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Efficacy of dupilumab in patients with moderate-to-severe asthma and persistent airflow obstruction

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ABSTRACT

Background: The 52-week, phase 3 LIBERTY ASTHMA QUEST study (NCT02414854) in patients aged above or equal to 12 years with uncontrolled, moderate-to-severe asthma demonstrated the efficacy and safety of dupilumab 200 mg and 300 mg every 2 weeks vs matched placebo.

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Objective: To assess whether dupilumab improves clinical outcomes in QUEST patients with persistent airflow obstruction (PAO) defined as post-bronchodilator forced expiratory volume in 1 second/forced vital capacity ratio less than 0.7 at baseline.

Methods: End points were annualized rate of severe exacerbations, pre and post-bronchodilator forced expiratory volume in 1 second over time, proportion achieving reversal of PAO, and quality of life. Efficacy was evaluated in patients with or without PAO at baseline in subpopulations with eosinophils ≥ 150 cells/μL or fractional exhaled nitric oxide (FeNO) ≥ 25 ppb or eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb.

Results: Of 1902 patients enrolled in QUEST, 1039 (55%) had PAO at baseline. Dupilumab vs placebo rapidly and significantly improved lung function in patients with PAO and elevated type 2 inflammatory biomarkers at baseline. Dupilumab improved probability of reversing airflow obstruction (hazard ratio vs placebo 1.616 [95% confidence interval, 1.272-2.052] and 1.813 [1.291-2.546]; both $P < .001$) and significantly reduced severe exacerbations by 69% (relative risk, 0.411; 95% confidence interval [0.327-0.516]; $P < .0001$) and by 75% (0.252 [0.178-0.356]; $P < .0001$) in patients with PAO with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb, respectively. Similar results were observed in patient subgroups without PAO.

Conclusion: In patients with uncontrolled moderate-to-severe asthma, treatment with dupilumab facilitates reversal of PAO status and improves clinical outcomes.

Trial Registration: ClinicalTrials.gov identifier: NCT02414854.

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Introduction

Asthma is typically characterized by airflow obstruction that is reversible either spontaneously or after adequate therapy with corticosteroids or bronchodilators.[1] This distinguishes it from chronic obstructive pulmonary disease, where airflow obstruction is not fully reversible and is usually progressive.[2,3] Persistent airflow obstruction (PAO), most often defined by a post-bronchodilator ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) less than or equal to 70%,[4,5] is persistent despite appropriate treatment for moderate or severe asthma, or owing to obstruction that is incompletely reversible despite adequate therapy. PAO develops in approximately 16% of patients with asthma, with a higher incidence in those with severe or difficult-to-treat asthma.[6-8] PAO in asthma is thought to occur through airway wall remodeling that occurs as the disease progresses and is characterized by increased airway smooth muscle mass, goblet cell hyperplasia, and airway wall fibrosis.[1,2] Eosinophilic airway inflammation may also contribute to tissue remodeling and PAO in asthma; eosinophils release mediators that target bronchial epithelium and reducing eosinophils in vivo results in a concomitant decrease in these mediators.[9]

PAO is an important feature in asthma because patients with asthma with PAO typically experience worse asthma outcomes than those without.[6-8] Patients with PAO have increased exacerbation frequency, decreased lung function, and a higher mortality rate.[6,10] Several studies have identified risk factors independently associated with PAO; these include older age, male sex, Black race, current or past smoking, aspirin sensitivity, and longer asthma duration.[4,7,8] Furthermore, patients with asthma who have elevated eosinophil counts in the sputum or blood have been found to have an increased risk of developing PAO, suggesting a potential pathophysiological link between type 2 inflammation and PAO.[10,11] This has important implications as approximately 80% of the patients with asthma have a type 2 inflammation-driven disease, which is characterized by elevated biomarkers, including blood eosinophils and fractional exhaled nitric oxide (FeNO).[1,12,13]

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.[14-17] In the LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab vs placebo significantly reduced severe asthma exacerbations, improved pre-bronchodilator FEV_1 in the overall population of patients with uncontrolled, moderate-to-severe asthma, and was generally well tolerated.[18] Treatment effects were greater in patients with elevated type 2 biomarkers at baseline (blood eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb).

Given the association between PAO and poor asthma outcomes, including decreased lung function, and the possibility for treatment to attenuate lung function decline, this post hoc analysis aimed to evaluate the efficacy of dupilumab in improving clinical outcomes in patients enrolled in QUEST who had PAO at baseline with elevated baseline type 2 biomarkers (eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb or eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb). The biomarker combinations and cutoffs used for this analysis were informed by Global Initiative for Asthma guidelines and previous analyses of QUEST. Patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb represent the Global Initiative for Asthma-defined type 2 population; in QUEST, the greatest clinical benefits were observed in patients with the highest levels of elevated type 2 biomarkers.[18-20]

Methods

Study Design

LIBERTY ASTHMA QUEST (NCT02414854) was a phase 3 randomized, double blind, placebo-controlled study that assessed the effect of dupilumab in patients with uncontrolled moderate-to-severe asthma.[18] A total of 1902 patients above or equal to 12 years of age with uncontrolled asthma were randomized in a 2:2:1:1 ratio to add-on dupilumab 200 mg or 300 mg subcutaneously administered every 2 weeks or matched-volume placebos for 52 weeks.

Clinical data, study design, patient population details, and CONSORT diagrams have been previously reported.[18]

Background Controller Medication Use During QUEST

Before and during the screening period, patients were required to be on a stable dose of medium- to high-dose inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta-agonists [LABAs], long-acting muscarinic antagonists, leukotriene receptor antagonists, methylxanthines). Patients requiring a third controller, if used for at least 3 months and on a stable dose more than or equal to 1 month before visit 1, were also eligible for the study. For pre-bronchodilator measured parameters, spirometry was to be performed after a washout period of bronchodilators according to their duration of action: for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours, withholding the last dose of LABA for at least 12 hours (ultra-long-acting LABAs such as vilanterol were withheld for at least 24 hours), and withholding the last dose of long-acting muscarinic antagonist for at least 24 hours. This was verified before performing

the measurements. During the randomized treatment period, patients continued taking their background controller medication(s) at the stable dose used during the screening period. Patients were allowed to use albuterol/salbutamol or levalbuterol/levosalbutamol metered-dose inhalers or nebulizer solutions as reliever medication as needed during the study. All use of controller and rescue medications was documented by the patient in an electronic diary.

Study End Points

Efficacy end point analysis included the annualized rate of severe exacerbations (AER) (defined as a deterioration of asthma requiring use of systemic corticosteroids for more than or equal to 3 days or hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids) over the treatment period and change from baseline in pre- and post-bronchodilator FEV_1 over time. Percentage of patients achieving reversal in PAO status (defined as post-bronchodilator FEV_1/FVC ratio $\geq$ 0.7) at weeks 2, 12, 24, and 52 and probability of achieving reversal of PAO over the treatment period were also assessed. Asthma-related quality of life was assessed using the Asthma Quality of Life Questionnaire (AQLQ; scale 1-7, with higher scores indicating better quality of life).

Populations and Subgroups Assessed

The primary populations of interest were patients from the overall intention-to-treat population of QUEST who had PAO at baseline, defined as a post-bronchodilator FEV_1/FVC ratio less than 0.7 (70%), with elevated type 2 biomarkers at baseline (eosinophils $\geq$ 150 cells/μL or FeNO $\geq$ 25 ppb; eosinophils $\geq$ 300 cells/μL and FeNO $\geq$ 25 ppb). Patients without PAO at baseline (post-bronchodilator FEV_1/FVC ratio $\geq$ 0.7) were also assessed.

For the purpose of this analysis, patients who received the 200 mg and 300 mg every 2 weeks dupilumab doses were pooled, as were those who received the matched placebos.

Statistical Analysis

Adjusted AER was derived using a negative binomial model with the total number of events onset from randomization up to visit 18 or last contact date (whichever was earlier) as the response variable, including treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year before the study as covariates, and log-transformed standardized observation duration as an offset variable.

The change from baseline in pre- and post-bronchodilator FEV_1 was analyzed with the use of a linear mixed-effect model with repeated measures, which included change from baseline in the respective end point values up to week 52 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, the pre- (or post)-bronchodilator FEV_1 baseline value of the respective end point, and baseline-by-visit interaction as covariates.

The change in AQLQ global score was analyzed with a mixed-effect model with repeated measures, which included treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline AQLQ global score, and baseline-by-visit interaction as covariates.

Efficacy was also assessed by subgroup analysis using longitudinal multivariable analysis with interaction effects incorporating baseline characteristics of exacerbation history ($\leq$ 1 vs > 1 prior year exacerbations); smoking history (former vs never smokers); age (< 18 vs 18 to $\leq$ 64 vs $\geq$ 65 years), with vs without comorbid chronic rhinosinusitis or nasal polyposis, with vs without asthma with an allergic phenotype, age of asthma onset (< 18 vs 18 to $\leq$ 40 vs > 40 years), and time since asthma diagnosis (< median vs $\geq$ median; median = 17.04 years); for exacerbations, lung functions, and quality of life end points in the above-mentioned populations.

The time-to-first post-bronchodilator FEV_1/FVC $\geq$ 0.7 event variable (defined as the date of the first event minus the randomization date + 1) was analyzed using a Cox proportional hazards regression model, which included the time-to-first event as the dependent variable, and included treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline post-bronchodilator FEV_1/FVC (%) value as covariates. Patients with no event on or before visit 18 or last contact date were censored at visit 18 or the last contact date, whichever was sooner.

Role of the Funding Source

The external authors and study sponsors participated in the study design, data collection, data analysis, data interpretation, and development of the report and gave approval to submit for publication. The report was written by an independent medical writing company, funded by the study sponsors. All authors had full access to the study data and had final responsibility for the decision to submit for publication.

Results

Demographic and Disease Characteristics

Of 1902 QUEST patients with moderate-to-severe asthma, 685 (54%) dupilumab-treated patients and 354 (55%) placebo-treated patients had PAO at baseline. Of these patients, most also had elevated type 2 biomarkers at baseline; 80% of dupilumab-treated and 85% of placebo-treated patients had eosinophils $\geq$ 150 cells/μL or FeNO $\geq$ 25 ppb; 32% of dupilumab-treated patients and 33% of placebo-treated patients had eosinophils $\geq$ 300 cells/μL and FeNO $\geq$ 25 ppb. The baseline demographics and disease characteristics of the 4 patient populations are found in Table 1. In patient subgroups with elevated type 2 biomarkers, those with PAO were more likely to be male, more likely to have been a smoker, experienced greater severe exacerbations in the previous year, were first diagnosed with asthma at an older age, and had a longer time since first diagnosis than those without PAO at baseline. Time since first diagnosis of asthma was 15.96 to 22.34 years across the patient subgroups, with age at onset from 24.8 to 31.3 years.

Lung Function

Dupilumab vs placebo significantly improved pre-bronchodilator FEV_1 as early as week 2 in patients with and without PAO at baseline (Fig 1A-D). Consistent and sustained improvements were observed with dupilumab in the 52-week treatment period over placebo responses. Among the patients with PAO and eosinophils $\geq$ 150 cells/μL or FeNO $\geq$ 25 ppb, the least squares (LS) mean difference vs placebo was 0.17 L (95% confidence interval [CI], 0.11-0.22; $P < .0001$) at week 12 and 0.21 L (0.15-0.27; $P < .0001$) at week 52 (Fig 1A). Among the patients with PAO and eosinophils $\geq$ 300 cells/μL and FeNO $\geq$ 25 ppb, the LS mean difference vs placebo was 0.32 L (95% CI, 0.23-0.42; $P < .0001$) at week 12 and 0.42 L (0.32-0.52; $P < .0001$) at week 52 (Fig 1C).

Similar improvements were observed in post-bronchodilator FEV_1 with dupilumab vs placebo in patients with elevated type 2 inflammatory biomarkers with and without PAO at baseline (Fig 2) which were also sustained over the 52-week treatment period. In the patients with PAO and eosinophils $\geq$ 150 cells/μL or FeNO $\geq$ 25 ppb

Table 1
Baseline Demographics and Disease Characteristics

Characteristic	≥150 eosinophils/μL or FeNO ≥ 25 ppb				≥300 eosinophils/μL and FeNO ≥ 25 ppb			
	With PAO[a] at BL		Without PAO at BL		With PAO at BL		Without PAO at BL	
	Combined placebo (n = 300)	Combined dupilumab (n = 547)	Combined placebo (n = 227)	Combined dupilumab (n = 445)	Combined placebo (n = 116)	Combined dupilumab (n = 217)	Combined placebo (n = 80)	Combined dupilumab (n = 142)
Age, mean (SD), y	50.9 (12.9)	51.0 (13.3)	44.0 (13.3)	42.9 (16.5)	49.1 (13.6)	50.8 (12.7)	44.4 (17.9)	41.2 (16.9)
Female sex, n (%)	170 (56.7)	316 (57.8)	163 (71.8)	279 (62.7)	60 (51.7)	119 (54.8)	49 (61.3)	98 (69.0)
BMI, mean (SD), kg/m^2	29.28 (6.27)	28.42 (5.66)	29.55 (8.04)	29.48 (7.30)	27.34 (4.92)	27.66 (5.36)	27.95 (6.19)	27.93 (6.15)
High-dose ICS, n (%)	172 (57.3)	295 (53.9)	109 (48.0)	209 (47.0)	68 (58.6)	118 (54.4)	43 (53.8)	77 (54.2)
Age at onset of asthma, mean (SD), y	29.0 (18.7)	28.6 (18.9)	26.0 (19.0)	24.8 (19.3)	30.3 (17.1)	31.3 (18.2)	27.8 (20.5)	25.3 (19.0)
Time since first diagnosis of asthma, mean (SD), y	21.92 (15.32)	22.34 (15.31)	18.07 (14.31)	18.23 (13.90)	18.83 (12.71)	19.62 (14.36)	16.62 (13.89)	15.96 (12.29)
Former smoker, n (%)	72 (24.0)	110 (20.1)	32 (14.1)	72 (16.2)	31 (26.7)	41 (18.9)	11 (13.8)	16 (11.3)
Proportion of patient with CRS/NP, n (%)	72 (24.0)	138 (25.2)	51 (22.5)	83 (18.7)	42 (36.2)	75 (34.6)	26 (32.5)	37 (26.1)
Time since last severe asthma exacerbation, mean (SD), mo	5.53 (2.95)	5.62 (3.01)	5.51 (2.83)	5.71 (2.91)	5.25 (3.08)	5.03 (2.91)	5.53 (2.65)	5.51 (2.90)
Severe asthma exacerbations in past year, mean (SD)	2.29 (1.96)	2.09 (2.00)	2.11 (1.76)	2.04 (2.79)	2.66 (2.29)	2.49 (2.59)	2.06 (1.58)	2.06 (1.57)
Pre-bronchodilator FEV_1, mean (SD), L	1.61 (0.58)	1.62 (0.58)	1.96 (0.56)	2.02 (0.58)	1.67 (0.58)	1.65 (0.64)	1.96 (0.61)	2.01 (0.56)
Pre-bronchodilator FEV_1 percent predicted, mean (SD), %	52.66 (12.96)	52.90 (13.13)	65.40 (10.51)	65.17 (0.46)	53.49 (12.71)	52.85 (13.39)	63.60 (11.48)	65.72 (10.75)
Post-bronchodilator FEV_1, mean (SD), L	1.94 (0.66)	1.92 (0.66)	2.46 (0.68)	2.51 (0.68)	2.00 (0.64)	1.97 (0.70)	2.51 (0.71)	2.52 (0.67)
FEV_1 reversibility, mean (SD), %	26.15 (18.86)	24.38 (17.43)	26.51 (17.72)	29.02 (25.85)	23.54 (18.79)	25.98 (19.85)	28.75 (18.93)	29.20 (21.56)
ACQ-5 score, mean (SD)	2.82 (0.81)	2.81 (0.77)	2.69 (0.68)	2.72 (0.82)	2.85 (0.81)	2.84 (0.83)	2.68 (0.66)	2.73 (0.87)
AQLQ score, mean (SD)	4.20 (0.99)	4.29 (1.04)	4.31 (1.04)	4.35 (1.11)	4.24 (0.94)	4.24 (1.06)	4.30 (1.09)	4.42 (1.15)
Post-BD FEV_1/FVC mean (SD), %	59.90 (7.56)	58.99 (7.94)	76.62 (5.45)	76.53 (5.70)	60.68 (5.90)	59.77 (7.60)	76.19 (5.21)	76.42 (5.16)
Blood eosinophils, median (Q1-Q3), cells/μL	350.0 (200.0-560.0)	340.0 (210.0-590.0)	330.0 (210.0-500.0)	290.0 (180.0-500.0)	615.0 (420.0-880.0)	540.0 (390.0-720.0)	530.0 (390.0-860.0)	535.0 (400.0-820.0)
Total IgE, median (Q1-Q3), IU/mL	225.5 (92.0-520.0)	188.0 (75.0-485.0)	168.0 (61.5-446.5)	190.0 (71.0-536.0)	277.0 (106.5-577.0)	202.0 (92.0-550.0)	237.0 (82.0-505.0)	242.0 (88.5-725.0)
FeNO, median (Q1-Q3), ppb	32.0 (17.0-51.0)	29.0 (18.0-50.0)	31.0 (19.0-53.0)	29.0 (17.0-49.0)	45.5 (34.0-67.0)	45.0 (31.0-67.0)	53.0 (38.0-81.5)	48.5 (35.0-74.0)

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; BL, baseline; BMI, body mass index; CRS/NP, chronic rhinosinusitis or bilateral nasal polyposis; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; PAO, persistent airflow obstruction; Q, quarter; SD, standard deviation.
[a]PAO defined as post-BD FEV_1/FVC < 0.7.

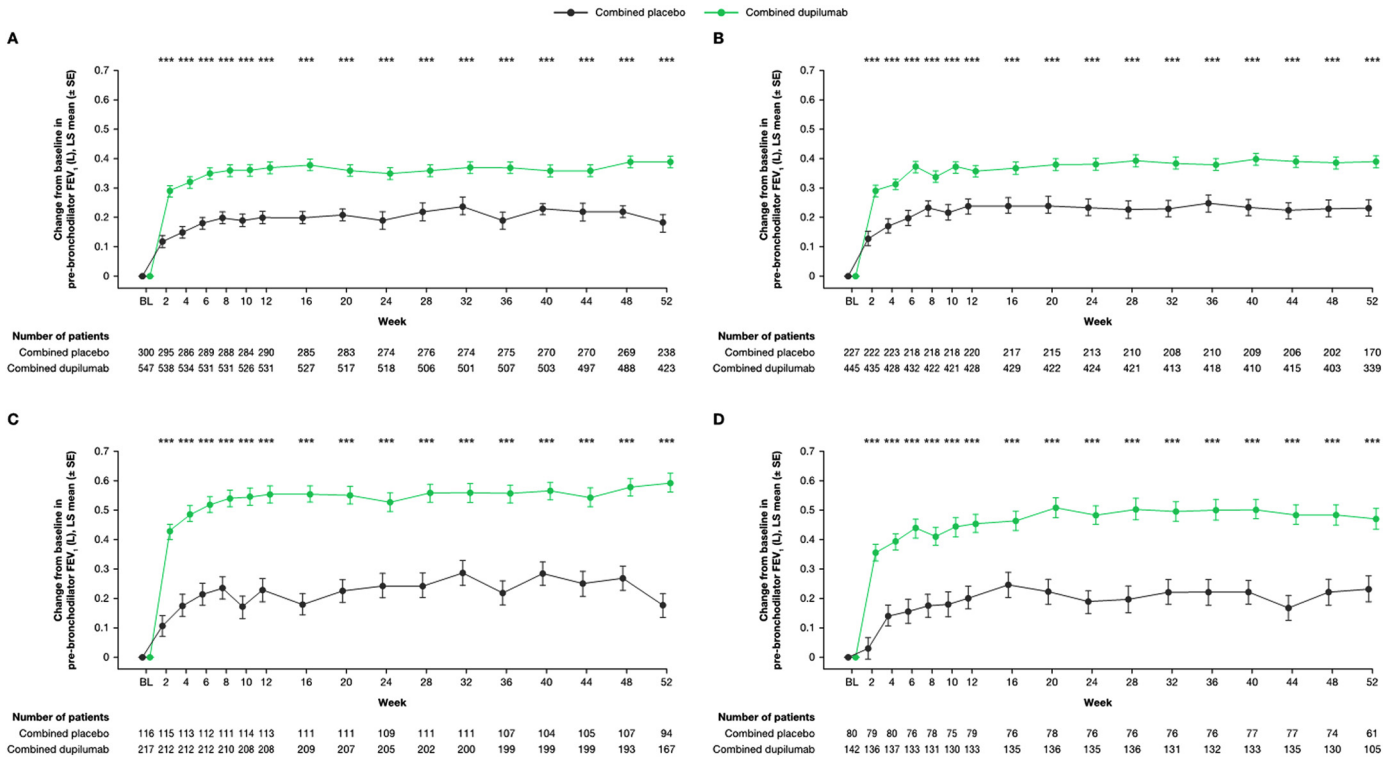


Figure 1. Change from baseline in pre-bronchodilator FEV_1 over time in patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb (A) with PAO, (B) without PAO, and in patients with eosinophils ≥ 300 cells/μL or FeNO ≥ 25 ppb (C) with PAO, and (D) without PAO. *** $P < 0.001$ FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; PAO, persistent airflow obstruction.

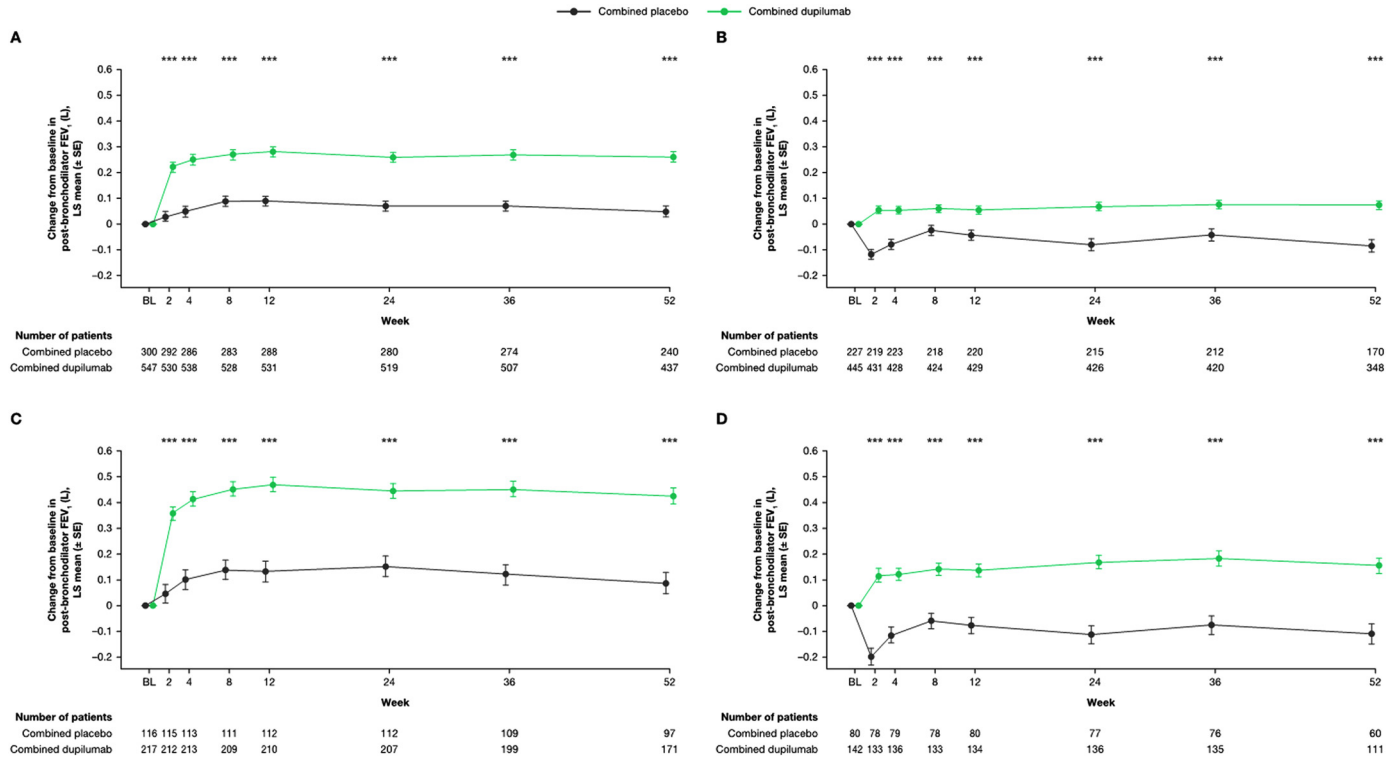


Figure 2. Change from baseline in post-bronchodilator FEV_1 over time in patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb (A) with PAO, (B) without PAO, and in patients with eosinophils ≥ 300 cells/μL or FeNO ≥ 25 ppb (C) with PAO, and (D) without PAO. *** $P < 0.001$. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; PAO, persistent airflow obstruction; SE, standard error.

at baseline, the LS mean difference vs placebo was 0.19 L (95% CI, 0.13-0.24; $P < .0001$) at week 12 and 0.21 L (0.16-0.27; $P < .0001$) at week 52 (Fig 2A). In the patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline, LS mean difference vs placebo was 0.34 L (95% CI, 0.24-0.43; $P < .0001$) at week 12 and 0.34 L (0.24-0.44; $P < .0001$) at week 52 (Fig 2C). Similar results were observed for pre- and post-BD FEV_1 in the subgroups without PAO (all $P < .0001$) (Fig 2B and D).

Subgroup analyses conducted to evaluate whether other baseline characteristics affected FEV_1 response revealed that, in both subgroups of patients with PAO at baseline, a greater improvement in pre-bronchodilator FEV_1 was observed in dupilumab-treated patients aged below 18 years and above or equal to 18 years to below 64 years (corresponding treatment-by-subgroup interaction *P* values all < .05) (eFig 1A and C). For all other subgroups analyzed, including populations without PAO, no significant interactions were observed that would affect pre-bronchodilator FEV_1 (eFig 1A-D).

There was a greater improvement in post-bronchodilator FEV_1, among the dupilumab-treated patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb who experienced a greater number of prior year exacerbations (*P* < .05) (eFig 1E). No other significant interactions were observed for any other subgroups or in the populations without PAO (eFig 1E-H).

Change in Airflow Obstruction Status (Forced Expiratory Volume in 1 Second/Forced Vital Capacity)

In both subgroups of patients with PAO at baseline, approximately twice as many dupilumab-treated than placebo-treated patients reversed PAO status as early as week 2 (Fig 3). The percentage of patients treated with dupilumab vs placebo achieving a post-bronchodilator FEV_1/FVC ratio ≥ 0.7 by week 2 was 23.6% vs 13.4% in patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb and 32.5% vs 18.3% in patients with eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb, respectively (Figs 3A and B). By week 52, these percentages increased to 31.1% vs 15.8% in patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb and 44.4% vs 16.5% in patients with eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline, respectively (Fig 3A and B). These intergroup differences were statistically significant over time indicating that compared with placebo, dupilumab improved the probability of changing PAO status in both subgroups with PAO at baseline (hazard ratio vs matched placebo 1.616 [95% CI, 1.272-2.052] for patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb and 1.813 [1.291-2.546] for patients with eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb, respectively, both *P* < .001) (Fig 4A and B).

Annualized Rate of Severe Exacerbations

Dupilumab vs placebo significantly reduced AER by 59% (risk ratio, 0.411; 95% CI, 0.327-0.516; *P* < .0001) in patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb at baseline and by 75% (0.252; 0.178-0.356; *P* < .0001) in patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline (Fig 5A and C), including in both subgroups without PAO (both *P* < .0001) (Fig 5B and D).

Subgroup analyses revealed that, in patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb at baseline, covariates associated with a significantly greater reduction in exacerbation risk in dupilumab-treated patients were the following: a greater number of exacerbations in the prior year, older age of asthma onset, and less time since diagnosis (all corresponding treatment-by-subgroup interaction *P* values < .05) (eFig 2A). The absence of an allergic asthma phenotype was associated with a significantly greater reduction in exacerbation risk in dupilumab-treated patients without PAO with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb at baseline (*P* = .04) (eFig 2B). Older age at asthma onset was associated with a significantly greater reduction in exacerbation risk in dupilumab-treated patients without PAO with eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb (*P* = .04) (eFig 2D). No other significant interactions with risk of exacerbations were observed (eFig 2).

Asthma-Related Quality of Life

Dupilumab improved health-related quality of life, as assessed by the AQLQ global score, compared with placebo in both subgroups with and without PAO (Fig 6). Significant improvements were

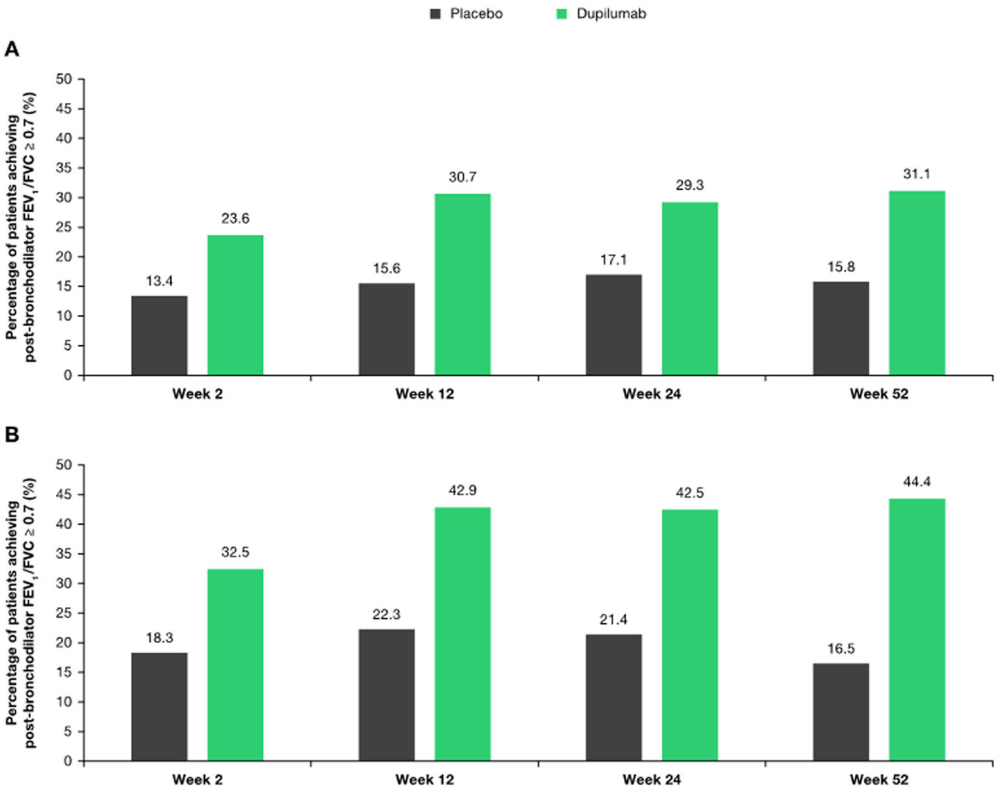


Figure 3. Percentage of patients achieving post-bronchodilator FEV_1/FVC ≥ 0.7 over time in (A) patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb, and (B) patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PAO, persistent airflow obstruction.

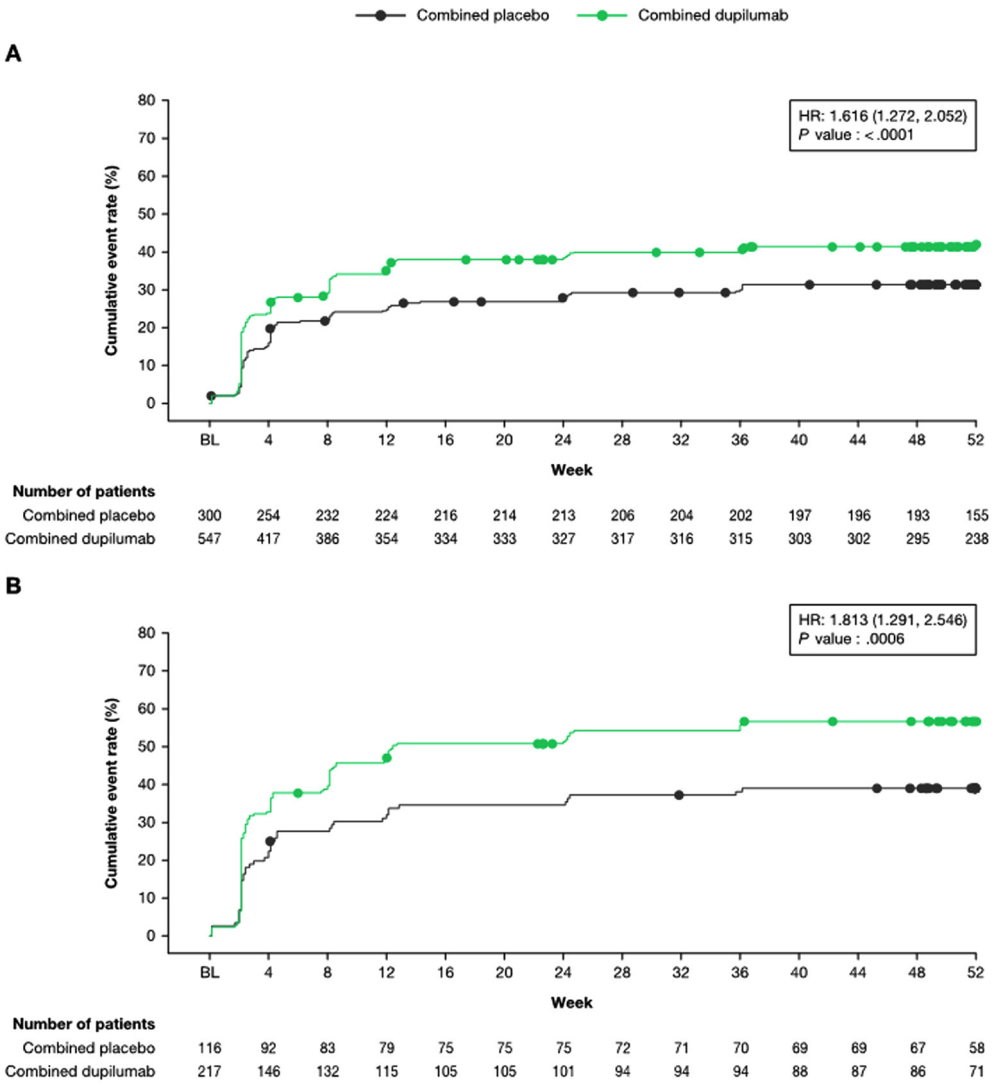


Figure 4. Kaplan–Meier plot of time-to-first post-bronchodilator $FEV_1/FVC \geq 0.7$ event in (A) patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb, and (B) patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HR, hazard ratio; PAO, persistent airflow obstruction.

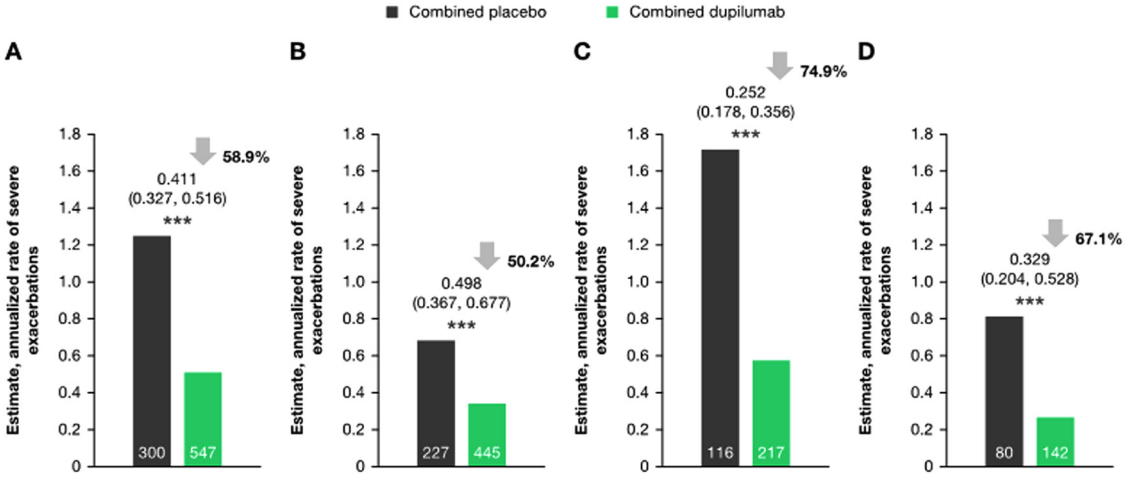


Figure 5. Annualized rate of severe exacerbations during the 52-week treatment period in patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb (A) with PAO, (B) without PAO, and in patients with eosinophils ≥ 300 cells/μL or FeNO ≥ 25 ppb (C) with PAO, and (D) without PAO. *** $P < 0.001$. FeNO, fractional exhaled nitric oxide; PAO, persistent airflow obstruction.

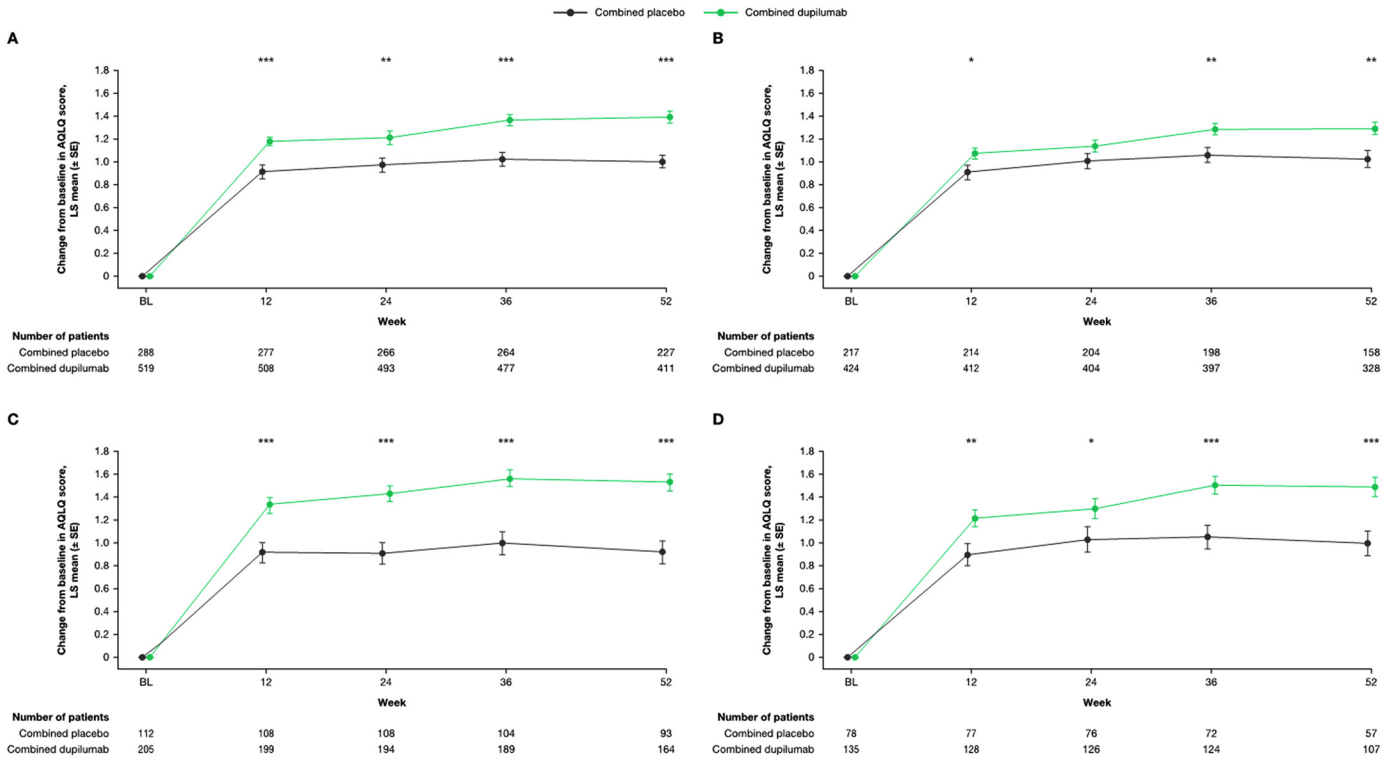


Figure 6. Change from baseline in AQLQ global score over time in patients with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb (A) with PAO, (B) without PAO, and in patients with eosinophils ≥ 300 cells/μL or FeNO ≥ 25 ppb (C) with PAO, and (D) without PAO. * $P < 0.05$, ** $P < 0.01$, *** $P < .001$. AQLQ, Asthma Quality of Life Questionnaire; FeNO, fractional exhaled nitric oxide; PAO, persistent airflow obstruction; SE, standard error.

observed by the first assessment at week 12, and these improved further throughout the 52-week treatment period. In patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb at baseline, LS mean difference vs placebo was 0.27 (95% CI, 0.13-0.40; $P < .0001$) at week 12 and 0.39 (0.24-0.54; $P < .0001$) at week 52 (Fig 6A). In patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb, LS mean difference vs placebo was 0.41 (0.19-0.63; $P = .0003$) at week 12 and 0.61 (0.37-0.86; $P < .0001$) at week 52 (Fig 6C). Similar results were observed in both subgroups without PAO (all $P < .05$) (Fig 6B and D).

Discussion

In this post hoc analysis of patients enrolled in QUEST, PAO at baseline (defined as post-bronchodilator FEV_1/FVC ratio < 0.7) was present in more than 50% of the overall intention-to-treat population of QUEST. Dupilumab significantly improved lung function and reduced severe asthma exacerbations in patients with evidence of type 2 inflammation, both with and without PAO at baseline. Despite a high placebo response, improvements in lung function were rapid and sustained in the 52-week treatment period. Dupilumab also significantly improved health-related quality of life in patients with type 2 asthma with and without PAO at baseline. Overall, improvements were of greater magnitude in the subpopulations of patients with higher elevated biomarkers of type 2 inflammation at baseline (eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb vs eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb).

Approximately twice as many dupilumab-treated vs placebo-treated patients achieved a post-bronchodilator FEV_1/FVC ratio of ≥ 0.7; with a difference observed as early as week 2 and sustained to week 52. These findings suggest that these patients experience a reversal of airflow obstruction.

In asthma, PAO occurs by progressive airway remodeling that is characterized by increased airway smooth muscle mass, goblet cell hyperplasia, and fibrosis.[2,21] Eosinophilic airway inflammation may also contribute to tissue remodeling and PAO in asthma by the release of mediators that target bronchial epithelium.[9] The proinflammatory cytokines IL-4 and IL-13 promote airway inflammation and airway remodeling, acting on mucus production, airway smooth muscle activity, and bronchial hyperresponsiveness by enhancing subepithelial fibrosis, goblet cell hyperplasia, and collagen deposition.[22] Dupilumab blocks the shared receptor component for IL-4 and IL-13, which are key and central drivers of type 2 inflammation in multiple diseases, including asthma,[16,17] thereby reducing underlying type 2 inflammation. This may contribute to PAO reversal both by blocking the direct inflammatory and remodeling effects of IL-4 and IL-13 and by reducing blood eosinophil counts. The reversal of airflow obstruction, as observed by a greater proportion of patients in the dupilumab arm achieving a normal FEV_1/FVC ratio, supports the concept that suppression of IL-4 and IL-13 may lead to reversal of airway remodeling. Further studies are needed to prospectively evaluate the impact of dupilumab on structural and functional changes in the airway. The VESTIGE study (NCT04400318) will evaluate the impact of dupilumab on radiographic features of patients with moderate-to-severe asthma and evidence of type 2 inflammation.

This study has several limitations. This is a post hoc analysis, and the primary QUEST study was not designed to evaluate the impact of baseline airflow obstruction on the response to dupilumab. Furthermore, as QUEST excluded patients with a smoking history of more than 10 pack-years, this analysis is limited in its ability to draw conclusions for patients with smoking-related airflow obstruction.

In conclusion, dupilumab vs placebo significantly improved clinical outcomes in patients with uncontrolled, moderate-to-severe asthma and elevated type 2 biomarkers with and without PAO at baseline. These data suggest the potential of dupilumab in reversing airflow obstruction and raise the possibility that dupilumab may contribute to reversing airway remodeling.

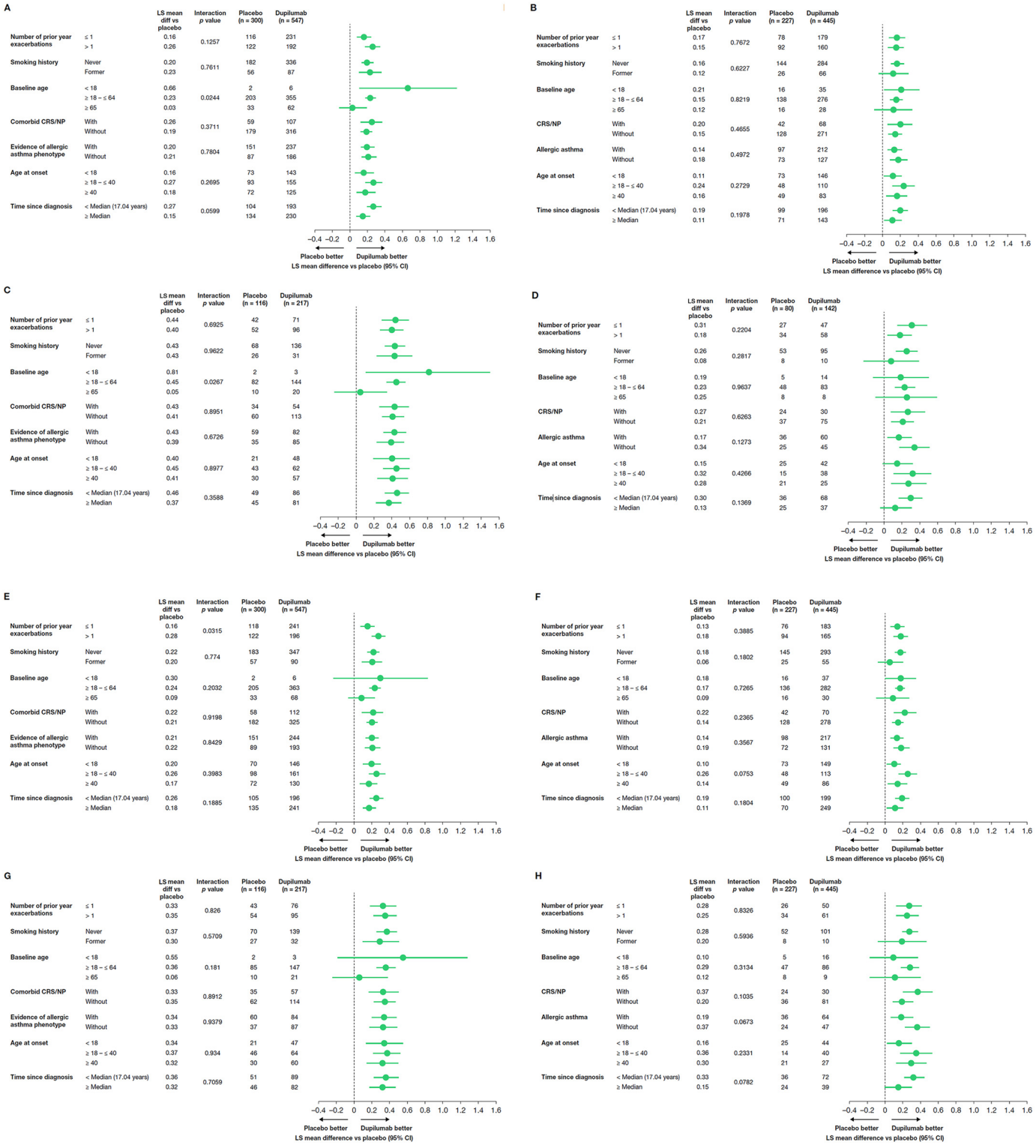
Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2022.10.018

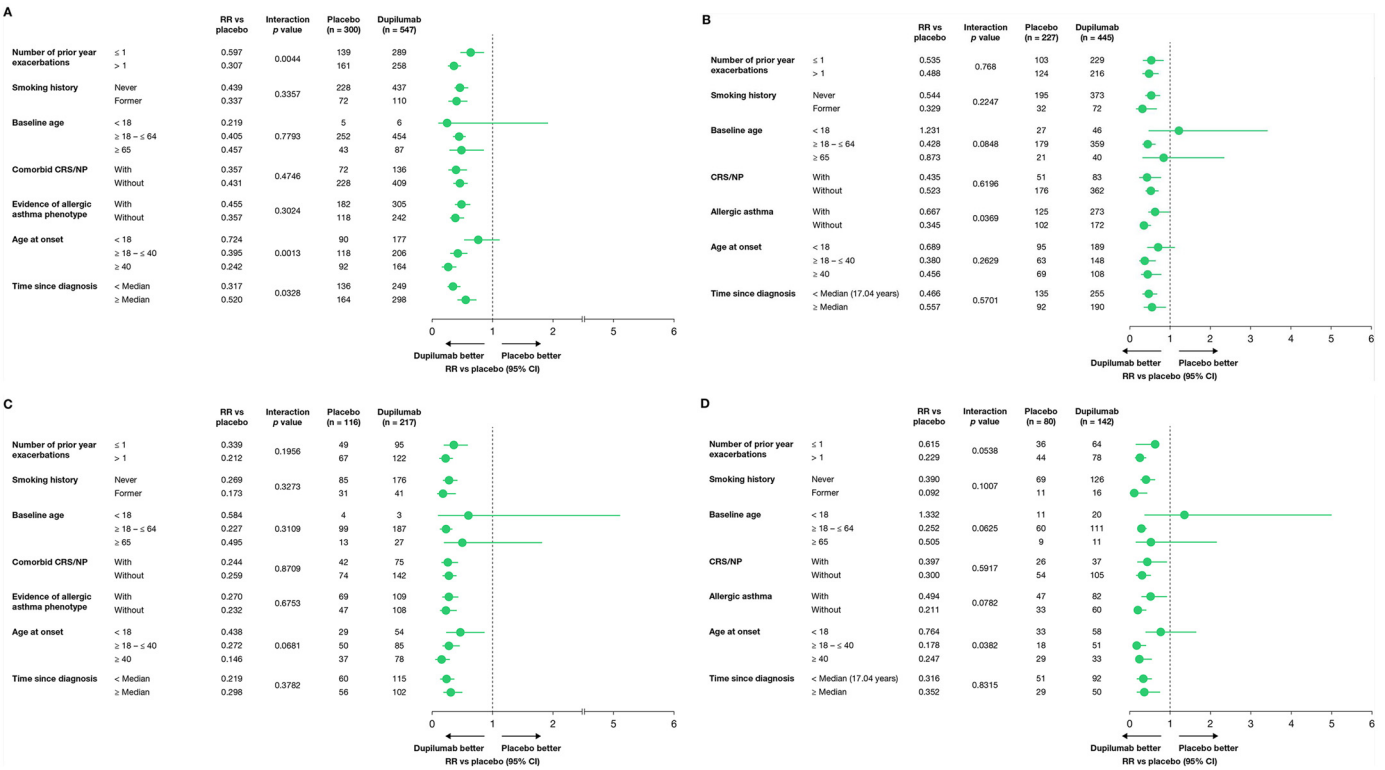
References

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2021. Available at: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. Accessed June 22, 2022.
2. Fehrenbach H, Wagner C, Wegmann M. Airway remodelling in asthma: what really matters. *Cell Tissue Res*. 2017;367(3):551–569.
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2021. Available at: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf. Accessed June 27, 2022.
4. Bennett GH, Carpenter L, Hao W, Song P, Steinberg J, Baptist AP. Risk factors and clinical outcomes associated with fixed airflow obstruction in older adults with asthma. *Ann Allergy Asthma Immunol*. 2018;120(2):164–168. e1.
5. Mirza S, Clay RD, Koslow MA, Scanlon PD. COPD guidelines: a review of the 2018 GOLD report. *May Clin Proc*. 2018;93(10):1488–1502.
6. Chipps BE, Hirsch I, Trudo F, Alacqua M, Zangrilli JG. Benralizumab efficacy for patients with fixed airflow obstruction and severe, uncontrolled eosinophilic asthma. *Ann Allergy Asthma Immunol*. 2020;124(1):79–86.
7. Zhang L, He L, Gong J, Liu C. Risk factors associated with irreversible airway obstruction in asthma: a systematic review and meta-analysis. *BioMed Res Int*. 2016;2016: 9868704.
8. Lee JH, Haselkorn T, Borish L, Rasouliyan L, Chipps BE, Wenzel SE. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. *Chest*. 2007;132(6):1882–1889.
9. Kostikas K, Brindicci C, Patalano F. Blood eosinophils as biomarkers to drive treatment choices in asthma and COPD. *Curr Drug Targets*. 2018;19(16):1882–1896.
10. Huang S, Vasquez MM, Halonen M, Martinez FD, Guerra S. Asthma, airflow limitation and mortality risk in the general population. *Eur Respir J*. 2015;45(2):338–346.
11. Mogensen I, Alving K, Dahlen SE, James A, Forsberg B, Ono J, et al. Fixed airflow obstruction relates to eosinophil activation in asthmatics. *Clin Exp Allergy*. 2019;49(2):155–162.
12. Schoettler N, Strek ME. Recent advances in severe asthma. From phenotypes to personalized medicine. *Chest*. 2020;157(3):516–528.
13. Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57–65.
14. MacDonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchak J, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci U S A*. 2014;111(14):5147–5152.
15. Murphy AJ, Macdonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci U S A*. 2014;111(14):5153–5158.
16. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol*. 2017;13(5):425–437.
17. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188–1204.
18. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–2496.
19. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2020. Available at: https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf. Accessed June 22, 2022.
20. Busse WW, Wenzel SE, Casale TB, Fitzgerald JM, Rice MS, Daizadeh N, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. *Lancet Respir Med*. 2021;9(10):1165–1173.
21. Joseph C, Tatler AL. Pathobiology of airway remodelling in asthma: the emerging role of integrins. *J Asthma Allergy*. 2022;15:595–610.
22. Hough KP, Curtiss ML, Blain TJ, Liu R-M, Tevor J, Deshane JS, et al. Airway remodeling in asthma. *Front Med (Lausanne)*. 2020;7:191.

Supplementary Data



eFigure 1. Change from baseline in pre- and post-bronchodilator FEV_1 at week 52 in (A, E) patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb, (B, F) patients without PAO with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb, (C, G) patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb, and (D, H) patients without PAO with eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline, stratified by selected baseline demographics and disease characteristics by subgroups. CRS/NP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LS, least squares; PAO, persistent airflow obstruction.



eFigure 2. Annualized rate of severe exacerbations during the 52-week treatment period in (A) patients with PAO and eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb, (B) patients without PAO with eosinophils ≥ 150 cells/μL or FeNO ≥ 25 ppb, (C) patients with PAO and eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb, and (D) patients without PAO with eosinophils ≥ 300 cells/μL and FeNO ≥ 25 ppb at baseline, stratified by selected baseline demographics and disease characteristics. CRS/NP, chronic rhinosinusitis with nasal polyps; FeNO, fractional exhaled nitric oxide; LS, least squares; PAO, persistent airflow obstruction .