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Efficacy of dupilumab on clinical outcomes in patients with asthma and perennial allergic rhinitis

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ABSTRACT

Background: Comorbid perennial allergic rhinitis (PAR) or year-round aeroallergen sensitivity substantially contributes to disease burden in patients with asthma. Dupilumab blocks the shared receptor for interleukin (IL) 4 and IL-13, key drivers of type 2 inflammation that play important roles in asthma and PAR. In the LIBERTY ASTHMA QUEST trial (NCT02414854), dupilumab reduced severe asthma exacerbations and improved forced expiratory volume in 1 second (FEV_1) in patients with uncontrolled, moderate-to-severe asthma, with greater efficacy observed in patients with elevated type 2 inflammatory biomarkers at baseline (blood eosinophils and fractional exhaled nitric oxide).
Objective: To assess dupilumab efficacy in LIBERTY ASTHMA QUEST patients with comorbid PAR.
Methods: Severe asthma exacerbation rates, FEV_1, asthma control (5-item Asthma Control Questionnaire), rhinoconjunctivitis-specific health-related quality of life (Standardized Rhinoconjunctivitis Quality of Life

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Questionnaire +12 scores), and type 2 inflammatory biomarkers during the 52-week treatment period were assessed.

Results: A total of 814 of the 1902 patients (42.8%) had comorbid PAR (defined as an allergic rhinitis history and ≥1 perennial aeroallergen specific immunoglobulin E (IgE) level ≥0.35 kU/L at baseline). Dupilumab, 200 and 300 mg every 2 weeks, vs placebo reduced severe exacerbations rates by 32.2% and 34.6% ($P < .05$ for both) and improved FEV_1 at week 12 by 0.14 L and 0.18 L ($P < .01$ for both); greater efficacy was observed in patients with elevated baseline blood eosinophil counts (≥300 cells/μL) and fractional exhaled nitric oxide. Dupilumab treatment also numerically improved the 5-item Asthma Control Questionnaire and Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12 scores and suppressed type 2 inflammatory biomarkers.

Conclusion: Dupilumab improved key asthma-related outcomes, asthma control, and rhinoconjunctivitis-specific health-related quality of life while suppressing type 2 inflammatory biomarkers and perennial allergen-specific IgE in patients with moderate-to-severe asthma and comorbid PAR, highlighting its dual inhibitory effects on IL-4 and IL-13 and its role in managing asthma and PAR.

Introduction

Allergic rhinitis (AR) is one of the most common types of atopic comorbidity in patients with uncontrolled, persistent asthma.[1] Perennial allergic rhinitis (PAR), which is often associated with sensitization to indoor allergens, such as dust mites and animal dander,[2] is generally considered more difficult to treat than seasonal allergic rhinitis (SAR), and symptoms of PAR often persist despite available treatment.[3] Individuals sensitized to mites or other indoor aeroallergens are more likely to have severe asthma than patients with seasonal allergies,[4,5] which adds to the disease burden in patients with asthma.[5,6] Indeed, comorbid AR is a marker of more severe asthma and contributes to poor asthma control. Uncontrolled severe asthma is associated with a greater likelihood of asthma-related hospital admissions, emergency department visits, inferior quality of life (QoL), and higher total annual medical costs.[5,7,8]

Epidemiologic, pathophysiologic, and clinical evidence supports the concept that asthma and AR are components of a united airway disease, in which symptoms of the upper and lower airways are manifestations of the allergic or type 2 inflammation common to both conditions.[5,9-12] Type 2 inflammation is mediated by inflammatory cells, including T cells, mast cells, basophils, and eosinophils, which infiltrate the nasal and bronchial mucosa and release inflammatory cytokines and chemokines.[12-14] Interleukin (IL) 4 and IL-13 are key drivers of type 2 inflammatory processes, including the immunoglobulin E (IgE)–mediated allergic inflammation typical of PAR. IL-4 is a pivotal cytokine that induces T_H2 polarization,[15,16] and IL-4 and IL-13 promote IgE synthesis and activation of mast cells and eosinophils.[17] IL-13 also induces mucus production and airway hyperreactivity.[18,19]

Dupilumab, a fully human VelocImmune-derived[20,21] monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, type 2 inflammatory cytokines implicated in several allergic diseases from asthma to atopic dermatitis, and inhibits signaling by both cytokines.[22] Dupilumab is approved by the US Food and Drug Administration[23] as add-on maintenance treatment in patients 12 years or older who have moderate-to-severe asthma and an eosinophilic phenotype or have oral corticosteroid-dependent asthma, is approved in Japan for patients 12 years or older who have severe or refractory bronchial asthma and symptoms inadequately controlled by existing therapies,[24] and is also approved by the European Medicines Agency[25] as an add-on maintenance treatment in patients 12 years or older with type 2 severe asthma characterized by increased blood eosinophils and/or increased fractional exhaled nitric oxide (FeNO) who have inadequate control with a high-dose inhaled corticosteroid plus another medicinal product for maintenance treatment.[26-29] Dupilumab is also approved in the United States as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps[24] and for the treatment of inadequately controlled, moderate-to-severe atopic dermatitis in patients 12 years or older in the United States[23] and in adults in the European Union[25] and other countries.[30-32]

In a pivotal, phase 2b study (NCT01854047), dupilumab improved key asthma outcomes in the overall population with uncontrolled, persistent asthma and improved AR-associated nasal symptoms in the subgroup of patients with comorbid PAR.[29,33] In the phase 3 LIBERTY ASTHMA QUEST study in patients 12 years or older with uncontrolled, moderate-to-severe asthma, compared with placebo, dupilumab again significantly improved key asthma outcomes and had greater efficacy in patients with elevated type 2 inflammatory biomarkers (blood eosinophils and FeNO) at baseline.[26] In that study, dupilumab also improved asthma symptoms and health-related quality of life (HRQoL) measures and was generally well tolerated in the intention-to-treat (ITT) population.[26]

In this study, post hoc analysis of the phase 3 LIBERTY ASTHMA QUEST study was conducted to determine the effects of dupilumab on outcomes of asthma and AR and the inhibitory effects of dupilumab on type 2 inflammatory biomarkers in patients with uncontrolled, moderate-to-severe asthma and comorbid PAR.

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 12 years or older with uncontrolled, moderate-to-severe asthma. The study design has been reported elsewhere.[26] Briefly, patients were randomized in a 2:2:1:1 ratio to receive add-on therapy with 200 mg of dupilumab (loading dose, 400 mg), 300 mg of dupilumab (loading dose, 600 mg), or matched-volume placebos. Treatment was administered every 2 weeks for 52 weeks.

In this post hoc analysis, efficacy of dupilumab was evaluated in the subgroup of patients with comorbid PAR, defined as a history of AR and sensitization to 1 or more perennial aeroallergen-specific IgEs (≥0.35 kU/L) at baseline. Perennial aeroallergens included house dust mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*); cat dander, dog dander, and ubiquitous molds (*Alternaria alternata*, *Aspergillus fumigatus*, and *Cladosporium herbarum*);

Table 1
Baseline Demographic and Disease Characteristics of Patients With Comorbid Perennial Allergic Rhinitis

Characteristic	1.14 mL, 200 mg every 2 weeks		2 mL, 300 mg every 2 weeks	
	Placebo (n = 133)	Dupilumab (n = 260)	Placebo (n = 145)	Dupilumab (n = 276)
Age, mean (SD), y	43.1 (16.8)	42.8 (16.0)	42.9 (15.4)	42.8 (15.7)
Female, No. (%)	78 (58.6)	145 (55.8)	98 (67.6)	167 (60.5)
White race, No. (%)	113 (85.0)	205 (78.8)	124 (85.5)	228 (82.6)
BMI, mean (SD), kg/m^2	28.81 (6.88)	28.78 (6.62)	29.09 (7.46)	28.86 (6.84)
Time since first asthma diagnosis, mean (SD), y	24.01 (15.65)	23.70 (16.23)	24.02 (16.26)	24.58 (15.33)
Age at asthma onset, mean (SD), y	19.1 (17.4)	19.2 (17.5)	18.9 (16.6)	18.2 (16.7)
Severe asthma exacerbations in past year, mean (SD)	1.91 (1.63)	1.90 (1.58)	2.17 (1.87)	1.73 (1.21)
High-dose ICSs, No. (%)[a]	69 (51.9)	126 (48.5)	77 (53.1)	127 (46.0)
Prebronchodilator FEV_1, mean (SD), L	1.90 (0.63)	1.89 (0.62)	1.89 (0.61)	1.91 (0.57)
FEV_1 predicted, mean (SD), %	59.71 (12.90)	59.36 (13.07)	60.20 (13.98)	60.81 (12.92)
Ongoing atopic medical condition, No. (%)[b]	133 (100)	260 (100)	145 (100)	276 (100)
Atopic dermatitis	17 (12.8)	44 (16.9)	28 (19.3)	37 (13.4)
Nasal polyposis	13 (9.8)	27 (10.4)	12 (8.3)	29 (10.5)
Food allergy	17 (12.8)	28 (10.8)	23 (15.9)	23 (8.3)
Former smoker, No. (%)	19 (14.3)	48 (18.5)	27 (18.6)	49 (17.8)
ACQ-5 score, mean (SD)[c]	2.68 (0.61)	2.79 (0.85)	2.69 (0.78)	2.73 (0.80)
RQLQ(S) +12 total score, mean (SD)[d]	2.00 (1.08)	2.00 (1.16)	1.87 (1.19)	1.88 (1.15)
Total serum IgE, median (IQR), IU/mL	321 (147-639)	305.5 (150-855)	272 (116-730)	315.5 (132-752)
Allergen-specific IgE, median (IQR), kU/L (exposed population)[e]				
Dermatophagoides farinae	4.26 (2.14-7.75)	5.095 (2.06-10.3)	4.22 (1.44-7.22)	7.19 (5.16-10.6)
Dermatophagoides pteronyssinus	12.50 (5.04-41.3)	19.05 (8.66-36.2)	12.0 (7.93-26)	23.4 (12-34.4)
Cat dander	3.52 (1.96-7.98)	4.59 (3.06-7.03)	5.69 (2.66-8.6)	3.87 (2.24-7.41)
Dog dander	2.89 (1.75-5.48)	2.1 (1.58-3.86)	4.2 (1.72-7.95)	2.67 (1.78-3.92)
Aspergillus fumigatus	1.10 (0.82-2.23)	1.46 (1.01-2.3)	1.49 (0.81-4.01)	0.87 (0.65-1.41)
German cockroach	0.84 (0.63-1.57)	0.98 (0.79-1.64)	1.71 (0.75-3.77)	1.21 (0.95-1.74)
Oriental cockroach	0.76 (NE)	1.46 (0.36-6.83)	NA	1.69 (1.11-3.29)
Alternaria alternata	4.26 (2.95-6.10)	3.26 (2.32-4.60)	2.82 (1.33-5.40)	3.19 (1.41-5.59)
Cladosporium herbarum	1.39 (0.6-2.51)	1.335 (0.71-2.50)	1.73 (0.82-5.34)	1.22 (0.72-2.30)
FeNO, median (IQR), ppb	28 (15-53)	24 (15-43)	29 (16-51)	24 (14-41)
TARC, median (IQR), pg/mL	334 (205-551)	352 (230.0-500.5)	302 (201-505)	321 (200-489)
Blood eosinophil count, median (IQR), cells/μL	290 (140-490)	240 (130-475)	260 (160-440)	250 (140-440)

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICSs, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not available; NE, not estimable; RQLQ(S) +12, Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12; TARC, thymus- and activation-regulated chemokine.

[a]Medium- to high-dose ICSs (≥250 μg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 μg/d of fluticasone propionate or equivalent).

[b]A patient is considered to have an ongoing atopic medical condition if he or she has a baseline total IgE level of 100 IU/mL or greater, 1 or more aeroallergen specific IgE test results are positive (≥0.35 kU/L) at baseline, or any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, or hives.

[c]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. A change in the ACQ-5 score of 0.5 or greater is regarded as clinically meaningful.

[d]The RQLQ(S) +12 is a self-administered questionnaire with standardized activities developed to measure health-related quality-of-life signs and symptoms that are most problematic in those aged 12 to 75 years, as a result of perennial or seasonal allergic rhinitis. Higher scores indicated greater health-related quality-of-life impairment. A change in RQLQ(S) +12 score of at least 0.5 is regarded as clinically meaningful.

[e]For patients with 1 or more aeroallergen-specific IgE–positive test results (≥0.35 kU/L) at baseline.

German cockroach (*Blatella germanica*); and Oriental cockroach (*Blatella orientalis*).

Study Outcomes and Procedures

The analyzed asthma-related outcome measures were annualized severe exacerbation rates during the 52-week treatment period, change from baseline in prebronchodilator forced expiratory volume in 1 second (FEV_1) to week 12, and change from baseline in 5-item Asthma Control Questionnaire (ACQ-5) score to week 12. FEV_1 and ACQ-5 were also assessed during the entire 52-week treatment period. A severe asthma exacerbation was defined as deterioration of asthma that led to treatment for 3 days or more with systemic glucocorticoids, hospitalization, or an emergency department visit that led to treatment with systemic glucocorticoids. 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. A change in ACQ-5 score of at least 0.5 is regarded as clinically meaningful.[34,35] Outcomes related to PAR were the change from baseline in the Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12 (RQLQ [S] +12) total score and subdomains during the 52-week treatment period.[34,35] The RQLQ(S) +12 is a self-administered questionnaire with standardized activities developed to measure HRQoL signs and symptoms that are most problematic in those 12 to 75 years of age as a result of PAR or SAR. Higher scores indicate greater HRQoL impairment. A change in RQLQ(S) +12 score of at least 0.5 is regarded as clinically meaningful.[34]

The effect of dupilumab treatment on biomarkers of type 2 inflammation (total serum IgE, FeNO, and serum thymus- and activation-regulated chemokine [CCL17 or TARC]) was also assessed. Treatment effects on allergen-specific IgE were also assessed in patients who tested positive (≥0.35 kU/L) for that specific allergen at baseline.

Statistical Analysis

Efficacy analyses were performed on the ITT population, defined as all randomized patients with comorbid PAR. Data were analyzed according to the assigned intervention, regardless of whether an

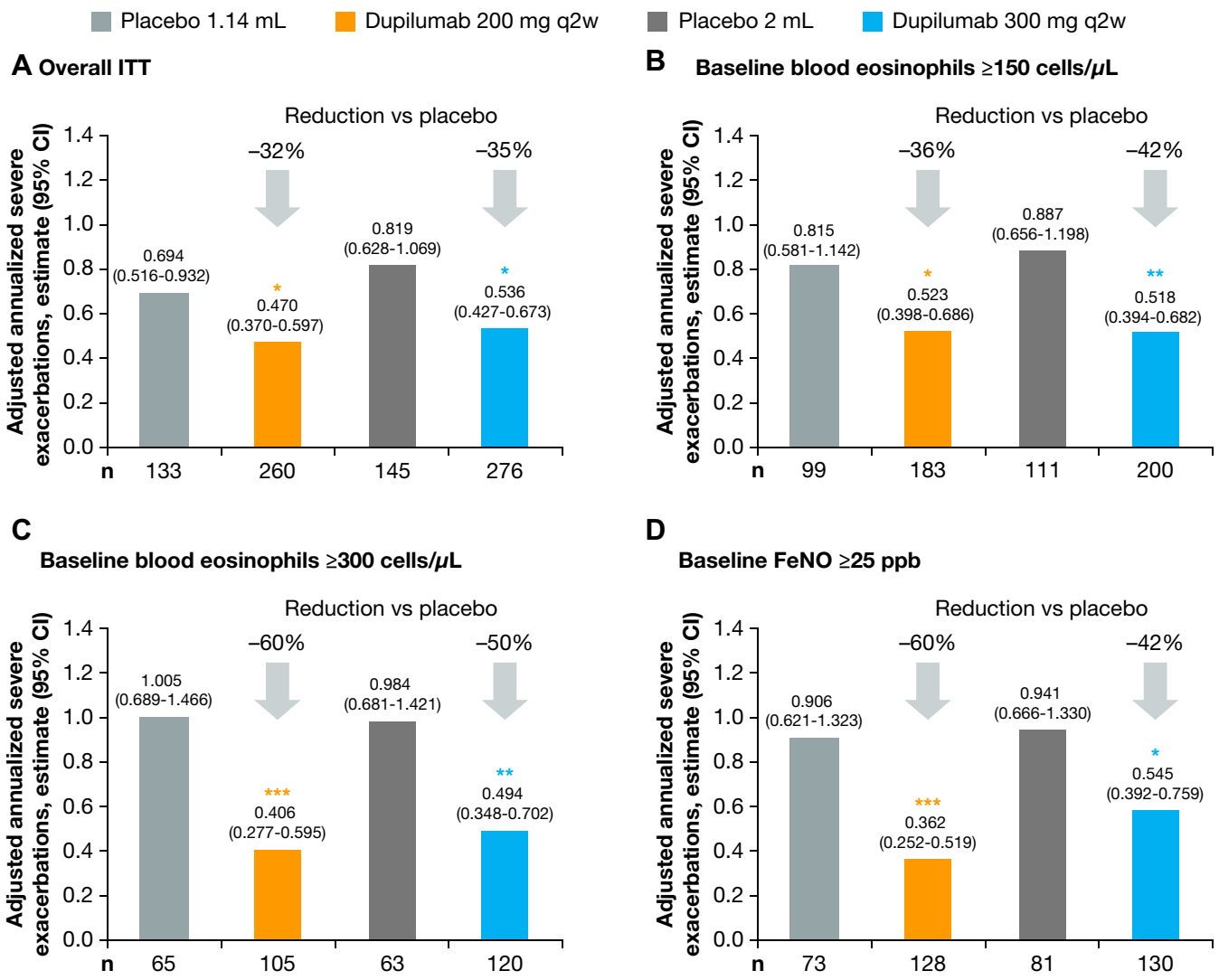


Figure 1. Effect of dupilumab on annualized severe exacerbation rates in patients with (A) comorbid PAR, (B) baseline blood eosinophil counts of 150 cells/μL or greater, (C) baseline blood eosinophil counts of 300 cells/μL or greater, or (D) FeNO levels of 25 ppb or greater. CI, confidence interval; FeNO, fractional exhaled nitric oxide levels; ITT, intent to treat; PAR, perennial allergic rhinitis; q2w, every two weeks. $^{*}P < .05$ vs matched placebo. $^{**}P < .01$ vs matched placebo. $^{***}P < .001$ vs matched placebo.

intervention was received. Annualized rates of severe exacerbation were analyzed using negative binomial regression models that included as covariates the 4 assigned intervention groups (age, geographic region, baseline eosinophil level, and baseline dose of inhaled corticosteroid) and number of exacerbations in the previous year. All severe exacerbations during the 52 weeks were included, regardless of whether the patient continued to receive treatment.

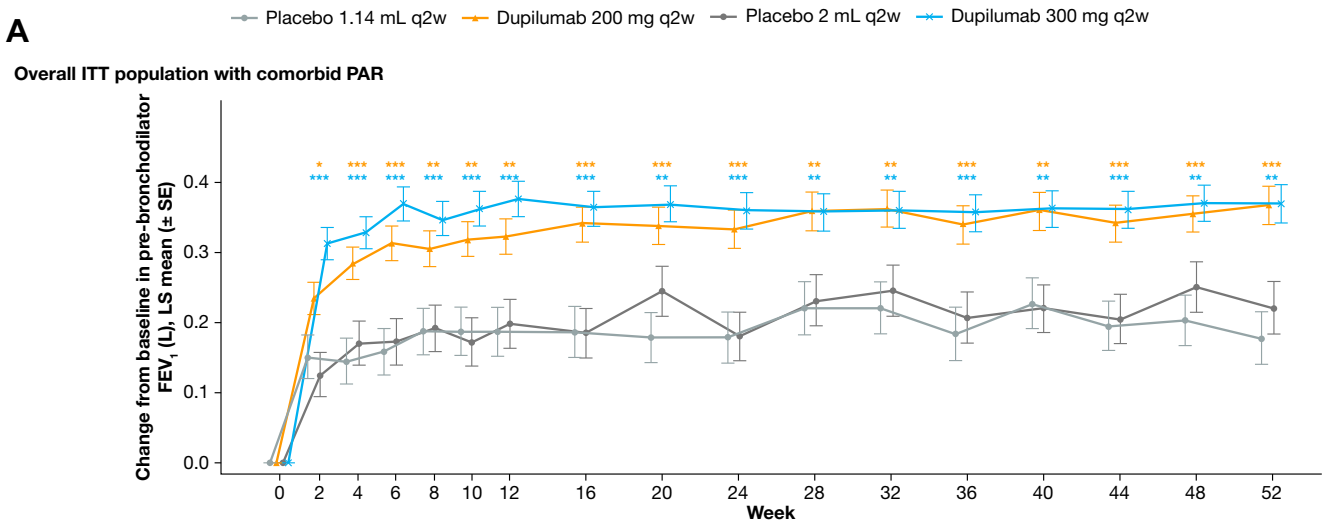
Change from baseline in prebronchodilator FEV_1, ACQ-5 score, and RQLQ(S) +12 scores were analyzed using mixed-effect models with repeated measures, including as covariates the 4 assigned intervention groups (as specified above), for visit, visit-by-intervention interaction, corresponding baseline value, and baseline-by-visit interaction. For FEV_1 analyses, sex and baseline height were included as covariates. If treatment was discontinued early, any measurements made during the 52-week study period but after discontinuation were included in the analyses.

Differences between dupilumab and matched placebo in the change from baseline for each of the selected biomarkers were analyzed in the population of all patients exposed to the study medication by using a rank analysis of covariance model, including as covariates the 4 assigned intervention groups and the corresponding baseline values. Nominal $P < .05$ was considered statistically significant. Least squares (LS) means and associated differences in LS means between treatment groups were reported for each of the outcomes. Statistical analysis was performed using SAS statistical software, version 9.4 (SAS Institute Inc, Cary, North Carolina).

Results

Baseline Demographic and Clinical Characteristics

Of the 1902 randomized patients with uncontrolled, moderate-to-severe asthma (ITT population), 1207 (63.5%) had a patient-reported history of AR. Of those with a history of AR, 814 (67.4%) met the criteria for PAR, and this group comprised 42.8% of all randomized patients. Baseline demographic and disease characteristics of the PAR population are given in Table 1 and were broadly balanced between the dupilumab and placebo populations. Of the 1088 patients (57.2% of the ITT population) who did not meet the criteria for PAR, 695 (63.9%) did not report a history of AR, 314 (28.9%) reported a history of AR but received negative test results



No. of patients

Placebo 1.14 mL q2w	133	133	132	131	130	130	132	128	130	127	125	122	124	123	124	122	105
Dupilumab 200 mg q2w	260	254	255	254	254	249	253	251	249	251	246	247	246	241	244	237	201
Placebo 2 mL q2w	145	143	140	140	140	141	142	138	137	134	140	136	139	136	133	129	116
Dupilumab 300 mg q2w	276	273	265	267	265	259	268	270	263	269	257	260	259	259	254	250	215

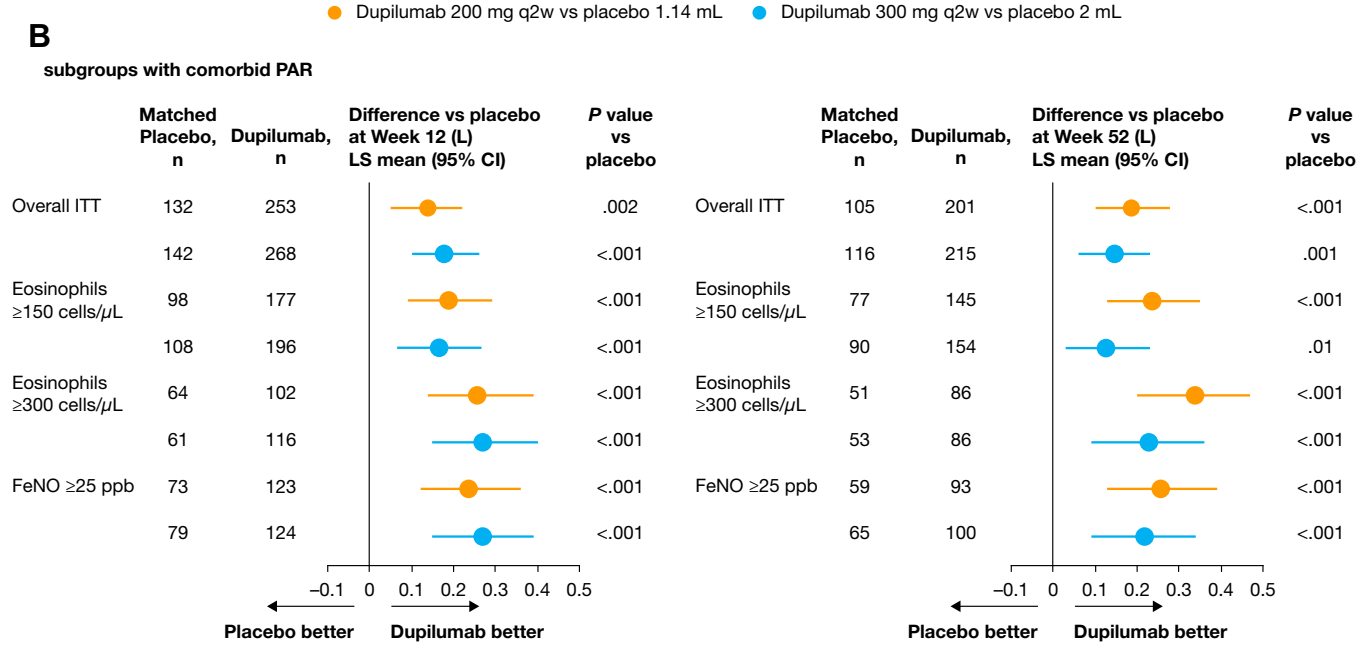
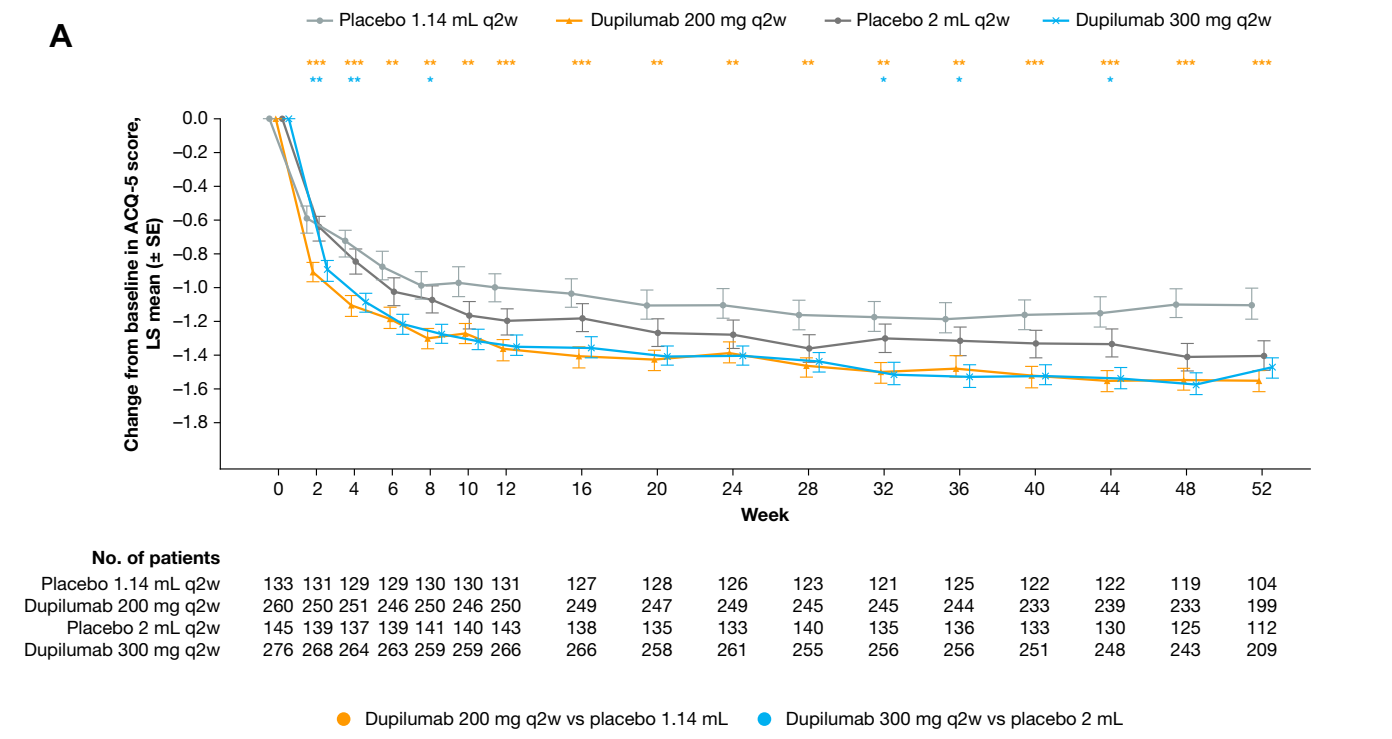


Figure 2. Effect of dupilumab on FEV1 during the 52-week treatment period in patients with (A) comorbid PAR and (B) baseline blood eosinophil counts of 150 or 300 cells/μL or greater or fractional exhaled nitric oxide (FeNO) of 25 ppb or higher. CI, confidence interval; FeNO, fractional exhaled nitric oxide levels; FEV_1, forced expiratory volume in 1 second; ITT, intent to treat; LS, least squares; PAR, perennial allergic rhinitis; q2w, every two weeks. $^{*}P < .05$ vs matched placebo. $^{**}P < .01$ vs matched placebo. $^{***}P < .001$ vs matched placebo.

for all perennial or seasonal allergens, and 79 (7.3%) reported a history of AR and received positive test results (≥0.35 IU/mL) for 1 or more of the seasonal (not perennial) allergens.

Annualized Rate of Severe Asthma Exacerbations

In patients with comorbid PAR, dupilumab (vs matched placebo) significantly reduced the annualized rate of severe exacerbation events during the 52-week treatment period by 32.2% (95% confidence interval [CI], 2.6%-52.8%, $P = .04$, for the 200 mg every 2 weeks regimen) and 34.6% (95% CI, 8.3%-53.3%, $P = .01$, for the 300 mg every 2 weeks regimen) (Fig 1A). The reductions in severe exacerbation rates in the dupilumab groups relative to those in the placebo groups were greater in several subgroups of patients than in the ITT population; those subgroups were patients with baseline blood eosinophil counts of 150 cells/μL or greater (severe exacerbation rate reduction, 35.8% with the 200 mg every 2 weeks regimen, $P = .04$; 41.6% with the 300 mg every 2 weeks regimen, $P = .007$) (Fig 1B), patients with baseline blood eosinophil counts of 300 cells/μL or greater (59.6%, $P < .001$; 49.8%, $P = .007$, respectively) (Fig 1C), and patients with baseline FeNO of 25 ppb or greater (60.1%, $P < .001$; 42.0%, $P = 0.02$, respectively) (Fig 1D).



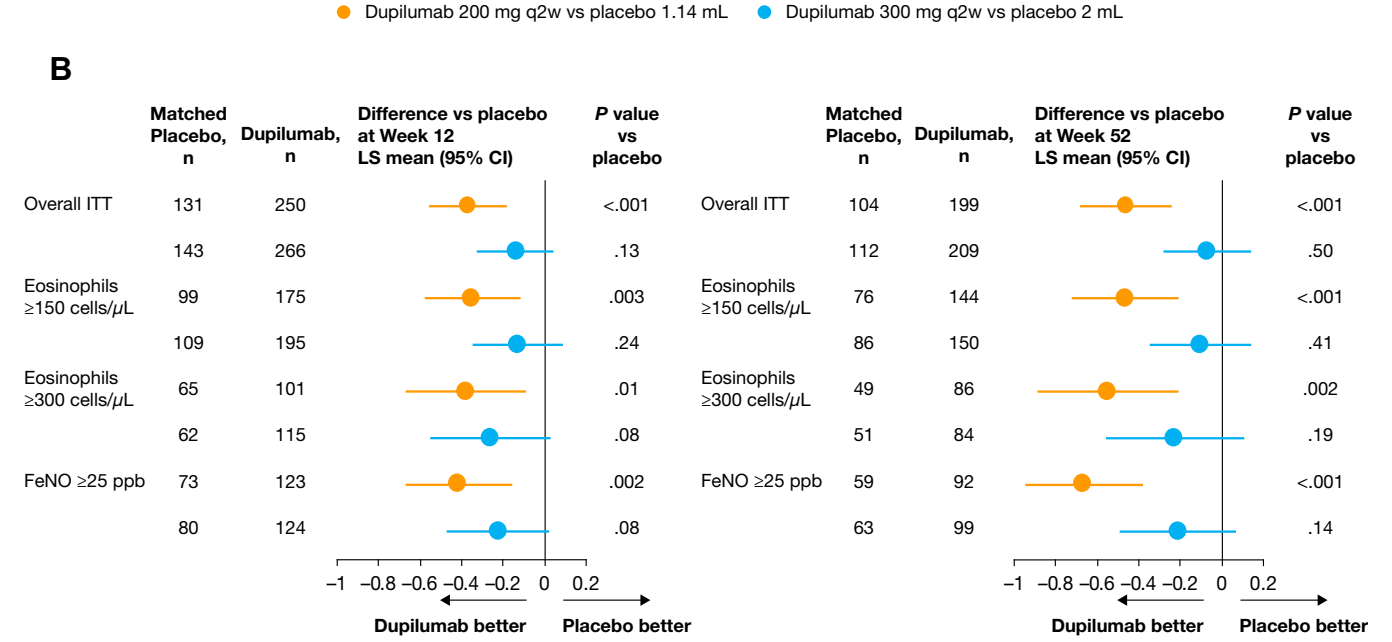


Figure 3. Effect of dupilumab on asthma control in patients with (A) comorbid PAR and (B) baseline blood eosinophil counts of 150 or 300 cells/μL or greater or FeNO of 25 ppb or greater. ACQ-5, 5-item Asthma Control Questionnaire; CI, confidence interval; FeNO, fractional exhaled nitric oxide levels; ITT, intent to treat; LS, least squares; PAR, perennial allergic rhinitis; q2w, every two weeks. $^{*}P < .05$ vs matched placebo. $^{**}P < .01$ vs matched placebo. $^{***}P < .001$ vs matched placebo.

Prebronchodilator forced expiratory volume in 1 second

At week 12, dupilumab, compared with placebo, significantly improved prebronchodilator FEV_1 by 0.14 L (200-mg regimen: 95% CI, 0.05-0.22 L; $P = .002$) and 0.18 L (300-mg regimen: 95% CI, 0.10-0.26 L; $P < .001$) (Fig 2A and B) in patients with comorbid PAR. These improvements were comparable or greater in patients with baseline blood eosinophil counts of 150 or 300 cells/μL or greater and patients with baseline FeNO of 25 ppb or greater ($P < .001$ for both regimens in each subgroup) (Fig 2B).

The FEV_1 improvements in the overall population with comorbid PAR were observed as early as week 2 with both dupilumab regimens (200-mg group vs placebo: 0.09 L; 95% CI, 0.01-0.16 L; $P = .03$; 300-mg group vs placebo: 0.19 L; 95% CI, 0.11-0.26 L; $P < .001$) and sustained through week 52 (200-mg group vs placebo: 0.19 L; 95% CI, 0.10-0.28 L; $P < .001$; 300-mg group vs placebo: 0.15 L; 95% CI, 0.06-0.23 L; $P < .001$).

Asthma Control (as Measured by 5-Item Asthma Control Questionnaire)

At week 12, patients receiving 200 mg of dupilumab every 2 weeks reported an improvement in asthma control (LS mean [SE] change from baseline in ACQ-5 score, −1.38 [0.06]; LS mean difference vs placebo, −0.37; 95% CI, −0.56 to −0.18; $P < .001$) (Fig 3A and B). In patients receiving a dose of 300 mg of dupilumab every 2 weeks, the LS mean (SE) change from baseline in ACQ-5 score at week 12 was −1.34 (0.06), and the LS mean

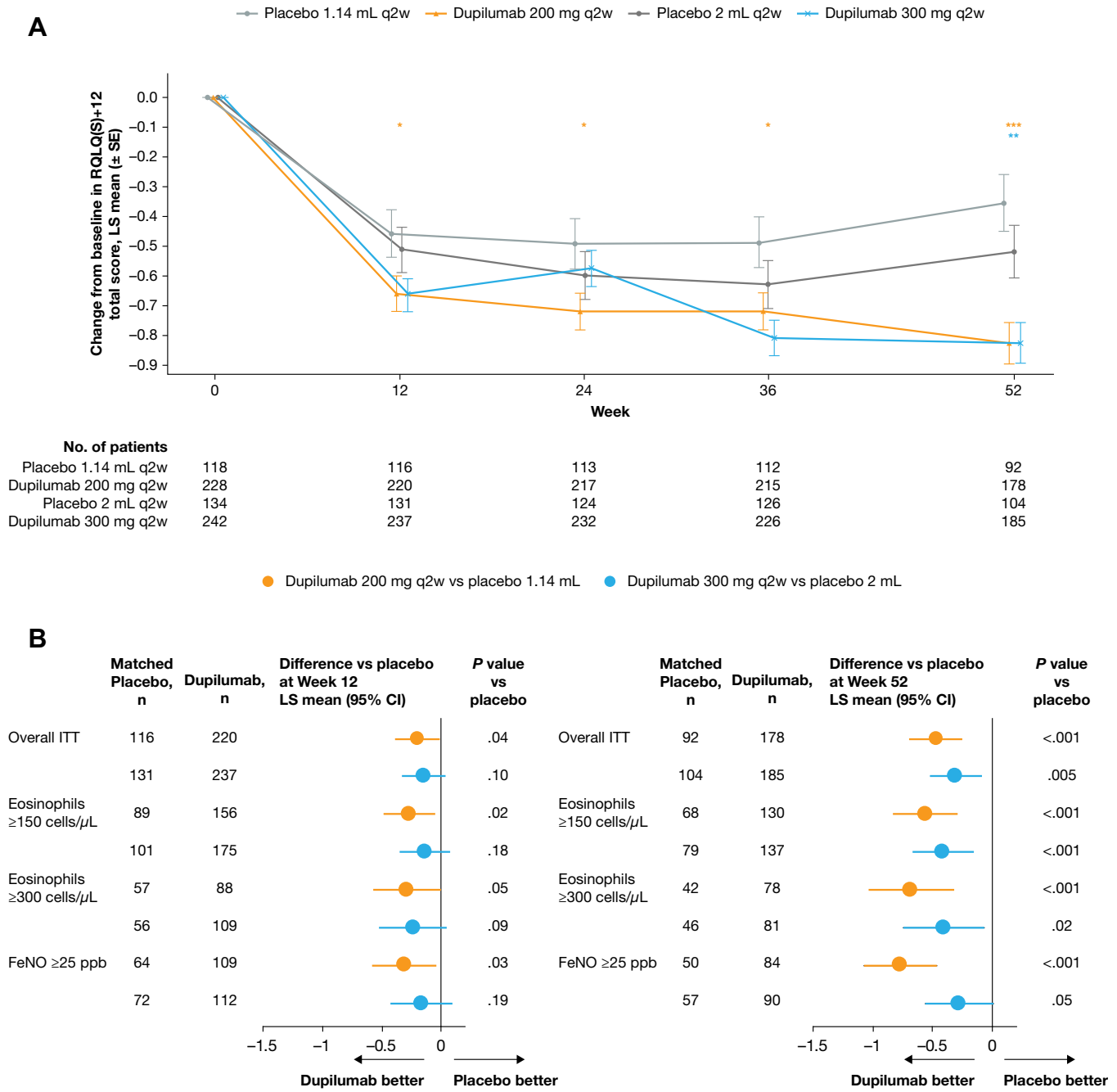


Figure 4. Effect of dupilumab on rhinoconjunctivitis-specific HRQoL in patients with (A) comorbid PAR and (B) baseline blood eosinophil counts of 150 or 300 cells/μL or greater or baseline FeNO of 25 ppb or greater. CI, confidence interval; FeNO, fractional exhaled nitric oxide levels; HRQoL, health-related quality of life; ITT, intent to treat; LS, least squares; PAR, perennial allergic rhinitis; q2w, every two weeks; RQLQ(S) +12, Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12. $^{*}P < .05$ vs matched placebo. $^{**}P < .01$ vs matched placebo. $^{***}P < .001$ vs matched placebo.

difference vs placebo was −0.14 (95% CI, −0.33 to 0.04; $P = .13$) (Fig 3A and B). These improvements in asthma control in the dupilumab and placebo groups exceeded the threshold for change in scores that are considered clinically important (0.5),[34,35] were observed as early as week 2, and were sustained throughout the 52-week treatment period. Significant improvements compared with placebo were also observed at weeks 12 and 52 in the subgroups of patients receiving 200 mg of dupilumab every 2 weeks with baseline blood eosinophil counts of 150 cells/μL or greater, 300 cells/μL or greater, or baseline FeNO of 25 ppb or greater (Fig 3B).

Rhinoconjunctivitis-Specific Health-Related Quality of Life (as Measured by Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12)

At week 12 patients with comorbid PAR who were receiving 200 mg of dupilumab every 2 weeks reported an improvement in rhinoconjunctivitis-specific HRQoL as measured by the RQLQ(S) +12 (LS mean [SE] change from baseline in total score, −0.06 (0.06); LS mean difference vs placebo, −0.20; 95% CI, −0.39 to −0.01; $P = .04$). Patients receiving 300 mg of dupilumab every 2 weeks had a LS mean (SE) improvement from

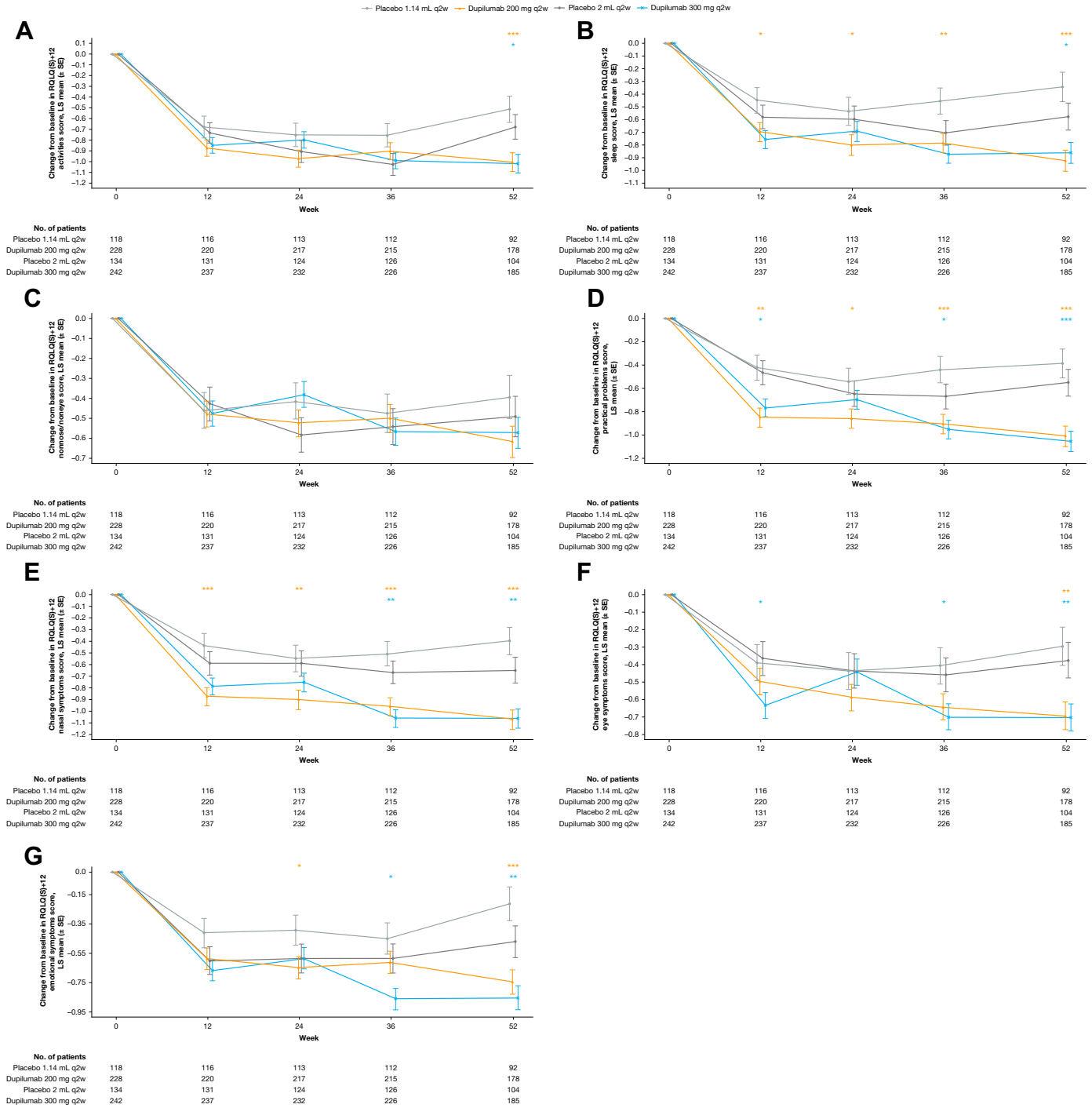
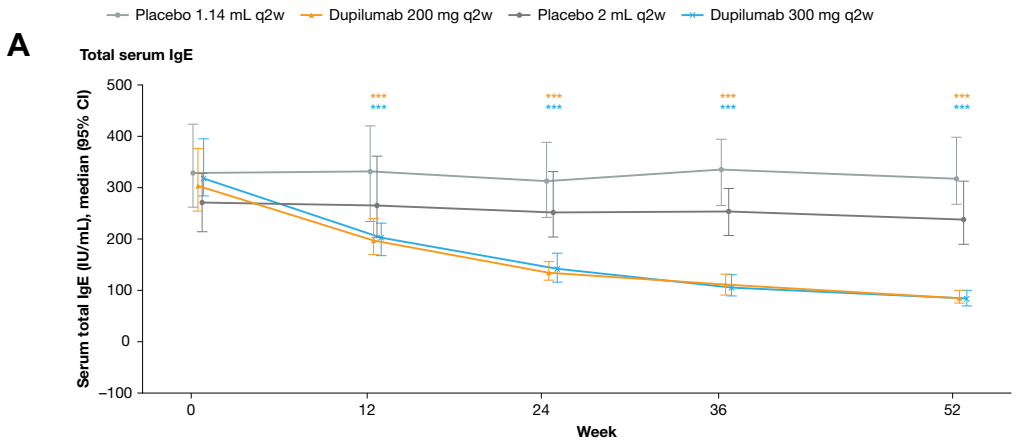


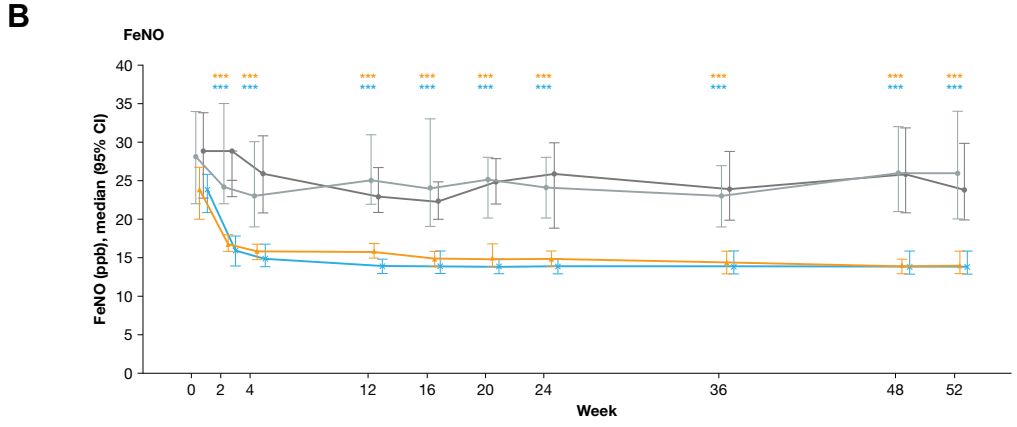
Figure 5. Effect of dupilumab on RQLQ(S) +12 domains: (A) activities, (B) sleep, (C) nonnose/noneye, (D) practical problems, (E) nasal symptoms, (F) eye symptoms, and (G) emotions in patients with comorbid PAR. LS, least squares; PAR, perennial allergic rhinitis; q2w, every two weeks; RQLQ(S) +12, Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12. $^{*}P < .05$ vs matched placebo. $^{**}P < .01$ vs matched placebo. $^{***}P < .001$ vs matched placebo.

baseline in total RQLQ(S) +12 score of −0.67 (0.06) and a LS mean difference vs placebo of −0.15 (95% CI, −0.33 to 0.03; $P = .10$) (Fig 4A and B). Rhinoconjunctivitis-specific HRQoL improved further during the 52-week treatment period, and by week 52, the LS mean (SE) change from baseline in total RQLQ(S) +12 score was −0.83 (0.07) (minimum clinically important difference = 0.5)[34,35] in both dupilumab groups (Fig 4A). Improvements vs placebo at week 12 were comparable for the subgroups of patients with baseline blood eosinophil counts of 150 or 300 cells/μL or greater and patients with baseline FeNO of 25 ppb or greater, and the magnitude of the improvement was comparable or greater at week 52 (Fig 4B).

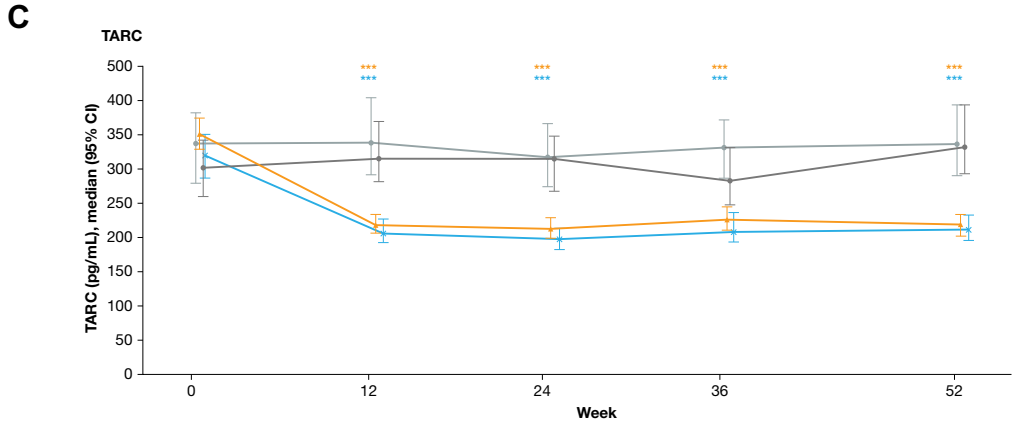
By week 52, treatment with 200 mg or 300 mg of dupilumab every 2 weeks vs placebo had improved RQLQ(S) +12 subscores in 6 of 7 domains (activities, sleep, practical problems, nasal symptoms, eye symptoms, and emotions; $P < .05$ for all) (Fig 5A-G).



No. of patients					
Placebo 1.14 mL q2w	132	131	127	123	103
Dupilumab 200 mg q2w	261	258	247	237	207
Placebo 2 mL q2w	145	142	136	132	110
Dupilumab 300 mg q2w	276	271	266	256	213



No. of patients										
Placebo 1.14 mL q2w	130	127	128	127	117	119	123	115	103	87
Dupilumab 200 mg q2w	260	239	245	238	238	232	235	224	201	186
Placebo 2 mL q2w	143	135	137	132	132	131	129	127	108	98
Dupilumab 300 mg q2w	275	259	258	252	252	250	253	239	211	187



No. of patients					
Placebo 1.14 mL q2w	129	131	126	123	103
Dupilumab 200 mg q2w	261	258	240	244	208
Placebo 2 mL q2w	145	144	131	133	108
Dupilumab 300 mg q2w	273	273	261	254	210

Figure 6. Effects of dupilumab on (A) total serum IgE, (B) FeNO, and (C) TARC in the ITT (exposed) population with comorbid PAR. CI, confidence interval; FeNO, fractional exhaled nitric oxide levels; IgE, immunoglobulin E; ITT, intent to treat; PAR, perennial allergic rhinitis; q2W, every two weeks; TARC, thymus- and activation-regulated chemokine. $^{***}P < .001$ vs matched placebo.

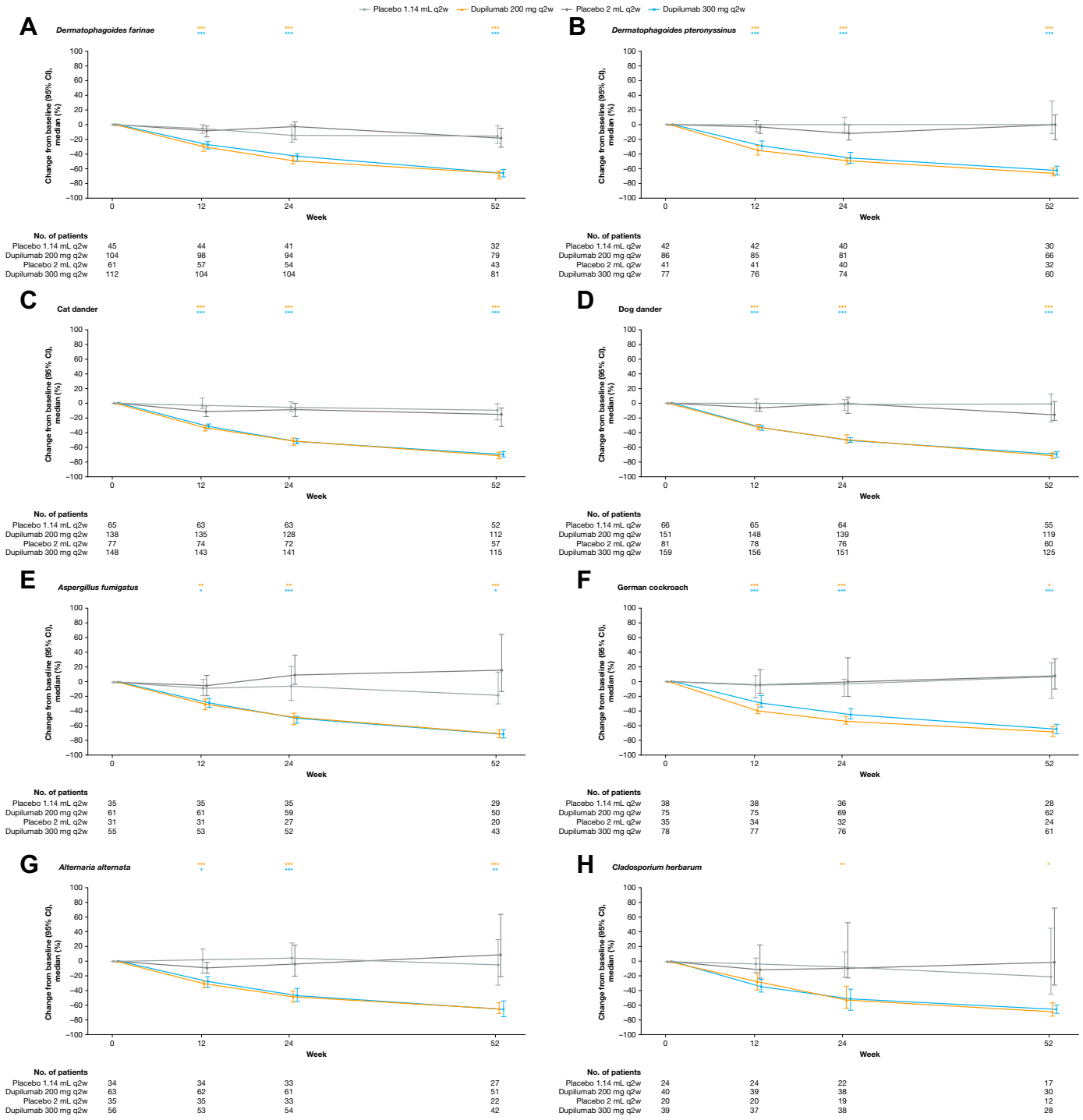


Figure 7. Effect of dupilumab, during the 52-week treatment period on allergen-specific IgE in patients who received positive test results (≥0.35 kU/L) at baseline for (A) *Dermatophagoides farinae*, (B) *Dermatophagoides pteronyssinus*, (C) Cat dander, (D) Dog dander, (E) *Aspergillus fumigatus*, (F) German cockroach, (G) *Alternaria alternata*, and (H) *Cladosporium herbarum*. CI, confidence interval; IgE, immunoglobulin E; q2w, every two weeks. $^{*}P < .05$ vs matched placebo. $^{**}P < .01$ vs matched placebo. $^{***}P < .001$ vs matched placebo.

Total Serum Immunoglobulin E and Allergen-Specific Immunoglobulin E

At baseline, the median total serum IgE concentration ranged from 272 to 321 IU/mL across the 4 treatment groups. Total serum IgE concentrations decreased progressively through the 52-week period in both dupilumab groups as follows: at week 52 median reductions were −198.00 IU/mL (95% CI, −255.00 to −159.00) with 200 mg of dupilumab every 2 weeks (vs −7.0 IU/mL [95% CI, −22.0 to 3.0] with matched placebo; $P < .001$) and −224.00 (95% CI, −270.00 to −172.00) with 300 mg of dupilumab every 2 weeks (vs −12.50 [95% CI, −41.00 to 0] with matched placebo; $P < .001$) (Fig 6A).

Percent change in allergen-specific IgE for 8 of the 9 perennial allergens analyzed (*A fumigatus*, *D farinae*, *D pteronyssinus*, cat dander, dog dander, German cockroach, *A alternata*, and *C*

herbarum) was evaluated (with the exception of Oriental cockroach allergens, for which too few patients received positive test results at baseline to allow a meaningful analysis). Among patients who received positive test results (≥0.35 kU/L) for each allergen-specific IgE at baseline, dupilumab reduced allergen-specific IgE levels for all 8 allergens. Reductions were significant compared with placebo from week 12 to week 52 ($P < .05$) for all allergens except for *C herbarum*, which was significantly reduced only for patients receiving 200 mg of dupilumab every 2 weeks at weeks 24 and 52 (Fig 7A-H). At week 52, median percent change from baseline in the respective allergen-specific IgEs ranged from −62% to −73% in patients treated with dupilumab compared with −22% to 15% in the placebo groups.

For each specific IgE, there was a consistent increase in the proportion of patients with comorbid PAR whose specific IgE concentration decreased to less than 0.35 kU/L between weeks 12 and 52 (eTable 1).

Fractional Exhaled Nitric Oxide and Serum Thymus- and Activation-Regulated Chemokine

Significant reductions in type 2 inflammatory biomarkers in the airways (FeNO) and blood (TARC) were observed in both dupilumab treatment groups compared with placebo ($P < .001$ for all time points) (Fig 6B and C). These reductions were observed at the earliest assessed time points and were sustained throughout the 52-week treatment period.

Discussion

In 814 patients with uncontrolled, moderate-to-severe asthma and comorbid PAR, dupilumab significantly reduced the annualized rate of severe exacerbations, provided a rapid and sustained improvement in FEV_1, and improved asthma control as measured by the ACQ-5. The magnitude of its effect on rates of severe asthma exacerbation was somewhat lower than that observed in the overall study population of 1902 patients in whom the exacerbation rate was reduced by approximately 48% with 200 mg of dupilumab every 2 weeks and 46% with 300 mg of dupilumab every 2 weeks.[26] However, the effect of dupilumab treatment on FEV_1 and asthma control (ACQ-5 scores) in patients with PAR was similar to that observed in the overall study population, and these improvements in asthma-related end points were accompanied by significant improvements in rhinoconjunctivitis-related QoL at week 52, as measured by total RQLQ(S) +12 scores. Among patients receiving dupilumab, improvements from baseline observed in asthma control scores and rhinoconjunctivitis-related QoL were greater than the minimum clinically important difference, and LS mean differences in change from baseline vs placebo were statistically significant.

Asthma and PAR have similar immunopathologic and functional features, including chronic type 2 inflammation of the airway and various degrees of bronchial hyperreactivity and mucosal hypersecretion.[5,12,36] The coexistence of upper and lower airway morbidity in patients with uncontrolled asthma and PAR adds to the overall burden of disease and the complexity of management using multiple treatment modalities.[5,6,8] The beneficial effect of dupilumab on both asthma- and PAR-related outcomes represents an opportunity to manage both diseases with a single treatment in this difficult-to-treat population.

In this phase 3 study of patients with uncontrolled, moderate-to-severe asthma, the proportion of patients who met the criteria for PAR (814 of 1902 patients [42.8%]) was smaller than the overall proportion of patients who reported a history of comorbid AR (1207 of 1902 [63.5%]). The remaining 393 patients (21% of the LIBERTY ASTHMA QUEST ITT population) had non-AR or PAR atributable to sensitization to 1 or more perennial allergens that were not included in our test panel. Compared with the overall LIBERTY ASTHMA QUEST study population,[26] the subset of patients with PAR were younger and had a higher prebronchodilator FEV_1 (data not shown). However, their baseline levels of asthma control (ACQ-5 scores), type 2 inflammatory biomarkers, and use of high-dose corticosteroids were similar to those in the overall study population.

Consistent with the mechanism of action of dupilumab,[22] the efficacy of dupilumab in patients with PAR was accompanied by a significant reduction in type 2 inflammatory markers, including total serum IgE, FeNO, and TARC. In patients who received positive test results for allergen-specific IgEs at baseline, dupilumab (compared with placebo) significantly reduced concentrations of specific IgE, a finding that supports an inhibitory effect of dupilumab on IgE-mediated allergic inflammation (or inflammatory processes). The progressive suppression of IgE over time may also contribute to the gradual improvement in RQLQ(S) +12 scores throughout the study, leading to significant improvements by week 52.

The results of this post hoc analysis complement those assessing the effect of dupilumab vs placebo in patients with asthma and comorbid PAR in a phase 2b study, in which 300 mg of dupilumab every 2 weeks statistically improved 22-item Sino-Nasal Outcome Test (SNOT-22) total scores and AR-associated symptoms compared with placebo.[33] Similarly, dupilumab also significantly improved SNOT-22 and the University of Pennsylvania Smell Identification Test sense of smell assessments in patients with chronic sinusitis and nasal polyposis.[37] Although significant improvements were observed with both dupilumab doses in the current analysis, the previous study in patients with PAR only reported significant improvements in SNOT-22 in patients receiving the higher dose of dupilumab, with numerical improvements in the 200 mg of dupilumab every 2 weeks group.[33] One advantage of this analysis is that it included a larger patient population than either of these previous studies, but direct comparisons of these studies cannot be made because of different outcome measures used (SNOT-22 vs RQLQ [S] +12), which vary in number of items measured (22 vs 28). Standardized Rhinoconjunctivitis Quality of Life Questionnaire +12 has been validated in patients with AR, whereas as SNOT-22 is validated in patients with chronic rhinosinusitis.

Some limitations of this analysis should be noted. This was a post hoc analysis performed using subgroups that were not predefined. The diagnosis of PAR was based on sensitization to a selected panel of perennial aeroallergens, and it is possible that some patients had been sensitized to perennial aeroallergens that were not included in the panel and were therefore excluded from the PAR subgroup. Comparisons were not made between the PAR subgroup and the complementary group who did not meet the PAR criteria, which was a heterogeneous population that potentially included patients with SAR, patients with AR because of allergens that were not included in the panel, and patients with non-AR. These confounding factors would probably have influenced efficacy outcomes and thus reduced the accuracy and usefulness of a comparison of those groups. Separately, the effect of allowed concomitant medications, such as antihistamines and intranasal corticosteroids, on efficacy outcomes was not assessed.

In conclusion, dupilumab improved key asthma-related outcomes, suppressed type 2 inflammatory biomarkers, and improved rhinoconjunctivitis-related QoL in patients with uncontrolled, moderate-to-severe asthma and comorbid PAR. Dupilumab was generally well tolerated in the overall study population.[26] These findings add to what is known about the clinical effects of dual inhibition of the IL-4 and IL-13 signaling pathways and suppression of type 2 inflammatory biomarkers by dupilumab in the treatment of asthma[26-29] and other related conditions, such as atopic dermatitis,[30-32,38] chronic rhinosinusitis with nasal polyposis,[37] and eosinophilic esophagitis.[39] Asthma and PAR, 2 common comorbid conditions, are linked by a systemic immunologic response

to airborne allergens. Dupilumab, with its inhibitory effects on the type 2 inflammatory processes underlying both conditions, may help to optimize management by providing simultaneous control of asthma and PAR.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2020.05.026.

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Supplementary Data

eTable 1
Patients With Comorbid Perennial Allegic Rhinitis and Specific IgE Levels of 0.35 IU/mL or Greater at Baseline Whose Specific IgE Levels Decreased to Less Than 0.35 IU/mL (Exposed Population)[a]

Aeroallergen	1.14 mL, 200 mg every 2 weeks		2.0 mL, 300 mg every 2 weeks	
	Placebo	Dupilumab	Placebo	Dupilumab
Cat dander	n = 65	n = 138	n = 77	n = 148
Week 12	2/63 (3.2)	14/135 (10.4)	0/74 (0.0)	15/143 (10.5)
Week 24	4/63 (6.3)	20/128 (15.6)	4/72 (5.6)	28/141 (19.9)
Week 52	6/52 (11.5)	31/112 (27.7)	2/57 (3.5)	30/115 (26.1)
Dermatophagoides farinae	n = 45	n = 104	n = 61	n = 112
Week 12	0/44 (0.0)	14/98 (14.3)	1/57 (1.8)	5/104 (4.8)
Week 24	0/41 (0.0)	18/94 (19.1)	1/54 (1.9)	8/104 (7.7)
Week 52	2/32 (6.3)	22/79 (27.8)	3/43 (7.0)	14/81 (17.3)
Aspergillus fumigatus	n = 35	n = 61	n = 31	n = 55
Week 12	3/35 (8.6)	9/61 (14.8)	2/31 (6.5)	9/53 (17.0)
Week 24	2/35 (5.7)	15/59 (25.4)	0/27 (0.0)	22/52 (42.3)
Week 52	0/29 (0.0)	21/50 (42.0)	1/20 (5.0)	24/43 (55.8)
Dermatophagoides pteronyssinus	n = 42	n = 86	n = 41	n = 77
Week 12	0/42 (0.0)	9/85 (10.6)	1/41 (2.4)	4/76 (5.3)
Week 24	0/40 (0.0)	13/81 (16.0)	0/40 (0.0)	7/74 (9.5)
Week 52	0/30 (0.0)	10/66 (15.2)	0/32 (0.0)	7/60 (11.7)
Dog dander	n = 66	n = 151	n = 81	n = 159
Week 12	2/65 (3.1)	25/148 (16.9)	2/78 (2.6)	16/156 (10.3)
Week 24	4/64 (6.3)	28/139 (20.1)	4/76 (5.3)	36/151 (23.8)
Week 52	6/55 (10.9)	43/119 (36.1)	4/60 (6.7)	44/125 (35.2)
German cockroach	n = 38	n = 75	n = 35	n = 78
Week 12	7/38 (18.4)	18/75 (24.0)	3/34 (8.8)	15/77 (19.5)
Week 24	8/36 (22.2)	23/69 (33.3)	3/32 (9.4)	20/76 (26.3)
Week 52	3/28 (10.7)	30/62 (48.4)	1/24 (4.2)	25/61 (41.0)
Cladosporium herbarum	n = 24	n = 40	n = 20	n = 39
Week 12	2/24 (8.3)	9/39 (23.1)	2/20 (10.0)	8/37 (21.6)
Week 24	1/22 (4.5)	12/38 (31.6)	2/19 (10.5)	13/38 (34.2)
Week 52	4/17 (23.5)	13/30 (43.3)	4/12 (33.3)	11/28 (39.3)
Alternaria alternata	n = 34	n = 63	n = 35	n = 56
Week 12	0/34 (0.0)	5/62 (8.1)	3/35 (8.6)	3/53 (5.7)
Week 24	0/33 (0.0)	8/61 (13.1)	2/33 (6.1)	7/54 (13.0)
Week 52	1/27 (3.7)	9/51 (17.6)	0/22 (0.0)	14/42 (33.3)

[a]Data are presented as number of patients/number of patients with specific IgE data at that corresponding week (percentage of patients).