

Original Article

Dupilumab Efficacy in Patients with Uncontrolled, Moderate-to-Severe Allergic Asthma

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What is already known about this topic? Type 2-high asthma includes the overlapping phenotypes, allergic asthma (characterized by increased expression of specific IgE to aeroallergens), and eosinophilic asthma (characterized by blood and/or airway/tissue eosinophilia).

What does this article add to our knowledge? Dupilumab is effective in patients with and without allergic asthma and suppresses type 2 inflammatory biomarkers, highlighting the key role of IL-4 and IL-13 in airway inflammation.

How does this study impact current management guidelines? Results support the roles of IL-4 and IL-13 in IgE- and non-IgE-mediated inflammatory pathways in asthma and IL-4/IL-13 inhibition by dupilumab therapy as beneficial for both the allergic and nonallergic asthma phenotypes.

BACKGROUND: Dupilumab blocks the shared receptor component for IL-4 and IL-13, key drivers of type 2 inflammation, including IgE-mediated allergic inflammation in asthma. In the LIBERTY ASTHMA QUEST (NCT02414854) study, dupilumab reduced severe asthma exacerbations and improved forced expiratory volume in 1 second (FEV₁) in

patients with uncontrolled, moderate-to-severe asthma with greater efficacy observed in patients with elevated type 2 inflammatory biomarkers (blood eosinophils and fractional exhaled nitric oxide) at baseline.

OBJECTIVE: We assessed dupilumab's effect on key asthma outcomes in QUEST patients with/without evidence of allergic

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Abbreviations used

ACQ- Asthma Control Questionnaire
 AD- Atopic dermatitis
 CI- Confidence interval
 FeNO- Fractional exhaled nitric oxide
 FEV₁- Forced expiratory volume in 1 second
 ITT- Intention-to-treat
 LS- Least squares
 q2w- Every 2 weeks
 SE- Standard error
 Th- T helper
 TARC- Thymus and activation-regulated chemokine

asthma (total serum IgE ≥ 30 IU/mL and ≥ 1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L at baseline).

METHODS: Severe exacerbation rates and change from baseline in FEV₁, asthma control, and markers of type 2 inflammation during the 52-week treatment period were assessed.

RESULTS: In the allergic asthma subgroup (n = 1083), dupilumab 200/300 mg every 2 weeks versus placebo reduced severe asthma exacerbation rates (−36.9%/−45.5%; both $P < .01$), improved FEV₁ at week 12 (0.13 L/0.16 L; both $P < .001$); improvements were evident by the first evaluation at week 2) with greater efficacy observed in patients with elevated type 2 inflammatory biomarkers at baseline, and improved asthma control. Dupilumab treatment also resulted in rapid and sustained reductions in type 2 inflammatory biomarkers.

Comparable results were observed in patients without evidence of allergic asthma (n = 819).

CONCLUSION: Dupilumab reduced severe exacerbation rates, improved FEV₁ and asthma control, and suppressed type 2 inflammatory biomarkers in patients with uncontrolled, moderate-to-severe asthma with or without evidence of allergic asthma, highlighting the key role of IL-4 and IL-13 in airway inflammation. © 2019 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>). (J Allergy Clin Immunol Pract 2019;■:■-■)

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Type 2-high asthma is the most prevalent type of persistent uncontrolled asthma.¹ It includes the overlapping phenotypes, allergic asthma (characterized by increased expression of specific IgE to aeroallergens), and eosinophilic asthma (characterized by blood and/or airway/tissue eosinophilia).¹⁻³

IL-4 and IL-13 are key drivers of type 2 inflammation, including IgE-mediated allergic inflammation in asthma. IL-4 is crucial for the differentiation of naive T helper (Th) 0 to Th2 cells, which induces the production of type 2 inflammatory cytokines (eg, IL-4, IL-5, IL-13) and chemokines (eg, eotaxin-3).⁴ IL-4 also induces B-lymphocyte isotype switching from IgG- to IgE-producing plasma cells, thereby increasing IgE production, and primes mast cells to degranulate on antigen exposure.^{5,6} IL-13 also induces goblet cell hyperplasia, mucus hypersecretion, and airway hyperresponsiveness.^{7,8} IL-4 and IL-13 cytokines are also the key drivers of other type 2 inflammatory diseases, including atopic dermatitis (AD), allergic rhinitis,

chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis,⁹ and food allergies.¹⁰

Dupilumab, a fully human VelocImmune-derived monoclonal antibody,^{11,12} blocks the shared receptor component for IL-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13 cytokines.¹⁰ Dupilumab is approved by the US Food and Drug Administration¹³ as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥ 12 years with an eosinophilic phenotype or with oral corticosteroid-dependent asthma; in Japan, for patients aged ≥ 12 years with severe or refractory bronchial asthma whose symptoms are inadequately controlled with existing therapy,¹⁴ and by the European Medicines Agency¹⁵ as an add-on maintenance treatment in patients aged ≥ 12 years with severe type 2 inflammation characterized by increased blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO) who are inadequately controlled with high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment.¹⁶⁻¹⁸ Dupilumab is also approved for inadequately controlled, moderate-to-severe AD, in patients aged ≥ 12 years in the United States and adults in the European Union and other countries.^{13,19-21} The efficacy and safety of dupilumab have also been demonstrated in patients with chronic rhinosinusitis with nasal polyps.²²

LIBERTY ASTHMA QUEST (NCT02414854) was a phase 3 study that demonstrated the efficacy and safety of dupilumab in patients ≥ 12 years of age with uncontrolled, moderate-to-severe asthma.¹⁷ Dupilumab significantly reduced the annualized rate of severe exacerbations and improved lung function in the overall population, with greater treatment effects observed in patients with higher baseline concentrations of type 2 inflammatory biomarkers.

We compared the effect of dupilumab on key asthma outcome measures in subgroups of patients with and without evidence of allergic asthma at baseline in the QUEST study. Allergic asthma was defined per the most commonly used criteria in clinical practice in the United States in determining eligibility for biologic therapy with omalizumab (ie, total serum IgE ≥ 30 IU/mL and ≥ 1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L at baseline).²³ Because dupilumab treatment is not limited by weight or serum levels of total IgE, no upper threshold for serum total IgE was specified.

METHODS

Study design

A complete description of the LIBERTY ASTHMA QUEST study design is provided in the primary manuscript.¹⁷ QUEST was a phase 3, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of dupilumab in patients with uncontrolled, moderate-to-severe asthma. A total of 1902 patients aged ≥ 12 years were randomized in a 2:2:1:1 ratio to add-on subcutaneous dupilumab 200 mg (loading dose 400 mg) or 300 mg (loading dose 600 mg) every 2 weeks (q2w) or matched-volume placebos for 52 weeks. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guideline and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study

TABLE I. Baseline demographic and disease characteristics

	Allergic asthma (n = 1083)				Did not meet the criteria for allergic asthma (n = 819)			
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo (n = 183)	Dupilumab (n = 360)	Placebo (n = 179)	Dupilumab (n = 361)	Placebo (n = 134)	Dupilumab (n = 271)	Placebo (n = 142)	Dupilumab (n = 272)
Age, mean (SD), y	44.0 (16.8)	45.5 (16.0)	44.1 (14.9)	43.9 (15.8)	54.0 (11.8)	51.0 (13.7)	53.2 (12.8)	52.7 (13.6)
Female, n (%)	101 (55.2)	196 (54.4)	114 (63.7)	216 (59.8)	97 (72.4)	191 (70.5)	104 (73.2)	178 (65.4)
BMI, mean (SD), kg/m ²	29.3 (7.35)	28.47 (6.35)	28.78 (6.88)	28.91 (6.91)	30.39 (7.09)	29.82 (6.67)	29.76 (7.02)	29.27 (6.37)
Age at asthma onset, mean (SD), y	20.9 (17.9)	23.0 (19.5)	20.9 (16.9)	20.8 (17.8)	35.9 (17.3)	32.5 (17.3)	35.7 (17.4)	34.2 (18.8)
With ongoing atopic medical condition,* n (%)	176 (96.2)	337 (93.6)	173 (96.6)	354 (98.1)	90 (67.2)	172 (63.5)	93 (65.5)	170 (62.5)
Atopic dermatitis	21 (11.5)	48 (13.3)	32 (17.9)	42 (11.6)	14 (10.4)	13 (4.8)	6 (4.2)	20 (7.4)
Allergic rhinitis	142 (77.6)	265 (73.6)	140 (78.2)	284 (78.7)	79 (59)	156 (57.6)	85 (59.9)	154 (56.6)
Food allergy	21 (11.5)	35 (9.7)	25 (14.0)	32 (8.9)	7 (5.2)	13 (4.8)	11 (7.7)	15 (5.5)
Hives	13 (7.1)	16 (4.4)	9 (5.0)	22 (6.1)	6 (4.5)	14 (5.2)	6 (4.2)	8 (2.9)
Former smokers, n (%)	27 (14.8)	75 (20.8)	38 (21.2)	67 (18.6)	32 (23.9)	51 (18.8)	29 (20.4)	49 (18.0)
Severe asthma exacerbations in the past year, mean (SD), n	1.89 (1.48)	1.98 (2.99)	2.22 (1.99)	1.79 (1.33)	2.32 (1.68)	2.18 (2.16)	2.43 (2.17)	2.33 (2.35)
Prebronchodilator FEV ₁ , mean (SD), L	1.84 (0.64)	1.85 (0.64)	1.84 (0.61)	1.88 (0.58)	1.66 (0.55)	1.70 (0.58)	1.64 (0.49)	1.66 (0.61)
ACQ-5 score, [†] mean (SD)	2.69 (0.69)	2.73 (0.82)	2.73 (0.76)	2.74 (0.78)	2.75 (0.77)	2.80 (0.77)	2.81 (0.79)	2.80 (0.74)
Total serum IgE, median (IQR), IU/mL; n	337.0 (147.0-629.0); 183	304.0 (137.0-835.5); 360	315.0 (142.0-763.0); 179	326.0 (152.0-762.0); 361	60.0 (24.0-147.0); 131	63.0 (24.0-135.0); 264	67.0 (24.0-154.0); 139	64.0 (24.0-150.0); 265
FeNO, median (IQR), ppb; n	27.0 (15.0-50.0); 180	25.0 (16.0-45.0); 358	30.0 (17.5-53.0); 176	24.0 (14.0-42.0); 358	24.0 (14.0-42.0); 131	22.0 (13.0-36.0); 266	22.5 (13.5-39.5); 140	24.0 (14.0-43.0); 269
Serum TARC, median (IQR), pg/mL; n	307.0 (218.0-508.0); 179	351.0 (224.5-478.5); 360	313.0 (206.0-525.0); 179	317.0 (198.0-456.0); 357	284.0 (196.0-421.0); 130	265.0 (187.5-402.5); 264	281.5 (186.0-449.0); 140	276.0 (178.0-386.0); 265
Blood eosinophil count, median (IQR), cells/μL; n	290.0 (150.0-490.0); 183	240.0 (120.0-470.0); 359	260.0 (160.0-440.0); 179	240.0 (140.0-430.0); 361	250.0 (130.0-470.0); 134	250.0 (120.0-460.0); 271	270.0 (120.0-470.0); 141	270.0 (130.0-510.0); 272

Baseline blood eosinophil data were missing for 1 randomized patient receiving dupilumab 200 mg q2w and 1 randomized patient receiving placebo 2 mL/300 mg q2w and were excluded from efficacy analyses.

ACQ-5, 5-Item Asthma Control Questionnaire; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; IQR, interquartile range; q2w, every 2 weeks; SD, standard deviation; TARC, thymus and activation-regulated chemokine.

*A patient was considered to have ongoing atopic medical condition if he/she had any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, or hives.

†The ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control; higher scores indicate less asthma control. Change in ACQ-5 score of at least 0.5 is regarded as clinically meaningful.

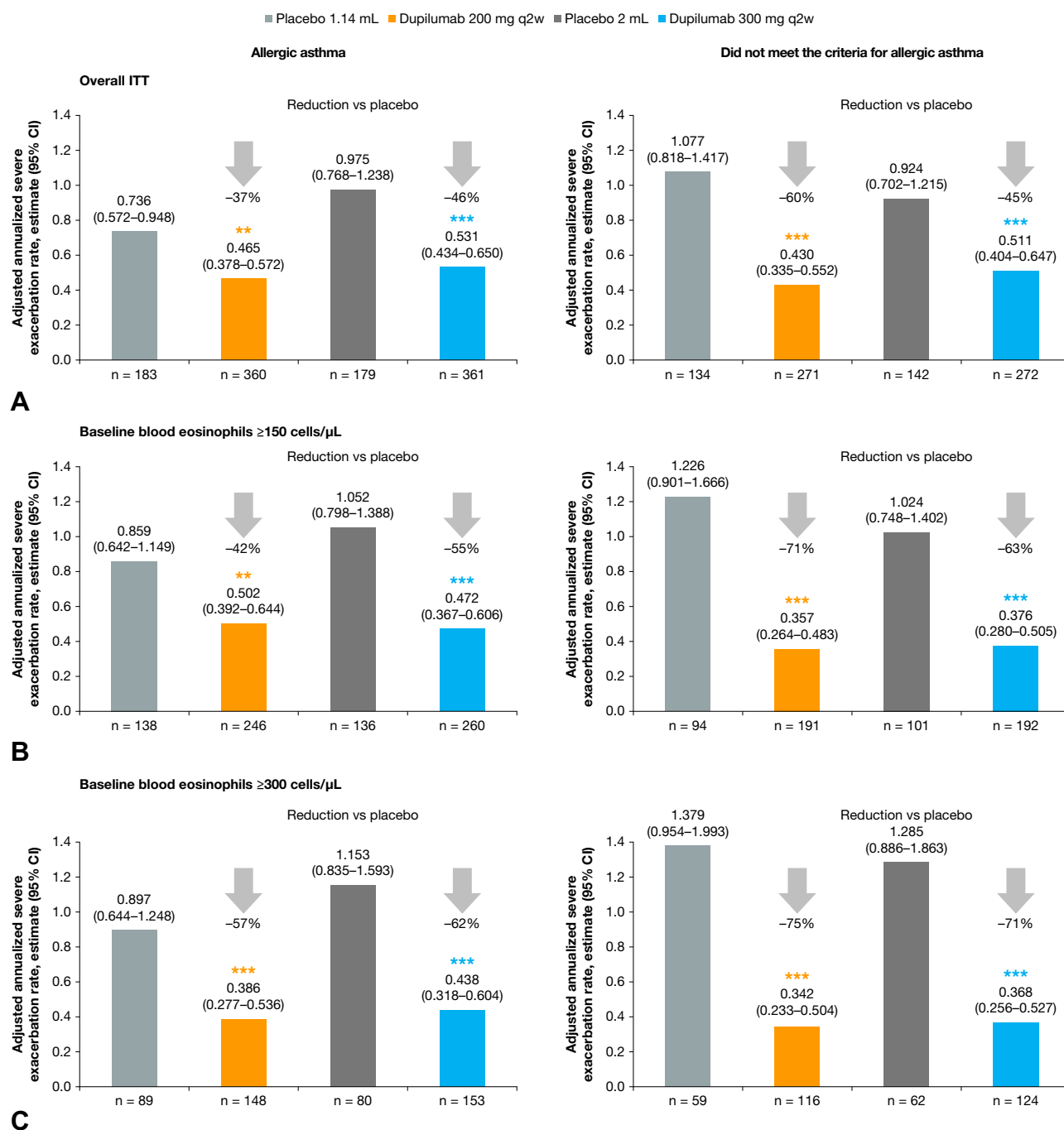


FIGURE 1. Effect of dupilumab on annualized severe exacerbation rates in the overall allergic subgroup and overall subgroup that did not meet the criteria for allergic asthma (A), and those with baseline blood eosinophils ≥ 150 cells/ μ L (B), ≥ 300 cells/ μ L (C), baseline FeNO ≥ 25 ppb (D), and baseline serum total IgE > 700 IU/mL (E) within these subgroups. CI, Confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; q2w, every 2 weeks.

center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

Patients

The study enrolled adults and adolescents (aged ≥ 12 years) with physician-diagnosed asthma for at least 12 months (based on Global

Initiative for Asthma 2014 guidelines²⁴) and receiving treatment with a medium-to-high dose inhaled glucocorticoid and up to 2 additional controllers. Eligible patients had forced expiratory volume in 1 second (FEV₁) before bronchodilator use $\leq 80\%$ of predicted normal value for adults and $\leq 90\%$ of predicted normal value for adolescents; FEV₁ reversibility of $\geq 12\%$ and 200 mL; a score of ≥ 1.5 on the 5-item

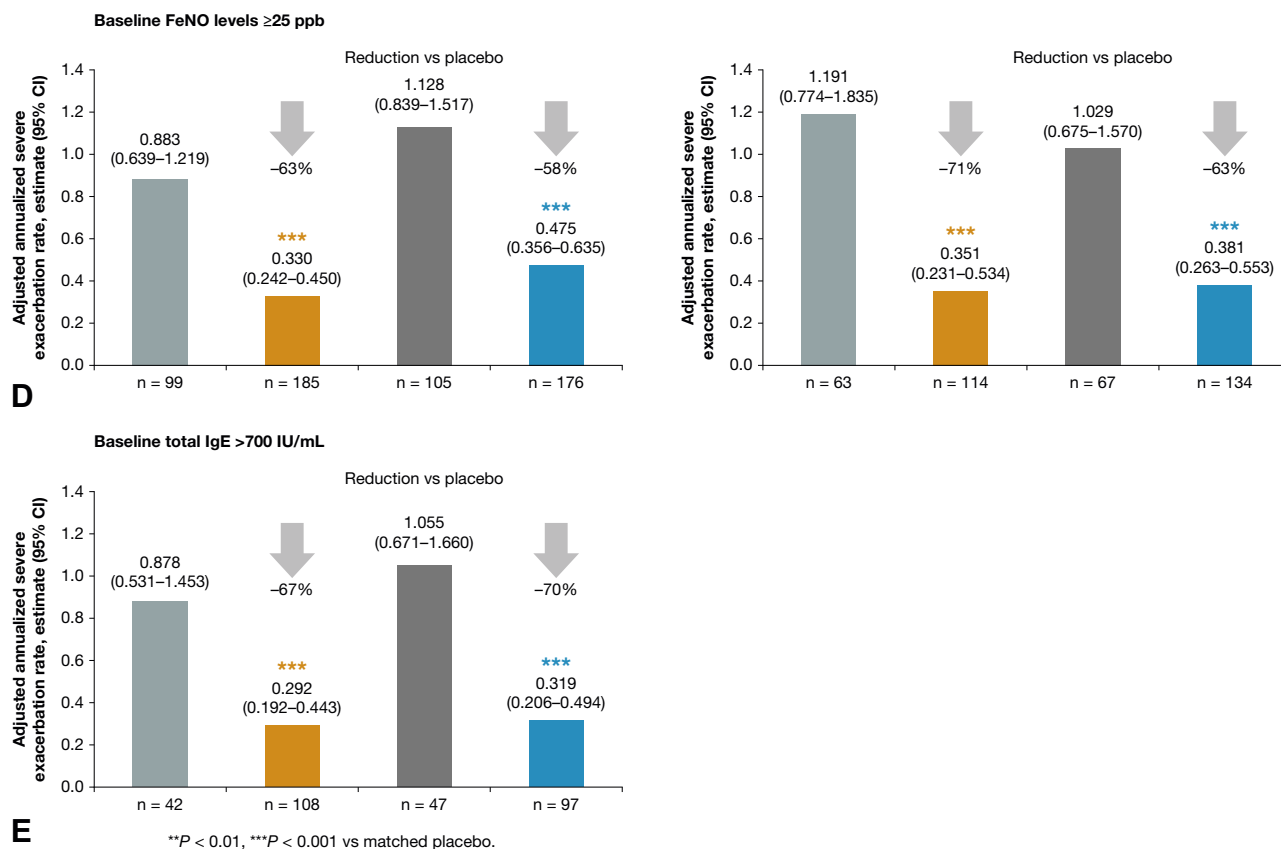


FIGURE 1. Continued.

Asthma Control Questionnaire (ACQ-5); and worsening of asthma in the previous year that led to hospitalization, emergency medical care, or treatment with systemic glucocorticoids for 3 or more days. Complete inclusion and exclusion criteria are provided in the Supplementary Appendix of the primary manuscript.¹⁷

For this *post hoc* analysis, we examined patients classified by whether or not they met the criteria for allergic asthma used by physicians to determine eligibility for biologic therapy with omalizumab: a total serum IgE ≥ 30 IU/mL and ≥ 1 positive perennial aeroallergen-specific IgE value (≥ 0.35 kU/L) at baseline.²³ The following perennial allergens were included: *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Cladosporium herbarum*, cat and dog danders, German cockroach, oriental cockroach, and *Aspergillus fumigatus*. Percutaneous allergy skin testing was not performed.

End points

End points analyzed were annualized severe exacerbation rates, change from baseline in prebronchodilator FEV₁ (L), and change from baseline in ACQ-5 score over the 52-week treatment period in the subgroups of patients who met and did not meet the allergic asthma criteria. Within each subgroup, severe exacerbations during the 52-week treatment period and change from baseline in prebronchodilator FEV₁ (L) at week 12 were also analyzed in populations of patients with baseline blood eosinophils ≥ 150 cells/ μ L, ≥ 300 cells/ μ L, and baseline FeNO ≥ 25 ppb. An additional analysis was performed on the subset of patients with allergic asthma with

baseline serum total IgE >700 IU/mL, for whom omalizumab therapy is not indicated in the United States.²³

The effect of dupilumab treatment on the following biomarkers of type 2 inflammation was also assessed in the allergic versus nonallergic subgroups: serum total IgE, FeNO, and serum thymus and activation-regulated chemokine (TARC). The effect of dupilumab treatment on serum specific IgE to each of the perennial aeroallergens tested during the 52-week treatment period was also examined in those patients who tested positive (≥ 0.35 kU/L) at baseline.

Statistical analysis

Efficacy analyses were performed in the intention-to-treat (ITT) population, defined as all randomized patients, separated into subgroups (ie, with or without total serum IgE ≥ 30 IU/mL and ≥ 1 positive perennial aeroallergen-specific IgE value [≥ 0.35 kU/L] at baseline). Data were analyzed for each subgroup according to the 4 assigned treatment groups (dupilumab vs placebo), whether or not an intervention was received.¹⁷ Annualized rates of severe exacerbations over the 52-week treatment period were analyzed using a negative binomial regression model, which included as covariates the assigned intervention groups, age, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, and number of severe exacerbations in the previous year. All severe exacerbations that occurred during the 52-week treatment period were included regardless of whether the patient remained on treatment.

The change from baseline in prebronchodilator FEV₁ (L) and ACQ-5 scores during the 52-week treatment period were analyzed using mixed-effect models with repeated measures, which included

as covariates the 4 assigned intervention groups, age, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, visit, visit-by-intervention interaction, corresponding baseline value, and baseline-by-visit interaction. In addition, sex and baseline height were also included as covariates for FEV₁ analyses. If treatment was discontinued, any measurements recorded after discontinuation were included throughout the 52-week treatment period.

Biomarker analyses were performed in the exposed population, defined as all patients exposed to study medication. For both patient subgroups, differences between dupilumab and matched placebo in the change from baseline in levels of eosinophils and FeNO, considered as key biomarkers of type 2 inflammation, were analyzed using a rank analysis of covariance model including the 4 assigned intervention groups, age, sex, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, and corresponding baseline value as covariates. For the analysis of specific IgEs, we restricted the analyses to patients who were positive (≥ 0.35 kU/L) for the specific IgEs at baseline.

A nominal P value of $<.05$ for the comparison between each dupilumab dose and matched placebo (within each subgroup) was considered statistically significant.

RESULTS

Patients

A total of 1083 patients (57% of the QUEST study ITT population) met the criteria used to define allergic asthma, namely total serum IgE ≥ 30 IU/mL and ≥ 1 positive perennial aeroallergen-specific IgE ≥ 0.35 kU/L at baseline. The remaining patients ($n = 819$; 43% of the ITT population) did not meet the criteria for allergic asthma. Of these 819 patients, 7% ($n = 55$) had ≥ 1 positive perennial aeroallergen-specific IgE at baseline but a total serum IgE of <30 IU/mL; 14% ($n = 114$) had ≥ 1 positive seasonal allergen but tested negative for all perennial allergens; 38% ($n = 314$) had a history of allergic rhinitis but tested negative for all perennial and seasonal allergens; and 41% ($n = 336$) did not have a history of allergic rhinitis and also tested negative for all perennial and seasonal allergens.

Patients who met the criteria for allergic asthma were generally younger (mean 44.5 years vs 52.5 years), had asthma onset at an earlier age (mean 21.6 years vs 34.2 years), and a higher proportion had comorbid atopic conditions (96% vs 64%) compared with the subgroup that did not meet the criteria for allergic asthma (Table 1). Furthermore, the allergic asthma subgroup had fewer mean severe exacerbations in the previous year (1.94 vs 2.30) and a higher mean prebronchodilator FEV₁ (1.85 L vs 1.67 L). These patients, compared with patients who did not meet the criteria for allergic asthma, also had higher serum TARC concentrations (median 327 pg/mL vs 277 pg/mL) and similar levels of FeNO (median 26 ppb vs 23 ppb) and blood eosinophil count (median 250 cells/ μ L vs 260 cells/ μ L).

Annualized rate of severe asthma exacerbations

In the allergic asthma subgroup, dupilumab reduced the adjusted annualized rate of severe exacerbations compared with matched placebo by 36.9% with 200 mg q2w (95% confidence interval [CI], 13.4% to 54.0%; nominal $P = .004$) and 45.5% with 300 mg q2w (95% CI, 26.0% to 59.9%; nominal $P < .001$; Figure 1, A). In patients who did not meet the criteria for allergic asthma, the adjusted annualized rate of severe

exacerbation events was also significantly reduced by 60.0% with dupilumab 200 mg q2w (95% CI, 42.7% to 72.1%; nominal $P < .001$), and by 44.6% with 300 mg q2w (95% CI, 21.5% to 60.9%; nominal $P < .001$) compared with placebo (Figure 1, A). In both the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, dupilumab 200 and 300 mg q2w significantly (all nominal $P < .01$) reduced the rate of severe exacerbations in patients with baseline blood eosinophils ≥ 150 and ≥ 300 cells/ μ L and in those with baseline FeNO ≥ 25 ppb, and the magnitude of effect was numerically greater compared with the respective overall subgroup (Figure 1, B-D). Among patients in the allergic asthma subgroup with baseline serum total IgE >700 IU/mL, both dupilumab doses significantly (nominal $P < .001$) reduced severe exacerbation rates during the 52-week treatment period compared with matched placebo, and the magnitude of effect was also numerically greater versus the overall allergic asthma subgroup (Figure 1, E).

Prebronchodilator FEV₁

At week 12, dupilumab 200 and 300 mg q2w treatment significantly improved prebronchodilator FEV₁ versus placebo by least-squares (LS) mean 0.13 L (95% CI, 0.05-0.20; nominal $P < .001$) and 0.16 L (95% CI, 0.09-0.23; nominal $P < .001$), respectively, in the allergic asthma subgroup, and by 0.14 L (95% CI, 0.07-0.22; nominal $P < .001$) and 0.09 L (95% CI, 0.01-0.16; nominal $P = .02$) versus placebo, respectively, in those patients who did not meet the criteria (Figure 2, A). As observed for severe exacerbations, the magnitude of improvement versus placebo in prebronchodilator FEV₁ at week 12 was equal to or greater than in patients with baseline blood eosinophils ≥ 150 and ≥ 300 cells/ μ L and those with baseline FeNO ≥ 25 ppb than in the respective overall subgroups (all nominal $P < .05$; Figure 2, B). Among patients in the allergic asthma subgroup with baseline serum total IgE >700 IU/mL, dupilumab 300 mg q2w showed a similar magnitude of effect on prebronchodilator FEV₁ at week 12 compared with the overall subgroup (LS mean difference vs placebo 0.12 L [95% CI, -0.03 to 0.26; nominal $P = .11$]), whereas a greater magnitude of effect was observed in patients treated with dupilumab 200 mg q2w (LS mean difference vs placebo 0.27 L [95% CI, 0.13 to 0.42]; nominal $P < .001$).

In both the allergic and nonallergic subgroups, improvements in prebronchodilator FEV₁ were observed as early as the first evaluation at week 2 and persisted through week 52 (Figure 2, A).

Asthma control

In the allergic asthma subgroup, the LS mean change from baseline in ACQ-5 score was improved by -1.39 (standard error [SE], 0.05) with a difference versus placebo of -0.28 (95% CI, -0.46 to -0.11; nominal $P < .01$) in dupilumab 200 mg q2w-treated patients and by -1.42 (SE, 0.05) with a difference versus placebo of -0.26 (95% CI, -0.44 to -0.08; nominal $P < .01$) at week 24 (Figure 3) in dupilumab 300 mg q2w-treated patients. In the subgroup that did not meet the allergic asthma criteria, the improvement in ACQ-5 score from baseline at week 24 was -1.51 (SE, 0.06) with a difference versus placebo of -0.44 (95% CI, -0.65 to -0.22; nominal $P < .0001$) in dupilumab 200 mg q2w-treated patients, and -1.35 (SE, 0.06) with a difference versus placebo of -0.08

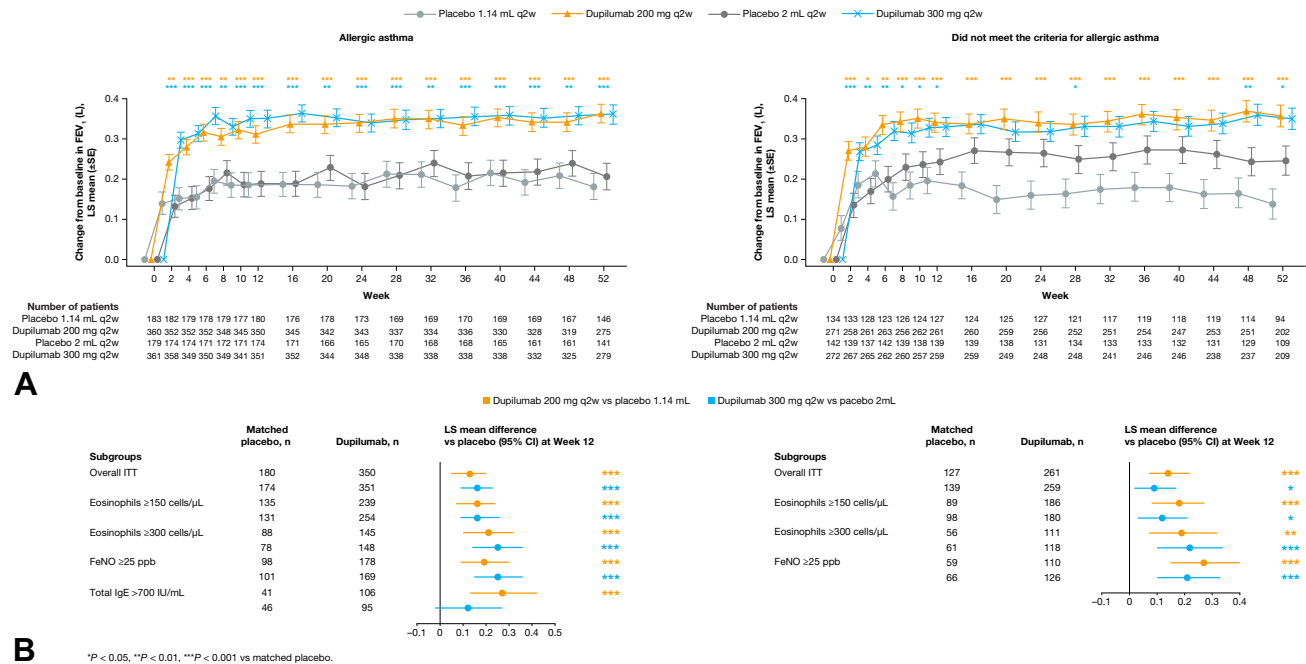


FIGURE 2. Effect of dupilumab on FEV_1 (L) during the 52-week treatment period in the overall allergic subgroup and overall subgroup that did not meet the criteria for allergic asthma (A) and the magnitude of effect by baseline blood eosinophils, FeNO, and baseline serum total IgE subgroups at week 12 (B). *FeNO*, Fractional exhaled nitric oxide; *FEV₁*, forced expiratory volume in 1 second; *ITT*, intention-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error.

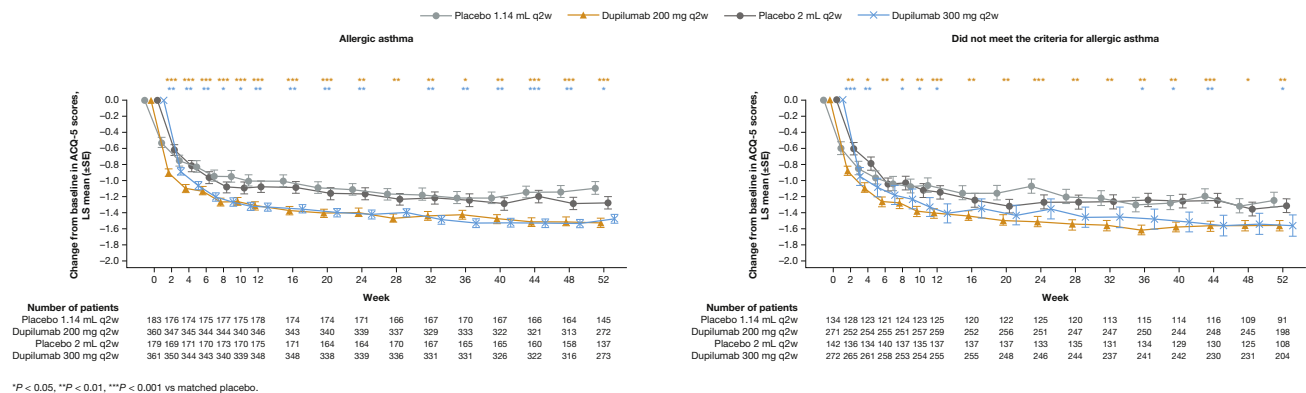


FIGURE 3. Effect of dupilumab on asthma control (as measured by ACQ-5) during the 52-week treatment period in the overall allergic subgroup and overall subgroup that did not meet the criteria for allergic asthma. *ACQ-5*, 5-Item Asthma Control Questionnaire; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error.

(95% CI, -0.29 to 0.12 ; nominal $P = .43$) observed in patients treated with dupilumab 300 mg q2w (Figure 3).

Serum total IgE and aeroallergen-specific IgE

In the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, both dupilumab 200 and 300 mg q2w dose regimens significantly reduced total serum IgE compared with matched placebo at week 12 (the earliest assessed time point; nominal $P < .001$; Figure 4, A). Reductions in total serum IgE occurred gradually throughout the treatment period (nominal $P < .001$ vs placebo at all time points).

In patients with allergic asthma who tested positive at baseline (≥ 0.35 kU/L) for the respective perennial aeroallergen,

significant reductions from baseline in percentage of antigen-specific serum IgE levels were observed over time for each of the 8 perennial aeroallergens that were assessed (Figure 5). These reductions were statistically significant at week 12 (the earliest assessed time point) compared with matched placebo (nominal $P < .05$) and continued over the 52-week treatment period. Too few patients tested positive for oriental cockroach allergens at baseline to allow for a meaningful analysis.

FeNO and serum TARC

In both the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, dupilumab 200 and 300 mg q2w dose regimens versus placebo were associated with a

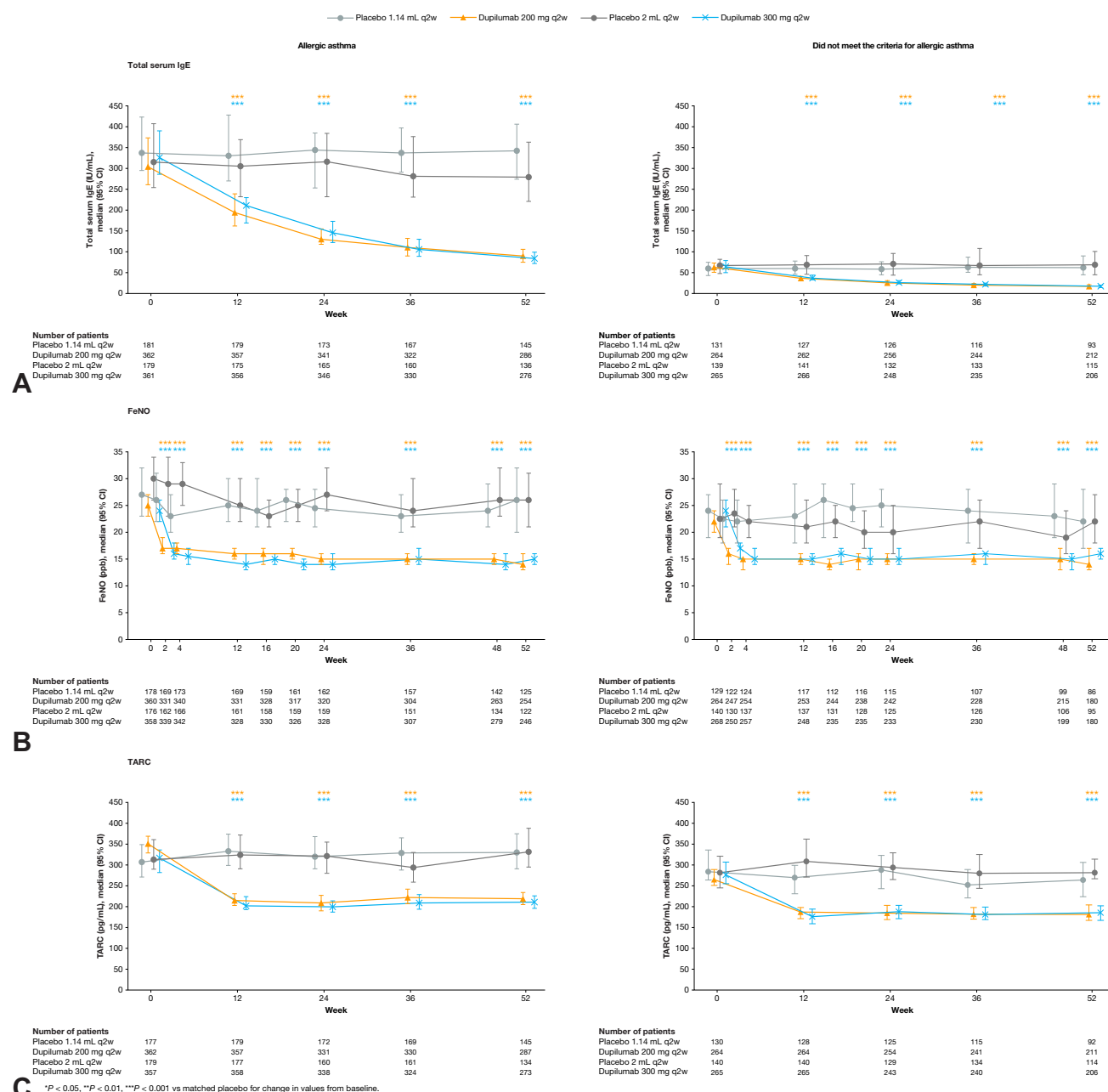


FIGURE 4. Effect of dupilumab on serum total IgE (A), FeNO (B), and serum TARC (C) during the 52-week treatment period in the overall allergic subgroup and overall subgroup that did not meet the criteria for allergic asthma (exposed population). *CI*, Confidence interval; *FeNO*, fractional exhaled nitric oxide; *q2w*, every 2 weeks; *TARC*, thymus and activation-regulated chemokine.

marked decrease in FeNO by the first evaluation, after 2 weeks of treatment. The decrease in FeNO was sustained throughout the 52-week treatment period (nominal $P < .001$ at all time points) (Figure 4, B). By week 52, median FeNO values for the dupilumab 200 and 300 mg q2w doses in both subgroups were similar to the published median value for healthy volunteers (16 ppb).²⁵

In both the allergic asthma subgroup and the subgroup that did not meet the criteria for allergic asthma, serum TARC concentrations were significantly reduced versus matched placebo at week 12 (the earliest assessed time point) in patients

treated with dupilumab 200 or 300 mg q2w. These reductions were sustained throughout the 52-week treatment period (nominal $P < .001$ at all time points) (Figure 4, C).

DISCUSSION

In this *post hoc* analysis of the pivotal phase 3 LIBERTY ASTHMA QUEST study, dupilumab significantly reduced severe exacerbation rates and improved FEV₁ and asthma control (as measured by ACQ-5) in patients with allergic asthma. Improvements in FEV₁ and asthma control were

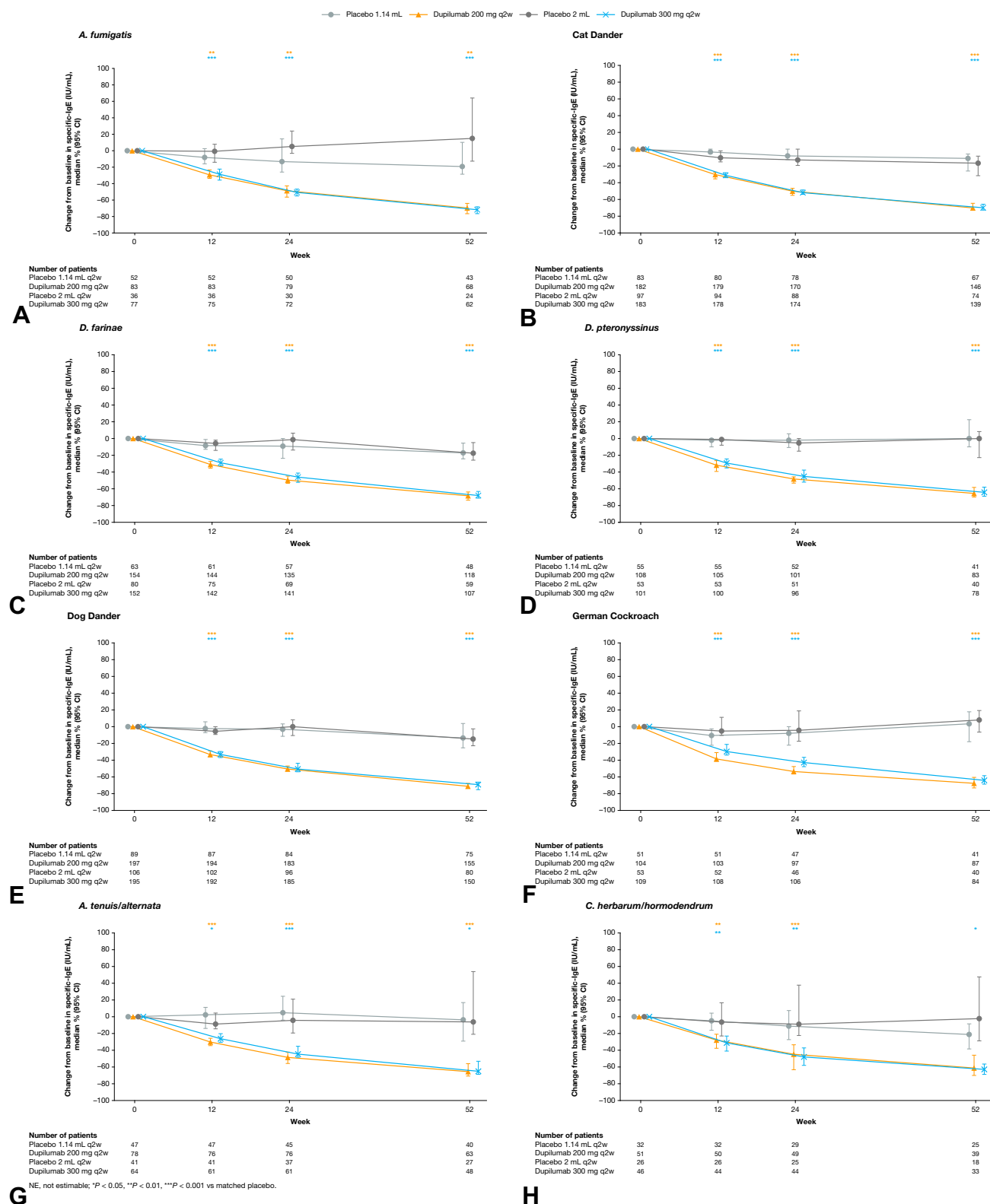


FIGURE 5. Effect of dupilumab on antigen-specific serum IgE levels during the 52-week treatment period in the allergic asthma subgroup with baseline antigen-specific serum IgE levels ≥ 0.35 kU/mL (exposed population). *Aspergillus fumigatus* (A), cat dander (B), *Derma-tophagoides farinae* (C), *Dermatophagoides pteronyssinus* (D), dog dander (E), German cockroach (F), *Alternaria tenuis/alternata* (G), and *Cladosporium herbarum/hormodendrum* (H). CI, Confidence interval; q2w, every 2 weeks.

evident by the first evaluation at week 2, and sustained throughout the 52-week treatment period. Reductions in severe exacerbation rates and improvement in FEV₁ were greater in patients with higher baseline levels of type 2 inflammatory biomarkers, which were consistent with previous dupilumab studies in asthma.¹⁶⁻¹⁸ The proportion of patients who met the criteria for allergic asthma (57%) in this study was significantly lower than patients who reported a history of ≥ 1 atopic condition in the overall QUEST population.¹⁷ This difference is primarily due to the exclusion of patients who had a history of allergic rhinitis but did not have evidence of hypersensitivity to aeroallergens; the exclusion of patients who had hypersensitivity only to seasonal allergens, to a lesser extent; and the exclusion of patients with perennial allergen sensitivity but whose total serum IgE was <30 IU/mL. It should be acknowledged that the timing of specific IgE measurements in this global study was not designed to coincide with peak seasonal allergen exposure in each country/region.

In this study, dupilumab is shown to be effective in patients with allergic asthma as well as those who did not meet the criteria for allergic asthma. These findings support the critical roles of IL-4 and IL-13 in driving IgE-mediated and non-IgE-mediated type 2 inflammation in asthma. The clinical benefits observed in this study extended to those patients with allergic asthma whose serum total IgE exceeded 700 IU/mL at baseline. This is a clinically relevant subset of allergic asthma patients for whom anti-IgE therapy with omalizumab is not indicated in the United States.²³ This subgroup was included in the analysis because dosing of dupilumab, unlike omalizumab, is not limited by body weight and serum total IgE in adolescent and adult patients with uncontrolled, moderate-to-severe asthma. It should be noted, however, that although omalizumab is not indicated in patients with total IgE ≥ 700 IU/mL, there have been reports of its effective use in such patients.²⁶

Consistent with the mechanism of action of dupilumab in suppressing IgE production, dupilumab significantly reduced serum total IgE and aeroallergen-specific IgE in patients with allergic asthma, and reduced serum total IgE in those who did not meet the criteria for allergic asthma.

Similarly, dupilumab significantly reduced levels of other type 2 inflammatory biomarkers including FeNO and serum TARC in both patient subgroups. The decline in total and specific IgE is slower relative to other biomarkers such as FeNO. The decline in IgE concentrations did not plateau during the 52-week treatment period.

The pathophysiological mechanisms that underlie allergic and eosinophilic inflammation in asthma are interconnected. There is increasing recognition of the complex relationship in asthma between adaptive immunity, including Th2 cells, and innate immunity, including type 2 innate lymphoid cells.^{2,6,7,9} The findings of this *post hoc* analysis reinforce the importance of inhibiting persistent type 2 inflammation as an important treatment paradigm for managing the majority of patients with uncontrolled asthma.

The strength of this study includes its randomized, double-blind design, large population size, and the inclusion of patients regardless of the baseline IgE level. A limitation is that this was a *post hoc* analysis in subgroups that were not defined *a priori*. The study was not powered specifically to investigate differences between patients with asthma with or without an allergic phenotype. The diagnosis of allergic asthma was based on the

criteria used to determine eligibility for omalizumab therapy (ie, high serum IgE levels and sensitization to at least 1 perennial allergen).²³ Although allowing a comparison with omalizumab efficacy, this definition did not include all possible perennial allergens, or indeed seasonal allergens, which can also trigger allergic asthma and may, therefore, have missed some patients with allergic asthma. Furthermore, the analysis also excluded patients without elevated IgE levels, which is not a strict requirement for a diagnosis of allergic asthma. A further limitation regarding diagnosis was that patients with a single positive allergen-specific IgE to animal dander were not assessed for any history of relevant animal exposure before being classified as having allergic asthma. Lastly, all patients were allowed to take antiallergic medications (including allergen immunotherapy in the maintenance phase) during the study, and their role in influencing the results is unclear.

In summary, this is the first report to describe the clinical and pharmacodynamic effects of dual IL-4 and IL-13 inhibition with dupilumab in patients with allergic asthma defined by the presence of total serum IgE ≥ 30 IU/mL and ≥ 1 perennial aeroallergen-specific IgE ≥ 0.35 kU/L at baseline. Dupilumab significantly reduced the rate of severe exacerbations, improved FEV₁, and demonstrated clinically meaningful improvements in asthma control (ACQ-5) during the 52-week treatment period regardless of subgroup, and treatment was generally well tolerated in the overall study population.¹⁷ Markers of type 2 inflammation, including FeNO, total IgE, and TARC, were also significantly reduced with dupilumab treatment in both subgroups. The findings from this study support the roles of IL-4 and IL-13 in IgE- and non-IgE-mediated inflammatory pathways in asthma, and IL-4/IL-13 inhibition by dupilumab therapy as beneficial for both the allergic and nonallergic asthma phenotypes.

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REFERENCES

1. Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol* 2015;15:57-65.
2. Campo P, Rodríguez F, Sánchez-García S, Barranco P, Quirce S, Pérez-Francés C, et al. Phenotypes and endotypes of uncontrolled severe asthma: new treatments. *J Investig Allergol Clin Immunol* 2013;23:76-88.
3. Wenzel S. Severe asthma: from characteristics to phenotypes to endotypes. *Clin Exp Allergy* 2012;42:650-8.
4. Chen L, Grabowski KA, Xin JP, Coleman J, Huang Z, Espiritu B, et al. IL-4 induces differentiation and expansion of Th2 cytokine-producing eosinophils. *J Immunol* 2004;172:2059-66.
5. Poulsen LK, Hummelshøj L. Triggers of IgE class switching and allergy development. *Ann Med* 2007;39:440-56.
6. Hall S, Agrawal DK. Key mediators in the immunopathogenesis of allergic asthma. *Int Immunopharmacol* 2014;23:316-29.
7. Rael EL, Lockett RF. Interleukin-13 signaling and its role in asthma. *World Allergy Organ J* 2011;4:54-64.
8. Gour N, Wills-Karp M. IL-4 and IL-13 signaling in allergic airway disease. *Cytokine* 2015;75:68-78.
9. Hirano I, Dellon ES, Hamilton JD, Collins MH, Peterson K, Chehade M, et al. Efficacy of dupilumab in a phase 2 randomized trial of adults with active eosinophilic esophagitis [published online ahead of print October 5, 2019]. *Gastroenterology*. <https://doi.org/10.1053/j.gastro.2019.09.042>.

10. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol* 2017;13:425-37.
11. 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 USA* 2014;111:5147-52.
12. 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 USA* 2014;111:5153-8.
13. US Food and Drug Administration. DUPIXENT® (dupilumab) injection, for subcutaneous use; 2017. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf. Accessed July 18, 2019.
14. Japan PMDA. DUPIXENT® (dupilumab). Available from: https://www.pmda.go.jp/PmdaSearch/iyakuDetail/ResultDataSetPDF/780069_4490405G1024_1_04. Accessed July 18, 2019.
15. EU EMA approval. New add-on treatment for patients with severe asthma. Available from: http://ec.europa.eu/health/documents/community-register/2019/20190506144541/anx_144541_en.pdf. Accessed July 18, 2019.
16. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016;388:31-44.
17. 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;378:2486-96.
18. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;378:2475-85.
19. Blauvelt A, de Bruin-Weller M, Gooderham M, Cather JC, Weisman J, Pariser D, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017;389:2287-303.
20. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016;375:2335-48.
21. Thaçi D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016;387:40-52.
22. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016;315:469-79.
23. US Food and Drug Administration. Xolair® (omalizumab). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/omalgen062003LB.pdf. Accessed April 2, 2019.
24. Global strategy for asthma management and prevention. Global Initiative for Asthma (GINA); 2015. Available from: https://ginasthma.org/wp-content/uploads/2016/01/GINA_Pocket_2015.pdf. Accessed April 2, 2019.
25. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602-15.
26. Maselli DJ, Singh H, Diaz J, Peters JJ. Efficacy of omalizumab in asthmatic patients with IgE levels above 700 IU/mL: a retrospective study. *Ann Allergy Asthma Immunol* 2013;110:457-61.