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ORIGINAL ARTICLE

Allergen-Specific Immunotherapy and Biologics

Dupilumab reduced impact of severe exacerbations on lung function in patients with moderate-to-severe type 2 asthma

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Abstract

Background: Severe asthma exacerbations increase the risk of accelerated lung function decline. This analysis examined the effect of dupilumab on forced expiratory volume in 1 s (FEV_1) in patients with moderate-to-severe asthma and elevated type 2 biomarkers from phase 3 LIBERTY ASTHMA QUEST (NCT02414854).

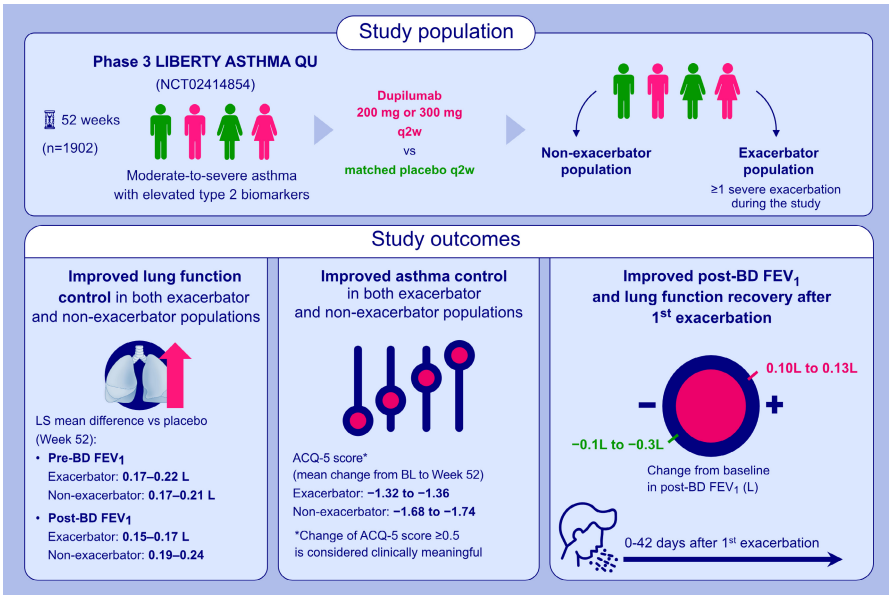
Methods: Changes from baseline in pre- and post-bronchodilator (BD) FEV_1 and 5-item Asthma Control Questionnaire (ACQ-5) scores were assessed in patients with elevated type 2 biomarkers at baseline (type 2–150/25: eosinophils ≥150 cells/μl and/or fractional exhaled nitric oxide [FeNO] ≥25 ppb; type 2–300/25: eosinophils ≥300 cells/μl and/or FeNO ≥25 ppb), stratified as exacerbators (≥1 severe exacerbation during the study) or non-exacerbators.

Results: In exacerbators and non-exacerbators, dupilumab increased pre-BD FEV_1 by Week 2 vs placebo; differences were maintained to Week 52 (type 2–150/25: LS mean difference (LSMD) vs placebo: 0.17 L (95% CI: 0.10–0.24) and 0.17 L (0.12–0.23); type 2–300/25: 0.22 L (0.13–0.30) and 0.21 L (0.15–0.28)), in exacerbators and non-exacerbators, respectively ($p < .0001$). Similar trends were seen for post-BD FEV_1. Dupilumab vs placebo also showed significantly greater improvements in post-BD FEV_1 0–42 days after first severe exacerbation in type 2–150/25 (LSMD vs placebo: 0.13 L [0.06–0.20]; $p = .006$) and type 2–300/25 (0.14 L [0.06–0.22]; $p = .001$) patients. ACQ-5 improvements were greater with dupilumab vs placebo in both groups.

Conclusion: Dupilumab treatment led to improvements in lung function independent of exacerbations and appeared to reduce the impact of exacerbations on lung function in patients who experienced a severe exacerbation during the study.

KEYWORDS
dupilumab, FEV_1, severe exacerbations, type 2 biomarkers

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; BD, bronchodilator; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LSMD, least squares mean difference; MMRM, mixed model repeated measures; q2w, every 2 weeks.



GRAPHICAL ABSTRACT

This analysis assessed the effect of dupilumab on FEV_1 in QUEST patients with moderate-to-severe asthma and elevated type 2 biomarkers. Dupilumab significantly increased FEV_1, regardless of number of severe exacerbations; FEV_1 recovery was more rapid in dupilumab- vs placebo-treated patients. Dupilumab produced rapid and sustained improvement in lung function, including in patients experiencing severe exacerbations.

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; BD, bronchodilator; BL, baseline; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LS, least squares; q2w, every 2 weeks

1 | INTRODUCTION

Patients with asthma are at an increased risk of accelerated loss of lung function compared with healthy individuals.[1] Although age-related decline in lung function is observed in adults without asthma, this is often accelerated in patients with asthma, and this may begin early in childhood.[1,2] A number of other risk factors are associated with loss of lung function, including biological sex, smoking, and exposure to pollutants.[3,4] Regardless of asthma status, blood and sputum eosinophil counts have been associated with accelerated lung function decline,[5] and in patients with asthma, predictors include elevated type 2 inflammatory biomarkers such as eosinophil counts and fractional exhaled nitric oxide (FeNO), low body mass index, and presence of nasal polyps.[6] In patients with either asthma or chronic obstructive pulmonary disease, the frequency of exacerbations has been linked to a more rapid decline in lung function.[7–9] The use of inhaled corticosteroids (ICS) reduces the frequency of exacerbations and degree of lung function decline,[7] but some patients with severe asthma fail to respond adequately to treatment with ICS or ICS plus additional controllers.[10]

Dupilumab, a fully human monoclonal antibody,[11,12] blocks the shared receptor component for IL-4 and IL-13. These type 2 inflammatory cytokines are implicated in numerous diseases such as asthma and atopic dermatitis.[13,14] In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 mg or 300 mg every 2 weeks (q2w) vs placebo significantly reduced severe asthma exacerbations and improved pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) in the overall population of patients with uncontrolled, moderate-to-severe asthma. Treatment effects were greater in patients with vs without elevated type 2 biomarkers at baseline (blood eosinophils ≥150 cells/μl or FeNO ≥25 ppb).[15]

Given the association between severe exacerbations and reductions in FEV_1 and the potential for treatment to attenuate decline in lung function, this post hoc analysis aimed to evaluate changes in lung function in patients with elevated type 2 biomarkers who experienced severe exacerbations during treatment with dupilumab or placebo during the QUEST study.

2 | METHODS

2.1 | Study design

Full details of the QUEST study design have been published previously.[15] In brief, QUEST was a phase 3, randomized, double-blind, placebo-controlled study assessing the efficacy and safety of dupilumab in patients with uncontrolled, moderate-to-severe asthma. The study was conducted in accordance with the Declaration of Helsinki, the principles of Good Clinical Practice, and all local applicable regulations. Patients or their parents/guardians provided informed consent/assent prior to enrollment in the study. Subgroup analysis of primary endpoints by number of asthma exacerbation events with 1 year prior to study was part of the pre-specified analysis in the study protocol. However, other parts of the analysis were conducted post hoc (e.g., analysis by baseline FeNO subgroups).

2.2 | Patients

Patients aged ≥12 years with physician-diagnosed persistent asthma for ≥12 months based on the Global Initiative for Asthma (GINA) recommendations,[16] who were receiving medium-to-high dose ICS plus up to 2 additional controllers (e.g., a long-acting β2-agonist or leukotriene receptor antagonist) were eligible for enrollment. Inclusion criteria included pre-BD FEV_1 ≤ 80% of the predicted normal value for adults (≤90% for adolescents); FEV_1 reversibility ≥12% and 200 ml; a 5-item Asthma Control Questionnaire (ACQ-5) score ≥1.5; and ≥1 asthma exacerbation in the past year, defined as a worsening of asthma in the preceding year that resulted in hospitalization, emergency medical care, or treatment with systemic glucocorticoids for ≥3 days. Full details of inclusion and exclusion criteria have been published previously.[15]

Patients were randomized 2:2:1:1 to receive add-on subcutaneous dupilumab 200 mg or 300 mg or matched placebo q2w for 52 weeks.

2.3 | Endpoints

Outcomes assessed in the current analysis include comparison of the baseline demographics and disease characteristics of exacerbators and non-exacerbators, change from baseline over the 52-week treatment period in pre- and post-BD FEV_1, including assessment after the first severe exacerbation (and prior to a second severe exacerbation event), and the duration between first severe exacerbation and the first available measurement of pre- and post-BD FEV_1 following the exacerbation event. Data were censored at onset of the potential second exacerbation event. A severe exacerbation during the study period was defined as a deterioration of asthma that required either the use of systemic corticosteroids for ≥3 days or a hospitalization or emergency room visit due to asthma and requiring systemic corticosteroids.

2.4 | Statistical analysis

Data for the two dupilumab and placebo arms were combined to create one data set for each treatment. Patients with type 2 asthma, defined as baseline blood eosinophil count ≥150 cells/μl and/or FeNO ≥25 ppb (type 2–150/25) were included in the current analysis. Analyses were also performed on the subgroup of patients with baseline blood eosinophil count ≥300 cells/μl and/or FeNO ≥25 ppb (type 2–300/25). Within the type 2–150/25 and type 2–300/25 groups, patients were stratified by whether or not they experienced a severe exacerbation during the 52-week study, with exacerbators defined as patients who experienced ≥1 exacerbation and non-exacerbators defined as patients who experience no exacerbations during the study treatment period.

Change from baseline in pre- and post-BD FEV_1 was assessed using a mixed model repeated measures (MMRM) design, with change from baseline in pre−/post-BD FEV_1 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, baseline pre−/post-BD FEV_1, and baseline-by-visit interactions as covariates. Additional analysis of change from baseline in pre- and post-BD FEV_1 was performed by smoking status (never smoked or former smoker). Analysis of change in post-BD FEV_1 after onset of the first severe exacerbation event using the same MMRM was conducted but with change from study baseline in post-BD FEV_1 values on or after the first severe exacerbation event and prior to second severe exacerbation event as the response variable. Duration between first severe exacerbation and first FEV_1 measurement available after onset of first severe exacerbation is presented as median and interquartile ranges.

Change from baseline in ACQ-5 was assessed using a MMRM design with change from baseline in ACQ-5 up to week 52 as the response variable and two pooled treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline ACQ-5, and baseline-by-visit interaction as covariates. Lower scores indicate greater improvements in asthma control.

3 | RESULTS

In total, 1902 patients were included in the QUEST study, of whom 1519 patients were included in the analysis reported in this manuscript. All 1519 patients were included in the type 2–150/25 group, and 1219 were also included in the type 2–300/25 group. Baseline pre- and post-BD FEV_1 and reversibility were higher in non-exacerbators vs exacerbators in both type 2 subgroups (both subgroups—$p < .0001$ for pre-BD and post-BD FEV1; $p < .05$ for reversibility) (Table 1). Across treatment groups, a higher percentage of exacerbators were on high-dose ICS at baseline (both subgroups—$p < .0001$). Similarly, the mean number of severe asthma exacerbations in the previous year was higher in patients in the exacerbator group (both subgroups—$p \leq .0001$) and a higher percentage of exacerbator patients had ≥2 exacerbations in the year prior to the study (both subgroups—$p \leq .0001$). No clear differences in baseline biomarkers were seen between exacerbators and non-exacerbators. As reported previously, exacerbations in the previous year were less common in dupilumab-treated patients than placebo-treated patients.[15]

3.1 | Change in pre- and post-BD FEV_1

Non-exacerbators compared with exacerbators had significantly higher pre- and post-BD FEV_1 at baseline ($p < .0001$), regardless of biomarker levels at baseline. Significantly greater increases in pre-BD FEV_1 were seen in both exacerbators and non-exacerbators for dupilumab vs placebo from Week 2 onwards. These differences were maintained through to Week 52 and were similar in

TABLE 1 Baseline demographics and patient characteristics

	Patients with blood eosinophils ≥150 cells/μl and/or FeNO ≥25 ppb at baseline				Patients with blood eosinophils ≥300 cells/μl and/or FeNO ≥25 ppb at baseline			
	Exacerbator[a]		Non-exacerbator[b]		Exacerbator[a]		Non-exacerbator[b]	
	Combined PBO	Combined DPL	Combined PBO	Combined DPL	Combined PBO	Combined DPL	Combined PBO	Combined DPL
n	231	280	296	712	189	215	239	576
Age, mean (SD), years	49.0 (14.5)	49.0 (15.4)	47.1 (15.5)	46.7 (15.3)	48.5 (15.1)	48.7 (15.2)	46.6 (15.8)	46.6 (15.2)
Female sex, *n* (%)	155 (67.1)	174 (62.1)	178 (60.1)	421 (59.1)	121 (64.0)	133 (61.9)	145 (60.7)	342 (59.4)
Body mass index mean (SD), kg/m^2	29.65 (7.39)	29.66 (7.13)	29.20 (6.84)	28.59 (6.16)	28.98 (7.13)	29.42 (7.10)	28.62 (6.46)	28.34 (5.82)
Pre-BD FEV_1, mean (SD), L	1.69 (0.54)	1.69 (0.56)	1.82 (0.63)	1.84 (0.63)	1.70 (0.56)	1.67 (0.54)	1.83 (0.64)	1.83 (0.63)
Percent predicted pre-BD FEV_1, mean (SD), %	56.77 (13.25)	55.97 (13.35)	59.22 (13.66)	59.36 (13.40)	56.50 (13.49)	55.36 (13.46)	59.59 (13.67)	59.05 (13.55)
Post-BD FEV_1, mean (SD), L	2.06 (0.62)	2.02 (0.67)	2.25 (0.77)	2.25 (0.75)	2.07 (0.64)	2.02 (0.64)	2.26 (0.78)	2.24 (0.76)
Post-BD FEV_1/FVC,mean (SD), %	65.91 (9.31)	65.07 (11.84)	68.03 (11.56)	67.56 (10.87)	65.30 (9.54)	64.50 (11.90)	68.42 (11.35)	67.31 (10.73)
FEV_1 reversibility, mean (SD), %	24.27 (15.79)	25.23 (19.40)	27.89 (20.03)	26.95 (22.58)	24.35 (16.20)	25.69 (18.98)	27.97 (20.28)	27.24 (22.87)
ICS dose, *n* (%)								
High	137 (59.3)	168 (60.0)	144 (48.6)	336 (47.2)	110 (58.2)	132 (61.4)	112 (46.9)	264 (45.8)
Medium	92 (39.8)	110 (39.3)	150 (50.7)	368 (51.7)	77 (40.7)	82 (38.1)	126 (52.7)	306 (53.1)
With ongoing atopic medical condition, *n* (%)	192 (83.1)	234 (83.6)	252 (85.1)	592 (83.1)	159 (84.1)	179 (83.3)	205 (85.8)	486 (84.4)
Former smoker, *n* (%)	58 (25.1)	52 (18.6)	46 (15.5)	130 (18.3)	48 (25.4)	40 (18.6)	39 (16.3)	92 (16.0)
Number of severe asthma exacerbations experienced in the year before QUEST								
Mean (SD)	2.62 (2.19)	2.26 (2.35)	1.89 (1.52)	1.99 (2.39)	2.63 (2.17)	2.40 (2.58)	1.95 (1.65)	1.95 (1.57)
Median (Q1–Q3)	2.00 (1.0–12.0)	2.00 (1.0–4.0)	1.00 (1.0–10.0)	1.00 (1.0–50.0)	2.00 (1.0–12.0)	2.00 (1.0–24.0)	1.00 (1.0–10.0)	1.00 (1.0–15.0)
1	84 (36.4)	133 (47.5)	158 (53.4)	385 (54.1)	69 (36.5)	96 (44.7)	128 (53.6)	306 (53.1)
≥2	147 (63.6)	147 (52.5)	138 (46.6)	327 (45.9)	120 (63.6)	119 (55.3)	111 (46.4)	270 (46.8)
Biomarkers								
Blood eosinophils, cells/μl	*n* = 231	*n* = 280	*n* = 295	*n* = 712	*n* = 189	*n* = 215	*n* = 238	*n* = 576
Median (Q1–Q3)	380.0 (220.0–690.0)	310.0 (190.0–500.0)	290.0 (190.0–480.0)	330.0 (200.0–560.0)	430.0 (310.0–790.0)	380.0 (230.0–590.0)	370.0 (190.0–530.0)	390.0 (235.0–620.0)
Total IgE, IU/ml	*n* = 231	*n* = 277	*n* = 291	*n* = 705	*n* = 189	*n* = 212	*n* = 235	*n* = 569
Median (Q1–Q3)	212.0 (76.0–515.0)	164.0 (65.0–420.0)	210.0 (73.0–477.0)	194.0 (76.0–542.0)	252.0 (96.0–563.0)	191.5 (81.5–486.5)	241.0 (81.0–496.0)	215.0 (88.0–579.0)
FeNO, ppb	*n* = 229	*n* = 276	*n* = 291	*n* = 707	*n* = 188	*n* = 213	*n* = 235	*n* = 571
Median (Q1–Q3)	34.0 (19.0–54.0)	27.0 (16.0–46.0)	30.0 (18.0–50.0)	30.0 (18.0–51.0)	38.0 (27.0–60.5)	33.0 (24.0–55.0)	34.0 (25.0–55.0)	37.0 (25.0–59.0)

Abbreviations: BD, bronchodilator; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IgE. immunoglobulin E; ICS, inhaled corticosteroid; PBO, placebo; ppb, parts per billion; Q, quarter; SD, standard deviation.

[a]Exacerbators were patients who experienced a severe asthma exacerbation during the QUEST study.

[b]Non-exacerbators were patients who did not experience any severe asthma exacerbations during the trial.

patients included in the type 2–150/25 and type 2–300/25 groups. In patients with type 2–150/25 asthma, by Week 52, least squares mean differences (LSMD) (95% CI) for dupilumab vs placebo were 0.17 L (0.10–0.24) and 0.17 L (0.12–0.23) in exacerbators and non-exacerbators, respectively (both $p < .0001$; Figure 1A). In patients with type 2–300/25 asthma, these differences were 0.22 L (0.13–0.30) and 0.21 L (0.15–0.28), respectively (both $p < .0001$; Figure 1B). It should be noted that whereas the LSMDs vs placebo were similar in exacerbators and non-exacerbators, the absolute pre-BD FEV_1 remained lower throughout the study in exacerbators compared with non-exacerbators in both treatment groups. Similar trends were observed in post-BD FEV_1, with significantly greater improvements in the dupilumab vs placebo groups by Week 2, sustained through to Week 52, irrespective of exacerbator status. In patients with type 2–150/25 asthma, by Week 52, LSMD (95% CI) vs placebo was 0.15 L (0.08–0.22) in exacerbators and 0.19 L (0.14–0.25) in non-exacerbators (both $p < .0001$; Figure 2A). In patients with type 2–300/25 asthma, by Week 52, LSMD vs placebo was 0.17 L (0.09–0.24) in exacerbators and 0.24 L (0.18–0.30) in non-exacerbators (both $p < .0001$; Figure 2B). As observed with pre-BD FEV_1, absolute post-BD FEV_1 remained lower throughout the study in exacerbators compared with non-exacerbators, irrespective of baseline biomarkers or treatment group.

3.2 | Smoking history

When stratified by smoking history, significantly greater changes from baseline in pre-BD FEV_1 were observed for patients from both subgroups who had never smoked when treated with dupilumab vs placebo, independent of exacerbator status (type 2–150/25 exacerbators – LSMD [95% CI] vs placebo: 0.19 L [0.11–0.28], $p < .0001$; type 2–150/25 non-exacerbators: 0.17 L [0.10–0.23], $p < .0001$; type 2–300/25 exacerbators: 0.26 L [0.16–0.36], $p < .0001$; type

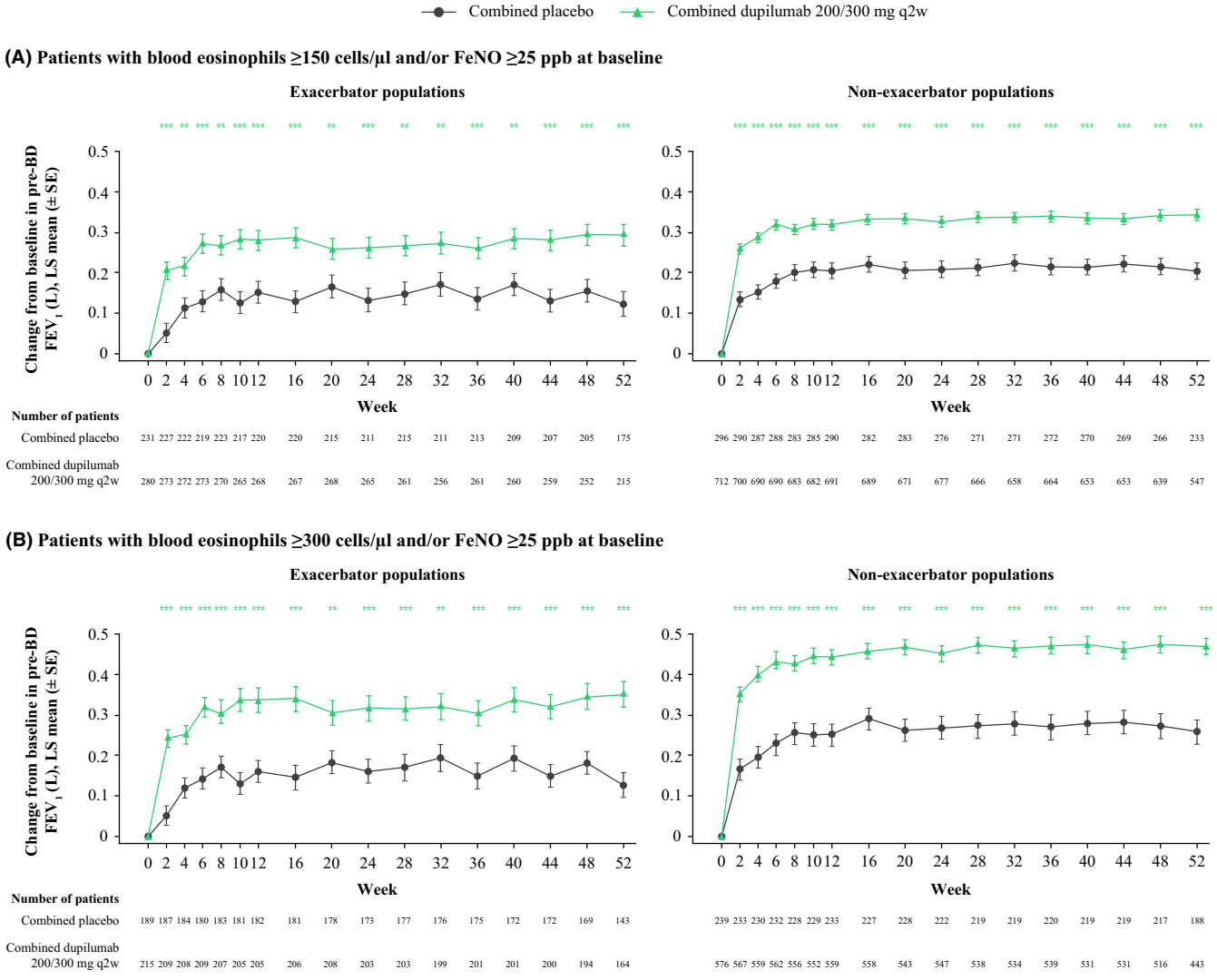


FIGURE 1 Change from baseline over time in pre-BD FEV_1 in (A) patients with eosinophil count ≥150 cells/µl and/or FeNO ≥25 ppb at baseline and (B) patients with eosinophil count ≥300 cells/µl and/or FeNO ≥25 ppb at baseline. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SE, standard error. *$p < .05$; **$p < .01$; ***$p < .001$ vs matched placebo

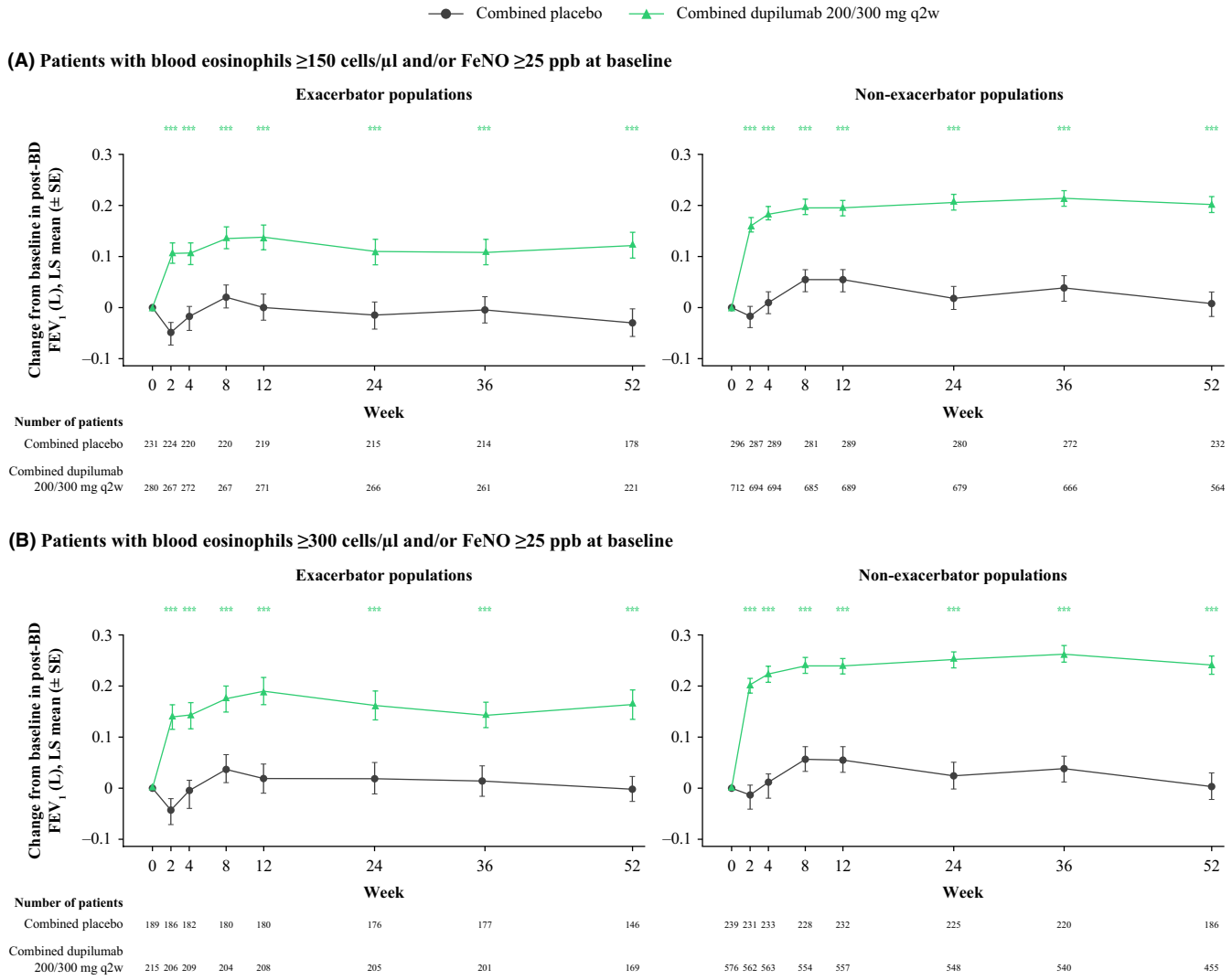


FIGURE 2 Change from baseline over time in post-BD FEV_1 during 52 weeks of treatment in (A) patients with eosinophil count ≥150 cells/μl and/or FeNO ≥25 ppb at baseline and (B) patients with eosinophil count ≥300 cells/μl and/or FeNO ≥25 ppb at baseline. *$p < .05$; **$p < .01$; ***$p < .001$ vs matched placebo. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SE, standard error

2–300/25 non-exacerbators: 0.20 L [0.12–0.27], $p < .0001$). Greater changes were also seen in non-exacerbators with a history of smoking who received dupilumab vs placebo (type 2–150/25 – LSMD [95% CI] vs placebo: 0.19 L [95% CI: 0.05–0.33], $p = .08$; type 2–300/25: 0.25 L [0.09–0.41], $p = .002$); however, differences between treatment groups were not significant in exacerbators who were former smokers (type 2–150/25 – LSMD [95% CI] vs placebo: 0.13 L [−0.04 to −0.30], $p = .143$; type 2–300/25: 0.12 L [−0.08 to −0.32], $p = .225$). Similar trends were also observed in post-BD FEV_1, with significant differences between treatment groups in both exacerbators (type 2–150/25 – LSMD [95% CI] vs placebo: 0.19 L [0.12–0.27], $p < .0001$; type 2–300/25: 0.22 L [0.13–0.31], $p < .0001$) and non-exacerbators (type 2–150/25: 0.19 L [0.13–0.25], $p < .0001$; type 2–300/25: 0.23 L [0.17–0.30], $p < .0001$) who had never smoked, and in non-exacerbators who were former smokers (type 2–150/25: 0.20 L [0.06–0.33], $p = .004$; type 2–300/25: 0.24 L [0.08–0.40], $p = .003$). In the group of exacerbators who were former smokers, change from baseline in post-BD FEV_1 was similar between dupilumab and placebo (type 2–150/25 – LSMD [95% CI] vs placebo: 0.03 L [−0.12 to 0.18], $p = .672$; type 2–300/25: −0.0002 [−0.17 to 0.17], $p = .998$).

3.3 | Change from baseline in post-BD FEV_1 after onset of the first exacerbation

Within the exacerbator population, significantly greater improvements from baseline in post-BD FEV_1 were observed 0–42 days after the first severe exacerbation event in dupilumab- vs placebo-treated patients with either type 2–150/25 (LSMD [95% CI] vs placebo: 0.13 L [0.06–0.20], $p = .0006$) or type 2–300/25 (0.14 L [0.06–0.22], $p = .001$) asthma (Figure 3). There was also a trend toward greater improvements from baseline in post-BD FEV_1 measured at either 43–125 or 126–210 days after the first severe exacerbation event

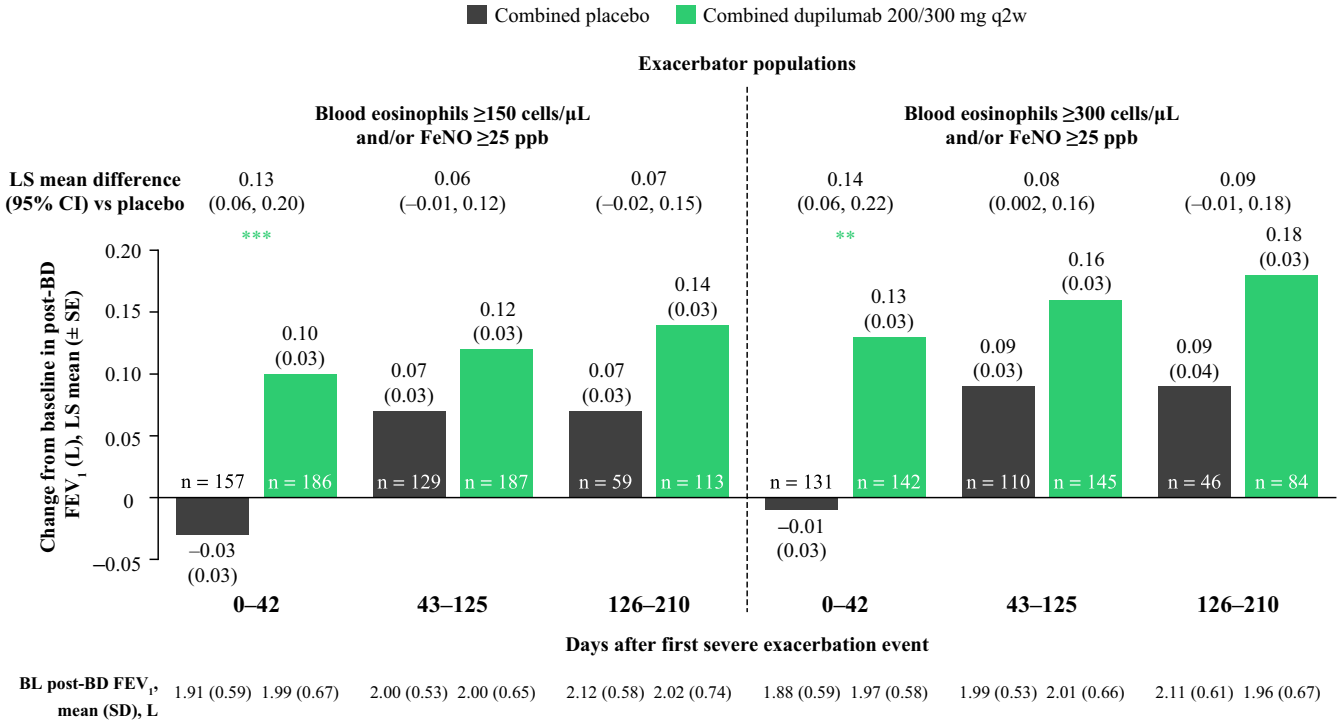


FIGURE 3 Change from baseline in post-BD FEV_1 after onset of the first severe exacerbation event. Two events are considered as different if the start dates are separated by at least 4 weeks. Post-BD FEV_1 measurements on or after the first severe exacerbation event are split into visits based on the days elapsed between the first severe exacerbation event and these measurements: 0–42 days, 43–125 days, and 126–210 days. The exacerbator group includes patients with ≥1 severe exacerbation event during the 52-week treatment period. Change from baseline in post-BD FEV_1 was derived from MMRM with change from study baseline in post-BD FEV_1 values on or after the first severe exacerbation event and prior to second severe exacerbation event 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, study baseline post-BD FEV_1 value and study baseline-by-visit interaction as covariates. BD, bronchodilator; BL, baseline; CI, confidence interval; FeNO: fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LS, least squares; MMRM, mixed model repeated measures; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation; SE, standard error. $^{**}p < .01$; $^{***}p < .001$

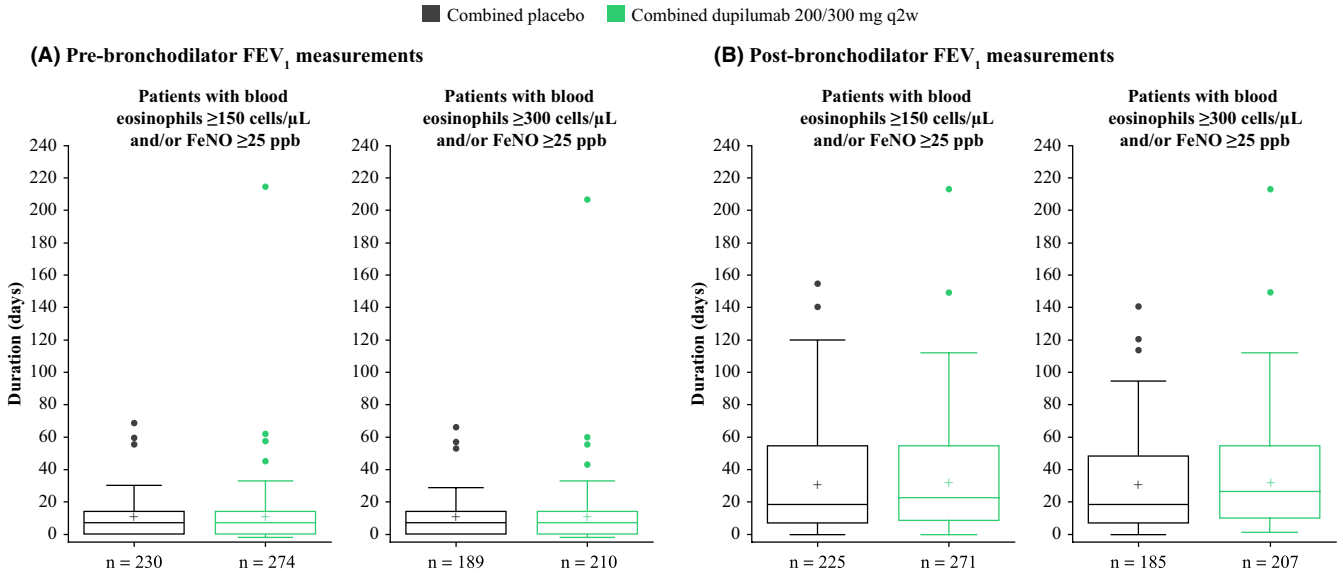


FIGURE 4 Duration (days) between the onset of first severe exacerbation event and the latest (A) pre- and (B) post-BD FEV_1 (L) measurement on or after the onset of first severe exacerbation. The exacerbator group includes patients with ≥1 severe exacerbation event during the 52-week treatment period. The duration (days) is calculated as (latest pre-BD measurement date on or after first severe exacerbation event—onset date of first severe exacerbation event +1). FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ppb, parts per billion; q2w, every 2 weeks

in dupilumab- vs placebo-treated patients, although these were not statistically significant (Figure 3). Overall, the median durations between first severe exacerbation event and the latest available pre- and post-BD FEV_1 data were similar in the placebo and dupilumab groups and for patients with type 2–150/25 and type 2–300/25 asthma (Figure 4A and B). Median duration between first severe exacerbation and pre-BD FEV_1 data was 8 days (IQR: 1–15 days) for placebo and 9 days (3–15) for dupilumab, for both subgroups of patients. For type 2–150/25 patients, median duration between first severe exacerbation and post-BD FEV_1 was 19 days (IQR: 7–54) in the placebo group and 23 days (IQR: 9–54) in the dupilumab group. Similar durations were observed in type 2–300/25 patients (18 days [IQR: 7–49] and 26 days [IQR: 9–54] for placebo- and dupilumab-treated patients, respectively).

3.4 | Change from baseline in ACQ-5 scores

In both the type 2–150/25 and type 2–300/25 groups, treatment with dupilumab in non-exacerbators resulted in significantly greater improvements in ACQ-5 scores vs placebo from Week 2, and these improvements were sustained through Week 52 (LSMD vs placebo $p < .0001$ at all time points) (Figure 5). In exacerbators in the type 2–150/25 and type 2–300/25 groups, treatment with dupilumab resulted in greater improvements in ACQ-5 scores vs placebo from Week 2; however, the LSMD vs placebo was only significant at some time points (Figure 5).

4 | DISCUSSION

The results presented here indicate that the degree of improvement in lung function for dupilumab- vs placebo-treated patients was similar for those who suffered breakthrough exacerbations and those who did not. However, absolute pre- and post-BD FEV_1 remained lower in exacerbators than non-exacerbators throughout the study. The observed improvements in lung function in both groups indicate that, despite differences in baseline FEV_1, treatment still improves lung function in patients who suffer breakthrough exacerbations during treatment. Compared with non-exacerbators, exacerbators had more frequent exacerbations during the year prior to study enrollment, indicating that they were at higher risk of future exacerbations and more rapid lung function decline, as indicated by a lower FEV_1 at baseline. Use of biologics such as dupilumab in patients with moderate-to-severe asthma has been shown to both improve lung function and reduce the number of severe exacerbations, thus slowing any further decline in lung function that may occur during an exacerbation.[15,17–19] As patients with frequent exacerbations often experience poorer pulmonary function and higher symptom burden than non-exacerbators,[20,21] this study indicates that optimizing biologic therapy can have substantial benefits for patients with a frequent exacerbator phenotype.

In the current analysis, differences in treatment effects were observed between exacerbators and non-exacerbators when stratified by smoking history; however, the difference between treatments in former smokers who were exacerbators was not significant. A previous study of the effect of smoking in adolescent and early adult patients with asthma demonstrated that lung function impairments were associated with asthma and smoking early in life and were not fully responsive to bronchodilators, indicating irreversible damage may have occurred.[22] However, this is unlikely to have been the case in the patients in the current study, as the absolute changes from baseline in the dupilumab group in pre-BD FEV_1 were similar regardless of smoking history. Caution is advised when interpreting this result as the small population sizes in the former-smoker group confounded clear interpretation of any population-specific impact.

In patients who experienced exacerbations during the study, a decline in lung function was observed in the first 42 days after the first exacerbation in the placebo group, but not in the dupilumab group. Patients who received dupilumab experienced continued improvement in lung function, even in the weeks following an exacerbation. The data from the placebo group are in line with the association between exacerbation frequency and accelerated lung function decline observed in previous studies.[7–9] In an analysis of patients with severe asthma enrolled in the DREAM and MENSA phase 3 mepolizumab studies, decline in lung function was observed in patients with more than 1 exacerbation and was greater in the placebo group. Across treatments and studies, linear regression analysis suggested that each exacerbation event was associated with a 50 ml decline in post-BD FEV_1.[6] However, these studies included patients on oral corticosteroids, whereas patients dependent on oral corticosteroids were excluded from the QUEST study, precluding direct comparisons of these analyses.

During severe exacerbation events, patients have worsening airway inflammation,[23] and this may at least partly explain why dupilumab can maintain lung function after an exacerbation. 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.[13,24] Reduction of this underlying type 2 inflammation may reduce the damage done to the airways by lessening the decline in lung function following an exacerbation as well as by reducing the likelihood of further severe exacerbations. Reduction by dupilumab in IL-13-driven mucus production, and thus airway mucus plugging, may also play a role in lessening the decline in lung function. The role of dupilumab in reducing underlying inflammation may also explain the greater benefits in patients with type 2–300/25 asthma compared with those with type 2–150/25. In a previous analysis of the QUEST study, the largest clinical benefits with dupilumab were observed in patients with the highest levels of elevated type 2 biomarkers.[25] It could be hypothesized this is due to more severe disease in patients with higher levels of type 2 biomarkers, who therefore have more potential room for improvement. However, no clear differences in the baseline exacerbation rates or FEV_1 were observed between the two type 2 populations studied in this analysis, suggesting that the degree of elevated type 2 biomarkers was not indicative of the likelihood of exacerbation or decline in lung function. Thus, this analysis demonstrates that treatment of underlying inflammation provides beneficial impacts on the disease course even

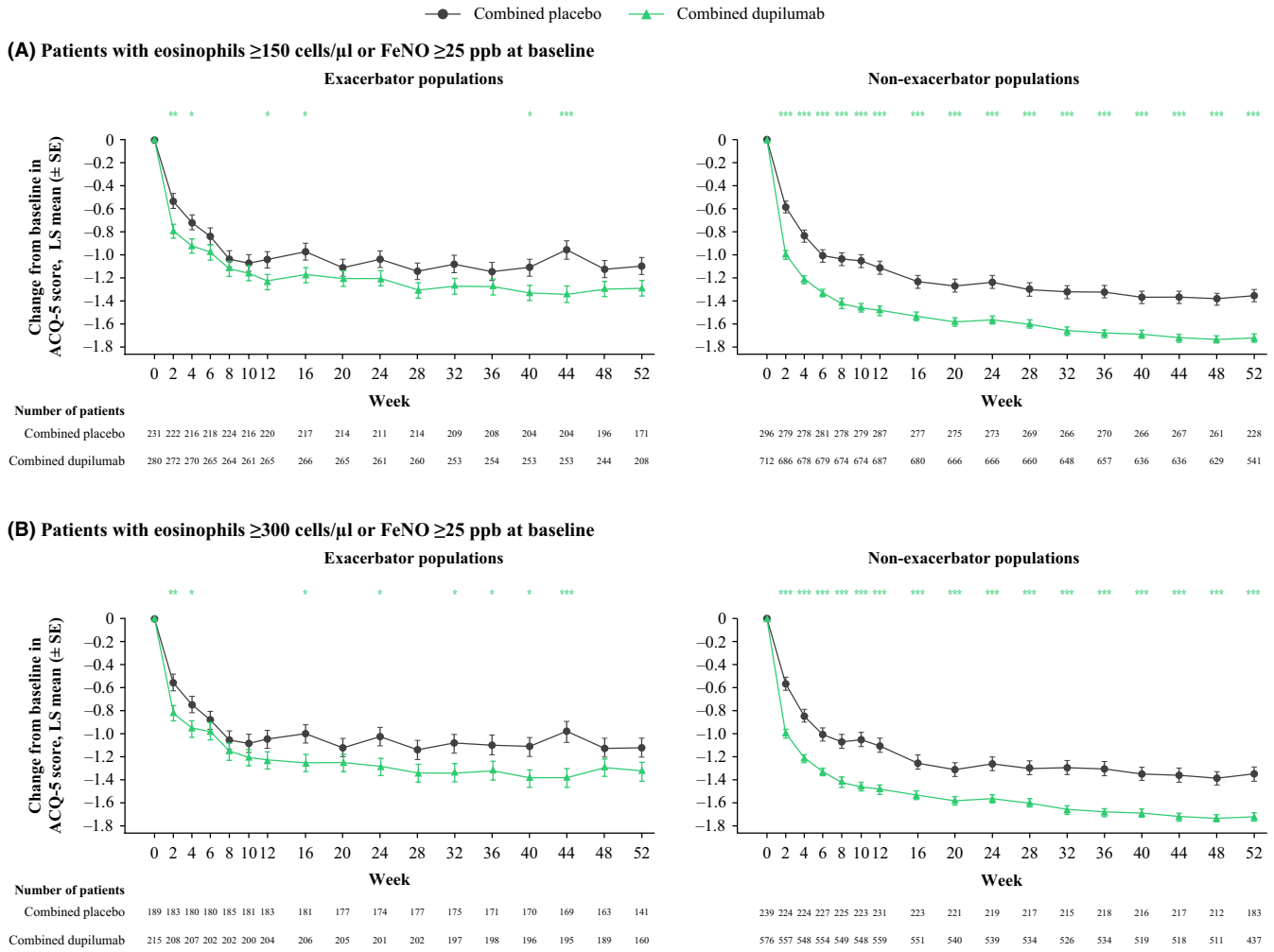


FIGURE 5 Change from baseline over time in ACQ-5 score during 52 weeks of treatment in (A) patients with eosinophil count ≥150 cells/μl or FeNO ≥25 ppb at baseline and (B) patients with eosinophil count ≥300 cells/μl or FeNO ≥25 ppb at baseline. ACQ-5, 5-item Asthma Control Questionnaire; FeNO, fractional exhaled nitric oxide; LS, least squares; ppb, parts per billion; SE, standard error

in patients with lower levels of type 2 biomarkers, as well as in those who continue to experience exacerbations during treatment.

Improvements from baseline in ACQ-5 scores were greater in patients on dupilumab vs placebo. In both exacerbators and non-exacerbators, improvements were observed as early as Week 2 and were sustained for the duration of the study, although significant differences were only consistent in the larger population of non-exacerbators.

There are a number of limitations to this study. First, as a post hoc analysis, the study was not powered to investigate differences between treatments in the subgroups of exacerbators and non-exacerbators. Small sample sizes in some subgroups may confound interpretation of the data. Second, our post-exacerbation spirometry testing was not conducted at pre-specified intervals relative to exacerbation events, but at times specified by the overall 52-week protocol. The higher incidence of exacerbation rates seen in placebo-treated patients might have increased the likelihood of spirometry occurring sooner after exacerbation events in these patients vs those treated with dupilumab, leading to higher probability of detecting lower FEV_1 values. However, we found no statistically or clinically important difference between placebo- and dupilumab-treated patients in terms of time from exacerbation to FEV_1 measurement. Therefore, our data point to dupilumab favoring a more rapid improvement in lung function after exacerbation events (as early as 0–42 days) compared with placebo (from 43 days onwards). A faster recovery after exacerbations is a priority for many patients. Nevertheless, the FEV_1 increase after exacerbations appears not to be the only determinant of the overall lung function improvement seen with dupilumab treatment, as non-exacerbators also benefitted from dupilumab therapy. Third, our study was not designed to examine the nature of the exacerbations that occurred. For example, it has been reported that patients receiving mepolizumab for severe eosinophilic asthma are heterogenous, with approximately half of exacerbations being non-eosinophilic events driven by infection.[26] Fourth, as this was a randomized controlled study, it may be that exacerbations were assessed and managed more rapidly than would have occurred in a real-world situation. Finally, the study design reflects previous rather than current GINA recommendations.

In summary, this analysis shows that treatment with dupilumab results in significant increases in both pre- and post-BD FEV_1 in patients with elevated type 2 biomarkers, regardless of whether severe exacerbations occurred. Although lung function in placebo-treated patients declined following severe exacerbation events, dupilumab-treated patients continued to experience improvements in lung function, suggesting sustained preservation of lung function after severe exacerbation can be achieved with dupilumab treatment.

AUTHOR CONTRIBUTIONS

AP, JC, MC, CD, LR, KRC, and DJJ contributed to the data collection, data analysis, data interpretation, and writing of this manuscript. ND, NPA, RG, JAJN, PJR, YC, and BO contributed to the study design, data analysis, data interpretation, and writing of this manuscript. ND accessed and verified the data and did statistical analyses. All authors had full access to all of the data; participated in interpretation of the data, provided critical feedback, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses; and took final responsibility to submit for publication.

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CONFLICT OF INTEREST

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