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Original Article

Dupilumab Efficacy in Uncontrolled, Moderate-to-Severe Asthma with Self-Reported Chronic Rhinosinusitis

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What is already known about this topic? Patients with asthma frequently have chronic rhinosinusitis (CRS) comorbidity, and these patients are often difficult to treat, with poor quality of life and few treatment options.

What does this article add to our knowledge? Dupilumab provides efficacy and quality-of-life benefits to patients with asthma and comorbid CRS.

How does this study impact current management guidelines? Patients with asthma and comorbid CRS may gain additional benefits from dupilumab treatment as it targets type 2 inflammation associated with these comorbid conditions.

BACKGROUND: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13 signaling, key drivers of type 2 inflammation. In the phase 3 study (NCT02414854), add-on dupilumab 200 mg/300 mg every 2 weeks, versus placebo, significantly reduced severe asthma exacerbations and improved pre-bronchodilator forced expiratory volume in 1 second (FEV_1) and quality-of-life measures in patients with uncontrolled, moderate-to-severe asthma, with greater efficacy observed in those with a high baseline type 2 phenotype.

OBJECTIVE: To assess the efficacy and safety of dupilumab in patients with uncontrolled, moderate-to-severe asthma with or without self-reported comorbid chronic rhinosinusitis (CRS or non-CRS).

METHODS: Comorbid CRS was self-reported by patients using an e-diary. Annualized severe exacerbation rates, changes from baseline in pre- and post-bronchodilator FEV_1, patient-reported outcomes, type 2 biomarkers, and safety were assessed.

RESULTS: CRS was self-reported by 382 of 1902 (20.1%) patients. Dupilumab 200 mg/300 mg reduced annualized severe

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Abbreviations used
ACQ-5- 5-Item Asthma Control Questionnaire
AQLQ(S)- Asthma Quality of Life Questionnaire (standardized version)
CI- Confidence interval
CRS- Chronic rhinosinusitis
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
HLT- High Level Term
HRQoL- Health-related quality of life
ICS- Inhaled corticosteroid
ITT- Intention-to-treat
LS- Least squares
MedDRA- Medical Dictionary for Regulatory Activities
NP- Nasal polyps
PRO- Patient-reported outcome
q2w- Every 2 weeks
SD- Standard deviation
SE- Standard error
SNOT-22- 22-Item Sino-Nasal Outcome Test
TARC- Thymus and activation-regulated cytokine
TEAE- Treatment-emergent adverse event

exacerbation rates by 63%/61%, respectively, in patients with CRS, and by 42%/40% in patients without CRS (all $P < .001$ vs placebo). Dupilumab also improved lung function and patient-reported asthma control and quality of life, and suppressed type 2 biomarkers versus placebo in both subgroups. Clinical responses were rapid, with near-maximal responses observed at the earliest measured time points and sustained at week 52. Improvements observed in the CRS subgroup were similar to or numerically greater than those in the non-CRS subgroup.

CONCLUSION: Dupilumab showed efficacy and was generally well tolerated in patients with uncontrolled, moderate-to-severe asthma with or without CRS. **(J Allergy Clin Immunol Pract 2020;8:527-39)**

Key words: *Chronic rhinosinusitis; Dupilumab; Efficacy; Safety; Asthma; Anti-IL-4; Anti-IL-13*

Chronic rhinosinusitis (CRS) and asthma frequently coexist[1]; CRS is associated with exacerbation-prone asthma, asthma persistence, and reduced health-related quality of life (HRQoL).[2-4] Specifically, comorbid CRS was associated with higher frequency of asthma exacerbations in an analysis of data from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program-3.[2] Comorbid CRS has been linked to lower HRQoL, as measured by the Mini Asthma Quality of Life Questionnaire (mini-AQLQ) and the Euro Quality of Life health questionnaire, compared with patients with asthma but no CRS.[4]

Type 2 cytokines, specifically IL-4, IL-5, and IL-13, are known to play important roles in the pathogenesis of CRS with nasal polyps (NP) and atopic asthma,[5-7] which represent type 2-mediated mucosal inflammation of the upper and lower airways, respectively.[8] CRS without NP has also been associated with type 2 inflammation in a subset of patients.[9]

Dupilumab is a fully human, VelocImmune-derived[10,11] monoclonal antibody that blocks the shared receptor component of IL-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, key drivers of type 2 inflammatory diseases such as atopic dermatitis, asthma, allergic rhinitis, and food allergies.[12] Dupilumab is approved by the US Food and Drug Administration[13] 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. Dupilumab is approved in Japan for patients aged ≥12 years with severe or refractory bronchial asthma whose symptoms are inadequately controlled with existing therapies,[14] and by the European Medicines Agency[15] as an add-on maintenance treatment in patients aged ≥12 years with type 2 severe asthma characterized by increased blood eosinophils and/or raised fractional exhaled nitric oxide (FeNO) who are inadequately controlled with high-dose inhaled corticosteroid (ICS) plus another medicinal product for maintenance treatment.[16-18] Dupilumab is approved in the USA as an add-on treatment in patients with inadequately controlled CRS with NP,[13] and adults in the European Union[15] and other countries.[19-21]

In the phase 3 LIBERTY ASTHMA QUEST study, dupilumab reduced severe asthma exacerbations and showed a rapid and sustained improvement in lung function in patients with uncontrolled, moderate-to-severe asthma, with greater treatment effects observed in patients with elevated baseline levels of blood eosinophils or FeNO.[17] In a phase 2a trial in patients with severe CRS with NP refractory to intranasal corticosteroids, dupilumab significantly reduced polyp size and sinus opacification/inflammation, improved nasal congestion, nasal peak inspiratory flow, sense of smell, and HRQoL, and improved asthma control and lung function in a subset of patients with comorbid asthma.[22] These findings were

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confirmed in 2 phase 3, placebo-controlled studies of dupilumab in patients with severe CRS and NP refractory to systemic corticosteroids and/or surgery (NCT02912468, NCT02898454). After 24 weeks, dupilumab significantly improved NP size, nasal opacification, nasal congestion, sense of smell, and HRQoL. In the subgroups with comorbid asthma (n = 276 [58%] and n = 448 [60%], 2 phase 3 studies), dupilumab significantly improved lung function and asthma control.[23,24]

This *post hoc* analysis of the phase 3 LIBERTY ASTHMA QUEST study[17] assessed the effect of dupilumab on severe exacerbations, lung function, patient-reported outcomes (PROs), and type 2 biomarkers in patients with moderate-to-severe asthma with and without comorbid CRS.

METHODS

Study design

LIBERTY ASTHMA QUEST (NCT02414854) is a previously reported, phase 3, randomized, double-blinded, placebo-controlled study assessing the effect of dupilumab in patients with uncontrolled, moderate-to-severe asthma.[17]

The study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data, and an institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients provided written informed consent before participating in the trial.

Study population

Complete inclusion and exclusion criteria are provided in this article's Online Repository at www.jaci-inpractice.org.[17]

This *post hoc* analysis reports data for the subgroup of patients with CRS, defined as patients with self-reported comorbid CRS with or without NP as recorded in an e-diary at baseline. Patients not meeting these criteria were defined as non-CRS. Data were also analyzed in subgroups of patients with baseline blood eosinophils ≥150 cells/μL or ≥300 cells/μL, and baseline FeNO ≥25 ppb.

Study endpoints

Efficacy endpoints were the annualized severe asthma exacerbation rate and change from baseline in pre- and post-bronchodilator forced expiratory volume in 1 second (FEV_1). In addition, PROs were assessed during the 52-week treatment period using the scores from 3 patient-reported questionnaires: the 5-item Asthma Control Questionnaire (ACQ-5), Asthma Quality of Life Questionnaire (standardized version) (AQLQ[S]), and 22-item Sino-Nasal Outcome Test (SNOT-22). The ACQ-5 is a measure of the level of asthma control (global score 0-6, with higher scores indicating less control), and the AQLQ(S) assesses the impact of asthma on HRQoL (global score 0-7, with higher scores indicating better HRQoL). The SNOT-22, administered only to patients self-reporting CRS, measures the impact of sino-nasal disorders on HRQoL (total score 0-110, with higher scores indicating greater HRQoL impairment). Within-patient improvement in ACQ-5, AQLQ(S), and SNOT-22 scores of at least 0.5, 0.5, and 8.9, respectively, were considered clinically meaningful as defined by the questionnaire developers.[25-28] Concentrations of the following biomarkers of type 2 inflammation were also measured over the 52-week treatment period in all patients: FeNO, serum total IgE, serum thymus and activation-regulated chemokines (TARCs), and peripheral blood eosinophils. Specific IgE for the following aeroantigens was assessed at baseline: *Aspergillus fumigatus*, cat dander, mite *Dermatophagoides farinae*, mite *Dermatophagoides pteronyssinus*, dog dander, German cockroach, Oriental cockroach, *Alternaria tenuis/alternata*, and *Cladosporium herbarum/Hormodendrum*.

Treatment-emergent adverse events (TEAEs) were reported for the CRS and non-CRS subgroups, and safety data were analyzed according to the treatment received.

Statistical analysis

Efficacy analyses were performed in the intention-to-treat (ITT) population, defined as all patients who underwent randomization, with data analyzed according to the assigned intervention.[19] Within each subgroup, annualized rates of severe exacerbations were derived from negative binomial regression models, which included the total number of events that occurred in the double-blind treatment period (regardless of whether the patient was on treatment) as the response variable. Covariates in the models included treatment group, age, baseline blood eosinophil level, baseline ICS dose level, geographic region, and number of severe exacerbations in the preceding year. Changes from baseline in pre- and post-bronchodilator FEV_1, ACQ-5, AQLQ(S), and SNOT-22 scores were analyzed in each subgroup using mixed-effects models with repeated measures, with age, geographic region, baseline eosinophil level, baseline ICS dose level, visit, treatment-by-visit interaction, baseline level of the corresponding variable, and baseline-by-visit interaction as covariates. Baseline height and sex were also included as covariates in analyses of change from baseline in FEV_1. Changes from baseline in type 2 inflammatory biomarkers in the exposed population, defined as all patients exposed to study medication, were summarized by descriptive statistics and compared based on a rank analysis of the covariance model adjusted for the baseline biomarker level, age, sex, geographic region, baseline eosinophil level, and baseline ICS dose level. A nominal P value of $<.05$ for the comparison between each dupilumab dose and matched-volume placebo (within each subgroup) was considered statistically significant.

RESULTS

Baseline characteristics

Of 1902 patients with uncontrolled, moderate-to-severe asthma in the ITT population, 382 (20.1%) self-reported comorbid CRS.

The baseline patient demographic and clinical characteristics of the CRS and non-CRS subgroups are shown in Table I. The subgroup with CRS was significantly older than the non-CRS subgroup at study baseline (mean [standard deviation, SD], 51.5 [12.1] vs 47.0 [15.9] years, respectively) and at asthma onset (mean [SD], 31.7 [18.0] vs 25.8 [19.2] years, respectively) (both comparisons $P < .0001$). Patients in this subgroup had also experienced more asthma exacerbations in the past year (mean [SD], 2.32 [2.29] vs 2.04 [2.12] non-CRS, $P = .03$) and had significantly higher levels of the type 2 biomarkers, FeNO, and peripheral blood eosinophils (both $P < .0001$), than those in the non-CRS subgroup. Baseline total IgE levels were similar between subgroups, with a smaller proportion of patients positive for ≥1 specific IgE in the CRS subgroup than in the non-CRS subgroup ($P < .0001$). In general, other baseline demographic and clinical characteristics were similar between the 2 subgroups.

TABLE I. Baseline demographic and disease characteristics

	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)				
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		
	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 254)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 510)	*P* value, with CRS vs without CRS
Age, mean (SD), y	52.3 (12.0)	51.0 (10.6)	49.6 (11.8)	52.7 (13.5)	47.2 (16.3)	47.1 (16.2)	47.8 (15.4)	46.5 (15.8)	<.0001
Female sex, n (%)	38 (60.3)	71 (56.3)	48 (68.6)	75 (61.0)	160 (63.0)	316 (62.6)	170 (67.7)	319 (62.5)	.32
BMI, mean (SD), kg/m^2	29.61 (5.86)	28.31 (5.47)	29.40 (6.18)	28.23 (5.67)	29.79 (7.57)	29.23 (6.75)	29.16 (7.16)	29.27 (6.89)	.07
Age at onset of asthma, mean (SD), y	33.4 (19.1)	32.3 (16.3)	29.7 (19.0)	31.3 (18.6)	25.7 (18.9)	25.8 (19.6)	26.8 (18.5)	25.4 (19.5)	<.0001
Pre-bronchodilator FEV_1, mean (SD), L	1.81 (0.62)	1.88 (0.57)	1.70 (0.59)	1.68 (0.53)	1.75 (0.61)	1.76 (0.63)	1.76 (0.56)	1.81 (0.62)	.82
Pre-bronchodilator FEV_1, mean (SD), % predicted	59.06 (12.92)	60.05 (12.92)	57.17 (13.66)	57.17 (14.05)	58.27 (13.31)	57.96 (13.64)	58.68 (13.94)	58.83 (13.38)	.99
FEV_1 reversibility, mean (SD), %	24.81 (15.06)	24.46 (18.74)	24.37 (15.71)	22.83 (16.64)	25.12 (19.60)	28.12 (23.66)	27.03 (18.14)	26.43 (25.17)	.006
Exacerbations in the past year, mean (SD), n	2.16 (1.58)	2.14 (1.91)	2.56 (2.38)	2.46 (2.84)	2.05 (1.58)	2.05 (2.82)	2.24 (1.97)	1.92 (1.51)	.03
With ongoing atopic medical condition,* n (%)	49 (77.8)	105 (83.3)	65 (92.9)	99 (80.5)	217 (85.4)	404 (80.0)	201 (80.1)	425 (83.3)	.58
AQLQ(S) score, mean (SD)†	4.26 (1.02)	4.39 (0.98)	4.30 (1.05)	4.31 (1.06)	4.26 (1.02)	4.29 (1.10)	4.31 (1.02)	4.27 (1.05)	.48
ACQ-5 score, mean (SD)	2.86 (0.70)	2.76 (0.80)	2.76 (0.73)	2.85 (0.76)	2.68 (0.73)	2.76 (0.80)	2.77 (0.78)	2.75 (0.76)	.16
SNOT-22 score, mean (SD)‡	44.77 (19.75)	41.30 (17.98)	43.81 (19.28)	42.76 (18.02)	—	—	—	—	—
FeNO, median (IQR), ppb§	31.00 (19.00-60.00)	32.00 (23.00-57.00)	35.00 (23.00-56.00)	26.00 (17.00-53.00)	24.00 (14.00-43.00)	21.00 (14.00-39.00)	24.00 (15.00-42.00)	24.00 (14.00-41.00)	<.0001
Serum total IgE, median (IQR), IU/mL‖	177.00 (75.00-337.00)	156.00 (75.00-438.00)	205.00 (76.00-564.00)	150.00 (67.00-392.00)	170.00 (60.00-465.00)	154.00 (55.00-459.00)	176.00 (53.00-414.00)	179.50 (61.50-467.00)	.83
With ≥1 positive specific IgE,¶ n (%)	30 (47.6)	68 (54.4)	34 (49.3)	60 (49.2)	161 (64.4)	306 (61.4)	159 (63.9)	320 (63.6)	<.0001
TARC, median (IQR), pg/mL#	335.00 (185.00-488.00)	293.00 (228.00-461.00)	349.00 (264.00-508.00)	308.50 (213.00-457.00)	295.50 (206.00-457.00)	317.00 (199.00-464.00)	288.00 (187.00-473.00)	292.00 (183.00-431.50)	.07
Blood eosinophil count, median (IQR), cells/μL**	410.00 (200.00-690.00)	365.00 (240.00-600.00)	470.00 (250.00-830.00)	360.00 (180.00-680.00)	240.00 (130.00-430.00)	200.00 (110.00-405.00)	240.00 (130.00-410.00)	220.00 (120.00-410.00)	<.0001

ACQ-5, 5-Item Asthma Control Questionnaire; *AQLQ(S)*, Asthma Quality of Life Questionnaire (standardized version); *BMI*, body mass index; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *IQR*, interquartile range; *q2w*, every 2 weeks; *SD*, standard deviation; *SNOT-22*, Sino-Nasal Outcome Test; *TARC*, thymus and activation-regulated chemokine.

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.

*Ongoing atopic medical condition defined as any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥100 IU/mL and at least 1 aeroantigen-specific IgE is positive (≥0.35 IU/mL) at baseline.

†n = 95 missing at baseline.

‡n = 45 missing at baseline.

§n = 24 missing at baseline.

‖n = 20 missing at baseline.

¶Specific IgE-positive defined as at least 1 aeroantigen ≥0.35 IU/mL at baseline: *Aspergillus fumigatus*, cat dander, mite *Dermatophagoides farinae*, mite *Dermatophagoides pteronyssinus*, dog dander, German cockroach, Oriental cockroach, *Alternaria tenuis/alternata*, *Cladosporium herbarum/Hormodendrum*. n = 23 missing at baseline.

#n = 28 missing at baseline.

**n = 2 missing at baseline.

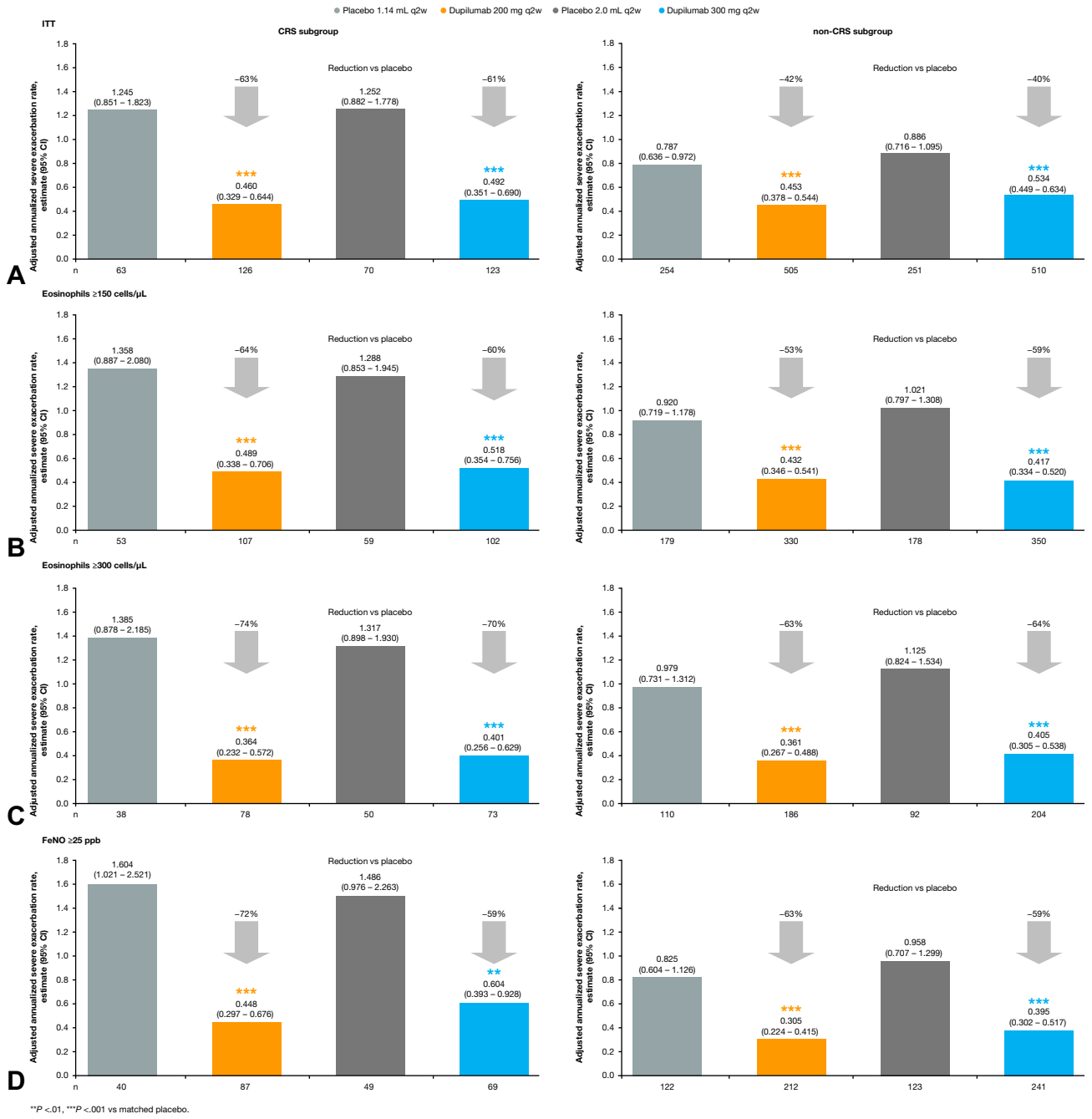

FIGURE 1. Effect of dupilumab on annualized severe exacerbation rates. **A**, In the overall ITT CRS and non-CRS subgroups. **B**, In those with baseline blood eosinophils ≥150 cells/μL. **C**, In those with baseline blood eosinophils ≥300 cells/μL. **D**, In those with baseline FeNO ≥25 ppb. *CI*, Confidence interval; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *ITT*, intention-to-treat; *q2w*, every 2 weeks.

Annualized rate of severe asthma exacerbations

Dupilumab 200 mg or 300 mg administered every 2 weeks (q2w) significantly reduced annualized rates of severe asthma exacerbations compared with a matched-volume placebo (1.14 mL or 2.0 mL, respectively) in patients with and without CRS (Figure 1, *A*), with overall reductions of 63% (200 mg q2w) and 61% (300 mg q2w) in the CRS subgroup (both $P < .001$), and 42% (200 mg q2w) and 40% (300 mg q2w) in the non-CRS subgroup (both $P < .001$). In placebo-treated patients, the CRS subgroup had numerically higher adjusted annualized rates of severe asthma exacerbations than the non-CRS subgroup: for 1.14 and 2.0 mL q2w, the CRS subgroup had rates (95% confidence interval [CI]) of 1.25 (0.85-1.82) and 1.25 (0.88-1.78), compared with the non-CRS subgroup's rates of 0.79 (0.64-0.97) and 0.89 (0.72-1.10).

In general, dupilumab 200 and 300 mg q2w versus a matched-volume placebo showed a numerically greater reduction

FIGURE 2. Effect of dupilumab on pre-bronchodilator FEV_1. **A**, In the overall ITT CRS and non-CRS subgroups. **B**, In those with baseline blood eosinophils ≥150 cells/μL, ≥300 cells/μL, and baseline FeNO ≥25 ppb. *CI*, Confidence interval; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ITT*, intention-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error.

in severe exacerbation rate in the CRS subgroup than in the non-CRS subgroup in patients with baseline blood eosinophils ≥150 cells/μL (Figure 1, *B*) and ≥300 cells/μL (Figure 1, *C*), and in those with baseline FeNO ≥25 ppb (Figure 1, *D*).

Pre-bronchodilator FEV_1

Dupilumab 200 and 300 mg q2w treatment resulted in rapid and sustained improvements in pre-bronchodilator FEV_1 versus a matched-volume placebo in both the CRS and non-CRS subgroups (Figure 2, *A*, and Table E1, available in this article's Online Repository at www.jaci-inpractice.org). In the CRS subgroup, dupilumab 200 and 300 mg q2w significantly improved pre-bronchodilator FEV_1 at week 2 with a least-squares (LS) mean change from baseline difference (95% CI) versus placebo of 0.20 L (0.10-0.31, $P = .0001$) and 0.21 L (0.11-0.31, $P < .0001$), respectively; at week 12, 0.18 L (0.06-0.30, $P = .004$) and 0.15 L (0.04-0.27, $P = .01$), respectively; and at week 52, 0.28 L (0.15-0.41, $P < .0001$) and 0.16 L (0.03-0.28, $P = .02$), respectively. Similar results were seen in the non-CRS subgroup at week 2 (LS mean change from baseline difference vs placebo [95% CI] for dupilumab 200 and 300 mg, respectively, 0.13 L [0.07-0.18], $P < .0001$; 0.13 L [0.08-0.19], $P < .0001$); week 12 (0.13 L [0.07-0.18], $P < .0001$; 0.12 L [0.06-0.18], $P < .0001$); and week 52 (0.17 L [0.11-0.24], $P < .0001$; 0.12 L [0.06-0.19], $P = .0002$).

In both the CRS and non-CRS subgroups, treatment effects with 300 mg dupilumab versus a matched-volume placebo on change from baseline in pre-bronchodilator FEV_1 at week 12 were numerically greater in patients with baseline blood eosinophils ≥300 cells/μL and with baseline FeNO ≥25 ppb (Figure 2, *B*).

Post-bronchodilator FEV_1

Dupilumab resulted in rapid and sustained improvements in post-bronchodilator FEV_1 versus a matched-volume placebo in both the CRS and non-CRS subgroups (Figure 3, *A*, and Table E2, available in this article's Online Repository at www.jaci-inpractice.org). In the CRS subgroup, dupilumab significantly improved post-bronchodilator FEV_1 by week 2 with an LS mean change from baseline difference (95% CI) versus placebo of 0.20 L (0.09-0.30, $P = .0002$) and 0.21 L (0.11-0.31, $P < .0001$) for dupilumab 200 and 300 mg q2w, respectively. These improvements continued through week 12 (0.12 L [0.01-0.23], $P = .03$; 0.18 L [0.07-0.28], $P = .0009$) and week 52 (0.27 L [0.15-0.39], $P < .0001$; 0.14 L [0.03-0.26], $P = .02$). Similarly, in the non-CRS subgroup, dupilumab significantly improved post-bronchodilator FEV_1 by week 2 (LS mean change from baseline difference vs placebo [95% CI] of 0.15 L [0.11-0.20], $P < .0001$; 0.11 L [0.06-0.16], $P < .0001$), and continued to

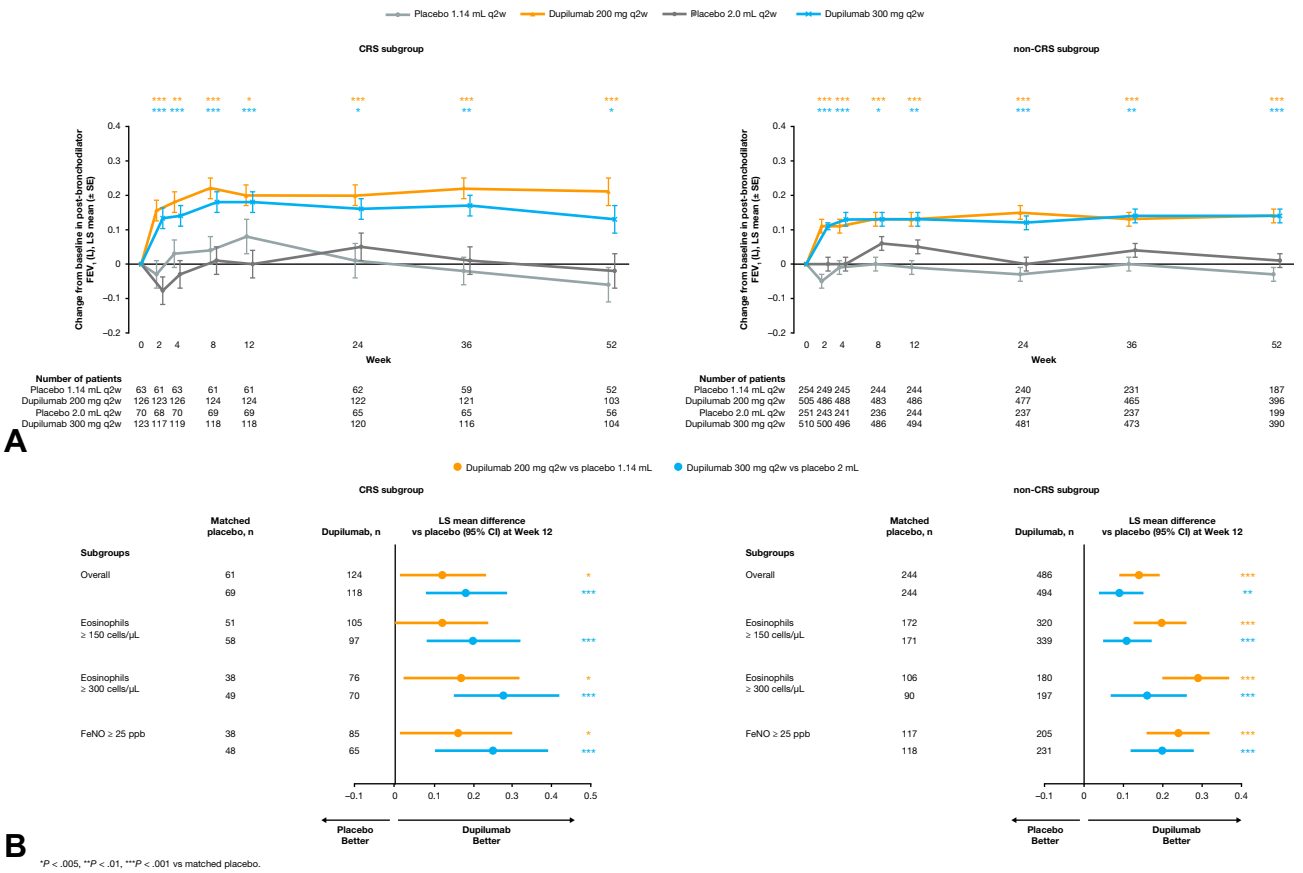

FIGURE 3. Effect of dupilumab on post-bronchodilator FEV_1. **A**, In the overall ITT CRS and non-CRS subgroups. **B**, In those with baseline blood eosinophils ≥150 cells/μL, ≥300 cells/μL, and baseline FeNO ≥25 ppb. *CI*, Confidence interval; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *ITT*, intention-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error.

week 12 (0.14 L [0.09-0.19], $P < .0001$; 0.09 L [0.03-0.14], $P = .001$) and week 52 (0.17 L [0.11-0.23], $P < .0001$; 0.13 L [0.07-0.18], $P < .0001$).

In both the CRS and non-CRS subgroups, treatment effects on post-bronchodilator FEV_1 at week 12 were numerically greater in patients with baseline blood eosinophils ≥300 cells/μL and with baseline FeNO ≥25 ppb (Figure 3, *B*).

ACQ-5 score

Dupilumab 200 and 300 mg q2w versus a matched-volume placebo improved asthma control as assessed by ACQ-5 scores in the CRS and non-CRS subgroups during the treatment period ($P < .05$, most comparisons) (Figure 4, *A*, and Table E3, available in this article's Online Repository at www.jaci-inpractice.org). In the CRS subgroup, the LS mean change from baseline at week 2 was −0.93 (standard error [SE] 0.08, difference vs placebo [95% CI] −0.32 [−0.59 to −0.05]; $P = .02$) and −1.14 (SE 0.08, difference vs placebo [95% CI] −0.63 [−0.89 to −0.37]; $P < .0001$) for dupilumab 200 and 300 mg, respectively. Improvement was sustained through week 52 by −1.75 (SE 0.09, difference vs placebo [95% CI] −0.60 [−0.90 to −0.30]; $P = .0001$) and −1.75 (SE 0.09, difference vs placebo [95% CI] −0.54 [−0.83 to −0.25]; $P = .0003$) for dupilumab 200 and 300 mg, respectively. Similar results were seen in the non-CRS subgroup at week 2 at −0.88 (SE 0.04, difference vs placebo [95% CI] −0.34 [−0.47 to −0.20]; $P < .0001$) and −0.86 (SE 0.04, −0.23 [−0.36 to −0.09]; $P = .001$) and week 52 at −1.48 (SE 0.05, difference vs placebo [95% CI] −0.33 [−0.49 to −0.18]; $P < .0001$) and −1.45 (SE 0.05, difference vs placebo [95% CI] −0.14 [−0.29 to 0.02]; $P = .09$) for dupilumab 200 and 300 mg, respectively.

For both dupilumab regimens, the change in ACQ-5 scores from baseline to week 52 in patients with asthma with CRS exceeded the clinically meaningful difference of 0.5 for this measure.[25,26] The observed effects of dupilumab on ACQ-5 scores at week 52 were numerically greater in the CRS subgroup than in the non-CRS subgroup.

AQLQ(S) score

In general, both dupilumab regimens significantly ($P < .05$, most comparisons) improved HRQoL as assessed by AQLQ(S) scores versus a matched-volume placebo in the CRS and non-CRS subgroups during the treatment period (Figure 4, *B*, and Table E4, available in this article's Online Repository at www.jaci-inpractice.org). In the CRS subgroup, the LS mean change from baseline at week 12 was improved by 1.23 (SE 0.08, difference vs placebo [95% CI] 0.39 [0.10-0.68]; $P = .008$) and 1.16 (SE 0.09, difference vs placebo [95% CI] 0.09 [−0.18 to 0.36]; $P = .52$) for

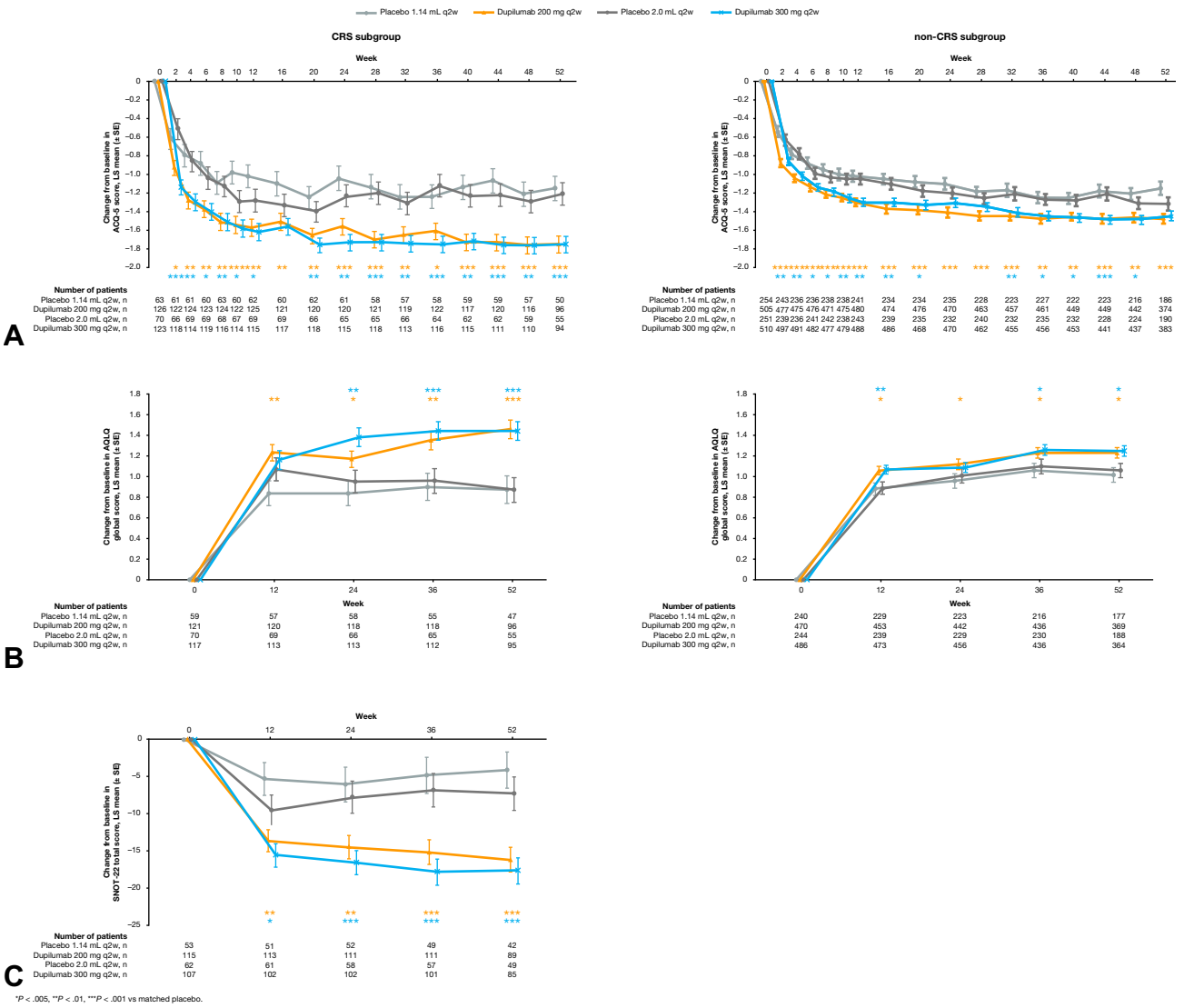

FIGURE 4. Effect of dupilumab on (**A**) asthma control and (**B**) quality of life in patients with asthma with and without CRS, and (**C**) on sinonasal outcomes in patients with CRS. *ACQ-5*, 5-Item Asthma Control Questionnaire; *AQLQ(S)*, Asthma Quality of Life Questionnaire (standardized version); *CRS*, chronic rhinosinusitis; *LS*, least squares; *q2w*, every 2 weeks; *SE*, standard error; *SNOT-22*, Sino-Nasal Outcome Test.

dupilumab 200 and 300 mg, respectively. Improvement was sustained through week 52 by 1.46 (SE 0.09, difference vs placebo [95% CI] 0.58 [0.28-0.88]; $P = .0002$) and 1.44 (SE 0.09, difference vs placebo [95% CI] 0.57 [0.29-0.86]; $P = .0001$) for dupilumab 200 and 300 mg, respectively. In the non-CRS subgroup, the LS mean change from baseline at week 12 was improved by 1.06 (SE 0.04, difference vs placebo [95% CI] 0.18 [0.04-0.32]; $P = .01$) and 1.07 (SE 0.04, difference vs placebo [95% CI] 0.19 [0.05-0.33]; $P = .009$) for dupilumab 200 and 300 mg, respectively. Improvement was sustained through week 52 by 1.23 (SE 0.05, difference vs placebo [95% CI] 0.21 [0.05-0.37]; $P = .01$) and 1.25 (SE 0.05, difference vs placebo [95% CI] 0.19 [0.03-0.35]; $P = .02$) for dupilumab 200 and 300 mg, respectively.

For both dupilumab regimens, the change in AQLQ(S) scores from baseline to week 52 in patients with asthma with CRS exceeded the clinically meaningful difference of 0.5 for this measure.[27] The observed effect of dupilumab on AQLQ(S) score at week 52 was numerically greater in the CRS subgroup than in the non-CRS subgroup.

SNOT-22 score

Patients treated with dupilumab versus placebo had significant improvement in CRS-specific symptoms and HRQoL as assessed by SNOT-22 scores during the treatment period ($P < .05$, all comparisons) (Figure 4, *C*, and Table E5, available in this article's Online Repository at www.jaci-inpractice.org). The LS mean change from baseline at week 12 was improved by −13.81 (SE 1.49, difference vs placebo [95% CI] −8.13 [−13.28 to −2.98]; $P = .002$) and −15.77 (SE 1.57, difference vs placebo [95% CI] −6.02 [−10.93 to −1.10]; $P = .02$) for dupilumab 200 and 300 mg, respectively. Improvement was

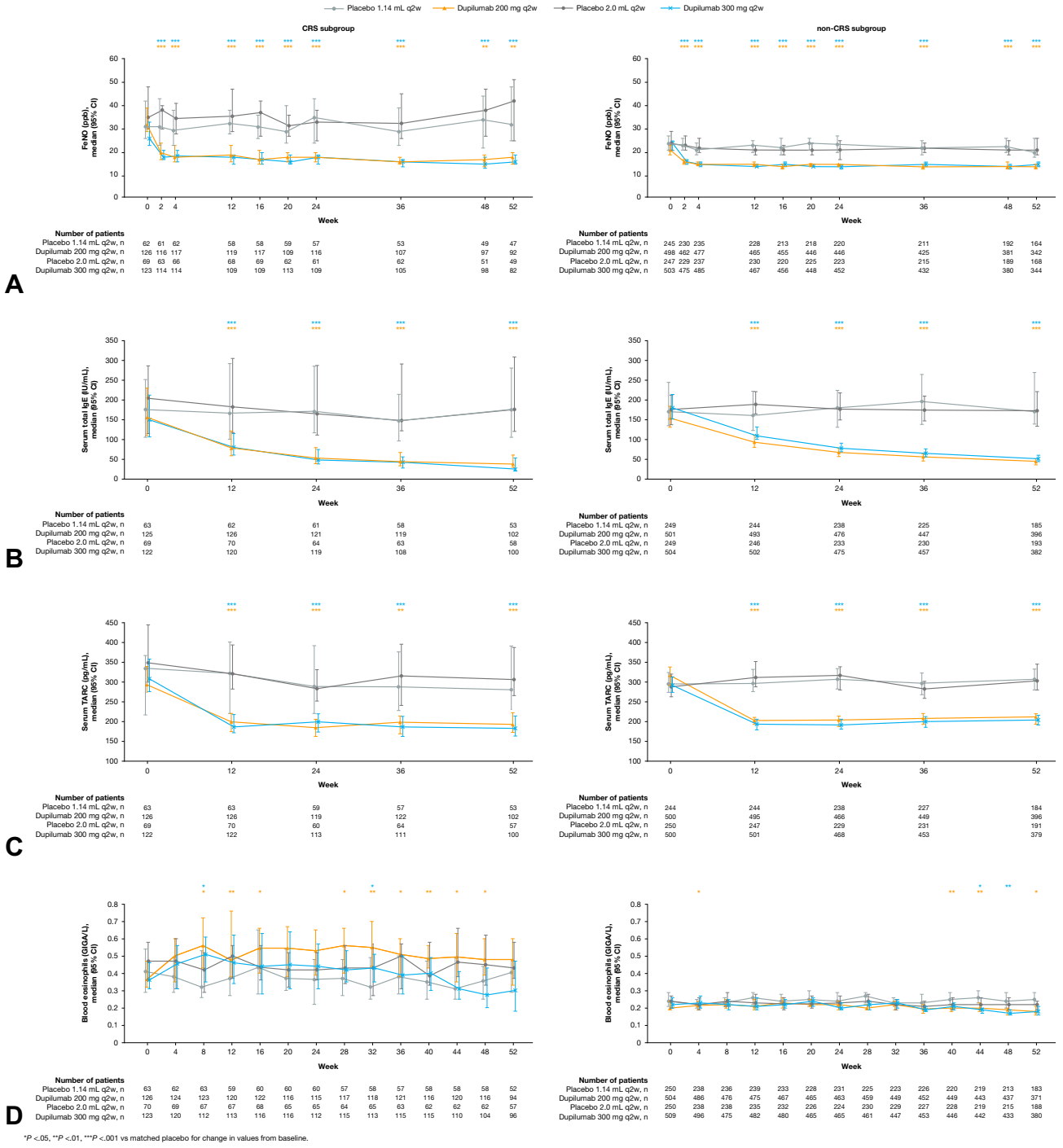

FIGURE 5. Effect of dupilumab on (**A**) FeNO, (**B**) serum total IgE, (**C**) TARC, and (**D**) blood eosinophils during the 52-week treatment period in CRS and non-CRS subgroups. *CI*, Confidence interval; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *q2w*, every 2 weeks; *SE*, standard error; *TARC*, thymus and activation-regulated cytokine.

sustained through week 52 by −16.35 (SE 1.65, difference vs placebo [95% CI] −11.88 [−17.59 to −6.18]; $P < .0001$) and −17.86 (SE 1.72, difference vs placebo [95% CI] −10.32 [−15.77 to −4.87]; $P = .0002$) for dupilumab 200 and 300 mg, respectively.

The magnitude of change in SNOT-22 scores from baseline to week 52 in dupilumab-treated patients exceeded 8.9, the difference regarded as clinically meaningful for this measure.[28]

Type 2 biomarkers

Rapid and sustained suppression of airway (FeNO) and systemic (total IgE, TARC) type 2 inflammatory biomarkers were observed in all dupilumab-treated patients. In both CRS and non-CRS subgroups, the change from baseline in FeNO levels with either dupilumab q2w dose regimen was significantly greater than in placebo-treated patients, in whom no change in FeNO was observed. These changes were evident by week 2 and

TABLE II. Summary of safety: CRS and non-CRS subgroups in the safety population

	Patients with asthma with CRS (n = 382)						Patients with asthma without CRS (n = 1515)					
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
n (%)	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 133)	Dupilumab (n = 249)	Placebo (n = 250)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 509)	Placebo (n = 501)	Dupilumab (n = 1014)
Any TEAE	54 (85.7)	106 (84.1)	65 (92.9)	102 (82.9)	119 (89.5)	208 (83.5)	203 (81.2)	402 (79.6)	205 (81.7)	413 (81.1)	408 (81.4)	815 (80.4)
Any serious TEAE	9 (14.3)	8 (6.3)	8 (11.4)	10 (8.1)	17 (12.8)	18 (7.2)	17 (6.8)	41 (8.1)	19 (7.6)	45 (8.8)	36 (7.2)	86 (8.5)
Any TEAE leading to death*	1 (1.6)	0 (0)	0 (0)	0 (0)	1 (0.8)	0 (0)	2 (0.8)	1 (0.2)	0 (0)	4 (0.8)	2 (0.4)	5 (0.5)
Any TEAE leading to permanent treatment discontinuation	3 (4.8)	2 (1.6)	2 (2.9)	10 (8.1)	5 (3.8)	12 (4.8)	16 (6.4)	17 (3.4)	8 (3.2)	34 (6.7)	24 (4.8)	51 (5.0)
Injection-site reactions (MedDRA HLT)	4 (6.3)	26 (20.6)	10 (14.3)	29 (23.6)	14 (10.5)	55 (22.1)	13 (5.2)	70 (13.9)	23 (9.2)	87 (17.1)	36 (7.2)	157 (15.5)

CRS, Chronic rhinosinusitis; *HLT*, High Level Term; *MedDRA*, Medical Dictionary for Regulatory Activities; *q2w*, every 2 weeks; *TEAE*, treatment-emergent adverse event.
*Causes of death in the dupilumab groups were pulmonary embolism, cardiopulmonary arrest in a patient with paraplegia due to spinal cord injury and multiple vertebral fractures due to osteoporosis, respiratory depression with cardiorespiratory arrest and ischemic encephalopathy, unwitnessed death attributed to myocardial infarction, and cardiac congestive failure with ventricular tachycardia in an obese patient with a history of obstructive sleep apnea. In the placebo groups, deaths were attributed to recurrence of thyroid cancer, postoperative pulmonary embolism after knee arthroplasty, and suicide.

sustained over the 52-week study period ($P < .01$ all comparisons; Figure 5, *A*, and Table E6, available in this article's Online Repository at www.jaci-inpractice.org).

For IgE and TARC (Figure 5, *B* and *C*, and Tables E7 and E8, available in this article's Online Repository at www.jaci-inpractice.org), significant differences in reductions from baseline versus placebo were observed in both subgroups by week 12, with these differences evident throughout the 52-week treatment period ($P < .01$ for all IgE and TARC comparisons). No changes in serum total IgE or TARC were observed in placebo-treated patients.

No changes from baseline in blood eosinophil levels were observed throughout the study in non-CRS patients irrespective of treatment, whereas mild elevations were observed in CRS patients treated with dupilumab (Figure 5, *D*, and Table E9, available in this article's Online Repository at www.jaci-inpractice.org).

Safety

Rates of TEAEs were similar across treatment groups (placebo 83.1%; dupilumab 81.0%) in the overall population, as reported previously.[19] Injection-site reactions (Medical Dictionary for Regulatory Activities [MedDRA] High Level Term [HLT]) were the most frequent TEAEs, occurring at higher rates in dupilumab-treated patients than in placebo-treated patients (dupilumab 16.8%; placebo 7.9%).[19]

In the CRS subgroup, serious TEAEs occurred in 12.8% of patients who received a placebo and in 7.2% of patients treated with dupilumab; in the non-CRS subgroup, the proportion of patients with serious TEAEs was similar in both treatment groups (7.2% placebo vs 8.5% dupilumab). Injection-site reactions (MedDRA HLT) occurred more frequently in dupilumab-treated patients (dupilumab vs placebo, 22.1% vs 10.5% and 15.5% vs 7.2% in the CRS and non-CRS subgroups, respectively) (Table II).

In this analysis, the incidence of TEAEs was higher in the CRS subgroup (placebo 89.5%; dupilumab 83.5%) than in the non-CRS subgroup (placebo 81.4%; dupilumab 80.4%). In both subgroups, irrespective of treatment, viral upper respiratory tract infections were the most frequently reported TEAE (MedDRA Preferred Term) (Table III).

DISCUSSION

This *post hoc* analysis of the LIBERTY ASTHMA QUEST study demonstrated that dupilumab treatment significantly reduced severe asthma exacerbations and improved pre- and post-bronchodilator FEV_1 in patients with moderate-to-severe asthma with and without comorbid CRS, with apparently greater improvements observed in the subgroups of patients with elevated baseline blood eosinophils and FeNO. Dupilumab improved patient-reported asthma control and HRQoL and suppressed type 2 inflammatory biomarkers in both subgroups. It also improved sino-nasal symptoms and HRQoL, as assessed by SNOT-22, in patients with CRS. The results obtained for the 2 subgroups of patients were consistent with the overall study results reported for the ITT population.[17]

Patients with asthma with CRS are difficult to treat and have more severe disease.[2,3] This was reflected by their significantly greater severe exacerbation history, and significantly higher levels of the type 2 inflammatory biomarkers, FeNO, and blood eosinophils, at baseline than those without CRS. These observations are

TABLE III. Treatment-emergent adverse events (MedDRA PT) in ≥5% of patients in the CRS and non-CRS subgroups in the safety population

	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
n (%)	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
TEAEs occurring in ≥5% of patients in any group*						
CRS (n = 382)	(n = 63)	(n = 126)	(n = 70)	(n = 123)	(n = 133)	(n = 249)
Viral upper respiratory tract infection	7 (11.1)	24 (19.0)	16 (22.9)	21 (17.1)	23 (17.3)	45 (18.1)
Injection site erythema	3 (4.8)	22 (17.5)	7 (10.0)	26 (21.1)	10 (7.5)	48 (19.3)
Bronchitis	12 (19.0)	15 (11.9)	10 (14.3)	18 (14.6)	22 (16.5)	33 (13.3)
Upper respiratory tract infection	11 (17.5)	13 (10.3)	16 (22.9)	17 (13.8)	27 (20.3)	30 (12.0)
Sinusitis	8 (12.7)	10 (7.9)	12 (17.1)	8 (6.5)	20 (15.0)	18 (7.2)
Influenza	7 (11.1)	11 (8.7)	6 (8.6)	12 (9.8)	13 (9.8)	23 (9.2)
Headache	7 (11.1)	8 (6.3)	7 (10.0)	9 (7.3)	14 (10.5)	17 (6.8)
Back pain	3 (4.8)	8 (6.3)	2 (2.9)	8 (6.5)	5 (3.8)	16 (6.4)
Non-CRS (n = 1515)	(n = 250)	(n = 505)	(n = 251)	(n = 509)	(n = 501)	(n = 1014)
Viral upper respiratory tract infection	53 (21.2)	95 (18.8)	48 (19.1)	90 (17.7)	101 (20.2)	185 (18.2)
Upper respiratory tract infection	26 (10.4)	56 (11.1)	33 (13.1)	60 (11.8)	59 (11.8)	116 (11.4)
Bronchitis	35 (14.0)	58 (11.5)	32 (12.7)	53 (10.4)	67 (13.4)	111 (10.9)
Injection site erythema	10 (4.0)	54 (10.7)	15 (6.0)	72 (14.1)	25 (5.0)	126 (12.4)
Headache	19 (7.6)	38 (7.5)	18 (7.2)	31 (6.1)	37 (7.4)	69 (6.8)
Accidental overdose†	16 (6.4)	29 (5.7)	14 (5.6)	31 (6.1)	30 (6.0)	60 (5.9)
Influenza	22 (8.8)	25 (5.0)	16 (6.4)	26 (5.1)	38 (7.6)	51 (5.0)
Sinusitis	19 (7.6)	26 (5.1)	17 (6.8)	18 (3.5)	36 (7.2)	44 (4.3)

CRS, Chronic rhinosinusitis; *MedDRA*, Medical Dictionary for Regulatory Activities; *PT*, Preferred Term; *q2w*, every 2 weeks; *TEAE*, treatment-emergent adverse event.
*Adverse events in this category were reported according to the preferred terms in the MedDRA, version 20.0.
†Accidental overdose is coded in MedDRA as an overdose arising from a medication error (eg, drug reconstitution error, incorrect dose, or incorrect dosing interval) and not associated with clinical symptoms.

consistent with previously published observations of increased expression of inflammatory biomarkers found in nasal polyp tissue of patients with CRS.[29]

Consistent with its mechanism of action, dupilumab treatment provided rapid and sustained suppression of both local and systemic type 2 inflammatory biomarkers. At week 52 in both subgroups, the median FeNO levels in dupilumab-treated patients were consistent with previously reported FeNO levels for healthy patients (≤25 ppb).[30] A transient increase in mean peripheral blood eosinophils was observed in the overall ITT population, and it declined to baseline levels during treatment.[17] However, in this analysis, patients with CRS had higher median blood eosinophil levels at baseline and throughout the treatment period than patients without CRS, consistent with a type 2 inflammatory phenotype.

Interestingly, with dupilumab treatment, the magnitude of reductions in severe asthma exacerbations and improvement in FEV_1 from baseline was greater in the CRS subgroup than the non-CRS subgroup. This greater reduction may be due to the simultaneous symptom control of type 2-mediated inflammation of both upper and lower airways by dupilumab, leading to improvements in both CRS (upper airway) and asthma (lower airway) outcome measures. Recent studies have demonstrated that targeting the IL-5 pathway may be efficacious in the treatment of asthma in a subgroup of patients with severe eosinophilic asthma with comorbid CRS.[31-33] The numerical difference in efficacy between the CRS and non-CRS groups could also result from between-group differences in baseline characteristics such as exacerbation rate and type 2 biomarkers. It is also noteworthy that dupilumab resulted in a numerically greater reduction in severe exacerbations in the subgroup with CRS, given that this subgroup had a higher severe exacerbation rate and type 2 burden at baseline compared with the non-CRS subgroup.

The findings reported here support and extend the data obtained from a previously published proof-of-concept, phase 2, randomized, placebo-controlled study of dupilumab in patients with CRS and NP.[22] Adding dupilumab 300 mg q2w to intranasal corticosteroid therapy significantly reduced the burden of NP while improving FEV_1 and asthma control, as well as sense of smell, sinus computed tomography scans, and quality of life in patients with CRS, NP, and comorbid asthma. Phase 3 studies of dupilumab in CRS and NP have recently been completed, confirming and extending these positive results.[23,24]

Consistent with safety in the overall population of the QUEST phase 3 study,[17] dupilumab had an acceptable safety profile in patients with and without CRS and was generally well tolerated. Injection-site reactions occurred more frequently in dupilumab-treated patients than in placebo-treated patients, being more frequent in patients with CRS than in those without CRS.

A major limitation of this analysis is that the diagnosis of CRS was based on patient self-reporting rather than clinician diagnosis. Patients with past but no current symptoms of CRS may not have reported themselves as having CRS and therefore may have been included in the non-CRS group. In addition, we were unable to evaluate any differences in outcomes between CRS with and without NP, as this level of data was not obtained.

Nonetheless, the significant baseline differences between the subgroups with and without a diagnosis of CRS (older age, more asthma exacerbations in the previous year, higher levels of type 2 biomarkers, smaller proportion positive for $\geq$1 specific IgE) suggest that patient self-reporting identified a specific phenotype. Recent evidence indicates that type 2 inflammation is present in patients with CRS with and without NP.[9] Although our study was not specifically designed to compare patients with and without CRS, the power was sufficient for a careful and rigorous evaluation of asthma clinical outcomes, biomarkers, and PROs in this population with comorbid disease. In addition, studies of reslizumab and benralizumab in patients with asthma also relied on self-reporting to identify patients with CRS with or without NP.[33,34]

This *post hoc* analysis suggests that adding dupilumab 200 or 300 mg q2w to medium-to-high-dose ICS plus long-acting β_2-agonist therapy was effective and well tolerated in patients with uncontrolled, moderate-to-severe asthma with and without comorbid CRS. Improvements in asthma control occurred rapidly and were sustained over the 52-week study period. Notably, the clinical benefits associated with dupilumab in terms of efficacy and improved quality of life were particularly evident in the subgroup of patients with comorbid asthma and CRS. These patients represent a difficult-to-treat subpopulation of patients with asthma, with high levels of inflammatory biomarkers and baseline disease burden, and increased risk of asthma exacerbations. Dupilumab was particularly efficacious in these patients, providing evidence of improving symptoms in comorbidities of both the upper and lower airways.

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TABLE E1. LS mean change from baseline in pre-bronchodilator FEV_1 (L) during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS

LS mean change from baseline	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 254)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 510)
Baseline, n	63	126	70	123	254	505	251	510
Mean (SD)	1.81 (0.62)	1.88 (0.57)	1.70 (0.59)	1.68 (0.53)	1.75 (0.61)	1.76 (0.63)	1.76 (0.56)	1.81 (0.62)
Week 2, n	63	122	68	121	252	488	245	504
LS mean (SE)	0.06 (0.04)	0.26 (0.03)	0.07 (0.04)	0.28 (0.03)	0.12 (0.02)	0.25 (0.02)	0.15 (0.02)	0.28 (0.02)
LS mean difference vs placebo (95% CI)		0.20 (0.10 to 0.31)		0.21 (0.11 to 0.31)		0.13 (0.07 to 0.18)		0.13 (0.08 to 0.19)
P value		.0001		<.0001		<.0001		<.0001
Week 12, n	62	124	70	116	245	487	243	494
LS mean (SE)	0.20 (0.05)	0.37 (0.04)	0.18 (0.05)	0.33 (0.04)	0.18 (0.02)	0.31 (0.02)	0.22 (0.03)	0.34 (0.02)
LS mean difference vs placebo (95% CI)		0.18 (0.06 to 0.30)		0.15 (0.04 to 0.27)		0.13 (0.07 to 0.18)		0.12 (0.06 to 0.18)
P value		.0039		.0107		<.0001		<.0001
Week 24, n	61	120	64	117	239	479	232	479
LS mean (SE)	0.14 (0.05)	0.41 (0.04)	0.23 (0.05)	0.34 (0.04)	0.18 (0.03)	0.32 (0.02)	0.21 (0.03)	0.33 (0.02)
LS mean difference vs placebo (95% CI)		0.27 (0.15 to 0.39)		0.11 (−0.01 to 0.22)		0.14 (0.08 to 0.20)		0.11 (0.05 to 0.17)
P value		<.0001		.0754		<.0001		.0005
Week 52, n	52	99	57	98	188	378	193	390
LS mean (SE)	0.14 (0.06)	0.42 (0.04)	0.19 (0.05)	0.34 (0.04)	0.17 (0.03)	0.34 (0.02)	0.24 (0.03)	0.36 (0.02)
LS mean difference vs placebo (95% CI)		0.28 (0.15 to 0.41)		0.16 (0.03 to 0.28)		0.17 (0.11 to 0.24)		0.12 (0.06 to 0.19)
P value		<.0001		.0156		<.0001		.0002

CI, Confidence interval; *CRS*, chronic rhinosinusitis; *FEV_1*, forced expiratory volume in 1 second; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.
P values are vs matched placebo.

TABLE E2. LS mean change from baseline in post-bronchodilator FEV_1 (L) during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS

	Patients with asthma patients with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
LS mean change from baseline	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 254)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 510)
Baseline, n	63	126	70	123	254	505	251	510
Mean (SD)	2.16 (0.70)	2.24 (0.70)	2.08 (0.69)	2.02 (0.64)	2.16 (0.71)	2.14 (0.75)	2.15 (0.69)	2.21 (0.74)
Week 2, n	61	123	68	117	249	486	243	500
LS mean (SE)	−0.03 (0.04)	0.17 (0.03)	−0.08 (0.04)	0.13 (0.03)	−0.05 (0.02)	0.11 (0.02)	0.00 (0.02)	0.11 (0.01)
LS mean difference vs placebo (95% CI)		0.20 (0.09 to 0.30)		0.21 (0.11 to 0.31)		0.15 (0.11 to 0.20)		0.11 (0.06 to 0.16)
P value		.0002		<.0001		<.0001		<.0001
Week 12, n	61	124	69	118	244	486	244	494
LS mean (SE)	0.08 (0.05)	0.20 (0.03)	−0.00 (0.04)	0.18 (0.03)	−0.01 (0.02)	0.13 (0.02)	0.05 (0.02)	0.13 (0.02)
LS mean difference vs placebo (95% CI)		0.12 (0.01 to 0.23)		0.18 (0.07 to 0.28)		0.14 (0.09 to 0.19)		0.09 (0.03 to 0.14)
P value		.0320		.0009		<.0001		.0011
Week 24, n	62	122	65	120	240	477	237	481
LS mean (SE)	0.01 (0.05)	0.20 (0.03)	0.05 (0.04)	0.16 (0.03)	−0.03 (0.02)	0.15 (0.02)	0.00 (0.02)	0.12 (0.02)
LS mean difference vs placebo (95% CI)		0.19 (0.08 to 0.30)		0.12 (0.01 to 0.22)		0.18 (0.12 to 0.23)		0.12 (0.06 to 0.18)
P value		.0008		.0367		<.0001		<.0001
Week 52, n	52	103	56	104	187	396	199	390
LS mean (SE)	−0.06 (0.05)	0.21 (0.04)	−0.02 (0.05)	0.13 (0.04)	−0.03 (0.02)	0.14 (0.02)	0.01 (0.02)	0.14 (0.02)
LS mean difference vs placebo (95% CI)		0.27 (0.15 to 0.39)		0.14 (0.03 to 0.26)		0.17 (0.11 to 0.23)		0.13 (0.07 to 0.18)
P value		<.0001		.0173		<.0001		<.0001

CI, Confidence interval; *CRS*, chronic rhinosinusitis; *FEV_1*, forced expiratory volume in 1 second; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.
P values are vs matched placebo.

TABLE E3. LS mean change from baseline in ACQ-5 scores during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS

	Patients with asthma patients with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
LS mean change from baseline	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 254)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 510)
Baseline, n	63	126	70	123	254	505	251	510
Mean (SD)	2.86 (0.70)	2.76 (0.80)	2.76 (0.73)	2.85 (0.76)	2.68 (0.73)	2.76 (0.80)	2.77 (0.78)	2.75 (0.76)
Week 2, n	61	122	66	118	243	477	239	497
LS mean (SE)	−0.62 (0.11)	−0.93 (0.08)	−0.51 (0.11)	−1.14 (0.08)	−0.54 (0.06)	−0.88 (0.04)	−0.63 (0.06)	−0.86 (0.04)
LS mean difference vs placebo (95% CI)		−0.32 (−0.59 to −0.05)		−0.63 (−0.89 to −0.37)		−0.34 (−0.47 to −0.20)		−0.23 (−0.36 to −0.09)
P value		.0201		<.0001		<.0001		.0010
Week 12, n	62	125	69	115	241	480	243	488
LS mean (SE)	−1.02 (0.12)	−1.57 (0.09)	−1.28 (0.12)	−1.62 (0.09)	−1.02 (0.06)	−1.30 (0.04)	−1.05 (0.06)	−1.30 (0.04)
LS mean difference vs placebo (95% CI)		−0.55 (−0.84 to −0.26)		−0.34 (−0.62 to −0.06)		−0.28 (−0.42 to −0.13)		−0.24 (−0.39 to −0.10)
P value		.0002		.0187		.0002		.0011
Week 24, n	61	120	65	115	235	470	232	470
LS mean (SE)	−1.04 (0.13)	−1.56 (0.09)	−1.23 (0.12)	−1.73 (0.09)	−1.10 (0.06)	−1.41 (0.05)	−1.20 (0.06)	−1.31 (0.05)
LS mean difference vs placebo (95% CI)		−0.52 (−0.82 to −0.21)		−0.50 (−0.80 to −0.20)		−0.31 (−0.46 to −0.15)		−0.11 (−0.26 to 0.04)
P value		.0009		.0010		<.0001		.1552
Week 52, n	50	96	55	94	186	374	190	383
LS mean (SE)	−1.15 (0.13)	−1.75 (0.09)	−1.21 (0.12)	−1.75 (0.09)	−1.15 (0.07)	−1.48 (0.05)	−1.32 (0.07)	−1.45 (0.05)
LS mean difference vs placebo (95% CI)		−0.60 (−0.90 to −0.30)		−0.54 (−0.83 to −0.25)		−0.33 (−0.49 to −0.18)		−0.14 (−0.29 to 0.02)
P value		.0001		.0003		<.0001		.0877

ACQ-5, 5-Item Asthma Control Questionnaire; *CI*, confidence interval; *CRS*, chronic rhinosinusitis; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.
P values are vs matched placebo.

TABLE E4. LS mean change from baseline in AQLQ(S) scores during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS

	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
LS mean change from baseline	**Placebo (n = 63)**	**Dupilumab (n = 126)**	**Placebo (n = 70)**	**Dupilumab (n = 123)**	**Placebo (n = 254)**	**Dupilumab (n = 505)**	**Placebo (n = 251)**	**Dupilumab (n = 510)**
Baseline, n	59	121	70	117	240	470	244	486
Mean (SD)	4.26 (1.02)	4.39 (0.98)	4.30 (1.05)	4.31 (1.06)	4.26 (1.02)	4.29 (1.10)	4.31 (1.02)	4.27 (1.05)
Week 12, n	57	120	69	113	229	453	239	473
LS mean (SE)	0.84 (0.12)	1.23 (0.08)	1.07 (0.11)	1.16 (0.09)	0.88 (0.06)	1.06 (0.04)	0.89 (0.06)	1.07 (0.04)
LS mean difference vs placebo (95% CI)		0.39 (0.10 to 0.68)		0.09 (−0.18 to 0.36)		0.18 (0.04 to 0.32)		0.19 (0.05 to 0.33)
P value		.0076		.5221		.0145		.0092
Week 24, n	58	118	66	113	223	442	229	456
LS mean (SE)	0.84 (0.12)	1.17 (0.08)	0.95 (0.11)	1.38 (0.09)	0.96 (0.07)	1.12 (0.05)	1.01 (0.07)	1.09 (0.05)
LS mean difference vs placebo (95% CI)		0.33 (0.05 to 0.62)		0.43 (0.16 to 0.70)		0.16 (0.01 to 0.32)		0.08 (−0.07 to 0.23)
P value		.0209		.0022		.0382		.2971
Week 52, n	47	96	55	95	177	369	188	364
LS mean (SE)	0.88 (0.13)	1.46 (0.09)	0.87 (0.12)	1.44 (0.09)	1.02 (0.07)	1.23 (0.05)	1.06 (0.07)	1.25 (0.05)
LS mean difference vs placebo (95% CI)		0.58 (0.28 to 0.88)		0.57 (0.29 to 0.86)		0.21 (0.05 to 0.37)		0.19 (0.03 to 0.35)
P value		.0002		.0001		.0118		.0215

AQLQ(S), Asthma Quality of Life Questionnaire (standardized version); *CI*, confidence interval; *CRS*, chronic rhinosinusitis; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.
P values are vs matched placebo.

TABLE E5. LS mean change from baseline in SNOT-22 scores during the 52-week treatment period in patients with asthma with CRS

	Patients with asthma with CRS (n = 382)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
LS mean change from baseline	**Placebo (n = 63)**	**Dupilumab (n = 126)**	**Placebo (n = 70)**	**Dupilumab (n = 123)**
Baseline, n	53	115	62	107
Mean (SD)	44.77 (19.75)	41.30 (17.98)	43.81 (19.28)	42.76 (18.02)
Week 12, n	51	113	61	102
LS mean (SE)	−5.68 (2.21)	−13.81 (1.49)	−9.75 (2.01)	−15.77 (1.57)
LS mean difference vs placebo (95% CI)		−8.13 (−13.28 to −2.98)		−6.02 (−10.93 to −1.10)
P value		.0021		.0166
Week 24, n	52	111	58	102
LS mean (SE)	−6.44 (2.29)	−14.71 (1.55)	−7.97 (2.11)	−16.76 (1.62)
LS mean difference vs placebo (95% CI)		−8.27 (−13.61 to −2.93)		−8.79 (−13.94 to −3.64)
P value		.0025		.0009
Week 52, n	42	89	49	85
LS mean (SE)	−4.47 (2.44)	−16.35 (1.65)	−7.54 (2.23)	−17.86 (1.72)
LS mean difference vs placebo (95% CI)		−11.88 (−17.59 to −6.18)		−10.32 (−15.77 to −4.87)
P value		<.0001		.0002

CI, Confidence interval; *CRS*, chronic rhinosinusitis; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error; *SNOT-22*, Sino-Nasal Outcome Test. *P* values are vs matched placebo.

TABLE E6. Median FeNO (ppb) levels during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS—exposed population

	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 250)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 509)
Baseline, n	62	126	69	123	245	498	247	503
Median (95% CI)	31.0 (26.0 to 42.0)	32.0 (29.0 to 39.0)	35.0 (30.0 to 48.0)	26.0 (23.0 to 33.0)	24.0 (21.0 to 27.0)	21.0 (19.0 to 23.0)	24.0 (21.0 to 29.0)	24.0 (21.0 to 25.0)
Week 2, n	61	116	63	114	230	462	229	475
Median (95% CI)	31.0 (23.0 to 43.0)	20.0 (17.0 to 24.0)	38.0 (30.0 to 40.0)	18.0 (17.0 to 21.0)	23.0 (21.0 to 26.0)	16.0 (15.0 to 17.0)	23.0 (21.0 to 27.0)	16.0 (15.0 to 17.0)
P value		<.0001		<.0001		<.0001		<.0001
Week 12, n	58	119	68	109	228	465	230	467
Median (95% CI)	32.5 (28.0 to 38.0)	19.0 (16.0 to 23.0)	35.5 (29.0 to 47.0)	18.0 (15.0 to 19.0)	23.0 (20.0 to 25.0)	15.0 (14.0 to 16.0)	21.0 (19.0 to 23.0)	14.0 (14.0 to 15.0)
P value		.0002		<.0001		<.0001		<.0001
Week 24, n	57	116	61	109	220	446	223	452
Median (95% CI)	35.0 (24.0 to 43.0)	18.0 (16.0 to 20.0)	33.0 (25.0 to 38.0)	18.0 (15.0 to 19.0)	23.5 (20.0 to 27.0)	15.0 (14.0 to 15.0)	21.0 (17.0 to 25.0)	14.0 (13.0 to 15.0)
P value		.0007		<.0001		<.0001		<.0001
Week 52, n	47	92	49	82	164	342	168	344
Median (95% CI)	32.0 (25.0 to 48.0)	18.0 (15.0 to 20.0)	42.0 (25.0 to 51.0)	16.0 (15.0 to 19.0)	20.0 (18.0 to 26.0)	14.0 (13.0 to 15.0)	21.0 (19.0 to 26.0)	15.0 (14.0 to 16.0)
P value		.0094		.0003		<.0001		<.0001

CI, Confidence interval; *CRS*, chronic rhinosinusitis; *FeNO*, fractional exhaled nitric oxide; *ICS*, inhaled corticosteroid; *q2w*, every 2 weeks.

P values are comparing dupilumab vs matched placebo for change in FeNO from baseline and are based on rank analysis of the covariance model adjusted for baseline FeNO, age, sex, geographic region, baseline eosinophil strata, and baseline ICS dose level.

TABLE E7. Median serum total IgE (IU/mL) levels during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS

	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 250)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 509)
Baseline, n	63	125	69	122	249	501	249	504
Median (95% CI)	177.00 (106.00 to 251.00)	156.00 (110.00 to 230.00)	205.00 (115.00 to 286.00)	150.00 (107.00 to 212.00)	170.00 (135.00 to 244.00)	154.00 (131.00 to 184.00)	176.00 (137.00 to 212.00)	179.50 (152.00 to 214.00)
Week 12, n	62	126	70	120	244	493	246	502
Median (95% CI)	167.50 (100.00 to 292.00)	79.50 (59.00 to 122.00)	182.00 (118.00 to 305.00)	81.50 (61.00 to 115.00)	161.00 (123.00 to 222.00)	93.00 (80.00 to 111.00)	188.50 (165.00 to 221.00)	109.50 (100.00 to 132.00)
P value		<.0001		<.0001		<.0001		<.0001
Week 24, n	61	121	64	119	238	476	233	475
Median (95% CI)	170.00 (117.00 to 285.00)	53.00 (39.00 to 80.00)	165.00 (111.00 to 287.00)	49.00 (38.00 to 75.00)	179.50 (131.00 to 224.00)	67.00 (57.00 to 78.00)	177.00 (149.00 to 218.00)	78.00 (69.00 to 91.00)
P value		<.0001		<.0001		<.0001		<.0001
Week 52, n	53	102	58	100	185	396	193	382
Median (95% CI)	176.00 (106.00 to 280.00)	38.50 (30.00 to 61.00)	176.00 (121.00 to 308.00)	26.50 (21.00 to 53.00)	170.00 (139.00 to 269.00)	45.00 (36.00 to 51.00)	173.00 (133.00 to 221.00)	51.00 (44.00 to 60.00)
P value		<.0001		<.0001		<.0001		<.0001

CI, Confidence interval; *CRS*, chronic rhinosinusitis; *ICS*, inhaled corticosteroid; *q2w*, every 2 weeks.

P values are comparing dupilumab vs matched placebo for change in serum total IgE from baseline and are based on rank analysis of the covariance model adjusted for baseline serum total IgE, age, sex, geographic region, baseline eosinophil strata, and baseline ICS dose level.

TABLE E8. Median serum TARC (pg/mL) levels during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS—exposed population

	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 250)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 509)
Baseline, n	63	126	69	122	244	500	250	500
Median (95% CI)	335.0 (217.0 to 367.0)	293.0 (274.0 to 339.0)	349.0 (300.0 to 444.0)	308.5 (276.0 to 358.0)	295.5 (274.0 to 324.0)	317.0 (291.0 to 338.0)	288.0 (263.0 to 320.0)	292.0 (274.0 to 313.0)
Week 12, n	63	126	70	122	244	495	247	501
Median (95% CI)	322.0 (221.0 to 401.0)	200.0 (175.0 to 221.0)	321.0 (282.0 to 394.0)	186.5 (172.0 to 218.0)	296.5 (276.0 to 332.0)	203.0 (193.0 to 211.0)	312.0 (288.0 to 352.0)	194.0 (179.0 to 206.0)
P value		.0002		<.0001		<.0001		<.0001
Week 24, n	59	119	60	113	238	466	229	468
Median (95% CI)	289.0 (221.0 to 392.0)	185.0 (163.0 to 206.0)	283.5 (252.0 to 331.0)	200.0 (174.0 to 220.0)	307.0 (283.0 to 334.0)	204.0 (188.0 to 214.0)	317.0 (280.0 to 339.0)	192.0 (181.0 to 206.0)
P value		.0003		<.0001		<.0001		<.0001
Week 52, n	53	102	57	100	184	396	191	379
Median (95% CI)	281.0 (231.0 to 391.0)	193.0 (173.0 to 223.0)	306.0 (266.0 to 387.0)	183.0 (164.0 to 214.0)	307.0 (280.0 to 333.0)	212.0 (194.0 to 220.0)	303.0 (280.0 to 345.0)	204.0 (192.0 to 216.0)
P value		.0002		.0001		<.0001		<.0001

CI, Confidence interval; *CRS*, chronic rhinosinusitis; *ICS*, inhaled corticosteroid; *q2w*, every 2 weeks; *TARC*, thymus and activation-regulated chemokine.
P values are comparing dupilumab vs matched placebo for change in serum TARC from baseline and are based on rank analysis of the covariance model adjusted for baseline TARC, age, sex, geographic region, baseline eosinophil strata, and baseline ICS dose level.

TABLE E9. Median blood eosinophil (Giga/L) count during the 52-week treatment period in patients with asthma with CRS and patients with asthma without CRS—exposed population

	Patients with asthma with CRS (n = 382)				Patients with asthma without CRS (n = 1520)			
	1.14 mL/200 mg q2w		2.0 mL/300 mg q2w		1.14 mL/200 mg q2w		2.0 mL/300 mg q2w	
	Placebo (n = 63)	Dupilumab (n = 126)	Placebo (n = 70)	Dupilumab (n = 123)	Placebo (n = 250)	Dupilumab (n = 505)	Placebo (n = 251)	Dupilumab (n = 509)
Baseline, n	63	126	70	123	250	504	250	509
Median (95% CI)	0.410 (0.290 to 0.540)	0.365 (0.320 to 0.470)	0.470 (0.360 to 0.580)	0.360 (0.310 to 0.460)	0.240 (0.210 to 0.290)	0.200 (0.190 to 0.240)	0.240 (0.200 to 0.270)	0.220 (0.200 to 0.260)
Week 4, n	62	124	69	120	238	486	238	496
Median (95% CI)	0.380 (0.290 to 0.490)	0.500 (0.350 to 0.600)	0.470 (0.310 to 0.600)	0.455 (0.310 to 0.560)	0.220 (0.200 to 0.250)	0.215 (0.190 to 0.240)	0.220 (0.190 to 0.260)	0.230 (0.200 to 0.270)
P value		.1136		.1586		.0314		.5775
Week 12, n	59	120	67	113	239	475	235	482
Median (95% CI)	0.370 (0.270 to 0.490)	0.475 (0.380 to 0.760)	0.500 (0.370 to 0.560)	0.460 (0.340 to 0.620)	0.260 (0.220 to 0.290)	0.210 (0.190 to 0.250)	0.230 (0.210 to 0.280)	0.210 (0.190 to 0.260)
P value		.0018		.0676		.7294		.7691
Week 24, n	60	115	65	112	231	463	224	465
Median (95% CI)	0.365 (0.220 to 0.480)	0.530 (0.390 to 0.650)	0.420 (0.360 to 0.520)	0.440 (0.310 to 0.570)	0.240 (0.210 to 0.290)	0.220 (0.190 to 0.240)	0.230 (0.200 to 0.270)	0.200 (0.190 to 0.230)
P value		.3222		.5364		.0768		.5150
Week 52, n	52	94	57	96	183	371	188	380
Median (95% CI)	0.405 (0.290 to 0.480)	0.480 (0.330 to 0.600)	0.430 (0.370 to 0.580)	0.300 (0.180 to 0.470)	0.250 (0.220 to 0.290)	0.180 (0.160 to 0.210)	0.220 (0.190 to 0.240)	0.180 (0.160 to 0.210)
P value		.0519		.7685		.0121		.2433

ANCOVA, Analysis of covariance; *CI*, confidence interval; *CRS*, chronic rhinosinusitis; *ICS*, inhaled corticosteroid; *q2w*, every 2 weeks.

P values are comparing dupilumab vs matched placebo for change in blood eosinophil count from baseline and are based on the rank ANCOVA model adjusted for baseline blood eosinophil count, age, sex, geographic region, baseline eosinophil strata, and baseline ICS dose level.