 52: Off-study intervention data will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: • Having missing data at Week 52: Participants will be considered as non-responders.	Logistic regression model, with treatment group, region (pooled country), ICS dose at baseline, smoking status at screening, and baseline SGRQ total score as covariates
Secondary objective: To evaluate the effect of dupilumab on moderate and severe COPD exacerbations				

Endpoint Category	Estimands			
	Endpoint(s) [a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary endpoint – Time-to-event	Time to AECOPD exacerbation events during the 52-week treatment period	ITT	The intercurrent events will be handled as follows: • Discontinuation of study intervention before Week 52: Off-study intervention data up to Week 52 will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up before Week 52: Analyses will be censored at the time of study discontinuation	Cox proportional hazards model using the time to the first event as the dependent variable, and treatment group, region (pooled country), ICS dose at baseline, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (i.e., continuous, proportion, event, time-to-event) at other weeks.

Multiplicity

The multiplicity procedure was proposed to control the overall type-I error rate for testing the primary and selected secondary endpoints listed below. The overall alpha was 0.05.

A non-binding futility interim analysis was planned in this study, and an administrative penalty of 0.001 was taken from the significance level used at final analysis and thus two-sided 0.049 was used. No further multiplicity adjustment was performed for the interim analysis.

At the final analysis, the comparisons with placebo were tested based on the hierarchical order below at 2-sided alpha=0.049.

1) Primary efficacy endpoint:

- Annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.

2) Secondary/exploratory efficacy endpoints:

- Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo
- Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo
- Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo in the subgroup of patients with baseline FENO $\geq$ 20 ppb
- Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo in the subgroup of patients with baseline FENO $\geq$ 20 ppb
- Change from baseline to Week 52 in SGRQ total score compared to placebo

- Proportion of patients with SGRQ improvement ≥4 points at Week 52 compared to placebo
- Change in E-RS COPD scores from baseline to Week 52 compared to placebo
- Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FENO ≥ 20 ppb

The study is considered positive when the primary endpoint achieves statistical significance.

Interim analysis

A pre-specified nonbinding futility interim analysis in the study was planned to be performed when approximately 408 patients would have completed Week 12 visit. The interim analysis was performed by independent statisticians that supported the DMC and were separated from personnel involved in the trial conduct. DMC reviewed the unblinded interim analysis results and recommended action based on the non-binding futility criterion that was specified in the DMC charter and DMC SAP. People involved in the conduct of the study (patients, Investigators, Study Team, and Project Team) had no access to the interim analysis results.

At the interim analysis, the efficacy endpoints were analyzed using the same methods as specified for the final efficacy analysis. The analysis population for the interim analysis was the first 408 patients randomized. The analysis of the endpoints used all the data collected for the analysis population up to the interim analysis cutoff time. An administrative penalty of 0.001 was taken from the significance level used at final analysis (i.e., two-sided 0.049 will be used for the final analysis).

Subgroup Analyses

Subgroup analyses were planned to be conducted for the primary efficacy endpoint with respect to:

- Age group (<65, ≥65 years)
- Gender (Male, Female)
- Region
- Territory
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, Others)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight (<70, ≥70- < 90, ≥ 90 kg; <60, ≥ 60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m2)
- ICS high dose level at baseline (Yes, No)
- Smoking status at screening (current smokers, former smokers)
- Number of moderate-or-severe COPD exacerbation events within one year prior to V1 (≤2, 3, or ≥ 4)
- Number of severe COPD exacerbation events within one year prior to V1 (0, 1, ≥ 2)
- Baseline predicted post-bronchodilator FEV1% (<50%, ≥50%)
- Baseline pre-bronchodilator FEV1 (< median, ≥ median)
- Baseline FEV1 reversibility (<12%, ≥ 12%; < median, ≥ median)
- Baseline fractional exhaled nitric oxide (FeNO) (<20, ≥20 ppb)

- Baseline eotaxin-3 (< median, ≥ median)
- Baseline IgE (< 100 , ≥ 100 IU/ml)
- Baseline PARC (< median, ≥ median)
- Baseline Fibrinogen (< 350, ≥ 350 mg/dL)
- Baseline mMRC (< median, ≥median)
- Maximum eosinophils counts during screening (≥ 0.3-<0.5, ≥0.5 Giga/L)

Treatment by subgroup interaction and its p-value were derived from a negative binomial model (using the same covariates as the model used for the primary analysis). If quantitative treatment by subgroup interaction was detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test was performed to evaluate possible qualitative interaction. Summary statistics of moderate or severe exacerbations are provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing dupilumab dose group vs. placebo for the subgroups are provided.

Results

Participant flow

Study EFC15804 was a multicenter study conducted at 275 centers that screened at least 1 participant in 24 countries worldwide (Asia: China, Japan, and South Korea; Latin America: Argentina, Chile, and Mexico; East Europe: Bulgaria, Czech Republic, Hungary, Poland, Romania, Russia, Slovakia, Turkey, and Ukraine; and Western Countries: Canada, Denmark, Finland, Germany, Israel, Italy, Spain, Sweden, and US).

Out of the 2599 participants screened for study eligibility, 1660 (63.9%) participants were screen failures. The 2 main reasons for screen failure were: not meeting inclusion criterion I03, blood eosinophils ≥300 cells/microliter at Visit 1 (33.7% of all screened participants) and not meeting the inclusion criterion of post-BD FEV1/FVC ratio <0.70 (10.5% of all screened participants). This clearly refers to the distinct subgroup of patients with eosinophilic COPD enrolled in this study.

A total of 939 participants were randomized to study intervention: 468 in the dupilumab 300 mg q2w group and 471 in the placebo group (Figure 10). All randomized participants were exposed to study intervention. There were no participants who were exposed but not randomized. One participant who was allocated to the placebo group inadvertently received a single dose of dupilumab on Day 40, which was reported as a major protocol deviation. The participant was included in the dupilumab group for the safety analyses.

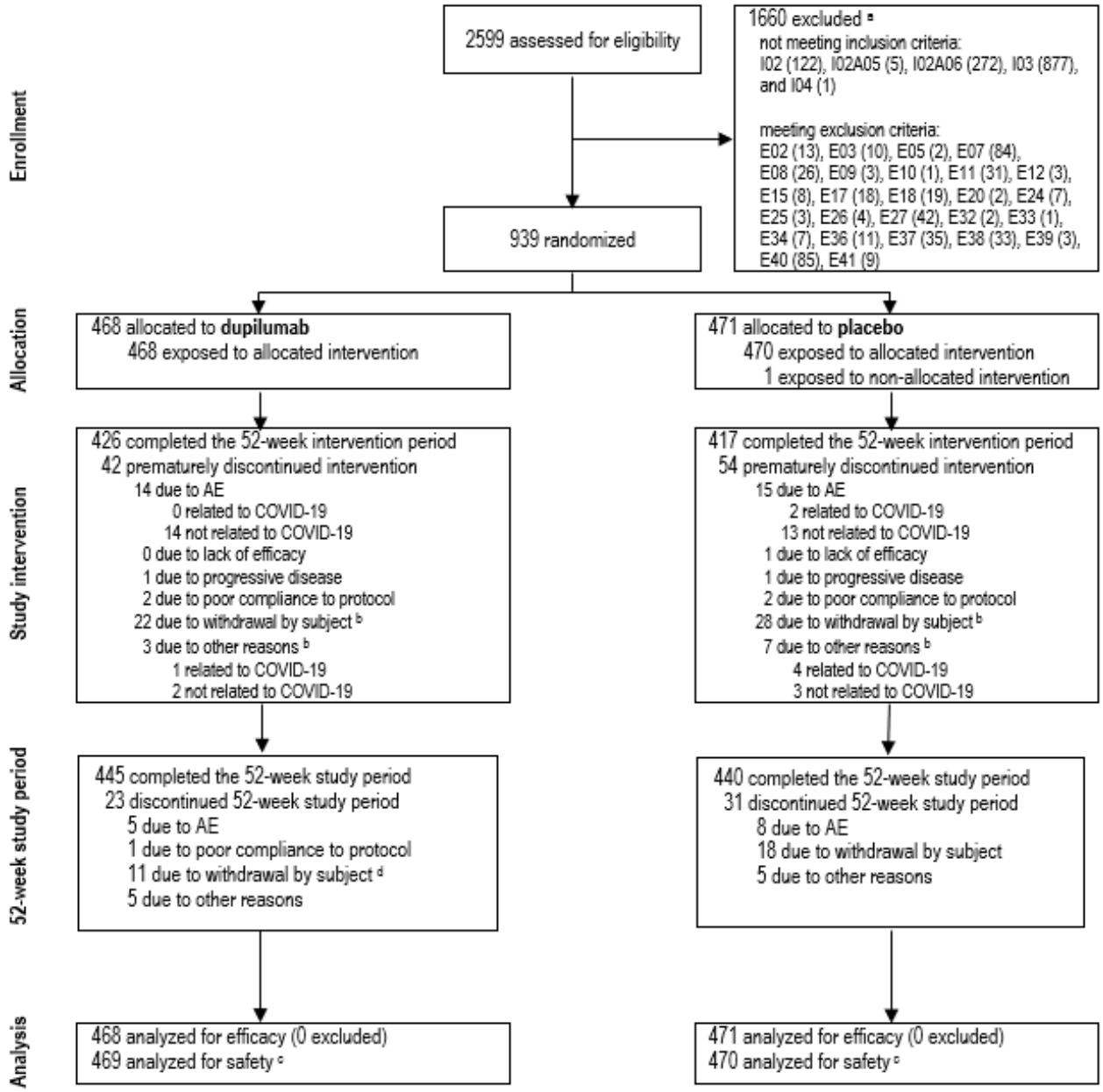
In the randomized population, 426 (91.0%) participants in the dupilumab group and 417 (88.5%) participants in the placebo group completed the 52-week study intervention period. The percentage of participants who permanently discontinued study intervention was 9.0% in the dupilumab group and 11.5% in the placebo group. The most frequently reported reason for permanent study intervention discontinuation, as per the Investigator, was "withdrawal by subject" (22 (4.7%) in the dupilumab group and 28 (5.9%) in the placebo group). The majority of these withdrawals by subject were due to "other" reasons (Figure 10).

Overall, 12 permanent study intervention discontinuations were related to COVID-19: 2 due to SAEs of COVID-19 pneumonia that led to death, both in the placebo group, and 10 due to "other" reasons related to COVID-19, either reported as the reason for permanent study intervention discontinuation by the

Investigator or as the reason for withdrawal by the participant (3 in the dupilumab group and 7 in the placebo group). Potential effects of the COVID-19 pandemic (e.g. public health measures) on the efficacy results and clinical safety assessment of COVID-19-related AEs are discussed in the report.

As of the data cut-off date (08 February 2023), 410 (87.6%) participants in the dupilumab group and 402 (85.4%) participants in the placebo group had completed the study (ie, the entire study intervention and post-intervention follow-up periods), while 30 (6.4%) participants in the dupilumab group and 33 (7.0%) in the placebo group were still ongoing in the post-intervention follow-up period and 28 (6.0%) participants in the dupilumab group and 36 (7.6%) participants in the placebo group had prematurely discontinued from the study. The data for the complete post-intervention follow-up period have been provided during the procedure and are presented in the efficacy and safety sections.

Figure 10 - Patient Disposition Study EF15804 (Flow Diagram)



Source: Table 7 and Appendix 16-2-1-disposition [16.2.1.1.1] and [16.2.1.1.3]

[a] A full description of the inclusion and exclusion criteria is provided in the protocol (16-1-1-protocol [5.1] and [5.2]).

[b] None of the "other" reasons for permanent study intervention discontinuation were related to safety.

[c] One participant who was allocated to the placebo group inadvertently received a single dose of dupilumab on Day 40 and was included in the dupilumab group for the safety analyses.

d One participant in the Dupilumab 300mg q2w group (015804-792-0004-08403) discontinued the study intervention and study prior to week 52, but the eCRF was marked as completed the study period and therefore not included in the discontinued from study period due to withdrawal by subject.

Recruitment

EFC15804 (BOREAS):

First participant enrolled:	09 May 2019
Last participant (end of treatment visit):	08 February 2023
The primary analysis data cut-off:	07 March 2023

Conduct of the study

Protocol amendments

The original protocol, dated 07 November 2018, was modified per 8 global amendments. Amendment 04 (18-March-2019), was implemented before any participants were enrolled to add clarification to inclusion criterion no. 2 that at least 1 exacerbation should have occurred on triple therapy, to add the exclusion of participants with a history of asthma in addition to those with a current diagnosis of asthma, to clarify that chronic use of systemic corticosteroids was prohibited, and to change stratification factor from asthma history to ICS dose. Enrollment cap for current smokers (30%) was added with Amendment 07 (06-Dec-2019). Amendment 08, dated 29 September 2020, was implemented to replace some on-site study visits and assessments by telephone visits to decrease the burden on participants, to minimize COVID-19 pandemic-related risks in this vulnerable and elderly population of patients with COPD, as well as to update the list of AESIs with the updated Sponsor safety information related to eye.

COVID-19 pandemic

Study EFC15804 was conducted during the global COVID-19 pandemic. In response to the COVID-19 pandemic, contingency measures in the study conduct were introduced in protocol amendment 08, which allowed implementation of temporary or alternative mechanisms such as phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff (as permitted per local regulation) to ensure study continuity and protect the participants' safety. No waivers to deviate from protocol enrollment criteria due to COVID-19 were granted. Remote monitoring was introduced when on-site monitoring was not allowed. All temporary mechanisms utilized and deviations from planned study procedures were documented as being related to the COVID-19 pandemic and were to remain in effect only for the duration of the public health emergency.

Ukraine/Russia conflict

Study EFC15804 was ongoing when the Ukraine/Russia conflict escalated in February 2022. Overall, 22 participants in Ukraine and 2 participants in Russia were receiving study intervention at that time. All 24 participants completed the study (ie, the entire study intervention and post-intervention follow-up periods).

Protocol deviations

Critical or major protocol deviation occurred in 167 (35.7%) and 176 (37.4%) participants in the dupilumab or placebo group, respectively.

The most frequently reported category of critical or major protocol deviations was "assessments/ procedures" (dupilumab: 70 (15.0%); placebo: 85 (18.0%) with the majority of classified as "Examination not performed" and "Study physical visit, phone call or safety contact not performed".

Critical or major deviations related to randomization procedures were reported in 53 (11.3%) participants in the dupilumab group and 55 (11.7%) in the placebo group (second most frequently reported category

of critical or major protocol deviations) and were mostly related "wrong stratum of randomization" (high-dose ICS [yes/no]) (53 [11.3%] participants in the dupilumab group and 55 [11.7%] in the placebo group). During the procedure, the MAH provided details on the randomisation errors and justified comprehensively that the impact on the efficacy result is rather small. One participant who was allocated to the placebo group and received dupilumab on Day 40 was reported with a major protocol deviation classified as "IMP administered but not as per protocol".

Critical or major protocol deviations related to "Inclusion/exclusion criteria" were reported for 35 (7.5%) participants in the dupilumab group and 27 (5.7%) participants in the placebo group with deviations related to inclusion criterion no. 2 (physician diagnosis of COPD; dupilumab: 10; placebo: 4), exclusion criterion no. 27 (<80% compliance with controller therapy; dupilumab: 6; placebo 6) and exclusion criterion no. 15 (prohibited concomitant medication; dupilumab: 8; placebo 2) being the most frequent.

Overall, 34 (7.3%) participants in the dupilumab group and 33 (7.0%) participants in the placebo group had at least 1 critical or major protocol deviation related to the COVID-19 pandemic. The majority of these protocol deviations were classified as "Examination not performed" (27 [5.8%] participants in the dupilumab group and 28 [5.9%] participants in the placebo group) and mainly related to spirometry assessments not performed. These critical/major protocol deviations are not considered to have an impact as they were low in number.

GCP violations

Potential GCP violations occurred at 5 Japanese study sites and were reported to EMA on 13-Nov-23 after the submission of the dossier. A limited number of patients may not have met the eligibility criteria for enrollment. In order to assess the data integrity, sensitivity analyses were provided. These analyses showed that exclusion of the Japanese patients does not change the efficacy conclusion of the study. There were no unique safety findings in the Japanese patients.

Baseline data

Demographics

As expected for the disease, more than half of participants had an age of 65 and older (58.1%). The mean age of the randomized population was 65.1 years with a range of 40 to 80 years. Male participants represented around two thirds of the population (66.0%). EFC15804 study enrolled participants in Asia (14.2%), Latin America (24.0%), Eastern Europe (33.4%), and Western countries (28.4%). Race representation included White (84.1%), Asian (14.3%), Black/of African descent (0.5%), and other races (1.1%). There was a very low number of participants with Black/of African descent that is potentially attributed to recruitment challenges in this patient group. The MAH provided further assessment of the efficacy in this subpopulation (see subgroup analysis by demographics) The mean BMI was 27.58 kg/m^2 with 29.4% of participants having a BMI of ≥30 kg/m2.

Table 16 - Demographics and participant characteristics at baseline - Randomized population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Age (years)			
Number	471	468	939
Mean (SD)	65.2 (8.1)	65.0 (8.0)	65.1 (8.1)
Median	66.0	66.0	66.0
Q1 ; Q3	60.0 ; 71.0	59.0 ; 70.5	60.0 ; 71.0
Min ; Max	41 ; 80	40 ; 80	40 ; 80
Age group (years) [n (%)]			

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Number	471	468	939
40-64	201 (42.7)	192 (41.0)	393 (41.9)
65-74	204 (43.3)	216 (46.2)	420 (44.7)
75-80	66 (14.0)	60 (12.8)	126 (13.4)
Sex [n (%)]			
Number	471	468	939
Male	322 (68.4)	298 (63.7)	620 (66.0)
Female	149 (31.6)	170 (36.3)	319 (34.0)
Region[a] [n (%)]			
Number	471	468	939
Asia	66 (14.0)	67 (14.3)	133 (14.2)
Latin America	112 (23.8)	113 (24.1)	225 (24.0)
East Europe	158 (33.5)	156 (33.3)	314 (33.4)
Western countries	135 (28.7)	132 (28.2)	267 (28.4)
Territory[b] [n (%)]			
Number	471	468	939
North America	60 (12.7)	60 (12.8)	120 (12.8)
European Union	156 (33.1)	150 (32.1)	306 (32.6)
Rest of World	255 (54.1)	258 (55.1)	513 (54.6)
Race [n (%)]			
Number	471	468	939
White	397 (84.3)	393 (84.0)	790 (84.1)
Black/of African descent	2 (0.4)	3 (0.6)	5 (0.5)
Asian	67 (14.2)	67 (14.3)	134 (14.3)
American Indian or Alaska Native	4 (0.8)	3 (0.6)	7 (0.7)
Native Hawaiian or other Pacific Islander	1 (0.2)	0	1 (0.1)
Multiple	0	2 (0.4)	2 (0.2)
Ethnicity [n (%)]			
Number	471	468	939
Hispanic or Latino	129 (27.4)	132 (28.2)	261 (27.8)
Not Hispanic or Latino	342 (72.6)	335 (71.6)	677 (72.1)
Unknown	0	1 (0.2)	1 (0.1)
Weight (kg)			
Number	471	468	939
Mean (SD)	77.51 (17.60)	76.51 (17.25)	77.02 (17.42)
Median	75.70	75.00	75.20
Q1 ; Q3	65.00 ; 88.00	64.65 ; 87.00	65.00 ; 87.10
Min ; Max	41.0 ; 158.3	38.6 ; 130.0	38.6 ; 158.3
Weight group (kg) [n (%)]			
Number	471	468	939
<50	14 (3.0)	21 (4.5)	35 (3.7)
≥50 - <100	410 (87.0)	399 (85.3)	809 (86.2)
≥100	47 (10.0)	48 (10.3)	95 (10.1)
Weight group 1 for efficacy (kg) [n (%)]			
Number	471	468	939
<60	75 (15.9)	78 (16.7)	153 (16.3)

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
≥60	396 (84.1)	390 (83.3)	786 (83.7)
Weight group 2 for efficacy (kg) [n (%)]			
Number	471	468	939
<70	161 (34.2)	171 (36.5)	332 (35.4)
≥70 - <90	203 (43.1)	203 (43.4)	406 (43.2)
≥90	107 (22.7)	94 (20.1)	201 (21.4)
Body mass index (BMI) (kg/m^2)			
Number	471	468	939
Mean (SD)	27.65 (5.73)	27.51 (5.44)	27.58 (5.59)
Median	26.80	26.81	26.81
Q1 ; Q3	23.66 ; 30.85	23.62 ; 30.97	23.62 ; 30.86
Min ; Max	16.0 ; 52.9	16.2 ; 47.3	16.0 ; 52.9
BMI group (kg/m^2) [n (%)]			
Number	471	468	939
<25	168 (35.7)	163 (34.8)	331 (35.3)
≥25 - <30	167 (35.5)	165 (35.3)	332 (35.4)
≥30 - <35	84 (17.8)	97 (20.7)	181 (19.3)
≥35	52 (11.0)	43 (9.2)	95 (10.1)

a Asia: Japan, China, South Korea; Latin America: Argentina, Chile and Mexico; East Europe: Russia, Ukraine, Turkey, Hungary, Poland, Czech Republic, Romania, Bulgaria, Slovakia; Western Countries: Finland, Denmark, Spain, Israel, Sweden, Germany, Italy, Canada, USA

b North America: Canada and USA; European Union: Hungary, Poland, Czech Republic, Romania, Bulgaria, Slovakia, Spain, Sweden, Germany, Italy, Finland, Denmark; Rest of World: Israel, Argentina, Chile, Japan, China, South Korea, Mexico, Russia, Ukraine, Turkey

Note: Number = Number of participants assessed. Percentages are calculated using number of participants assessed as denominator.

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/dem_demo_r_t.sas
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Baseline disease characteristics

The mean age at onset of COPD (based on reported date of diagnosis) was 56.9 years. The mean number of moderate or severe AECOPD events in the prior year was 2.3 overall and similar between intervention groups (2.2 in the dupilumab group and 2.3 in the placebo group), with 129 (27.6%) participants in the dupilumab group and 114 (24.2%) participants in the placebo group experiencing ≥1 severe exacerbation in the prior year. All participants had a history of smoking with 30.0% of participants being current smokers. The mean (SD) number of pack-years of cigarette smoking was 40.48 (23.35) and was similar between the intervention groups (Table 17).

At baseline, there were 448 (47.7%) and 442 (47.1%) participants, respectively, with moderate (GOLD grade 2; % predicted post-BD FEV1 of 50 to <80%) and severe airflow limitation (GOLD grade 3; % predicted post-BD FEV1 of 30 to <50%). The values are balanced between the dupilumab and the placebo group. A total of 25 (2.7%) participants had airflow limitation categorized as very severe (ie, GOLD grade 4; % predicted post-BD FEV1 of <30% at baseline). A small number of participants (dupilumab: 3; placebo: 3), had a GOLD Grade 4 at screening but were reported as major protocol deviations. Similarly, a total of 24 participants were grade GOLD grade 1 (FEV1 ≥80%) at baseline indicating participants with improvement in FEV1 by at least 10 percent points regardless of dupilumab treatment. However, these patients were low in number and balanced between treatment groups. The overall mean pre-BD FEV1 was 1.30 L and mean % predicted pre-BD FEV1 was 47.09%. As defined in the inclusion criteria, participants had a participant-reported history of signs and symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year up to screening in the absence of other known causes of chronic cough history.

COPD-related phenotypes including emphysema and chronic bronchitis were well balanced between the intervention groups. A total of 309 (32.9%) participants had a history of emphysema, which was ongoing at study baseline for 306 (32.6%) of participants.

Randomization was stratified by ICS dose at baseline. Overall, 27.4% of participants were on high dose ICS while 72.6% of participants did not receive high-dose ICS at baseline. This latter group also included participants for whom ICS was contraindicated (see Section 2.1.2.5). Despite maximal standard-of-care therapy, the participants enrolled in EFC15804 had uncontrolled COPD (high risk of exacerbation and presence of respiratory symptoms).

The mean (SD) SGRQ score was 48.42 (17.42) (scale range: 0-100 with 100 indicating the largest impact on health status/HRQoL); the mean (SD) EQ VAS score was 65.5 (16.4) (values between 0 [worst imaginable health] and 100 [best imaginable health], and the mean (SD) E-RS: COPD RS-Total score was 12.9 (7.1) (scale range of 0 to 40, with higher values indicating more severe respiratory symptoms). The mean (SD) baseline BODE index score was 4.062 (1.659), with 42.4% of participants having a score of 3-4, 30.6% of participants having a score of 5-6, and 7.6% of participants having a score of 7-10. An overview of the scale ranges of the patient reported outcome questionnaires has been provided in the dossier.

Table 17 - Selected disease characteristics at baseline - Randomized population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Baseline high-dose ICS from medication history			
Number	471	468	939
Yes	126 (26.8)	131 (28.0)	257 (27.4)
No	345 (73.2)	337 (72.0)	682 (72.6)
Baseline high-dose ICS from IVRS			
Number	471	468	939
Yes	173 (36.7)	170 (36.3)	343 (36.5)
No	298 (63.3)	298 (63.7)	596 (63.5)
Baseline pre-bronchodilator FEV1(L)			
Number	471	467	938
Mean (SD)	1.32 (0.46)	1.28 (0.45)	1.30 (0.46)
Median	1.22	1.20	1.21
Q1 ; Q3	0.98 ; 1.58	0.94 ; 1.57	0.96 ; 1.57
Min ; Max	0.5 ; 3.4	0.4 ; 3.4	0.4 ; 3.4
Baseline post-bronchodilator FEV1(L)			
Number	471	468	939
Mean (SD)	1.41 (0.47)	1.39 (0.47)	1.40 (0.47)
Median	1.33	1.31	1.32
Q1 ; Q3	1.08 ; 1.71	1.03 ; 1.68	1.05 ; 1.70
Min ; Max	0.5 ; 3.4	0.5 ; 3.1	0.5 ; 3.4
Baseline pre-bronchodilator FEV1 percent predicted			
Number	471	467	938
Mean (SD)	47.27 (13.17)	46.91 (13.56)	47.09 (13.36)
Median	46.35	46.22	46.28
Q1 ; Q3	37.09 ; 56.34	36.79 ; 55.56	36.99 ; 55.96
Min ; Max	22.6 ; 95.1	21.9 ; 115.2	21.9 ; 115.2

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Baseline post-bronchodilator FEV1 percent predicted			
Number	471	468	939
Mean (SD)	50.63 (12.97)	50.57 (13.26)	50.60 (13.11)
Median	49.40	50.40	50.17
Q1 ; Q3	40.56 ; 60.40	40.24 ; 59.06	40.36 ; 59.88
Min ; Max	19.2 ; 98.7	23.8 ; 105.1	19.2 ; 105.1
Baseline pre-bronchodilator FVC(L)			
Number	471	467	938
Mean (SD)	2.83 (0.90)	2.71 (0.74)	2.77 (0.83)
Median	2.76	2.66	2.69
Q1 ; Q3	2.17 ; 3.38	2.15 ; 3.17	2.17 ; 3.27
Min ; Max	0.8 ; 6.6	1.0 ; 4.9	0.8 ; 6.6
Baseline pre-bronchodilator FEV1/FVC Ratio			
Number	471	467	938
Mean (SD)	0.48 (0.11)	0.48 (0.12)	0.48 (0.12)
Median	0.47	0.47	0.47
Q1 ; Q3	0.39 ; 0.56	0.39 ; 0.56	0.39 ; 0.56
Min ; Max	0.2 ; 0.8	0.2 ; 0.8	0.2 ; 0.8
Baseline post-bronchodilator FEV1/FVC Ratio			
Number	471	468	939
Mean (SD)	0.49 (0.11)	0.49 (0.12)	0.49 (0.12)
Median	0.48	0.48	0.48
Q1 ; Q3	0.39 ; 0.57	0.40 ; 0.57	0.40 ; 0.57
Min ; Max	0.2 ; 1.0	0.2 ; 0.8	0.2 ; 1.0
Baseline pre-bronchodilator forced expiratory flow (FEF) 25-75% (L/s)			
Number	471	467	938
Mean (SD)	0.50 (0.30)	0.50 (0.34)	0.50 (0.32)
Median	0.42	0.42	0.42
Q1 ; Q3	0.30 ; 0.60	0.28 ; 0.63	0.29 ; 0.61
Min ; Max	0.2 ; 3.2	0.1 ; 3.9	0.1 ; 3.9
Baseline FEV1 reversibility (%)			
Number	471	467	938
Mean (SD)	8.84 (12.48)	9.30 (13.08)	9.07 (12.78)
Median	6.93	7.58	7.26
Q1 ; Q3	1.52 ; 13.47	2.17 ; 14.21	1.84 ; 13.82
Min ; Max	-26.0 ; 110.8	-23.2 ; 159.3	-26.0 ; 159.3
Baseline FEV1 reversibility > 12% and > 0.2 L			
Number	471	467	938
Yes	81 (17.2)	80 (17.1)	161 (17.2)
No	390 (82.8)	387 (82.9)	777 (82.8)
Baseline SGRQ total score			
Number	461	461	922
Mean (SD)	48.41 (17.80)	48.42 (17.04)	48.42 (17.42)

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Median	48.20	48.58	48.29
Q1 ; Q3	35.87 ; 60.89	36.22 ; 60.55	35.95 ; 60.64
Min ; Max	3.0 ; 97.1	2.4 ; 97.0	2.4 ; 97.1
Time since first diagnosis of COPD (years)			
Number	471	468	939
Mean (SD)	8.96 (6.10)	8.59 (5.96)	8.77 (6.03)
Median	8.00	7.25	7.67
Q1 ; Q3	4.42 ; 12.00	4.00 ; 11.00	4.00 ; 11.42
Min ; Max	1.0 ; 40.0	1.0 ; 36.0	1.0 ; 40.0
Age at onset of COPD (years)			
Number	471	468	939
Mean (SD)	56.8 (9.2)	57.0 (8.8)	56.9 (9.0)
Median	58.0	57.0	57.0
Q1 ; Q3	51.0 ; 63.0	51.0 ; 64.0	51.0 ; 63.0
Min ; Max	27 ; 78	29 ; 77	27 ; 78
Smoking history at screening			
Number	471	468	939
Former	323 (68.6)	334 (71.4)	657 (70.0)
Current	148 (31.4)	134 (28.6)	282 (30.0)
Smoking quantities (pack-years)			
Number	377	389	766
Mean (SD)	41.38 (24.36)	39.60 (22.32)	40.48 (23.35)
Median	39.00	35.00	37.00
Q1 ; Q3	22.50 ; 50.00	23.00 ; 48.00	23.00 ; 50.00
Min ; Max	10.0 ; 153.0	10.0 ; 172.0	10.0 ; 172.0
Number of moderate or severe COPD exacerbation[a] experienced within 1 year before visit 1			
Number	471	468	939
Mean (SD)	2.3 (1.0)	2.2 (1.1)	2.3 (1.0)
Median	2.0	2.0	2.0
Q1 ; Q3	2.0 ; 3.0	2.0 ; 2.0	2.0 ; 2.0
Min ; Max	1 ; 8	1 ; 16	1 ; 16
1	46 (9.8)	59 (12.6)	105 (11.2)
2	303 (64.3)	312 (66.7)	615 (65.5)
3	90 (19.1)	57 (12.2)	147 (15.7)
≥4	32 (6.8)	40 (8.5)	72 (7.7)
Number of moderate COPD exacerbation[a] experienced within 1 year before visit 1			
Number	471	468	939
Mean (SD)	2.0 (1.1)	1.9 (1.3)	1.9 (1.2)
Median	2.0	2.0	2.0
Q1 ; Q3	2.0 ; 2.0	2.0 ; 2.0	2.0 ; 2.0
Min ; Max	0 ; 7	0 ; 16	0 ; 16
1	30 (6.4)	30 (6.4)	60 (6.4)
2	280 (59.4)	280 (59.8)	560 (59.6)
3	77 (16.3)	51 (10.9)	128 (13.6)
≥4	25 (5.3)	29 (6.2)	54 (5.8)

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Number of severe COPD exacerbation[a] experienced within 1 year before visit 1			
Number	471	468	939
Mean (SD)	0.3 (0.6)	0.4 (0.7)	0.3 (0.7)
Median	0.0	0.0	0.0
Q1 ; Q3	0.0 ; 0.0	0.0 ; 1.0	0.0 ; 1.0
Min ; Max	0 ; 5	0 ; 5	0 ; 5
≥1	114 (24.2)	129 (27.6)	243 (25.9)
1	95 (20.2)	107 (22.9)	202 (21.5)
2	13 (2.8)	15 (3.2)	28 (3.0)
3	4 (0.8)	3 (0.6)	7 (0.7)
≥4	2 (0.4)	4 (0.9)	6 (0.6)
Baseline EQ visual analog scale score[b]			
Number	459	457	916
Mean (SD)	65.7 (16.0)	65.3 (16.7)	65.5 (16.4)
Median	67.0	67.0	67.0
Q1 ; Q3	54.0 ; 79.0	51.0 ; 79.0	52.0 ; 79.0
Min ; Max	20 ; 100	17 ; 100	17 ; 100
Baseline BODE index score			
Number	470	464	934
Mean (SD)	4.006 (1.659)	4.119 (1.659)	4.062 (1.659)
Median	4.000	4.000	4.000
Q1 ; Q3	3.000 ; 5.000	3.000 ; 5.000	3.000 ; 5.000
Min ; Max	1.00 ; 9.00	1.00 ; 10.00	1.00 ; 10.00
Baseline BODE			
Number	470	464	934
0-2	95 (20.2)	86 (18.5)	181 (19.4)
3-4	204 (43.4)	192 (41.4)	396 (42.4)
5-6	139 (29.6)	147 (31.7)	286 (30.6)
7-10	32 (6.8)	39 (8.4)	71 (7.6)
Baseline Evaluating Respiratory Symptoms (E-RS): COPD RS-Total score[c]			
Number	467	461	928
Mean (SD)	13.0 (6.9)	12.9 (7.2)	12.9 (7.1)
Median	13.0	12.4	12.6
Q1 ; Q3	8.6 ; 17.7	7.9 ; 17.6	8.1 ; 17.7
Min ; Max	0 ; 35	0 ; 35	0 ; 35
Baseline E-RS: COPD domain scores			
E-RS: COPD RS-Breathlessness			
Number	467	461	928
Mean (SD)	6.3 (3.6)	6.4 (3.7)	6.4 (3.7)
Median	6.0	6.4	6.2
Q1 ; Q3	4.0 ; 9.0	4.0 ; 9.0	4.0 ; 9.0
Min ; Max	0 ; 15	0 ; 16	0 ; 16
E-RS: COPD RS-Cough and Sputum			
Number	467	461	928
Mean (SD)	3.5 (1.8)	3.4 (1.9)	3.4 (1.8)

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Median	3.4	3.4	3.4
Q1 ; Q3	2.4 ; 4.7	2.3 ; 4.7	2.3 ; 4.7
Min ; Max	0 ; 9	0 ; 9	0 ; 9
E-RS: COPD RS-Chest Symptoms			
Number	467	461	928
Mean (SD)	3.1 (2.2)	3.2 (2.3)	3.2 (2.2)
Median	3.1	3.0	3.0
Q1 ; Q3	1.1 ; 4.8	1.1 ; 4.7	1.1 ; 4.7
Min ; Max	0 ; 11	0 ; 10	0 ; 11
Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity at screening			
Number	471	468	939
GOLD Grade 1	0	0	0
GOLD Grade 2	218 (46.3)	233 (49.8)	451 (48.0)
GOLD Grade 3	250 (53.1)	232 (49.6)	482 (51.3)
GOLD Grade 4	3 (0.6)	3 (0.6)	6 (0.6)
Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity at baseline			
Number	471	468	939
GOLD Grade 1	12 (2.5)	12 (2.6)	24 (2.6)
GOLD Grade 2	219 (46.5)	229 (48.9)	448 (47.7)
GOLD Grade 3	229 (48.6)	213 (45.5)	442 (47.1)
GOLD Grade 4	11 (2.3)	14 (3.0)	25 (2.7)

ICS: Inhaled Corticosteroid; IVRS: Interactive Voice Response System; FEV1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; FEF 25-75%: Forced Expiratory Flow at 25% to 75% of forced vital capacity; SGRQ: St. George's Respiratory Questionnaire; COPD: Chronic Obstructive Pulmonary Disease; BODE: Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity

a Moderate exacerbations are recorded by the Investigator and defined as AECOPD that require either systemic corticosteroids (such as intramuscular, intravenous or oral) and/or antibiotics. Severe exacerbations are recorded by the Investigator and defined as AECOPD requiring hospitalization, or treatment for >24 hours in emergency department/urgent care facility or result in death.

For both moderate and severe events to be counted as separate events, they must be separated by at least 14 days.

b The EQ VAS records the respondent's self-rated health on a vertical VAS. A high score indicates good outcome.

c The E-RS: COPD utilizes the 11 respiratory symptom items contained in the 14-item EXACT, with higher values indicating more severe respiratory symptoms.

Note: Number = Number of participants assessed. Percentages are calculated using number of participants assessed as denominator.

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/dem_disease_sl_r_t.sas
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Medical history and concurrent illnesses

The percentages of participants with a type 2 comorbidity were well balanced between the intervention groups. Approximately 22% of participants had a history of at least 1 other type 2 inflammatory disease, with allergic rhinitis being the most frequent (13.0%). The COPD population enrolled in Study EFC15804 had a low prevalence of comorbid type 2 conditions. As per protocol, none of the participants had a current diagnosis or history of asthma, with the exception of 2 participants, 1 in the placebo group with an ongoing medical history of asthma and 1 in the dupilumab group with an ongoing medical history of asthma-COPD overlap syndrome; both were reported as major protocol deviations.

Biomarkers at baseline

All participants had eosinophil count ≥0.3 Giga/L at screening as per protocol (the maximum eosinophil count during screening was used for eligibility), except for 2 participants in the placebo group and 1 participant in the dupilumab group; these were reported as major protocol deviations. At baseline, and the mean (SD) eosinophil count at baseline was 0.40 (0.30) Giga/L (401.00 [298.29] cells/µL). While all participants had a maximum eosinophil count ≥0.3 Giga/L at screening with a mean (SD) maximum value of 0.52 (0.31) Giga/L, eosinophil levels dropped to a mean (SD) 0.40 (0.30) at baseline with the majority (61.0%) of participants having an eosinophil count that remained ≥0.3 Giga/L and a total of 39% of participants being below the targeted eosinophil screening threshold at baseline. Mean (SD) FeNO levels at baseline were elevated (24.33 [22.40] ppb) and similar between the intervention groups. Overall, 383 (43.8%) of participants had baseline FeNO levels ≥20 ppb (45.0% in the dupilumab group and 42.5% in the placebo group). Other markers of type 2 inflammation (e.g. plasma eotaxin-3, serum total IgE, serum PARC) were elevated and similar between the intervention groups.

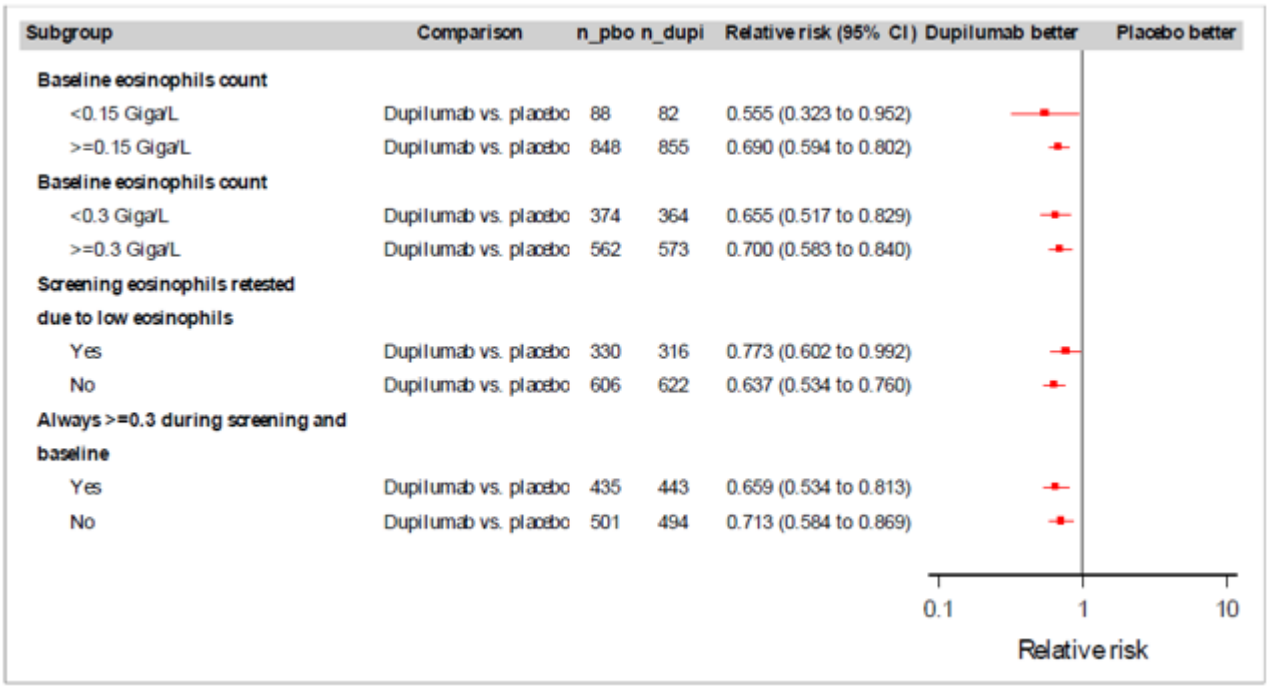
Table 18 - Biomarkers at baseline - Randomized population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Max eosinophil at screening (giga/L)			
Number	471	468	939
Mean (SD)	0.53 (0.33)	0.51 (0.28)	0.52 (0.31)
Median	0.43	0.42	0.42
Q1 ; Q3	0.34 ; 0.60	0.35 ; 0.54	0.35 ; 0.57
Min ; Max	0.1 ; 3.2	0.3 ; 2.6	0.1 ; 3.2
Geometric Mean (Geometric SD)	0.48 (1.53)	0.47 (1.47)	0.47 (1.50)
Max eosinophil at screening category (giga/L) [n (%)]			
Number	471	468	939
<0.5	298 (63.3)	310 (66.2)	608 (64.7)
≥0.5	173 (36.7)	158 (33.8)	331 (35.3)
Baseline blood eosinophil (giga/L)			
Number	471	468	939
Mean (SD)	0.41 (0.33)	0.39 (0.26)	0.40 (0.30)
Median	0.33	0.34	0.34
Q1 ; Q3	0.23 ; 0.46	0.25 ; 0.46	0.24 ; 0.46
Min ; Max	0.0 ; 3.2	0.0 ; 2.6	0.0 ; 3.2
Geometric Mean (Geometric SD)	0.33 (1.84)	0.34 (1.77)	0.33 (1.80)
Baseline blood eosinophil category (giga/L) [n (%)]			
Number	471	468	939
<0.30	186 (39.5)	180 (38.5)	366 (39.0)
≥0.30	285 (60.5)	288 (61.5)	573 (61.0)
Baseline fractional exhaled nitric oxide (FeNO) (ppb)			
Number	442	433	875
Mean (SD)	23.51 (22.00)	25.18 (22.79)	24.33 (22.40)
Median	17.00	17.00	17.00
Q1 ; Q3	11.00 ; 30.00	10.00 ; 31.00	10.00 ; 30.00
Min ; Max	5.0 ; 179.0	5.0 ; 140.0	5.0 ; 179.0

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Baseline fractional exhaled nitric oxide (FeNO) category (ppb) [n (%)]			
Number	442	433	875
<20	254 (57.5)	238 (55.0)	492 (56.2)
≥20	188 (42.5)	195 (45.0)	383 (43.8)

Additional data for patients with retesting were provided during the procedure. The subgroup analysis provided in Figure 11 below overall indicate that the reductions in exacerbations were overall similar in participants with retesting of blood eosinophils or low blood eosinophils (<0.15 cells/µL) at baseline as compared to participants that always showed blood eosinophils above the threshold.

Figure 11 – Forest plot of relative risk in the annualized rate of moderate of severe COPD exacerbations during the 52-week treatment period by screening and baseline eosinophils – Pooled ITT population



Prior and concomitant medications

The 10 most frequently used prior medications by standardized medication name were salbutamol (73.7% of participants), tiotropium bromide monohydrate (40.6%), fluticasone propionate/salmeterol xinafoate (25.6%), budesonide/formoterol fumarate (24.9%), acetylsalicylic acid (17.1%), budesonide (12.6%), fluticasone furoate/umeclidinium bromide/vilanterol trifenatate (11.6%), prednisone (10.3%), tiotropium bromide (10.0%), and atorvastatin (8.4%).

All participants were receiving background COPD controller therapy at study entry and continued with these medications throughout the study. Both intervention groups were well balanced with respect to the use of controller medications. Overall, 97.6% of participants were on triple therapy LABA+LAMA+ICS. Among participants receiving ICS, 27.4% were on high-dose ICS, while 70.5% of participants received non-high-dose (ie, low or medium-dose) ICS at baseline. Additional add-on therapy included PDE-4

inhibitors in 1.2%, methylxanthines in 3.0%, supplemental oxygen therapy for <12 hours per day in 2.3%, and chronic azithromycin therapy in 0.7% of the overall population.

Table 19 - Controller medication at randomization by type - Randomized population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Participants with ICS controller medication	463 (98.3)	456 (97.4)	919 (97.9)
High-dose ICS [n (%)]	126 (26.8)	131 (28.0)	257 (27.4)
Non-high-dose ICS [n (%)]	337 (71.5)	325 (69.4)	662 (70.5)
ICS dose (in fluticasone propionate equivalent dose) (mcg)			
Number	463	456	919
Mean (SD)	547.49 (303.91)	553.83 (293.65)	550.64 (298.72)
Median	500.00	500.00	500.00
Q1 ; Q3	255.56 ; 513.61	255.56 ; 750.00	255.56 ; 625.00
Min ; Max	100.0 ; 3000.0	62.5 ; 1750.0	62.5 ; 3000.0
Participants with controller medication other than ICS	471 (100)	468 (100)	939 (100)
LABA [n (%)]	471 (100)	468 (100)	939 (100)
LAMA [n (%)]	469 (99.6)	467 (99.8)	936 (99.7)
Anti-leukotrienes [n (%)]	7 (1.5)	11 (2.4)	18 (1.9)
Methylxanthines [n (%)]	16 (3.4)	12 (2.6)	28 (3.0)
Phosphodiesterase-4 (PDE4) inhibitor [n (%)]	9 (1.9)	2 (0.4)	11 (1.2)
Other[a] [n (%)]	1 (0.2)	1 (0.2)	2 (0.2)
Participants with combinations of controller medications	469 (99.6)	467 (99.8)	936 (99.7)
ICS+LABA+LAMA [n (%)]	461 (97.9)	455 (97.2)	916 (97.6)
LABA+LAMA (no ICS) [n (%)]	8 (1.7)	12 (2.6)	20 (2.1)

ICS: Inhaled corticosteroid, LABA: Long-acting beta-agonist, LAMA: Long-Acting Muscarinic Antagonist, LTRA: Leukotriene Receptor Antagonist

a Includes Ipratropium and Salbutamol sulfate.

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Outcomes and estimation

A summary of the primary, key secondary and other selected efficacy endpoints in study EFC15804 is given below.

Table 20- Summary of the primary and key secondary/other efficacy endpoints in the hierarchical testing procedure - ITT population

Parameter	Hierarchy	Placebo[a] (N=471)	Dupilumab[a] (N=468)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Primary endpoint					
Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period	1	1.101	0.776	0.705 (0.581 to 0.857)	**0.0005**
Key secondary/other endpoints					
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo	2	0.077 (0.018)	0.160 (0.018)	0.083 (0.042 to 0.125)	**<.0001**
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo	3	0.070 (0.019)	0.153 (0.019)	0.083 (0.038 to 0.128)	**0.0003**
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo in the subgroup of participants with baseline FeNO ≥ 20 ppb[d]	4	0.108 (0.035)	0.232 (0.034)	0.124 (0.045 to 0.203)	**0.0022**
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo in the subgroup of participants with baseline FeNO ≥ 20 ppb[d]	5	0.120 (0.037)	0.247 (0.036)	0.127 (0.042 to 0.212)	**0.0034**
Change from baseline to Week 52 in SGRQ total score compared to placebo	6	-6.369 (0.816)	-9.732 (0.810)	-3.363 (-5.459 to -1.266)	**0.0017**
Proportion of participants with SGRQ improvement ≥ 4 points at Week 52 compared to placebo	7	203 (43.1)	241 (51.5)	1.439 (1.096 to 1.890)	**0.0089**
Change in E-RS: COPD RS-Total Score from baseline to Week 52 compared to placebo	8	-1.558 (0.256)	-2.694 (0.257)	-1.137 (-1.823 to -0.450)	**0.0012**
Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of participants with baseline FeNO ≥ 20 ppb[d]	9	1.117	0.699	0.625 (0.450 to 0.869)	**0.0052**

FEV1: Forced Expiratory Volume in one second; FeNO; Fractional Exhaled Nitric Oxide; SGRQ: St. George's Respiratory Questionnaire; E-RS: COPD: Evaluating Respiratory Symptoms (E-RS) in COPD; LS: least squares.

a Values presented are event rates derived using negative binomial model for event type variables, LS mean change from baseline with standard error for continuous variables, and number and percent of responders for binary variables.

b Difference is relative risk for event type variables, LS mean difference for continuous variables, and odds ratio for binary variables.

c All values in bold font are statistically significant according to the hierarchical testing procedure.

d The subgroup of baseline FeNO ≥20 ppb included N=188 in placebo and N=195 in dupilumab intervention groups.

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Primary efficacy endpoint

Annualized rate of moderate or severe exacerbation events in the ITT population

At baseline, the participants had a mean (SD) of 2.3 (1.0) moderate or severe AECOPD events in the year prior to enrollment. The adjusted annualized rate of moderate or severe AECOPD events over the 52-week intervention period in the ITT population was lower in the dupilumab group than in the placebo group: 0.776 (95% CI: 0.645 to 0.934) versus 1.101 (95% CI: 0.931 to 1.301). A reduction of 30% in the annualized rate of moderate or severe AECOPD compared to placebo (p=0.0005) was observed (Table 21. Sensitivity analyses provided results consistent with the primary analysis.

The total number of moderate or severe AECOPD events reported during the 52-week intervention period was lower in the dupilumab group as compared to the placebo group (296 versus 422) with a mean (SD) of 0.6 (1.0) and 0.9 (1.4), respectively.

The percentage of participants who did not experience any moderate or severe AECOPD events during the 52-week intervention period was greater in the dupilumab group as compared with the placebo group

(61.1% versus 55.0%). A lower percentage of participants in the dupilumab group had multiple exacerbations (≥2), compared with the placebo group. This overall indicates that the number of exacerbations may have been incrementally reduced based on the individual exacerbation baseline values.

However, the number of exacerbation events of 1 or 2 is in contrast similar between placebo and dupilumab.

The MAH provided further data for the whole range of exacerbations events including data for patients with up to 8 moderate or severe SOPC exacerbations. The data show that patients with multiple exacerbation events were more often observed in the placebo group.

Table 21 - Primary analysis: analysis of the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period - ITT population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)
Number of participants with >=1 moderate or severe exacerbation event		
Number	471	468
No	259 (55.0)	286 (61.1)
Yes	212 (45.0)	182 (38.9)
Number of moderate or severe exacerbation events		
Number	471	468
Mean (SD)	0.9 (1.4)	0.6 (1.0)
Median	0.0	0.0
Q1 ; Q3	0.0 ; 1.0	0.0 ; 1.0
Min ; Max	0 ; 8	0 ; 8
0	259 (55.0)	286 (61.1)
1	106 (22.5)	113 (24.1)
2	55 (11.7)	47 (10.0)
3	25 (5.3)	9 (1.9)
≥4	26 (5.5)	13 (2.8)
Total number of moderate or severe exacerbation events	422	296
Total patient-years followed	454.8	458.2
Unadjusted annualized moderate or severe exacerbation event rate[a]	0.93	0.65
Adjusted annualized moderate or severe exacerbation event rate[b]		
Estimate (95% CI)	1.101 (0.931 to 1.301)	0.776 (0.645 to 0.934)
Relative risk vs. placebo (95% CI)		0.705 (0.581 to 0.857)
P-value		0.0005
Risk difference vs. placebo (95% CI)[c]		-0.324 (-0.508, -0.140)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week treatment period are included, regardless of whether the participant was on-treatment or not.

a The total number of events 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 the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

c Derived using delta method.

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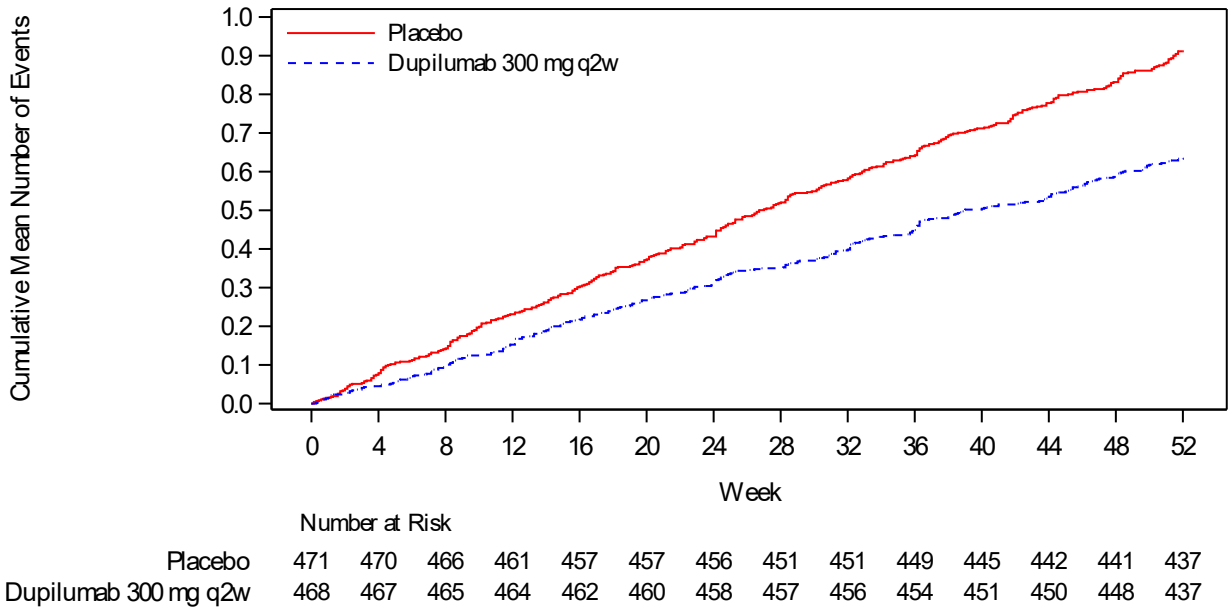
During the 52-week intervention period, a lower mean cumulative number of moderate or severe AECOPD events was observed in the dupilumab group as compared to the placebo group. The difference between the 2 intervention groups was apparent as early as Week 4 and progressively increased up to Week 52.

Figure 12 - Plot of cumulative mean number of moderate or severe COPD exacerbation events during the 52-week treatment period - ITT population



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Supportive analyses

Exacerbations by severity

The majority of the AECOPD events in both intervention groups were moderate. The total number of severe AECOPD events was low in the dupilumab and placebo groups (28 and 37 events). This decline is consistent with the reduction of severe exacerbation events observed during the COVID-19 pandemic. The adjusted annualized rate of severe AECOPD events over the 52-week treatment period in the ITT population was 0.072 in the dupilumab group and 0.086 in the placebo group (nominal p=0.6085). There was no difference between the dupilumab and placebo groups in the time to first severe COPD exacerbation event (hazard ratio: 0.744 [95% CI: 0.416 to 1.331]; nominal p=0.3185). In both intervention groups, all severe AECOPD events required hospitalization or emergency medical care visit, and none led to death.

Table 22 - Summary of occurrence of moderate or severe COPD exacerbations during the 52-week treatment period by individual criterion - ITT population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)
Total number of moderate or severe events	422	296
Number of severe events	37	28
Requiring hospitalization	36 (97.3)	27 (96.4)
Requiring emergency medical care visit	1 (2.7)	1 (3.6)
Resulting in death	0	0
Number of moderate events	385	268

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)
Only requiring use of systemic corticosteroid medications	130 (33.8)	84 (31.3)
Only requiring use of systemic antibiotics	68 (17.7)	52 (19.4)
Requiring use of both systemic corticosteroid medications and systemic antibiotics	187 (48.6)	132 (49.3)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week treatment period are included, regardless of whether the participant was on-treatment or not.

Note: Percentages are calculated using the number of events as the denominator.

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Table 23 - Summary of annualized rate of COPD exacerbation overall and by components during the 52-week treatment period - ITT population

Parameter	Placebo[a] (N=471)	Dupilumab[a] (N=468)	Difference (95% CI) for Dupilumab vs. Placebo	P-value[b]
Primary endpoint				
moderate or severe COPD exacerbation	1.101	0.776	0.705 (0.581 to 0.857)	**0.0005**
Components of the primary endpoint				
moderate COPD exacerbation	0.973	0.673	0.692 (0.564 to 0.848)	0.0004
severe COPD exacerbation	0.086	0.072	0.847 (0.447 to 1.602)	0.6085

a Values presented are event rates derived using negative binomial model.

b Nominal p-values except for the primary endpoint

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Time to first moderate or severe exacerbations

Dupilumab treatment delayed the time to first moderate or severe COPD exacerbation event as compared to placebo (hazard ratio: 0.803 [95% CI: 0.658 to 0.980]; nominal p=0.0309). The KM curves for first occurrence of moderate or severe COPD exacerbation event for the dupilumab and placebo groups started to diverge as early as Week 4.

Key secondary efficacy endpoint

Annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period in the subgroup of patients with baseline FeNO ≥20 ppb

The adjusted annualized rate of moderate or severe AECOPD events over the 52-week intervention period in the subgroup of participants with baseline FeNO ≥20 ppb was lower in the dupilumab group as compared with the placebo group: 0.699 (95% CI: 0.510 to 0.958) versus 1.117 (95% CI: 0.831 to 1.502). The magnitude of the treatment effect was numerically higher than that observed in the ITT population. In this subgroup of participants with baseline FeNO ≥20 ppb, a 37% reduction in the annualized rate of moderate or severe AECOPD as compared to placebo was observed (p=0.0052).

Table 24 - Analysis of the annualized rate of moderate or severe COPD exacerbations during the 52week treatment period among participants with baseline FeNO>= 20 ppb - ITT population

	Placebo (N=188)	Dupilumab 300 mg q2w (N=195)
Number of participants with >=1 moderate or severe exacerbation event		
Number	188	195
No	106 (56.4)	126 (64.6)
Yes	82 (43.6)	69 (35.4)
Number of moderate or severe exacerbation events		

Number	188	195
Mean (SD)	0.9 (1.5)	0.6 (1.1)
Median	0.0	0.0
Q1 ; Q3	0.0 ; 1.0	0.0 ; 1.0
Min ; Max	0 ; 8	0 ; 8
0	106 (56.4)	126 (64.6)
1	41 (21.8)	49 (25.1)
2	18 (9.6)	12 (6.2)
3	8 (4.3)	2 (1.0)
≥4	15 (8.0)	6 (3.1)
Total number of moderate or severe exacerbation events	178	110
Total patient-years followed	180.8	188.1
Unadjusted annualized moderate or severe exacerbation event rate[a]	0.98	0.58
Adjusted annualized moderate or severe exacerbation event rate[b]		
Estimate (95% CI)	1.117 (0.831 to 1.502)	0.699 (0.510 to 0.958)
Relative risk vs. placebo (95% CI)		0.625 (0.450 to 0.869)
P-value		0.0052
Risk difference vs. placebo (95% CI)[c]		-0.418 (-0.728, -0.109)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week treatment period are included, regardless of whether the participant was on-treatment or not.

a The total number of events 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 the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

c Derived using delta method.

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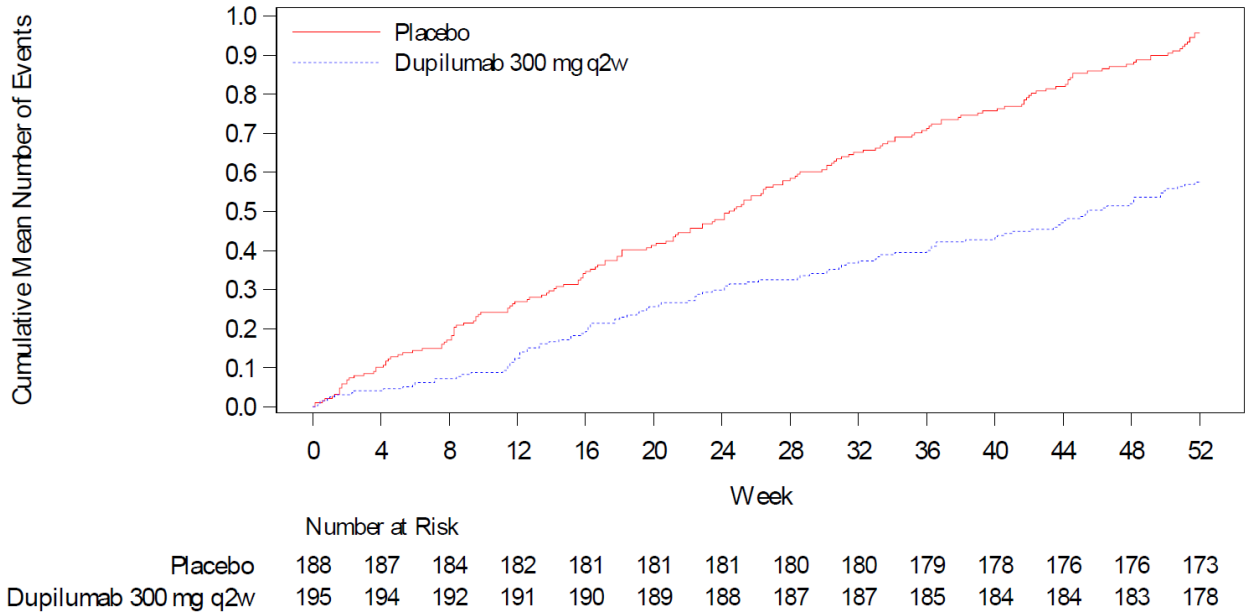
A lower mean cumulative number of moderate or severe AECOPD in the the subgroup of participants with baseline FeNO ≥20 ppb was observed in the dupilumab group as compared to the placebo group; the difference between the 2 intervention groups was apparent by Week 4 and progressively increased up to Week 52.

Figure 13- Plot of cumulative mean number of moderate or severe COPD exacerbation events during the 52-week treatment period among participants with baseline FeNO >=20 ppb - ITT



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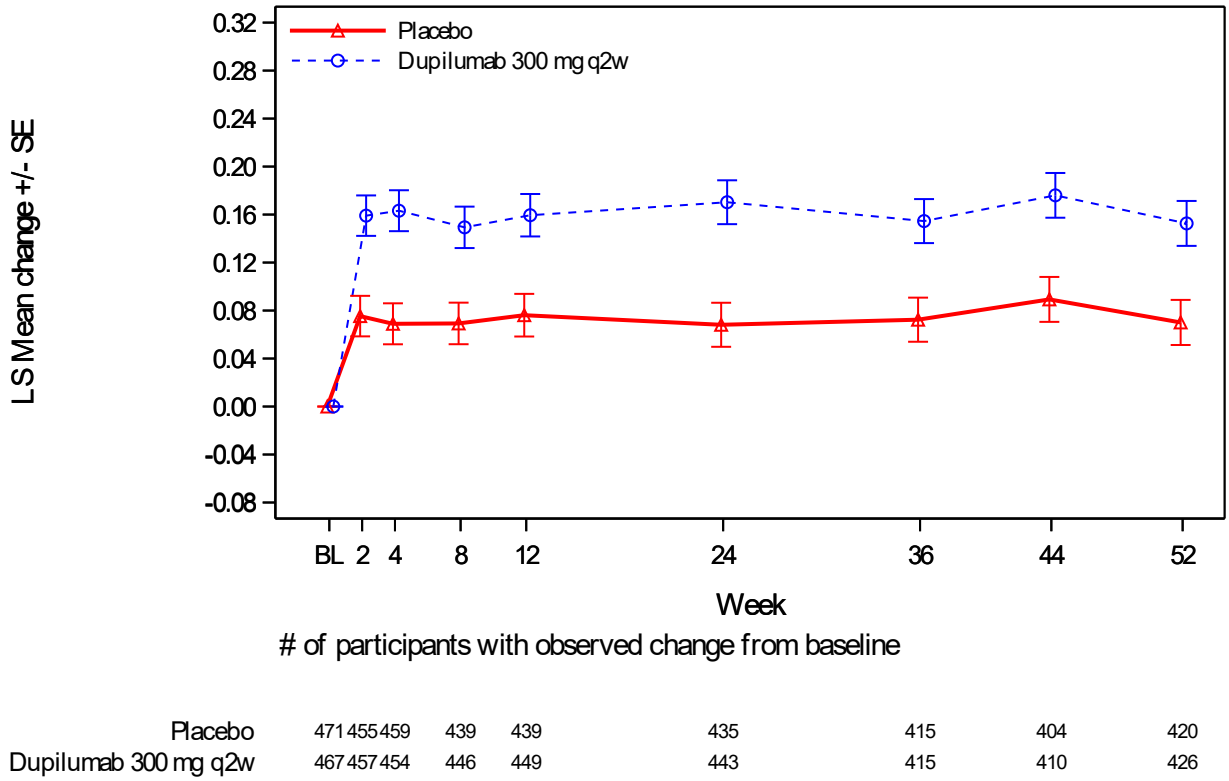
Change from baseline in pre-BD FEV1 at Week 12 and Week 52

Change in pre-bronchodilator FEV1 from baseline to Week 12 and Week 52 compared to placebo was specified as key secondary endpoint to evaluate improvements in airflow obstruction.

The LS mean change from baseline in pre-BD FEV1 at Week 12 was +0.160 L in the dupilumab group versus +0.077 L in the placebo group (+0.083 L, 95% CI: 0.042 L to 0.125 L; p <0.0001). The improvement in pre-BD FEV1 was rapid, with an onset of a difference between the intervention groups observed as early as Week 2 (nominal p<0.0001) and sustained over the 52-week intervention period (Figure 14). The LS mean change in pre-BD FEV1 from baseline to Week 52 was +0.153 L in the dupilumab group and +0.070 L in the placebo group, resulting in an LS mean difference versus placebo of +0.083 L (95% CI: 0.038 L to 0.128 L, p=0.0003). Notably, there is a prominent improvement in the placebo group as well. The MAH clarified that FEV1 improvements also in placebo patients are observed in both studies but are not a unique observation for the COPD development program. Similar placebo responses in lung function have been also observed in the asthma indication. Further, it was clarified that, considering the duration of the screening phase (which lasted 3-5 weeks), patients included were on a stable dose of triple therapy for no less than approximately 2 months in order to reduce potential confounding effects on FEV1 improvements due to changes in background medication prior to the begin of dupilumab treatment. Notably, there is no later decline in lung function in either the dupilumab or placebo group.

Although, the treatment is intended for long-term therapy, no clinical data for maintenance of lung function improvements beyond 52 weeks were submitted. Therefore, section 4.2 of the SmPC has been revised to include that dosing beyond 52 weeks has not been studied. Also, guidance that discontinuation of treatment should be considered if no response to treatment is observed has been included in section 4.2 of the SmPC.

Figure 14 - LS mean change from baseline in pre-bronchodilator FEV_1 (L) up to Week 52 by visit - ITT population



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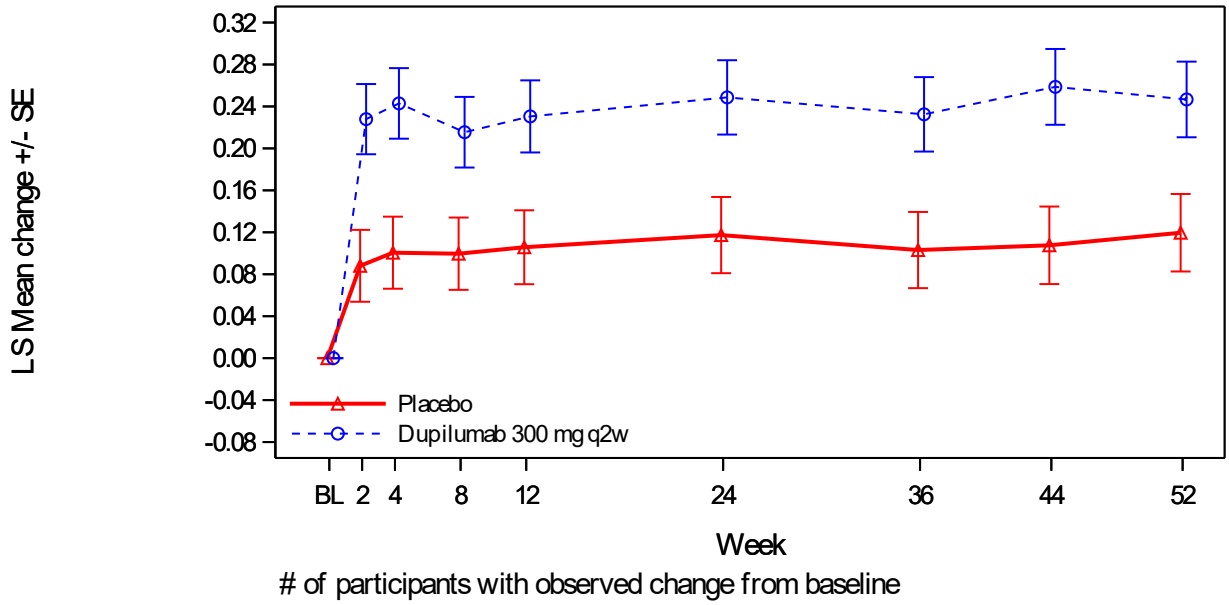
Change from baseline in pre-BD FEV1 at Week 12 and Week 52 in the subgroup of participants with baseline FeNO ≥20 ppb

In the subgroup of participants with baseline FeNO ≥20 ppb the LS mean change from baseline to Week 12 in pre-BD FEV1 was +0.232 L in the dupilumab group versus +0.108 L in the placebo group (+0.124 L, 95% CI: 0.045 to 0.203 L; p=0.0022). The improvement in pre-BD FEV1 was rapid, with an onset of a difference between the intervention groups observed as early as Week 2, and the effect was maintained over the 52-week intervention period (Figure 15). The LS mean change from baseline to Week 52 in pre-BD FEV1 was +0.247 L in the dupilumab group versus +0.120 L in the placebo group; (+0.127 L, 95% CI: 0.042 to 0.212 L; p=0.0034).

Figure 15 - LS mean change from baseline in pre-bronchodilator FEV_1 (L) up to Week 52 by visit among participants with baseline FeNO ≥20 ppb - ITT population



# of participants with observed change from baseline

Placebo	188	177	184	176	176	173	167	163	167
Dupilumab 300 mg q2w	194	187	187	185	188	184	175	167	177

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/eff_fev1_ls_i_g.sas
OUT=REPORT/OUTPUT/eff_fev1_pre_ls_wk52_fenoh_i_g_i.rtf (22MAR2023 4:15)

Supportive analyses to key secondary endpoints: other lung function parameters

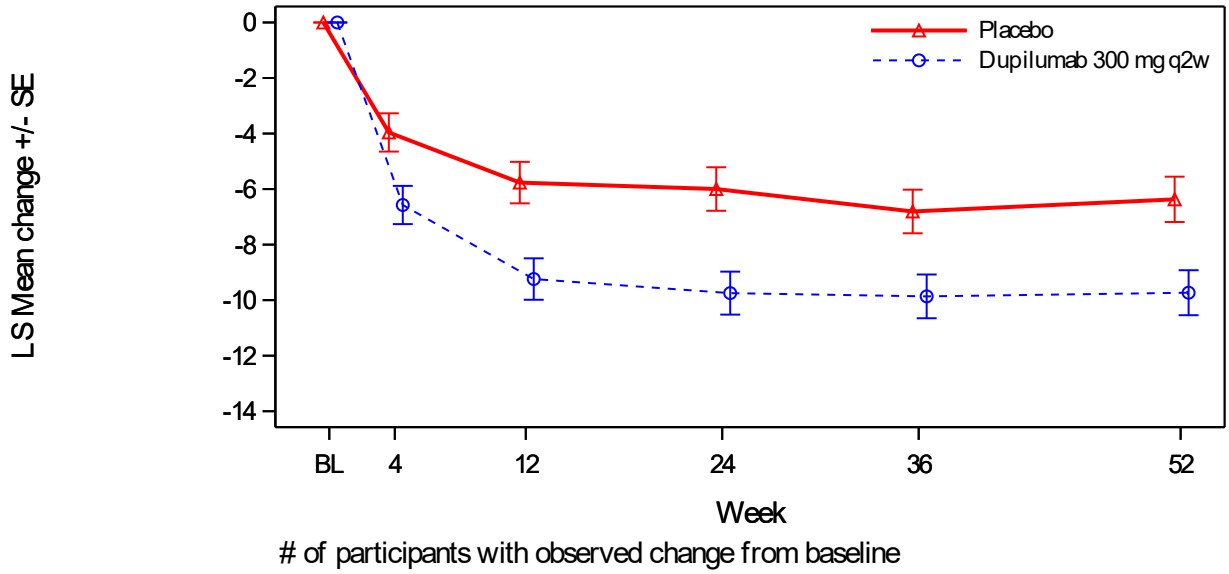
Dupilumab treatment demonstrated nominally significant and clinically meaningful improvements across multiple measures of lung function over time up to Week 52 including changes in post-bronchodilator FEV1, pre-bronchodilator FVC, post-bronchodilator FEV1/FVC, and Pre-bronchodilator FEF 25-75%.

Notably, no difference in the rate of change from baseline in post-BD FEV1 was observed between the dupilumab and placebo groups after Week 4 during the 52-week intervention period as assessed by post-BD FEV1 slope analysis.

Change from baseline in the SGRQ total score at Week 52

The overall health status was assessed using the established St George's Respiratory Questionnaire (SGRQ). At Week 52, a significantly greater reduction in SGRQ total scores was observed in the dupilumab group as compared to the placebo group, with LS mean changes from baseline to Week 52 of -9.732 and -6.369, respectively, and an LS mean difference versus placebo of 3.363 (95% CI: -5.459 to -1.266; p=0.0017). Similar to the improvements in lung function (change in pre-BD FEV1), the reduction and improvement in SGRQ total score was rapid, with a difference in favor of dupilumab as compared to placebo observed as early as the first post-baseline measurement at Week 4 (nominal p=0.0029), and sustained throughout the 52-week intervention period (Figure 16).

Figure 16 - LS mean change from baseline in SGRQ total score up to Week 52 by visit - ITT population



# of participants with observed change from baseline

Placebo	461	439	430	407	414	400
Dupilumab 300 mg q2w	461	444	436	434	407	415

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/eff_sgrq_ls_i_g.sas
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Similar to the treatment effect observed on the SGRQ total score, reductions (improvements) in all 3 SGRQ domains scores at Week 52 were observed in the dupilumab group as compared to the placebo group: Symptoms (nominal p=0.0121), Activity (nominal p=0.0005), and Impacts (nominal p=0.0242) Differences were observed as early as Week 4.

Proportion of participants with SGRQ improvement by ≥4 points at Week 52

The proportion of participants who achieved a clinically meaningful response in SGRQ total score (ie, reduction [improvement] by ≥4 points) was higher in the dupilumab group as compared to the placebo group (51.5% versus 43.1%); the difference was statistically significant (odds ratio: 1.439 [95% CI: 1.096 to 1.890]; p=0.0089). It should be noted that the mean (SD) change in the placebo group was 6.16 (17.59), exceeding the defined minimal important difference of -4 points in 43.1%. Still, a greater number of these responders was observed in the dupilumab group (51.5%).

Additionally, empirical cumulative distribution function curves of the change from baseline in SGRQ total score at Week 52, were created to evaluate the meaningfulness of the within-patient changes. The curves were well separated across a wide range of thresholds (in particular in the improvement area, including above -4 threshold) demonstrating a higher proportion of responders in the dupilumab versus placebo group.

Overall, the SGRQ data are supportive for the treatment effect of dupilumab on lung function.

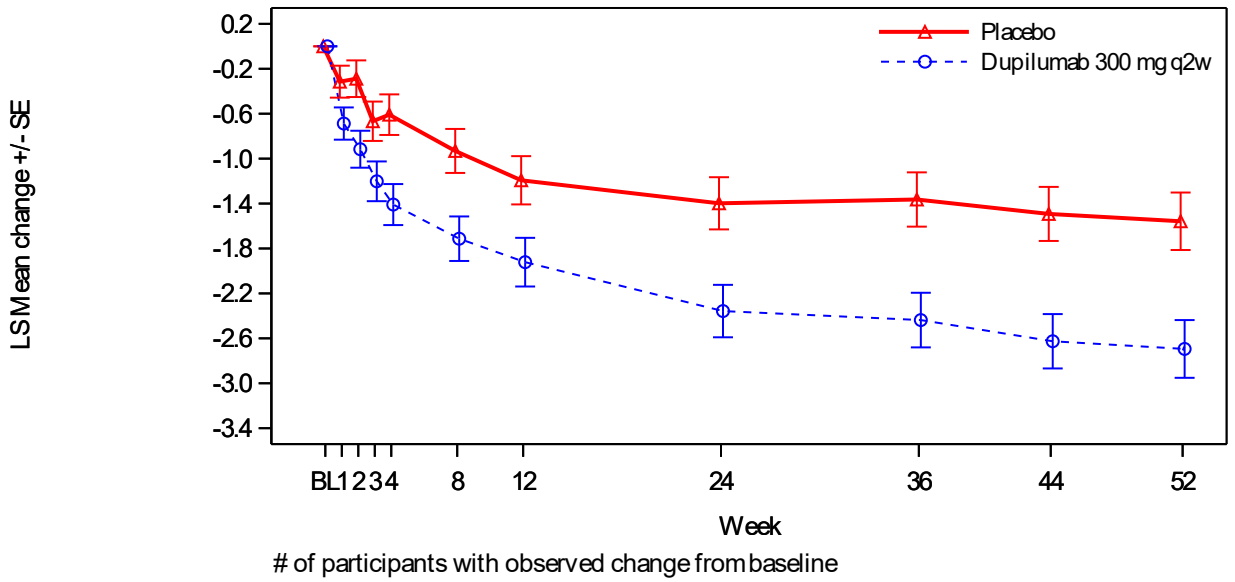
Other efficacy endpoints

Change in E-RS: COPD scores from baseline to Week 52

A significantly greater reduction in E-RS: COPD RS-Total scores, indicating an improvement in the severity of COPD-related respiratory symptoms, was observed in the dupilumab group as compared to

the placebo group, with LS mean changes from baseline to Week 52 of 2.694 and 1.558, respectively, and an LS mean difference versus placebo of 1.137 (95% CI: 1.823 to 0.450; p=0.0012).

Figure 17 - LS mean change from baseline in E-RS: COPD RS-Total Score up to Week 52 by visit - ITT population



# of participants with observed change from baseline

Placebo	467	454	448	443	424	414	404	379
Dupilumab 300 mg q2w	461	446	435	439	428	412	403	380

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Additional efficacy analysis

Efficacy in participants without moderate or severe COPD exacerbations

A post-hoc analysis on the subgroup of participants who did not experience AECOPD during the 52-week treatment period (dupiluman:286; placebo:259) was performed. The LS mean change in pre-BD FEV1 from baseline to Week 12 was +0.189 L in the dupilumab group versus +0.104 L in the placebo group, corresponding to an LS mean difference versus placebo of +0.085 L ([95% CI: 0.024 to 0.147]; nominal p=0.0065). The LS mean change in SGRQ total score from baseline to Week 52 was 12.289 in the dupilumab group versus 8.225 in the placebo group, corresponding to an LS mean difference versus placebo of 4.064 ([95% CI: -6.821 to -1.307]; nominal p=0.0039). The LS mean change in E-RS: COPD RS-Total score from baseline to Week 52 was 2.826 in the dupilumab group versus 1.643 in the placebo group, corresponding to an LS mean difference versus placebo of 1.183 ([95% CI: 2.043 to 0.323]; nominal p=0.0071). Results suggest similar treatment effect with regard to improvements in lung function and health status.

Use of corticosteroids or antibiotics

Systemic corticosteroids in case of acute exacerbation were allowed as rescue medication for up to a maximum of 6 weeks. The proportion of participants who required treatment with SCS for COPD exacerbations was lower in the dupilumab group (dupilumab: 153 (32.7%); placebo: 179 (38.0%)). Accordingly, the adjusted annualized total number of SCS courses for COPD exacerbations was lower in the dupilumab group as compared to the placebo group (0.667 [95% CI: 0.536 to 0.829] versus 0.948 [95% CI: 0.780 to 1.151]). Similarly, the adjusted annualized total number of antibiotic courses for COPD

exacerbations was lower in the dupilumab group as compared to the placebo group (0.594 [95% CI: 0.476 to 0.742] versus 0.818 [95% CI: 0.671 to 0.996]).

Treatment effect after study intervention discontinuation

During the 12-week post-intervention follow-up period, no difference in the annualized rate of moderate or severe COPD exacerbations was observed between the dupilumab and placebo groups (nominal p=0.7800). The change in mean pre-BD FEV1 from baseline in the dupilumab group diminished toward the level observed in the placebo group. In the same manner, between Weeks 52 and 64, the decrease observed in the SGRQ total score from baseline in the dupilumab group lessened to a similar level as observed in the placebo group. There was no rebound (worsening of disease above baseline) observed in the dupilumab treatment group for any of the endpoints evaluated during the follow-up period.

Table 25 - Analysis of annualized rate of moderate or severe COPD exacerbations during the follow-up period - ITT population who completed the Week 52 study period

	Placebo (N=440)	Dupilumab 300 mg q2w (N=445)
Number of participants with >=1 moderate or severe exacerbation event		
Number	440	445
No	376 (85.5)	372 (83.6)
Yes	64 (14.5)	73 (16.4)
Number of moderate or severe exacerbation events		
Number	440	445
Mean (SD)	0.2 (0.4)	0.2 (0.4)
Median	0.0	0.0
Q1 ; Q3	0.0 ; 0.0	0.0 ; 0.0
Min ; Max	0 ; 3	0 ; 3
0	376 (85.5)	372 (83.6)
1	57 (13.0)	67 (15.1)
2	6 (1.4)	4 (0.9)
3	1 (0.2)	2 (0.4)
≥4	0	0
Total number of moderate or severe exacerbation events	72	81
Total patient-years followed	97.7	98.5
Unadjusted annualized moderate or severe exacerbation event rate[a]	0.74	0.82
Adjusted annualized moderate or severe exacerbation event rate[b]		
Estimate (95% CI)	0.821 (0.607 to 1.111)	0.921 (0.685 to 1.238)
Relative risk vs. placebo (95% CI)		1.121 (0.813 to 1.548)
P-value		0.4855
Risk difference vs. placebo (95% CI)[c]		0.100 (-0.181, 0.381)

All moderate or severe exacerbation events during the follow-up period (week 52 to week 64) are included.
[a] The total number of events that occurred during the follow-up period (week 52 to week 64) divided by the total number of patient-years followed in the follow-up period.
[b] Derived using negative binomial model with the total number of the events occurring as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.
[c] Derived using delta method.
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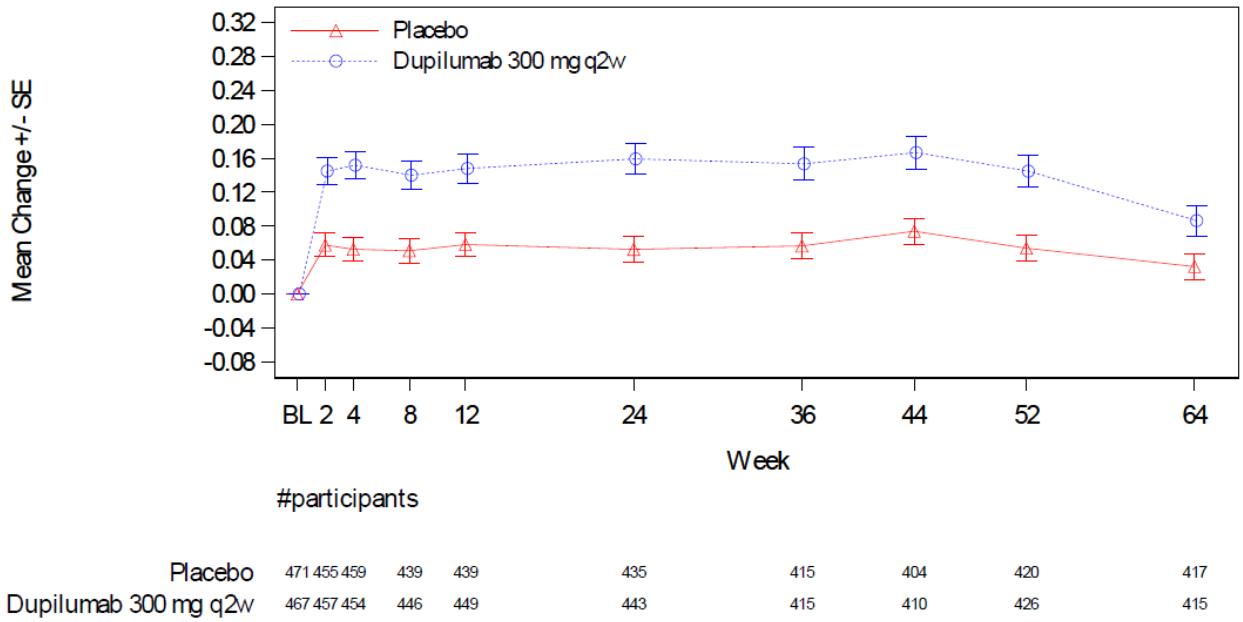
OUT=REPORT/OUTPUT/eff_copd_rate_fup_cp_i_t_i.rtf (18OCT2023 4:57)

Figure 18 - Mean change from baseline in pre-bronchodilator FEV_1 (L) up to Week 64 by visit - ITT population



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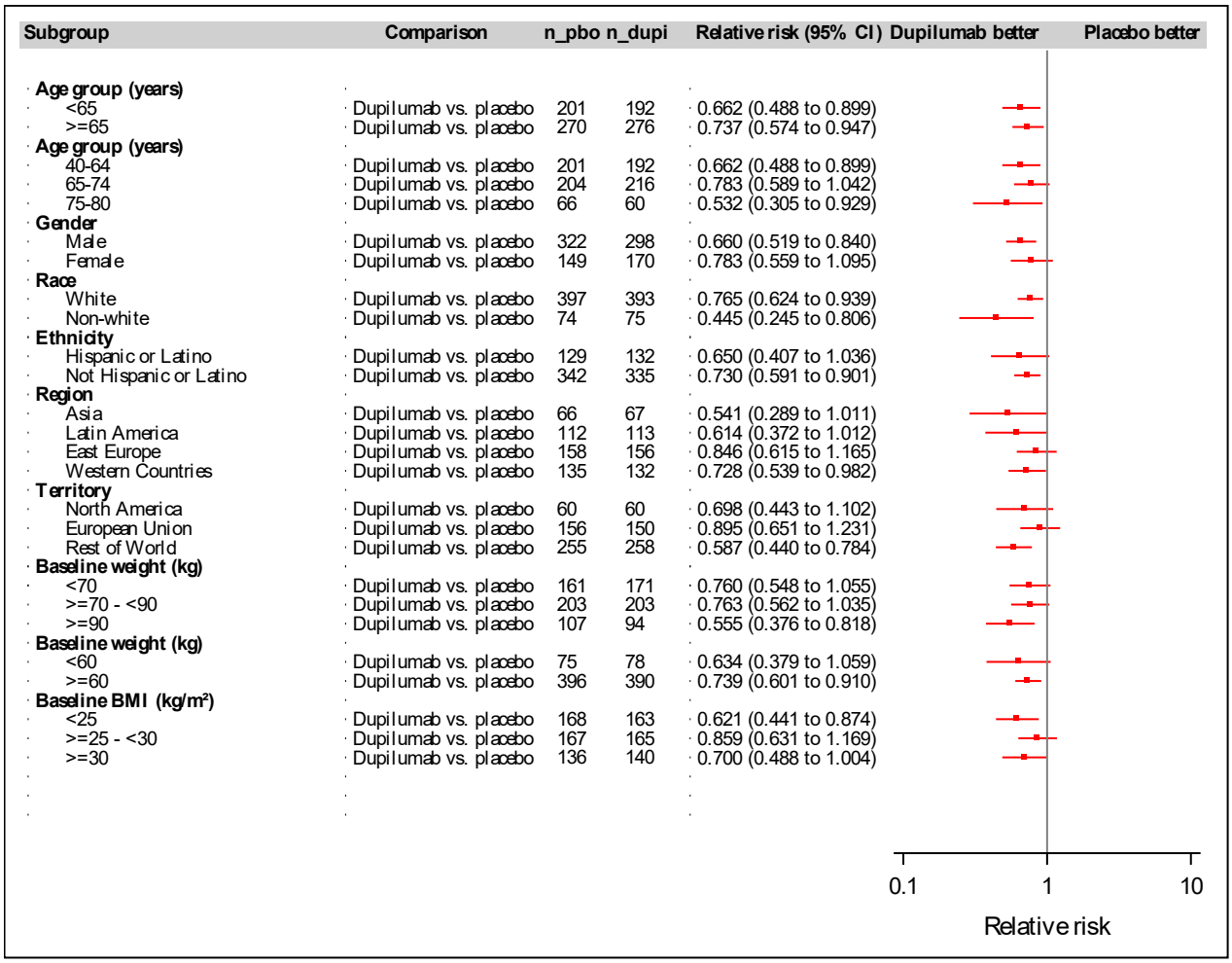
Subgroup analysis

Subgroup analyses based on demographics

Annualized rate of moderate or severe exacerbation events

There was a reduction in the rate of moderate or severe AECOPD events with dupilumab versus placebo across all prespecified subgroups based on demographic characteristics including age, gender, race, ethnicity, region, body weight, and BMI.

Figure 19 - Forest plot of relative risk in the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period by demographic subgroups - ITT population



PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/eff_copd_rate_forest_sub_i_g.sas
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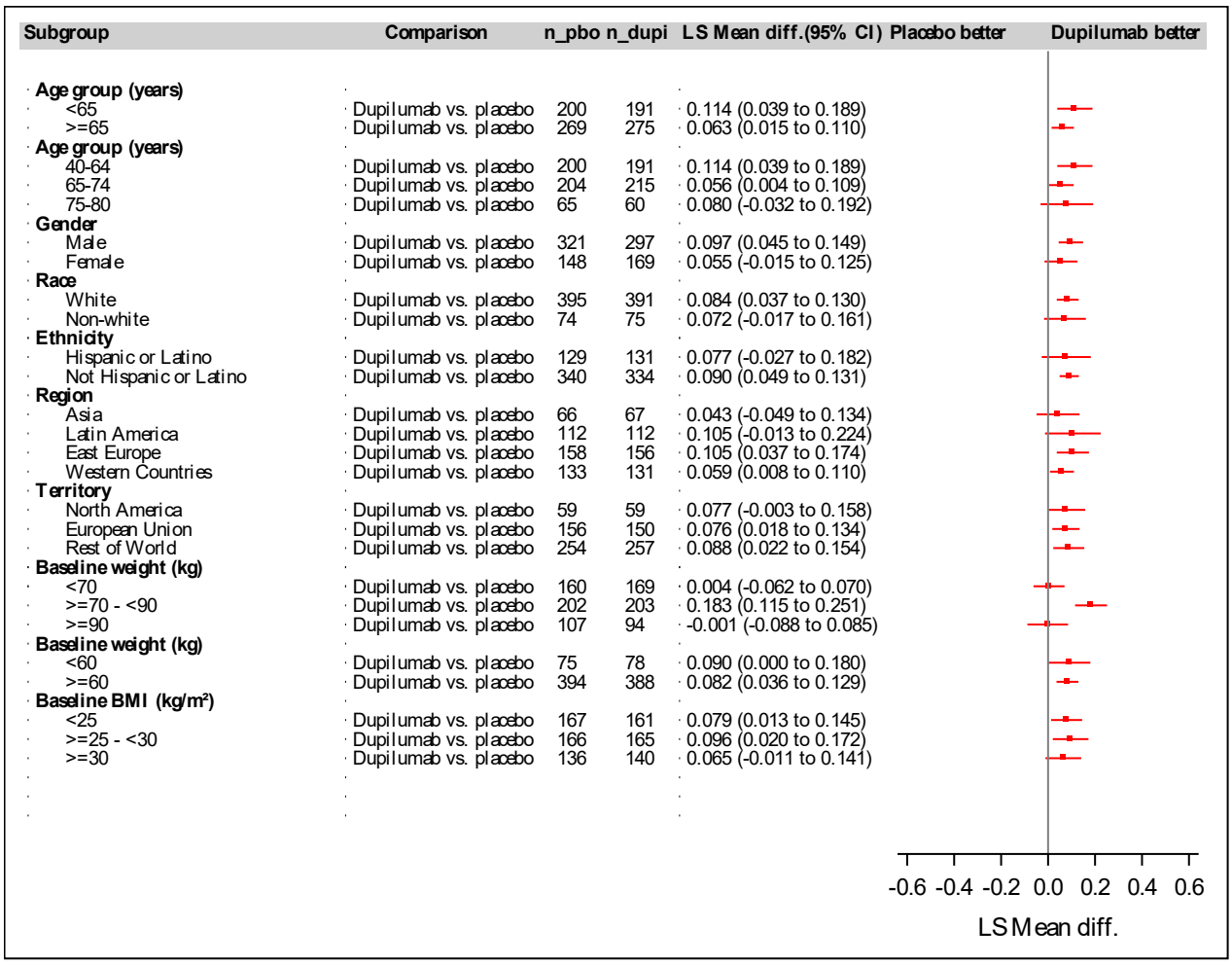
Change from baseline in pre-BD FEV1 at Week 12

Subgroup data for pre-BD FEV1 at Week 12 for demographics including age, gender, race, ethnicity, region, body weight, and BMI, and weight are shown below.

Figure 20 - Forest plot of LS mean difference in the change from baseline in pre-bronchodilator FEV_1 at Week 12 by demographic subgroups - ITT population



PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/eff_fev1_forest_sub_i_g.sas
OUT=REPORT/OUTPUT/eff_fev1_pre_fr_lsmd_dem_i_g_i.rtf (04MAY2023 9:47)

Elderly patients (≥65 years of age)

Participants ≥65 years of age at study entry comprised the majority (58.1%) of the study population and were similarly represented in the 2 intervention groups (dupilumab: 59.0%, placebo: 57.3%), 13.4% of participants were ≥75 years of age (dupilumab: 12.8%, placebo: 14.0%).

The reduction in the annualized rate of moderate or severe exacerbations observed in the dupilumab group compared to the placebo group was consistent between the subgroups of participants <65 and ≥65 years while the improvement in pre-BD FEV1 observed in the dupilumab group compared to the placebo group was less pronounced in the subgroup of participants ≥65 years. This might be attributed to a more severe disease as with regard to post-BD FEV1 values at and the respective GOLD grading at baseline.

The treatment benefit observed in the subgroup of participants ≥65 years of age (N=546) was nominally significant across all endpoints in the hierarchical testing procedure and was similar to that observed in the ITT population.

Black/Of African descent participants

A limited number of patients of Black/African descent were included in the study despite no major differences in disease prevalence for this patient population. In total 5 randomized participants were Black/of African descent (3 [0.6%] participants in the dupilumab and 2 [0.4%] participants in the placebo

group). One of the participants in the placebo group permanently discontinued study intervention on Day 241 per the participant's decision.

A description of the main efficacy parameters in these patients is provided in the following. During the 52-week treatment period, none of the participants in the dupilumab group experienced any moderate or severe COPD exacerbations, while multiple COPD exacerbations were reported for the 2 participants in the placebo group. For all 3 participants in the dupilumab group, improvements in pre-BD FEV1 were observed at Weeks 12 and 52. In the placebo group, an improvement in pre-BD FEV1 was observed for 1 participant and a decline in pre-BD FEV1 was observed for the other participant.

Due to the highly limited number of patients included in the BOREAS study do not allow any clear conclusion on whether the treatment effect is different. The MAH provided further data from study NOTUS.

Differences by regions

There appears to be notable trend towards a lower reduction in exacerbation events in European and Western Countries as compared to Asia and Latin America. Of note, participants from European Union showed the lowest effect in subgroups defined by region or territory (adjusted annualized exacerbation event rate 1.113 (95% CI: 0.866 to 1.430) vs. 0.996 (95% CI: 0.762 to 1.303) resulting in a difference of 10.5 percent as compared to 30 percent as observed for the total study population. As further described in the PK/PD assessment (Section 5.3), territory was found to be significant covariate for exacerbations and participants from the EU were predicted to have lower exacerbation reductions. Still, the treatment regarding lung function improvement effect was similar in the subgroups defined by region. As already discussed for the primary endpoint, the study was conducted during the COVID-19 pandemic which has potentially affected the number of exacerbation events observed during the study. The reasons for the diverging reduction in exacerbation rates in different regions might be due to different public health measures in the participating countries or different timepoints of patient recruitment (before, during, after the pandemic). For the primary endpoint, no treatment-by-subgroup interactions were observed by region (nominal p-value for interaction = 0.3340) or territory (nominal p-value for interaction = 0.1023) indicating no meaningful differences in the annualized rate of moderate or severe exacerbations according to region or territory were observed.

Body weight

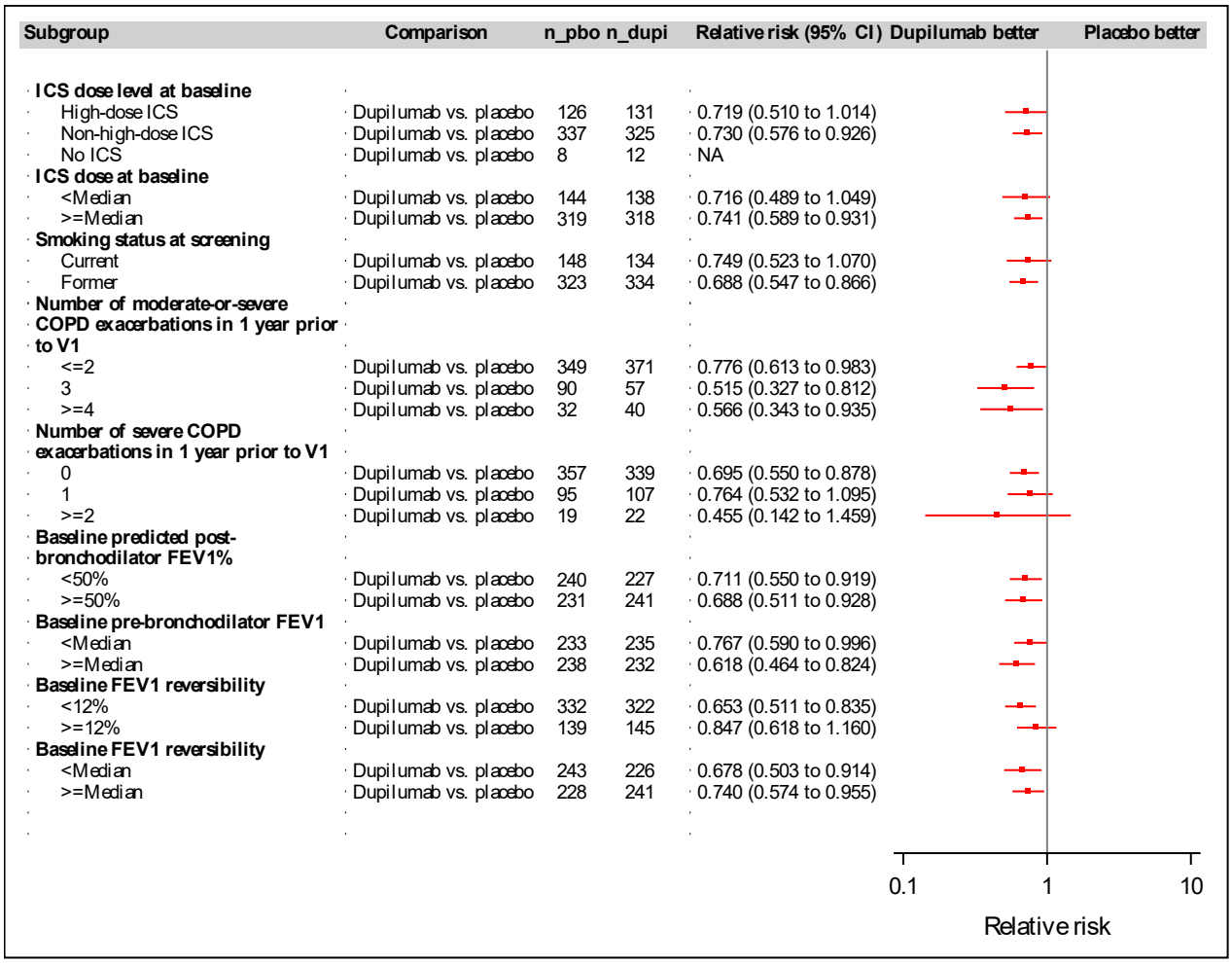
There appears to be lower improvements in lung function in participants with a body weight <70 kg and ≥ 90 kg. However, this effect was not seen for the other weight categories (e.g. BMI).

Subgroup analyses based on disease characteristics

Annualized rate of moderate or severe exacerbation events

Results of the subgroup analysis by disease characteristics are shown below.

Figure 21 - Forest plot of relative risk on the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period by disease characteristics subgroups - ITT population



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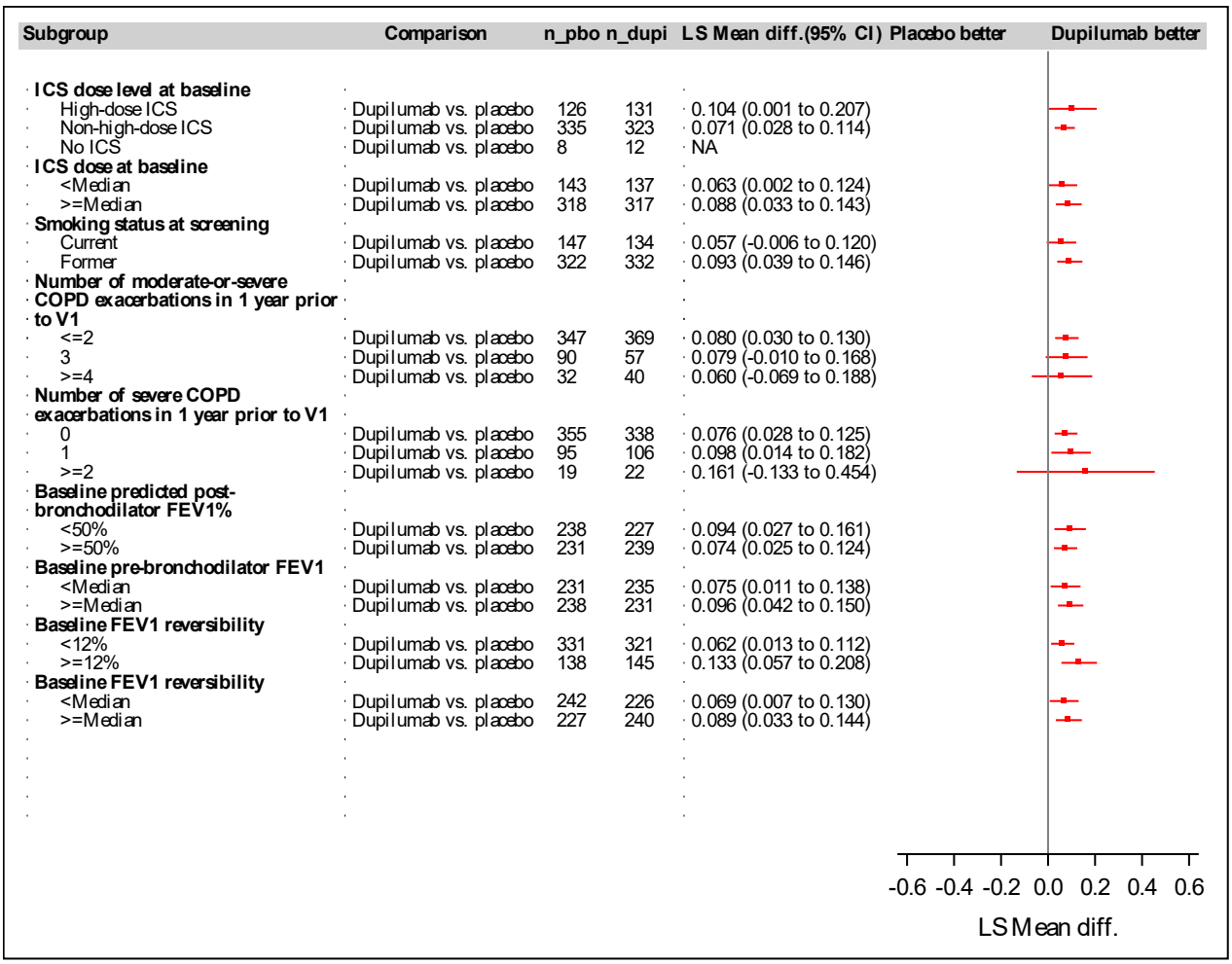
OUT=REPORT/OUTPUT/eff_copd_rate_fr_rr_dis_i_g_i.rtf (04MAY2023 9:47)

Change from baseline in pre-BD FEV1 at Week 12

Similiar improvements in pre-BD FEV1 at Week 12 with dupilumab versus placebo was observed across all subgroups based on baseline disease characteristics.

Figure 22 - Forest plot of LS mean difference in the change from baseline in pre-bronchodilator FEV1 at Week 12 by disease characteristics subgroups - ITT population



Participants with a history of severe exacerbations

In the subgroup of participants with at least 1 severe COPD exacerbation within the year prior to inclusion, a reduction of 29% in the annualized rate of moderate or severe AECOPD was observed in the dupilumab group as compared to placebo (nominal p=0.0639). This reduction was similar to that observed in the participants without a severe exacerbation in the year prior to inclusion and in the overall ITT population**.**

Participants with emphysema

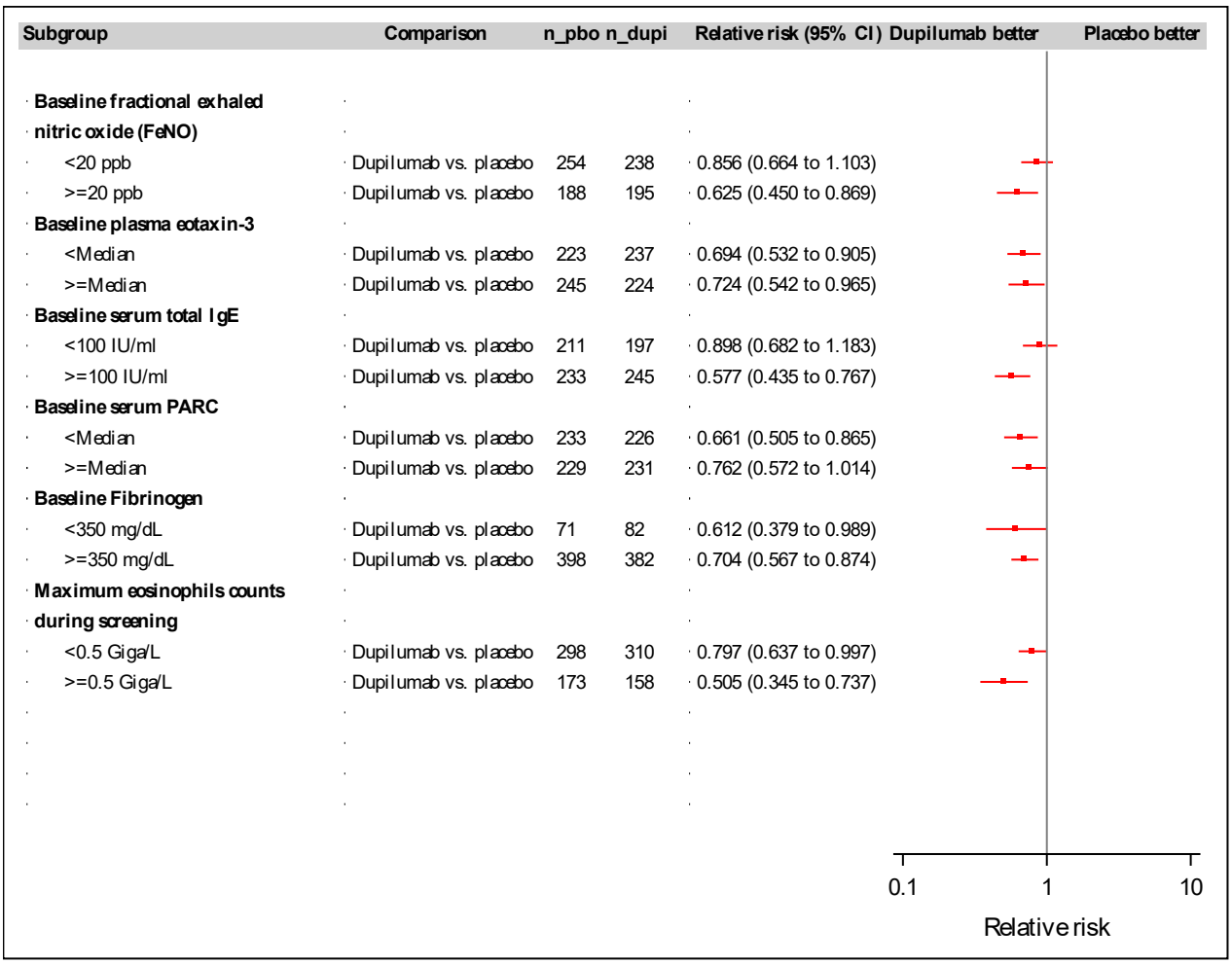
The treatment effect was overall consistent in the subgroup of patients with emphysema. In the subgroup of participants with emphysema (32.6% of participants), a nominally significant reduction of 29% in the annualized rate of moderate or severe COPD exacerbations was observed in the dupilumab group as compared to the placebo group (nominal p=0.0190). A nominally significant improvement in pre-BD FEV1 at Week 12 of +0.071 L was observed in the dupilumab group over the placebo group (nominal p=0.0436).

Subgroup analyses based on biomarkers

Annualized rate of moderate or severe exacerbation events

A reduction in the rate of moderate or severe AECOPD events with dupilumab versus placebo was observed across all subgroups based on baseline biomarker values (Figure 23) including biomarkers of type 2 inflammation. Nominally significant treatment-by-subgroup quantitative interactions were observed for baseline serum total IgE (nominal p=0.0298) and maximum eosinophils counts during screening (nominal p=0.0141). A greater treatment benefit of dupilumab versus placebo was observed in those subgroups of participants with higher levels of eosinophils (≥0.5 Giga/L during screening), total IgE (≥100 IU/mL at baseline) and FENO (≥20 ppb at baseline).

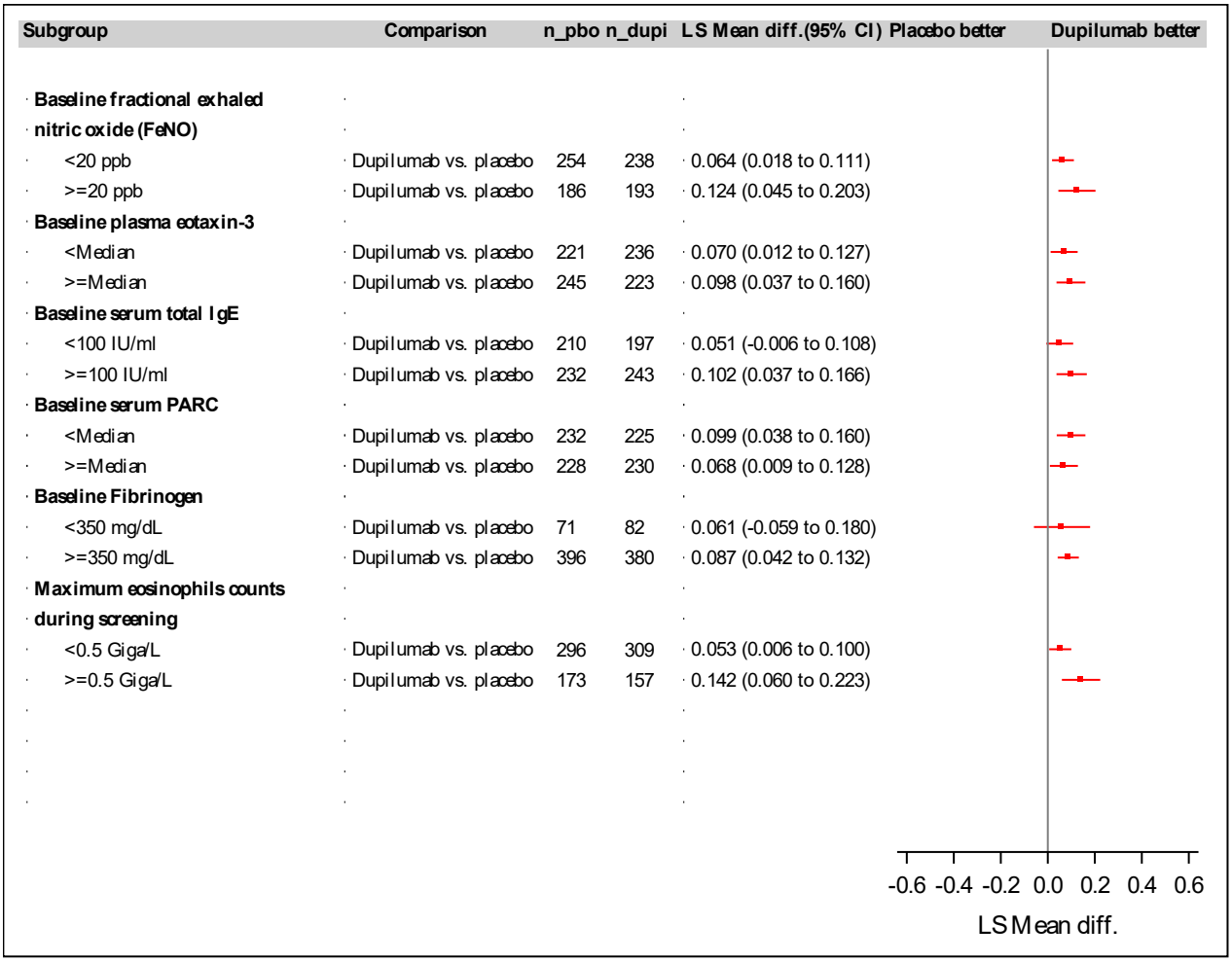
Figure 23 - Forest plot of relative risk on the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period by biomarker subgroups - ITT population



Change from baseline in pre-BD FEV1 at Week 12

An improvement in pre-BD FEV1 at Week 12 with dupilumab versus placebo was observed across all subgroups based on biomarker values at baseline (Figure 24), including biomarkers of type 2 inflammation. A nominally significant treatment-by-subgroup quantitative interaction was observed for maximum eosinophils count during screening (nominal p=0.0382) and a greater treatment benefit of dupilumab versus placebo was observed in the subgroup of participants with higher levels of eosinophils (≥0.5 Giga/L during screening).

Figure 24 - Forest plot of LS mean difference in the change from baseline in pre-bronchodilator FEV_1 at Week 12 by biomarker subgroups - ITT population



Additional treatment-by-biomarker interaction testing

For each biomarker, the effect of dupilumab on the annualized rate of moderate or severe exacerbation events as a function of the biomarker was evaluated using a negative binominal model which includes the covariates from the primary analysis model and a first-degree fractional polynomial transformation of the biomarker as a continuous variable, and biomarker-by-treatment interaction. To account for the high skewness of baseline total IgE and baseline eotaxin-3 in the study, these 2 variables were natural logarithm transformed in the model.

Nominally significant treatment-by-biomarker interactions on the annualized rate of moderate or severe exacerbation events were observed for baseline blood eosinophils (nominal p=0.006), maximum eosinophil counts during screening (nominal p=0.010), and baseline FeNO level (nominal p=0.043). The subgroup analysed based on biomarkers showed an increased treatment response in terms of reduction in exacerbation rates and improvements in lung function (pre-BD FEV1 at Week 12) in participants with strongly increased blood eosinophils (≥0.5 Giga/L) and elevated FeNO levels (≥20 ppb).

Correlation of blood eosinophils or FeNO over time

To explore the stability of blood eosinophils and FeNO over time, an evaluation of the overall correlation coefficient for these biomarkers in the placebo-exposed population was conducted.

The overall correlation coefficient between the observed screening eosinophil value and multiple timepoints through week 64 is 0.636, with the overall correlation coefficient between screening and baseline eosinophil levels at 0.795. The overall correlation coefficient between the observed baseline FeNO at multiple timepoints through week 64 is 0.685. These overall correlation coefficients indicate that the within-patient measurements of both blood eosinophils and FeNO were stable and similar.

2.5.2.2. Study EFC15805 (NOTUS)

The Clinical Study Report of the second pivotal study EFC15805 was provided during the procedure. Study EFC15805 was a multinational, randomized, double-blind, placebo-controlled, parallel group (2 groups), 52-week, pivotal Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in participants with uncontrolled COPD (ie, ≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2), moderate-to-severe airflow obstruction (ie, post-BD FEV1 >30% to ≤70% of predicted), and evidence of type 2 inflammation, on top of an established background therapy of LABA, LAMA, and ICS (unless ICS was contraindicated).

The study was a replicate study with mainly the same design and objectives as study EFC15804 (BOREAS).

Methods

See EFC15804 (BOREAS)

Study participants

The same inclusion and exclusion criteria as for study EFC15804 were used with the following exception:

- Study EFC15805 enrolled participants with an age between 40 and 85 years

Treatments

Same treatment and background or reliver medication as within study EFC15804.

Objectives / Outcomes and Endpoints

Same objectives and endpoints as within study EFC15804.

Sample size

The sample size of the study was determined based on power calculations for the primary endpoint of annualized rate of acute moderate or severe COPD exacerbations over the 52-week treatment period. Assuming the number of exacerbations follows a negative binomial distribution with a dispersion parameter of 1, a placebo annualized rate of exacerbations of 1.5, an average treatment duration of 0.95 year (to account for an average of 5% of the planned treatment period with missing data), and a randomization ratio of 1:1 to the two treatment arms, with 924 randomized patients (462 for each treatment arm), the study will have 90% power to detect a 25% relative risk reduction (ie, annualized rate of 1.125 for the dupilumab group) in the annualized rate of moderate or severe COPD exacerbations at the 2-tailed significance level of α=0.05. With the addition of an interim analysis, the final alpha may be reduced to 0.049, which maintains approximately 90% power.

Randomisation

After a run-in period of 4 weeks ±1 week, patients will be centrally randomized using a permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 1:1 randomization ratio for dupilumab 300 mg q2w and a matching placebo q2w for SC administration. Randomization will be stratified by country, by ICS dose (high dose ICS [yes/no]) at baseline, and smoking status at screening (current smokers or not). Enrollment will be capped at 30% current smokers (as defined by smoking status at screening visit).

Blinding (masking)

Dupilumab and placebo were provided in identically matched 2 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) glass pre-filled syringes was prepared such that the treatments (dupilumab and its matching placebo) are identical and indistinguishable and were labeled with a treatment kit number.

In accordance with the double-blind design, study patients, Investigators, and study site personnel remained blinded to study treatment and had no access to the randomization arm or to the IMP content (dupilumab or placebo) except under circumstances described as follows.

In case of an AE, the randomization code had only to be broken in circumstances when knowledge of the IMP was required for treating the patient. Code breaking could be performed at any time by using the proper module of the IVRS/IWRS and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind was broken, the Investigator had to document the date, time of day, and reason for code breaking. Patient withdrawal only occurred when the code break call was made at the site level, not the study level. This means that if the Emergency Unblinding transaction was performed by the Investigator (ie, at the site level), then the patient would be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the patient will not be withdrawn from treatment. Patients who were withdrawn from treatment were encouraged to remain in the study and the Investigator should discuss with them the key visits to attend.

Statistical methods

Analysis Populations/Sets
The intent-to-treat (ITT) population was defined as the randomized population analyzed according to the treatment group allocated by randomization.

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

Primary Estimand / Primary Analysis strategy
The primary efficacy variable was annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.
The following null hypothesis and alternative were tested for dupilumab arm against placebo:
H0: No treatment difference between the dupilumab dose regimen and placebo in annualized rate of COPD exacerbation.
H1: There is a treatment difference between the dupilumab dose regimen and placebo in annualized rate of COPD exacerbation.

The primary analysis of the annualized rate of moderate or severe exacerbation events during the 52-week placebo-controlled treatment period was to assess the efficacy of dupilumab in an intention-to-treat setting. Adjudicated COPD exacerbation events data were used.

The primary estimand was described in the following table:

Endpoint Category	Estimands			
	Endpoint(s)	**Population**	**Intercurrent event(s) handling strategy and missing data handling**	**Population-level summary**
Primary objective: The primary objective of this study is to evaluate the efficacy of dupilumab 300 mg every 2 weeks compared to placebo in reducing annualized rate of acute moderate or severe COPD exacerbation (AECOPD) over the 52-week treatment period in patients with moderate or severe COPD.				
Primary endpoint – Event	Annualized rate of AECOPD exacerbation events over the 52-week treatment period.	ITT	The intercurrent events will be handled as follows: • Discontinuation of study treatment before Week 52: Off-study treatment data up to Week 52 will be included in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: • Discontinuing the study follow-up before Week 52: Analyses will be censored at the time of study discontinuation.	Negative binomial regression model using the total number of events occurred during the 52-week planned treatment period as the response variable, with the treatment group, region (pooled country), ICS dose at baseline, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates. Log-transformed observation duration will be used as offset variable.

If a patient withdrew from study prior to the end of 52-week treatment period, all observed moderate or severe exacerbation events up to the last contact date or the end date of the planned 52-week treatment period (whichever is earlier) were included in the analysis, and the observation duration was defined as from randomization to the last contact date or the end date of the planned 52-week treatment period whichever was earlier. No imputation was performed for the unobserved events that may happen after study discontinuation and up to Week 52.

The annualized rate of moderate or severe COPD exacerbation events was analyzed using a negative binomial regression model. The negative binomial regression model includes the total number of events occurred during the 52-week planned treatment period as the response variable, with the treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4) as covariates. Log-transformed observation duration was used as offset variable. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals were derived. The event rate ratio of the dupilumab group against placebo, its two-sided 95% confidence interval and p-value are provided.

The rate difference between dupilumab and placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

Supplementary Analysis for Primary Endpoint

If patients withdraw from the study before Visit 16 (Week 52), moderate or severe exacerbation events that may occur after study discontinuation were not observed. These patients are considered as patients with missing data on moderate or severe exacerbation. Number of patients with missing data, reasons and timing for patient withdrawals are summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics are provided for patients with missing data and patients with complete data separately. In addition, the following sensitivity analyses were conducted to assess the robustness of the conclusion based on the primary analysis.

Pattern mixture model - multiple imputation (PMM-MI): For each patient with missing data of moderate or severe exacerbation events, individual bi-weekly event probability was estimated using observed data with adjustment of for the same variables as in primary analysis model the planned treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted postbronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4). The total number of AECOPD moderate or severe events (on bi-weekly basis) was calculated based on data imputed using multiple imputation.

Control-based PMM-MI: For each patient with missing data of moderate or severe exacerbation events, individual bi-weekly event probability was estimated using observation in the placebo arms only, with adjustment for the same variables as in primary analysis model except treatment group of region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted postbronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4). The total number of AECOPD moderate or severe events (on bi-weekly basis) was calculated based on data imputed using multiple imputation.

Tipping point analysis: For each patient with missing data of moderate or severe exacerbation events, the bi-weekly event was imputed in a similar fashion as PMM-MI based on various odds values. If the patient was on dupilumab, the predicted odds were increased; if the patient was on Placebo, the predicted odds value were decreased. The adjusted rate then was used to impute the number of events that would occur during the missing observation period. A sequence of increasing/decreasing ratio was used to generate different imputed datasets.

For each of the above methods, a negative binomial model was fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the same covariates as in the primary analysis model the treatment group, region (pooled country), ICS dose at baseline (high dose ICS [yes/no]), smoking status at screening (current smokers or not), baseline disease severity (as % predicted post-bronchodilator FEV1), and number of moderate or severe COPD exacerbation events within one year prior to the study (≤2, 3, or ≥4) as covariates. Log transformed observation duration was the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 16 (Week 52). SAS MIANALYZE procedure was used to generate statistical inferences by combining results from the analysis with each dataset using Rubin’s formula.

Secondary Estimand(s)/ Secondary Analysis strategy

The analysis of secondary endpoints was based on the ITT population.

The secondary estimands are described in the following table:

Endpoint Category	Estimands			
	Endpoint(s) [a]	Population	Intercurrent event(s) handling strategy and missing data handling	Population-level summary
Secondary objective: To demonstrate the efficacy of dupilumab on spirometry and health related quality of life endpoints, separately, at various time points or population				
Secondary endpoint – Continuous	Change from baseline in FEV_1 at Week 12 Change from baseline in FEV_1 at Week 52 Change from baseline in SGRQ at Week 52 Change from baseline in E-RS at Week 52 [b]	ITT (For FEV_1 endpoints, also patients with baseline FeNO ≥20 ppb)	The intercurrent events will be handled as follows: • Discontinuing the study intervention prior to Week 12 or Week 52: all data collected after discontinuation will be used in the analysis (treatment policy strategy). In addition, the missing data imputation rules are as follows: • Missing data will be imputed latently by MMRM based on missing at random assumption	MMRM model using change from baseline in corresponding endpoint values up to corresponding weeks as response variables, and factors for treatment group, age, sex, height (age, sex and height are only included for spirometry endpoints analyses), region (pooled country), ICS dose at baseline, smoking status at screening, visit, treatment-by-visit interaction, baseline value of the endpoint, and baseline-by-visit interaction as covariates.

a Additional secondary objectives/endpoints are not included in this table but would be handled with a similar strategy as the endpoint type (ie, Continuous, proportion, event, time-to-event) at other weeks.

b Exploratory endpoint

Multiplicity

Multiplicity was considered for performing an interim analysis and for testing multiple endpoints. The overall Type-I error rate was controlled at the two-sided 0.05 level.

An interim analysis was planned to be performed using the Kim-DeMets spending function when the information fraction was ≥0.92 based on follow-up time for the primary endpoint of annualized rate of moderate or severe COPD exacerbations over 52-week treatment period.

A hierarchical testing procedure was used for testing primary, key secondary and other endpoints. If the primary endpoint would not demonstrate efficacy at this interim analysis, then the study would remain blinded and the primary endpoint would be retested at the 52-week final analysis time point with an α=0.049. If the primary endpoint would demonstrate efficacy at this interim analysis based on the alpha allocated, then the rest of the multiplicity-controlled endpoints would be tested with α=0.05. The comparisons were tested based on the hierarchical order below.

1. Primary efficacy endpoints:
    - Annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period compared to placebo.
2. Secondary/exploratory efficacy endpoints:
    - Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo
    - Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo
    - Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo in the subgroup of patients with baseline FeNO ≥20 ppb
    - Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo in the subgroup of patients with baseline FeNO ≥20 ppb
    - Change from baseline to Week 52 in SGRQ total score compared to placebo
    - Proportion of patients with SGRQ improvement ≥4 points at Week 52 compared to placebo
    - Change in E-RS COPD total score from baseline to Week 52 compared to placebo
    - Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of patients with baseline FeNO ≥20 ppb

The study was considered positive when the primary endpoint achieved statistical significance.

Interim analysis

An interim analysis was planned when the information fraction was ≥0.92 based on follow-up time for the primary endpoint of annualized rate of moderate or severe COPD exacerbations over a 52-week treatment period. The information fraction at the time of interim analysis was estimated using a conservative approach assuming all ongoing patients complete the 52-week treatment period. All participants would have complete follow-up for the key secondary endpoint of change from baseline in FEV1 at Week 12. The purpose of this interim analysis was to potentially demonstrate efficacy when ≥92% of the information fraction for the primary endpoint was available, but prior to all patients have completed the 52-week treatment period, as COPD is a disease with a high unmet medical need.

To control the overall type I error at α=0.05, the Kim DeMets approach was used with the power parameter rho (ρ) determined based on the information fraction observed at the time of the interim analysis and to maintain an α=0.049 at the final analysis (Table 26).

Table 26 – Kim-DeMets alpha spending function to control the overall alpha at 0.05

Information fraction	Rho (ρ)	α at interim analysis	α at final analysis
0.92 to <0.93	12	0.018	0.049
0.93 to <0.94	12	0.020	0.049
0.94 to <0.95	13	0.022	0.049
0.95 to <0.96	14	0.024	0.049
0.96 to <0.97	15	0.027	0.049

Subgroup Analyses

Subgroup analyses were planned to be conducted for the primary efficacy endpoint with respect to:

- Age group (<65, ≥65 years; 40-64, 65-74, 75-85)
- Gender (Male, Female)
- Region
- Territory
- Race (White, Non-white)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Baseline weight (<70, ≥70- < 90, ≥ 90 kg; <60, ≥ 60 kg)
- Baseline BMI (<25, ≥25- <30, ≥30 kg/m2)
- ICS high dose level at baseline (High-dose ICS, Non-high-dose ICS, No ICS)
- ICS high dose level at baseline (Yes, No)
- Smoking status at screening (current smokers, former smokers)
- Number of moderate-or-severe COPD exacerbation events within one year prior to V1 (≤2, 3, or ≥4)
- Number of severe COPD exacerbation events within one year prior to V1 (0, 1, ≥ 2; 0, ≥1)
- Baseline predicted post-bronchodilator FEV1% (<50%, ≥50%)
- Baseline pre-bronchodilator FEV1 (< median, ≥ median)
- Baseline FEV1 reversibility (<12%, ≥ 12%; < median, ≥ median)
- Baseline fractional exhaled nitric oxide (FeNO) (<20, ≥20 ppb)
- Baseline eotaxin-3 (< median, ≥ median)
- Baseline IgE (< 100, ≥ 100 IU/ml)
- Baseline PARC (< median, ≥ median)
- Baseline Fibrinogen (< 350, ≥ 350 mg/dL)
- Baseline mMRC (< median, ≥median)
- Maximum eosinophils counts during screening (<0.5, ≥0.5 Giga/L)
- Emphysema ongoing at baseline (Yes, No)

Results

Participant flow

Out of the 2769 participants screened for study eligibility, 1834 (66.2%) participants were screen failures. The 2 main reasons for screen failure were: not meeting inclusion criterion I 03, ie, evidence of type 2 inflammation based on blood eosinophils ≥300 cells/microliter at Visit 1 (33.6% of all screened participants) and not meeting inclusion criterion I 02, ie, participants with a physician diagnosis of COPD

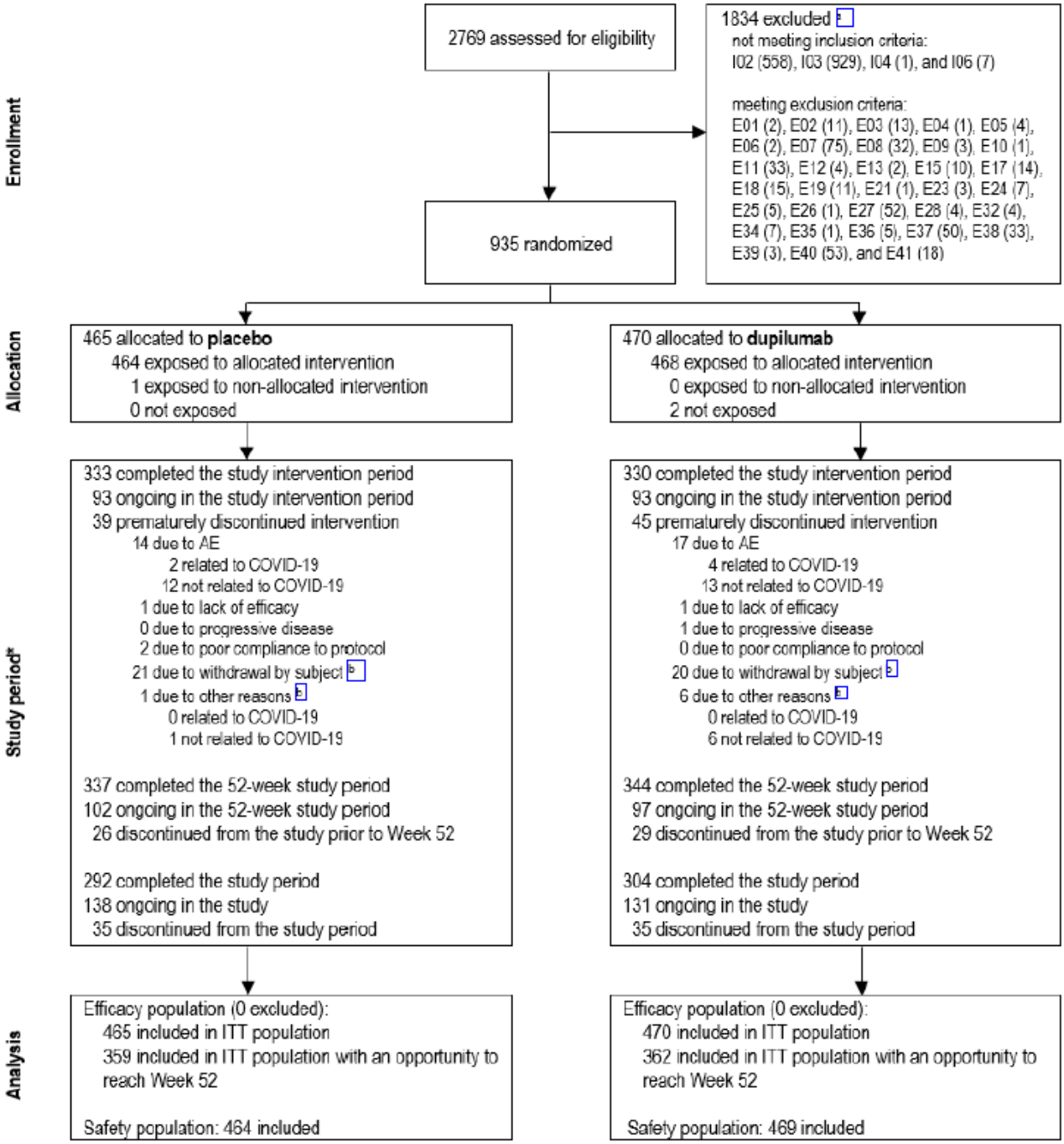
who met specific criteria at screening related to smoking history, lung function, symptoms, exacerbations, and background therapy (20.2% of all screened participants).

A total of 935 participants were randomized to study intervention: 470 in the dupilumab 300 mg q2w group and 465 in the placebo group (Figure 25). All participants were exposed to study intervention, with the exception of 2 participants in the dupilumab group who were randomized by error but not exposed to the study intervention. In addition, 1 participant allocated to the placebo group inadvertently received a single dose of dupilumab on Day 113, which was reported as a major protocol deviation; the participant was included in the dupilumab group for the safety analyses.

As of the IA data cut-off date of the CSR (29 September 2023), 935 participants were enrolled in the study; the first 721 randomized participants (362 [77.0%] participants in the dupilumab group and 359 [77.2%] participants in the placebo group) had the opportunity to reach Week 52. A total of 330 (70.2%) randomized participants in the dupilumab group and 333 (71.6%) randomized participants in the placebo group had completed the 52-week study intervention period. A total of 93 (19.8%) participants in the dupilumab group and 93 (20.0%) participants in the placebo group were still ongoing in the 52-week study intervention period, while 45 (9.6%) participants in the dupilumab group and 39 (8.4%) participants in the placebo group had permanently discontinued study intervention. The most frequently reported reason for permanent study intervention discontinuation, as per the Investigator, was "withdrawal by subject" (20 [4.3%] in the dupilumab group and 21 [4.5%] in the placebo group).

Of the 45 participants in the dupilumab group and 39 participants in the placebo group who permanently discontinued study intervention, 29 and 26 participants in the dupilumab and placebo groups, respectively, also withdrew from the study prior to Week 52. Overall, 304 (64.7%) participants in the dupilumab group and 292 (62.8%) participants in the placebo group had completed the study period as of the IA data cut-off date of this CSR (29 September 2023) (ie, the entire study intervention and post-intervention follow-up periods).

Figure 25 - Patient Disposition Study EF15805 (Flow Diagram



Source: Table 8 and Appendix 16-2-1-disposition [16.2.1.1.1] and [16.2.1.1.3]

* Study period = study intervention period + post-intervention follow-up period

a A full description of the inclusion and exclusion criteria is provided in the protocol (16-1-1-protocol [5.1] and [5.2])

b None of the "other" reasons for permanent study intervention discontinuation were related to safety.

Recruitment

EFC15805 (NOTUS):

First participant enrolled: 06 July 2020

Interim Analysis cut-off date:	29 September 2023
Database lock:	01 Nov 2023

Conduct of the study

Protocol amendments

The original protocol, dated 06 December 2019, was modified per 3 global amendments. Amendment 01 (29 September 2020) was implemented to replace some on-site study visits and assessments with telephone visits to decrease the burden on participants, to minimize the COVID-19 pandemic-related risks in this vulnerable and elderly population of patients with COPD, as well as to update the list of AESIs. Amendment 02 (16 December 2021) was implemented to provide flexibility for participant enrolment criteria (i.e., allowing patients up to 85 years old with COPD and patients with COPD on long-term oxygen therapy to participate in the study). Amendment 03 (28 October 2023) was implemented to add an IA to determine if the primary efficacy endpoint (ie, annualized rate of moderate or severe exacerbations) is met at the time of the IA (see "Statistical methods" for more details).

Impact of the COVID-19 pandemic

Study EFC15805 was conducted during the global COVID-19 pandemic. In response to the COVID-19 pandemic, contingency measures in the study conduct were introduced in protocol amendment 01, which allowed implementation of temporary or alternative mechanisms such as phone contact, virtual visits, online meetings, use of local clinic or laboratory locations, and home visits by skilled staff (as permitted per local regulation) to ensure study continuity and protect the participants' safety. No waivers to deviate from protocol enrollment criteria due to COVID-19 were granted. Remote monitoring was introduced when on-site monitoring was not allowed. All temporary mechanisms utilized and deviations from planned study procedures were documented as being related to the COVID-19 pandemic and were to remain in effect only for the duration of the public health emergency.

Impact of the Ukraine/Russia conflict

Study EFC15805 was ongoing when the Ukraine/Russia conflict escalated in February 2022. Overall, 32 participants in Ukraine and 44 participants in Russia were receiving study intervention at that time. Of these, 31 participants in Ukraine and 44 participants in Russia completed the study (ie, the entire study intervention and post-intervention follow-up periods).

Protocol deviations

As of the IA data cut-off date, the number (%) of participants with at least 1 critical or major protocol deviation was 141 (30.0%) in the dupilumab group and 132 (28.4%) in the placebo group.

Three protocol deviations (2 in the dupilumab group and 1 in the placebo group), related to "Informed consent procedures", were assessed as critical.

The most frequently reported category of critical or major protocol deviations was "randomization procedure" (64 [13.6%] participants in the dupilumab group and 62 [13.3%] in the placebo group), mainly related to "Wrong stratum of randomization" (high-dose ICS [yes/no]).

Critical or major protocol deviations related to "Inclusion/exclusion criteria" were reported for 34 (7.2%) participants in the dupilumab group and 26 (5.6%) participants in the placebo group. The 2 most common inclusion/exclusion criteria (not) met were I 02 (ie, participants with a physician diagnosis of COPD who met specific criteria at screening related to the disease status such as MRC, post-BD FEV1 or post-BD FEV1/FVC, exacerbation history, or background therapy reported in 13 participants in the

dupilumab group and 7 participants in the placebo group, and E 27 (ie, Participants who were <80% compliant with controller therapy during screening) reported in 10 participants in the dupilumab group and 6 participants in the placebo group.

Breaking of the blind

The blind was broken for regulatory purposes, one participant experienced an SAE of severe keratitis, which was reassessed as non-serious by the Investigator prior to the IA data cut-off date. The event led to permanent study intervention discontinuation.

Baseline data

Demographics

The mean age of the randomized population was 65.0 years with a range of 40 to 85 years. There were more participants aged 65-74 years in the dupilumab group compared to the placebo group (46.4% versus 40.9%) and fewer participants aged 40-64 years (41.7% versus 45.8%). Overall, 67.6% of participants were male and 32.4% were female, and 89.6% were White with 1.3% Black/of African descent and 1.1% Asian. The mean BMI was 27.94 kg/m², with 19.0% of participants having a BMI ≥30 - <35 kg/m2 and 11.1% of participants having a BMI ≥35 kg/m2. Out of the 3 regions included in this study, the highest number of enrolled participants were from East Europe (43.3%), followed by Latin America (30.6%), and Western Countries (26.1%). By territory, most of the participants were enrolled in the European Union (45.7%), followed by the Rest of the World (44.6%) and North America (9.7%).

Baseline disease characteristics

The mean age at onset of COPD was 56.3 years. All participants had a history of smoking with 29.5% of participants being current smokers. The mean number of pack-years of cigarette smoking was 40.33 overall, and similar between the 2 intervention groups. The mean number of moderate or severe AECOPD events in the prior year was 2.2 in the dupilumab group and 2.1 in the placebo group. A total of 113 (24.1%) participants in the dupilumab group and 100 (21.5%) participants in the placebo group had experienced ≥1 severe exacerbation in the prior year.

The percentage of participants with moderate airflow limitation (GOLD grade 2; % predicted post-BD FEV1 between ≥50% and <80%) was lower in the dupilumab group compared with the placebo group (45.6% versus 49.4%) while the percentage of participants with severe airflow limitation (GOLD grade 3; % predicted post-BD FEV1 between ≥30% and <50%) was higher (51.2 versus 46.6%). A total of 23 (2.5%) participants had airflow limitation categorized as very severe (ie, GOLD grade 4; % predicted post-BD FEV1 <30%).

COPD-related phenotypes including emphysema and chronic bronchitis were well balanced between the 2 intervention groups. A total of 287 (30.7%) participants had a history of emphysema, which was ongoing for 284 (30.4%) of participants.

Randomization was stratified by ICS dose at baseline. Overall, 27.9% of participants were on high dose ICS while 72.1% of participants were not on high-dose ICS at baseline. This latter group also included participants who were on double therapy (LABA+LAMA) (1.1% of all participants).

Medical history and concurrent illnesses

The percentages of participants with a type 2 inflammatory disease history were well balanced between intervention groups. Overall, 12.4% of participants had an history of at least one other type 2 inflammatory disease, with allergic rhinitis being the most frequent (6.5%). Two participants in the dupilumab group had an ongoing medical history of asthma, which were reported as a major protocol deviation.

Biomarkers at baseline

All participants had an eosinophil count of ≥0.3 Giga/L at screening as per protocol (the maximum eosinophil count during screening was used for eligibility), with the exception of 3 participants in the dupilumab group which were all reported as major protocol deviations. At baseline, the majority of participants (60.2%) had an eosinophil count that remained ≥0.3 Giga/L. The mean (SD) blood eosinophil count was 0.41 (0.34) Giga/L.

Mean (SD) FeNO levels at baseline were elevated (24.56 [25.96] ppb) and similar between the intervention groups. Overall, 41.7% of participants had baseline FeNO levels of ≥20 ppb. The median serum total IgE level at baseline was 128 IU/mL and similar between the dupilumab and placebo groups.

Prior and concomitant medications

The 10 most frequently used prior medications by standardized medication name were salbutamol (69.2% of participants), tozinameran (32.2%), tiotropium bromide monohydrate (27.6%), budesonide (26.8%), fluticasone propionate (25.7%), fluticasone furoate (24.3%), formoterol fumarate (24.1%), glycopyrronium bromide (21.1%), vilanterol trifenatate (20.9%), and beclomethasone dipropionate (19.5%) and umeclidinium bromide (19.5%).

Most participants in both intervention groups (98.8% overall) were on triple therapy LABA+LAMA+ICS and 1.1% were on LABA+LAMA. Overall, 27.9% of participants were on high-dose ICS while 71.0% of participants received non-high-dose (ie, low or medium dose) ICS at baseline.

Outcomes and estimation

A summary of the primary, key secondary and other selected efficacy endpoints in study EFC15805 based on the interim analysis cut-off data are shown below.

Table 27- Summary of the primary and key secondary/other efficacy endpoints in the hierarchical testing procedure - ITT population – EFC15805

Parameter	Hierarchy	Placebo[a] (N=465)	Dupilumab[a] (N=470)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]
Primary endpoint					
Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period	1	1.295	0.859	0.664 (0.535 to 0.823)	**0.0002**
Key secondary/other endpoints					
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo	2	0.057 (0.017)	0.139 (0.017)	0.082 (0.040 to 0.124)	**0.0001**
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo[e]	3	0.054 (0.020)	0.115 (0.021)	0.062 (0.011 to 0.113)	**0.0182**
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo in the subgroup of participants with baseline FeNO ≥20 ppb[d]	4	0.081 (0.037)	0.221 (0.037)	0.141 (0.058 to 0.223)	**0.0010**
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo in the subgroup of participants with baseline FeNO ≥20 ppb[de]	5	0.095 (0.043)	0.176 (0.043)	0.081 (-0.019 to 0.181)	0.1111
Change from baseline to Week 52 in SGRQ total score compared to placebo[e]	6	-6.444 (0.922)	-9.816 (0.920)	-3.371 (-5.811 to -0.931)	0.0068
Proportion of participants with SGRQ improvement ≥4 points at Week 52 compared to placebo[e]	7	167 (46.5)	186 (51.4)	1.164 (0.856 to 1.581)	0.3329
Change in E-RS: COPD RS-Total Score from baseline to Week 52 compared to placebo[e]	8	-1.770 (0.300)	-2.388 (0.301)	-0.618 (-1.430 to 0.193)	0.1351
Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of participants with baseline FeNO ≥20 ppb[d]	9	1.571	0.740	0.471 (0.328 to 0.675)	<.0001

FEV1: Forced Expiratory Volume in one second; FeNO; Fractional Exhaled Nitric Oxide; SGRQ: St. George's Respiratory Questionnaire; E-RS: COPD: Evaluating Respiratory Symptoms (E-RS) in COPD; LS: least squares.

a Values presented are event rates derived using negative binomial model for event type variables, LS mean change from baseline with standard error for continuous variables, and number and percent of responders for binary variables

b Difference is relative risk for event type variables, LS mean difference for continuous variables, and odds ratio for binary variables

c Values in bold font are statistically significant according to the hierarchical testing procedure.

d The subgroup of baseline FeNO ≥20 ppb included N=183 in placebo and N=172 in dupilumab intervention groups.

e Only participants who have opportunity to reach Week 52 assessments are analyzed for the continuous and proportion type endpoints at Week 52. This includes N=359 in placebo and N=362 in dupilumab intervention groups. (N=132 in placebo and N=132 in dupilumab intervention groups for the subgroup of baseline FeNO ≥20 ppb)

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Primary efficacy endpoint

At baseline, the mean (SD) of moderate or severe AECOPD events in the year prior to screening was 2.2 (1.0) and 2.1 (0.7) in the dupilumab and placebo groups, respectively.

The adjusted annualized rate of moderate or severe AECOPD events over the 52-week intervention period in the ITT population was lower in the dupilumab group as compared with the placebo group: 0.859 (95% CI: 0.699 to 1.057) versus 1.295 (95% CI: 1.048 to 1.600). Dupilumab 300 mg q2w led to a reduction of 34% in the annualized rate of moderate or severe AECOPD events as compared to placebo (p=0.0002).

Table 28 - Primary analysis: analysis of the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period - ITT population - EFC15805

	Placebo (N=465)	Dupilumab 300 mg q2w (N=470)
Number of participants with >=1 moderate or severe exacerbation event		
Number	465	470
No	283 (60.9)	314 (66.8)
Yes	182 (39.1)	156 (33.2)
Number of moderate or severe exacerbation events		
Number	465	470
Mean (SD)	0.8 (1.3)	0.6 (1.0)
Median	0.0	0.0
Q1 ; Q3	0.0 ; 1.0	0.0 ; 1.0
Min ; Max	0 ; 7	0 ; 6
0	283 (60.9)	314 (66.8)
1	98 (21.1)	93 (19.8)
2	41 (8.8)	36 (7.7)
3	18 (3.9)	15 (3.2)
≥4	25 (5.4)	12 (2.6)
Total number of moderate or severe exacerbation events	352	263
Total patient-years followed	417.3	422.5
Unadjusted annualized moderate or severe exacerbation event rate[a]	0.84	0.62
Adjusted annualized moderate or severe exacerbation event rate[b]		
Estimate (95% CI)	1.295 (1.048 to 1.600)	0.859 (0.699 to 1.057)
Relative risk vs. placebo (95% CI)		0.664 (0.535 to 0.823)
P-value		0.0002
Risk difference vs. placebo (95% CI)[c]		-0.435 (-0.682, -0.188)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week treatment period (up to the interim cut-off date) are included, regardless of whether the participant was on-treatment or not.

a The total number of events 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 the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

c Derived using delta method.

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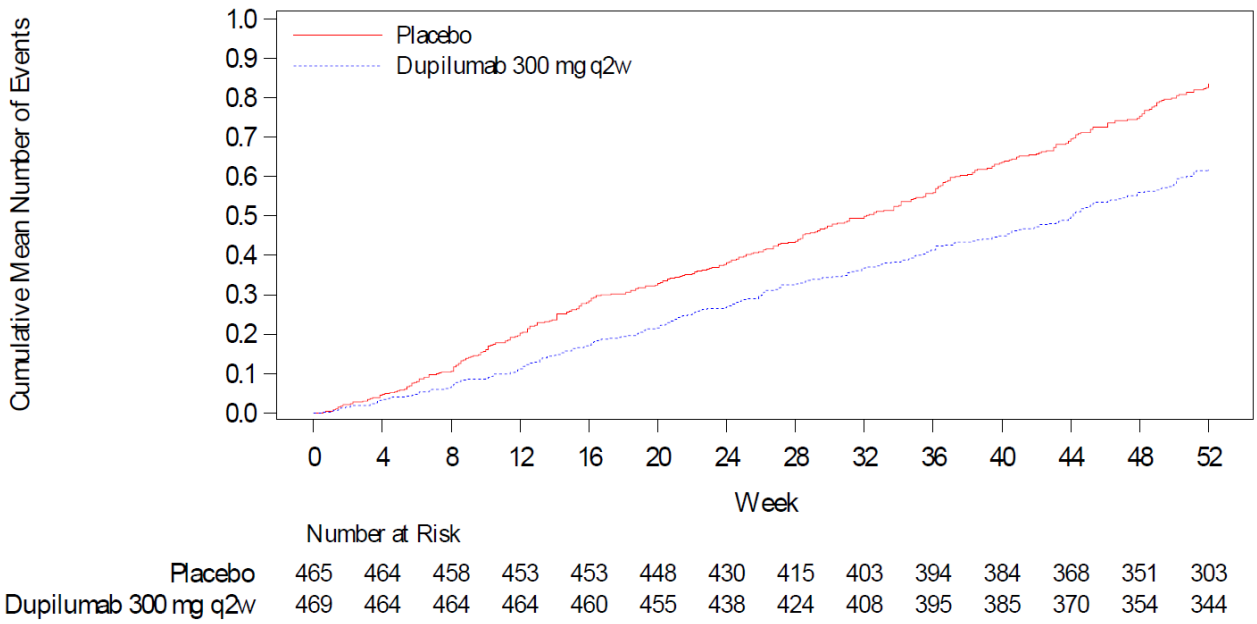
During the 52-week intervention period, a lower mean cumulative number of moderate or severe AECOPD events was observed in the dupilumab group as compared to the placebo group. The difference between the 2 intervention groups was apparent after Week 4 and progressively increased up to Week 52.

Figure 26 - Plot of cumulative mean number of moderate or severe COPD exacerbation events during the 52-week treatment period - ITT population – EFC15805



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OUT=REPORT/OUTPUT/eff_copd_cmf_i_g_i.rtf (19NOV2023 16:41)

Supportive analyses

Exacerbations by severity

The majority of the AECOPD events in both intervention groups were moderate and required treatment with both systemic corticosteroids and antibiotics. The total number of severe AECOPD events was low in the dupilumab and placebo groups (26 and 39 events, respectively). The adjusted annualized rate of severe AECOPD events over the 52-week treatment period in the ITT population was 0.070 (95% CI: 0.039 to 0.123) in the dupilumab group and 0.124 (95% CI: 0.072 to 0.215) in the placebo group.

Time to first moderate or severe exacerbations

Dupilumab treatment delayed the time to first moderate or severe COPD exacerbation event and reduced the risk of first moderate or severe COPD exacerbation event by 29% compared to placebo (hazard ratio: 0.714 [95% CI: 0.574 to 0.887]; nominal p=0.0024). The Kaplan-Meier curves for first occurrence of moderate or severe COPD exacerbation event for the dupilumab and placebo groups started to diverge after Week 4.

Key secondary efficacy endpoints

Annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period in the subgroup of patients with baseline FeNO ≥20 ppb

The adjusted annualized rate of moderate or severe AECOPD events over the 52-week intervention period in the subgroup of participants with baseline FeNO ≥20 ppb was lower in the dupilumab group as compared with the placebo group: 0.740 (95% CI: 0.530 to 1.033) versus 1.571 (95% CI: 1.119 to

2.206). Dupilumab 300 mg q2w led to a reduction of 53% in the annualized rate of moderate or severe AECOPD events as compared to placebo (nominal p<0.0001).

Table 29 - Analysis of the annualized rate of moderate or severe COPD exacerbations during the 52week treatment period among participants with baseline FeNO>= 20 ppb - ITT population – EFC15805

	Placebo (N=183)	Dupilumab 300 mg q2w (N=172)
Number of participants with >=1 moderate or severe exacerbation event		
Number	183	172
No	104 (56.8)	122 (70.9)
Yes	79 (43.2)	50 (29.1)
Number of moderate or severe exacerbation events		
Number	183	172
Mean (SD)	0.9 (1.4)	0.5 (1.0)
Median	0.0	0.0
Q1 ; Q3	0.0 ; 1.0	0.0 ; 1.0
Min ; Max	0 ; 7	0 ; 6
0	104 (56.8)	122 (70.9)
1	41 (22.4)	32 (18.6)
2	15 (8.2)	7 (4.1)
3	11 (6.0)	8 (4.7)
≥4	12 (6.6)	3 (1.7)
Total number of moderate or severe exacerbation events	165	84
Total patient-years followed	160.6	156.8
Unadjusted annualized moderate or severe exacerbation event rate[a]	1.03	0.54
Adjusted annualized moderate or severe exacerbation event rate[b]		
Estimate (95% CI)	1.571 (1.119 to 2.206)	0.740 (0.530 to 1.033)
Relative risk vs. placebo (95% CI)		0.471 (0.328 to 0.675)
P-value		<.0001
Risk difference vs. placebo (95% CI)[c]		-0.831 (-1.314, -0.348)

All moderate or severe adjudicated exacerbation events that occurred during the 52-week treatment period (up to the interim cut-off date) are included, regardless of whether the participant was on-treatment or not.

a The total number of events 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 the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

c Derived using delta method.

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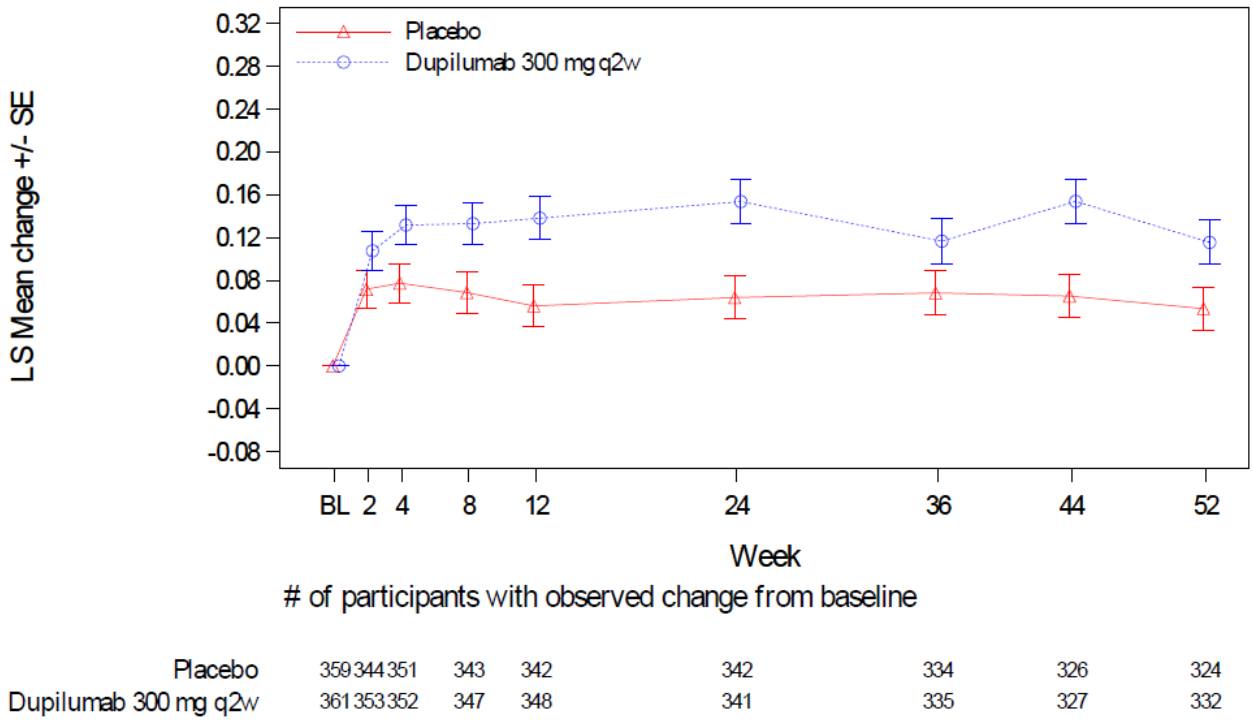
Change from baseline in pre-BD FEV1 at Week 12 and Week 52

The LS mean change from baseline to Week 12 in pre-BD FEV1 was +0.139 L in the dupilumab group versus +0.057 L in the placebo group; the LS mean difference versus placebo was statistically significant (+0.082 L [95% CI: 0.040 to 0.124], p=0.0001).

The LS mean change from baseline to Week 52 in pre-BD FEV1 was +0.115 L in the dupilumab group versus +0.054 L in the placebo group; the LS mean difference versus placebo was statistically significant (+0.062 L [95% CI: 0.011 to 0.113], p=0.0182).

Figure 27 - LS mean change from baseline in pre-bronchodilator FEV1 (L) up to Week 52 by visit - ITT population with an opportunity to reach Week 52 – EFC15805



PGM=PRODOPS/SAR231893/EFC15805/CSR/REPORT/PGM/eff_fev1_ls_ia_i_g.sas
OUT=REPORT/OUTPUT/eff_fev1_pre_ls_wk52_ia_i_g_i.rtf (19NOV2023 16:04)

Change from baseline in pre-BD FEV1 at Week 12 and Week 52 in the subgroup of participants with baseline FeNO ≥20 ppb

In the subgroup of participants with baseline FeNO ≥20 ppb, dupilumab treatment resulted in a non-significant improvement in pre-BD FEV1 at Week 52 compared with placebo. The LS mean change from baseline to Week 52 in pre-BD FEV1 was +0.176 L in the dupilumab group versus +0.095 L in the placebo group; the LS mean difference versus placebo was +0.081 L [95% CI: -0.019 to 0.181 L], p=0.1111). the statistical hierarchical testing procedure broke at this endpoint. The change from baseline in pre-BD FEV1 in the dupilumab group as compared to the placebo group reached nominal significance in this subgroup at Weeks 4, 8, 12, 24, 36, and 44.

Change from baseline in the SGRQ total score at Week 52

A greater reduction (improvement) in SGRQ total score at Week 52 was observed in the dupilumab group as compared to the placebo group, with LS mean changes from baseline to Week 52 of -9.816 and -6.444, respectively. The LS mean difference versus placebo was nominally significant (-3.371 [95% CI: -5.811 to -0.931], nominal p=0.0068). The reduction in SGRQ total score was observed as early as Week 12 (LS mean difference versus placebo: -2.819; nominal p=0.0071).

Additional efficacy analysis

Efficacy in participants without moderate or severe COPD exacerbations

In Study EFC15805, 597 participants did not experience a COPD exacerbation during the study (dupilumab: 314; placebo: 283). In this subgroup, the LS mean change from baseline to Week 12 in pre-BD FEV1 was +0.150 L in the dupilumab group versus +0.057 L in the placebo group, corresponding to a LS mean difference versus placebo of +0.092 L ([95% CI: 0.036 to 0.149]; nominal p=0.0013). The LS

mean change from baseline to Week 52 in SGRQ total score was -12.899 in the dupilumab group versus -9.727 in the placebo group, corresponding to an LS mean difference versus placebo of -3.172 ([95% CI: -6.112 to -0.231]; nominal p=0.0346).

Use of corticosteroids or antibiotics

The adjusted annualized total number of SCS courses for COPD exacerbations was lower in the dupilumab group as compared to the placebo group (0.682 [95% CI: 0.527 to 0.883] versus 1.114 [95% CI: 0.856 to 1.451]), corresponding to a reduction of 39% in the annualized total number of SCS courses for COPD exacerbations with dupilumab treatment as compared to placebo (nominal p=0.0003). The adjusted annualized total number of antibiotic courses for COPD exacerbations was lower in the dupilumab group as compared to the placebo group (0.470 [95% CI: 0.344 to 0.642] versus 0.723 [95% CI: 0.526 to 0.995]), corresponding to a reduction of 35% in the annualized total number of antibiotic courses for COPD exacerbations with dupilumab treatment as compared to placebo (nominal p=0.0092).

Subgroup analysis

Subgroup analyses based on demographics

A consistent reduction in the rate of moderate or severe AECOPD events with dupilumab versus placebo was observed across all subgroups based on demographics. No treatment-by-subgroup interaction was observed.

A consistent improvement in pre-BD FEV1 with dupilumab versus placebo was observed across the majority of subgroups based on demographics. No treatment-by-subgroup interaction was observed.

In Study EFC15805, no treatment-by-subgroup interactions were observed by region (nominal p-value for interaction = 0.4267) or territory (nominal p-value for interaction = 0.2511). The treatment effect on the annualized rate of moderate or severe COPD exacerbations was similar between Europe and North America.

Subgroup analyses based on baseline disease characteristics

A consistent reduction in the rate of moderate or severe AECOPD events with dupilumab versus placebo was observed across all subgroups based on baseline disease characteristics. No treatment-by-subgroup interaction was observed.

A consistent improvement in pre-BD FEV1 with dupilumab versus placebo was generally observed across all subgroups based on baseline disease characteristics. A nominally significant treatment-by-subgroup quantitative interaction was observed for baseline FeNO (nominal p=0.0265). A nominally significant quantitative treatment-by-subgroup interaction was observed for BODE (nominal p=0.0268) with a greater treatment benefit of dupilumab versus placebo observed in the subgroup of participants with BODE $\leqslant$4 compared to those with BODE >4.

Subgroup analyses based on biomarkers

A reduction in the rate of moderate or severe AECOPD events with dupilumab versus placebo was observed across all subgroups based on baseline biomarker values, including biomarkers of type 2 inflammation.

An improvement in pre-BD FEV1 at Week 12 with dupilumab versus placebo was observed across all subgroups based on biomarker values at baseline, including biomarkers of type 2 inflammation. No treatment-by-subgroup interaction was observed.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application.

Table 30 - Summary of Efficacy for Study EFC15804

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety, and Tolerability of Dupilumab in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) with Type 2 inflammation			
Study identifier	EFC15804, EudraCT: 2018-001953-28		
Design	Multinational, randomized, double-blind, placebo-controlled, parallel group (2 groups), 52-week Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe COPD with type 2 inflammation on an established background of triple therapy (LABA, LAMA and ICS unless ICS contraindicated). Study treatments are dupilumab 300 mg q2w or placebo q2w administered SC over a 52-week treatment period.		
	Duration of main phase:		68 weeks
	Duration of run-in phase:		Not applicable
	Duration of extension phase:		Not applicable
Hypothesis	Superiority		
Treatments groups	Dupilumab		Dupilumab 300 mg Q2W, 52-week treatment period, 468 randomized participants
	Placebo		Matching placebo Q2W, 52-week treatment period, 471 randomized participants
Endpoints and definitions	Primary endpoint	AECOPD	Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period
	Key Secondary endpoint	Pre-BD FEV1 at Week 12	Change from baseline in pre-bronchodilator FEV1 at Week 12
	Key Secondary endpoint	Pre-BD FEV1 at Week 52	Change from baseline in pre-bronchodilator FEV1 at Week 52
	Key Secondary endpoint	Pre-BD FEV1 at Week 12 in high FeNO	Change from baseline in pre-bronchodilator FEV1 at Week 12 in participants with baseline FeNO ≥20 ppb
	Key Secondary endpoint	Pre-BD FEV1 at Week 52 in high FeNO	Change from baseline in pre-bronchodilator FEV1 at Week 52 in participants with baseline FeNO ≥20 ppb
	Key Secondary endpoint	SGRQ total score at Week 52	Change from baseline in SGRQ total score at Week 52
	Key Secondary endpoint	SGRQ response at Week 52	Proportion of participants with SGRQ improvement ≥ 4 points at Week 52
	Key Secondary endpoint	AECOPD in high FeNO	Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period in participants with baseline FeNO ≥20 ppb
	Other endpoint	E-RS: COPD RS-total score at Week 52	Change from baseline in E-RS: COPD RS-total score at Week 52
Database lock	07 March 2023		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population Baseline to Week 52		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	468	471
	AECOPD – adjusted annualized moderate or severe event rate	0.776	1.101
	95% CI	(0.645, 0.934)	(0.931, 1.301)
Effect estimate per comparison	Annualized rate of moderate or severe COPD	Comparison groups	Dupilumab vs Placebo
		Risk ratio (95% CI)	0.705 (0.581, 0.857)
		p-value	0.0005
Analysis description	**Key Secondary/Other Analysis**		
Analysis population and time point description	Intent to treat population		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	468	471
	Change from baseline in pre-BD FEV1 at Week 12 (LS Mean Change)	0.160	0.077
	95% CI	(0.126, 0.195)	(0.042, 0.112)
	Change from baseline in pre-BD FEV1 at Week 52 (LS Mean Change)	0.153	0.070
	95% CI	(0.116, 0.189)	(0.033, 0.107)
	Change from baseline in SGRQ total score at Week 52 (LS Mean Change)	-9.732	-6.369
	95% CI	(-11.322, -8.142)	(-7.971, -4.768)
	Proportion of participants with SGRQ improvement ≥ 4 points at Week 52 (%)	241 (51.5)	203 (43.1)
	95% CI (%)	(46.9, 56.1)	(38.6, 47.7)
	Change from baseline in E-RS: COPD RS-total score at Week 52 (LS Mean Change)	-2.694	-1.558

	95% CI	(-3.199, -2.190)	(-2.060, -1.056)
Effect estimate per comparison	Change in pre-BD FEV1 at Week 12	Comparison groups	Dupilumab vs Placebo
		Least square means (95% CI)	0.083 (0.042, 0.125)
		p-value	< 0.0001
	Change in pre-BD FEV1 at Week 52	Least square means (95% CI)	0.083 (0.038, 0.128)
		p-value	0.0003
	Change in SGRQ total score at Week 52	Least square means (95% CI)	-3.363 (-5.459, -1.266)
		p-value	0.0017
	Proportion of participants with SGRQ improvement ≥ 4 points at Week 52	Odds ratio (95% CI)	1.439 (1.096, 1.890)
		p-value	0.0089
	Other endpoint Change from baseline in E-RS: COPD RS-total score at Week 52	Least square means (95% CI)	-1.137 (-1.823, -0.450)
		p-value	0.0012
Analysis description	**Key Secondary Analysis**		
Analysis population and time point description	Intent to treat population in participants with baseline FeNO ≥ 20 ppb		

Table 31 - Summary of Efficacy for Study EFC15805

Title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, 52-week Pivotal Study to Assess the Efficacy, Safety, and Tolerability of Dupilumab in Patients With Moderate-to-severe Chronic Obstructive Pulmonary Disease (COPD) with Type 2 inflammation		
Study identifier	EFC15805, EudraCT: 2018-001954-91	
Design	Multinational, randomized, double-blind, placebo-controlled, parallel group (2 groups), 52-week Phase 3 study to assess the efficacy, safety, and tolerability of dupilumab in patients with moderate-to-severe COPD with type 2 inflammation on an established background of triple therapy (LABA, LAMA and ICS unless ICS contraindicated). Study treatments are dupilumab 300 mg q2w or placebo q2w administered SC over a 52-week treatment period.	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	68 weeks Not applicable Not applicable
Hypothesis	Superiority	
Treatments groups	Dupilumab	Dupilumab 300 mg Q2W, 52-week treatment period, 470 randomized participants

	Placebo		Matching placebo Q2W, 52-week treatment period, 465 randomized participants
Endpoints and definitions	Primary endpoint	AECOPD	Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period
	Key Secondary endpoint	Pre-BD FEV1 at Week 12	Change from baseline in pre-bronchodilator FEV1 at Week 12
	Key Secondary endpoint	Pre-BD FEV1 at Week 52	Change from baseline in pre-bronchodilator FEV1 at Week 52
	Key Secondary endpoint	Pre-BD FEV1 at Week 12 in high FeNO	Change from baseline in pre-bronchodilator FEV1 at Week 12 in participants with baseline FeNO ≥20 ppb
	Key Secondary endpoint	Pre-BD FEV1 at Week 52 in high FeNO	Change from baseline in pre-bronchodilator FEV1 at Week 52 in participants with baseline FeNO ≥20 ppb
	Key Secondary endpoint	SGRQ total score at Week 52	Change from baseline in SGRQ total score at Week 52
	Key Secondary endpoint	SGRQ response at Week 52	Proportion of participants with SGRQ improvement ≥ 4 points at Week 52
	Key Secondary endpoint	AECOPD in high FeNO	Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period in participants with baseline FeNO ≥20 ppb
	Other endpoint	E-RS: COPD RS-total score at Week 52	Change from baseline in E-RS: COPD RS-total score at Week 52
Database lock	01 Nov 2023		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat population Baseline up to Week 52		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	470	465
	AECOPD – adjusted annualized moderate or severe event rate	0.859	1.295
	95% CI	(0.699, 1.057)	(1.048, 1.600)
Effect estimate per comparison	Annualized rate of moderate or severe COPD	Comparison groups	Dupilumab vs Placebo
		Risk ratio (95% CI)	0.664 (0.535, 0.823)
		p-value	0.0002
Analysis description	**Key Secondary Analysis**		
Analysis population and	Intent to treat population		

time point description	Baseline to Week 12		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	470	465
	Change from baseline in pre-BD FEV1 at Week 12 (LS Mean Change)	0.139	0.057
	95% CI	(0.105, 0.173)	(0.023, 0.091)
Effect estimate per comparison	Change in pre-BD FEV1 at Week 12	Comparison groups	Dupilumab vs Placebo
		Least square means (95% CI)	0.082 (0.040, 0.124)
		p-value	0.0001
Analysis description	**Key Secondary/Other Analysis**		
Analysis population and time point description	Intent to treat population with opportunity to reach Week 52 Baseline to Week 52		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	362	359
	Change from baseline in pre-BD FEV1 at Week 52 (LS Mean Change)	0.115	0.054
	95% CI	(0.075, 0.156)	(0.014, 0.093)
	Change from baseline in SGRQ total score at Week 52 (LS Mean Change)	-9.816	-6.444
	95% CI	(-11.623, -8.008)	(-8.225, -4.634)
	Proportion of participants with SGRQ improvement ≥ 4 points at Week 52 (%)	186 (51.4%)	167 (46.5%)
	95% CI (%)	(46.1, 56.6)	(41.3, 51.8)

	Change from baseline in E-RS: COPD RS-total score at Week 52 (LS Mean Change)	-2.388	-1.770
	95% CI	(-2.979, -1.797)	(-2.359, -1.181)
Effect estimate per comparison	Change in pre-BD FEV1 at Week 52	Comparison groups	Dupilumab vs Placebo
		Least square means (95% CI)	0.062 (0.011, 0.113)
		p-value	0.0182
	Change in SGRQ total score at Week 52	Least square means (95% CI)	-3.371 (-5.811, -0.931)
		p-value	0.0068
	Proportion of participants with SGRQ improvement ≥ 4 points at Week 52	Odds ratio (95% CI)	1.164 (0.856, 1.581)
		p-value	0.3329
	Other endpoint Change from baseline in E-RS: COPD RS-total score at Week 52	Least square means (95% CI)	-0.618 (-1.430, 0.193)
		p-value	0.1351
Analysis description	**Key Secondary Analysis**		
Analysis population and time point description	Intent to treat population in participants with baseline FeNO ≥ 20 ppb Baseline to Week 12		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	172	183
	Change from baseline in pre-BD FEV1 at Week 12 (LS Mean Change) in high FeNO	0.221	0.081
	95% CI	(0.148, 0.294)	(0.008, 0.153)
Effect estimate per comparison	Change in pre-BD FEV1 at Week 12 in high FeNO	Comparison groups	Dupilumab vs Placebo
		Least square means (95% CI)	0.141 (0.058, 0.223)
		p-value	0.0010

Analysis description	**Key Secondary Analysis**		
Analysis population and time point description	Intent to treat population with opportunity to reach Week 52 in participants with baseline FeNO ≥ 20 ppb Baseline to Week 52		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	132	132
	Change from baseline in pre-BD FEV1 at Week 52 (LS Mean Change) in high FeNO	0.176	0.095
	95% CI	(0.091, 0.261)	(0.011, 0.179)
Effect estimate per comparison	Change in pre-BD FEV1 at Week 52 in high FeNO	Comparison groups	Dupilumab vs Placebo
		Least square means (95% CI)	0.081 (-0.019, 0.181)
		p-value	0.1111
Analysis description	**Key secondary Analysis**		
Analysis population and time point description	Intent to treat population in participants with baseline FeNO ≥ 20 ppb Baseline up to Week 52		
Descriptive statistics and estimate variability	Treatment group	Dupilumab	Placebo
	Number of subjects	172	183
	AECOPD – adjusted annualized moderate or severe event rate in high FeNO	0.740	1.571
	95% CI	(0.530, 1.033)	(1.119, 2.206)
Effect estimate per comparison	Annualized rate of moderate or severe COPD in high FeNO	Comparison groups	Dupilumab vs Placebo
		Risk ratio (95% CI)	0.471 (0.328, 0.675)
		p-value	< 0.0001
Notes			

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

Pooled ITT population of the BOREAS and NOTUS

Data from both studies demonstrated clinically meaningful and statistically significant reductions of 30% (EFC15804) and 34% (EFC15805) reductions in the annualized rate of moderate or severe exacerbations.

In the pooled ITT population, dupilumab demonstrated benefits over placebo in all endpoints included in the hierarchy of the individual studies (Table 32).

Table 32 – Summary of the primary and key secondary/other efficacy endpoints in the hierarchical testing procedure – ITT population from EFC 15804 and EFC 15085 and pooled ITT population

Parameter	EFC15804					EFC15805					Pooled			
	Hierarchy	Placebo[a] (N=471)	Dupilumab[a] (N=468)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Hierarchy	Placebo[a] (N=465)	Dupilumab[a] (N=470)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=936)	Dupilumab[a] (N=938)	Difference (95% CI) [b]for Dupilumab vs. Placebo	P-value[c]
Primary endpoint														
Annualized rate of moderate or severe COPD exacerbation over the 52-week treatment period	1	1.101	0.776	0.705 (0.581 to 0.857)	**0.0005**	1	1.295	0.859	0.664 (0.535 to 0.823)	**0.0002**	1.156	0.794	0.687 (0.595 to 0.793)	<.0001
Key secondary/other endpoints														
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo	2	0.077 (0.018)	0.160 (0.018)	0.083 (0.042 to 0.125)	**<.0001**	2	0.057 (0.017)	0.139 (0.017)	0.082 (0.040 to 0.124)	**0.0001**	0.064 (0.013)	0.147 (0.013)	0.083 (0.053 to 0.112)	<.0001
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo	3	0.070 (0.019)	0.153 (0.019)	0.083 (0.038 to 0.128)	**0.0003**	3	0.054 (0.020)	0.115 (0.021)	0.062 (0.011 to 0.113)	**0.0182**	0.059 (0.015)	0.133 (0.015)	0.073 (0.040 to 0.107)	<.0001
Change in pre-bronchodilator FEV1 from baseline to Week 12 compared to placebo in the subgroup of participants with baseline FeNO ≥ 20 ppb[e]	4	0.108 (0.035)	0.232 (0.034)	0.124 (0.045 to 0.203)	**0.0022**	4	0.081 (0.037)	0.221 (0.037)	0.141 (0.058 to 0.223)	**0.0010**	0.089 (0.027)	0.219 (0.027)	0.131 (0.074 to 0.187)	<.0001
Change in pre-bronchodilator FEV1 from baseline to Week 52 compared to placebo in the subgroup of participants with baseline FeNO ≥ 20 ppb[e]	5	0.120 (0.037)	0.247 (0.036)	0.127 (0.042 to 0.212)	**0.0034**	5	0.095 (0.043)	0.176 (0.043)	0.081 (-0.019 to 0.181)	0.1111	0.104 (0.029)	0.210 (0.029)	0.106 (0.042 to 0.170)	0.0012
Change from baseline to Week 52 in SGRQ total score compared to placebo	6	-6.369 (0.816)	-9.732 (0.810)	-3.363 (-5.459 to -1.266)	**0.0017**	6	-6.444 (0.922)	-9.816 (0.920)	-3.371 (-5.811 to -0.931)	0.0068	-6.579 (0.640)	-9.945 (0.636)	-3.366 (-4.953 to -1.778)	<.0001
Proportion of participants with SGRQ improvement ≥ 4 points at Week 52 compared to placebo	7	203 (43.1)	241 (51.5)	1.439 (1.096 to 1.890)	**0.0089**	7	167 (46.5)	186 (51.4)	1.164 (0.856 to 1.581)	0.3329	370 (44.6)	427 (51.4)	1.311 (1.070 to 1.607)	0.0089

Parameter	EFC15804					EFC15805					Pooled			
	Hierarchy	Placebo[a] (N=471)	Dupilumab[a] (N=468)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Hierarchy	Placebo[a] (N=465)	Dupilumab[a] (N=470)	Difference (95% CI)[b] for Dupilumab vs. Placebo	P-value[c]	Placebo[a] (N=936)	Dupilumab[a] (N=938)	Difference (95% CI) [b]for Dupilumab vs. Placebo	P-value[c]
Change in E-RS: COPD RS-Total Score from baseline to Week 52 compared to placebo	8	-1.558 (0.256)	-2.694 (0.257)	-1.137 (-1.823 to -0.450)	**0.0012**	8	-1.770 (0.300)	-2.388 (0.301)	-0.618 (-1.430 to 0.193)	0.1351	-1.605 (0.200)	-2.519 (0.201)	-0.914 (-1.438 to -0.389)	0.0006
Annualized rate of moderate or severe COPD exacerbation compared to placebo over the 52-week treatment period in the subgroup of participants with baseline FeNO ≥ 20 ppb[e]	9	1.117	0.699	0.625 (0.450 to 0.869)	**0.0052**	9	1.571	0.740	0.471 (0.328 to 0.675)	<.0001	1.321	0.729	0.552 (0.434 to 0.701)	<.0001

FEV1: Forced Expiratory Volume in one second; FeNO; Fractional Exhaled Nitric Oxide; SGRQ: St. George's Respiratory Questionnaire, E-RS: COPD: Evaluating Respiratory Symptoms (E-RS) in COPD; LS: least squares.

a Values presented are event rates derived using negative binomial model for event type variables, LS mean change from baseline with standard error for continuous variables, and number and percent of responders for binary variables

b Difference is relative risk for event type variables, LS mean difference for continuous variables, and odds ratio for binary variables.

c Values in bold font are statistically significant according to the hierarchical testing procedure.

d Nominal p-values. No hierarchical testing procedure for pooled data.

e The subgroup of baseline FeNO ≥20 ppb included N=371 in placebo and N=367 in dupilumab intervention groups in the pooled ITT population.

Note: For the continuous and proportion type endpoints at Week 52, only participants who have opportunity to reach Week 52 assessments in EFC15805 are analyzed in EFC15805 interim analyses, and are pooled with participants with EFC15804 and analyzed in the summary of clinical efficacy.

PGM=PRODOPS/SAR231893/OVERALL/ISE_COPD_2023/REPORT/PGM/eff_hierarchy_test_i_t.sas OUT=REPORT/OUTPUT/eff_hierarchy_test_i_t_i.rtf (20NOV2023 10:54)

Since the proportion of participants who experienced severe COPD exacerbations was low, data from both studies were pooled to gain a more precise estimate of the treatment effect. In the pooled ITT population, the adjusted annualized rate of severe AECOPD events over the 52-week treatment period was 0.084 in

the dupilumab group and 0.124 in the placebo group, with a 33% reduction (nominal p=0.0725) (Table 33).

Table 33 – Summary of annualized rate of COPD exacerbation overall and by components during the 52-week treatment period – Pooled ITT population

Parameter	Placebo[a] (N=936)	Dupilumab[a] (N=938)	Difference (95% CI) for Dupilumab vs. Placebo[b]	P-value[c]
Primary endpoint				
moderate or severe COPD exacerbation	1.156	0.794	0.687 (0.595 to 0.793)	<.0001
Components of the primary endpoint				
moderate COPD exacerbation	1.001	0.690	0.689 (0.592 to 0.801)	<.0001
severe COPD exacerbation	0.124	0.084	0.674 (0.438 to 1.037)	0.0725

a Values presented are event rates derived using negative binomial model.

b Difference is relative risk for event type variables

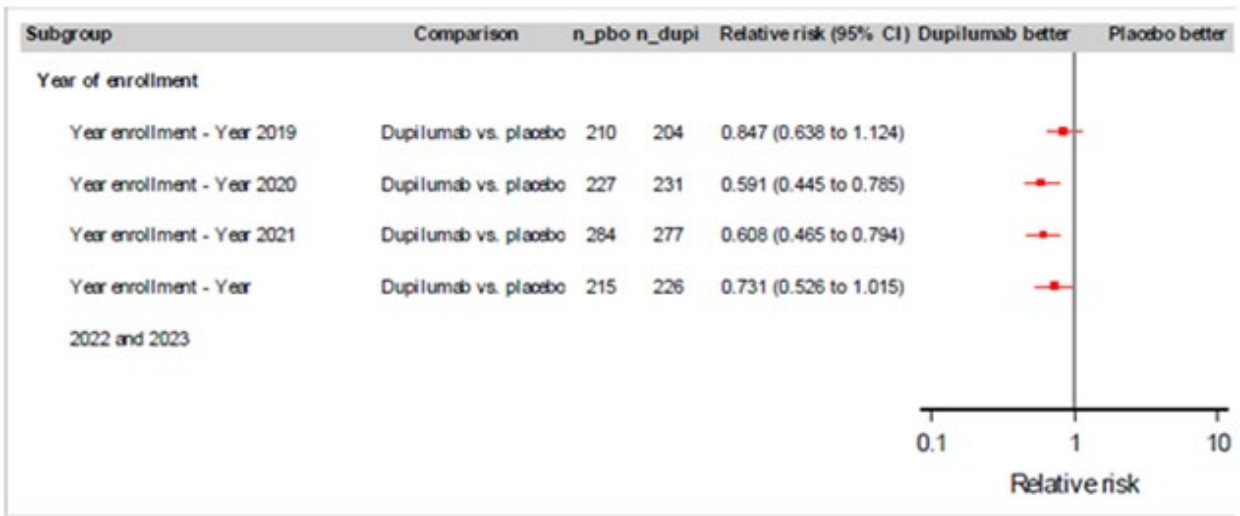
c Nominal p-values

PGM=PRODOPS/SAR231893/OVERALL/ISE_COPD_2023/REPORT/PGM/eff_copd_summary_sp_i_t.sas
OUT=REPORT/OUTPUT/eff_copd_summary_ovcom_i_t_i.rtf (20NOV2023 10:47)

Primary and Key Secondary Endpoint as per year of enrolment, post hoc analysis

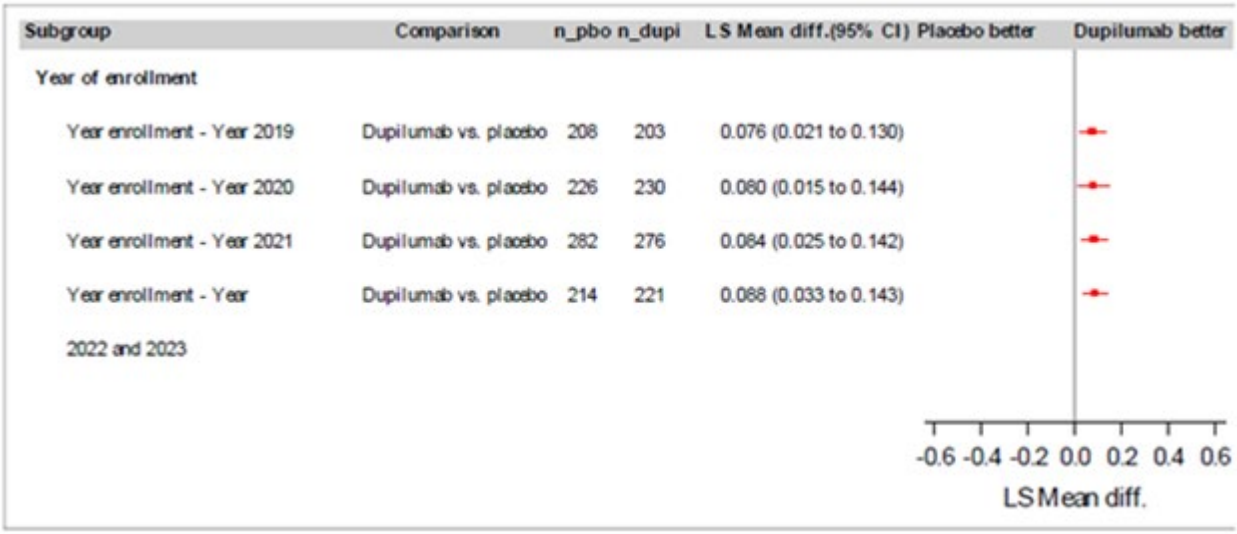
The relative risk in annualized rate of moderate or severe exacerbations by year of enrolment for the pooled ITT of EFC15804 and EFC15805 is provided in Figure 28. These analyses were requested during the review and are post hoc.

Figure 28 - Forest plot relative risk in the annualized rate of moderate or severe COPD exacerbations during the 52-week treatment period by year of enrolment – Pooled ITT population – post hoc analysis



The improvement in pre-BD FEV1 at Week 12 by year of enrolment is provided in Figure 29.

Figure 29 – Forest plot of LS mean difference in the change from baseline in pre-bronchodilator FEV1(L) at Week 12 by year enrolment – Pooled ITT population – Post hoc analysis



A reduction in exacerbation rates was observed throughout all years of enrolment in the pooled ITT population of both studies. Notably, reductions were lowest in participants enrolled in 2019, highest in 2020 and 2021 and appear to be again lower in 2022/2023. The MAH states that the study was not powered to detect differences in subgroups. The presented data indicate that reductions in exacerbation rates where highest during the peak of the COVID-19 pandemic. It is unclear whether pandemic related public measures may or may not have influenced the magnitude of the treatment effect.

This is further supported by the fact that improvements in lung function appear to be unaffected by the year of enrolment which seems reasonable as lung function parameters are not as dependent on environmental triggers as the occurrence of exacerbations. A reduction in exacerbations of >30 percent may not be achieved in a post-pandemic scenario. Still, clear differences between dupilumab and placebo were observed in both studies. Overall, clinically meaningful reductions in exacerbation rates and improvements in lung function were seen in both studies throughout all years of enrolment.

Black/African descent participants

The MAH provided an additional analysis with data from 26 participants that are Black or of African descent within the pooled ITT population.

During the 52-week treatment period, 9 out of the 12 participants in the dupilumab group did not experience any moderate or severe COPD exacerbation event, versus 8 out of 14 participants in the placebo group. The other 3 participants in the dupilumab group had 1 to 2 moderate or severe COPD exacerbation events each, and the remaining 6 participants in the placebo group had 1 to 4 moderate or severe COPD exacerbation events each during the 52-week treatment period. The annualized rate of moderate or severe exacerbations was lower in the dupilumab group (0.750) than the placebo group (1.528) with a relative risk reduction of 0.491 (95% CI: 0.113 to 2.125) in this small subgroup of Black or African American patients (Table 34)

These larger data set indicate similar efficacy results in this subpopulation. However, due to the low patient number statistical significance was not reached.

Table 34 – Analysis of annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period in participants with Black or African American race – Pooled ITT population with Black or African American race

	Placebo (N=14)	Dupilumab 300 mg q2w (N=12)
Total number of moderate or severe exacerbation events	14	5
Total patient-years followed	12.7	10.5
Unadjusted annualized moderate or severe exacerbation event rate[a]	1.10	0.48
Adjusted annualized moderate or severe exacerbation event rate[b]		
Estimate (95% CI)	1.528 (0.455 to 5.126)	0.750 (0.164 to 3.440)
Relative risk vs. placebo (95% CI)		0.491 (0.113 to 2.125)
P-value		0.3188

All moderate or severe adjudicated exacerbation events that occurred during the 52-week treatment period are included, regardless of whether the participant was on-treatment or not.
Participants with multiple races including Black or African American are included
[a] The total number of events that occurred during the 52-week 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 the events occurring during the 52-week treatment period as the response variable, and treatment group, region (pooled country), ICS dose, smoking status at screening, baseline disease severity, and number of moderate or severe COPD exacerbation events within one year prior to the study as covariates, and log-transformed treatment duration as an offset variable.

2.5.3. Discussion on clinical efficacy

Data for clinical efficacy are based on the results from the single pivotal phase 3 study EFC15804 (BOREAS), a multinational, placebo-controlled, 52-week study, with uncontrolled COPD on triple therapy (LABA+LAMA+ICS; unless contraindicated), with increased blood eosinophils (≥0.3 cells/microliter). Dupilumab was administered with a dose regimen 300mg, Q2W (without a loading dose) as also used for other approved indications. Efficacy data from the second phase 3 study, EFC15805 (NOTUS), which was part of the dupilumab COPD development program, were provided during the procedure.

Design and conduct of the clinical study (EFC15804)

The BOREAS study was conducted at the time of the global COVID-19 pandemic (first participant enrolled: 09-May-2019; last participant (end of treatment visit :08-Feb-2023) including study sites in Asia, Latin America, East Europe, and Western Countries.

The study enrolled adult patients (age: 40-80 years) with moderate-to-severe COPD as defined by a FEV1/FVC ratio <70% and a post-BD FEV1 within a range between 30 and 70%, corresponding to a GOLD grading of GOLD 2 and GOLD 3. Patients with a very severe disease (i.e. GOLD grade 4; FEV1 <30%) were not included. Current or former smokers with a smoking history of ≥10 pack-years with a cap of 30% for current smokers were included.

Participants needed to be on a background triple therapy consisting of ICS+LABA+LAMA for 3 months prior to randomization. During the procedure, "triple therapy" in the indication as proposed by the MAH was replaced with more specific information: a combination of an inhaled corticosteroid and a long-acting beta2-agonist and a long-acting muscarinic antagonist. A double therapy with LABA+LAMA was allowed if ICS was contraindicated. Further, it was considered that to better reflect the clinical practice and cases of patients that are not treated with ICS based on reasons other than known contraindications, the wording of the indication should be modified from 'if ICS was contraindicated' to 'if ICS is not appropriate'.

The background therapy needed to be stable for at least one month prior to screening. Throughout the study, participants were required to continue their established background therapy at the same dose and

regimen. Use of PDE-4 inhibitors and methylxanthines was allowed during the study if the dose was stable >6 months prior to the screening visit. After 1 severe or 2 moderate exacerbations of COPD, dose adjustment of background therapy was permitted for symptom control and as needed for the rest of the study.

Participants with an uncontrolled COPD as evidenced by a documented history of high exacerbation risk defined as exacerbation history of ≥2 moderate or ≥1 severe exacerbations within the year prior to inclusion and the presence of symptoms of COPD with MRC dyspnea scale ≥2, despite receiving maximal standard-of-care treatment (triple therapy LABA+LAMA+ICS unless ICS was contraindicated) as well as presence of increased blood eosinophils ≥300 cells/microliter during the screening period were included. Retesting of blood eosinophils was allowed up to three times.

The primary efficacy endpoint was the annualized rate of moderate or severe COPD exacerbations (AECOPD) over the 52-week treatment period compared to placebo. A moderate exacerbation was defined as an exacerbation event that required either systemic corticosteroids and/or antibiotics whereas a severe exacerbation was defined as an event requiring hospitalization or observation for >24 hours in an emergency department/urgent care facility or that results in death. Key secondary endpoints included changes in pre-BD FEV1 from baseline to Week 12 and Week 52 compared to placebo to evaluate changes in lung function as well as quality of life assessment by the SGRQ and the E-RS: COPD scale. Evaluation of the annualized rate of moderate or severe COPD exacerbation events and change from baseline in FEV1 at Week 12 and Week 52 in the subgroup of patients with baseline FeNO ≥20 ppb was later added as key secondary endpoints in the SAP prior to database lock and unblinding.

A total of 2599 subjects were screened for eligibility with 939 participants finally randomized to study intervention (dupilumab: 468; placebo: 471). There was a high number of screen failures (63.9%), with around one third of cases attributed to not meeting the inclusion criteria (blood eosinophils ≥300 cells/microliter) indicating the distinct subgroup of patients with eosinophilic COPD enrolled in this study.

In general, COPD patients with an increase in blood eosinophils are more likely to respond to corticosteroids and blood eosinophil counts predict the magnitude of the effect of ICS, while a threshold of a blood eosinophil count ≥300 cells/microliter identifies the top of the continuous relationship between eosinophils and ICS and can be used to identify patients with the greatest likelihood of treatment benefit with ICS (GOLD 2023). The study was thus conducted in a more severe patient population of patients (i.e. those who are not responding to ICS). During the procedure, the MAH provided an estimate of what percentage of the COPD population dupilumab is targeting which indicated that a very small subset of patients would satisfy the criteria that indicate a benefit with treatment (i.e. GOLD group E on triple therapy, with evidence of increased blood eosinophils).

As per study protocol, retesting of blood eosinophils was allowed up to three times to meet the inclusion threshold indicating a fluctuating stability of the blood eosinophil measurement. Notably, at baseline, eosinophil blood levels had dropped below the threshold of ≥300 cells/microliter in 39% of participants. Additional data and discussion were provided by the MAH upon request. Fluctuating blood eosinophil counts were observed in both pivotal phase 3 studies (BOREAS and NOTUS). Still, in patients with high or lower eosinophil counts at baseline, similar reductions in exacerbations were observed. Given the fluctuating stability of the blood eosinophil measurement over time a precise cut-off to be included in the indication is considered not feasible. The CHMP agreed that the wording of the indication should capture instead that the medicine is intended for patients with COPD characterised by raised blood eosinophils. The threshold used for screening in the phase 3 studies is included in Section 5.1 of the SmPC.

The majority of participants completed the study (dupilumab: 426 (91.0%); placebo 417 (88.5%) group completed the 52-week study intervention period. The most frequently reported reason for permanent study intervention discontinuation, as per the Investigator, was “withdrawal by subject” (22 (4.7%) in the dupilumab group and 28 (5.9%) in the placebo group). The majority of these withdrawals by subject

were due to "other" reasons. 12 permanent study intervention discontinuations were related to COVID 19. Only a small number of patients discontinued treatment due to COVID-19 restrictions (e.g. patient cannot come to site) in both treatment groups. The majority of withdrawal by subject was not COVID-19-related (see additional assessment on the study conduct during the COVID-19 pandemic further below).

Around two thirds of the study population were male (66%). The majority of participants was White (84.1%). Asian participants contributed to 14.3 % of the study population. Of note, there was a very low number of participants with Black/of African descent (0.5%) (see efficacy in other subgroups below). As expected for the disease, more than half of participants had an age of 65 and older (58.1%). 29.4 % of participants had a BMI of 30 kg/m2 and higher. One third of the study population was enrolled in the European Union (32.6%).

The mean (SD) number of patients with a moderate or severe exacerbation within the year before screening was 2.3 (1.0) in the entire study population. The majority of participants had two moderate exacerbations with a limited number of participants that have experienced multiple moderate exacerbations before the study. Around 1/4 of participants experienced a severe exacerbation prior to study enrolment.

At screening, the majority of participants had a severity grade of GOLD 2 or GOLD 3 and were nearly equally distributed (48% vs. 51.3% in the ITT population). A small number of participants (dupilumab: 3; placebo: 3), had a GOLD Grade 4 at screening. At baseline 14 participants in the dupilumab group and 11 participants in the placebo group had disease severity of GOLD Grade 4. Similarly, a total of 24 participants were grade GOLD grade 1 (FEV1 ≥80%) indicating participants with improvement in FEV1 by at least 10 percent points regardless of dupilumab treatment. Still, these patients were low in number and balanced between treatment groups.

Efficacy data and additional analyses (EFC15804)

The study met its primary endpoint and all other multiplicity-controlled endpoints of the hierarchical testing strategy.

Primary Endpoint

The adjusted annualized rate of moderate or severe AECOPD events at 52 weeks was lower in the dupilumab as compared to placebo (0.776, 95% CI:0.645-0.934; 1.101, 95% CI:0.931-1.301) resulting in a reduction of the exacerbation rate by 30 percent (rate ratio vs. placebo: 0.705 (95% CI: 0.581-0.857).

A trend towards loss of response after the end of treatment can be observed in the dupilumab group apparent by similar exacerbation event rates as compared to placebo during the 12-week follow-up period.

Overall, intercurrent events and missing values not defined in detail rise to some uncertainties regarding the magnitude and interpretation of the primary (and important secondary) endpoints. Requested additional information on the underlying intercurrent events have shown that this uncertainty is rather negligible.

Secondary Endpoints

Change in pre-bronchodilator FEV1 from baseline to Week 12 and Week 52 compared to placebo were specified as key secondary endpoints to evaluate improvements in lung function. There's an apparent improvement in pre-bronchodilator FEV1 in the placebo group as well. Similar placebo responses in lung function have been also observed in the asthma indication. Despite the FEV1 improvements in the placebo group, a clinically meaningful difference between dupilumab and placebo was observed in both studies.

The improvement in pre-BD FEV1 was rapid, with an onset of difference between dupilumab and placebo starting at Week 2 which was maintained until Week 52 (mean difference: +83 ml) with no signs of later decline in the placebo or dupilumab group. After the end of treatment, the pre-BD FEV1 started to decline in the dupilumab group. The maintenance of the effect was demonstrated for 52 weeks but not for longer time periods as dosing beyond 52 weeks has not been studied. This is reflected in section 4.2 of the SmPC.

The overall health status was assessed using the established St George's Respiratory Questionnaire (SGRQ). Similar to the improvements in lung function (change in pre-BD FEV1), improvements in SGRQ started early and were maintained through the 52-week treatment period. The LS mean difference between dupilumab placebo was -3.363 (-5.459 to -1.266). Notably, the mean (SD) change in the placebo group was 6.16 (17.59), exceeding the defined minimal important difference of -4 points in 43.1%. Still, a greater number of these responders was observed in the dupilumab group (51.5%). Overall, these data are supportive for the treatment effect of dupilumab on lung function.

The treatment effect was also reflected in other relevant measures of lung function over time up to Week 52 including changes in post-bronchodilator FEV1, pre-bronchodilator FVC and post-bronchodilator FEV1/FVC.

Efficacy in subpopulations based on biomarkers of type 2 inflammation (e.g. FeNO)

The MAH initially proposed an indication to treat COPD patients with "type 2 inflammation" which is a broad term that would potentially allow treatment based on other type 2 biomarkers besides increased blood eosinophils such as increased FeNO. Of note, as per current GOLD guidelines the term "type 2 inflammation" is not established in the context of diagnosis and management of COPD.

Subgroup data for the primary and secondary endpoint in patients with increased FeNO at baseline (FeNO ≥20 ppb) were provided. In the BOREAS study, the annualized rate of moderate or severe AECOPD events over 52 weeks was higher in participants with baseline FeNO ≥20 ppb as compared to the overall ITT population (37% vs 30%). An enhanced improvement in lung function was also observed in patients with increased FeNO (LS mean difference +0.127). Further subgroup analysis showed greater reductions in exacerbation rates and greater improvements in lung function (pre-BD FEV1 at Week 12) in participants with strongly increased blood eosinophils (≥0.5 Giga/L) or participants with elevated FeNO levels (≥20 ppb). Similar results with regard to efficacy in relation to baseline FeNO values were also observed in the second phase 3 study NOTUS. These data indicate the strong relevance of the extent of airway inflammation to the treatment effect of dupilumab and are considered overall highly supportive.

It must however be noted that in both phase 3 studies enrolment was restricted to COPD patients with raised blood eosinophils (i.e. ≥300 cells/microliter) only. Thus, the provided subgroup analysis regarding baseline FeNO levels is not able to demonstrate efficacy in patients with elevated FeNO alone as these patients were not part of the study population. To which extent blood eosinophils and FeNO levels do correlate in COPD is not evident from the data obtained in study EFC15804 and EFC15805. While a strong correlation of eosinophilia and FeNO has been demonstrated for other indications, such as asthma, this correlation is not clearly established in COPD. It is also important to note that for the asthma indication efficacy was also shown for patients with blood eosinophils <150 cells/microliter and FeNO ≥25 ppb. Such data are not available for the COPD population as all patients had to have blood eosinophils ≥300 cells/microliter at screening. Further, current GOLD guidelines do not include any treatment recommendations based on FeNO. A broad indication that may allow treatment based on type 2 biomarkers irrespective of blood eosinophils is therefore not supported by the data. Overall, the indication needs to reflect the study population included in the BOREAS study; that is COPD patients with raised blood eosinophils. Therefore the MAH updated the indication to 'COPD characterised by raised blood eosinophils'.

Conduct during the COVID-19 pandemic

Study EFC15804 was partially conducted during the COVID-19 pandemic with the first participant enrolled on 09-May-2019 and the last participant completing the treatment period on 08-Feb-2023. In response to the emerging COVID-19 pandemic in 2020 several measures (telephone visits, earlier possibility for at-home administration and home visits etc.) were included per protocol amendment. These implemented measures can be considered to not have significantly affected the evaluation of the primary objective of the study (rate of exacerbations) as information on exacerbation could also be recorded by remote visits. Still, some spirometry assessments (secondary objective) were not performed due to COVID-19 measures. These critical/major protocol deviations were, however, low in number. The majority of participants enrolled in this study (92.0%) were considered without trial impact (disruption) due to COVID-19.

However, since COPD exacerbations are often triggered by (viral) infections, the general public health measures put in place during the conduct of the study (i.e. social distancing, protection masks, increased hygiene, behavioural changes) have largely affected the number and potentially also the quality of exacerbations that occurred during the study. This was apparent by a large reduction in the numbers of moderate or severe AECOPD events in the placebo group comparing the year before and after the 52-week treatment period (2.3 vs. 0.9). Moreover, despite the recruitment of patients with a high exacerbation risk that had experienced at least one exacerbation in the year before enrolment, more than half of all participants did not experience any exacerbation during the study.

To account for this, the MAH provided a post-hoc analysis in the subgroup of participants without moderate or severe exacerbations. The results suggest similar treatment effect with regard to improvements in lung function and health status.

In the placebo group, numbers of severe exacerbations before and after the 52-week treatment period were reduced by more than 65%. Accordingly, the effect observed for the primary endpoint was mainly driven by the difference in moderate exacerbations while no statistical difference was observed for severe exacerbations. Additional analysis with the pooled ITT population of the BOREAS and NOTUS study provided by the MAH during the procedure showed a trend toward similar magnitude of reduction in severe exacerbations (33%).

Overall, as environmental triggers for exacerbations were apparently largely reduced during the conduct of the study there was some level of uncertainty as to whether the observed effect of dupilumab on exacerbation rates in the single pivotal BOREAS study represented the true clinical effect that would be achieved in a real-world "post-pandemic" scenario. During the procedure, further data were requested, and the MAH submitted the results of another ongoing study (NOTUS) together with a pooled analysis. The additional analysis performed across trials by the MAH indicated that in the pooled ITT population of the BOREAS and the NOTUS study reductions in exacerbations were lowest in patients enrolled in 2019, highest in 2020 and 2021 and appear to be again lower in 2022/2023 leading to assume that a reduction in exacerbations of >30 percent may not be achieved in a post-pandemic scenario. Still, clear differences between dupilumab and placebo were observed in both phase 3 studies throughout all years of enrolment.

Efficacy in other subgroups

The majority of participants was at age 65 and older with 44.7% in the age group of 65-74 and 13.4% in the age group of 75-80 years. The reduction in exacerbation events was overall similar between the different age groups while improvement in lung function were pronounced in older patients.

At baseline, the majority of participants were either GOLD grade 2 (FEV1 ≥50% and <80%) or GOLD grade 3 (FEV1 ≥30% and <50%) (see baseline data). The reduction in exacerbation events and lung improvements were similar in the subgroup of patients with FEV1 < or ≥ 50 %. The reduction in

exacerbation events was similar in current or former smokers while current smokers appear to have lower improvements in lung function. The treatment effect was overall consistent in the subgroup of patients with emphysema. The effect of dupilumab in COPD was similar in patients with or without reversibility of FEV1 at baseline. The study mainly enrolled patients with moderate-to-severe COPD (post-BD FEV1/FVC ratio >0.70 and post BD FEV1 % predicted >30% and ≤70%). There is very limited data available on patients with GOLD 1 and GOLD 4 treated with dupilumab which is mentioned in section 5.1 of the SmPC.

A total of only 5 participants with Black/African descent were included in the study despite no major differences in disease prevalence for this patient population which is the lowest number ever enrolled throughout the different indications previously investigated. During the procedure, the MAH provided an additional analysis with data from 26 participants that are Black or of African descent (including new data from the NOTUS study). These larger data set indicates similar efficacy results in this subpopulation.

Design and conduct of the clinical study EFC15805 (NOTUS)

During the procedure, the MAH provided the efficacy data from the second phase 3 study EFC15805 (NOTUS) based on an interim analysis. The data comprised 77% of the initially randomized patients (721/935) that had reached Week 52 by the time of the analysis. As for the BOREAS study, this second pivotal study was conducted at the time of the global COVID-19 pandemic but with start of enrolment about one year later than the BOREAS study (first participant enrolled: 06-July-2020). Efficacy data included in the provided CSR are based on the interim analysis cut-off date 29 September 2023.

The study was a replicate study with mainly the same design and objectives as study EFC15804 and enrolled the same study population of moderate-to-severe COPD patients with a high exacerbation risk, despite maximal standard-of-care and presence of increased blood eosinophils at screening. Baseline demographics and disease characteristic are overall consistent with the BOREAS study. Of note, the NOTUS study was amended to include patients up to 85 years of age. Most of NOTUS participants (45.7 %) were enrolled in the EU.

As during the BOREAS study, there was a high number of screening failures due to participants not meeting the blood eosinophil threshold at screening. Retesting of blood eosinophils for screening purposes was allowed and a considerable number of participants (39.8%) had eosinophil counts below ≥ 300 cells/microliter at baseline again indicating the fluctuating nature of blood eosinophil measurement.

Efficacy data and additional analyses (EFC15805)

Results for the primary endpoints and the main secondary endpoints were overall consistent with the BOREAS study and are summarized below.

Primary Endpoint

The adjusted annualized rate of moderate or severe AECOPD events over the 52-week intervention period in the ITT population was lower in the dupilumab group as compared to the placebo group (0.859 (95% CI: 0.699 to 1.057) vs. 1.295 (95% CI: 1.048 to 1.600) resulting in a 34 percent reduction of the exacerbation rate (rate ratio vs. placebo: 0.664 (95% CI: 0.535- 0.823).

Secondary Endpoints

A rapid improvement in pre-BD FEV1 was observed with a mean difference of +82 ml. As within the BOREAS study, there was a fast onset of the response during the first weeks. Notably, the effect was slightly reduced at Week 52 (+62 ml). Larger FEV1 improvements were seen in patients with baseline FeNO ≥20 ppb at Week 12. At week 52, statistical significance was however not reached and FEV1 improvements tended to be similar compared to the overall population.

As within the BOREAS study, the treatment effect seen for the primary and secondary endpoints was also reflected in improvements in relevant health status and quality of life measures and other relevant

measures of lung function including changes in post-bronchodilator FEV1, pre-bronchodilator FVC and post-bronchodilator FEV1/FVC.

Pooled ITT population

Results for the pooled ITT population were overall consistent with the results of the individual phase 3 studies. The difference in the adjusted annualized rate of moderate or severe AECOPD events over the 52-week between dupilumab and placebo group was (0.687 (95% CI: 0.595 to 0.793). Consistent improvements in pre-BD FEV1 as compared to placebo were observed at week 12 (+83ml (95% CI: 53 to 112). At week 52, pre-BD FEV1 improvements were +73ml (95%CI: 40 to 107) in the pooled ITT population. The pooled ITT population of the BOREAS and NOTUS showed a trend toward similar magnitude of reduction in severe exacerbations The data on the reduction of severe exacerbation have been included in the SmPC (section 5.1).

2.5.4. Conclusions on the clinical efficacy

Efficacy results from study EFC15804 demonstrate a beneficial treatment effect of dupilumab in patients with uncontrolled COPD and increased blood eosinophils when added to triple background therapy (LABA+LAMA+ ICS, unless ICS was contraindicated) as seen by the profound reduction in exacerbation events and rapid improvements in lung function in both studies. The effect was also reflected in other additional efficacy measures. Overall, the effects seen at Week 52 in the primary and secondary endpoints of study EFC15804 are considered clinically meaningful and do support the approval of dupilumab in patients with COPD.

While efficacy data were initially based only on one single pivotal study EFC15804 (BOREAS) replication of the results with additional data from the second pivotal study EFC15805 (NOTUS) was demonstrated during the procedure.

The MAH also agreed to update the indication to better reflect the COPD population studied in the 2 pivotal studies. Therefore the CHMP concluded that the efficacy data support the following indication:

Dupixent is indicated in adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate (see Section 5.1).

2.6. Clinical safety

Introduction

Safety Data for COPD

Main safety data

Safety data for the COPD indication are derived from phase 3 study EFC15804 (BOREAS; safety data from the second phase 3 study EFC15805 (NOTUS) have been provided. The pooled safety population of both studies consists of 1872 (dupilumab: 938; placebo: 934) patients.

Table 35- Study evaluated in the Summary of Clinical Safety and study status

Study number/Status at study cut-off date	Summary of key study information	Planned study duration	Participants randomized/ treated
EFC15804 (BOREAS) 52-week intervention period completed 12-week post-intervention follow-up period completed Date last participant last visit: 02 May 2023 (5.3.5.1 [Study EFC15804])	A randomized, multi-center, 52-week treatment, parallel group, double-blind, placebocontrolled pivotal study to evaluate the use of dupilumab in participants with moderatetosevere airflow obstruction and uncontrolled COPD (≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2) with type 2 inflammation (blood eosinophil counts ≥0.3 Giga/L at screening) on an established LABA, LAMA and/or ICS background therapy Population: adults (40 to 80 years of age) Dose regimen: 300 mg q2w SC	52 weeks of treatment + 12 weeks of post-intervention followup	Randomized=939 (dupilumab: 468; placebo: 471) Treated=939 (dupilumab: 469[a]; placebo: 470)
EFC15805 (NOTUS) 52-week intervention period completed 12-week post-intervention follow-up period ongoing at the interim analysis data cut-off date 29 Sep 2023 (5.3.5.1 [Study EFC15805])	A randomized, multi-center, 52-week treatment, parallel group, double-blind, placebocontrolled pivotal study to evaluate the use of dupilumab in participants with moderatetosevere airflow obstruction and uncontrolled COPD (≥2 moderate or ≥1 severe exacerbations in the previous year and MRC ≥2) with type 2 inflammation (blood eosinophil counts ≥0.3 Giga/L at screening) on an established LABA, LAMA and/or ICS background therapy Population: adults (40 to 85 years of age) Dose regimen: 300 mg q2w SC	52 weeks of treatment + 12 weeks of post-intervention follow-up	Randomized= 935 (dupilumab: 470; placebo: 465) Treated= 933 (dupilumab: 469 ; placebo: 464)

COPD: chronic obstructive pulmonary disease; EOT: end of treatment; ICS: inhaled corticosteroids; LABA: longacting beta agonist; LAMA: longacting muscarinic antagonist; MRC: Medical Research Council; SC: subcutaneously.

a One participant randomized to the placebo group received 1 dose of dupilumab and was considered as part of the dupilumab group for safety analyses.

Supportive safety data

SUSARs and deaths reported from:

- study EFC15804 (BOREAS): 08 February 2023 - and 31 May 2023
- study EFC15805 (NOTUS): 14 January 2023 – 31 May 2023
- other ongoing Phase 2/3 studies and Phase 4 interventional studies: 14 January 2023 - 31 May 2023

2.6.1. Study EFC15804 (BOREAS)

Patient exposure

Disposition

A total of 939 participants were randomized to study intervention: 468 in the dupilumab 300 mg q2w group and 471 in the placebo group. All randomized participants were exposed to at least 1 dose of IMP. There were no participants who were exposed but not randomized. One participant was randomized to

placebo but inadvertently received a single dose of dupilumab; this participant is analyzed in the dupilumab group for all safety analyses.

Most of the randomized participants completed the 52-week study intervention period (dupilumab: 91.0% of participants; placebo: 88.5% of participants). In both groups, the most frequent reason for permanent study intervention discontinuation, as per the Investigator, was withdrawal by participant (dupilumab: 4.7%; placebo: 5.9%). The category "adverse event" was reported by the Investigator as the reason for permanent study intervention discontinuation prior to Week 52 similarly in both intervention groups (dupilumab: 14 [3.0%] participants; placebo: 15 [3.2%] participants). A total of 16 (3.4%) participants permanently discontinued the study intervention due to AE.

Overall, 12 permanent study intervention discontinuations were related to COVID-19: 2 in the placebo group due to SAEs of COVID-19 pneumonia that led to death and 10 due to "other" reasons related to COVID 19 (3 in the dupilumab group and 7 in the placebo group).

Participants who permanently discontinued study intervention were encouraged to remain in the study. Of the 42 participants in the dupilumab group and 54 participants in the placebo group who permanently discontinued study intervention, 23 and 31 participants in the dupilumab and placebo groups, respectively, withdrew from the study prior to Week 52.

As of the primary completion date for this study (08 February 2023), 410 (87.6%) participants in the dupilumab group and 402 (85.4%) participants in the placebo group had completed the study (ie, the entire study intervention and post-intervention follow-up periods), 30 (6.4%) participants in the dupilumab group and 33 (7.0%) in the placebo group were ongoing in the post intervention follow-up period and 28 (6.0%) participants in the dupilumab group and 36 (7.6%) participants in the placebo group had prematurely discontinued from the study.

Table 36 - Participant disposition - Randomized population

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)
Randomized and not exposed [n(%)]	0	0
Randomized and exposed [n(%)]	471 (100)	468 (100)
Completed the study intervention period	417 (88.5)	426 (91.0)
Discontinued the study intervention period	54 (11.5)	42 (9.0)
Reason for study intervention discontinuation		
Adverse event	15 (3.2)	14 (3.0)
Related to COVID-19	2 (0.4)	0
Not related to COVID-19	13 (2.8)	14 (3.0)
Lack of efficacy	1 (0.2)	0
Progressive disease	1 (0.2)	1 (0.2)
Poor compliance to protocol	2 (0.4)	2 (0.4)
Withdrawal by subject	28 (5.9)	22 (4.7)
Other reason[a]	7 (1.5)	3 (0.6)
Related to COVID-19	4 (0.8)	1 (0.2)
Not related to COVID-19	3 (0.6)	2 (0.4)
Subject's reason for withdrawal[b]		
Adverse event	2 (0.4)	2 (0.4)
Related to COVID-19	0	0
Not related to COVID-19	2 (0.4)	2 (0.4)
Study procedures	2 (0.4)	4 (0.9)
Inconvenience of device use	1 (0.2)	1 (0.2)

	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)
Other[a]	23 (4.9)	15 (3.2)
Related to COVID-19	3 (0.6)	2 (0.4)
Not related to COVID-19	20 (4.2)	13 (2.8)
Completed the 52-week study period [n(%)]	440 (93.4)	445 (95.1)
Discontinued from the study prior to Week 52 [n(%)]	31 (6.6)	23 (4.9)
Reason for study discontinuation prior to Week 52		
Adverse event	8 (1.7)	5 (1.1)
Poor compliance to protocol	0	1 (0.2)
Study terminated by sponsor	0	0
Withdrawal by subject	18 (3.8)	11 (2.4)[c]
Other reason[a]	5 (1.1)	5 (1.1)
Related to COVID-19	0	0
Not related to COVID-19	5 (1.1)	5 (1.1)
Ongoing in study [n(%)]	33 (7.0)	30 (6.4)
Completed the study period [n(%)]	402 (85.4)	410 (87.6)[c]
Discontinued from the study period [n(%)]	36 (7.6)	28 (6.0)[c]
Reason for study discontinuation		
Adverse event	9 (1.9)	7 (1.5)
Poor compliance to protocol	0	1 (0.2)
Study terminated by sponsor	0	0
Withdrawal by subject	22 (4.7)	11 (2.4)[c]
Other reason[a]	5 (1.1)	9 (1.9)
Related to COVID-19	0	1 (0.2)
Not related to COVID-19	5 (1.1)	8 (1.7)
Status at last study contact		
Alive	427 (90.7)	426 (91.0)
Dead	8 (1.7)	9 (1.9)

a Verbatim terms for these discontinuations are provided in the listings of participants with permanent study intervention discontinuation or study discontinuation respectively

b This is a further breakdown of the reasons for withdrawal by subject reported above, as collected in the standard CRF form

c One participant in the Dupilumab 300mg q2w group discontinued the study intervention and study prior to week 52, but the eCRF was marked as completed the study period and therefore not included in the discontinued from study period due to withdrawal by subject.

One participant in the Dupilumab 300mg q2w group completed the study alive but died after completion of the end of the study. Death was not related to IMP per investigator and was not related to TEAE or post-treatment AE.

Note: percentages are calculated using the number of participants randomized as denominator

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/dis_dispo_r_t.sas OUT=REPORT/OUTPUT/dis_dispo_r_t_i.rtf (29APR2023 5:05)

Note: The study intervention period (also referred to as 52-week intervention period) corresponds to the period during which the participant was treated with the IMP. The study period corresponds to the entire study intervention and post-intervention follow-up periods. The 52-week study period corresponds to the period up to the Week 52/EOT visit, regardless of premature discontinuation of the study intervention.

Exposure

The mean (SD) duration of IMP exposure was 346.07 (66.55) and 340.78 (76.25) days for dupilumab and placebo, respectively. Cumulative exposure to dupilumab was 444 participant-years. Overall, a total of 469 participants were exposed to dupilumab of which 446 (95.1%) were exposed for >6 months (24 weeks) and 325 (69.3%) for >1 year (52 weeks).

Table 37 - Exposure to investigational product - Safety population

	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Cumulative duration to treatment exposure (participant years)	439	444
Duration of IMP exposure (days)		
Number	470	469
Mean (SD)	340.78 (76.25)	346.07 (66.55)
Median	365.00	365.00
Min ; Max	15.0 ; 392.0	15.0 ; 393.0
Duration of IMP exposure by category [n (%)]		
>0 and ≤2 weeks	0	0
>2 and ≤4 weeks	3 (0.6)	3 (0.6)
>4 and ≤8 weeks	9 (1.9)	5 (1.1)
>8 and ≤12 weeks	4 (0.9)	3 (0.6)
>12 and ≤16 weeks	8 (1.7)	5 (1.1)
>16 and ≤20 weeks	6 (1.3)	3 (0.6)
>20 and ≤24 weeks	2 (0.4)	4 (0.9)
>24 and ≤28 weeks	4 (0.9)	6 (1.3)
>28 and ≤32 weeks	0	3 (0.6)
>32 and ≤36 weeks	6 (1.3)	3 (0.6)
>36 and ≤40 weeks	4 (0.9)	3 (0.6)
>40 and ≤44 weeks	2 (0.4)	2 (0.4)
>44 and ≤48 weeks	4 (0.9)	2 (0.4)
>48 and ≤52 weeks	100 (21.3)	102 (21.7)
>52 weeks and ≤52 weeks + 3 days	274 (58.3)	285 (60.8)
>52 weeks + 3 days	44 (9.4)	40 (8.5)
Number of participants with duration of IMP exposure by category [n (%)]		
>0 week	470 (100)	469 (100)
>2 weeks	470 (100)	469 (100)
>4 weeks	467 (99.4)	466 (99.4)
>8 weeks	458 (97.4)	461 (98.3)
>12 weeks	454 (96.6)	458 (97.7)
>16 weeks	446 (94.9)	453 (96.6)
>20 weeks	440 (93.6)	450 (95.9)
>24 weeks	438 (93.2)	446 (95.1)
>28 weeks	434 (92.3)	440 (93.8)
>32 weeks	434 (92.3)	437 (93.2)
>36 weeks	428 (91.1)	434 (92.5)
>40 weeks	424 (90.2)	431 (91.9)
>44 weeks	422 (89.8)	429 (91.5)
>48 weeks	418 (88.9)	427 (91.0)
>52 weeks	318 (67.7)	325 (69.3)
>52 weeks + 3 days	44 (9.4)	40 (8.5)
Number of injections [n(%)]		
1 injection	3 (0.6)	3 (0.6)
2 injections	2 (0.4)	1 (0.2)
3 injections	5 (1.1)	4 (0.9)
4 injections	4 (0.9)	1 (0.2)
5 injections	3 (0.6)	2 (0.4)
6 injections	6 (1.3)	3 (0.6)
7 injections	0	2 (0.4)
8 injections	5 (1.1)	1 (0.2)

	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
9 injections	2 (0.4)	1 (0.2)
10 injections	0	5 (1.1)
11 injections	1 (0.2)	1 (0.2)
12 injections	2 (0.4)	3 (0.6)
13 injections	3 (0.6)	1 (0.2)
14 injections	0	2 (0.4)
15 injections	1 (0.2)	3 (0.6)
16 injections	0	2 (0.4)
17 injections	5 (1.1)	1 (0.2)
18 injections	4 (0.9)	1 (0.2)
19 injections	1 (0.2)	1 (0.2)
20 injections	2 (0.4)	1 (0.2)
21 injections	1 (0.2)	1 (0.2)
22 injections	8 (1.7)	3 (0.6)
23 injections	9 (1.9)	15 (3.2)
24 injections	24 (5.1)	17 (3.6)
25 injections	70 (14.9)	49 (10.4)
26 injections	308 (65.5)	345 (73.6)
27 injections	1 (0.2)	0

Note: participants are counted in a treatment group based on the treatment actually received.
PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/cdc_exposure_s_t.sas
OUT=REPORT/OUTPUT/cdc_exposure_s_t_i.rtf (21MAR2023 5:23)

Compliance to study and background intervention

Compliance to study intervention was high (⩾98.4%) in both intervention groups. Overdose was reported for 27 (5.8%) participants in the dupilumab group and 31 (6.6%) participants in the placebo group in the safety population. None of these participants experienced any symptoms associated with overdose.

Participants were required to remain on their standard of care background therapy for COPD (ICS+LABA+LAMA or LABA+LAMA if ICS contraindicated) throughout the study. Mean compliance to controller medications including those with ICS component, was high (>90% of days) in both intervention groups.

2.6.1.1. Demographics, Baseline Characteristics, Medical History

Demographics and Baseline Characteristics

Overall, demographic and baseline characteristics in the safety population were generally similar between the dupilumab and placebo groups (see Table 16 and Table 17, Section 2.5.2.1, Baseline data). The mean (SD) age of the randomized participants was 65.1 (8.1) years with a majority of the participants being ≥65 years of age. There were more males (66.0%) than females randomized in the study. Race representation included White (84.1%), Asian (14.3%), Black/of African descent (0.5%), and other races (1.1%). A majority of participants had a BMI <30 kg/m2 (70.6%). Participants were enrolled from East Europe (33.4%), followed by Western Countries (28.4%), Latin America (24.0%), and Asia (14.2%).

The mean age at onset of COPD (based on reported date of diagnosis) was 56.9 years. All participants had a history of smoking and approximately 30% were current smokers at study entry; the mean cigarette consumption was 40.48 pack-years and was similar between intervention groups.

Baseline COPD characteristics were similar between treatment groups, with an overall mean post BD FEV1/FVC ratio of 0.49. The mean % predicted post BD FEV1 was 50.60%. Overall, 47.7% of the participants had airflow limitation classified as moderate (GOLD grade 2; % predicted post BD FEV1

between ≥30% and <50%) and 47.1% had airflow limitation classified as severe (GOLD grade 3; % predicted post BD FEV1 between ≥30% and <50%). A total of 25 (2.7%) participants had airflow limitation classified as very severe (GOLD grade 4; % predicted post-BD FEV1 of <30%) at baseline. The mean pre-BD FEV1 was 1.30 L and mean % predicted pre-BD FEV1 was 47.09%.

The overall mean (SD) number of moderate or severe COPD exacerbations within the year prior to the study was 2.3 (1.0). A majority of the participants (59.6%) had 2 moderate COPD exacerbations within the year prior to the study and 25.9% of the participants had ≥1 severe COPD exacerbation.

Almost all the participants had COPD-related conditions including chronic bronchitis and/or emphysema, which were generally reported similarly between the 2 intervention groups. A total of 309 (32.9%) participants had a history of emphysema, which was ongoing at study entry for all but 3 of these 309 participants (32.6%).

Medical history and concurrent illnesses

Medical and surgical history was representative of a population with uncontrolled COPD and moderate to severe airflow limitation, which is associated with increased risk of comorbid conditions including cardiovascular diseases and metabolic disorders such as diabetes and osteoporosis. Apart from the SOC Respiratory, thoracic and mediastinal disorders, the most common SOCs (>20% of participants) in which a participant reported a medical or surgical history were Vascular disorders (60.6% of participants), Metabolism and nutrition disorders (52.3%), Surgical and medical procedures (37.5%), Musculoskeletal and connective tissue disorders (28.5%), Gastrointestinal disorders (28.9%), and Cardiac disorders (26.2%). The medical history profiles were generally similar between intervention groups, except for the following SOCs: Musculoskeletal and connective tissue disorders (dupilumab: 32.1%; placebo: 25.1%) mainly due to osteoarthritis and osteoporosis, and Surgical and medical procedures (dupilumab: 40.6%; placebo: 34.4%).

Apart from COPD, the most common preferred terms (PTs) (>10% of participants) reported for medical, or surgery history were hypertension (56.0% of participants), obesity (25.5%), and type 2 diabetes mellitus and gastroesophageal reflux disease (11.6%, each), that were all reported similarly in the 2 intervention groups.

A participant was considered to have a type 2 inflammatory disease history if he/she had or has any of the following diseases: nasal polyps, chronic sinusitis, atopic dermatitis, allergic conjunctivitis, allergic rhinitis, hives, food allergy, EoE, hypersensitivity to aspirin, or hypersensitivity to NSAID. Asthma was not included as a type 2 inflammatory disease, as participants with a current diagnosis or history of asthma were excluded per protocol (1 participant in the placebo group had an ongoing medical history of asthma and 1 participant in the dupilumab group had an ongoing medical history of asthma-COPD overlap syndrome, which were reported as major deviations to the protocol). The percentages of participants with a type 2 inflammatory disease history were well balanced between the 2 intervention groups. Approximately 22% of participants had a history of at least 1 other type 2 inflammatory disease, with allergic rhinitis being the most frequent (13.0%) (Table 38).

Comorbid medical history was generally consistent between participants taking high doses of ICS and those taking non high ICS doses.

Table 38 - COPD-related comorbid history and type 2 disease history - Randomized population

n (%)	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Any COPD related history[a, c]	457 (97.0)	444 (94.9)	901 (96.0)
Chronic bronchitis history	451 (95.8)	441 (94.2)	892 (95.0)
Ongoing	438 (93.0)	437 (93.4)	875 (93.2)

n (%)	Placebo (N=471)	Dupilumab 300 mg q2w (N=468)	All (N=939)
Emphysema history	153 (32.5)	156 (33.3)	309 (32.9)
Ongoing	151 (32.1)	155 (33.1)	306 (32.6)
Bronchiectasis history	2 (0.4)	7 (1.5)	9 (1.0)
Ongoing	0	6 (1.3)	6 (0.6)
Any type 2 disease history[b, c]	96 (20.4)	109 (23.3)	205 (21.8)
Allergic rhinitis history	54 (11.5)	68 (14.5)	122 (13.0)
Ongoing	51 (10.8)	68 (14.5)	119 (12.7)
Chronic sinusitis history	17 (3.6)	19 (4.1)	36 (3.8)
Ongoing	16 (3.4)	19 (4.1)	35 (3.7)
Nasal polyps history	11 (2.3)	19 (4.1)	30 (3.2)
Ongoing	10 (2.1)	12 (2.6)	22 (2.3)
Food allergy history	13 (2.8)	11 (2.4)	24 (2.6)
Ongoing	12 (2.5)	11 (2.4)	23 (2.4)
Atopic dermatitis history	5 (1.1)	11 (2.4)	16 (1.7)
Ongoing	5 (1.1)	10 (2.1)	15 (1.6)
Hives history	6 (1.3)	5 (1.1)	11 (1.2)
Ongoing	6 (1.3)	2 (0.4)	8 (0.9)
Hypersensitivity to NSAID history	3 (0.6)	7 (1.5)	10 (1.1)
Ongoing	3 (0.6)	7 (1.5)	10 (1.1)
Allergic conjunctivitis history	4 (0.8)	5 (1.1)	9 (1.0)
Ongoing	4 (0.8)	5 (1.1)	9 (1.0)
Hypersensitivity to aspirin history	3 (0.6)	3 (0.6)	6 (0.6)
Ongoing	3 (0.6)	3 (0.6)	6 (0.6)
Eosinophilic esophagitis history	1 (0.2)	0	1 (0.1)
Ongoing	1 (0.2)	0	1 (0.1)

NSAID: Nonsteroidal Anti-inflammatory Drug

a A participant is considered with comorbidity history or ongoing comorbid disease related to COPD if the participant had or has any of the following diseases: emphysema, chronic bronchitis, bronchiectasis.

b A participant will be considered with comorbidity history or ongoing comorbid disease not related to COPD if the participant had or has any of the following diseases: nasal polyps, chronic sinusitis, atopic dermatitis, allergic conjunctivitis, allergic rhinitis, hives, food allergy, eosinophillic esophagitis, hypersensitivity to aspirin, hypersensitivity to NSAID.

c Medical or surgical history other than disease being treated in this study as pre-defined in eCRF

n (%) = number and percentage of participants with at least one medical or surgical history. A participant can be counted in several categories. Events are sorted by decreasing frequency based on incidence in the overall intervention group

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/dem medhis preprint r t.sas
OUT=REPORT/OUTPUT/dem_medhis_preprint_r_t_i.rtf (21MAR2023 4:15)

Adverse events

Overall summary of treatment emergent adverse events

The percentage of participants who had at least 1 TEAE was 77.4% and 76.0% in the dupilumab and placebo group, respectively. Severe TEAEs were reported in 10.2% (dupilumab) and 11.7% (placebo) of

participants. Treatment-emergent SAEs occurred in 13.6% (dupilumab) and 15.5% (placebo) of participants. Deaths were reported for 7 (1.5%) participants in the dupilumab group and 8 (1.7%) participants in the placebo group.

When adjusted by exposure, the numbers of participants with at least 1 TEAE per 100 PY was 146.0 in the dupilumab group and 153.0 in the placebo group.

Table 39 - Overview of adverse event profile: Treatment-emergent adverse events - Safety population

n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Participants with any TEAE	357 (76.0)	363 (77.4)
Participants with any severe TEAE	55 (11.7)	48 (10.2)
Participants with any treatment emergent SAE	73 (15.5)	64 (13.6)
Participants with any TEAE leading to death	8 (1.7)	7 (1.5)
Participants with any TEAE leading to permanent study intervention discontinuation	16 (3.4)	14 (3.0)
Participants with any treatment emergent AESI	43 (9.1)	40 (8.5)
Participants with any treatment emergent other selected AE	20 (4.3)	26 (5.5)
Participants with any TEAE related to IMP	18 (3.8)	35 (7.5)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, IMP: Investigational medicinal product, AESI: adverse event of special interest

n (%) = number and percentage of participants with at least one TEAE

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/ae_overview_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_s_t_i.rtf (07JUL2023 4:29)

The most frequently reported TEAEs by SOC were Infections and infestations (dupilumab: 43.7%; placebo: 48.3%), Gastrointestinal disorders (dupilumab: 17.3%; placebo: 14.9%), and Respiratory, thoracic, and mediastinal disorders (dupilumab: 16.0%; placebo: 17.0%).

The incidence of TEAEs at the SOC level was generally similar in the dupilumab and the placebo groups, with the exception of the following SOCs (≥5% in either intervention group) for which TEAEs were more frequently reported (≥1% difference) in the dupilumab group than in the placebo group:

- Gastrointestinal disorders (17.3% versus 14.9%); the imbalance was mainly driven by the PTs of diarrhea (5.3% versus 3.6%), toothache (2.6% versus 1.1%), and gastritis (2.3% versus 0.4%).
- Musculoskeletal and connective tissue disorders (14.7% versus 13.2%); the imbalance was mainly driven by the HLGT of Muscle disorders (3.0% versus 1.1%) and HLGT of Musculoskeletal and connective tissue disorders NEC (8.5% versus 6.4%). At the PT level, back pain was reported more frequently with dupilumab than with placebo (5.1% versus 3.4%).
- General disorders and administration site conditions (9.6% versus 6.0%); the imbalance was mainly driven by the HLT of injection site reactions (3.0% versus 0.4%). At the PT level, injection site reaction was also reported more frequently with dupilumab than with placebo (1.5% versus 0.4%).

By contrast, the SOCs (≥5% in either intervention group) with TEAEs less frequently reported (≥1% difference) in the dupilumab group compared to placebo were Infections and infestations (43.7% versus 48.3%), Respiratory, thoracic, and mediastinal disorders (16.0% versus 17.0%), Injury, poisoning and procedural complications (13.6% versus 16.4%), Vascular disorders (7.0% versus 9.6%), Cardiac disorders (7.0% versus 8.5%), Metabolism and nutrition disorders (6.2% versus 7.2%), and Investigations (5.3% versus 6.6%).

At the PT level, the following TEAEs were more frequently reported in the dupilumab group as compared to the placebo group (≥2% in the dupilumab group and a difference of ≥1% versus the placebo group):

- Headache (8.1% vs. 6.8%)

- Diarrhea (5.3% vs. 3.6%)
- Back pain (5.1% vs. 3.4%)
- Urinary tract infection (4.9% vs. 2.1%)
- Toothache (2.6% vs. 1.1%)
- Gastritis (2.3% vs. 0.4%)

TEAEs that were reported with a lower frequency in the dupilumab group as compared to the placebo group were:

- Upper respiratory tract infection (7.9% vs. 9.8%)
- Hypertension (3.6% vs. 6.0%)
- COVID 19 (4.1% vs. 5.7%)
- Pneumonia (2.8% vs. 4.0%)
- Lower respiratory tract infection (1.3% vs. 2.3%)
- Gastroenteritis (1.1% vs. 2.3%)

At the time of the submission of the extension of indication application, 63 participants were still ongoing in the 12-week follow up period of study EFC15804. During the procedure, the MAH provided updated safety data including new data that was obtained after 08-Feb-2023 (Table 40). Overall, no new safety concerns were identified in Study EFC15804 from the additional safety data collected after the cut-off date of the main CSR.

Table 40 - Overview of adverse event profile: New treatment-emergent adverse events reported after the core database lock – Safety population

n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Participants with any TEAE	5 (1.1)	6 (1.3)
Participants with any severe TEAE	1 (0.2)	1 (0.2)
Participants with any treatment emergent SAE	1 (0.2)	1 (0.2)
Participants with any TEAE leading to death	0	1 (0.2)
Participants with any TEAE leading to permanent study intervention discontinuation	0	0
Participants with any treatment emergent AESI	1 (0.2)	1 (0.2)
Participants with any treatment emergent other selected AE	0	0
Participants with any TEAE related to IMP	0	0

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, IMP: Investigational medicinal product, AESI: adverse event of special interest

n (%) = number and percentage of participants with at least one TEAE

PGM=PRODOPS/SAR231893/EFC15804/CSR_2/REPORT/PGM/ae_overview_s_t.sas

OUT=REPORT/OUTPUT/ae_overview_new_s_t_i.rtf (10OCT2023 5:35)

Table 41 - Number (%) of participants with TEAE(s) that occurred with a frequency >=2% in any treatment group by Primary SOC and PT - Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Any Class	357 (76.0)	363 (77.4)
INFECTIONS AND INFESTATIONS	227 (48.3)	205 (43.7)
Nasopharyngitis	45 (9.6)	44 (9.4)
Upper respiratory tract infection	46 (9.8)	37 (7.9)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Urinary tract infection	10 (2.1)	23 (4.9)
Bronchitis	22 (4.7)	19 (4.1)
COVID-19	27 (5.7)	19 (4.1)
Pneumonia	19 (4.0)	13 (2.8)
Rhinitis	12 (2.6)	9 (1.9)
Lower respiratory tract infection	11 (2.3)	6 (1.3)
Gastroenteritis	11 (2.3)	5 (1.1)
NERVOUS SYSTEM DISORDERS	60 (12.8)	61 (13.0)
Headache	32 (6.8)	38 (8.1)
VASCULAR DISORDERS	45 (9.6)	33 (7.0)
Hypertension	28 (6.0)	17 (3.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	80 (17.0)	75 (16.0)
Chronic obstructive pulmonary disease	28 (6.0)	27 (5.8)
GASTROINTESTINAL DISORDERS	70 (14.9)	81 (17.3)
Diarrhoea	17 (3.6)	25 (5.3)
Toothache	5 (1.1)	12 (2.6)
Gastritis	2 (0.4)	11 (2.3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	62 (13.2)	69 (14.7)
Back pain	16 (3.4)	24 (5.1)
Arthralgia	12 (2.6)	12 (2.6)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	77 (16.4)	64 (13.6)
Accidental overdose	30 (6.4)	26 (5.5)
Fall	10 (2.1)	6 (1.3)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 25.1
n (%) = number and percentage of participants with at least one TEAE
Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group
Only PTs with at least one 2% in at least one group are presented
PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/ae_socpt_s_t.sas OUT=REPORT/OUTPUT/ae_socpt_freq2_s_t_i.rtf (17APR2023 4:49)

Treatment-emergent adverse events by Investigator causality assessment

The percentage of participants with TEAEs assessed by the Investigator as related to IMP was higher with dupilumab than with placebo (dupilumab: 7.5%; placebo: 3.8%). The difference was primarily driven by TEAEs in the HLT Injection site reactions (dupilumab: 3.0%; placebo: 0.4%). The SOCs that had the highest proportion of participants with IMP-related TEAEs were General disorders and administration site conditions (dupilumab: 4.1%; placebo: 0.6%) followed by Investigations (1.3% in each intervention group). At the PT level, the most frequently reported IMP-related TEAE was injection site reaction (dupilumab: 1.5%; placebo: 0.4%). Most IMP related TEAEs were reported in 1 participant in either intervention group.

Serious adverse event/deaths/other significant events

Serious adverse events

Treatment-emergent SAEs were reported in 13.6% (dupilumab) and 15.5% (placebo) of participants. The SOCs with the highest proportion of participants with treatment emergent SAEs (≥2% in either

intervention group) were Respiratory, thoracic and mediastinal disorders (dupilumab: 6.4%; placebo: 6.8%), Infections and infestations (dupilumab: 4.1%; placebo: 5.5%), and Cardiac disorders (dupilumab: 1.9%; placebo: 2.6%). Worsening of COPD condition was not considered an AE unless it met seriousness criteria. Treatment-emergent SAEs of chronic obstructive pulmonary disease (acute exacerbation of COPD) were reported with similar incidence in both intervention groups (dupilumab: 5.8% of participants; placebo: 5.5% of participants). At the PT level, apart from COPD, the most frequently reported treatment-emergent SAE was pneumonia reported less frequently with dupilumab than with placebo (dupilumab: 1.1%; placebo: 2.6%).

Most of all treatment-emergent SAEs were assessed as by the investigator as non-related to the IMP with the exception of 2 SEAs, both in the dupilumab group. One participant experienced a treatment emergent SAE of **rhabdomyolysis** that led to permanent discontinuation of the study intervention.

Other concomitant medications including amlodipine, rosuvastatin, theophylline and telmisartan, started about 2 years prior to study entry, were also discontinued the same day and were not reintroduced since causality of these drugs in rhabdomyolysis could not be ruled out. The participant recovered with corrective treatment.

Another participant experienced 2 treatment emergent SAEs of **pneumonia** (approximately 3 months apart) involving both lungs with concomitant acute exacerbation of COPD. Dupilumab was temporarily discontinued in both cases. The participant recovered with corrective treatment.

Treatment emergent SAEs led to permanent discontinuation of the study intervention in 9 participants in the dupilumab group and 13 participants in the placebo group. Apart from the SAE of rhabdomyolysis, none of these events were assessed by the Investigator as related to the IMP and the events were mostly from the SOC Neoplasms benign, malignant, and unspecified (including cysts and polyps) (dupilumab: 6; placebo: 4). Four participants in the dupilumab group and 7 participants in the placebo group had a fatal outcome as described further below. Other events included acute myocardial infarction, chronic respiratory failure, pneumonia, and cancers (lung neoplasm malignant, invasive ductal breast carcinoma, and pancreatic carcinoma metastatic).

Table 42 - Number (%) of participants with treatment emergent SAEs by Primary SOC and PT - Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Any Class	73 (15.5)	64 (13.6)
INFECTIONS AND INFESTATIONS	26 (5.5)	19 (4.1)
Pneumonia	12 (2.6)	5 (1.1)
COVID-19	4 (0.9)	3 (0.6)
Lower respiratory tract infection	2 (0.4)	3 (0.6)
COVID-19 pneumonia	5 (1.1)	2 (0.4)
Abdominal wall abscess	0	1 (0.2)
Bronchopulmonary aspergillosis	0	1 (0.2)
Cholecystitis infective	0	1 (0.2)
Epiglottitis	0	1 (0.2)
Herpes zoster	0	1 (0.2)
Pulmonary tuberculosis	0	1 (0.2)
Respiratory tract infection	0	1 (0.2)
Upper respiratory tract infection	0	1 (0.2)
Urinary tract infection	1 (0.2)	1 (0.2)
Appendicitis	1 (0.2)	0
Bronchitis bacterial	1 (0.2)	0
Influenza	1 (0.2)	0
Pneumonia bacterial	1 (0.2)	0
Pneumonia pneumococcal	2 (0.4)	0

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Septic shock	1 (0.2)	0
Subcutaneous abscess	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	7 (1.5)	7 (1.5)
Bladder transitional cell carcinoma	0	1 (0.2)
Glioblastoma	0	1 (0.2)
Lung carcinoma cell type unspecified stage IV	0	1 (0.2)
Lung neoplasm	0	1 (0.2)
Lung neoplasm malignant	1 (0.2)	1 (0.2)
Rectal cancer	0	1 (0.2)
Squamous cell carcinoma of lung	0	1 (0.2)
Ductal adenocarcinoma of pancreas	1 (0.2)	0
Invasive ductal breast carcinoma	1 (0.2)	0
Lung adenocarcinoma	1 (0.2)	0
Pancreatic carcinoma metastatic	1 (0.2)	0
Prostate cancer	1 (0.2)	0
Squamous cell carcinoma of skin	1 (0.2)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.2)	2 (0.4)
Anaemia	0	1 (0.2)
Polycythaemia	0	1 (0.2)
Blood loss anaemia	1 (0.2)	0
IMMUNE SYSTEM DISORDERS	1 (0.2)	1 (0.2)
Hypersensitivity	0	1 (0.2)
Anaphylactic reaction	1 (0.2)	0
ENDOCRINE DISORDERS	1 (0.2)	0
Hyperparathyroidism	1 (0.2)	0
METABOLISM AND NUTRITION DISORDERS	3 (0.6)	1 (0.2)
Diabetes mellitus inadequate control	0	1 (0.2)
Hypokalaemia	1 (0.2)	0
Hyponatraemia	1 (0.2)	0
Type 2 diabetes mellitus	1 (0.2)	0
PSYCHIATRIC DISORDERS	1 (0.2)	0
Psychotic disorder	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	6 (1.3)	5 (1.1)
Cerebral haemorrhage	0	2 (0.4)
Generalised tonic-clonic seizure	0	1 (0.2)
Ischaemic stroke	2 (0.4)	1 (0.2)
Syncope	0	1 (0.2)
Basal ganglia haemorrhage	1 (0.2)	0
Cerebral infarction	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	0
Presyncope	1 (0.2)	0
Transient ischaemic attack	1 (0.2)	0
CARDIAC DISORDERS	12 (2.6)	9 (1.9)
Cardiac failure	2 (0.4)	2 (0.4)
Coronary artery disease	1 (0.2)	2 (0.4)
Acute coronary syndrome	0	1 (0.2)
Acute myocardial infarction	2 (0.4)	1 (0.2)
Atrial fibrillation	1 (0.2)	1 (0.2)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Atrioventricular block second degree	0	1 (0.2)
Nodal rhythm	0	1 (0.2)
Angina unstable	1 (0.2)	0
Arrhythmia	1 (0.2)	0
Atrioventricular block complete	1 (0.2)	0
Cardiac failure congestive	2 (0.4)	0
Cor pulmonale acute	1 (0.2)	0
Myocardial infarction	1 (0.2)	0
Tachycardia	1 (0.2)	0
VASCULAR DISORDERS	3 (0.6)	1 (0.2)
Hypertensive crisis	0	1 (0.2)
Deep vein thrombosis	1 (0.2)	0
Hypertensive emergency	1 (0.2)	0
Peripheral artery occlusion	1 (0.2)	0
Peripheral vascular disorder	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	32 (6.8)	30 (6.4)
Chronic obstructive pulmonary disease	26 (5.5)	27 (5.8)
Acute pulmonary oedema	0	1 (0.2)
Acute respiratory failure	2 (0.4)	1 (0.2)
Atelectasis	0	1 (0.2)
Pneumothorax	1 (0.2)	1 (0.2)
Respiratory failure	3 (0.6)	1 (0.2)
Acute respiratory distress syndrome	1 (0.2)	0
Bronchospasm	1 (0.2)	0
Chronic respiratory failure	1 (0.2)	0
Pneumothorax spontaneous	1 (0.2)	0
Pulmonary oedema	1 (0.2)	0
GASTROINTESTINAL DISORDERS	4 (0.9)	5 (1.1)
Colitis	0	1 (0.2)
Intestinal polyp	0	1 (0.2)
Pancreatitis acute	0	1 (0.2)
Umbilical hernia	0	1 (0.2)
Upper gastrointestinal haemorrhage	0	1 (0.2)
Abdominal pain	1 (0.2)	0
Gastritis	1 (0.2)	0
Intestinal ischaemia	1 (0.2)	0
Pancreatitis	1 (0.2)	0
Rectal haemorrhage	1 (0.2)	0
HEPATOBILIARY DISORDERS	2 (0.4)	3 (0.6)
Cholecystitis	0	1 (0.2)
Cholecystitis acute	0	1 (0.2)
Cholelithiasis	0	1 (0.2)
Hepatic failure	0	1 (0.2)
Hepatorenal syndrome	0	1 (0.2)
Bile duct stone	1 (0.2)	0
Hepatic function abnormal	1 (0.2)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0	1 (0.2)
Rhabdomyolysis	0	1 (0.2)
RENAL AND URINARY DISORDERS	3 (0.6)	3 (0.6)
Chronic kidney disease	0	1 (0.2)
Haematuria	0	1 (0.2)
Renal failure	0	1 (0.2)

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Acute kidney injury	1 (0.2)	0
Glomerulonephritis	1 (0.2)	0
Nephritis	1 (0.2)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	1 (0.2)	0
Ovarian cyst	1 (0.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.4)	2 (0.4)
Chest pain	0	1 (0.2)
Pyrexia	1 (0.2)	1 (0.2)
Sudden cardiac death	1 (0.2)	0
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	6 (1.3)	4 (0.9)
Ankle fracture	0	1 (0.2)
Fibula fracture	1 (0.2)	1 (0.2)
Head injury	0	1 (0.2)
Pneumothorax traumatic	1 (0.2)	1 (0.2)
Road traffic accident	0	1 (0.2)
Skin abrasion	0	1 (0.2)
Tibia fracture	1 (0.2)	1 (0.2)
Femoral neck fracture	1 (0.2)	0
Femur fracture	1 (0.2)	0
Rib fracture	2 (0.4)	0
Spinal compression fracture	1 (0.2)	0

SAE: Serious adverse event, SOC: System organ class, PT: Preferred term

MedDRA 25.1

n (%) = number and percentage of participants with at least one treatment emergent SAE

Note: Table sorted by SOC internationally agreed order and decreasing percentage of PT in dupilumab 300 mg q2w group

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/ae_socpt_s_t.sas OUT=REPORT/OUTPUT/ae_socpt_sae_s_t_i.rtf (17APR2023 4:50)

Deaths

Main safety population (Study EFC15804)

A total of 16 deaths were reported during study EFC15804 until the study completion date (08 February 2023). 15 were due to TEAEs with fatal outcome (dupilumab: 7; placebo: 8) and 1 (dupilumab group) was due to a post treatment AE with fatal outcome. Of the 16 deaths, 11 occurred during the treatment period and 5 occurred during the post-treatment period (including 4 deaths due to TEAEs and 1 death due to a post treatment AE). All TEAEs leading to death were adjudicated by an external independent blinded committee to determine if these were CV deaths. None of the TEAEs leading to death were assessed by the Investigator as related to the IMP.

Table 43 - Number (%) of participants who died by study period - Safety population

n (%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Death on-study[a]	8 (1.7)	8 (1.7)
Death occurred during the TEAE period[b]	7 (1.5)	4 (0.9)
Death occurred during post-treatment period[c]	1 (0.2)	4 (0.9)
TEAE leading to death in the post-treatment period	1 (0.2)	3 (0.6)
Post-treatment AE leading to death in the post-treatment period	0	1 (0.2)

IMP: Investigational medicinal product, TEAE: Treatment emergent adverse event

a Includes all deaths that occurred after the start of treatment up to end of study (defined as last protocol planned visit or the resolution/stabilization of all treatment emergent SAE and adverse event of pre-specified monitoring).

b Includes all deaths that occurred after the start of treatment up to last IMP date + 98 days.

n (%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)

c Includes all deaths that occurred after the last IMP date + 98 days.

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/ae_deathbyphase_s_t.sas
OUT=REPORT/OUTPUT/ae_deathbyphase_s_t_i.rtf (21MAR2023 7:01)

Table 44 - Number (%) of participants with TEAE(s) leading to death (death as an outcome of the AE as reported by the Investigator in the AE page) by Primary SOC and PT - Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Any Class	8 (1.7)	7 (1.5)
INFECTIONS AND INFESTATIONS	3 (0.6)	1 (0.2)
COVID-19	0	1 (0.2)
COVID-19 pneumonia	2 (0.4)	0
Septic shock	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	1 (0.2)	4 (0.9)
Bladder transitional cell carcinoma	0	1 (0.2)
Lung carcinoma cell type unspecified stage IV	0	1 (0.2)
Lung neoplasm	0	1 (0.2)
Lung neoplasm malignant	0	1 (0.2)
Lung adenocarcinoma	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	0	1 (0.2)
Cerebral haemorrhage	0	1 (0.2)
CARDIAC DISORDERS	3 (0.6)	0
Arrhythmia	1 (0.2)	0
Cardiac failure congestive	1 (0.2)	0
Tachycardia	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.2)	1 (0.2)
Acute respiratory failure	0	1 (0.2)
Respiratory failure	1 (0.2)	0
RENAL AND URINARY DISORDERS	1 (0.2)	0
Acute kidney injury	1 (0.2)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (0.2)	0
Sudden cardiac death	1 (0.2)	0

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 25.1
n (%) = number and percentage of participants with at least one TEAE leading to death; death is per investigator
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency in dupilumab 300 mg q2w group
PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/ae_socpt_s_t.sas
OUT=REPORT/OUTPUT/ae_socpt_death_s_t_i.rtf (17APR2023 4:50)

Death events were grouped by cause as presented above (cause by infection, cancer, cardiovascular reasons, and other). All TEAEs leading to death were adjudicated by an external independent blinded committee to determine if these were CV deaths.

Death due to infections

Four participants (1 in the dupilumab group and 3 in the placebo group) died due to infections during the study. One death event in the placebo group was adjudicated as a CV death (see #16 below).

Dupilumab group:

1) A male participant (<65 years old) with an ongoing medical history of chronic bronchitis and emphysema, experienced a treatment emergent SAE of **COVID-19** on Day 364 (ie, 13 days after the last IMP dose), which led to death the following day.

Placebo group:

2/3) Two male participants (>65 years old) with an ongoing history of chronic bronchitis, experienced a treatment emergent SAE of **COVID-19 pneumonia** finally leading to death.

The enrolled COPD population has an increased risk to develop a severe COVID-19 infection. The study was conducted within the onset and peak phase of the COVID-19 pandemic and respective protocol measures (e.g. home visits) were implemented in the study protocol together with the public health measures (masks, social distancing) as well as COVID-19 vaccination upon availability to protect the vulnerable study participants.

Only, 3 participants (dupilumab: 1; placebo 2) died due to COVID-19 infections potentially reflecting the effectiveness of the protective measures.

Death due to cancer

Five participants (4 in the dupilumab group and 1 in the placebo group) died due to cancer; the majority of the cancers (4 of them) were lung cancer. All 5 participants were former or current smokers.

Dupilumab group:

4) A male participant (>65 years old) former smoker with a smoking history of 90 pack-years, with an ongoing medical history of chronic bronchitis, experienced a treatment emergent SAE of **bladder transitional cell carcinoma** on Day 99 (ie, the day of the 8th IMP dose), which led to death on Day 654.

5) A male participant (>65 years old), former smoker with a smoking history of 23 pack-years, experienced a treatment emergent SAE of **lung carcinoma cell type unspecified stage IV** on Day 161 (i.e., 3 days after the 10th IMP dose), which led to death on Day 322. The case was adjudicated as a non-CV death.

6) A female participant (>65 years old), former smoker with a smoking history of 39 pack-years, occupational exposure to chemical fumes, with an ongoing medical history of chronic bronchitis and emphysema, experienced a treatment emergent SAE of **lung neoplasm** on Day 343 (ie, 4 days after the 24th IMP dose), which led to death on Day 471.

7) A male participant (>65 years old), current smoker with a smoking history of 75 pack-years, with an ongoing medical history of chronic bronchitis, experienced a treatment emergent SAE of **lung neoplasm malignant** on Day 154 (i.e., 13 days after the 11th IMP dose), which led to death on Day 166. The case was adjudicated as a non-CV death due to end stage lung cancer with liver metastases.

Placebo group:

8) A male participant (<65 years old), current smoker with ongoing medical history of chronic bronchitis and with benign lung neoplasm for 2 years, experienced a treatment emergent SAE of **lung adenocarcinoma** leading to death.

Only 1 participant in the placebo group experienced death due to malignancies while this was the case for 4 participants in the dupilumab group. Given the so far known risk profile of dupilumab from other indications, there are no signs for an increased risk for malignancies.

Cardiovascular death (adjudicated)

All TEAEs leading to death were adjudicated by an external independent blinded committee to determine if these were CV deaths. Four cases (1 in the dupilumab group and 3 in the placebo group) were adjudicated as CV deaths. All participants with adjudicated CV deaths had comorbid cardiopulmonary conditions and or noted with confounding factors.

Dupilumab group:

9) A male participant (>65 years old) experienced a treatment emergent SAE of **cerebral hemorrhage** on Day 196 (ie, 1 day after the 15th IMP dose), which led to death on Day 239. The case was adjudicated as a CV death due to hemorrhagic stroke. The participant had a medical history of tachycardia treated with metoprolol, a smoking history of 22.5 pack years, and elevated blood pressure 1 day prior to the event, which might be possible confounding factors.

Placebo group:

10) A male participant (<65 years old) with an ongoing medical history of chronic bronchitis and emphysema, experienced treatment emergent SAEs of **arrhythmia** and acute kidney injury on Day 50 (ie, 7 days after the 4th IMP dose), which led to death on Day 57.

11) A male participant (>65 years old) with an ongoing medical history of chronic bronchitis experienced treatment emergent SAEs of respiratory failure and **cardiac failure congestive**, on Day 262 (ie, 23 days after the 17th IMP), which led to death on Day 263.

12) A female participant (>65 years old) with an ongoing medical history of chronic bronchitis experienced intestinal ischemia resulting in a treatment emergent SAE of **septic shock** on Day 53 (i.e., 14 days after the 4th IMP dose), and which led to death on Day 56. The event was adjudicated as a CV death (other CV death with ischemic and gangrenous colon leading to septic shock and death).

Other reasons for death

Other cases of deaths consisted of the following (1 in the dupilumab group and 2 in the placebo group):

Dupilumab group:

13) In the dupilumab group, a male participant (<65 years old) with an ongoing medical history of chronic bronchitis and emphysema, experienced a treatment emergent SAE of **acute respiratory failure** on Day 273 (ie, 20 days after the 18th IMP dose), which led to death on the same day. The IMP had been permanently discontinued prior to the emergence of the SAE by the Investigator's decision as the study participant's health was deteriorating due to progressive disease.

Placebo group:

14) In the placebo group, a male participant (>65 years old) with an ongoing medical history of chronic bronchitis and comorbid cardiovascular conditions, experienced a treatment emergent SAE of sudden cardiac death on Day 232 (ie, 8 days after the 17th IMP dose). The case was adjudicated as a non-CV death and the cause of death attributed to acute respiratory failure occurring 1.5 months after COVID-19 pneumonia.

15) In the placebo group, a female participant (>65 years old) with an ongoing medical history of chronic bronchitis, experienced a treatment emergent SAE of tachycardia on Day 100 (ie, day of the 8th IMP dose), which led to death on the same day. The case was adjudicated as a non-CV death. The rational

provided by the adjudicator was that in a context of dyspnea history and hypoxia /hypercarbia, the primary cause of death was respiratory failure and abnormality in gas exchange, with secondary wide complex tachycardia > 200/min; negative troponin essentially ruled out MI as the cause of death; primary ventricular arrhythmia as cause of respiratory arrest was assessed as much less likely.

16) One additional participant in the dupilumab group experienced a post-treatment AE of cardiogenic shock leading to death during the on-study period; the event was assessed by the Investigator as not related to the IMP.

Supportive safety population

Study EFC15804 post-intervention follow-up period

From the primary study completion date (08 February 2023) to 31 May 2023, 3 new deaths were reported in Study EFC15804, 2 in the dupilumab group (metastatic gastric cancer; pneumoniae/acute respiratory failure) and 1 in the placebo group (pancreatic adenocarcinoma metastatic). None of the deaths were assessed by the Investigator as related to the IMP.

Study EFC15805

During the period from 14 January 2023 (cut-off date for the most recent application in the US [AD hand and foot application]) to 31 May 2023, 1 new death (PT: sudden death, verbatim: "cardiovascular failure") was reported in the ongoing Phase 3 Study EFC15805 in participants with COPD; the event was assessed by the Investigator as not related to the IMP. The male participant (>65 years old) on blinded IMP, former smoker, had an ongoing medical history of emphysema and chronic bronchitis. The primary cause of death was reported as sudden death possibly related to heart rhythm disorder and the secondary cause of death was reported as COPD.

Studies in other indications

During the period from 14 January 2023 to 31 May 2023, no new deaths and no new SUSARs were reported in the ongoing clinical studies conducted in other dupilumab indications.

2.6.1.2. Adverse events of special interest and other selected AE groupings

Adverse events of special interest and other selected AE groupings were searched in the database using predefined search criteria, in addition, a medical review was conducted for specific AESIs. A summary of the number (%) of participants with treatment-emergent AESIs or events in other selected AE groupings for the safety population is provided by category and PT in Table 45. There were no reports of parasitic infections, pregnancies, symptomatic overdoses, clinically symptomatic eosinophilia, severe conjunctivitis, severe blepharitis or helminthic infections reported during the study. Descriptions of treatment-emergent AESIs or events in other selected AE groupings is provided in the following.

Table 45 - Number (%) of participants with treatment emergent AESIs and other selected AE grouping events by category - Safety population

Category n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Any treatment emergent AESI	43 (9.1)	40 (8.5)
Systemic hypersensitivity reactions (medically reviewed)	2 (0.4)	2 (0.4)
Anaphylactic reactions (medically reviewed)	1 (0.2)	0
Severe injection site reactions that last longer than 24 hours	0	1 (0.2)
AESI infections	39 (8.3)	37 (7.9)
Serious infections	26 (5.5)	19 (4.1)
Parasitic infections	0	0
Infection requires parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy	30 (6.4)	29 (6.2)
Infection requires oral antimicrobial therapy for longer than 2 weeks	11 (2.3)	6 (1.3)
Opportunistic infection	2 (0.4)	4 (0.9)
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	0	0
Symptomatic overdose with IMP	0	0
Symptomatic overdose with NIMP	0	0
Clinically symptomatic eosinophilia (medically reviewed)	0	0
Any severe type of conjunctivitis	0	0
Any severe type of blepharitis	0	0
Keratitis	0	0
Significant ALT elevation	2 (0.4)	0
Other selected AEs	20 (4.3)	26 (5.5)
Injection site reaction	2 (0.4)	14 (3.0)
Malignancy	9 (1.9)	8 (1.7)
Conjunctivitis (narrow)	7 (1.5)	4 (0.9)
Conjunctivitis (broad)	9 (1.9)	5 (1.1)
Conjunctivitis (FDA)[a]	7 (1.5)	4 (0.9)
Helminthic infections	0	0

AESI: Adverse event of special interest

MedDRA 25.1

a Labeling subgroup of preferred terms included in the USPI for Dupixent.

n (%) = number and percentage of participants with at least one treatment emergent AESI/other AE grouping event

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Adverse events of special interest and other selected AEs of interest including anaphylactic reactions, hypersensitivity and different infections (e.g. *conjunctivitis, blepharitis, keratitis, herpes*) were evaluated. Numbers of treatment emergent adverse events of special interest were balanced with 40 (8.5%) events occurring in the dupilumab group and 43 (9.1%) events in the placebo group, respectively.

Systemic hypersensitivity reactions (medically reviewed)

Treatment emergent systemic hypersensitivity reactions that were confirmed after medical review were reported in 4 participants, 2 [0.4%] in each intervention group. The rate of systemic hypersensitivity reactions was low in both groups. Two of these events, 1 in each intervention group, were assessed as serious. In the dupilumab group, the SAE, a hypersensitivity due to a bee sting, was assessed by the Investigator as not related to IMP. The event resolved with corrective treatment and did not lead to permanent discontinuation of the study intervention. In the placebo group, the SAE was an anaphylactic reaction (see description below). One event, in the dupilumab group, an urticaria of mild intensity, was assessed by the Investigator as related to the IMP and resulted in permanent discontinuation of the study

intervention; the event of urticaria resolved with corrective treatment. The remaining event, in the placebo group (dermatitis allergic reported as adverse reaction to ciprofloxacin), was assessed as nonserious and not related to the IMP and did not lead to permanent discontinuation of the study intervention. All 4 participants were ADA negative.

Anaphylactic reactions (medically reviewed)

Anaphylactic reaction attributed to diclofenac was reported in 1 participant in the placebo group. The event was assessed by the Investigator as serious, severe in intensity and not related to the IMP. There was no action taken with the IMP and the participant recovered with corrective treatment.

Injection site reactions HLT (other selected AE groupings)

Treatment emergent injection site reactions (HLT) were reported in a higher proportion of participants in the dupilumab group as compared to the placebo group. In total, 65 events were reported in 14 (3.0%) participants in the dupilumab group and 24 events in 2 (0.4%) participants in the placebo group. All the injection site reactions in both intervention groups were assessed by the Investigator as related to the IMP. None of the injection site reactions were assessed as serious. One event, in the dupilumab group, met the AESI criterion of severe injection site reaction that last longer than 24 hours, and led to permanent discontinuation of the study intervention (see description below). Two participants, both in the dupilumab group, including the participant with the severe injection site reaction, were ADA-positive. Most of the participants (dupilumab: 10 of 14 [71.4%] participants; placebo: 1 of 2 [50.0%] participants) reported a single injection site reaction during the study. Most events lasted less than 24 hours. In both groups, the highest incidence of events was observed within the first 2 weeks of IMP administration and thereafter decreased and remained low throughout the study.

Severe injection site reactions that lasted longer than 24 hours (AESI)

One injection site reaction that lasted longer than 24 hours was reported in 1 participant in the dupilumab group (injection site rash of severe intensity). The event was assessed by the Investigator as related to the IMP and led to permanent discontinuation of the study intervention. The participant recovered without corrective treatment.

Infections

The percentage of participants with AESI infections was similar between the dupilumab and placebo groups (dupilumab: 7.9%; placebo: 8.3%).

Serious infections (AESI)

The most common AESIs were related to infections (dupilumab: 37 (7.9%); placebo: 39 (8.3%)). In total, 24 treatment emergent AESIs of serious infections were reported in 19 (4.1%) participants in the dupilumab group and 33 events were reported in 26 (5.5%) participants in the placebo group (Table 45).

Most of the serious infections were respiratory infections (PTs: pneumonia, COVID-19, lower respiratory tract infection, COVID-19 pneumonia, bronchopulmonary aspergillosis, pulmonary tuberculosis, respiratory tract infection, upper respiratory tract infection, bronchitis bacterial, pneumonia bacterial, and pneumonia pneumococcal). Three of the serious respiratory infections had a fatal outcome (dupilumab: 1; placebo 2) and were related to COVID-19 infections (see 5.5.4). Serious respiratory infections led to permanent discontinuation of the study intervention in 4 participants: 1 in the dupilumab group (pulmonary tuberculosis) and 3 in the placebo group (COVID-19 pneumonia with fatal outcome [2 participants], and pneumonia). Serious respiratory infections were assessed by the Investigator as related to the IMP in 1 participant, in the dupilumab group (pneumonia); the participant recovered with corrective therapy. Most of the serious respiratory infections required parenteral antimicrobial therapy and all non-fatal events resolved, with sequelae (dependence on oxygen therapy) in 1 participant (see

Section 3.1.8.3.2). Serious infections other than respiratory infections had a fatal outcome in 1 participant, in the placebo group (septic shock). The event led to permanent discontinuation of the study intervention and was assessed by the Investigator as not related to the IMP.

TEAEs due to COVID-19 infections

TEAEs due to COVID-19 were reported in a lower percentage of participants with dupilumab than with placebo (dupilumab: 6.2%; placebo: 8.1%). Reported PTs were COVID-19, COVID-19 pneumonia, suspected COVID-19, asymptomatic COVID-19, and SARS-CoV-2 test positive.

The TEAEs were assessed by the Investigator as serious in 5 participants in the dupilumab group and 9 participants in the placebo group and led to death in 3 participants: 1 in the dupilumab group and 2 in the placebo group (see 5.5.4; Deaths). None of the TEAEs due to COVID-19 were assessed by the Investigator as related to the IMP. All the participants with non-fatal events recovered, with sequelae (dependence on oxygen therapy) in 1 participant in the dupilumab group.

Among the participants who experienced TEAEs due to COVID-19, 13 (44.8%) participants in the dupilumab group and 15 (39.5%) participants in the placebo group received at least 1 dose of COVID-19 vaccine prior to TEAE. Among the 14 participants with COVID-19 SAEs, 1 participant in each intervention group received at least 1 dose of COVID-19 vaccine prior to SAEs. None of the 3 participants who had a TEAE leading to death had received a dose of a COVID-19 vaccine prior to the event.

Infections requiring parenteral antimicrobial therapy (AESI)

Treatment emergent infections requiring parenteral antimicrobial therapy were reported in a similar percentage of participants in the 2 intervention groups. A total of 37 infections in 29 (6.2%) participants in the dupilumab group and 40 infections in 30 (6.4%) participants in the placebo group required parenteral (intravenous, intramuscular subcutaneous) antimicrobial therapy. The majority of these infections were classified as serious, of which 3, in the placebo group, had a fatal outcome (COVID-19 pneumonia in 2 participants and septic shock in 1 participant (see 5.5.4; Deaths).

Infections requiring oral antimicrobial therapy for longer than 2 weeks (AESI)

A total of 8 infections in 6 (1.3%) participants in the dupilumab group and 11 infections in 11 (2.3%) participants in the placebo group required oral antimicrobial therapy for longer than 2 weeks. Approximately half of these infections were classified as serious, of which 1, in the placebo group, had a fatal outcome (see 5.5.4; Deaths).

Opportunistic infections (AESI)

The incidence of treatment-emergent opportunistic infections was low and similar in both intervention groups. In total, 4 events were reported in 4 (0.9%) participants in the dupilumab group, and 2 events were reported in 2 (0.4%) participants in the placebo group. All the participants who experienced opportunistic infections recovered, with corrective treatment.

In the dupilumab group, opportunistic infections were classified as serious in 2 participants (pulmonary tuberculosis & bronchopulmonary aspergillosis) and nonserious in 2 participants (herpes zoster & oral candidiasis). None of these 4 events were assessed by the Investigator as related to the IMP. In the placebo group, opportunistic infections were classified as nonserious in the 2 participants (both ophthalmic herpes zoster); in 1 participant, the event led to permanent discontinuation of the study intervention.

Severe conjunctivitis (AESI) and other conjunctivitis events

No events of severe conjunctivitis were reported during the study.

The incidence of non-severe types of conjunctivitis (CMQ broad criteria) was low and similar in both intervention groups. A total of 6 events were reported in 5 (1.1%) participants in the dupilumab group and 9 events were reported in 9 (1.9%) participants in the placebo group. None of the TEAEs were assessed by the Investigator as serious, severe, related to the IMP and none resulted in permanent discontinuation of the study intervention. All the participants recovered, with corrective therapy in 9 of the participants. The most common reported event was conjunctivitis in 4 (0.9%) participants in the dupilumab group and in 6 (1.3%) participants in the placebo group. Other events (blepharitis, conjunctivitis allergic, eye pruritus and ocular hyperemia) were reported in 1 participant each. Of the 14 participants who reported conjunctivitis events (CMQ broad criteria), in the dupilumab group, 1 participant (with TEAE of blepharitis) had an ongoing medical history of AD, and 1 participant (with TEAE of conjunctivitis) had an ongoing medical history of conjunctivitis allergic.

Significant ALT elevation (AESI)

Significant ALT elevation (defined as ALT >5 x ULN in participants with baseline ALT ≤2 x ULN; or ALT >8 x ULN if baseline ALT >2 x ULN) was reported as TEAE in 2 (0.4%) participants, both in the placebo group. Both events were reported as non-severe TEAEs of alcohol abuse. None of the TEAEs were classified by the Investigator as serious and none were assessed as related to IMP. One event led to permanent discontinuation of the study intervention (see Section 4.3.2).

There were no cases of abnormal liver function tests meeting the Hy's law criteria (ALT >3 x ULN and total bilirubin >2 x ULN).

Malignancy

Malignancy (other selected AE groupings)

Malignancies (i.e. "Malignant or unspecified tumors") were reported in a low and similar number of participants in both intervention groups. In total, 8 events were reported in 8 (1.7%) participants in the dupilumab group, and 9 events were reported in 9 (1.9%) participants in the placebo group. Of these treatment emergent events, 14 were classified by the Investigator as serious (7 in each intervention group) with a fatal outcome in 5 participants (dupilumab: 4 participants [bladder transitional cell carcinoma, lung carcinoma cell type unspecified stage IV, lung neoplasm, and lung neoplasm malignant]; placebo: 1 participant [lung adenocarcinoma]; see 5.5.4). In addition, 6 TEAEs resulted in permanent discontinuation of the study intervention (dupilumab: 3 participants [glioblastoma, rectal cancer; and squamous cell carcinoma of lung]; placebo: 3 participants [lung neoplasm malignant, invasive ductal breast carcinoma, and pancreatic carcinoma metastatic]). None of the malignancies were assessed by the Investigator as related to the IMP.

The most frequently reported TEAEs were from the HLGT Respiratory and mediastinal neoplasms malignant and unspecified and included lung neoplasm malignant (dupilumab: 4 participants [squamous cell carcinoma of lung, lung neoplasm, lung carcinoma cell type unspecified stage IV, and lung neoplasm malignant]; placebo: 2 participants [lung adenocarcinoma and lung neoplasm malignant]) consistent with the increased risk of patients with COPD and smoking history to develop lung cancer. Other malignancies showed heterogeneity of tumor types.

Other important adverse events

Herpes viral infections

Herpes viral infections (HLT) were reported in a low and similar number of participants in both intervention groups (dupilumab: 7 [1.5%] participants; placebo: 4 [0.9%] participants) and included the following TEAEs: herpes zoster (dupilumab: 5 [1.1%]; placebo: 1 [0.2%] participant), oral herpes (dupilumab: 2 [0.4%] participants; placebo: 1 [0.2%] participant), and ophthalmic herpes zoster (dupilumab: no participants; placebo: 2 [0.4%] participants). For 3 of the participants, the event was

reported as an opportunistic infection (1 participant in the dupilumab group with herpes zoster and 2 participants in the placebo group with ophthalmic herpes zoster).

Major cardiovascular adverse events (MACE)

Treatment-emergent CV events adjudicated by an external independent blinded committee.

A total of 20 (4.3%) participants in the dupilumab group and 25 (5.3%) in the placebo group had events that were submitted for assessment to an independent blinded adjudication committee. Of these, 11 (2.3%) participants in the dupilumab group and 16 (3.4%) participants in the placebo group had events that were adjudicated as CV events.

The incidence rate for MACE was lower for dupilumab than for placebo (0.9% versus 1.9%), with a risk difference of -1.06% (95% CI: -2.85% to 0.50%). The majority of the MACE events were non-fatal MI or non-fatal stroke.

In 4 participants, including 1 participant in the dupilumab group and 3 participants in the placebo group, the cause of death was adjudicated as cardiovascular. None of these deaths were assessed by the Investigator as related to the IMP. In the dupilumab group, the CV death was classified as hemorrhagic stroke. In the placebo group, CV deaths were classified as heart failure in 1 participant, as cardiac arrhythmia, heart failure and renal failure (unspecified order) in 1 participant, and as ischemic and gangrenous colon leading to septic shock and death in 1 participant (see Section 3.1.5). In all 4 cases, death could be explained by comorbid cardiopulmonary conditions or confounding factors. The incidence rates for cardiovascular death were 0.2% for dupilumab and 0.6% for placebo, with a risk difference of 0.43% (95% CI: 1.67% to 0.61%).

In 3 participants, 2 (0.4%) in the dupilumab group and 1 (0.2%) in the placebo group, cardiovascular events were adjudicated as hospitalization for unstable angina. All 3 participants required PCI, and all recovered.

Table 46 - Number (%) of participants with treatment-emergent potential cardiovascular events submitted for independent, blinded adjudication according to final classification - Safety population

Classification n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Number of participants with events submitted for adjudication	25 (5.3)	20 (4.3)
Number of participants with events adjudicated as cardiovascular	16 (3.4)	11 (2.3)
MACE	9 (1.9)	4 (0.9)
MACE - Cardiovascular Death	3 (0.6)	1 (0.2)
Death - Myocardial infarction	0	0
Death - Heart failure	1 (0.2)	0
Death - Stroke	0	1 (0.2)
Ischemic stroke	0	0
Hemorrhagic stroke	0	1 (0.2)
Undetermined etiology	0	0
Death - Procedure-related	0	0
Death - Pulmonary Embolism	0	0
Other Cardiovascular death	2 (0.4)	0
MACE - non-fatal MI	3 (0.6)	1 (0.2)
ST-elevation	0	0
Non-ST elevation	1 (0.2)	1 (0.2)
Type 2 MI	0	0
MACE - non-fatal stroke	3 (0.6)	2 (0.4)
Ischemic	2 (0.4)	1 (0.2)
Hemorrhagic	1 (0.2)	1 (0.2)
Undetermined	0	0
MACE and/or hospitalization for unstable angina	10 (2.1)	6 (1.3)
Hospitalization for Unstable Angina	1 (0.2)	2 (0.4)
Requiring PCI	1 (0.2)	2 (0.4)
Requiring CABG	0	0
Requiring medical treatment only	0	0
Hospitalization for atrial fibrillation/flutter	1 (0.2)	1 (0.2)
Hospitalization for other symptomatic arrhythmias	0	2 (0.4)
Hospitalization for transient ischemic attack	1 (0.2)	0
Other non-fatal cardio/cerebrovascular events	6 (1.3)	3 (0.6)
Heart failure	2 (0.4)	2 (0.4)
New Heart failure	1 (0.2)	2 (0.4)
Worsening of previously known heart failure	1 (0.2)	0
Peripheral arterial event	1 (0.2)	0
Pulmonary embolism	0	0
Non acute coronary syndrome/myocardial ischemia requiring PCI	1 (0.2)	0
Non acute coronary syndrome/myocardial ischemia requiring CABG	0	0
Others	2 (0.4)	1 (0.2)
Non cardiovascular death	5 (1.1)	6 (1.3)
Undetermined cause of death	0	0
Adjudicated as non-cardiovascular event	3 (0.6)	4 (0.9)

Classification n(%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Not an event to be considered for adjudication	4 (0.9)	0
Not able to adjudicate	0	0

MACE: Major adverse cardiovascular event; includes cardiovascular death, non-fatal MI, and/or non-fatal stroke, MI: Myocardial infarction, PCI: Percutaneous coronary intervention, CABG: Coronary artery bypass graft

n (%) = number and percentage of participants with at least one event; n = number of participants

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Overall, no additional safety signal emerges from the AESI events reported.

2.6.1.3. Adverse drug reactions

The primary assessment for ADRs was conducted on the safety population, which comprised of all participants who received at least one dose of study intervention (n=939).

Identification of ADRs was based on the following criteria:

- Quantitative criteria: The PTs with incidence ≥2% in the dupilumab group and difference ≥1% versus the placebo group and with lower bound of the 95% CI of relative risk >1 compared to placebo were identified.
- Qualitative criteria: The PTs with incidence ≥2% in the dupilumab group and difference ≥1% versus placebo group were reviewed for potential causal relationship taking into consideration biologic plausibility, presence of potential confounders and/or alternative explanation, and plausible exposure relationship.
- Adverse events of special interest and selected AEs/AE grouping with incidence ≥2% in the dupilumab group and difference ≥1% versus placebo group were also assessed.
- Adverse events which have been previously established as ADRs for approved indications (AD, asthma, CRSwNP, EoE, and PN) occurring with incidence ≥2% in the dupilumab group were also assessed for a numerical imbalance between intervention groups.
- Less frequent PTs were also evaluated to see if any PT could qualify as an ADR based on pathobiological mechanisms or medical judgment.

The following PTs had an incidence ≥2% in the dupilumab group and difference ≥1% versus placebo group with lower bound of the 95% CI of relative risk >1 compared to placebo being met for the PT Urinary Tract infection and Gastritis.

PT: Headache	38 (8.1%) vs. 32 (6.8%)	RR: 1.19 (95%CI: 0.76 - 1.87)
PT: Diarrhoea	25 (5.3%) vs. 17 (3.6%)	RR: 1.47 (95%CI: 0.81 - 2.69)
PT: Back pain	24 (5.1%) vs. 16 (3.4%)	RR: 1.50 (95%CI: 0.81 - 2.79)
PT: Urinary tract infection	23 (4.9%) vs. 10 (2.1%)	RR: 2.30 (95%CI: 1.11 - 4.79)
PT: Toothache	12 (2.6%) vs. 5 (1.1%)	RR: 2.41 (95%CI: 0.85 - 6.77)
PT: Gastritis	11 (2.3%) vs. 2 (0.4%)	RR: 5.51 (95%CI: 1.23 - 24.73)

Urinary tract infection was not considered an ADR for dupilumab in participants with uncontrolled COPD. No temporal association was observed in the occurrence of urinary tract infections and dupilumab exposure. Time to onset of the events in the dupilumab group ranged between 1 and 449 days. In addition, none of the TEAEs resulted in permanent discontinuation of the study intervention and all but 1

event resolved, while the participants continued their treatment with dupilumab. Upon medical review of all events, possible alternative etiology/confounder were identified in 13 of 23 participants in the dupilumab group and in 6 of 10 participants in the placebo group. Most common alternative etiology/confounder included diabetes in perimenopausal women, urinary incontinence, nephrolithiasis, and benign prostatic hyperplasia.

Gastritis was not considered an ADR for dupilumab in participants with uncontrolled COPD. No temporal association was observed in the occurrence of gastritis and dupilumab exposure. The time to onset of the events in the dupilumab group ranged between 48 and 405 days. None of the TEAEs resulted in permanent discontinuation of the study intervention and all but 1 event resolved, while the participants continued their treatment with dupilumab. None of the participants had recurrent events of gastritis. In the dupilumab group, none of the events were assessed by the Investigator as serious, severe, or related to the IMP. In the placebo group, gastritis was serious in 1 participant who was hospitalized for a worsening of gastritis (erythematous gastropathy). Possible alternative etiology/confounder were identified in 6 of the 11 participants in the dupilumab group and in 1 of the 2 participants in the placebo group. Most notable confounders were treatment with NSAIDs and systemic antibiotics prior to occurrence of gastritis; medical history of gastroesophageal reflux disease/gastritis, and use of steroids

Amongst AESIs and selected AEs/AE grouping which have been established as ADRs for approved indications as per the CCDS, and occurring with an incidence ≥2% in the dupilumab group, numerical imbalance (≥1% versus placebo) was observed for:

HLT: Injection site reactions* 14 (3.0%) vs. 2 (0.4%) RR: 7.01 (95%CI: 1.60 - 30.70)

*including the PTs of injection site reaction, injection site pain, injection site erythema, injection site induration, and injection site rash

Other AESIs and selected AEs/AE groupings previously established as ADRs (as per the CCDS) for approved indications were either not reported in the dupilumab group (keratitis, ulcerative keratitis, facial rash, angioedema, dry eye, eye pruritus, anaphylactic reaction or conjunctivitis allergic) or were reported similarly in the 2 intervention groups including arthralgia (dupilumab: 12 [2.6%] participants; placebo: 12 [2.6%] participants), blepharitis (dupilumab: 1 [0.2%] participant; placebo: no participants), oral herpes (dupilumab: 2 [0.4%] participants; placebo: 1 [0.2%] participant) and eosinophilia (dupilumab: 3 [0.6%] participants; placebo: 1 [0.2%] participant).

In summary, based on consideration of previously established ADRs in other indications and analysis of safety data from Study EFC15804, **injection site reactions** (including the PTs of injection site reaction, injection site pain, injection site erythema, injection site induration, and injection site rash) were identified as an ADR for dupilumab in participants with uncontrolled COPD.

No new ADRs were identified in the population with uncontrolled COPD.

Table 47 - Adverse drug reactions occurring in ≥2% of participants with COPD treated with dupilumab

Adverse drug reaction n (%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Injection site reactions [a]	2 (0.4)	14 (3.0)

a Injection site reactions include injection site reaction, injection site pain, injection site erythema, injection site induration, and injection site rash

The MAH included a comprehensive assessment for ADR identification together with a justification for not including PTs that had formally fulfilled the defined quantitative criteria.

Laboratory findings

Hematology

Red blood cells, platelets and coagulation

No relevant changes from baseline mean values were observed over time for hematology parameters (hemoglobin, hematocrit, RBCs, platelets) in either intervention group.

The overall number of participants with potentially clinically significant abnormalites for RBC, platelets, or coagulation during the TEAE period (regardless of baseline values) was generally similar in both intervention groups. Similar results were observed among the participants with normal or missing baseline values.

No participants had PCSAs related to RBC, platelets or coagulation that were considered SAEs or were TEAEs that led to permanent intervention discontinuation. Two treatment-emergent SAEs of anemia and polycythemia were reported for two individual participants in the dupilumab group. Both events were assessed by the Investigator as not related to IMP and did not lead to permanent discontinuation of the study intervention.

White blood cells

No meaningful mean changes from baseline were observed over time for WBC parameters (WBC count, neutrophils, lymphocytes, monocytes, basophils, and eosinophils) in either intervention group.

The overall number of participants with PCSAs for WBC parameters (regardless of baseline values) during the TEAE period was generally similar between the intervention groups, with the exception of eosinophils (see additional description below) (Table 48). No participants had PCSAs related to changes in WBC parameters that were serious TEAEs or were TEAEs that led to permanent intervention discontinuation.

Table 48 - White blood cells - Number (%) of participants with abnormalities (PCSA) according to baseline PCSA status - Safety population

Laboratory parameter Baseline, PCSA criteria n/N1 (%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Leukocyte Count (WBC)		
Total[a]		
< 3 Giga/L (Non-Black); < 2 Giga/L (Black)	4/467 (0.9)	3/466 (0.6)
≥ 16 Giga/L	20/467 (4.3)	19/466 (4.1)
Normal/Missing		
< 3 Giga/L (Non-Black); < 2 Giga/L (Black)	4/464 (0.9)	3/462 (0.6)
≥ 16 Giga/L	19/464 (4.1)	17/462 (3.7)
< 3 Giga/L (Non-Black); < 2 Giga/L (Black)		
≥ 16 Giga/L	0/0	0/1
≥ 16 Giga/L		
< 3 Giga/L (Non-Black); < 2 Giga/L (Black)	0/3	0/3
Neutrophils		
Total[a]		
< 1.5 Giga/L (Non-Black); < 1 Giga/L (Black)	7/458 (1.5)	8/460 (1.7)
Normal/Missing		
< 1.5 Giga/L (Non-Black); < 1 Giga/L (Black)	7/457 (1.5)	8/460 (1.7)
Lymphocytes		
Total[a]		
> 4 Giga/L	27/467 (5.8)	27/466 (5.8)
Normal/Missing		
> 4 Giga/L	21/457 (4.6)	20/458 (4.4)

Laboratory parameter Baseline, PCSA criteria n/N1 (%)	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
Monocytes		
Total[a]		
> 0.7 Giga/L	288/467 (61.7)	268/466 (57.5)
Normal/Missing		
> 0.7 Giga/L	166/331 (50.2)	163/343 (47.5)
Basophils		
Total[a]		
> 0.1 Giga/L	134/467 (28.7)	129/466 (27.7)
Normal/Missing		
> 0.1 Giga/L	81/406 (20.0)	99/426 (23.2)
Eosinophils		
Total[a]		
> 0.5 Giga/L or > ULN (if ULN ≥ 0.5 Giga/L)	56/465 (12.0)	86/465 (18.5)
Normal/Missing		
> 0.5 Giga/L or > ULN (if ULN ≥ 0.5 Giga/L)	34/433 (7.9)	68/439 (15.5)

PCSA: Potentially clinically significant abnormalities

a Regardless of baseline status

Note: The number (n) represents the subset of the total number of participants who met the criterion at least once during the TEAE period

The denominator (/N1) for each parameter within the treatment group is the number of participants who had that parameter assessed post-baseline (not missing) during the TEAE period, by baseline PCSA status

For PCSA including condition based only on change from baseline, the denominator is restricted on participants having (not missing) baseline and a post-baseline values during the TEAE period

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Blood eosinophils

The mean blood eosinophil count transiently increased with dupilumab between baseline and Week 8 (mean [SD] change from baseline: 0.09 [0.64] Giga/L) and returned to the baseline levels by Week 24. The median change from baseline in blood eosinophil count was close to 0 and remained unchanged throughout the treatment period in the dupilumab group (Figure 30).

Figure 30 - Eosinophils (Giga/L): Mean change (+/- SE) and median change (with Interquartile range) from baseline - Safety population

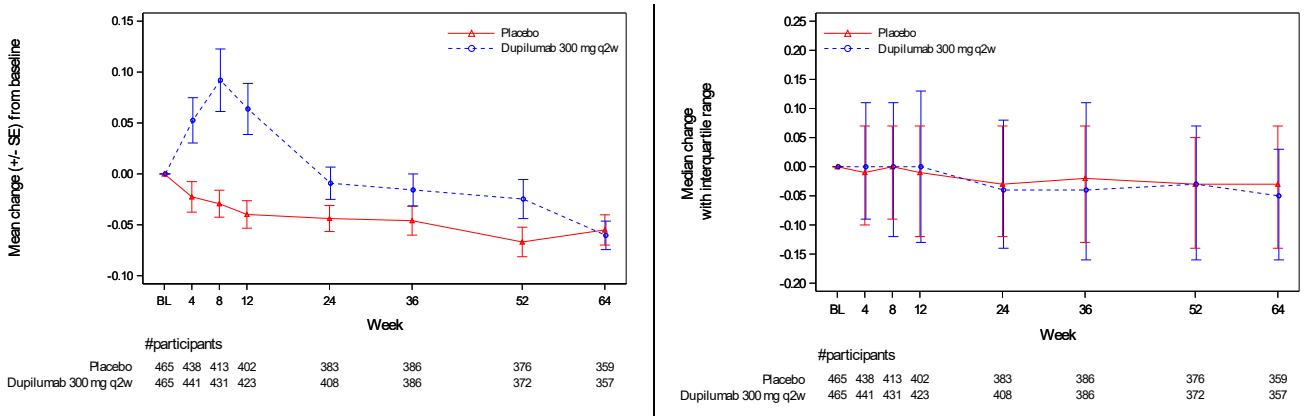
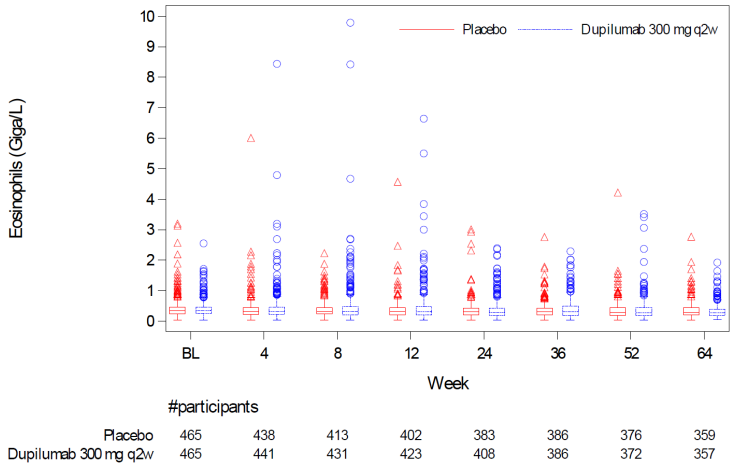


Figure 31 - Box plot of eosinophils over time - Safety Population



Among the participants with baseline values in the normal range, the percentage of participants with a PCSA for eosinophil count (>0.5 Giga/L or >ULN [if ULN ⩾0.5 Giga/L]) was higher with dupilumab than with placebo (dupilumab: 68 [15.5%] participants; placebo: 34 [7.9%] participants). Four participants, 3 in the dupilumab group and 1 in the placebo group had TEAE of eosinophilia, none being serious or leading to permanent discontinuation of the study intervention. No events of clinically symptomatic eosinophilia were reported and confirmed through medical review at the time of the data cut-off date of Study EFC15804.

Post-baseline peak blood eosinophil count ≥1 Giga/L (regardless of baseline value) were reported in a higher percentage of participants with dupilumab than with placebo (dupilumab: 12.7%; placebo: 6.7%) (Table 49). Post-baseline peak blood eosinophil counts ≥3 Giga/L were reported by 1.9% and 0.4% participants in the dupilumab and placebo groups, respectively and post baseline peak blood eosinophil counts ≥5 Giga/L were reported by 0.9% and 0.2% participants in the dupilumab and placebo groups, respectively.

Table 49 - Peak post-baseline blood eosinophil (Giga/L) during TEAE period by baseline blood eosinophil level - Safety population

Baseline Maximum post-baseline value	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)
All		
⩾1 Giga/L	31/465 (6.7)	59/465 (12.7)
≥3 Giga/L	2/465 (0.4)	9/465 (1.9)
≥5 Giga/L	1/465 (0.2)	4/465 (0.9)
<0.5 Giga/L		
≥1 Giga/L	9/373 (2.4)	19/372 (5.1)
≥3 Giga/L	0/373	2/372 (0.5)
≥5 Giga/L	0/373	0/372
≥0.5 Giga/L		
≥1 Giga/L	22/92 (23.9)	40/93 (43.0)
≥3 Giga/L	2/92 (2.2)	7/93 (7.5)
≥5 Giga/L	1/92 (1.1)	4/93 (4.3)

PGM=PRODOPS/SAR231893/EFC15804/CSR/REPORT/PGM/lab_peak_eos_s_t.sas
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The median change in blood eosinophils over time was overall small, while mean numbers increased starting with the begin of dupilumab treatment indicating highly elevated eosinophil counts in some individual patients (see Figure 25) preferentially in those with high eosinophil baseline levels ≥0.5 Giga/L (Table 49). However, this increase was only transient.

In both groups (dupilumab and placebo) blood eosinophils start to decline after beginning of treatment that may be related to participants that had initial high eosinophil counts at screening (retesting was allowed up to 3 times to meet the inclusion criteria) that declined afterwards.

Clinical Chemistry

Metabolic parameters

No meaningful mean changes from baseline were observed over time for metabolic parameters (glucose, cholesterol, total protein, and creatine phosphokinase) in either intervention group.

The proportion of participants with PCSAs for metabolic parameters (regardless of baseline values) during the TEAE period was similar between the intervention groups.

Increased CK levels were reported in a higher number dupilumab-treated patients (13 (2.8% vs. 9 (1.9%) with 3 participants reporting CK levels >10 ULN. None of these events were serious TEAEs or TEAEs that led to permanent intervention discontinuation. Of note, of the 3 participants with CK >10 ULN, 1 participant with normal CK value at baseline had a concomitant treatment-emergent SAE of rhabdomyolysis.

No participants had PCSAs related to changes in metabolic parameters that were serious TEAEs or TEAEs that led to permanent intervention discontinuation.

Electrolytes

No meaningful mean changes from baseline in electrolytes (sodium, potassium, chloride, or bicarbonate) were observed in either intervention group.

The number of participants with PCSAs was overall similar across intervention groups for all electrolyte parameters (regardless of baseline values) during the TEAE period.

Two participants in the placebo group had TEAEs related to electrolyte abnormalities that were reported as SAEs. None of the events were assessed by the Investigator as related to the IMP or led to permanent discontinuation of the study intervention.

Renal function

No meaningful mean changes from baseline were observed for renal function parameters (creatinine, creatinine clearance, uric acid, and blood urea nitrogen) in either intervention group.

The proportion of participants with PCSAs for renal function parameters (regardless of baseline values) was generally comparable between intervention groups during the TEAE period except for PCSAs for creatinine and creatinine clearance.

Among participants with normal/missing values at baseline, PCSAs for creatinine (≥30% change from baseline) were reported with a higher incidence with dupilumab than with placebo (dupilumab: 19.3% of participants; placebo: 15.7% of participants); PCSAs for creatinine clearance (≥60 - <90 mL/min [mild decrease in GFR]) were also reported more frequently with dupilumab than with placebo (dupilumab: 32.7% of participants; placebo: 28.2% of participants). Four participants with normal values at baseline, 3 in the dupilumab group and 1 in the placebo group had PCSAs for creatinine clearance <15 mL/min.

No participants had PCSAs for abnormalities in renal function parameters that were considered serious TEAEs or were TEAEs that led to permanent intervention discontinuation.

Liver function

The number of participants with PCSAs for liver function parameters was low and similar between intervention groups regardless of their baseline PCSA status (Table 44). No participants experienced a PCSA that met the Hy's law criteria (ALT >3 x ULN and total bilirubin >2 x ULN).

One participant in the placebo group had a treatment-emergent SAE of hepatic function abnormal on Day 313 (ie, 5 days after the 23rd IMP dose) (ALT at 46 IU/L versus 21 IU/L at baseline). The participant recovered from this event within 3 days. The event was assessed by the Investigator as not related to the IMP and did not lead to permanent discontinuation of the study intervention. No other participants had PCSAs for abnormalities in liver function parameters that were considered serious TEAEs or were TEAEs that led to permanent intervention discontinuation.

Two participants, both in the placebo group, had PCSAs that met the AESI criteria for significant ALT elevation. Both participants had non-severe TEAEs of alcohol abuse. In 1 of the participants, alcohol abuse led to permanent discontinuation of the study intervention. The participant had normal liver function parameters at baseline. On Day 170, ALT was at 102 IU/L (11 IU/L at baseline) and total bilirubin at 10.6 µmol/L (5.3 µmol/L at baseline). The values had further increased on Day 176 leading to permanent discontinuation of the study intervention. The values returned to normal and the TEAE was considered as resolved 23 days after the onset of the event.

Urinalysis

During the 52-week intervention period, the percentage of participants with positive results for urine protein in the dipstick urinalysis was generally similar between intervention groups.

Vital signs

Blood pressure and orthostatic changes

There were no clinically meaningful patterns or trends observed in the mean actual value or mean change from baseline over time in any of the vital sign parameters (SBP, DBP, HR, respiratory rate, and body temperature) across intervention groups. At Week 52 there was a small increase in body weight in both intervention groups, slightly greater in the dupilumab group as compared to the placebo group (mean [SD] change from baseline: 0.60 [3.34] kg versus 0.15 [3.62] kg).

The proportion of participants with PCSAs for SBP or HR was generally similar between the intervention groups (Table 45). Overall, PCSAs for weight increase (≥5 kg increase from baseline) were reported more frequently with dupilumab than with placebo (dupilumab: 16.8%; placebo: 14.1%). The PCSAs for weight increase were more frequent than PCSAs for weight decrease (≥5 kg decrease from baseline), especially in the dupilumab group (PCSAs for weight increase reported in 16.8% of participants; PCSAs for weight decrease reported in 8.7% of participants).

One participant in the dupilumab group with an ongoing medical history of hypertension, coronary artery disease and type 2 diabetes, was hospitalized for a treatment emergent SAE of hypertensive crisis on Day 398 (ie, 47 days after the last IMP dose as planned) associated with retrosternal pain that was assessed by the Investigator as not related to the IMP. The event did not lead to permanent discontinuation of the study intervention and resolved within 1 day. The participant had concomitant SAEs of acute coronary syndrome and pancreatitis acute, both assessed as not related to the IMP. One participant in the placebo group with medical history of hypertension and coronary acute disease, was hospitalized for a treatment emergent SAE of hypertensive emergency (worsening of hypertension) on Day 343 (ie, 20 days after the 22nd IMP dose) that was assessed by the Investigator as not related to the IMP and that did not lead to permanent discontinuation of the study intervention. The participant had a concomitant SAE of COPD.

Two participants, 1 in each intervention group, were hospitalized for a treatment-emergent SAE of pyrexia (etiology unknown), assessed by the Investigator as not related to the IMP; none of the SAEs led to permanent discontinuation of the study intervention.

Electrocardiogram

There were no clinically meaningful changes observed in the mean actual value or mean change from baseline over time in any of the ECG parameters across intervention groups.

Among participants with normal/missing values at baseline, prolonged QTc Fridericia >480 msec was reported in 1 participant in the dupilumab group. The participant with abnormal value at screening (QTcF: 468 ms) and normal value at baseline (447 ms) had prolonged QTcF on Day 84 (486.33 ms); QTcF values decreased at subsequent visits and returned to baseline level at the EOS visit. The participant had relevant medical history of hypertension, right bundle branch block, type 2 diabetes, obesity, and dyslipidemia. This participant experienced a TEAE of cardiac failure and a treatment-emergent SAE of acute pulmonary oedema on Day 281 adjudicated as "Other non-fatal cardio/cerebrovascular event - New heart failure".

One participant in the dupilumab group and 3 participants in the placebo group had TEAEs related to ECG parameter abnormalities that were reported as SAEs (PTs: atrioventricular block second degree, arrhythmia, tachycardia, and atrioventricular block complete).

Immunogenicity

Incidence and characterization of anti-dupilumab antibodies

During the study (up to Week 64), 46 (10.0%) participants in the dupilumab group and 11 (2.4%) in the placebo group, had treatment emergent ADAs.

During the on-treatment period (up to Week 52), the percentage of participants with treatment emergent ADA was low overall; it was higher in the dupilumab group than in the placebo group (dupilumab: 6.5%; placebo: 1.5%). The majority of the participants had a transient response; 10 (2.2%) participants in the dupilumab group and 1 (0.2%) in the placebo group developed a persistent response. No participants had treatment boosted ADA in either intervention group.

Most of the participants with treatment emergent ADA had low ADA titers (<1000). Two (0.4%) participants in the dupilumab group had high ADA titers (>10 000). Both participants had serum concentration of dupilumab below the quantification limit. None of these participants had concomitant AESIs of systemic hypersensitivity reactions or injection site reactions (HLT).

Among participants positive for ADA, the number of participants who developed treatment emergent NAb was low and similar in both intervention groups (dupilumab: 5 [1.1%] participants; placebo: 4 [0.9%] participants). Among the participants positive for NAb, 2 (0.4%) participants, both in the dupilumab group, had a high titer response (>10 000).

Association of anti-dupilumab antibodies to adverse events

Analysis of the potential influence of treatment-emergent ADA response on the incidence of TEAEs was limited by the small sample size of the participants with treatment emergent ADA (dupilumab: 46 participants; placebo: 11 participants).

In participants with treatment-emergent ADAs, the percentage of participants who had at least 1 TEAE was similar in both intervention groups (dupilumab: 76.1%; placebo: 81.8%). Among participants negative for ADA, the percentages of participants who experienced TEAEs were similar in both intervention groups (dupilumab: 77.6%; placebo: 76.7%).

Among participants from the safety population who experienced injection site reactions (HLT) (dupilumab: 14 [0.3%] participants; placebo: 2 [0.4%] participants), 2 participants, both in the dupilumab group had treatment emergent ADAs. Of these, 1 participant had a severe injection site reaction (injection site rash) that lasted longer than 24 hours and led to permanent discontinuation of the study intervention. The participant had a persistent ADA response on Day 89 with a moderate titer of 1920 and tested positive in the NAb assay. The other participant had a moderate injection site reaction on Day 61 that did not lead to permanent discontinuation of the study intervention. The participant had a transient ADA response with a low ADA titer of 30 on Day 169 and tested negative for the NAb assay.

No cases of anaphylactic reaction or hypersensitivity reaction occurred in participants with treatment emergent ADAs in either intervention group.

Safety in special populations

Intrinsic factors

Subgroup analyses of TEAEs, treatment-emergent SAEs and TEAEs leading to permanent intervention discontinuation by predefined intrinsic factors (including demographic, disease, and biomarker characteristics) were generally consistent with analyses in the overall study population. The limited number of participants who experienced AESIs/other selected AE groupings across subgroups did not allow meaningful interpretation of results. As described in the sections above, the incidence of injection site reactions was higher with dupilumab than with placebo.

Participants ≥65 years of age

A majority (58.1%) of the participants were ≥65 years of age at study entry and the percentage of participants ≥65 years of age was similar in the 2 intervention groups (dupilumab: 59.0%; placebo: 57.3%). Overall, 13.4% of the participants were ≥75 years of age (dupilumab: 12.8%; placebo: 14.0%).

The safety profile in the subgroup of participants aged 65 years or older was similar to that of the overall study population. In the participants ≥75 years of age, the safety profile was also generally similar to that of the overall study population.

Participants with emphysema

Approximately one third (32.6%) of the participants had an ongoing emphysema at study entry and the percentages of participants with ongoing emphysema were similar in both intervention groups (dupilumab: 33.3%; placebo: 32.5%). The safety profile of dupilumab in the subgroup of participants with ongoing emphysema at study entry was generally similar to that of the overall study population and did not suggest any safety concerns in these participants.

Participants with high BODE index

The score has a range of 0-10 with higher score corresponding to a higher risk of mortality over time. Overall, 38.2% of the participants had a high BODE index score (>4) at baseline, and the percentages of participants with a high score were similar in both intervention groups (dupilumab: 40.1%; placebo: 36.4%). The safety profile of dupilumab in the subgroup of participants with a high BODE score (>4) at baseline was generally similar to that of the overall study population and did not suggest any safety concerns in these participants.

Participants with history of severe exacerbation

Overall, 25.9% of the participants experienced at least 1 severe exacerbation in the year prior to study entry, and the percentages of participants with severe exacerbations were similar in both intervention groups (dupilumab: 27.6%; placebo: 24.2%). The safety profile of dupilumab in the subgroup of

participants with an history of severe exacerbations was generally similar to that of the overall study population.

Black/African descent participants

Despite recruitment efforts to ensure a diverse and representative study population in the global Study EFC15804, there was a low percentage (0.5%) of Black or African descent participants enrolled in this study: 5 participants in total including 3 (0.6%) participants in the dupilumab group and 2 (0.4%) in the placebo group.

Treatment-emergent AEs occurred in all 5 participants. Treatment-emergent AEs were more commonly reported in the SOC Infections and infestations and included in the dupilumab group: COVID-19 (2 participants), acute sinusitis, gastroenteritis, and pharyngitis streptococcal (1 participant, each), and in the placebo group: nasopharyngitis (3 episodes in 1 participant). None of the TEAEs were assessed by the Investigator as related to the IMP and none led to permanent discontinuation of the study intervention. The TEAEs were assessed as serious in a single participant (dupilumab group), who experienced chest pain, adjudicated by an independent blinded adjudication committee as a non-CV event, and ischemic stroke, adjudicated as a non-fatal stroke. Of the 5 Black or African descent participants, 1 participant, in the placebo group, permanently discontinued the study intervention on Day 241, as per the participant's decision (no safety related issue).

No differences in the safety profile of dupilumab had been reported across races in the approved indications. Safety data pooled across the completed pivotal placebo-controlled studies and across the approved indications (ie, asthma, AD, PN, EoE, and CRSwNP) were used to assess the safety in the pooled Black population. Of the 4847 participants included in the pooled safety population across the completed pivotal studies, 233 were Black (dupilumab: 145 participants; placebo: 88 participants). The safety profile was generally similar in the pooled Black population and the overall pooled safety population (Table 50). Notably, in the pooled Black population and as in the overall study populations, TEAEs of injection site reaction, injection site erythema, injection site edema, injection site pruritus, and injection site inflammation were noted more frequently in the dupilumab group than in the placebo group.

Table 50 - Overview of treatment-emergent adverse events in Pivotal Completed Placebo-Controlled Dupilumab Studies - Safety population

	Safety population			Black population		
n (%)	Placebo (N=1726)	Dupilumab (N=3121)	Total (N=4847)	Placebo (N=88)	Dupilumab (N=145)	Total (N=233)
Patients with any TEAE	1327 (76.9%)	2391 (76.6%)	3718 (76.7%)	58 (65.9%)	103 (71.0%)	161 (69.1%)
Patients with any severe TEAE	142 (8.2%)	218 (7.0%)	360 (7.4%)	11 (12.5%)	8 (5.5%)	19 (8.2%)
Patients with any treatment emergent SAE	138 (8.0%)	189 (6.1%)	327 (6.7%)	6 (6.8%)	10 (6.9%)	16 (6.9%)
Patients with any TEAE leading to death	3 (0.2%)	8 (0.3%)	11 (0.2%)	0	0	0
Patients with any TEAE leading to permanent study intervention discontinuation	65 (3.8%)	100 (3.2%)	165 (3.4%)	4 (4.5%)	2 (1.4%)	6 (2.6%)

n (%)	Safety population			Black population		
	Placebo (N=1726)	Dupilumab (N=3121)	Total (N=4847)	Placebo (N=88)	Dupilumab (N=145)	Total (N=233)
Patients with any TEAE related to IMP	294 (17.0%)	770 (24.7%)	1064 (22.0%)	13 (14.8%)	33 (22.8%)	46 (19.7%)

Asthma studies: DRI12544 (200 mg q2w/300 mg q2w/placebo), EFC13579 (200 mg q2w/300 mg q2w/placebo). CRSwNP studies: EFC14146 and EFC14280. Atopic dermatitis studies: R668-AD-1334, R668-AD-1416. PN studies: EFC16459 and EFC16460. EoE studies: R668-EE-1774 part A and part B.

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, IMP: Investigational medicinal product

n (%) = number and percentage of patients with at least one AE

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Extrinsic factors (region and territory)

Subgroup analyses of TEAEs, treatment-emergent SAEs and TEAEs leading to permanent intervention discontinuation by predefined extrinsic factors (region and territory) were generally consistent with analyses in the overall study population. The limited number of participants who experienced AESIs/other selected AE groupings across subgroups did not allow meaningful interpretation of results.

Discontinuation due to adverse events

The percentage of participants who had at least 1 TEAE reported by the Investigator as the reason for permanent study intervention discontinuation was low and similar in the 2 intervention groups (dupilumab: 14 (3.0%); placebo: 16 (3.4%)). The SOCs with the highest proportion of participants with TEAEs leading to permanent discontinuation of the study intervention were Neoplasms benign, malignant, and unspecified (dupilumab: 6 [1.3%] participants; placebo: 4 [0.9%] participants) and Infections and infestations (dupilumab: 2 [0.4%] participants; placebo: 5 [1.1%] participants). At the PT level, COVID-19 pneumonia led to permanent discontinuation of the study intervention in 2 participants, both in the placebo group. All other TEAEs were reported in 1 participant in either intervention group.

4 participants, 2 in each intervention group, permanently discontinued the study intervention due to AE per participant's decision.

Post-marketing experience

Dupilumab was first approved by the US FDA on 28 March 2017 for the treatment of adults with moderate-to-severe AD and has received subsequent approvals in other indications (asthma, CRSwNP, PN, and EoE) in multiple countries/regions. Dupilumab is not approved for the treatment of COPD in any country. No new safety concerns have been identified from the post-marketing data in the most recently submitted PBRER for dupilumab which covered the period from 29 March 2022 to 28 March 2023.

2.6.2. Study EFC15805 (NOTUS)

Safety data from the second phase 3 study EFC15805 (NOTUS) were provided during the procedure and are summarized below.

As of the interim data cut-off date (29 September 2023) for Study EFC15805 (NOTUS), a total of 933 participants were randomized and exposed to the study intervention: 468 in the dupilumab 300 mg q2w

group and 465 in the placebo group. Overall, 70.2% of the participants in the dupilumab group and 71.6% in the placebo group had completed the 52-week study intervention period.

Adverse events

The percentage of participants with any TEAE was similar between the dupilumab and placebo groups (66.7% versus 65.9%, respectively) (Table 51). The SOC with the highest percentage of participants with TEAEs among both intervention groups was Infections and infestations (42.0% participants in the dupilumab group and 38.6% participants in the placebo group).

Table 51 - Overview of adverse event profile: Treatment-emergent adverse events – Safety population – EFC15805

n(%)	Placebo (N=464)	Dupilumab 300 mg q2w (N=469)
Participants with any TEAE	306 (65.9)	313 (66.7)
Participants with any severe TEAE	62 (13.4)	60 (12.8)
Participants with any treatment emergent SAE	74 (15.9)	61 (13.0)
Participants with any TEAE leading to death	7 (1.5)	12 (2.6)
Participants with any TEAE leading to permanent study intervention discontinuation	12 (2.6)	18 (3.8)
Participants with any treatment emergent AESI	33 (7.1)	39 (8.3)
Participants with any treatment emergent other selected AE	11 (2.4)	23 (4.9)
Participants with any TEAE related to IMP	18 (3.9)	15 (3.2)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, IMP: Investigational medicinal product, AESI: adverse event of special interest
n (%) = number and percentage of participants with at least one TEAE
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Serious adverse events

Treatment-emergent SAEs were less frequently reported in the dupilumab group as compared to the placebo group (13.0% versus 15.9%). All treatment-emergent SAEs were considered not related to IMP by the Investigator.

Table 52 - Number (%) of participants with treatment emergent SAEs by Primary SOC and PT - Safety population– EFC15805

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=464)	Dupilumab 300 mg q2w (N=469)
Any Class	74 (15.9)	61 (13.0)
INFECTIONS AND INFESTATIONS	19 (4.1)	27 (5.8)
Pneumonia	4 (0.9)	7 (1.5)
COVID-19 pneumonia	2 (0.4)	6 (1.3)
COVID-19	4 (0.9)	3 (0.6)
Pneumonia bacterial	1 (0.2)	2 (0.4)
Viral upper respiratory tract infection	0	2 (0.4)
Bacterial colitis	0	1 (0.2)
Clostridium difficile colitis	0	1 (0.2)
Diverticulitis	0	1 (0.2)
Gastrointestinal infection	0	1 (0.2)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.2)
Influenza	0	1 (0.2)
Orchitis	0	1 (0.2)
Pneumonia pneumococcal	0	1 (0.2)
Pneumonia streptococcal	0	1 (0.2)
Respiratory tract infection	0	1 (0.2)
Suspected COVID-19	0	1 (0.2)
Anal abscess	1 (0.2)	0
Bronchitis	1 (0.2)	0

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=464)	Dupilumab 300 mg q2w (N=469)
Lower respiratory tract infection bacterial	1 (0.2)	0
Nasal candidiasis	1 (0.2)	0
Oropharyngeal candidiasis	1 (0.2)	0
Pneumonia klebsiella	1 (0.2)	0
Pneumonia pseudomonal	2 (0.4)	0
Urinary tract infection	1 (0.2)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	5 (1.1)	4 (0.9)
Adenocarcinoma of colon	1 (0.2)	1 (0.2)
Papillary thyroid cancer	0	1 (0.2)
Prostate cancer	1 (0.2)	1 (0.2)
Squamous cell carcinoma of skin	0	1 (0.2)
Chronic myelomonocytic leukaemia	1 (0.2)	0
Invasive ductal breast carcinoma	1 (0.2)	0
Squamous cell carcinoma of lung	1 (0.2)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.2)	2 (0.4)
Autoimmune haemolytic anaemia	0	1 (0.2)
Iron deficiency anaemia	0	1 (0.2)
Anaemia	1 (0.2)	0
IMMUNE SYSTEM DISORDERS	1 (0.2)	0
Anaphylactic reaction	1 (0.2)	0
ENDOCRINE DISORDERS	1 (0.2)	0
Inappropriate antidiuretic hormone secretion	1 (0.2)	0
METABOLISM AND NUTRITION DISORDERS	1 (0.2)	2 (0.4)
Decreased appetite	0	1 (0.2)
Hyponatraemia	0	1 (0.2)
Hyperkalaemia	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	7 (1.5)	2 (0.4)
Cerebral infarction	0	1 (0.2)
Cerebrovascular accident	1 (0.2)	1 (0.2)
Headache	1 (0.2)	0
Ischaemic stroke	2 (0.4)	0
Lacunar stroke	1 (0.2)	0
Syncope	1 (0.2)	0
Transient ischaemic attack	1 (0.2)	0
Vocal cord paralysis	1 (0.2)	0
EYE DISORDERS	0	1 (0.2)
Cataract	0	1 (0.2)
CARDIAC DISORDERS	12 (2.6)	9 (1.9)
Cardiac failure congestive	1 (0.2)	2 (0.4)
Atrial fibrillation	1 (0.2)	1 (0.2)
Cardiac arrest	0	1 (0.2)

Deaths

A total of 19 participants experienced TEAEs leading to death in the study (12 [2.6%] participants in the dupilumab group and 7 [1.5%] participants in the placebo group). There were 2 additional deaths in the post-treatment period (1 in each intervention group) which were attributed to post treatment AEs. None of the deaths were considered related to IMP by the Investigator.

Table 53 - Number (%) of participants with TEAE(s) leading to death (death as an outcome of the AE as reported by the Investigator in the AE page) by Primary SOC and PT - Safety population – EFC15805

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Placebo (N=464)	Dupilumab 300 mg q2w (N=469)
Any Class	7 (1.5)	12 (2.6)
INFECTIONS AND INFESTATIONS	3 (0.6)	4 (0.9)
Pneumonia	0	2 (0.4)
COVID-19 pneumonia	1 (0.2)	1 (0.2)
Infective exacerbation of chronic obstructive airways disease	0	1 (0.2)
Suspected COVID-19	0	1 (0.2)
COVID-19	1 (0.2)	0
Pneumonia klebsiella	1 (0.2)	0
NERVOUS SYSTEM DISORDERS	1 (0.2)	0
Cerebrovascular accident	1 (0.2)	0
CARDIAC DISORDERS	1 (0.2)	3 (0.6)
Cardiac arrest	0	1 (0.2)
Cardiac failure congestive	0	1 (0.2)
Cardiogenic shock	0	1 (0.2)
Cardiovascular disorder	1 (0.2)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	1 (0.2)
Pneumothorax	0	1 (0.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (0.4)	4 (0.9)
Sudden death	2 (0.4)	2 (0.4)
Death	0	1 (0.2)
Sudden cardiac death	0	1 (0.2)

TEAE: Treatment emergent adverse event, SOC: System organ class, PT: Preferred term
MedDRA 26.0
n (%) = number and percentage of participants with at least one TEAE leading to death; death is per investigator
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency in dupilumab 300 mg q2w group
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Adverse events of special interest

The percentage of participants with any treatment-emergent AESI or other selected AE was higher in the dupilumab group compared to the placebo group: 8.3% versus 7.1% for AESIs, and 4.9% versus 2.4% for other selected AEs, respectively. The difference between the intervention groups was mostly driven by AESIs of serious infection and other selected AEs of injection site reaction (HLT) and conjunctivitis (broad). None of the serious infection events were considered related to IMP by the Investigator.

The most frequently reported treatment-emergent AESIs were infections requiring parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy (dupilumab: 5.1%; placebo: 5.2%) and serious infections (dupilumab: 5.8%; placebo: 4.1%). There were no reports of severe injection site reactions that lasted longer than 24 hours, pregnancy, helminthic infections, symptomatic overdose with IMP/NIMP, clinically symptomatic eosinophilia, severe blepharitis, or significant ALT elevation in any intervention group.

The number (%) of participants with a treatment-emergent AESI of systemic hypersensitivity reaction that was confirmed by blinded medical review was low in both intervention groups (1 [0.2%] in the dupilumab group and 2 [0.4%] in the placebo group). The event in the dupilumab group (PT: rash) was non-serious and did not lead to permanent study intervention discontinuation. Treatment emergent AESIs of anaphylactic reaction confirmed by medical review were reported for 0 participants in the dupilumab group and 1 (0.2%) participant in the placebo group due to exposure to stinging insect venom.

Injection site reactions (other selected AE) were more frequently reported in the dupilumab group as compared to the placebo group (1.9% versus 0.4%).

Treatment-emergent AESIs of infection were more frequently reported in the dupilumab group as compared to the placebo group (8.1% versus 6.7%), mainly due to treatment-emergent AESIs of serious infection (5.8% versus 4.1%). The most frequently reported TEAEs of serious infection, at the PT level, were pneumonia (dupilumab: 1.5%, placebo: 0.9%), COVID-19 pneumonia (dupilumab: 1.3%, placebo: 0.4%), and COVID-19 (dupilumab: 0.6%, placebo: 0.9%); none of the events were considered related to IMP by the Investigator. Serious infections led to permanent study intervention discontinuation in 6 participants: 4 participants in the dupilumab group (PTs: COVID-19, COVID-19 pneumonia [2 participants], and suspected COVID-19) and 2 participants in the placebo group (PTs: COVID-19 pneumonia and COVID-19).

A total of 10 (2.1%) participants in the dupilumab group and 4 (0.9%) participants in the placebo group experienced an event of conjunctivitis (based on CMQ broad criteria). All were considered non-serious. One participant in the dupilumab group experienced an AESI of severe conjunctivitis as well as an AESI of severe keratitis (as searched by keratitis CMQ). Both events were considered related to IMP by the Investigator and led to permanent study intervention discontinuation.

Parasitic infection (AESI) was reported in 1 participant in the dupilumab group (PT: acarodermatitis; due to scabies). The TEAE was of mild intensity, considered not related to IMP by the Investigator, and did not lead to permanent study intervention discontinuation.

Treatment-emergent AEs of malignancy (as analyzed by SMQ "Malignant or unspecified tumors") were balanced between the dupilumab and placebo groups (5 [1.1%] participants in each intervention group). None led to death or were considered related to IMP by the Investigator.

The percentage of participants with adjudicated CV events was lower in the dupilumab group as compared to the placebo group (1.5% versus 3.4%) and low in both intervention groups for adjudicated MACE events (0.6% and 1.5%, respectively). Cardiovascular deaths were reported in 1 participant in each intervention group; both events were considered not related to IMP by the Investigator.

A total of 5 (1.1%) participants in the dupilumab group and 2 (0.4%) participants in the placebo group experienced events of herpes viral infection (HLT). All herpes viral infections were nonserious and of mild or moderate intensity. The majority of the events were considered not related to IMP by the Investigator, did not lead to permanent study intervention discontinuation, and were resolved as of the interim analysis data cut-off date of the CSR.

Table 54 - Number (%) of participants with treatment emergent AESIs and other selected AE grouping events by category - Safety population– EFC15805

Category n(%)	Placebo (N=464)	Dupilumab 300 mg q2w (N=469)
Any treatment emergent AESI	33 (7.1)	39 (8.3)
Systemic hypersensitivity reactions (medically reviewed)	2 (0.4)	1 (0.2)
Anaphylactic reactions (medically reviewed)	1 (0.2)	0
Severe injection site reactions that last longer than 24 hours	0	0
AESI infections	31 (6.7)	38 (8.1)
Serious infections	19 (4.1)	27 (5.8)
Parasitic infections	0	1 (0.2)
Infection requires parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy	24 (5.2)	24 (5.1)
Infection requires oral antimicrobial therapy for longer than 2 weeks	8 (1.7)	12 (2.6)
Opportunistic infection	0	2 (0.4)
Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP	0	0
Symptomatic overdose with IMP	0	0
Symptomatic overdose with NIMP	0	0
Clinically symptomatic eosinophilia (medically reviewed)	0	0
Any severe type of conjunctivitis	0	1 (0.2)
Any severe type of blepharitis	0	0
Keratitis	0	1 (0.2)
Significant ALT elevation	0	0
Other selected AEs	11 (2.4)	23 (4.9)
Injection site reaction	2 (0.4)	9 (1.9)
Malignancy	5 (1.1)	5 (1.1)
Conjunctivitis (narrow)	2 (0.4)	9 (1.9)
Conjunctivitis (broad)	4 (0.9)	10 (2.1)
Conjunctivitis (FDA)[a]	2 (0.4)	9 (1.9)
Helminthic infections	0	0

AESI: Adverse event of special interest
MedDRA 26.0
a Labeling subgroup of preferred terms included in the USPI for Dupixent.
n (%) = number and percentage of participants with at least one treatment emergent AESI/other AE grouping event
PGM=PRODOPS/SAR231893/EFC15805/CSR/REPORT/PGM/ae_aesi_sum_cat_s_t.sas
OUT=REPORT/OUTPUT/ae_aesi_sum_cat_s_t_i.rtf (20NOV2023 4:23)

Laboratory findings

A small transient increase in mean blood eosinophil count was observed in the dupilumab group as compared to the placebo group at the first post-baseline assessment at Week 4 (mean change from baseline: 0.07 Giga/L). The mean eosinophil count returned to near-baseline levels by Week 36, while the median blood eosinophil count remained relatively unchanged throughout the 52-week intervention period in the dupilumab group.

2.6.3. Pooled safety data (BOREAS and NOTUS)

In the pooled safety population, a total of 1872 participants were randomized and exposed to the study intervention: 938 in the dupilumab 300 mg q2w group and 934 in the placebo group. Among 938 participants exposed to dupilumab 872 (93.0%) were exposed for >6 months (24 weeks) and 588 (62.7%) for >1 year (52 weeks). In the pooled safety population, cumulative exposure to IMP was similar

in the 2 intervention groups: 855 PY in the dupilumab group and 847 PY in the placebo group. The mean (SD) duration of IMP exposure was similar in both intervention groups (dupilumab: 332.83 [77.81] days; placebo: 331.39 [80.99] days).

In the pooled safety population, the percentage of participants with any TEAE was balanced between the dupilumab and placebo groups (72.1% and 71.0%, respectively). The percentage of participants with any treatment-emergent SAE was lower in the dupilumab group as compared to the placebo group (13.3% and 15.7%, respectively). Treatment-emergent AEs leading to death were reported in a similar percentage of participants in both dupilumab and placebo groups (2.0% and 1.6%, respectively). None of these fatal events were considered related to IMP by the Investigator. The overall permanent study intervention discontinuation rate due to TEAEs was low in both intervention groups (3.4% in the dupilumab group and 3.0% in the placebo group).

Table 55 - Overview of adverse event profile: Treatment-emergent adverse events – Safety population for EFC15804, Safety population for EFC15805 and Pooled Safety population

n(%)	EFC15804		EFC15805		Pooled	
	Placebo (N=470)	Dupilumab 300 mg q2w (N=469)	Placebo (N=464)	Dupilumab 300 mg q2w (N=469)	Placebo (N=934)	Dupilumab 300 mg q2w (N=938)
Participants with any TEAE	357 (76.0)	363 (77.4)	306 (65.9)	313 (66.7)	663 (71.0)	676 (72.1)
Participants with any severe TEAE	55 (11.7)	48 (10.2)	62 (13.4)	60 (12.8)	117 (12.5)	108 (11.5)
Participants with any treatment emergent SAE	73 (15.5)	64 (13.6)	74 (15.9)	61 (13.0)	147 (15.7)	125 (13.3)
Participants with any TEAE leading to death	8 (1.7)	7 (1.5)	7 (1.5)	12 (2.6)	15 (1.6)	19 (2.0)
Participants with any TEAE leading to permanent study intervention discontinuation	16 (3.4)	14 (3.0)	12 (2.6)	18 (3.8)	28 (3.0)	32 (3.4)
Participants with any treatment emergent AESI	43 (9.1)	40 (8.5)	33 (7.1)	39 (8.3)	76 (8.1)	79 (8.4)
Participants with any treatment emergent other selected AE	20 (4.3)	26 (5.5)	11 (2.4)	23 (4.9)	31 (3.3)	49 (5.2)
Participants with any TEAE related to IMP	18 (3.8)	35 (7.5)	18 (3.9)	15 (3.2)	36 (3.9)	50 (5.3)

TEAE: Treatment-emergent adverse event, SAE: Serious adverse event, IMP: Investigational medicinal product, AESI: adverse event of special interest
n (%) = number and percentage of participants with at least one TEAE
PGM=PRODOPS/SAR231893/OVERALL/COPD_EMA_2024/REPORT/PGM/ae_overview_all_s_t.sas
OUT=REPORT/OUTPUT/ae_overview_all_s_t_i.rtf (26FEB2024 7:01)

In the pooled safety population, the incidence of treatment-emergent ADA responses was 1.8% (n=16) and 8.4% (n=77) for the placebo and dupilumab group, respectively, during the 52-week treatment period. A total of 0.4% (placebo) and 2.6% (dupilumab) of participants had persisting ADA responses. Neutralizing antibodies were observed in 1.1% and 3.0% of participants in the placebo and dupilumab group, respectively.

2.6.4. Discussion on clinical safety

Dupilumab is currently approved for treatment of atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, prurigo nodularis, and eosinophilic esophagitis.

Safety data for the COPD indication are derived from phase 3 study EFC15804 (BOREAS). Safety data from the second phase 3 study EFC15805 (NOTUS) were provided during the procedure. The pooled safety population of both studies consists of 1872 (dupilumab: 938; placebo: 934) patients.

Study EFC15804 (BOREAS)

The study included 939 participants that were randomized and exposed to dupilumab 300mg Q2W (without loading dose). The cut-off date for the safety analysis is 08-Feb-2023. The study included a 52-week treatment period and a 12-week follow-up. Follow-up data from remaining 63 participants (~7%)

were provided in the Response to the RSI. Additional SUSARs and fatal events from EFC15804 as well as the second phase 3 study in COPD (EFC15805; NOTUS) and from studies in other indications were included with a cut-off date of 31-May-2023.

A total of 939 participants were exposed (dupilumab: 468; placebo: 471) within study EFC15804. The mean exposure in the dupilumab and placebo group was 346.07 and 340.78 days with a cumulative exposure of 444 and 439 pty, respectively. The majority of participants completed the 52-week study intervention period (dupilumab: 91.0% of participants; placebo: 88.5% of participants).

There is extensive exposure to dupilumab, including long-term data up to 5 years for some of the currently approved indications (e.g. atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis). The 300 mg q2w dose used in the BOREAS study is the marketed dose for some of the approved indications. The demographics, comorbidities and concomitant treatments of the COPD population, although balanced across treatment groups in this study, do not align with those of the other approved indications. The ≥65 years of age group is less well represented in the other approved indications. The safety of dupilumab in patients over 65 will continue to be monitored with routine pharmacovigilance measures in future PSURs.

The percentage of participants with any TEAE was similar between the dupilumab group (77.4%) and the placebo group (76.0%). The most frequent TEAEs by SOC were *infections and infestations* (dupilumab: 43.7%; placebo: 48.3%), *gastrointestinal disorders* (dupilumab: 17.3%; placebo: 14.9%), and *respiratory/thoracic/and mediastinal disorders* (dupilumab: 16.0%; placebo: 17.0%).

Frequent (≥2%) TEAEs in the dupilumab group with a difference of greater 1% as compared to placebo were *Headache*, *Diarrhea*, *back pain*, *urinary tract infection*, *toothache*, and *gastritis*. In contrast, *upper respiratory tract infection, hypertension*, *COVID-19*, *pneumonia*, *lower respiratory tract infection* and *gastroenteritis* occurred less frequent (≤2%) in the dupilumab group.

Treatment-emergent SAEs were reported for 64 (13.6%) participants in the dupilumab group and for 73 (15.5%) participants in the placebo group with no apparent pattern for specific PT or HLTs. Comorbidities of the enrolled study population potentially have contributed to the distinct number of SAEs during the study. There was no difference in the occurrence of serious COPD exacerbations (dupilumab: 27; placebo: 26). Serious exacerbations include acute exacerbation of COPD unless they were classified as SAE (e.g. life threatening, requires hospitalisation). All SAEs were assessed by the Investigator as non-related to the IMP expect for one event of *rhabdomyolysis* and two consecutive events of *pneumonia* in a total two individual participants, both in the dupilumab group. Both participants recovered from the events. The events were assessed by the MAH as not-related to the IMP. Regarding the event of *rhabdomyolysis*, it is not possible to fully exclude dupilumab from having a role in this event. Musculoskeletal and connective tissue disorders were reported slightly more frequently in the dupilumab treated population (14.7% versus 13.2%) which is further reflected in in the HLGT of Muscle disorders (3.0% versus 1.1%) and HLGT of Musculoskeletal and connective tissue disorders NEC (8.5% versus 6.4%). There were 5 reports of myalgia, of which 2 reports of myalgia and 1 muscle pain were reported as related to IMP by the investigator. None were reported as severe. There were only 2 TEAEs of blood CPK raised in the dupilumab treated group and 1 in the placebo group. Increased CK levels were reported in a higher number of dupilumab-treated patients (13 (2.8% vs. 9 (1.9%) with 3 participants reporting CK levels >10 ULN). None of these events were serious TEAEs or TEAEs that led to permanent intervention discontinuation. Overall, there appears to be no clear signal of rhabdomyolysis and background rates of musculoskeletal disorders are likely to be generally high in this older population. Muscle disorders should continue to be monitored in future PSURs.

A total of 16 deaths occurred in study EFC15804 until the cut-off date 08-Feb-2023 (dupilumab: 8; placebo: 8). None of these deaths were assessed as related to the IMP which, upon review of the narratives, is endorsed. Only 3 participants (dupilumab: 1; placebo 2) died due to COVID-19 infections

potentially reflecting the implementation of protective measures to protect the vulnerable study population. Of note, none of these 3 participants had received a dose of a COVID-19 vaccine prior to the event. Four participants in the dupilumab group experienced death due to malignancies (placebo: 1). Overall, these death events are most likely linked the underlying comorbidities, the age and the extensive smoking history of the patient included. Some of these patients may already had lung cancer at the time of entry to the study. However, these patients should have been excluded from the study. Four cases (dupilumab: 1; placebo: 3) were adjudicated as CV deaths. Three new death events from study EFC15804 as well as one death event from study EFC15805 (NOTUS) were additionally reported with a cut-off date 31-May-2023. Overall, no new safety signals emerge from the reported fatal events. Updated data on death events from study EFC15804 and a complete analysis of death events occurring in the NOTUS study were be provided by the MAH during the procedure and do not raise major concerns.

Adverse events of special interest and other selected AEs of interest including anaphylactic reactions, hypersensitivity and different infections (e.g. conjunctivitis, blepharitis, keratitis, herpes) were evaluated. Numbers of treatment emergent adverse events of special interest were balanced with 40 (8.5%) events occurring in the dupilumab group and 43 (9.1%) events in the placebo group, respectively.

One anaphylactic reaction was reported in 1 participant in the placebo group. The rate of systemic hypersensitivity reactions was low in both groups (0.4% in each group). Severe injection site reaction lasting more than 24 hours was reported for one dupilumab-treated participant. Injection site reactions (HLT) (other selected AEs) were more frequently reported in the dupilumab group as compared to the placebo group (3.0% versus 0.4%). In both groups, the highest incidence of events was observed within the first 2 weeks of IMP administration and thereafter decreased and remained low throughout the study.

The most common AESIs were related to infections (dupilumab: 37 (7.9%); placebo: 39 (8.3%)). Serious infections were reported in 19 (4.1%) participants in the dupilumab group and for 26 (5.5%) participants in the placebo group. 4 infection events led to death. Most of the serious infections were respiratory infections. Consistent results were observed in study EFC15805. In the pooled safety population AESIs related to infections were reported in 75 (8.0%) and 70 (7.5%) in the dupilumab and placebo group, respectively. There was no difference in the occurrence of serious infections (dupilumab: 46 (4.9%); placebo: 45 (4.8%)).

No events of severe conjunctivitis were reported during the study. The incidence of non-severe types of conjunctivitis (CMQ broad criteria) was low (dupilumab: 5; placebo: 9). None of the conjunctivitis events were assessed by the Investigator as serious, severe, related to the IMP and none resulted in permanent discontinuation of the study intervention. All the participants recovered. Other eye disorders (i.e. blepharitis, conjunctivitis allergic, eye pruritus and ocular hyperemia) were reported in 1 participant each (dupilumab: 1; placebo: 3).

Malignancies were reported in a low number in both treatment groups (dupilumab: 8; placebo: 9). 5 events led to death. A total of 11 (2.3%) participants in the dupilumab group and 16 (3.4%) participants in the placebo group adjudicated by an external independent blinded committee as CV events. The incidence rate for Major cardiovascular adverse events (MACE) was low and similar between the groups (dupilumab: 1.9%; placebo: 0.9%) with a total of 4 cardiovascular deaths. Herpes viral infections (HLT) were reported in a low numbers in both intervention groups (dupilumab: 1.5%; placebo: 0.9%).

No events of clinically symptomatic eosinophilia (or eosinophilia associated with clinical symptoms) were reported. Blood eosinophils increased in individual patients upon start of dupilumab treatment preferentially in those with high eosinophil count at baseline ≥0.5 Giga/L. However, this increase was only transient.

The subgroup analysis by intrinsic (including demographic, disease, and biomarker characteristics) or extrinsic factors (territory and region) showed an overall consistent safety profile as compared to the

total population. The safety profile in the subgroup of patients aged 65 years or older was similar to that of the overall population. The higher number of TEAEs occurring in female patients was discussed by the MAH. Safety data for the very limited number of participants with Black/African (n=5) were provided together with a comparison on the safety profile obtained in Black patients across the different approved indications that indicate an overall similar safety profile in this subpopulation.

Study EFC15805 (NOTUS)

Safety data from the second phase 3 study EFC15805 (NOTUS) were provided by the MAH during the procedure.

As of the interim data cut-off date (29 September 2023) for Study EFC15805 (NOTUS), a total of 933 participants were randomized and exposed to the study intervention: 468 in the dupilumab 300 mg q2w group and 465 in the placebo group. Overall, 70.2% of the participants in the dupilumab group and 71.6% in the placebo group had completed the 52-week study intervention period.

Overall, the safety profile observed in study EFC15805 was similar to what have been observed in the BOREAS study. The new data do not give rise to any new safety finding.

ADR assessment

The MAH provided a comprehensive assessment for identification of any new or existing ADR based on defined quantitative and qualitative criteria. Based on data the data from study EFC15804, injection site reactions (including the PTs of injection site reaction, injection site pain, injection site erythema, injection site induration, and injection site rash) were identified as an ADR for dupilumab in participants with uncontrolled COPD. The new PT (injection site dermatitis) was identified in Study EFC15805. Injections site reactions has been also established as ADR for other approved dupilumab indications. No new ADRs were identified in both phase 3 studies. The ADR classification performed by the MAH is endorsed.

Overall, based on the provided data from study EFC15804 and EFC15804, dupilumab appears to have an acceptable safety profile in COPD that is similar to the safety profile known for other indications for which dupilumab is already approved. No new relevant new safety signals were apparent in the COPD population.

2.6.5. Conclusions on clinical safety

Overall, dupilumab treatment appears to be well tolerated with the proposed dose and method of administration (300 mg Q2W SC) in patients with COPD. The safety profile obtained in both studies appears consistent with the important identified risks mentioned in the safety specification and the so far known safety profile of dupilumab established during the AD, asthma and CRSwNP, PN, and EoE development programs.

2.6.6. PSUR cycle

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.

2.7. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 10.3 with the following content:

Safety concerns

Important identified risk	Systemic hypersensitivity (including events associated with immunogenicity)
Important potential risk	None
Missing information	Use in pregnant and lactating women
	Long-term safety in paediatric patients

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1- Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2- Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3- Required additional pharmacovigilance activities				
Pregnancy registry (R668-AD-1639) Ongoing	To evaluate the effect of exposure to dupilumab on pregnancy and infant outcomes.	Use in pregnant and lactating women	Protocol submission	Submitted to PRAC in Jan-2018 (and amendment #1 in Sep-2018)
			Amended protocol (asthma cohorts)	Submitted for information with EU-RMP v5.0
			Final report	Jan-2027
Pregnancy Outcomes Database Study (R668-AD-1760) Ongoing	To measure the prevalence of adverse pregnancy and infant outcomes in a cohort of women with AD exposed to dupilumab during pregnancy compared to a disease matched cohort exposed to systemic medication or phototherapy (but unexposed to dupilumab) in AD patients and a disease matched	Use in pregnant and lactating women	Protocol submission (amendment 1)	Submitted for information with EU-RMP v5.0
			Final report	Apr-2027

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	cohort who were not exposed to these treatments during pregnancy.			
An open-label extension study to assess the long-term safety of dupilumab in patients ≥6 months to <18 years of age with AD (Phase III) (LTS1434) (R668AD1434) Ongoing	To assess the long-term safety of dupilumab in pediatric patients with AD.	Long-term safety of dupilumab in paediatric patients with AD	Final report	Q4 2024
A registry-based nonintervention al post-authorisation safety study to evaluate the long-term safety of dupilumab in children aged ≥6 months to <6 years with moderate-to-severe atopic dermatitis using the PEDISTAD registry: a cohort design CSA0014 Planned	To assess the long-term safety of dupilumab in paediatric patients with moderate-to-severe AD.	Long-term safety of dupilumab in paediatric patients (≥6 months to <6 years) with AD	Synopsis v1.0 provided in Annex 3.1 of EU-RMP submitted within procedure EMEA/H/C/004390/II/0060 Protocol submitted to PRAC on Annual progress report Final Report	 18-Sep-2023 Q4 2024-2030 Q3 2032

AD: Atopic Dermatitis; EU: European Union; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; RMP: Risk Management Plan.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Systemic hypersensitivity (including events associated with immunogenicity)	**Routine risk minimization measures:** • SmPC sections 4.3, 4.4 and 4.8 • PIL sections 2 and 4 • Prescription only medicine **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity questionnaire **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	
Use in pregnant and lactating women	**Routine risk minimization measures:** • SmPC sections 4.6 and 5.3 • PIL section 2 • Prescription only medicine A**dditional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Pregnancy questionnaire **Additional pharmacovigilance activities:** Pregnancy registry study (R668-AD-1639), Pregnancy Outcomes Database Study (R668-AD-1760)
Long-term safety in paediatric patients	**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:** LTS1434 (R668-AD-1434) and DUPI PEDISTAD registry-based study (CSA0014)

PIL: Patient Information Leaflet; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC have been updated to extend the indication of the presentations Dupixent 300 mg solution for injection in pre-filled syringe or pre-filled pen related to the add-on maintenance treatment for uncontrolled COPD characterised by raised blood eosinophils on triple or double therapy if inhaled corticosteroids are not appropriate. The Package Leaflet (PL) is updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative(s) of Poland.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The changes of the product information are related to amendments of section 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 resulting in minor changes of the package leaflet in section 1, 2, 3, 4. Therefore, neither a full user testing nor an abridged testing is necessary for the current changes. The conclusion that the favourable results of the previous consultation with target patient groups are applicable here as well is endorsed.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COPD is a complex heterogeneous lung condition characterized by chronic respiratory symptoms (dyspnea, cough, and sputum production) due to abnormalities of the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction. COPD often coexists with other diseases (comorbidities) that may have a significant impact on disease course.

The disease results from gene-environment interactions and occurs in response to chronic exposure to noxious stimuli including tobacco smoke, pollutants, biomass, and gases. Periods of acute worsening of respiratory symptoms, called acute exacerbations of COPD (AECOPD) can occur that lead to further disease progression by means of airflow obstruction.

One of the main environmental exposures leading to COPD are tobacco smoking and other environmental exposures such as inhalation of toxic particles and gases from household and outdoor air pollution. Host factors (including abnormal lung development and accelerated lung aging) can also contribute. Exacerbations are often triggered by respiratory viral infections although bacterial infections and environmental factors such as pollution and ambient temperature may also initiate and/or amplify these events. When associated with viral infections, exacerbations are often more severe, last longer and precipitate more hospitalizations, as seen during the winter season.

3.1.2. Available therapies and unmet medical need

As per current GOLD 2023 guidelines, in addition to smoking cessation, the standard of care for patients at high risk of COPD exacerbation (GOLD group E) includes inhaled bronchodilators (LABA+LAMA). The addition of inhaled corticosteroids to comprise 'triple therapy' (i.e., ICS+LABA+LAMA) is strongly recommended for those with blood eosinophils ≥0.3 cells/microliter. Still, patients with blood eosinophils ≥ 0.1 cells/microliter may also be considered for ICS therapy given the continuous relationship of eosinophils on the disease pathogenesis and the variability of blood eosinophils measurements.

Though treatment recommendations for the management of severe COPD exist, no currently approved therapy is able to prevent the decline in lung function. While inhaled corticosteroids have a consistent effect in reducing the risk of moderate COPD exacerbations there is no consistent benefit on severe exacerbations.

Among severe COPD patients with high exacerbation risk on maximal standard-of-care "triple therapy" (ICS+LABA+LAMA) patients with an eosinophilic COPD phenotype may continue to experience exacerbations and disease progression providing important unmet need for new treatment options in this patient population.

3.1.3. Main clinical studies

Data for clinical efficacy and safety are based on the results from the two pivotal multinational, placebo-controlled, 52-week phase 3 studies EFC15804 (BOREAS) and EFC15805 (NOTUS) in participants with uncontrolled COPD (i.e. ≥2 moderate or ≥1 severe exacerbation in the previous year (GOLD Group E) and MRC ≥2) on triple therapy (LABA+LAMA+ICS; unless contraindicated), with presence of increased blood eosinophils (≥300 cells/microliter). The studies enrolled adult patients (age: 40-85 years) with moderate-

to-severe COPD (GOLD grade 2 and 3). Study EFC15804 included 939 participants that were randomized and exposed to dupilumab 300mg Q2W (without loading dose). Patients were treated for 52 weeks and were followed up for 12 weeks afterwards. Results from EFC15805 (NOTUS) that included data from 935 participants were provided by the MAH during the procedure.

3.2. Favourable effects

The number of COPD exacerbations that occurred in study EFC15804 was lower in the dupilumab group. Accordingly, the adjusted annualized rate of moderate or severe acute COPD exacerbations at 52 weeks (primary endpoint) was reduced by 30 percent as compared to placebo (0.776, 95% CI:0.645-0.934 vs. 1.101, 95% CI:0.931-1.301). A similar reduction of 34 percent was observed in the second pivotal study EFC15805 (0.859, 95% CI: 0.699-1.057 vs. 1.295 (95% CI: 1.048 to 1.600). The pooled results showed a reduction of 31 percent (risk difference: 0.687 (95%CI: 0.595 to 0.793)).

In both studies, patients showed an improvement in lung function as determined by change in pre-bronchodilator FEV1 from baseline to Week 12 and Week 52 (secondary endpoint). The improvement in pre-BD FEV1 was rapid, with an onset of difference between dupilumab and placebo starting at Week 2 which was maintained until Week 52 (mean difference: +83 ml; 95% CI: 38-128; +82ml; 95% CI: 11-113).

The treatment effect seen for the primary and secondary endpoints was also reflected in improvements in relevant health status and quality of life measures (SGRQ and E-RS: COPD).

Subgroup analysis based on type 2 inflammation biomarkers showed greater reductions in exacerbation rates and greater improvements in lung function (pre-BD FEV1 at Week 12) in participants with strongly increased blood eosinophils (≥0.5 Giga/L) or participants with elevated FeNO levels (≥20 ppb) indicating that patients with increased systemic or airway inflammation show enhanced benefit.

The reduction in exacerbation events and improvements in lung function were similar in patients with GOLD severity grade GOLD 2 (FEV1 ≥50%) or 3 (FEV1 <50%). An overall similar treatment effect was observed in current or former smokers and in elderly patients (>65 years).

3.3. Uncertainties and limitations about favourable effects

Both studies were partially conducted during the COVID-19 pandemic. Additional subgroup analysis for reductions in exacerbations by participant's year of enrolment (provided during the procedure) suggest that the absence or reduction in environmental triggers for COPD exacerbations due to public health measures could have influenced the strength of the treatment effect. Still, meaningful reductions in exacerbation rates and improvements in lung function were seen in both studies throughout all years of enrolment.

A post-hoc analysis in the subgroup of participants without moderate or severe exacerbations suggest a similar treatment effect with regard to improvements in lung function (FEV1) and health status.

Some intercurrent events and missing values not defined in detail give rise to some uncertainties regarding the magnitude and interpretation of the primary (and important secondary) endpoints. Requested additional details on the reasons for study discontinuation have shown that this uncertainty is rather negligible.

The study mainly enrolled patients with moderate-to-severe COPD (post-BD FEV1/FVC ratio >0.70 and post BD FEV1 % predicted >30% and ≤70%). However, there was a limited number of patients with GOLD 1 and GOLD 4 grade who participated in the study due to protocol deviations. Therefore, there is

very limited data available on those patients treated with dupilumab. This has been reflected accordingly in the SmPC.

The reduction in exacerbation events was mainly driven by a difference in moderate exacerbations while no statistically significant difference was observed for severe exacerbations. Additional analysis with the pooled ITT population of the BOREAS and NOTUS study provided by the MAH during procedure showed a trend toward a similar magnitude of reduction in severe exacerbations.

Only 0.5% and 1.3% of subjects enrolled in study EFC15804 or EFC15805 were Black or African American. An additional analysis with data from 26 participants that are Black or of African descent (including new data from the NOTUS study) indicate similar efficacy in this subpopulation.

3.4. Unfavourable effects

Safety data for this application are derived from the pivotal study EFC15804 (BOREAS). Additional safety data from the second pivotal study EFC15805 (NOTUS) were provided during the procedure.

In Study EFC15804, the percentage of participants with any TEAE was similar (77.4% vs. 76.0%). The most frequently reported TEAEs by SOC were Infections and infestations (43.7% vs. 48.3%), Gastrointestinal disorders (17.3% vs. 14.9%), and Respiratory, thoracic, and mediastinal disorders (16.0% vs. 17.0%) and were overall similar between dupilumab and placebo.

Frequent (≥2%) TEAEs in the dupilumab group with a difference of greater 1% as compared to placebo were headache, diarrhea, back pain, urinary tract infection, toothache, and gastritis. All these TEAEs were not considered as ADR.

In Study EFC15804, treatment-emergent SAEs were reported in 13.6% or 15.5% participants in the dupilumab and placebo group, respectively, with no apparent pattern for specific PT or HLTs. All SAEs were assessed by the Investigator as non-related to the IMP expect for one event of rhabdomyolysis and two consecutive events of pneumonia in a total of two individual participants, both in the dupilumab group. Both participants recovered from the events. The events were assessed as not-related to the IMP.

A total of 16 deaths occurred in study EFC15804 (8 vs. 8) (cut-off date: 08-Feb-2023). None of these deaths are considered to be related to the IMP. Three new death events from study EFC15804 as well as one death event from study EFC15805 (NOTUS) were additionally reported (cut-off date: 31-May-2023). Overall, no new safety signals emerge from the reported fatal events.

Adverse events of special interest and other selected AEs of interest were further evaluated in Study EFC15804. Numbers of treatment emergent adverse events of special interest were balanced with (8.5% vs. 9.1%). Injection site reactions (HLT) (other selected AEs) were more frequently reported in the dupilumab group (3.0% vs. 0.4%) and were identified as an ADR for dupilumab in COPD participants. The most common AESIs were related to infections (7.9% vs. 8.3%). Serious infections were reported in 4.1% participants in the dupilumab group and 5.5% participants in the placebo group. Most of the serious infections were respiratory infections. TEAEs due to COVID-19 were reported in a lower percentage of participants with dupilumab than with placebo (6.2% vs. 8.1%). No events of severe conjunctivitis were reported during the study. The incidence of non-severe types of conjunctivitis (CMQ broad criteria) was low (1.1% vs. 1.9%). Malignancies were reported in a low number in both treatment groups (1.7% vs. 1.9%). A total of 2.3% of participants in the dupilumab group and 3.4% participants in the placebo group had adjudicated CV events. Herpes viral infections (HLT) were reported in a low number in both intervention groups (1.5% vs. 0.9%).

Safety analysis in subgroups showed an overall consistent safety profile as compared to the total population. The safety profile in the subgroup of patients aged 65 years or older was similar to that of the

overall population. The incidence of ADAs was overall low incidence with no relevant impact on safety and efficacy. In the pooled safety population, the incidence of treatment-emergent ADA responses during the 52-week treatment period was 8.4% and 1.8% for the dupilumab and placebo group, respectively.

Safety data from the replicate study EFC15805 (NOTUS) were overall similar to the BOREAS study.

Based on the data from study EFC15804 and EF15805, dupilumab has an acceptable safety profile in COPD that is similar to the other indications for which dupilumab is already approved.

3.5. Uncertainties and limitations about unfavourable effects

There is extensive exposure to dupilumab, including long-term data up to 5 years for some of the currently approved indications (e.g. atopic dermatitis, asthma and chronic rhinosinusitis with nasal polyposis). The demographics, comorbidities and concomitant treatments of the COPD population, although balanced across treatment groups in this study, do not align with that of the other approved indications. The ≥65 years of age group is less well represented in the other approved indications. The safety of dupilumab in patients over 65 will continue to be monitored with routine pharmacovigilance measures in future PSURs.

Safety data for participants with Black/African descent are limited. Safety data for patients included were provided together with a comparison of the safety profile in Black patients across the different approved indications which suggest an overall similar safety profile in this subpopulation.

3.6. Effects Table

Effects Table for Dupixent (data cut-off: 07 March 2023 (EFC15804); 01 Nov 2023 (EFC15805)

Effect	Short description	Unit	DUPI 300 mg Q2W*[1]	PCB*[1]	Uncertainties / Strength of evidence	References
Favourable Effects						
AECOPD	Annualized rate of moderate or severe COPD exacerbations over the 52-week treatment period	R	0.776	1.101	- Clinically meaningful reduction of 30% and 34% - Studies conducted during COVID-19 pandemic	ITT EFC15804 (BOREAS)
		R	0.859	1.295		ITT EFC15805 (NOTUS)
		R	0.794	1.156		Pooled ITT
FEV1	Change in pre-bronchodilator FEV1 from baseline to week 52	ml	0.153	0.070	- Clinically meaningful improvement of +83ml and +82ml - early onset of effect - Maintenance data beyond week 52 not available	ITT EFC15804 (BOREAS)
		ml	0.115	0.054		ITT EFC15805 (NOTUS)
Unfavourable Effects						
TEAE	Injection site reactions (HLT)	%	3.0	0.4	- considered as ADR	EFC15804
		%	1.9	0.4	- one serious event in dupilumab group. All others mild or moderate	EFC15805
	SAE	%	13.6	15.5	- no specific pattern for specific PTs or HLTs	EFC15804
		%	13.0	15.9		EFC15805

Effect	Short description	Unit	DUPI 300 mg Q2W*[1]	PCB*[1]	Uncertainties / Strength of evidence	References
	Death	%	1.5	1.7	- all non-related to the IMP	EFC15804
		%	2.6	1.5		EFC15805
	ADAs	%	8.4	1.8	- No correlation with safety findings	Pooled ADA population

Abbreviations: ADA, anti-drug antibodies; AECOPD, acute exacerbation of COPD; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; ml, milliliter; PCB, placebo; R, rate; SAE, severe adverse event

Notes: *[1] participants on background therapy including LABA+LAMA+ICS (unless ICS was contraindicated)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary goals in COPD treatment are to control lung symptoms (i.e. airflow obstruction), reduce the number of exacerbations and improve overall quality of life. Based on data from two pivotal studies in uncontrolled COPD patients at high risk of exacerbation with an eosinophilic phenotype, dupilumab treatment led to a clear reduction in the annualized rate of moderate or severe exacerbations. The effect is clinically meaningful and relevant for the patient as exacerbation events are associated with increased disease progression, decline in lung function and overall morbidity and mortality. Dupilumab also improved lung function in pre-BD FEV1 at week 12 and week 52. This is relevant, also considering the severity of the targeted population, and represents a reversal of the typical FEV1 decline seen in this COPD population within 1-2 years. The effect was maintained throughout the 52-week treatment period of the study, while no additional maintenance data are available. The treatment effect was reflected in improvements in relevant health status and quality of life measures. The benefits of dupilumab were also observed in participants with potentially higher morbidity and mortality including elderly participants (≥65 years), participants with emphysema, and current smokers. Overall, these data demonstrate a beneficial treatment effect of dupilumab in the studied COPD population.

The initially proposed broad indication based on the term "COPD with type 2 inflammation" was not considered sufficiently supported by the data and insufficiently reflected the studied population that is characterized by raised blood eosinophils. Indeed, the study population in the BOREAS and NOTUS studies was restricted to participants with eosinophilic COPD (i.e. blood eosinophils ≥300 cells/microliter). During the procedure, upon the CHMP request the applicant agreed to update the indication to better reflect the studied population characterised by raised blood eosinophils.

Within study EFC15804, dupilumab treatment showed a similar safety profile as within the other dupilumab indications AD, asthma and CRSwNP, PN and EoE. The percentage of participants with any TEAE was similar. The most frequently reported TEAEs by SOC were Infections and infestations, Gastrointestinal disorders, and Respiratory, thoracic, and mediastinal disorders and were overall similar between dupilumab and placebo. Injection site reactions (HLT) (other selected AEs) were more frequently reported in the dupilumab group and were identified as an ADR. No new ADRs were identified. Treatment-emergent SAEs were reported in similar numbers in the dupilumab and placebo group, respectively, with no apparent pattern for specific PT or HLTs. A total of 16 deaths occurred in study EFC15804. None of these deaths were considered to be related to the IMP. Overall, no new safety signals emerge from the reported fatal events. The most common AESIs were related to infections (7.9% vs. 8.3%). Serious

infections were reported in 4.1% participants in the dupilumab group and 5.5% participants in the placebo group. Most of the serious infections were respiratory infections. TEAEs due to COVID-19 were reported in a lower percentage of participants with dupilumab than with placebo (6.2% vs. 8.1%). No events of severe conjunctivitis were reported during the study. The incidence of non-severe types of conjunctivitis (CMQ broad criteria) was low. Malignancies and adjudicated CV events were also reported in low numbers. ADA-formation was observed after dupilumab treatment with an overall low incidence while a relevant impact on safety and efficacy data was not noted.

Safety data from the second phase 3 study (EFC15805) were provided during the procedure and were consistent with the safety profile observed in study EFC15804. Overall, as compared to other indications no new safety signal is apparent based on the safety data from both COPD studies.

3.7.2. Balance of benefits and risks

Based on the efficacy and safety data provided from two pivotal phase 3 studies, the therapeutic need of dupilumab in patients with uncontrolled COPD is acknowledged. Efficacy data obtained in two phase 3 studies overall demonstrate a beneficial treatment effect of dupilumab in the studied COPD population with an acceptable safety profile that is overall similar to the other approved indications.

3.7.3. Additional considerations on the benefit-risk balance

Third party intervention during the evaluation of the procedure

On 4 June, the CHMP received, after the adoption of the CHMP positive opinion, a correspondence from a professor of pneumology (hereinafter referred to as "third party") which expressed concerns about the efficacy of Dupixent in patients with COPD.
The CHMP considered those interventions and concluded that the arguments put forward by the third-party did not impact the CHMP conclusions.

3.8. Conclusions

The overall B/R of Dupixent is positive as add-on maintenance treatment in adults for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**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 and IIIB

Extension of indication for DUPIXENT to include treatment of adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate, based on final results from study EFC15804 (BOREAS) and interim results from study EFC15805 (NOTUS); these are phase 3, randomized, double blind, placebo-controlled, multi-center, parallel group, 52-week studies to assess the efficacy, safety and tolerability of dupilumab in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) with elevated blood eosinophils (i.e. ≥300 cells/microliter). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 10.3 of the RMP has also been submitted.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Dupixent-H-C-004390-II-Var.0079'

Attachments

1. SmPC, Package Leaflet (changes highlighted) as adopted by the CHMP on 30 May 2024.