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Effect of Exacerbation History on Clinical Response to Dupilumab in Moderate-Severe Uncontrolled Asthma

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Summary (251/256 characters): Dupilumab reduced severe exacerbations and improved lung function and asthma control in patients with type 2–high asthma, irrespective of exacerbation history and baseline ICS dose. These data will aid clinicians managing patients with severe disease.

Abstract

Background: The phase 3 QUEST study (NCT02414854) in patients with uncontrolled, moderate-to-severe asthma has demonstrated the efficacy and safety of dupilumab 200 and 300 mg every 2 weeks *versus* placebo. This *post hoc* analysis assessed the effect of dupilumab on efficacy outcomes and asthma control across a range of historical exacerbation rates in patients with type 2–high asthma.

Methods: Annualised severe exacerbation rates over the 52-week treatment period, pre-bronchodilator forced expiratory volume in 1 second (FEV_1) at weeks 12/52, and the 5-item Asthma Control Questionnaire (ACQ-5) score at 24/52 were assessed in patients with ≥1, ≥2, or ≥3 exacerbations in the previous year. Subgroups were stratified by baseline blood eosinophils ≥150 or ≥300 cells·μL^{-1} or baseline fractional exhaled nitric oxide ≥25 ppb and baseline inhaled corticosteroid dose.

Results: Across all type 2–high subgroups, dupilumab *versus* placebo significantly reduced severe exacerbations by 54 to 90%, with greater improvements in patients with more exacerbations prior to study initiation. Similarly, improvements in FEV_1 (least squares [LS] difference *versus* placebo: ≥1 exacerbation, 0.15 to 0.25 L; ≥2 exacerbations, 0.12 to 0.32 L; ≥3 exacerbations, 0.09 to 0.38 L; majority $p<0.05$) and ACQ-5 score (LS mean difference range: ≥1 exacerbation, −0.30 to −0.57; ≥2 exacerbations, −0.29 to −0.56; ≥3 exacerbations, −0.43 to −0.61; all $p<0.05$) were observed, irrespective of prior exacerbation history, across all subgroups.

Conclusions: Dupilumab significantly reduced severe exacerbations and improved FEV_1 and asthma control in patients with elevated type 2 biomarkers irrespective of exacerbation history and baseline ICS dose.

Word count: 247 (including headings)/250

Keywords: Dupilumab, Asthma, Type 2 biomarkers, FEV_1, ACQ-5, Exacerbation history

Introduction

Asthma exacerbations, which may sometimes necessitate a change in a patient's current treatment, account for significant mortality and present a considerable economic burden due to the healthcare costs associated with their management [1, 2]. Patients with type 2 asthma and/or patients receiving higher doses of inhaled corticosteroids (ICS) have more severe disease and require higher doses of steroids to maintain asthma control. These subpopulations are therefore at greater risk of future exacerbations [3]. Moreover, asthma exacerbation history, particularly of recent events, has been shown to be a significant independent predictor of future exacerbation risk [4, 5].

Dupilumab is a fully human VelocImmune®-derived monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signalling of both IL-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases [6–9]. These cytokines, together with IL-5, play important roles in the pathogenesis of asthma [9, 10]. Dupilumab is approved for patients aged ≥12 years with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma, for adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps and for the treatment of patients with inadequately controlled, moderate-to-severe atopic dermatitis aged >6 years in the USA, and adults in the European Union and other countries [11–20].

In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), dupilumab 200 mg and 300 mg every 2 weeks (Q2W) *versus* matched placebo significantly reduced severe exacerbation rates and improved pre-bronchodilator (BD) forced expiratory volume in one second (FEV_1), asthma control, and quality of life measures in patients with uncontrolled, moderate-to-severe asthma [15]. Treatment effects were generally of greater magnitude in patients with elevated baseline levels of type 2 inflammatory biomarkers (blood eosinophils ≥150 cells·μL^{-1} or fractional exhaled nitric oxide [FeNO] ≥25 parts per billion [ppb]) [15].

Understanding the efficacy of treatments such as dupilumab in patients with high disease burden (evidenced by frequent, recent exacerbations and high-dose ICS use) is of considerable relevance to clinicians treating patients with severe disease. The aim of this *post hoc* analysis of the QUEST study was to assess the effect of dupilumab on severe exacerbations, lung function, and asthma control in subgroups of patients with a type 2–high phenotype, who had experienced a range of exacerbations in the previous year (≥1, ≥2 or ≥3), and who were further stratified by baseline ICS dose (high *versus* medium).

Methods

Study design and patients

LIBERTY ASTHMA QUEST (NCT02414854) was a phase 3 multinational, multicentre, randomised, double-blind, placebo-controlled study that assessed the effect of dupilumab in patients with uncontrolled, moderate-to-severe asthma [15]. Patients aged ≥12 years with physician-diagnosed asthma for 12 months (based on the Global Initiative for Asthma 2014 guidelines) were eligible to participate [21]. The study was open to all patients, irrespective of eosinophilic status or any other biomarker requirement. Patients were randomised in a 2:2:1:1 ratio to add-on subcutaneously (SC) administered dupilumab 200 mg (loading dose 400 mg) or 300 mg (loading dose 600 mg) Q2W or matched-volume placebos for 52 weeks. Full details of the study's design and methodology have been reported previously [15, 22]; complete patient eligibility criteria, including the requirement for all patients to have had $\geqslant$1 exacerbation within the year before enrolment, can be found in the Supplementary Appendix of the primary manuscript [15].

The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Study conduct and documentation were monitored by local institutional review boards or ethics committees, and all patients provided written informed consent before participating in the trial.

Study endpoints and populations analysed

The endpoints analysed in this *post hoc* analysis of QUEST were: annualised rate of severe exacerbations during the 52-week treatment period, least squares (LS) mean change from baseline in pre-BD FEV_1 (L) at weeks 12 and 52, and LS mean change from baseline in the 5-item Asthma Control Questionnaire (ACQ-5) score at weeks 24 and 52. A severe asthma exacerbation was defined as a deterioration of asthma requiring treatment with systemic corticosteroids for >3 days, or hospitalisation or emergency room visit because of asthma requiring systemic corticosteroids. ACQ-5 is a patient-reported measure of the adequacy of asthma control and of change in asthma control; higher scores indicate less asthma control [23].

Subgroup analysis was performed for patients stratified by number of exacerbations in the previous year (≥1, ≥2 or ≥3), baseline blood eosinophils (≥150 cells·μL^{-1} or ≥300 cells·μL^{-1}), baseline FeNO (≥25 ppb), and baseline ICS dose (medium- or high-dose). Analyses were also performed in the subgroup of

patients without elevated levels of type 2 biomarkers at baseline (eosinophils <150 cells·μL^{-1} and FeNO <25 ppb).

Statistical analysis

The estimates for adjusted annualised severe exacerbation rates were derived using a negative binomial regression model, with total number of events occurring during the 52-week treatment period as the response variable, and the four intervention groups, age, geographic region, baseline eosinophil strata (<300 cells·μL^{-1}, ≥300 cells·μL^{-1}), baseline ICS dose level, and number of exacerbations in the previous year as covariates. Change from baseline in pre-BD FEV_1 and ACQ-5 scores were analysed using mixed-effects models with repeated measures, including assigned intervention, age, baseline eosinophil strata, visit, intervention-by-visit interaction, region (pooled country), corresponding baseline pre-BD FEV_1 or ACQ-5 value and baseline-by-visit interaction as covariates. Sex and baseline height were included as additional covariates in the models for FEV_1. For patients who discontinued the assigned intervention and remained in the trial, measurements after the intervention were discontinued and were included in the analysis.

A p-value of <0.05 for the comparison between each dupilumab dose and placebo (within each subgroup) was considered statistically significant.

Results

Patient characteristics

1902 patients were enrolled in the QUEST trial (1264 assigned to dupilumab, 638 to placebo), all of whom had experienced ≥1 severe exacerbation event in the previous year [15]. There were no major differences in baseline characteristics across the subgroups, although patients who had experienced ≥3 exacerbations in the year prior to study entry had relatively lower pre-BD FEV_1 and a higher requirement for ICS use at baseline than did those who had experienced fewer exacerbations. Patients who had experienced ≥3 exacerbations also had higher mean baseline levels of blood eosinophils and FeNO (table).

Annualised rate of severe asthma exacerbations

Dupilumab Q2W (combined treatment groups) significantly reduced severe exacerbation rates *versus* placebo in patients with elevated baseline blood eosinophils irrespective of exacerbation history or ICS dose at baseline, with a greater magnitude of improvement observed in patients with ≥2 or ≥3 prior exacerbations (figure 1). Reductions in exacerbation rates *versus* placebo ranged from 58–71% in the

intention-to-treat (ITT) and 54–65% in the ICS high-dose subgroup of patients with baseline eosinophils ≥150 cells·μL^{-1}; 67–75% (ITT) and 63–67% (high-dose ICS) in patients with baseline eosinophils ≥300 cells·μL^{-1}; and 63-80% (ITT) and 62–76% (high-dose ICS) in patients with baseline FeNO ≥25 ppb (all p<0.001; figure 1A-C). Similar trends were observed in patients on medium-dose ICS at baseline (supplementary figure S1A). Across all high type 2 biomarker subgroups, adjusted annualised rates of exacerbation following dupilumab treatment ranged from 0.16 (in patients with ≥300 cells·μL^{-1} and medium-dose ICS treated with combined dupilumab 200 mg and 300 mg) to 0.65 (patients with ≥150 cells·μL^{-1} and high-dose ICS treated with combined dupilumab 200 mg and 300 mg) compared to rates ranging from 0.86 to 2.35 in placebo-treated patients.

In the subgroup of patients with baseline eosinophils <150 cells·μL^{-1} and baseline FeNO <25 ppb, numerical improvements *versus* placebo in annualised exacerbation rates were observed although these were not statistically significant (supplementary figure S1B).

Pre-BD FEV_1

Dupilumab 200 mg and 300 mg Q2W (combined treatment groups) *versus* matched placebo improved pre-BD FEV_1 at week 12, irrespective of exacerbation history across all subgroups, stratified by baseline eosinophils, FeNO or ICS dose (figure 2, supplementary figure S2); these improvements were statistically significant in a majority of cases, and the level of improvement increased with the number of prior exacerbations. In the subpopulation of patients who had elevated baseline biomarker levels (blood eosinophils ≥150 cells·μL^{-1}, ≥300 cells·μL^{-1} or baseline FeNO ≥25 ppb), further stratified by baseline ICS dose groups, and who had experienced ≥1 exacerbation in the previous year, LS mean change from baseline at week 12 in pre-BD FEV_1 ranged from 0.35 to 0.46 L with dupilumab and 0.20 to 0.23 L with placebo (LS mean difference *versus* placebo ranged from 0.15 L to 0.25 L; all p<0.001; figure 2A–C supplementary figure S2A–B). Improvements with dupilumab were also evident in the elevated biomarker subgroups with ≥2 and ≥3 prior exacerbations. In the former group, dupilumab treatment increased pre-BD FEV_1 by a range of 0.37 to 0.56 L compared with changes of 0.19 to 0.28 L with placebo (LS mean difference *versus* placebo ranging from 0.12 to 0.32 L; all p<0.01; figure 2A–C, supplementary figure 2A). In the subgroups of patients with elevated biomarker levels and ≥3 prior exacerbations, improvements with dupilumab and placebo at week 12 were between 0.36 and 0.66 L and 0.19 and 0.33 L, respectively (LS mean difference *versus* placebo ranged from 0.09 to 0.38 L; all p<0.01 *versus* placebo except in patients with baseline blood eosinophils ≥150 cells·μL^{-1} and high ICS dose [p=0.0679; figure 2A]

and patients with baseline blood eosinophils ≥300 cells·μL^{-1} and high ICS dose [p=0.1717; figure 2B]). Improvements were sustained at week 52 (supplementary figure S2A–B).

In the subgroup of patients without elevated baseline biomarkers (*i.e.* baseline blood eosinophils <150 cells·μL^{-1} and baseline FeNO <25 ppb), numerical improvements with dupilumab treatment *versus* placebo were observed at weeks 12 and 52, although these were largely not statistically significant (supplementary figure S2C).

ACQ-5 scores

Dupilumab Q2W (combined treatment groups) *versus* matched placebo improved asthma control (ACQ-5 score) at week 24 irrespective of exacerbation history across all subgroups stratified by baseline eosinophils, FeNO or ICS dose (figure 3, supplementary figure S3). As with the FEV_1 endpoint, these improvements *versus* placebo were statistically significant in a majority of cases, with greater improvements observed in the patients who had elevated biomarker levels at baseline and who had ≥3 prior exacerbations. In the subgroups of these patients who had experienced ≥1 exacerbation in the previous year, LS mean change in ACQ-5 score at week 24 ranged from −1.47 to −1.70 for dupilumab and −1.05 to −1.24 for placebo (LS mean difference *versus* placebo ranging from −0.30 to −0.57; all p<0.001) (figure 3A–C, supplementary figure S3A–B). In those who had ≥2 and ≥3 exacerbations in the previous year, improvements with dupilumab ranged from −1.51 to −1.83 and −1.58 to −1.90, respectively; patients receiving placebo reported lower improvements in asthma control, ranging from −1.12 to −1.45 and −1.07 to −1.47, respectively (LS mean difference *versus* placebo ranged from −0.29 to −0.56 and −0.43 to −0.61 in patients with ≥2 and ≥3 prior exacerbations, respectively; all p<0.05). Improvements were sustained at week 52 (supplementary figure S3A–B).

As with exacerbation rate and FEV_1 endpoints, in the subgroup of patients without elevated baseline biomarkers, numerical improvements with dupilumab *versus* placebo were observed at weeks 24 and 52 (supplementary figure S3C), although these were largely not statistically significant.

Discussion

This *post hoc* analysis of the LIBERTY ASTHMA QUEST phase 3, randomised, placebo-controlled trial assessed the effect of add-on dupilumab treatment on annualised rates of severe exacerbations, lung function (pre-BD FEV_1) and asthma control (ACQ-5 score) in subgroups of patients categorised by exacerbation history, *i.e.* ≥1, ≥2 or ≥3 exacerbations in the year prior to study enrolment. These subpopulations were further stratified by elevated baseline levels of blood eosinophils (≥150 or ≥300

cells·μL^{-1}) and FeNO (≥25 ppb)—two biomarkers of type 2 inflammation—and ICS dose at study entry (medium or high). The rationale for selecting these strata was based on the knowledge that recent exacerbations independently predict future exacerbation risk [4, 5], and that patients who have elevated type 2 biomarkers and/or are receiving high-dose ICS have more severe disease, and are therefore at greater risk of asthma exacerbations [3, 24]. Indeed, these observations were corroborated by the baseline characteristics of the patients, with the subgroup of patients who had experienced ≥3 exacerbations in the year prior to study entry displaying relatively worse lung function (pre-BD FEV_1) and a higher requirement for ICS use. Moreover, there also appeared to be a strong link between the number of previous exacerbations experienced and baseline type 2 biomarker levels, indicating that patients with a stronger type 2 signature have higher exacerbation risk.

Across all subgroups, dupilumab 200 mg and 300 mg Q2W (combined) *versus* matched placebo significantly reduced severe annualised exacerbation rates, irrespective of the number of exacerbations the patients had experienced in the year prior to the study start. Additionally, there was a trend showing that the magnitude of the improvements compared with placebo increased along with the number of severe asthma exacerbation events experienced in the previous year. Because the risk of exacerbations tends to increase proportionally to the number of recent exacerbations [4, 5], this finding suggests that dupilumab suppresses this increased exacerbation risk—a phenomenon that has also been reported for other asthma biologics [22, 25]. Across all high type 2 biomarker subgroups—even in those considered to be the most severe and difficult to treat due to high rates of prior exacerbations coupled with a high type 2 signature—dupilumab treatment exhibited considerable efficacy in improving lung function, with improvements of up to 0.38 L compared with placebo. Clinically meaningful improvements were also observed in ACQ-5 score [23], indicating better asthma control, regardless of the number of severe asthma exacerbations patients had experienced in the previous year, or their baseline level of type 2 biomarkers or ICS dose. Even in the most severe patients with a high type 2 signature who had experienced ≥3 exacerbations in the previous year, clinically meaningful and statistically significant improvements in ACQ-5 score were observed at week 24 in dupilumab compared with placebo.

For all endpoints, numerical improvements with dupilumab compared with placebo treatment were observed in the subgroup of patients who did not display a type 2 phenotype (*i.e.* who had baseline biomarker concentrations of <150 eosinophils·μL^{-1} and FeNO <25 ppb). However, most of these improvements were not statistically significant, and the magnitude of the treatment effects was minimal compared with those observed in type 2–high subpopulations. That greater treatment effects were

observed in patients with elevated type 2 biomarkers is consistent with the mechanism of action of dupilumab, which by binding to IL4Rα, inhibits the type 2 cytokines IL-4 and IL-13 and thus the type 2 inflammation exhibited by these patients [9]. Similar findings have been reported in other dupilumab asthma studies [14–16].

Although the data analysed in this study were collected in a large, randomised, stringently controlled clinical trial, a limitation of the analysis presented is its *post hoc* nature, as the parent study was not powered to specifically investigate differences in the subpopulations described. Accordingly, sample sizes for many of the subgroups analysed and described were low. Additionally, the aetiology of many of the exacerbations assessed in this study, whether in the year prior to study start or during the study itself, were unknown. Exacerbations can be triggered by multiple factors, including viral or bacterial respiratory infection, environmental allergens, pollutants and occupational exposures [26]. With hindsight, better characterisation of the causes of the exacerbations studied could have facilitated a comparative examination of dupilumab efficacy in each of these phenotypes.

In conclusion, this *post hoc* analysis confirms that the significant reduction in severe exacerbation rates and improvements in asthma control and lung function observed with dupilumab in the overall ITT population of QUEST extend to patients with elevated type 2 inflammation biomarkers, irrespective of exacerbation history and ICS dose at baseline. These findings suggest that prior history of exacerbations adds no further value to prognostication for the treating clinician but is of considerable value to clinicians in order to understand the efficacy of dupilumab, particularly among patients with a very severe disease burden.

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Data sharing statement

Qualified researchers may request access to patient level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymised, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data-sharing criteria, eligible studies, and process for requesting access can be found at: www.clinicalstudydatarequest.com/

Conflict of interest:

J. Corren reports receiving research support from Sanofi, outside the submitted work. **C.H. Katelaris** reports being an advisory board member and principal investigator of the dupilumab asthma phase 2b study for Sanofi, outside the submitted work. **M. Castro** reports receiving research support from American Lung Association, AstraZeneca, Boehringer Ingelheim, Gossamer, NIH, Novartis, PCORI, Sanofi and Shionogi; being a consultant for Boston Scientific, Genentech, Novartis, Sanofi, Teva and Vida Pharma; receiving speakers' honoraria from AstraZeneca, Boehringer Ingelheim, Genentech, Regeneron Pharmaceuticals Inc., Sanofi and Teva; and receiving royalties from Elsevier, outside the submitted work. **J.F. Maspero** reports being a speaker for AstraZeneca, GlaxoSmithKline, Menarini, Novartis, Sanofi, Teva and Uriach; and has received research grants from Novartis, outside the submitted work. **L.B. Ford** reports receiving research support from AstraZeneca, DBV, Genentech, Gossamer, Novartis and Teva; and being a consultant for Sanofi, outside the submitted work. **D.M.G. Halpin** reports receiving speaker fees and being an advisory board member of AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, Novartis, Pfizer, Sandoz and Sanofi, outside the submitted work. **M.S. Rice**, **P. Rowe and M. Djandji** are employees of Sanofi and may hold stock and/or stock options in the company. **A. Teper** is a former employee of Sanofi. **A. Radwan and Y. Deniz** are employees and shareholders of Regeneron Pharmaceuticals, Inc.

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TABLE: Baseline demographic and clinical characteristics of QUEST patients by exacerbation history and type 2 biomarkers

Baseline	≥1 exacerbations in the past year						≥2 exacerbations in the past year						≥3 exacerbations in the past year					
	Eosinophils ≥150 cells·μL^{-1}		Eosinophils ≥300 cells·μL^{-1}		FeNO ≥25 ppb		Eosinophils ≥150 cells·μL^{-1}		Eosinophils ≥300 cells·μL^{-1}		FeNO ≥25 ppb		Eosinophils ≥150 cells·μL^{-1}		Eosinophils ≥300 cells·μL^{-1}		FeNO ≥25 ppb	
Combined treatment	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**	**PBO**	**DPL**
N	**469**	**889**	**290**	**541**	**334**	**609**	**260**	**425**	**159**	**286**	**183**	**303**	**119**	**200**	**83**	**140**	**87**	**141**
Age mean±SD years	47.8 (15.0)	47.4 (15.4)	47.5 (15.3)	47.0 (15.2)	47.2 (15.8)	47.2 (15.3)	47.7 (14.4)	47.7 (14.7)	47.8 (14.6)	48.0 (14.5)	47.0 (15.5)	47.2 (14.6)	47.4 (13.6)	49.0 (14.6)	47.2 (13.6)	49.0 (14.3)	47.0 (14.2)	47.7 (14.7)
Female sex %	63.3	60.1	60.7	61.2	59.6	59.3	64.6	61.9	62.3	63.6	59.0	61.4	65.5	65.5	62.7	65.7	60.9	64.5
Severe asthma exacerbations experienced in the past year mean±SD n	2.24 (1.87)	2.09 (2.47)	2.34 (1.99)	2.19 (2.03)	2.27 (1.94)	2.11 (2.02)	3.23 (2.02)	3.28 (3.17)	3.45 (2.12)	3.26 (2.32)	3.32 (2.11)	3.24 (2.38)	4.69 (2.23)	4.72 (4.18)	4.78 (2.21)	4.56 (2. 76)	4.77 (2.32)	4.67 (2.90)
High-dose ICS use %	53.9	50.7	54.8	50.3	50.0	49.9	59.6	60.2	61.0	58.4	51.9	58.1	60.5	63.5	63.9	62.9	55.2	62.4
Medium-dose ICS use %	45.2	48.1	44.5	48.6	49.4	49.3	39.2	39.3	38.4	41.3	47.0	41.6	38.7	36.0	34.9	37.1	43.7	37.6
Pre-BD FEV_1 mean±SD L	1.76 (0.59)	1.80 (0.61)	1.76 (0.61)	1.78 (0.62)	1.79 (0.61)	1.80 (0.62)	1.73 (0.54)	1.76 (0.61)	1.71 (0.55)	1.71 (0.60)	1.78 (0.57)	1.76 (0.64)	1.69 (0.50)	1.67 (0.61)	1.68 (0.48)	1.63 (0.62)	1.73 (0.50)	1.67 (0.62)
Post-BD FEV_1 mean ±SD L	2.16 (0.71)	2.19 (0.72)	2.17 (0.71)	2.17 (0.72)	2.21 (0.73)	2.20 (0.75)	2.13 (0.65)	2.13 (0.72)	2.10 (0.66)	2.08 (0.70)	2.19 (0.69)	2.14 (0.74)	2.05 (0.56)	2.04 (0.75)	2.04 (0.55)	2.00 (0.75)	2.11 (0.58)	2.03 (0.72)
ACQ-5 score mean±SD	2.79 (0.77)	2.78 (0.80)	2.82 (0.73)	2.79 (0.82)	2.71 (0.76)	2.74 (0.80)	2.88 (0.79)	2.84 (0.86)	2.87 (0.75)	2.84 (0.86)	2.76 (0.80)	2.79 (0.81)	2.99 (0.88)	2.96 (0.94)	2.93 (0.86)	2.93 (0.96)	2.84 (0.89)	2.96 (0.90)
Baseline blood eosinophil mean±SD cells·μL^{-1}	487.93 (391.22)	462.31 (371.85)	654.86 (416.61)	623.66 (399.43)	485.38 (442.92)	457.11 (427.30)	520.15 (446.84)	525.25 (451.58)	712.26 (480.34)	676.89 (481.57)	544.12 (509.07)	522.28 (514.99)	608.74 (499.18)	562.35 (547.84)	779.88 (509.71)	713.36 (593.56)	610.69 (554.79)	579.29 (632.32)
Baseline FeNO mean±SD ppb	39.28 (32.79)	38.73 (35.01)	45.85 (36.48)	45.46 (39.37)	55.27 (36.73)	54.74 (36.19)	42.09 (36.44)	41.42 (38.47)	49.35 (41.01)	47.25 (42.30)	58.74 (43.19)	57.29 (40.23)	40.09 (28.04)	44.34 (42.95)	44.75 (28.67)	50.15 (47.19)	52.82 (27.01)	60.55 (45.33)

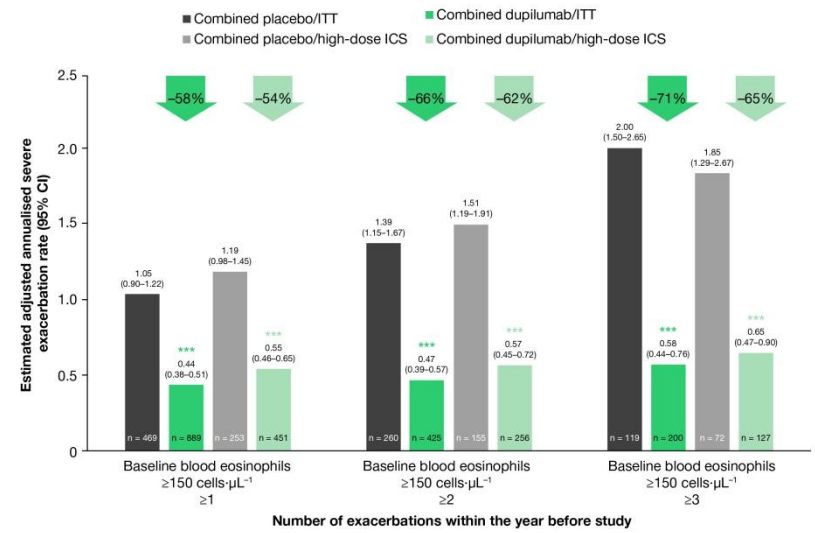
ACQ-5: 5-item Asthma Control Questionnaire; BD: bronchodilator; DPL: dupilumab; FeNO, fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; PBO, placebo; ppb: parts per billion; SD: standard deviation.

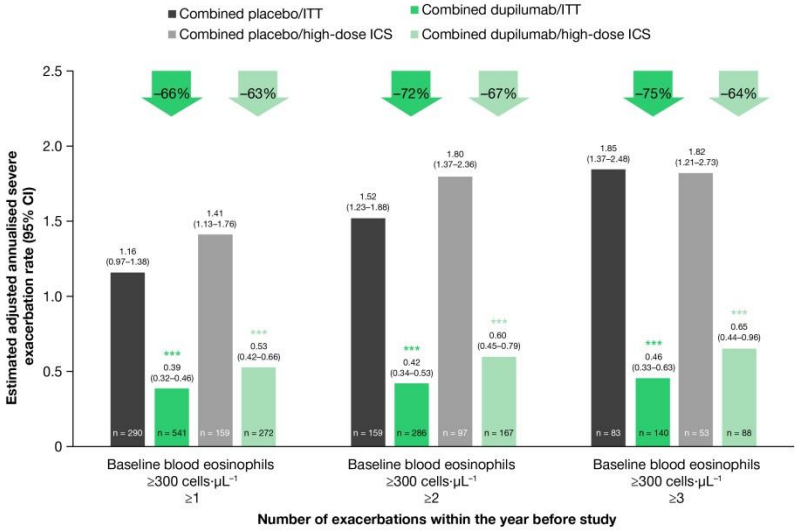
FIGURES

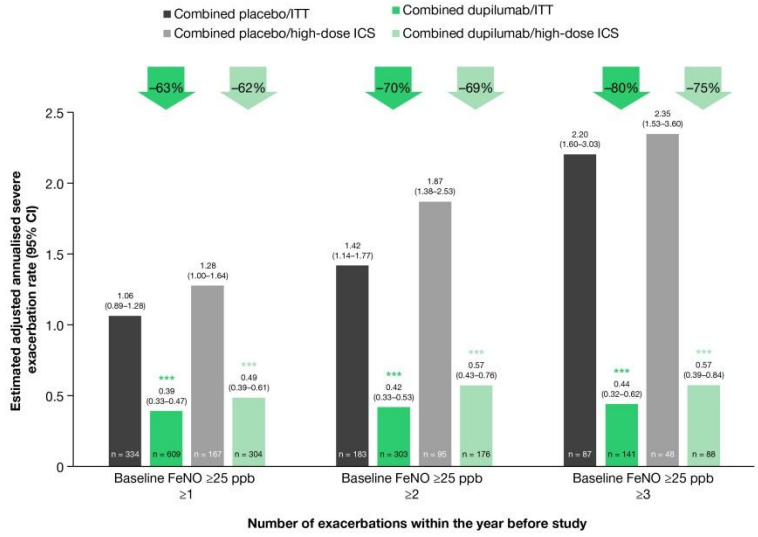
FIGURE 1 Reduction of annualised rate of severe exacerbations during the 52-week intervention period in subgroups of QUEST patients categorised by a) baseline blood eosinophils ≥150 cells·µL^{-1} ITT/with high-dose ICS, b) baseline blood eosinophils ≥300 cells·µL^{-1} ITT/with high-dose ICS, and c) baseline FeNO ≥25 ppb ITT/with high-dose ICS. CI: confidence interval; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; ITT, intention-to-treat; ppb: parts per billion. * p<0.05 *versus* placebo; ** p<0.01 *versus* placebo; *** : p<0.001 *versus* placebo.

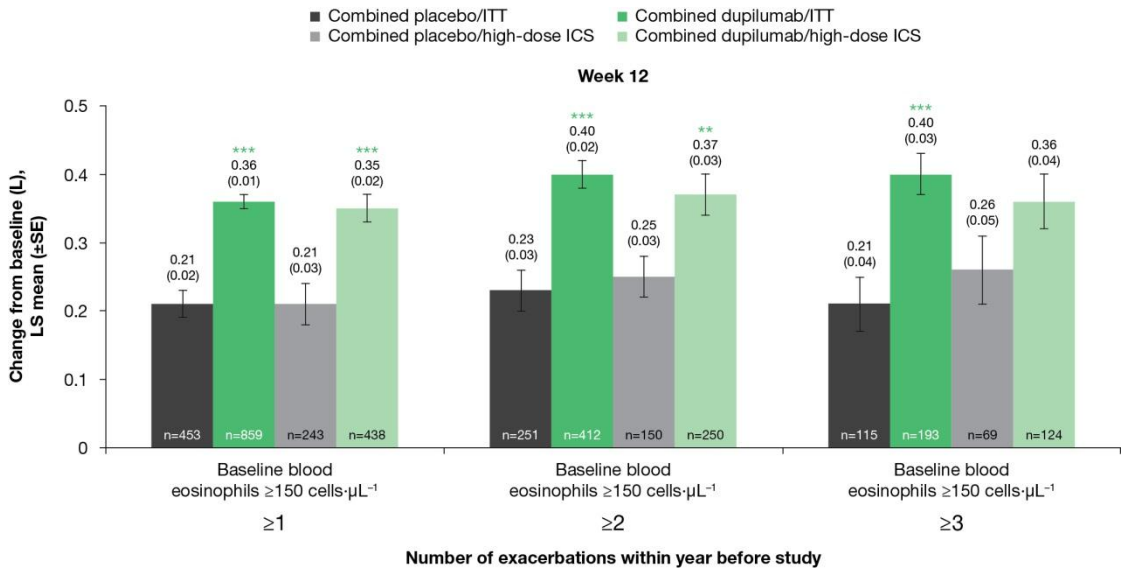
FIGURE 2 LS mean change from baseline at week 12 in pre-BD FEV_1 in patients categorised by a) baseline blood eosinophils ≥150 cells·µL^{-1} ITT/with high-dose ICS, b) baseline blood eosinophils ≥300 cells·µL^{-1} ITT/with high-dose ICS, and c) baseline FeNO ≥25 ppb ITT/with high-dose ICS.
BD: bronchodilator; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; ITT: intention-to-treat; LS: least squares; ppb: parts per billion; SE, standard error. * : p<0.05 *versus* placebo; ** : p<0.01 *versus* placebo; *** : p<0.001 *versus* placebo.

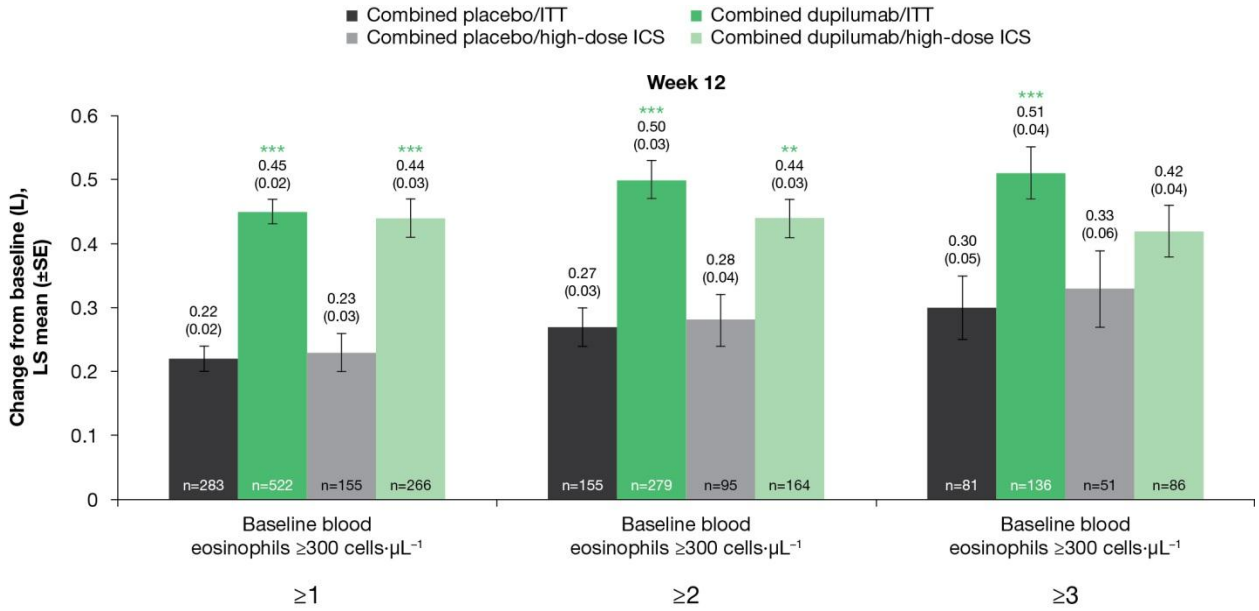
FIGURE 3 LS mean change from baseline at week 24 in ACQ-5 score in patients categorised by a) baseline blood eosinophils ≥150 cells·µL^{-1} ITT/with high-dose ICS, b) baseline blood eosinophils ≥300 cells·µL^{-1} ITT/with high-dose ICS, and c) baseline FeNO ≥25 ppb ITT/with high-dose ICS**.**
ACQ-5: 5-item Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; ICS: inhaled corticosteroid; ITT: intention-to-treat; LS: least squares; ppb: parts per billion; SE, standard error. * : p<0.05 *versus* placebo; ** : p<0.01 *versus* placebo; *** : p<0.001 *versus* placebo.

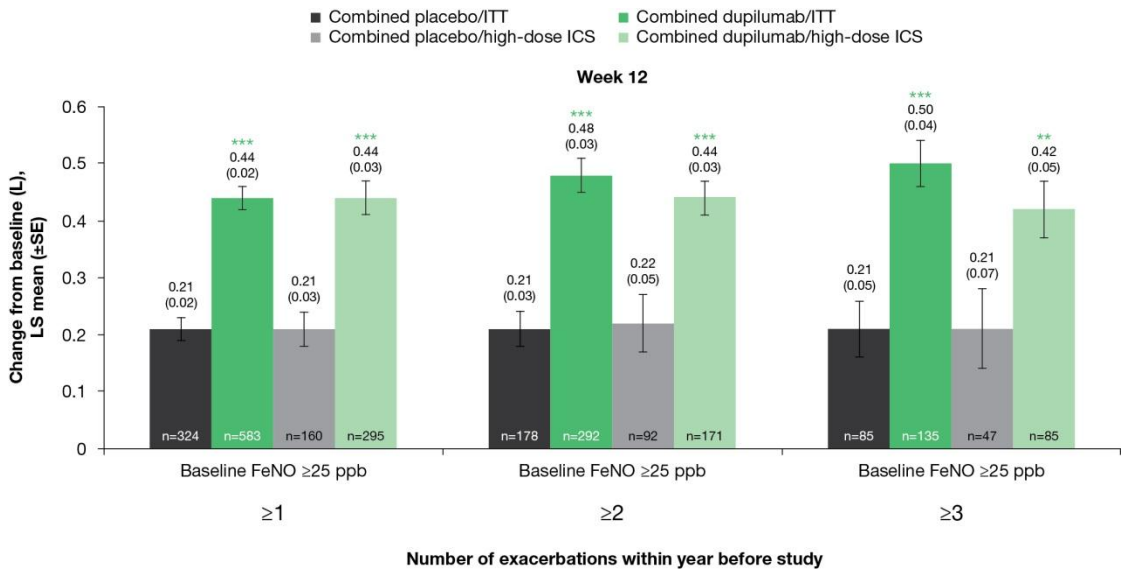

Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Estimated adjusted annualised severe exacerbation rate (95% CI)
2.5
2.0
1.5
1.0
0.5
0
–58%
–54%
–66%
–62%
–71%
–65%
1.05 (0.90–1.22)
0.44 (0.38–0.51)
1.19 (0.98–1.45)
0.55 (0.46–0.65)
1.39 (1.15–1.67)
0.47 (0.39–0.57)
1.51 (1.19–1.91)
0.57 (0.45–0.72)
2.00 (1.50–2.65)
0.58 (0.44–0.76)
1.85 (1.29–2.67)
0.65 (0.47–0.90)
***
n = 469
n = 889
n = 253
n = 451
n = 260
n = 425
n = 155
n = 256
n = 119
n = 200
n = 72
n = 127
Baseline blood eosinophils ≥150 cells·µL⁻¹
≥1
≥2
≥3
Number of exacerbations within the year before study

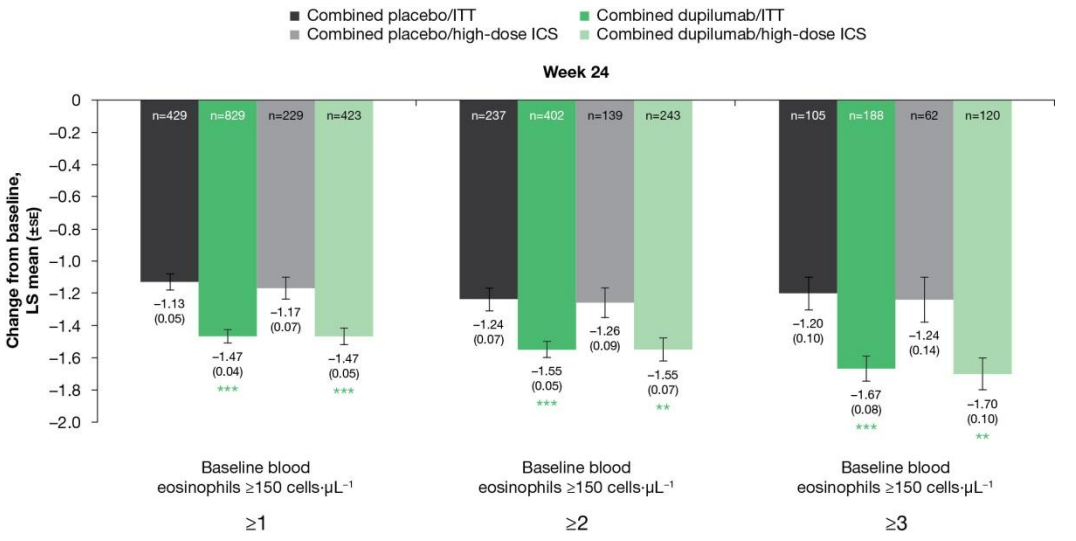

Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Estimated adjusted annualised severe exacerbation rate (95% CI)
2.5
2.0
1.5
1.0
0.5
0
–66%
–63%
–72%
–67%
–75%
–64%
1.16 (0.97–1.38)
0.39 (0.32–0.46)
1.41 (1.13–1.76)
0.53 (0.42–0.66)
1.52 (1.23–1.88)
0.42 (0.34–0.53)
1.80 (1.37–2.36)
0.60 (0.45–0.79)
1.85 (1.37–2.48)
0.46 (0.33–0.63)
1.82 (1.21–2.73)
0.65 (0.44–0.96)
***
n = 290
n = 541
n = 159
n = 272
n = 159
n = 286
n = 97
n = 167
n = 83
n = 140
n = 53
n = 88
Baseline blood eosinophils ≥300 cells·µL⁻¹
≥1
≥2
≥3
Number of exacerbations within the year before study

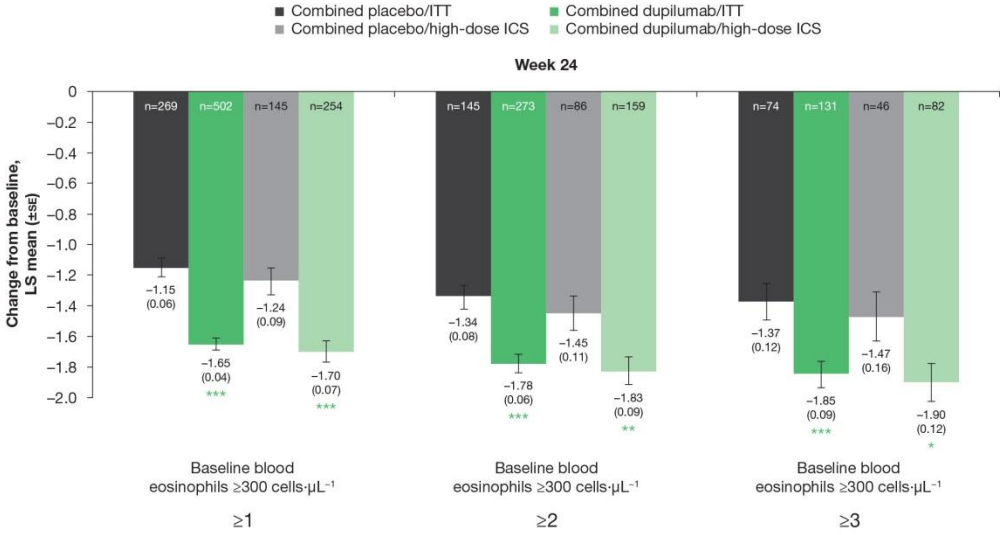

Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Estimated adjusted annualised severe exacerbation rate (95% CI)
2.5
2.0
1.5
1.0
0.5
0
–63%
–62%
–70%
–69%
–80%
–75%
1.06 (0.89–1.28)
0.39 (0.33–0.47)
1.28 (1.00–1.64)
0.49 (0.39–0.61)
1.42 (1.14–1.77)
0.42 (0.33–0.53)
1.87 (1.38–2.53)
0.57 (0.43–0.76)
2.20 (1.60–3.03)
0.44 (0.32–0.62)
2.35 (1.53–3.60)
0.57 (0.39–0.84)
***
n = 334
n = 609
n = 167
n = 304
n = 183
n = 303
n = 95
n = 176
n = 87
n = 141
n = 48
n = 88
Baseline FeNO ≥25 ppb
≥1
≥2
≥3
Number of exacerbations within the year before study

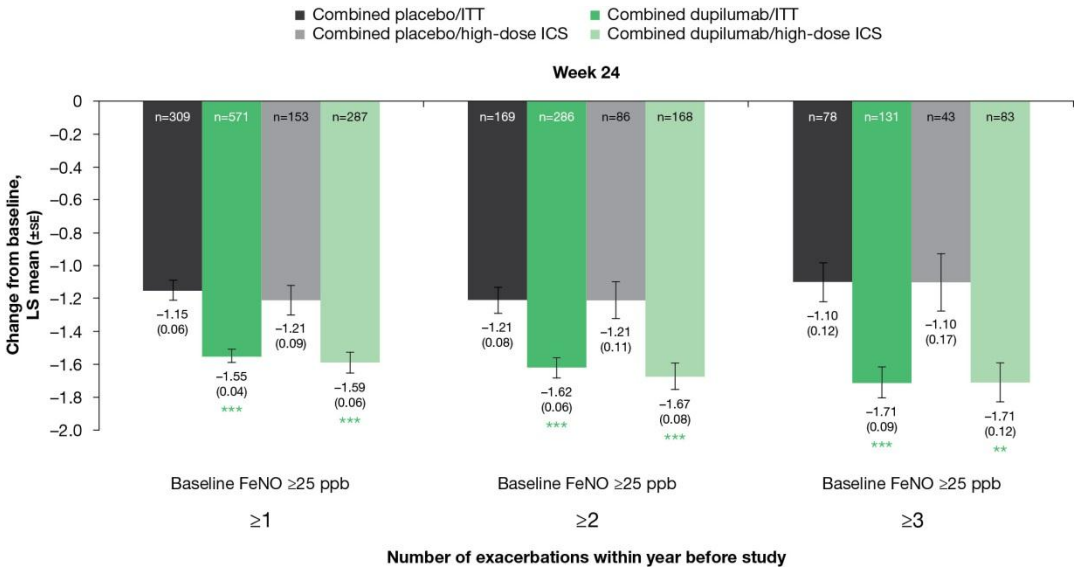

Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Week 12
Change from baseline (L), LS mean (±SE)
0.5
0.4
0.3
0.2
0.1
0
0.21 (0.02)
*** 0.36 (0.01)
0.21 (0.03)
*** 0.35 (0.02)
0.23 (0.03)
*** 0.40 (0.02)
0.25 (0.03)
** 0.37 (0.03)
0.21 (0.04)
*** 0.40 (0.03)
0.26 (0.05)
0.36 (0.04)
n=453
n=859
n=243
n=438
n=251
n=412
n=150
n=250
n=115
n=193
n=69
n=124
Baseline blood eosinophils ≥150 cells·μL⁻¹
≥1
≥2
≥3
Number of exacerbations within year before study


Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Week 12
Change from baseline (L), LS mean (±SE)
0.6
0.5
0.4
0.3
0.2
0.1
0
0.22 (0.02)
*** 0.45 (0.02)
0.23 (0.03)
*** 0.44 (0.03)
0.27 (0.03)
*** 0.50 (0.03)
0.28 (0.04)
** 0.44 (0.03)
0.30 (0.05)
*** 0.51 (0.04)
0.33 (0.06)
0.42 (0.04)
n=283
n=522
n=155
n=266
n=155
n=279
n=95
n=164
n=81
n=136
n=51
n=86
Baseline blood eosinophils ≥300 cells·μL⁻¹
≥1
≥2
≥3
Number of exacerbations within year before study

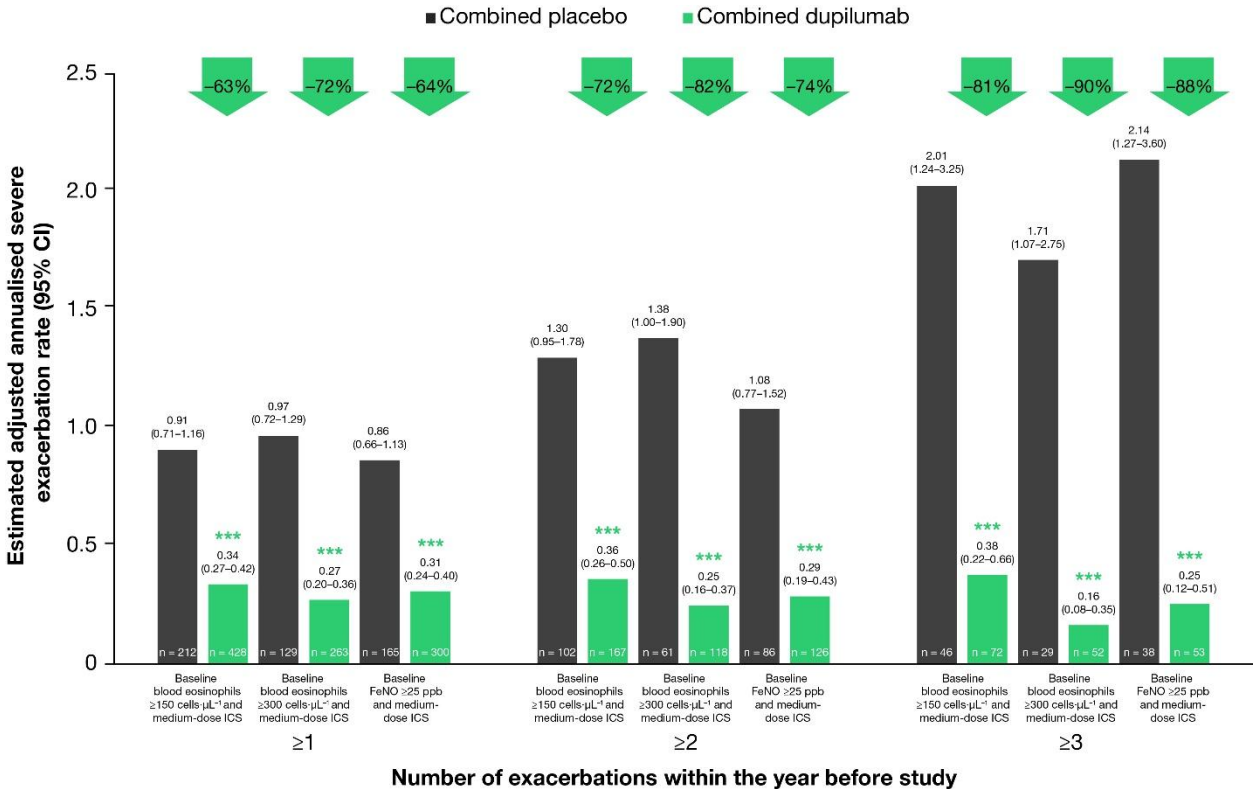

Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Week 12
Change from baseline (L), LS mean (±SE)
0.6
0.5
0.4
0.3
0.2
0.1
0
0.21 (0.02)
*** 0.44 (0.02)
0.21 (0.03)
*** 0.44 (0.03)
0.21 (0.03)
*** 0.48 (0.03)
0.22 (0.05)
*** 0.44 (0.03)
0.21 (0.05)
*** 0.50 (0.04)
0.21 (0.07)
** 0.42 (0.05)
n=324
n=583
n=160
n=295
n=178
n=292
n=92
n=171
n=85
n=135
n=47
n=85
Baseline FeNO ≥25 ppb
≥1
≥2
≥3
Number of exacerbations within year before study

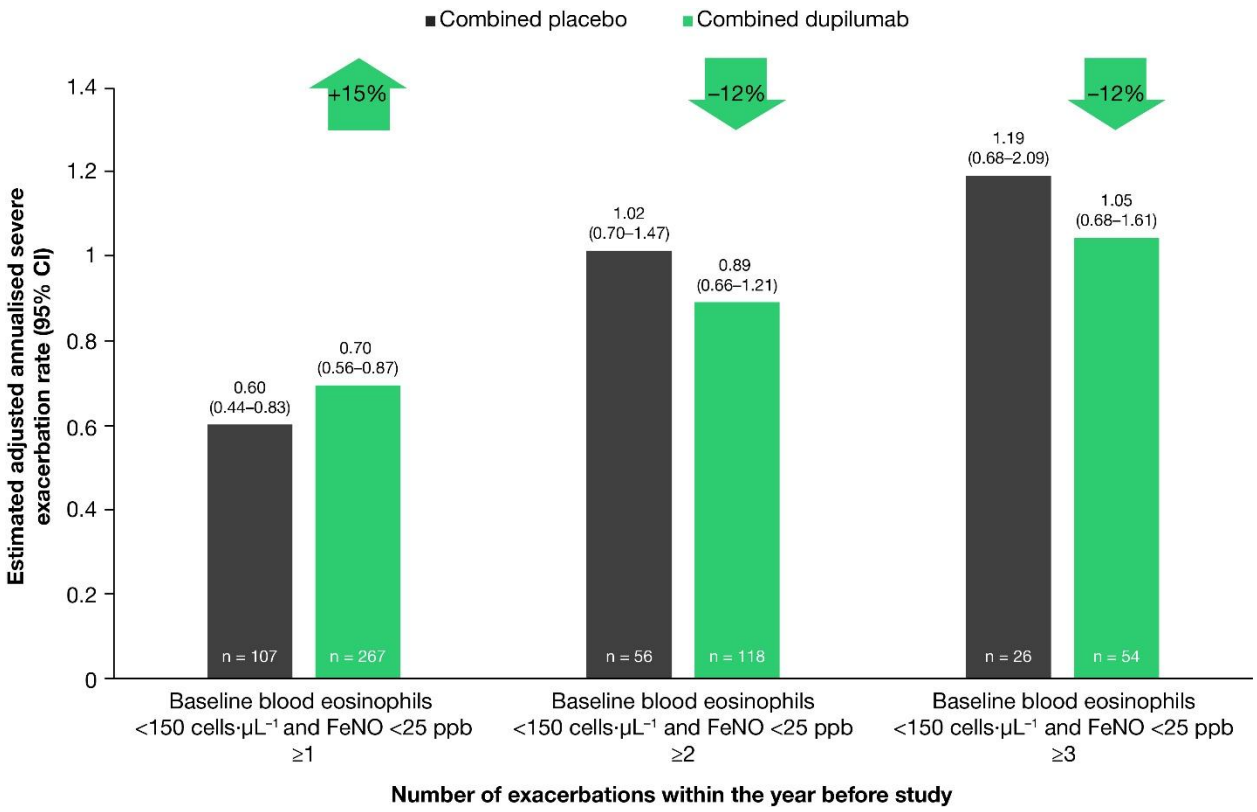

Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Week 24
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
−1.8
−2.0
n=429
n=829
n=229
n=423
n=237
n=402
n=139
n=243
n=105
n=188
n=62
n=120
−1.13 (0.05)
−1.47 (0.04) ***
−1.17 (0.07)
−1.47 (0.05) ***
−1.24 (0.07)
−1.55 (0.05) ***
−1.26 (0.09)
−1.55 (0.07) **
−1.20 (0.10)
−1.67 (0.08) ***
−1.24 (0.14)
−1.70 (0.10) **
Baseline blood eosinophils ≥150 cells·µL⁻¹
≥1
≥2
≥3
Number of exacerbations within year before study


Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Week 24
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
−1.8
−2.0
n=269
n=502
n=145
n=254
n=145
n=273
n=86
n=159
n=74
n=131
n=46
n=82
−1.15 (0.06)
−1.65 (0.04) ***
−1.24 (0.09)
−1.70 (0.07) ***
−1.34 (0.08)
−1.78 (0.06) ***
−1.45 (0.11)
−1.83 (0.09) **
−1.37 (0.12)
−1.85 (0.09) ***
−1.47 (0.16)
−1.90 (0.12) *
Baseline blood eosinophils ≥300 cells·µL⁻¹
≥1
≥2
≥3
Number of exacerbations within year before study


Combined placebo/ITT
Combined dupilumab/ITT
Combined placebo/high-dose ICS
Combined dupilumab/high-dose ICS
Week 24
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
−1.8
−2.0
n=309
n=571
n=153
n=287
n=169
n=286
n=86
n=168
n=78
n=131
n=43
n=83
−1.15 (0.06)
−1.55 (0.04) ***
−1.21 (0.09)
−1.59 (0.06) ***
−1.21 (0.08)
−1.62 (0.06) ***
−1.21 (0.11)
−1.67 (0.08) ***
−1.10 (0.12)
−1.71 (0.09) ***
−1.10 (0.17)
−1.71 (0.12) **
Baseline FeNO ≥25 ppb
≥1
≥2
≥3
Number of exacerbations within year before study

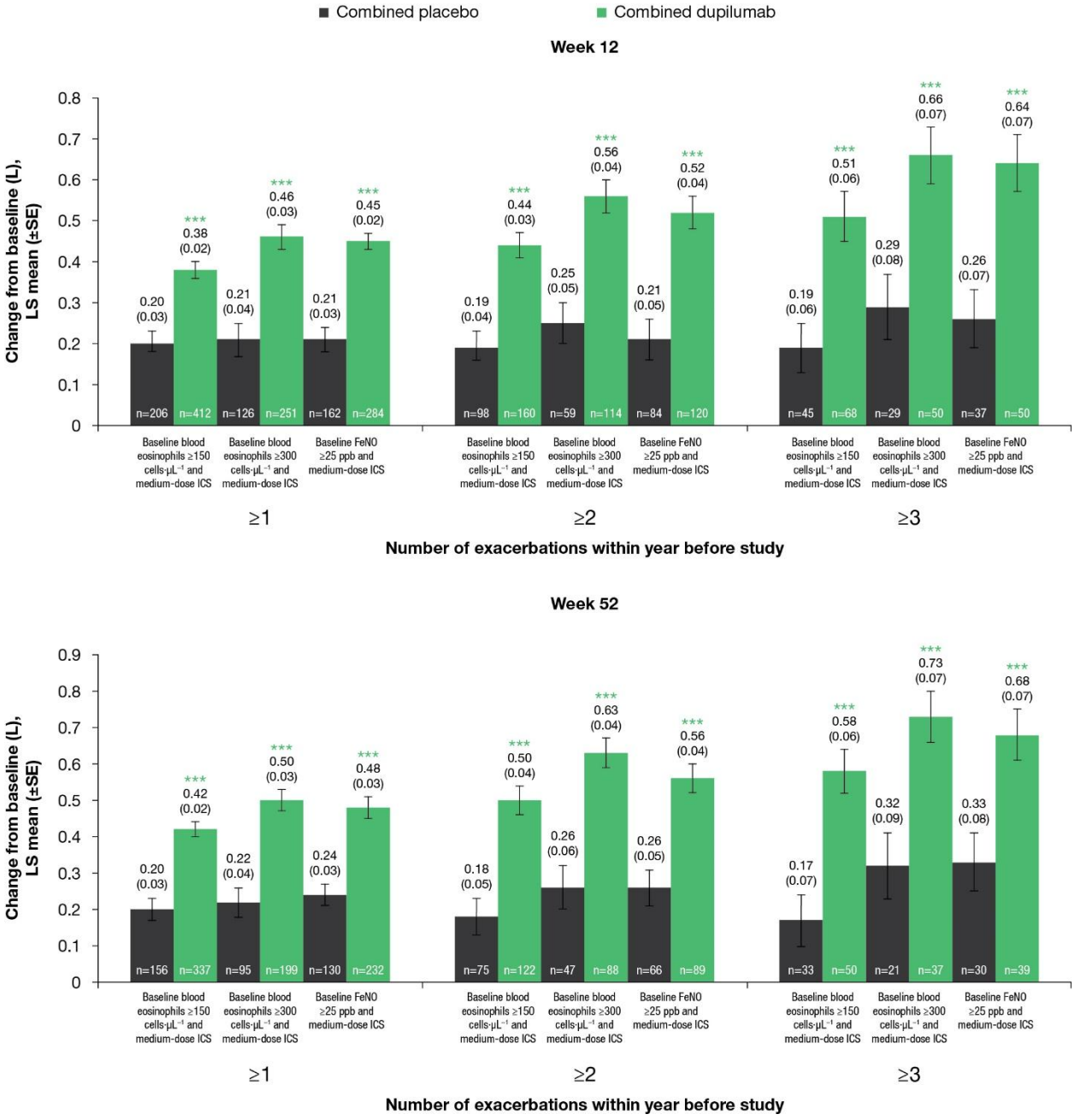
SUPPLEMENTARY FIGURE S1 Reduction of annualised rate of severe exacerbations during the 52-week intervention period by exacerbation history (≥1, ≥2 or ≥3) in the subgroups of patients with a) baseline blood eosinophils ≥150 cells·µL^{-1}, baseline blood eosinophils ≥300 cells·µL^{-1}, baseline FeNO ≥25 ppb and medium-dose ICS and b) baseline blood eosinophils <150 cells·µL^{-1} and FeNO <25 ppb.
CI: confidence interval; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; LS: least squares; ppb: parts per billion; Q2W: every 2 weeks. *** : p<0.001 *versus* placebo.

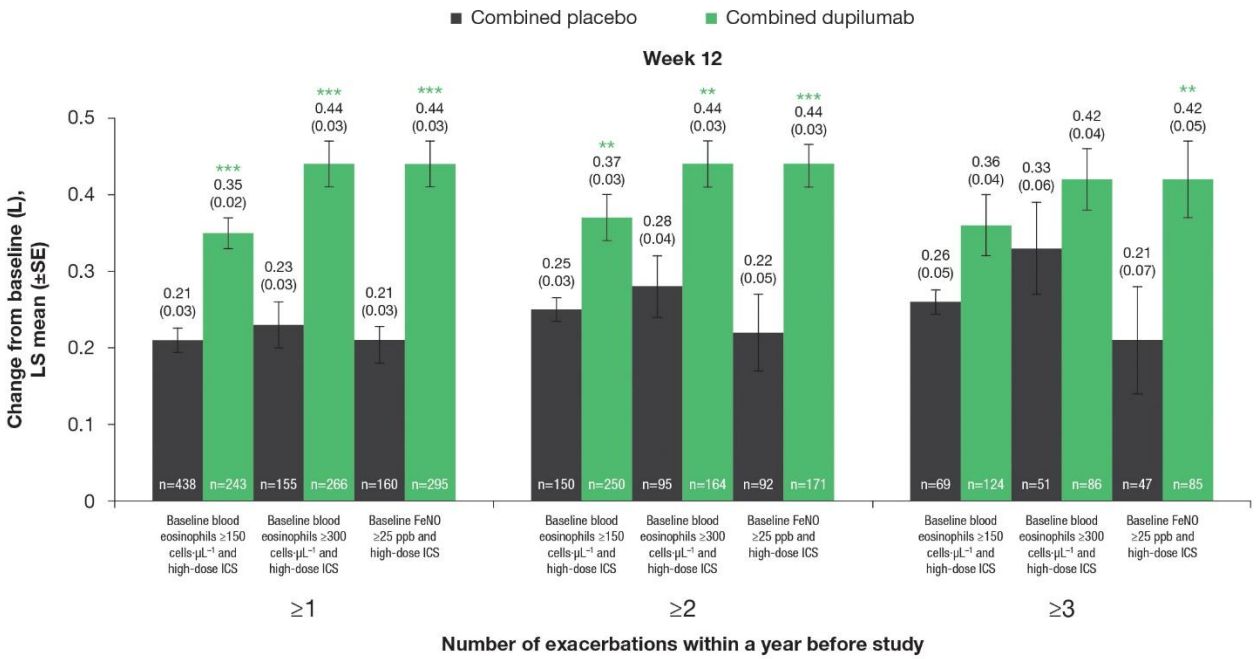


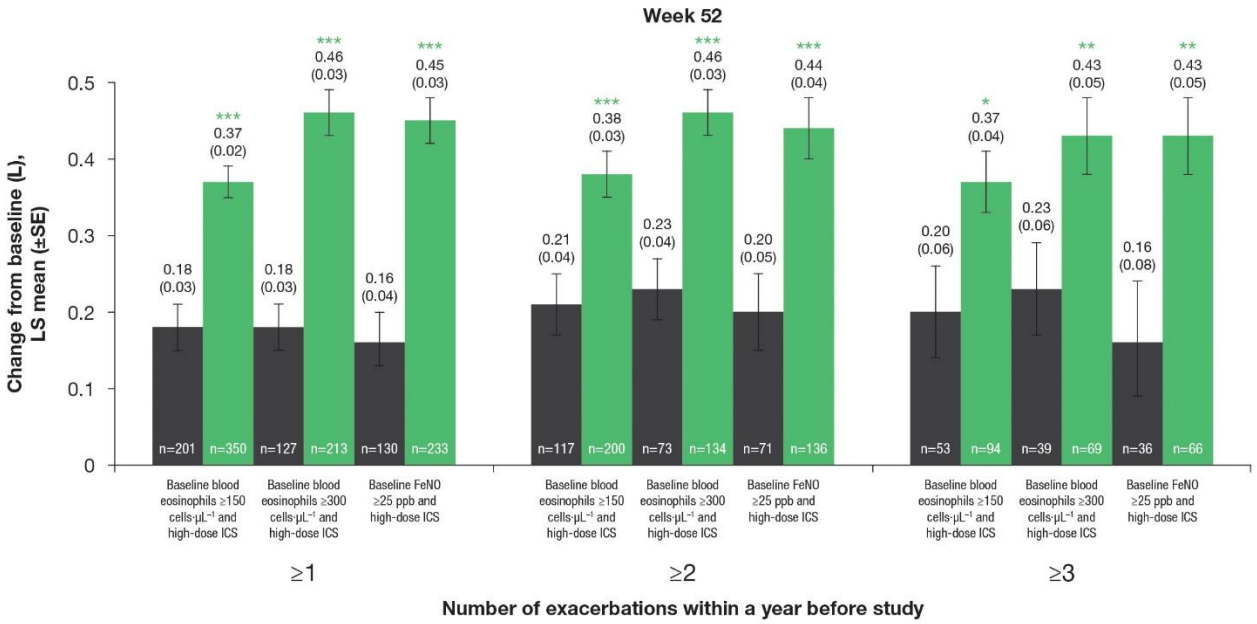

Combined placebo
Combined dupilumab
Estimated adjusted annualised severe exacerbation rate (95% CI)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
+15%
−12%
−12%
0.60 (0.44–0.83)
0.70 (0.56–0.87)
1.02 (0.70–1.47)
0.89 (0.66–1.21)
1.19 (0.68–2.09)
1.05 (0.68–1.61)
n = 107
n = 267
n = 56
n = 118
n = 26
n = 54
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥1
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥2
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥3
Number of exacerbations within the year before study

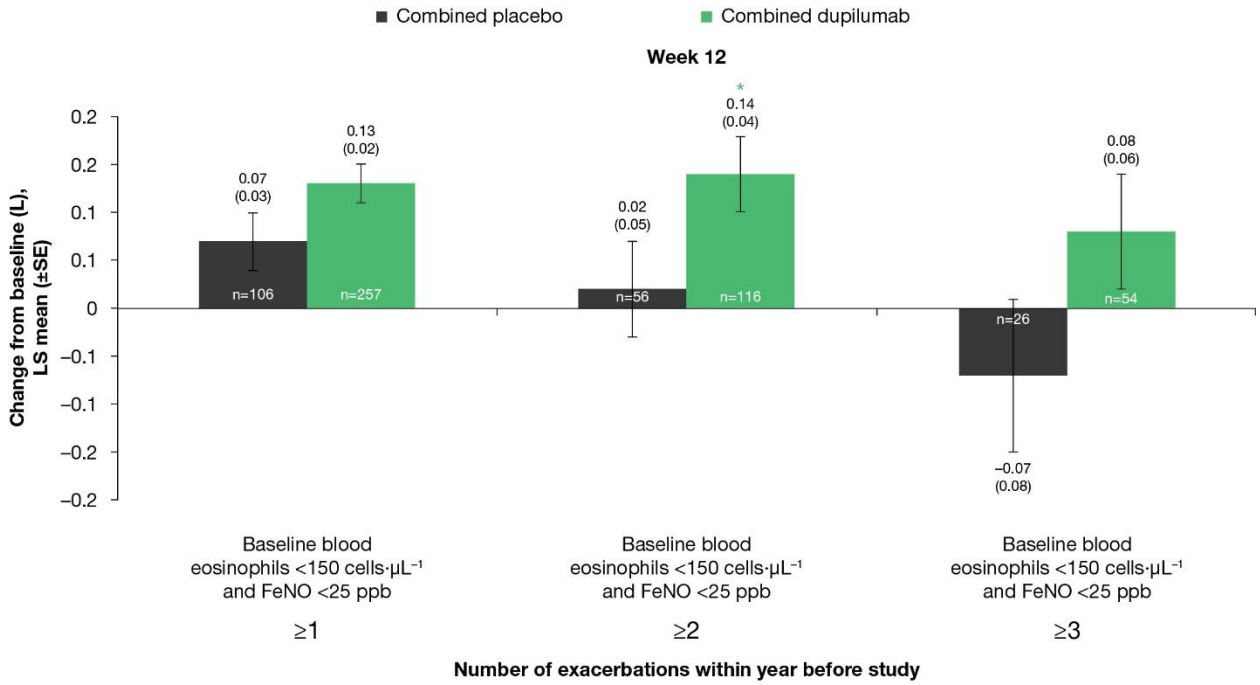
SUPPLEMENTARY FIGURE S2 LS mean change from baseline at week 12 and week 52 in pre-BD FEV_1 (L) by exacerbation history (≥1, ≥2 or ≥3) in the subgroups of patients with a) baseline blood eosinophils ≥150 cells·µL^{-1}, baseline blood eosinophils ≥300 cells·µL^{-1}, baseline FeNO ≥25 ppb and medium-dose ICS, b) baseline blood eosinophils ≥150 cells·µL^{-1}, baseline blood eosinophils ≥300 cells·µL^{-1}, baseline FeNO ≥25 ppb and high-dose ICS, and c) baseline blood eosinophils <150 cells·µL^{-1} and FeNO <25 ppb.

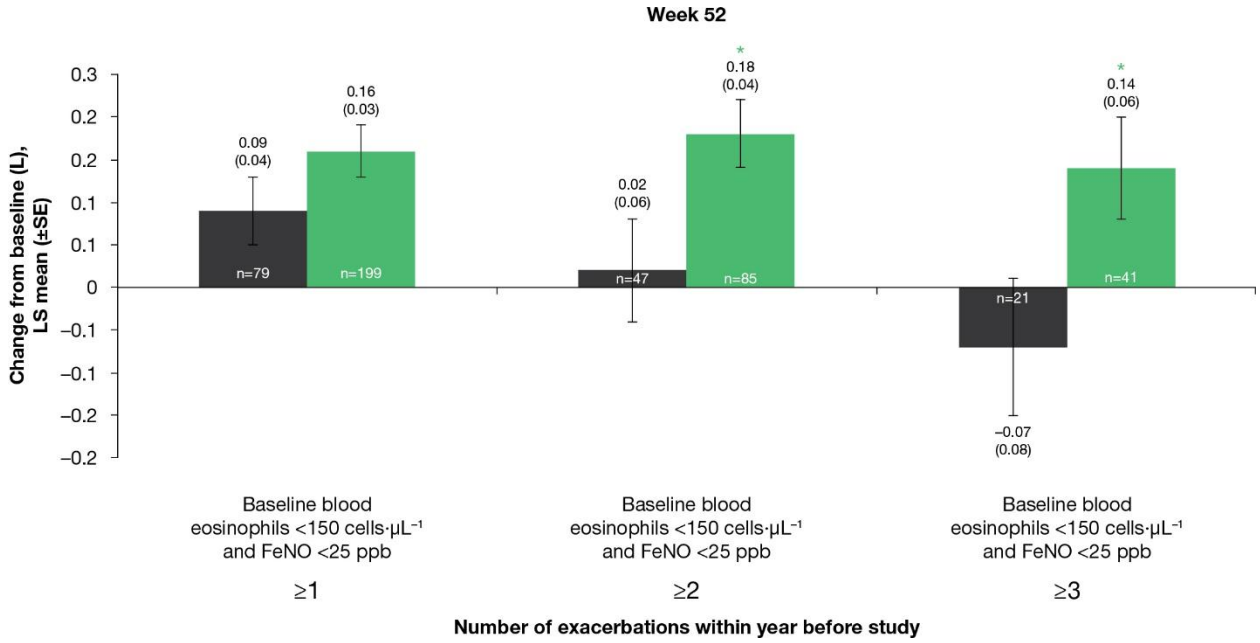
BD: bronchodilator; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LS: least squares; ppb: parts per billion; SE, standard error. * : p<0.05 *versus* placebo, *** : p<0.001 *versus* placebo.




Combined placebo
Combined dupilumab
Week 12
Change from baseline (L), LS mean (±SE)
0.5
0.4
0.3
0.2
0.1
0
0.21 (0.03)
*** 0.35 (0.02)
0.23 (0.03)
*** 0.44 (0.03)
0.21 (0.03)
*** 0.44 (0.03)
0.25 (0.03)
** 0.37 (0.03)
0.28 (0.04)
** 0.44 (0.03)
0.22 (0.05)
*** 0.44 (0.03)
0.26 (0.05)
0.36 (0.04)
0.33 (0.06)
0.42 (0.04)
0.21 (0.07)
** 0.42 (0.05)
n=438 n=243 n=155 n=266 n=160 n=295
n=150 n=250 n=95 n=164 n=92 n=171
n=69 n=124 n=51 n=86 n=47 n=85
Baseline blood eosinophils ≥150 cells·µL⁻¹ and high-dose ICS
Baseline blood eosinophils ≥300 cells·µL⁻¹ and high-dose ICS
Baseline FeNO ≥25 ppb and high-dose ICS
≥1
≥2
≥3
Number of exacerbations within a year before study

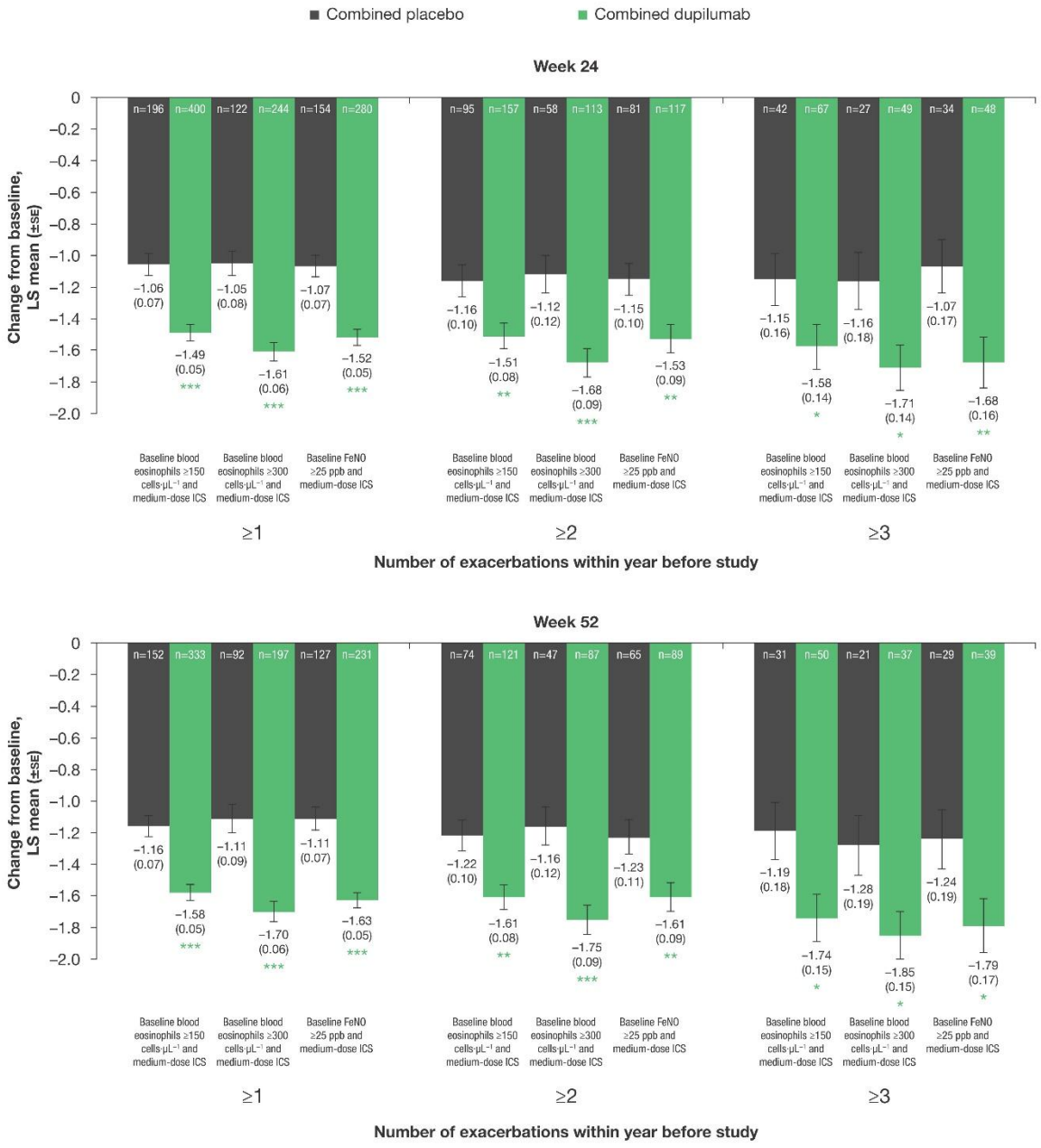

Week 52
Change from baseline (L), LS mean (±SE)
0.5
0.4
0.3
0.2
0.1
0
0.18 (0.03)
*** 0.37 (0.02)
0.18 (0.03)
*** 0.46 (0.03)
0.16 (0.04)
*** 0.45 (0.03)
0.21 (0.04)
*** 0.38 (0.03)
0.23 (0.04)
*** 0.46 (0.03)
0.20 (0.05)
*** 0.44 (0.04)
0.20 (0.06)
* 0.37 (0.04)
0.23 (0.06)
** 0.43 (0.05)
0.16 (0.08)
** 0.43 (0.05)
n=201 n=350 n=127 n=213 n=130 n=233
n=117 n=200 n=73 n=134 n=71 n=136
n=53 n=94 n=39 n=69 n=36 n=66
Baseline blood eosinophils ≥150 cells·µL⁻¹ and high-dose ICS
Baseline blood eosinophils ≥300 cells·µL⁻¹ and high-dose ICS
Baseline FeNO ≥25 ppb and high-dose ICS
≥1
≥2
≥3
Number of exacerbations within a year before study

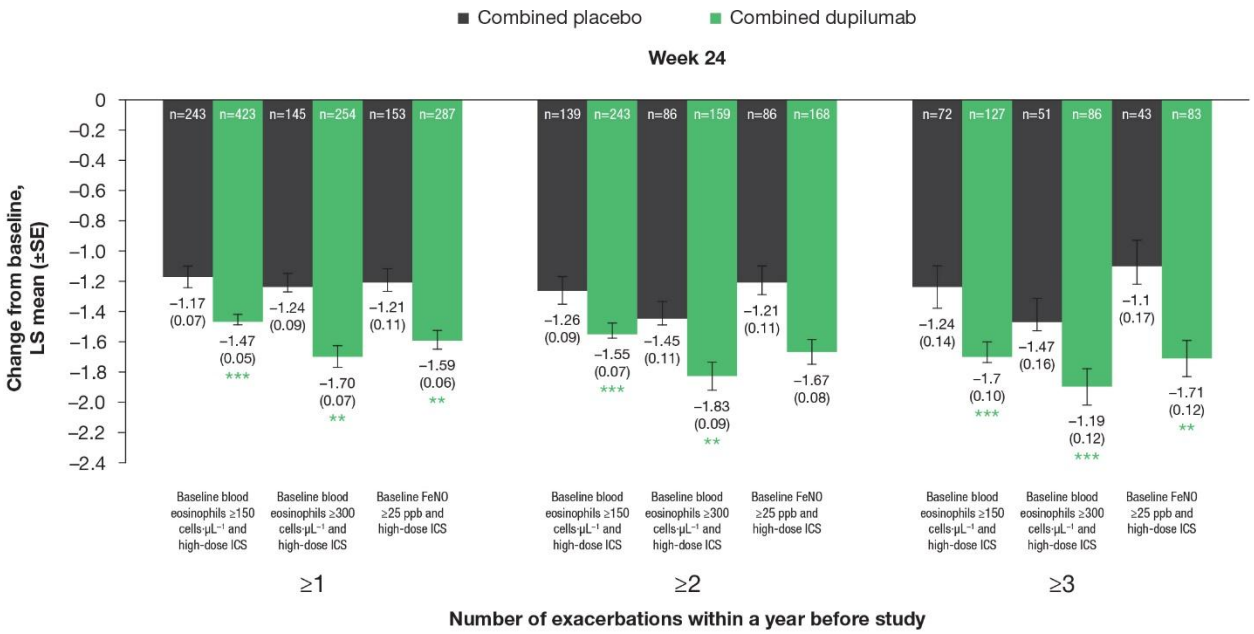

Combined placebo
Combined dupilumab
Week 12
Change from baseline (L), LS mean (±SE)
0.2
0.1
0
−0.1
−0.2
0.07 (0.03)
n=106
0.13 (0.02)
n=257
0.02 (0.05)
n=56
* 0.14 (0.04)
n=116
−0.07 (0.08)
n=26
0.08 (0.06)
n=54
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥1
≥2
≥3
Number of exacerbations within year before study

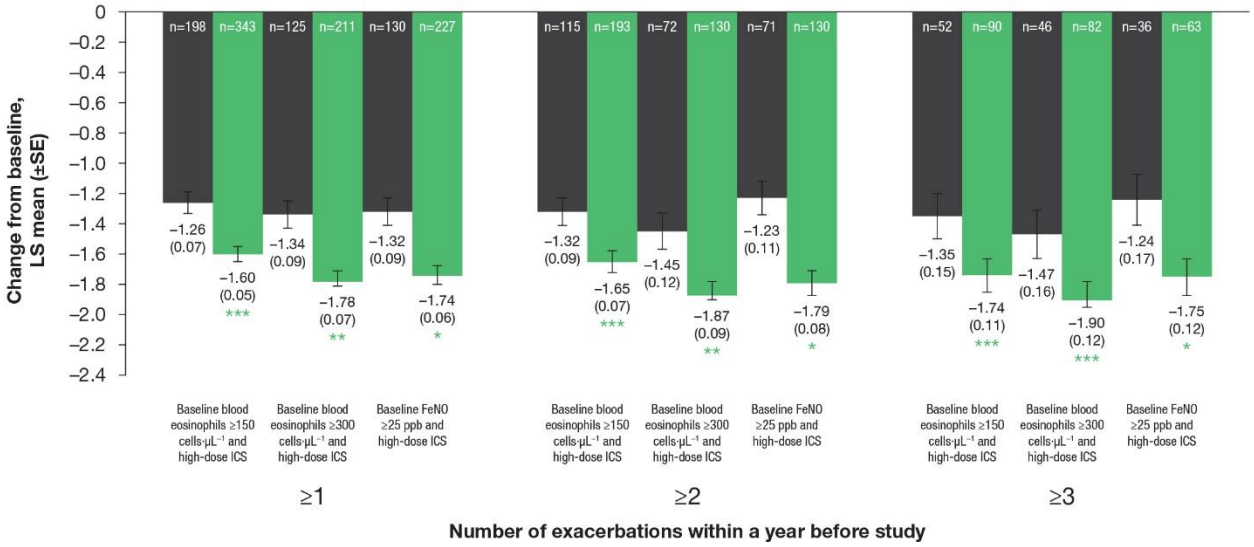

Week 52
Change from baseline (L), LS mean (±SE)
0.3
0.2
0.1
0
−0.1
−0.2
0.09 (0.04)
n=79
0.16 (0.03)
n=199
0.02 (0.06)
n=47
* 0.18 (0.04)
n=85
−0.07 (0.08)
n=21
* 0.14 (0.06)
n=41
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥1
≥2
≥3
Number of exacerbations within year before study

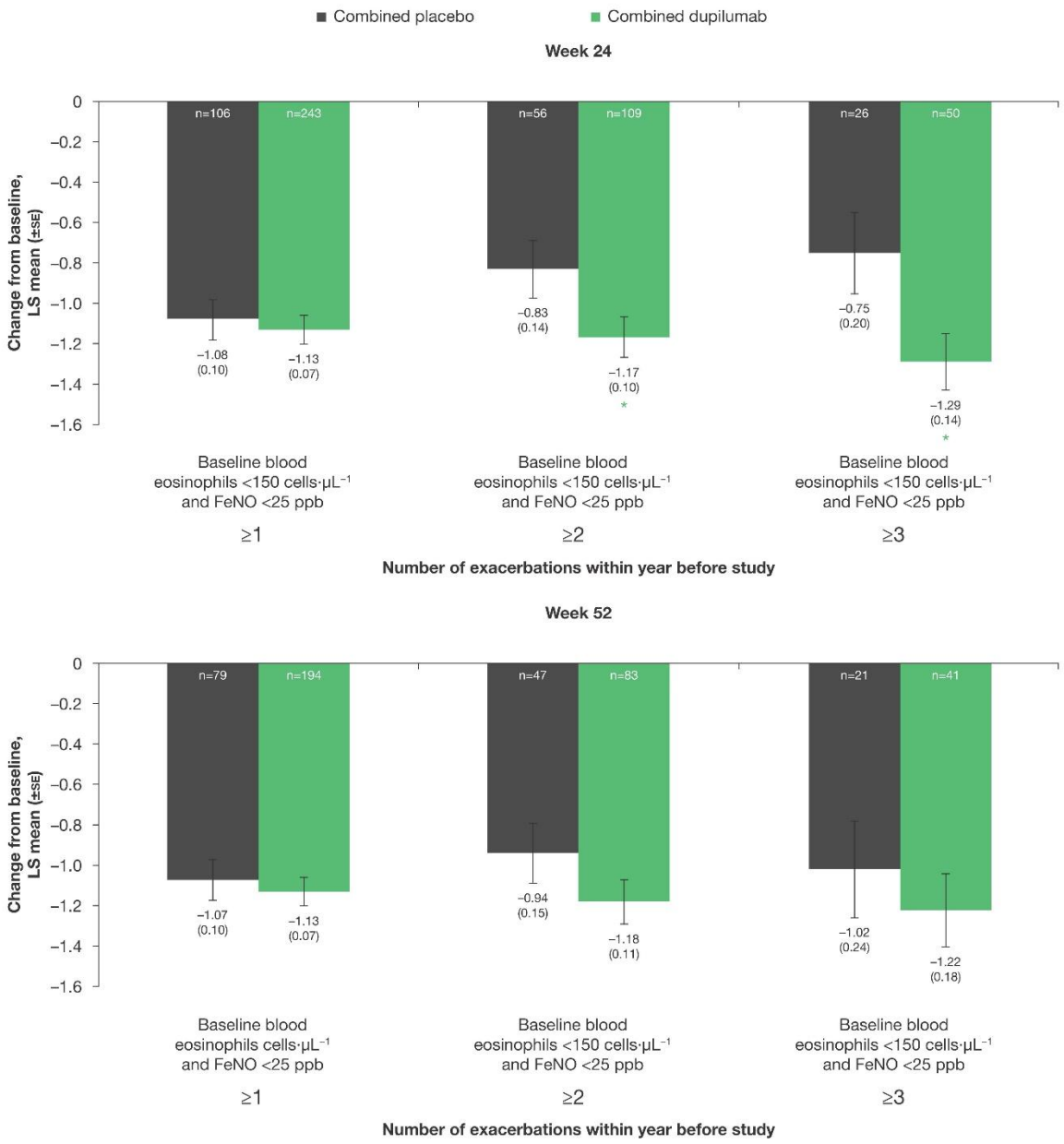
SUPPLEMENTARY FIGURE S3 LS mean change from baseline at week 24 and week 52 in ACQ-5 score by exacerbation history (≥1, ≥2 or ≥3) in the subgroup of patients with a) baseline blood eosinophils ≥150 cells·µL^{-1}, baseline blood eosinophils ≥300 cells·µL^{-1}, baseline FeNO ≥25 ppb and medium-dose ICS, b) baseline blood eosinophils ≥150 cells·µL^{-1}, baseline blood eosinophils ≥300 cells·µL^{-1}, baseline FeNO ≥25 ppb and high-dose ICS, and c) baseline blood eosinophils <150 cells·µL^{-1} and FeNO <25 ppb.

ACQ-5: 5-item Asthma Control Questionnaire; FeNO: fractional exhaled nitric oxide; ICS: inhaled corticosteroid; LS: least squares; ppb: parts per billion; SE, standard error. * : p<0.05 *versus* placebo, ** : p<0.01 *versus* placebo, *** : p<0.001 *versus* placebo.




Combined placebo
Combined dupilumab
Week 24
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
−1.8
−2.0
−2.2
−2.4
n=243 n=423 n=145 n=254 n=153 n=287
−1.17 (0.07)
−1.47 (0.05) ***
−1.24 (0.09)
−1.70 (0.07) **
−1.21 (0.11)
−1.59 (0.06) **
n=139 n=243 n=86 n=159 n=86 n=168
−1.26 (0.09)
−1.55 (0.07) ***
−1.45 (0.11)
−1.83 (0.09) **
−1.21 (0.11)
−1.67 (0.08)
n=72 n=127 n=51 n=86 n=43 n=83
−1.24 (0.14)
−1.7 (0.10) ***
−1.47 (0.16)
−1.19 (0.12) ***
−1.1 (0.17)
−1.71 (0.12) **
Baseline blood eosinophils ≥150 cells·μL⁻¹ and high-dose ICS
Baseline blood eosinophils ≥300 cells·μL⁻¹ and high-dose ICS
Baseline FeNO ≥25 ppb and high-dose ICS
≥1
≥2
≥3
Number of exacerbations within a year before study


Week 52
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
−1.8
−2.0
−2.2
−2.4
n=198 n=343 n=125 n=211 n=130 n=227
−1.26 (0.07)
−1.60 (0.05) ***
−1.34 (0.09)
−1.78 (0.07) **
−1.32 (0.09)
−1.74 (0.06) *
n=115 n=193 n=72 n=130 n=71 n=130
−1.32 (0.09)
−1.65 (0.07) ***
−1.45 (0.12)
−1.87 (0.09) **
−1.23 (0.11)
−1.79 (0.08) *
n=52 n=90 n=46 n=82 n=36 n=63
−1.35 (0.15)
−1.74 (0.11) ***
−1.47 (0.16)
−1.90 (0.12) ***
−1.24 (0.17)
−1.75 (0.12) *
Baseline blood eosinophils ≥150 cells·μL⁻¹ and high-dose ICS
Baseline blood eosinophils ≥300 cells·μL⁻¹ and high-dose ICS
Baseline FeNO ≥25 ppb and high-dose ICS
≥1
≥2
≥3
Number of exacerbations within a year before study


Combined placebo
Combined dupilumab
Week 24
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
n=106
n=243
n=56
n=109
n=26
n=50
−1.08 (0.10)
−1.13 (0.07)
−0.83 (0.14)
−1.17 (0.10)
*
−0.75 (0.20)
−1.29 (0.14)
*
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥1
≥2
≥3
Number of exacerbations within year before study
Week 52
Change from baseline, LS mean (±SE)
0
−0.2
−0.4
−0.6
−0.8
−1.0
−1.2
−1.4
−1.6
n=79
n=194
n=47
n=83
n=21
n=41
−1.07 (0.10)
−1.13 (0.07)
−0.94 (0.15)
−1.18 (0.11)
−1.02 (0.24)
−1.22 (0.18)
Baseline blood eosinophils cells·µL⁻¹ and FeNO <25 ppb
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
Baseline blood eosinophils <150 cells·µL⁻¹ and FeNO <25 ppb
≥1
≥2
≥3
Number of exacerbations within year before study