Original Article

Dupilumab Efficacy in Patients With Uncontrolled or Oral Corticosteroid–Dependent Allergic and Nonallergic Asthma

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What is already known about this topic? IL-4/-13 play a key role in airway inflammation. Dupilumab can suppress type 2 inflammatory biomarkers in patients with uncontrolled, moderate-to-severe asthma with or without evidence of allergic asthma, one of the most common forms of asthma.

What does this article add to our knowledge? In this analysis of patients with uncontrolled, moderate-to-severe, or oral corticosteroid–dependent severe asthma, dupilumab reduced severe exacerbation rates and improved lung function, asthma control, and quality of life in patients with or without evidence of allergic asthma.

How does this study impact current management guidelines? The results of this study indicate that dupilumab is beneficial in reducing the clinical burden of disease in patients with uncontrolled, moderate-to-severe, or corticosteroid-dependent severe asthma with and without evidence of allergic asthma.

BACKGROUND: Type 2 cytokines IL-4/IL-5/IL-13 play an important role in pathogenesis of type 2 conditions, including asthma. Dupilumab, a human monoclonal antibody, blocks the shared receptor component for IL-4/IL-13, inhibiting signaling. In phase 2b (P2B) (NCT01854047) and phase 3 VENTURE (NCT02528214), dupilumab reduced annualized severe exacerbation rates (AER), improved forced expiratory volume in 1 second (FEV_1), and was generally well tolerated in patients with uncontrolled, moderate-to-severe, or oral corticosteroid (OCS)–dependent severe asthma.

OBJECTIVE: The *post hoc* assessment of dupilumab efficacy versus placebo in P2B and VENTURE in patients stratified by allergic status.

METHODS: Allergic asthma was defined as total serum IgE ≥30 IU/mL and ≥1 perennial aeroallergen–specific IgE ≥0.35 kU/L at baseline. AER, prebronchodilator (BD) FEV_1, FEV_1/forced

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Abbreviations used
ACQ-5- Asthma Control Questionnaire
AER- Annualized severe exacerbations rate
ANCOVA- Analysis of covariance
AQLQ- Asthma Quality of Life Questionnaire
BD- Bronchodilator
CI- Confidence interval
FeNO- Fractional exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
FVC- Forced vital capacity
GINA- Global Initiative for Asthma
HRQoL- Health-related quality of life
ICS- Inhaled corticosteroid
ITT- Intent-to-treat
LS- Least squares
LSMD- Least-squares mean difference
OCS- Oral corticosteroid
P2B- Phase 2b
q2w- Every 2 weeks
QoL- Quality of life
SCS- Systemic corticosteroids
TARC- Thymus and activation-regulated chemokine
Th- T helper

vital capacity (FVC) ratio, asthma control (5-item Asthma Control Questionnaire), health-related quality of life (HRQoL; Asthma Quality of Life Questionnaire), type 2 biomarkers, specific IgE, and OCS reduction (VENTURE only) were assessed.

RESULTS: In patients with allergic asthma, dupilumab (P2B: pooled 200/300 mg; VENTURE: 300 mg) every 2 weeks versus placebo reduced AER (P2B: −60%, $P < .01$; VENTURE: −72%, $P < .001$), and, in P2B, increased pre-BD FEV_1 ($P < .01$) and FEV_1/FVC ($P < .05$). In both studies, dupilumab significantly improved asthma control and HRQoL and reduced most type 2 biomarkers. Dupilumab significantly reduced OCS use in VENTURE. Similar benefits were observed in patients without evidence of allergic asthma.

CONCLUSIONS: Dupilumab significantly reduced AER and improved lung function, asthma control, and HRQoL in patients with or without evidence of allergic asthma. **(J Allergy Clin Immunol Pract 2023;11:873-84)**

Key words: *Dupilumab; Allergic asthma; Exacerbation; IL-4; IL-13; IgE; Biomarkers; ACQ-5; AQLQ; FEV_1*

Allergic asthma is characterized by increased levels of total and allergen-specific IgE in serum.[1] Type 2 inflammatory cytokines, particularly IL-4, IL-5, and IL-13, play key roles in the pathogenesis of multiple type 2 inflammatory conditions, including atopic dermatitis, chronic rhinosinusitis with nasal polyps, and allergic asthma. One of the many roles of IL-4 in type 2 inflammatory responses is in differentiation of naive T helper (Th) cells into Th2 cells, which then produce type 2 inflammatory cytokines and chemokines.[2] In addition, IL-4 induces B-cell class switching from the production of IgG to IgE.[3] IL-5 stimulates eosinopoiesis and activates eosinophils, and IL-13 plays a key role in goblet cell hyperplasia, mucus hypersecretion, airway hyperresponsiveness, and eosinophil migration into the lung.[4,5]

Biomarkers modulated by IL-4 and IL-13 have been linked to type 2 inflammatory processes in patients with asthma, including thymus and activation-regulated chemokine (TARC), fractional exhaled nitric oxide (FeNO), and serum total and allergen-specific IgE levels. TARC plays a role in the recruitment of Th2 cells in allergic diseases such as allergic asthma. IL-4 induces the expression of TARC as part of the signal transducer and activator of transcription 6 signaling pathway,[6] and elevated levels of TARC have been observed in both serum and sputum of patients with asthma.[7] Nitric oxide acts as an important inflammatory mediator in the respiratory tract and is regulated in part by IL-13.[8] IgE has multiple effects in the pathogenesis of allergic processes, including activation and degranulation of mast cells, basophils, and eosinophils, leading to the release of proinflammatory mediators, recruitment of eosinophils, and bronchoconstriction.[9,10] Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, thus inhibiting their signaling.[11,12] It is indicated for use in patients with type 2 inflammatory diseases, including atopic dermatitis, asthma (regardless of allergic status), and chronic rhinosinusitis with nasal polyps.[13,14] In the phase 2b dose-ranging study (P2B; NCT01854047), add-on dupilumab 200/300 mg every 2 weeks (q2w) versus placebo reduced annualized rates of severe exacerbations and improved lung function, and was generally well tolerated, in patients with uncontrolled, moderate-to-severe asthma.[15] In addition, in the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), add-on dupilumab 300 mg therapy significantly reduced oral corticosteroid (OCS) use while simultaneously reducing the rate of severe asthma exacerbations and improving lung function in patients with OCS-dependent severe asthma.[16]

In a previous *post hoc* analysis of the phase 3 LIBERTY ASTHMA QUEST study, dupilumab significantly reduced the rate of severe exacerbations and improved forced expiratory volume in 1 second (FEV_1) and asthma control, in moderate-to-severe asthma patients with or without evidence of allergic asthma.[17]

This *post hoc* analysis aims to confirm outcomes observed in QUEST[17] in patients with and without evidence of allergic asthma with uncontrolled, moderate-to-severe asthma from the P2B study and with OCS-dependent severe asthma from the VENTURE study.

METHODS

Study design

Full details of the P2B and VENTURE study design have been published previously.[15,16] In brief, the P2B dose-ranging study was a phase 2b randomized, double-blind, placebo-controlled, parallel group study performed in adult patients with uncontrolled, moderate-to-severe asthma despite the use of medium- to high-dose inhaled corticosteroids (ICS). Patients were randomized 1:1:1:1:1 to receive subcutaneous dupilumab 200 mg (n = 150) or 300 mg (n = 157) q2w or 200 mg (n = 154) or 300 mg (n = 157) every 4 weeks, or placebo (n = 158) for a 24-week treatment period. This *post hoc* analysis included the combined dupilumab 200 mg and 300 mg q2w population (n = 307). VENTURE was a phase 3 randomized, double-blind, placebo-controlled study in adolescents and adults with OCS-dependent severe asthma. Patients were randomized 1:1

to receive dupilumab 300 mg q2w (n = 103) or placebo (n = 107) for 24 weeks. The OCS dose was adjusted every 4 weeks from week 4 to week 20 according to a protocol-prespecified algorithm. Both studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines and applicable regulatory requirements. All patients or their legal guardians/parents provided written informed consent before participating in the studies. Protocol and consent forms were approved by local institutional review boards and ethics committees before the commencement of the studies.

Patients

P2B enrolled adult patients with a diagnosis of asthma for ≥12 months based on Global Initiative for Asthma (GINA) 2009 guidelines:[18] existing treatment with medium- to high-dose ICS plus a long-acting β_2-agonist, prebronchodilator (BD) FEV_1 of 40% to 80% predicted at baseline, 5-item Asthma Control Questionnaire (ACQ-5) score ≥1.5 at screening and baseline, and FEV_1 reversibility of ≥12% and ≥200 mL after 200 to 400 μg of salbutamol at screening. VENTURE enrolled adolescent and adult patients with physician-diagnosed asthma for ≥12 months based on GINA 2014 guidelines:[19] regular OCS treatment in the previous 6 months (5-35 mg of prednisone or equivalent), high-dose ICS in combination with up to 2 controllers for ≥3 months, pre-BD FEV_1 ≤80% predicted (≤90% for adolescents), and reversibility ≥12% and 200 mL in FEV_1. Further details of inclusion and exclusion criteria have been published previously.[15,16]

No prick test was used in either study. For this *post hoc* analysis, patients were categorized as meeting or not meeting the criteria for allergic asthma as used by physicians to determine eligibility for biologic therapy with omalizumab: total serum IgE ≥30 IU/mL and at least 1 perennial aeroallergen−specific IgE ≥0.35 kU/L at baseline.[20] Perennial allergens analyzed in both studies were *Alternaria tenuis/alternata, Cladosporium herbarum/hormodendrum, Aspergillus fumigatus*, cat and dog dander, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, oriental cockroach, and, for P2B only, German cockroach.

End points

End points assessed for both studies were annualized severe exacerbation rates (defined as events leading to hospitalization or an emergency department visit requiring systemic corticosteroids [SCS] or treatment for ≥3 days of SCS [at ≥2 times the current dose of oral glucocorticoid for patients in VENTURE]), change from baseline in pre-BD FEV_1, FEV_1/forced vital capacity (FVC) ratio, ACQ-5 score, Asthma Quality of Life Questionnaire (AQLQ) global score, type 2 biomarkers (total IgE, FeNO, and serum TARC), and specific IgE for each of the perennial allergens over the 24-week treatment periods. Percentage reduction in OCS use was also assessed for patients in VENTURE.

Statistical analysis

Data were analyzed for subgroups of patients with allergic asthma versus those not meeting criteria for allergic asthma for each study separately in the intent-to-treat (ITT) population for efficacy parameters and in the exposed population for biomarkers. In P2B, data were combined across dupilumab q2w doses.

Annualized severe exacerbation rates over the 24-week study periods were analyzed using a negative binomial regression model; total number of events onset between first dose date and last dose date + 14 days for P2B and between first dose date and week 24 or last contact date (whichever came earlier) for VENTURE were the response variables, with treatment group, pooled countries/regions, number of severe exacerbation events before the study, and baseline eosinophil strata (plus baseline optimized OCS dose for VENTURE) as covariates, and log-transformed standardized treatment duration as an offset variable, for both studies.

Change from baseline in pre-BD FEV_1 and FEV_1/FVC ratios, ACQ-5 score, and AQLQ global score were assessed in each subgroup using mixed-effect models with repeated measures. Treatment group, pooled countries/regions, baseline eosinophil strata, visits, baseline optimized OCS dose (for VENTURE), treatment-by-visit interaction, baseline values, and baseline-by-visit interaction were covariates; age, gender, and height were added as covariates for pre-BD FEV_1 and FEV_1/FVC ratio in VENTURE.

For VENTURE, absolute and percentage reductions of the OCS dose at week 24 were analyzed in each subgroup using an analysis of covariance (ANCOVA) model; treatment group, baseline optimized OCS dose, pooled countries/regions, and baseline eosinophil strata were covariates. For patients who discontinued or had missing data on oral glucocorticoid dose at week 24, missing data were handled with the use of a pattern-mixture model by multiple imputations.

For VENTURE, the proportion of patients with a ≥50% reduction in the OCS dose—achieving the reduction of the OCS dose to <5 mg/d, achieving the maximum possible reduction of the OCS dose per protocol, and no longer requiring OCS at week 24 (for patients with the baseline OCS dose ≤30 mg/d)—were compared in each subgroup using a logistic regression model; treatment group, optimized OCS dose at baseline, pooled countries/regions, and baseline eosinophil level subgroup were covariates. Missing data were imputed the same way as for the percentage reduction of the OCS dose.

Change from baseline in type 2 biomarkers and specific IgE were assessed in the exposed population, and separately in each subgroup, using rank ANCOVA models due to non-normal distribution of the end points; baseline biomarker level, pooled countries/regions, baseline eosinophil strata, and baseline optimized OCS dose for VENTURE were covariates. Similar analyses were performed in patients with evidence of allergic asthma for percent change from baseline in IgE-specific allergens (only patients with positive specific allergens at baseline were included in the analyses).

Across all analyses, significance was attributed as $P < .05$. As all predictive analyses were *post hoc*, all P values were not adjusted for multiple testing and should be considered nominal. Analyses were performed using SAS version 9.4 (SAS Institute, Inc, Cary, NC).

RESULTS

Patients

In total, 271 patients with (placebo: n = 95; dupilumab: n = 176; 58.3% of the ITT population) and 194 patients without evidence of allergic asthma (placebo: n = 63; dupilumab: n = 131) from P2B, and 86 patients with (placebo: n = 40; dupilumab: n = 46; 41.0% ITT) and 124 patients without evidence of allergic asthma (placebo: n = 67; dupilumab: n = 57) from VENTURE were included in the analysis. Of the patients without evidence of allergic asthma in P2B, 48 versus 96 patients had baseline total IgE ≥ 30 IU/mL but no positive perennial allergen, 6 versus 8 had total IgE < 30 IU/mL but ≥1 positive perennial allergen, and 9 versus 27 had total IgE < 30 IU/mL and no positive perennial allergens for the placebo and dupilumab groups, respectively. In VENTURE, these numbers of patients were 48 versus 47, 2 versus 0, and 17 versus 10 for the 2 treatment groups, respectively.

TABLE I. Baseline characteristics of patients meeting and not meeting criteria for allergic asthma in the phase 2b and VENTURE study (intent-to-treat population)

	Phase 2b (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
Baseline characteristics	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 63)	Combined dupilumab (N = 131)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N = 57)
Age (y), mean (SD)	47.6 (12.5)	46.6 (13.5)	51.0 (13.0)	52.7 (11.4)	46.5 (14.5)	47.7 (14.5)	53.3 (11.1)	55.3 (9.3)
Female, n (%)	56 (58.9)	105 (59.7)	48 (76.2)	94 (71.8)	20 (50.0)	29 (63.0)	45 (67.2)	33 (57.9)
BMI (kg/m^2), mean (SD)	29.00 (6.86)	29.69 (6.12)	29.37 (5.65)	29.51 (6.15)	29.11 (5.90)	29.81 (6.66)	30.16 (6.07)	28.13 (5.16)
Age at asthma onset (y), mean (SD)	21.6 (16.9)	21.9 (18.1)	35.2 (16.8)	34.0 (15.1)	24.9 (16.8)	24.2 (19.3)	35.5 (14.9)	36.9 (16.6)
High-dose ICS use, n (%)	43 (45.7)	85 (49.4)	34 (55.7)	69 (55.2)	40 (100)	46 (100)	67 (100)	57 (100)
With ongoing atopic medical condition, n (%) (self-reported)	75 (79.8)	131 (75.3)	38 (63.3)	91 (70.5)	37 (92.5)	44 (95.7)	40 (59.7)	30 (52.6)
Atopic dermatitis	9 (9.6)	11 (6.3)	3 (5.0)	9 (7.0)	7 (17.5)	6 (13.0)	1 (1.5)	2 (3.5)
Allergic rhinitis	66 (70.2)	114 (65.5)	33 (55.0)	73 (56.6)	26 (65.0)	30 (65.2)	35 (52.2)	26 (45.6)
Food allergy	13 (13.8)	20 (11.5)	2 (3.3)	8 (6.2)	6 (15.0)	5 (10.9)	4 (6.0)	4 (7.0)
Hives	6 (6.4)	12 (6.9)	2 (3.3)	5 (3.9)	2 (5.0)	3 (6.5)	2 (3.0)	2 (3.5)
Severe asthma exacerbations in the past year, mean (SD), n	1.89 (1.32)	2.05 (1.65)	2.84 (3.10)	2.21 (2.26)	2.43 (2.36)	2.50 (2.55)	2.01 (2.16)	1.61 (1.51)
Pre-BD FEV_1 (L), mean (SD)	1.90 (0.58)	1.90 (0.57)	1.71 (0.49)	1.72 (0.45)	1.62 (0.66)	1.59 (0.46)	1.63 (0.58)	1.49 (0.58)
Percent predicted FEV_1 (%)	61.22 (10.48)	60.88 (10.77)	60.56 (11.13)	61.14 (10.58)	49.90 (15.82)	52.83 (13.61)	54.36 (14.59)	50.68 (16.57)
FEV_1/FVC ratio (%), mean (SD)	64.07 (9.48)	65.20 (9.49)	64.12 (10.51)	63.33 (9.75)	58.26 (13.02)	61.43 (9.78)	58.91 (10.23)	56.71 (11.41)
Daily OCS dose at visit 1 (ie, preoptimization) (mg/d), mean (SD)	–	–	–	–	11.76 (5.77)	11.79 (5.91)	11.87 (6.21)	11.79 (6.83)
Optimized daily OCS dose at baseline (mg/d), mean (SD)	–	–	–	–	12.31 (6.66)	10.71 (5.62)	11.42 (6.11)	10.79 (6.16)
ACQ-5 score,* mean (SD)	2.62 (0.80)	2.73 (0.82)	2.79 (0.78)	2.82 (0.83)	2.52 (1.13)	2.40 (1.22)	2.62 (1.07)	2.43 (1.26)
AQLQ score,† mean (SD)	4.24 (1.11)	4.10 (1.13)	3.93 (1.07)	3.79 (1.12)	4.34 (1.16)	4.35 (1.21)	4.30 (1.10)	4.40 (1.26)
Blood eosinophil count (GIGA/L), median (Q1-Q3)	0.260 (0.160-0.410)	0.250 (0.170-0.405)	0.240 (0.150-0.440)	0.280 (0.160-0.510)	0.265 (0.110-0.565)	0.240 (0.170-0.350)	0.220 (0.120-0.410)	0.350 (0.150-0.560)
FeNO (ppb), median (Q1-Q3)	32.0 (16.0-49.0)	27.5 (16.0-53.0)	24.5 (16.0-42.0)	30.0 (15.0-47.0)	30.0 (21.0-55.0)	23.0 (13.0-39.0)	23.5 (14.5-57.5)	36.5 (17.5-54.5)
Total serum IgE (IU/mL), median (Q1-Q3)	302.0 (138.0-523.0)	293.0 (129.5-646.0)	94.5 (31.0-216.0)	90.0 (25.0-178.0)	340.0 (187.0-820.0)	305.0 (150.0-941.0)	68.0 (23.0-164.0)	131.0 (48.0-244.0)
Serum TARC (pg/mL), median (Q1-Q3)	377.28 (267.87-577.82)	423.31 (305.64-641.77)	330.58 (228.79-502.92)	402.64 (282.77-598.68)	291.00 (161.00-550.00)	234.50 (134.00-475.00)	281.50 (170.00-402.00)	275.00 (232.00-448.00)

ACQ-5, Asthma Control Questionnaire-5; *AQLQ*, Asthma Quality of Life Questionnaire; *BD*, bronchodilator; *BL*, baseline; *BMI*, body mass index; *FeNO*, fractional exhaled nitric oxide; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *ICS*, inhaled corticosteroid; *OCS*, oral corticosteroid; *Q*, quartile; *q2w*, every 2 weeks; *SD*, standard deviation; *TARC*, thymus and activation-regulated chemokine.

*ACQ-5 scores range between 0 (totally controlled) and 6 (severely uncontrolled).

†AQLQ(S) scores are rated on a 7-point Likert-like scale (7 = not impaired at all − 1 = severely impaired).

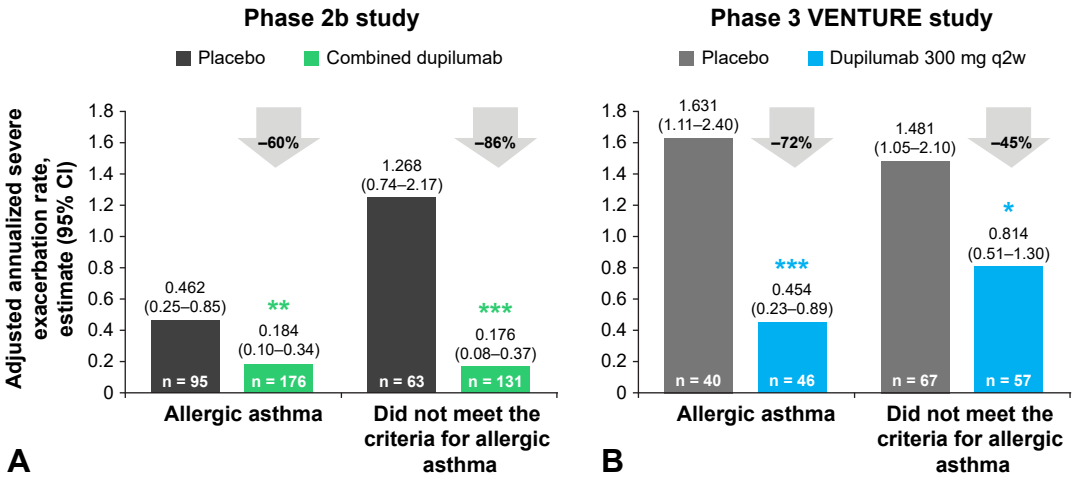

FIGURE 1. Annualized severe exacerbation rates over time in (**A**) the phase 2b dose ranging, and (**B**) VENTURE studies in patients meeting and not meeting criteria for allergic asthma (intent-to-treat population). *$P < .05$, **$P < .01$, ***$P < .001$, versus placebo. *CI*, Confidence interval; *q2w*, every 2 weeks.

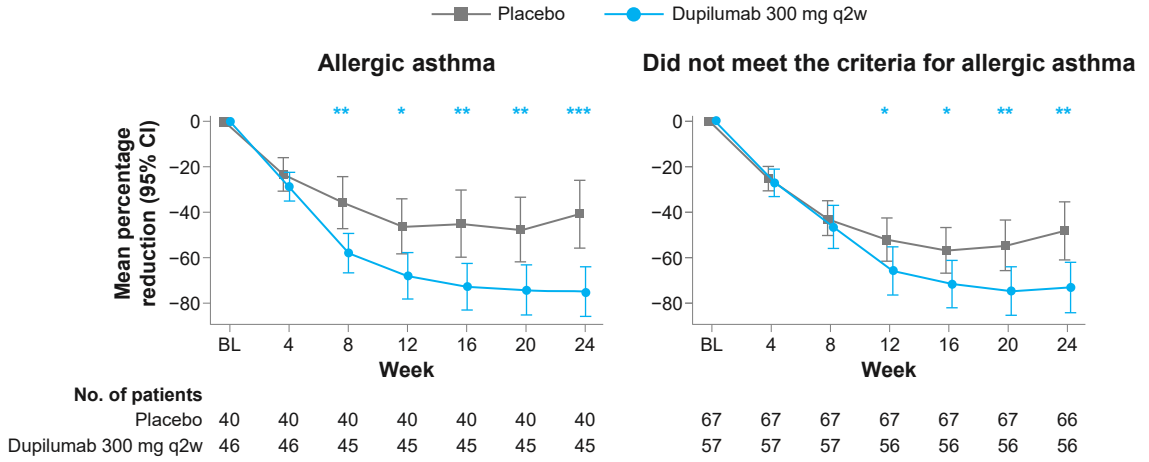

FIGURE 2. Percentage reduction in oral corticosteroids (OCS) from baseline over the course of VENTURE in OCS-dependent severe asthma patients meeting and not meeting criteria for allergic asthma (intent-to-treat population). *$P < .05$, **$P < .01$, ***$P < .001$, versus placebo. *BL*, Baseline; *CI*, confidence interval; *q2w*, every 2 weeks.

Patients with allergic asthma tended to be younger and had earlier age of asthma onset than patients without evidence of allergic asthma (Table I). Rates of atopic medical conditions were also higher in patients with allergic asthma. No clear differences in baseline type 2 biomarkers (except for total and allergen-specific IgE) were observed between groups of patients stratified by allergic status (Table E1, available in this article's Online Repository at www.jaci-inpractice.org).

Annualized severe exacerbation rate

In both studies, significantly lower rates of severe exacerbations were seen in the dupilumab versus placebo groups, irrespective of allergic status (Figure 1). In patients with allergic asthma, a 60% (risk ratio: 0.38; 95% confidence interval [CI]: 0.21, 0.77; $P = .0063$) reduction versus placebo was observed in P2B, and 72% (risk ratio: 0.28; 95% CI: 0.13, 0.58; $P = .0008$) in VENTURE; in patients without evidence of allergic asthma, these reductions were 86% (risk ratio: 0.14; 95% CI: 0.06, 0.34; $P < .0001$) and 45% (risk ratio: 0.55; 95% CI: 0.31, 0.96; $P = .0358$), respectively (Figure 1). Although the most pronounced disease burden (exacerbation rate) can be observed in patients with uncontrolled, moderate-to-severe asthma without evidence of allergic asthma (Figure 1, *A*), it is worth noting that exacerbation frequency in patients with OCS-dependent severe asthma is high irrespective of allergic status (Figure 1, *B*).

Effect of dupilumab on OCS use (VENTURE only)

Dupilumab versus placebo led to a greater reduction in OCS use from baseline to week 24 in both patients with (least-squares [LS] mean [standard error]: 73.1% [7.4] vs 40.6% [7.2]; $P = .0007$) and without (69.3% [6.7] vs 41.8% [6.1]; $P = .0015$) evidence of allergic asthma. When assessed over time, differences between the treatment groups were evident from week 12 onward for patients with or without evidence of allergic asthma.

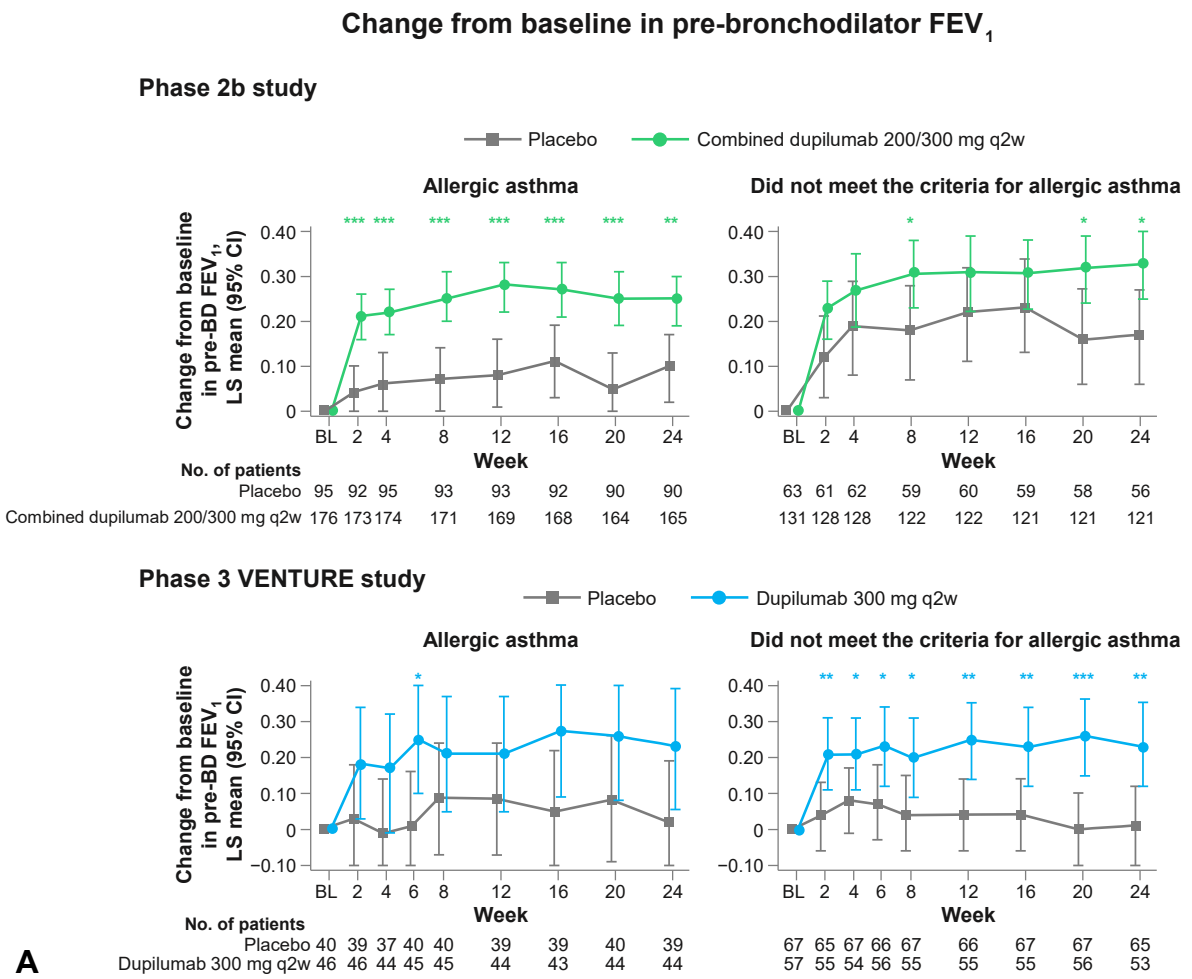

FIGURE 3. Change from baseline in (**A**) prebronchodilator FEV_1 and (**B**) prebronchodilator FEV_1/FVC ratio over time in patients meeting and not meeting criteria for allergic asthma (intent-to-treat population). $*P < .05$, $**P < .01$, $***P < .001$, versus placebo. *BD*, Bronchodilator; *BL*, baseline; *CI*, confidence interval; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *LS*, least squares; *q2w*, every 2 weeks.

Significant absolute reductions from baseline in OCS use were observed in patients with allergic asthma (LS mean difference [LSMD] vs placebo [95% CI]: 3.87 [1.65, 6.09] mg/d; $P = .0006$) and in patients without evidence of allergic asthma (LSMD [95% CI]: 2.27 [0.26, 4.28] mg/d; $P = .0268$) (Figure 2). Overall, the proportion of patients achieving at least 50% OCS dose reductions, reductions to <5 mg/d, maximum possible reductions per protocol, and no longer requiring OCS at week 24 were similar to patients treated with dupilumab regardless of allergic status, with significantly greater reductions for dupilumab versus placebo in all outcomes ($P < .05$; Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Lung function

In P2B, significantly greater improvements in pre-BD FEV_1 were observed for dupilumab versus placebo in patients with allergic asthma as early as week 2 (LSMD [95% CI]: 0.18 L [0.10, 0.26]; $P < .0001$); these were sustained until week 24 (LSMD [95% CI]: 0.15 L [0.06, 0.24]; $P = .0011$) (Figure 3, *A*). The difference between treatment groups in patients without evidence of allergic asthma was 0.16 L (0.04, 0.28) (LSMD [95% CI]; $P = .0104$) at week 24. In VENTURE, by the end of the treatment (week 24), dupilumab versus placebo improved pre-BD FEV_1 by 0.20 L (95% CI: −0.02, 0.43; $P = .0710$) in patients with allergic asthma. A significantly greater improvement from baseline in dupilumab versus placebo was observed in patients without evidence of allergic asthma as early as week 2, and this was sustained to week 24 (LSMD [95% CI]: 0.22 [0.07, 0.37] L; $P = .0046$) (Table E3, available in this article's Online Repository at www.jaci-inpractice.org).

The ratio of pre-BD FEV_1 to FVC is an important marker for airway obstruction. In P2B, significantly greater improvements in the pre-BD FEV_1/FVC ratio were observed for dupilumab versus placebo in patients with allergic asthma as early as week 2; these were sustained over the treatment period (week 24; LSMD [95% CI]: 1.89 [0.36, 3.43%]; $P = .0159$) (Figure 3, *B*). Numerically greater improvements between treatment groups were observed in patients without evidence of allergic asthma at week 2; a significant difference was seen by the end of the

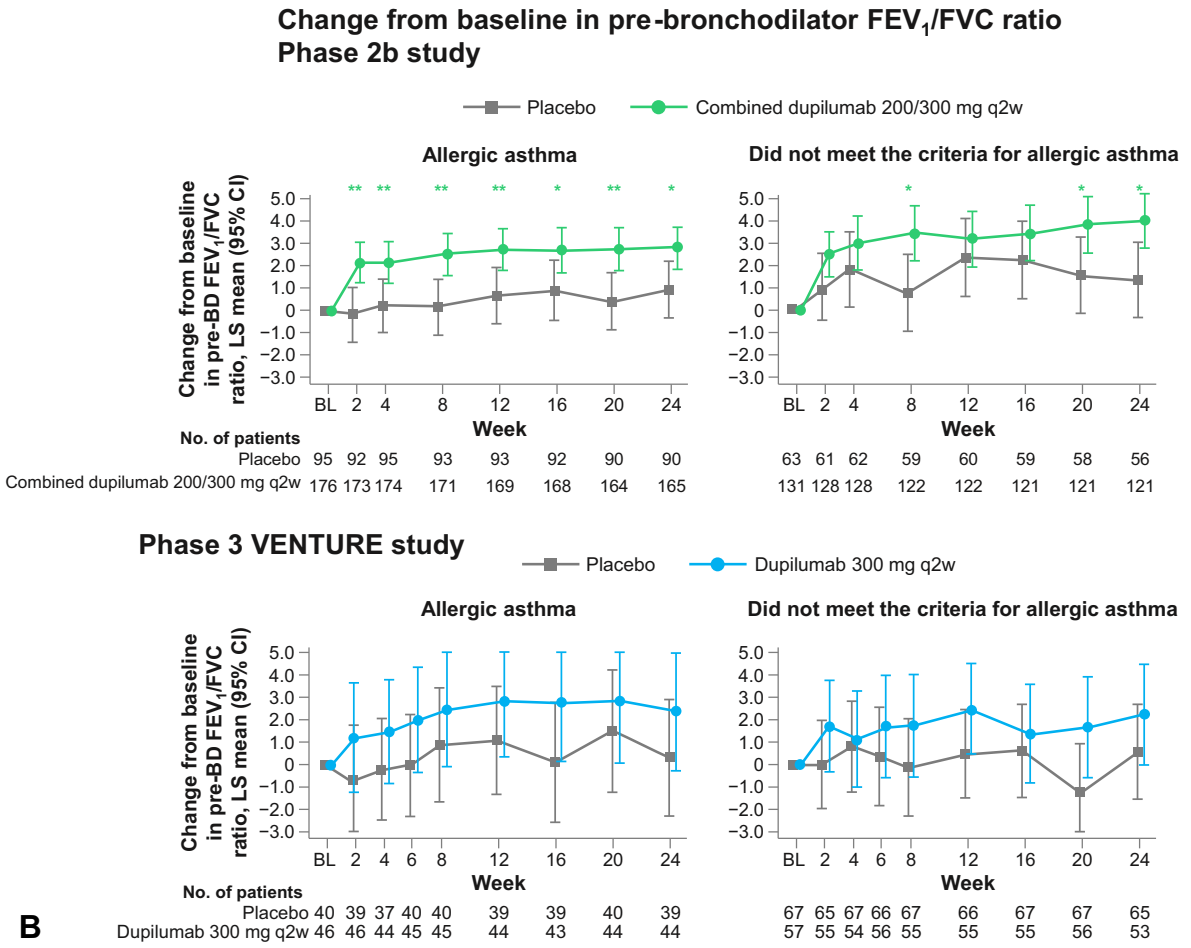

FIGURE 3. Continued

treatment (week 24; LSMD [95% CI]: 2.66 [0.64, 4.67]; $P = .0101$). In VENTURE, although not significant, numerically greater differences in dupilumab versus placebo were observed in the pre-BD FEV_1/FVC ratio between the treatment groups in patients with OCS-dependent severe asthma regardless of evidence of allergic asthma (Figure 3, *B*; see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Patient-reported outcomes

In P2B, significantly greater improvements from baseline in asthma control (ACQ-5 score) for dupilumab compared with placebo were seen from week 2 up to week 24 (LSMD [95% CI]: −0.35 [−0.60, −0.11]; $P = .0045$) in patients with allergic asthma; in patients without allergic asthma, numerically greater reductions were observed from week 2 until the end of the treatment (week 24; LSMD [95% CI]: −0.29 [−0.60, 0.03; $P = .0760$) (Figure 4, *A*; see Table E5 in this article's Online Repository at www.jaci-inpractice.org). In VENTURE, dupilumab- versus placebo-treated patients with allergic asthma showed significantly greater reductions from baseline in ACQ-5 score as early as week 2, and a mean score improvement >0.5 by week 24 (LSMD [95% CI]: −0.61 [−1.01, −0.22]; $P = .0029$). Numerically greater improvements were observed in patients without evidence of allergic asthma at week 24 (LSMD [95% CI]: −0.40 [−0.83, 0.02]; $P = .0600$) (Figure 4, *A*; see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

Similarly, significantly greater improvements from baseline in AQLQ global score for dupilumab compared with placebo were seen at week 24 in patients with allergic asthma in both P2B (LSMD [95% CI]: 0.34 [0.08, 0.61]; $P = .0112$) and VENTURE (LSMD [95% CI]: 0.43 [0.04, 0.81]; $P = .0315$). There were also numerically greater improvements in AQLQ scores in patients without evidence of allergic asthma in both studies at week 24 (P2B; LSMD [95% CI]: 0.35 [−0.01, 0.71], $P = .0548$; VENTURE: LSMD [95% CI]: 0.34 [−0.03, 0.70], $P = .0706$) (Figure 4, *B*; see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

Type 2 biomarkers

Dupilumab versus placebo significantly reduced total IgE from baseline as early as week 4 in patients with or without evidence of allergic asthma in both studies; these reductions were sustained over the 24-week treatment period (Figure 5, *A*; see Table E6 in this article's Online Repository at www.jaci-inpractice.org), with median change (95% CI) in total IgE from baseline in response to dupilumab treatment at week 24 in patients with (P2B: −152 IU/mL [−178, −119];

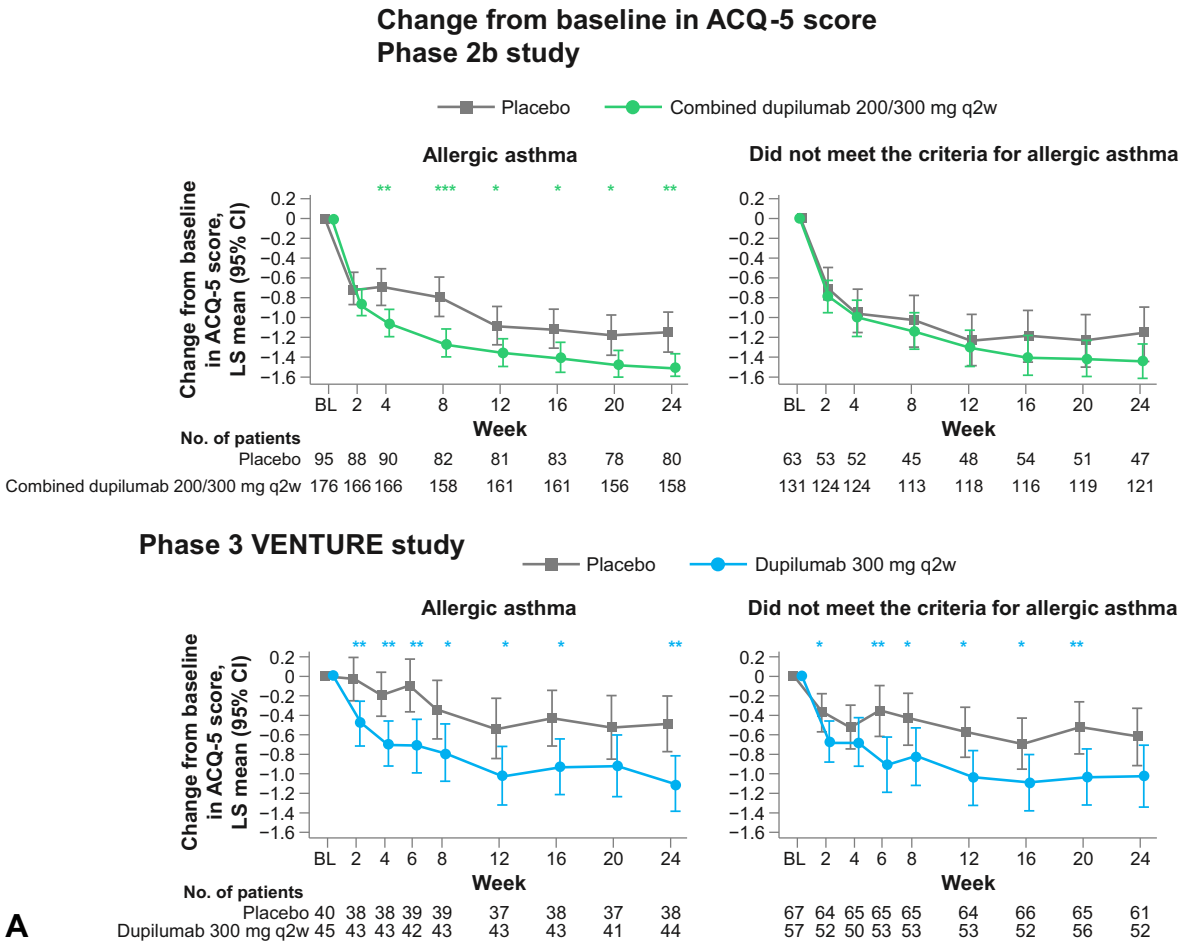

FIGURE 4. Change from baseline in (**A**) 5-item Asthma Control Questionnaire score and (**B**) Asthma Quality of Life Questionnaire score in patients meeting and not meeting criteria for allergic asthma (intent-to-treat population). $*P < .05$, $**P < .01$, $***P < .001$, versus placebo. *BL*, Baseline; *CI*, confidence interval; *LS*, least squares; *FEV_1*, forced expiratory volume in 1 second; *FVC*, forced vital capacity; *q2w*, every 2 weeks.

VENTURE: −189 IU/mL [−269, −111]) compared with those without evidence of allergic asthma (P2B: −45 IU/mL [−63.00, −9.00]; VENTURE to −67.5 IU/mL [−100, −42]) (all $P < .001$).

In patients with or without allergic asthma, significantly greater improvements in FeNO were seen for dupilumab versus placebo throughout both studies (Figure 5, *B*; see Table E7 in this article's Online Repository at www.jaci-inpractice.org).

Similarly, dupilumab rapidly reduced serum TARC levels, with a significant difference versus placebo from week 2 in P2B and week 4 in VENTURE for patients with or without evidence of allergic asthma (Figure 5, *C*; see Table E8 in this article's Online Repository at www.jaci-inpractice.org).

Specific IgE in patients with allergic asthma

In patients who met the criteria for allergic asthma and were positive for a given allergen at baseline, significant reductions versus placebo in allergen-specific IgE were observed at week 24 in both studies for all aeroallergens in VENTURE (Figure 6). Due to low patient numbers, results for *A. fumigatus* (placebo n = 5; dupilumab n = 7) and oriental cockroach (placebo n = 4; dupilumab n = 5) in P2B and for *C. herbarum/hormodendrum* (placebo n = 3; dupilumab n = 9) in VENTURE were excluded. Data from VENTURE indicated that differences for dupilumab versus placebo were seen during treatment from as early as week 4 for some aeroallergens (Figure E1, available in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

In this *post hoc* analysis of the P2B and phase 3 LIBERTY ASTHMA VENTURE studies, dupilumab reduced severe exacerbation rates; improved pre-BD FEV_1, pre-BD FEV_1/FVC ratio, asthma control, and asthma-related quality of life (QoL); and led to reductions in most type 2 biomarkers (IgE, FeNO, and TARC) in patients with or without evidence of allergic asthma. In addition, dupilumab significantly reduced OCS use versus placebo in patients with OCS-dependent severe asthma in VENTURE, irrespective of allergic status.

These results are consistent with those previously observed in patients with moderate-to-severe asthma enrolled in the QUEST study.[17] Findings from all 3 studies support the important roles of IL-4 and IL-13 in type 2 inflammation in patients with or without evidence of allergic asthma and the underlying impact of

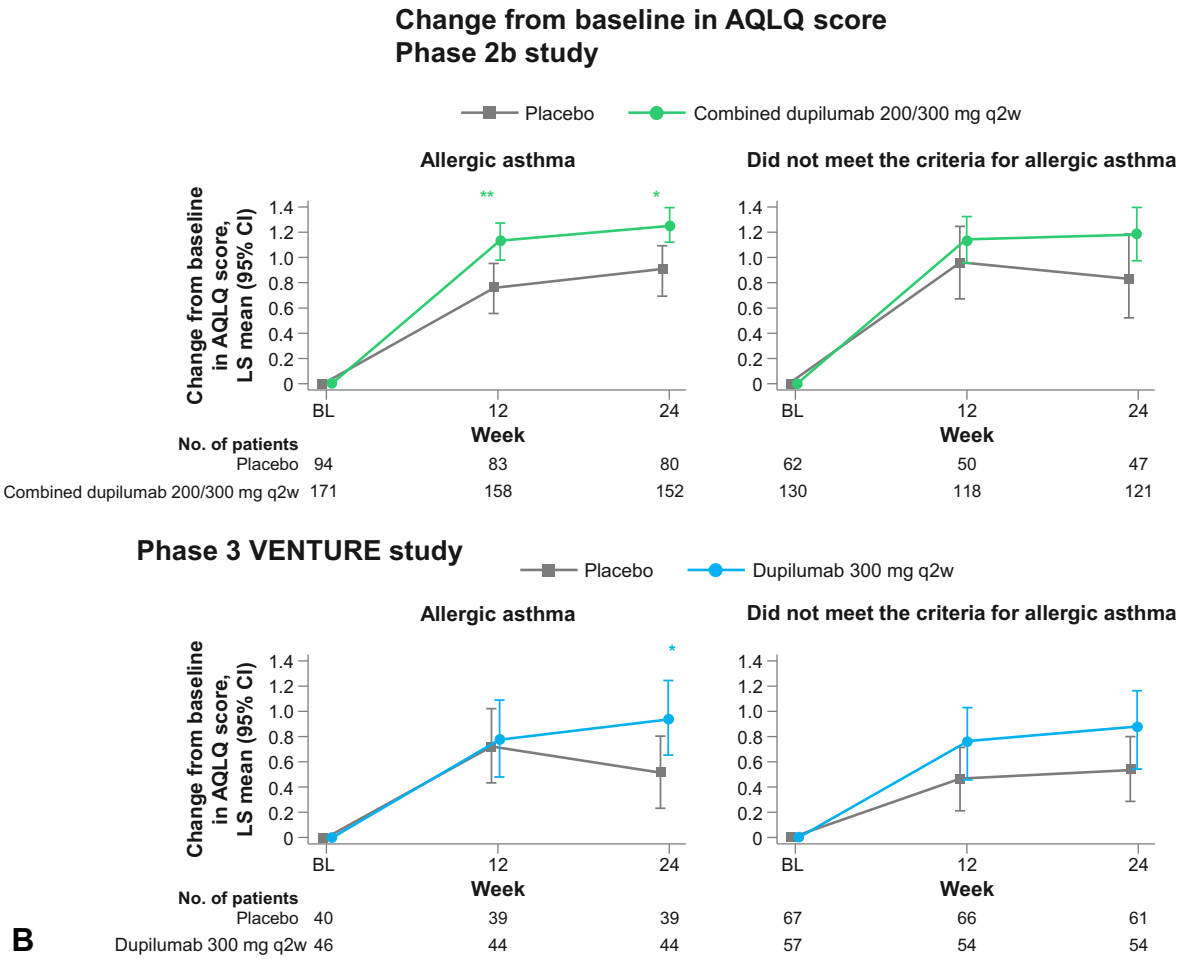

FIGURE 4. Continued

both cytokines in asthma pathogenesis.[21] In line with its mode of action, dupilumab suppressed both total IgE and allergen-specific IgE in patients with allergic asthma and also reduced IgE in patients not meeting allergic asthma criteria.[4,22] This is an important consideration, as the definition of allergic asthma for this analysis was based on a serum total IgE level ≥30 IU/mL and positive allergen-specific IgE for at least one of the tested aeroallergens (ie, specific IgE ≥0.35 kU/L). As not every potential allergen could be tested, the group without evidence of allergic asthma may have included patients with allergic asthma who were not sensitized to any of the allergens tested in the study. The reduction in serum IgE in patients with or without evidence of allergic asthma continued progressively throughout the treatment period, indicating a benefit of longer-term treatment with dupilumab. The observed efficacy in patients both with and without allergic asthma indicates that the baseline IgE level is not a relevant biomarker when considering the suitability of dupilumab for individual patients, with key biomarkers being blood eosinophil counts and FeNO.[23]

Although significant improvements in rates of severe exacerbations were observed in both studies in patients with or without evidence of allergic asthma and in multiple other outcome measures for certain subgroups, numerical differences versus placebo were observed in change from baseline FEV_1 in VENTURE patients with allergic asthma, but these did not reach statistical significance, possibly due to the relatively small sample size and the associated reduction in statistical power. Similarly, although there was a trend toward improvement versus placebo in ACQ-5 score in patients without evidence of allergic asthma in P2B, these differences were not statistically significant. At week 24, significant improvements versus placebo in asthma-related QoL were only observed in patients with allergic asthma. As with the other measures, there was a trend favoring dupilumab treatment versus placebo in patients without evidence of allergic asthma. The benefits of dupilumab on asthma control and health-related QoL in patients in P2B and VENTURE have been demonstrated for the overall study populations previously.[24,25] We hypothesize that determination of asthma control and QoL using a different test (such as the St Georges Respiratory Questionnaire with increased sensitivity for detecting changes) and a larger sample size could have resulted in statistical significance in the analysis of these patients with severe asthma.

The results of this *post hoc* analysis, and that of a similar analysis in patients with moderate-to-severe uncontrolled asthma from the phase 3 QUEST study,[17] highlight the benefits of reducing underlying type 2 inflammation in those patients, regardless of their allergic status. Another *post hoc* analysis of QUEST also showed that dupilumab was effective in patients

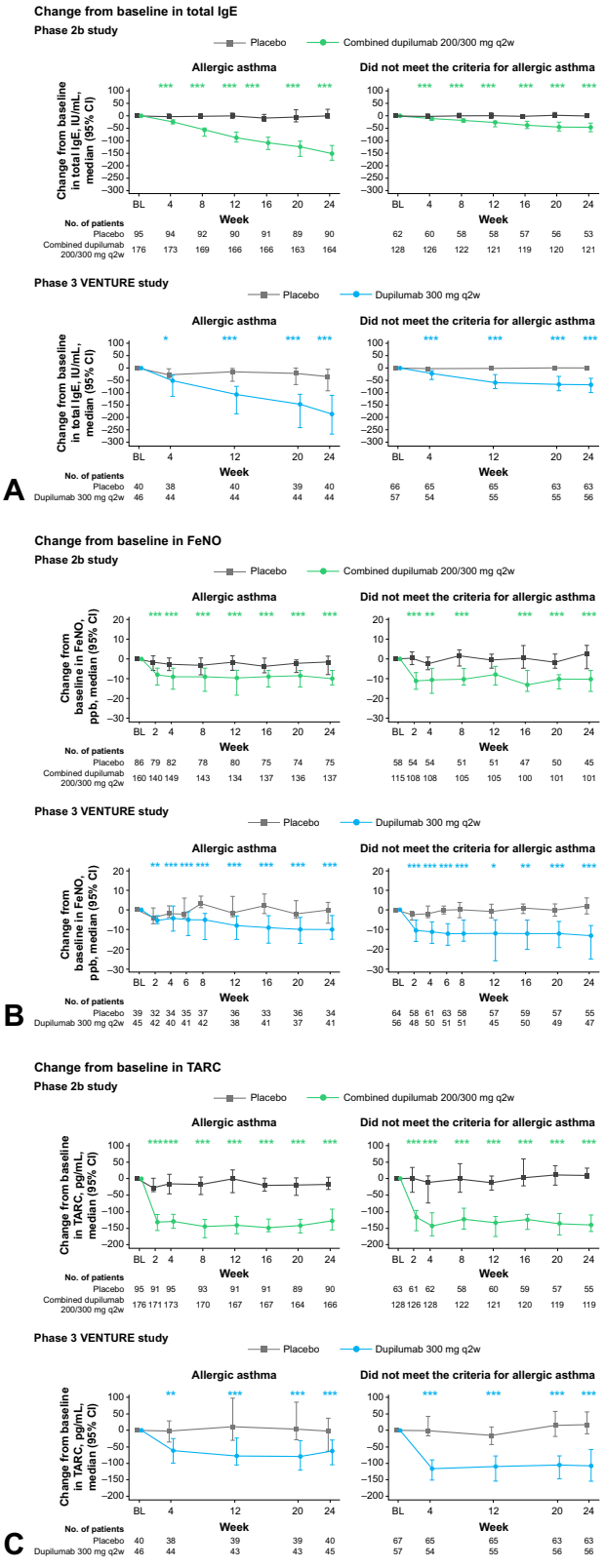

FIGURE 5. Change from baseline in (**A**) total IgE, (**B**) FeNO, and (**C**) TARC in patients meeting and not meeting criteria for allergic asthma (exposed population). $*P < .05$, $**P < .01$, $***P < .001$, versus placebo. *BL*, Baseline; *CI*, confidence interval; *FeNO*, fractional exhaled nitric oxide; *TARC*, thymus and activation-regulated chemokine; *q2w*, every 2 weeks.

FIGURE 6. Median percent changes from baseline at week 24 with 95% confidence intervals (CI) in specific IgE in the allergic asthma subgroup with baseline serum specific-IgE levels ≥0.35 kU/mL for each allergen (exposed population) in the (**A**) phase 2b dose ranging study and in the (**B**) VENTURE study. $*P < .05$, $**P < .01$, $***P < .001$, versus placebo. Due to low patient numbers, in P2B, results for *Aspergillus fumigatus* (placebo n = 5; dupilumab n = 7) and oriental cockroach (placebo n = 4; dupilumab n = 5), and in VENTURE, results for *Cladosporium herbarum/hormodendrum* (placebo n = 3; dupilumab n = 9) were excluded. *q2w*, every 2 weeks.

with uncontrolled moderate-to-severe asthma and comorbid perennial allergic rhinitis.[26] The strengths of this analysis include large study populations from randomized, double-blind, placebo-controlled clinical trials, and inclusion of patients irrespective of baseline IgE levels. As this analysis was performed *post hoc*, the trials were not specifically designed for the assessment of these subgroups and are subject to the same potential confounders and biases as other *post hoc* analyses. Criteria for allergic asthma were based on threshold total serum IgE level and specific IgE levels against at least one of the tested aeroallergens. As the test panel did not include all allergens to which patients with allergic asthma may be sensitized, some patients enrolled in the 2 studies who were allergic to other aeroallergens may have been misclassified into the subgroup without evidence of allergic asthma.

In summary, treatment with dupilumab reduced rates of severe exacerbations and improved lung function, asthma control, and QoL in patients with or without evidence of allergic asthma. Biomarkers of type 2 inflammation were reduced in both subgroups across the studies. The findings from this analysis, and a similar analysis of a separate study in patients with moderate-to-severe uncontrolled asthma, indicate that dupilumab is beneficial in reducing the clinical burden of disease in patients both with and without evidence of allergic asthma.

Acknowledgments

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TABLE E1. Baseline-specific IgE allergen concentrations in patients with and without evidence of an allergic asthma phenotype

	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
IgE allergens	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 63)	Combined dupilumab (N = 131)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N = 57)
Aspergillus fumigatus								
≥0.35 kU/L at BL, n (%)	5 (5.3)	7 (4.0)	0	0	17 (42.5)	15 (32.6)	0	0
kU/L, median (Q1-Q3)	0.05 (0.05-1.33)	0.05 (0.05-0.40)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.12 (0.05-0.91)	0.05 (0.05-0.49)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
Alternaria tenuis/alternata								
≥0.35 kU/L at BL, n (%)	19 (20.0)	37 (21.0)	4 (6.3)	0	8 (20.0)	12 (26.1)	0	0
kU/L, median (Q1:Q3)	0.05 (0.05-0.16)	0.05 (0.05-0.18)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.05 (0.05-0.19)	0.05 (0.05-0.35)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
Cladosporium herbarum/hormodendrum								
≥0.35 kU/L at BL, n (%)	8 (8.4)	25 (14.2)	2 (3.2)	0	3 (7.5)	9 (19.6)	0	0
kU/L, median (Q1-Q3)	0.05 (0.05-0.11)	0.05 (0.05-0.15)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.05 (0.05-0.16)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
Dermatophagoides farinae								
≥0.35 kU/L at BL, n (%)	46 (48.4)	82 (46.6)	1 (1.6)	3 (2.3)	13 (32.5)	17 (37.0)	1 (1.5)	0
kU/L, median (Q1-Q3)	1.38 (0.21-14.90)	1.35 (0.18-8.48)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	1.19 (0.15-9.08)	0.48 (0.05-2.03)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
Dermatophagoides pteronyssinus								
≥0.35 kU/L at BL, n (%)	25 (26.3)	46 (26.1)	0	1 (0.8)	12 (30.0)	12 (26.1)	0	0
kU/L, median (Q1-Q3)	4.08 (0.55-31.60)	3.46 (0.68-21.50)	0.05 (0.05-0.13)	0.05 (0.05-0.11)	1.69 (0.05-20.70)	1.66 (0.22-19.00)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
Cat dander								
≥0.35 kU/L at BL, n (%)	54 (56.8)	95 (54.0)	1 (1.6)	3 (2.3)	15 (37.5)	21 (45.7)	1 (1.5)	0
kU/L, median (Q1-Q3)	0.65 (0.05-5.23)	0.59 (0.05-3.89)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.13 (0.05-2.87)	0.18 (0.05-5.09)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
Dog dander								
≥0.35 kU/L at BL, n (%)	51 (53.7)	100 (56.8)	1 (1.6)	2 (1.5)	19 (47.5)	26 (56.5)	1 (1.5)	0
kU/L, median (Q1-Q3)	0.49 (0.10-2.52)	0.54 (0.08-4.10)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.41 (0.05-2.02)	0.51 (0.10-5.26)	0.05 (0.05-0.05)	0.05 (0.05-0.05)
German cockroach								
≥0.35 kU/L at BL, n (%)	28 (29.5)	48 (27.3)	0	0	–	–	–	–
kU/L, median (Q1-Q3)	0.22 (0.05-0.51)	0.16 (0.05-0.60)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	–	–	–	–
Oriental cockroach								
≥0.35 kU/L at BL, n (%)	4 (4.2)	5 (2.8)	0	0	11 (27.5)	18 (39.1)	0	0
kU/L, median (Q1-Q3)	0.05 (0.05-0.37)	0.05 (0.05-0.11)	0.05 (0.05-0.05)	0.05 (0.05-0.05)	0.09 (0.05-0.40)	0.23 (0.05-1.22)	0.05 (0.05-0.05)	0.05 (0.05-0.05)

BL, Baseline; *q2w*; every 2 weeks.

TABLE E2. Percent reduction in OCS use from baseline to week 24 (VENTURE) in OCS-dependent severe asthma patients meeting and not meeting criteria for allergic asthma (ITT population)

	Allergic asthma		Did not meet the criteria for allergic asthma	
OCS related outcomes	**Placebo (n = 40)**	**Dupilumab 300 mg q2w (n = 46)**	**Placebo (n = 67)**	**Dupilumab 300 mg q2w (n = 57)**
Proportion of patients achieving reduction in OCS at week 24				
Patients achieving a reduction of OCS dose to ≥50% (%)	47.5	81.5	56.7	80.6
Adjusted probability of achieving the reduction (95% CI)	0.46 (0.30, 0.63)	0.80 (0.63, 0.90)	0.51 (0.37, 0.64)	0.82 (0.68, 0.91)
Odds ratio vs placebo (95% CI)	–	4.63 (1.69, 12.71)	–	4.43 (1.76, 11.13)
P value		.0029		.0015
Patients achieving a reduction of OCS dose to <5 mg/d (%)	32.5	72.8	40.3	72.9
Adjusted probability of achieving the reduction (95% CI)	0.28 (0.15, 0.46)	0.69 (0.50, 0.83)	0.33 (0.21, 0.47)	0.70 (0.55, 0.82)
Odds ratio vs placebo (95% CI)	–	5.77 (2.08, 15.98)	–	4.84 (2.03, 11.53)
P value		.0008		.0004
Risk ratio vs placebo (95% CI)	–	1.93 (2.08, 15.98)	–	1.68 (1.2, 2.36)
P value		.0008		.0027
Patients achieving their maximum possible reduction of OCS dose per protocol (%)	25.0	52.8	32.8	52.8
Adjusted probability of achieving the reduction (95% CI)	0.22 (0.11, 0.39)	0.46 (0.29, 0.64)	0.27 (0.17, 0.41)	0.48 (0.34, 0.63)
Odds ratio vs placebo (95% CI)	–	3.08 (1.16, 8.18)	–	2.48 (1.11, 5.54)
P value		.0240		.0266
Risk ratio vs placebo (95% CI)	–	1.91 (1.06, 3.43)	–	1.44 (0.95, 2.17)
P value		.0313		.0826
Patients no longer requiring OCS at week 24 in patients with baseline OCS dose ≤30 mg/d (%)	25.0	52.8	31.8	52.8
Adjusted probability of achieving the reduction (95% CI)	0.22 (0.11, 0.39)	0.46 (0.29, 0.64)	0.26 (0.16, 0.39)	0.48 (0.33, 0.64)
Odds ratio vs placebo (95% CI)	–	3.08 (1.16, 8.18)	–	2.71 (1.18, 6.21)
P value		.0240		.0188
Risk ratio vs placebo (95% CI)	–	1.91 (1.06, 3.43)	–	1.43 (0.95, 2.16)
P value		.0313		.0851

CI, Confidence interval; *ITT,* intention-to-treat; *OCS*, oral corticosteroid; *q2w*, every 2 weeks

TABLE E3. Change from baseline in FEV_1 at weeks 2 and 24 in patients meeting and not meeting criteria for allergic asthma (ITT population)

	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
FEV1 related outcomes	**Placebo (N = 95)**	**Combined dupilumab (N = 176)**	**Placebo (N = 63)**	**Combined dupilumab (N = 131)**	**Placebo (N = 40)**	**Dupilumab 300 mg q2w (N = 46)**	**Placebo (N = 67)**	**Dupilumab 300 mg q2w (N = 57)**
FEV_1 at BL (L), mean (SD)	1.90 (0.58)	1.90 (0.57)	1.71 (0.49)	1.72 (0.45)	1.62 (0.66)	1.59 (0.46)	1.63 (0.58)	1.49 (0.58)
Change from baseline in FEV_1 at week 2								
	n = 92	**n = 173**	**n = 61**	**n = 128**	**n = 39**	**n = 46**	**n = 65**	**n = 55**
LS mean (95% CI)	0.04 (−0.03, 0.10)	0.21 (0.16, 0.26)	0.12 (0.03, 0.21)	0.23 (0.16, 0.29)	0.03 (−0.13, 0.18)	0.18 (0.02, 0.34)	0.04 (−0.06, 0.13)	0.21 (0.11, 0.31)
LS mean difference vs placebo (95% CI)	—	0.18 (0.10, 0.26)	—	0.10 (0.00, 0.21)	—	0.15 (−0.06, 0.36)	—	0.17 (0.04, 0.30)
P value vs placebo		<.0001		.0564		.1517		.0097
Change from baseline in FEV_1 at week 24								
	n = 90	**n = 165**	**n = 56**	**n = 121**	**n = 39**	**n = 44**	**n = 65**	**n = 53**
LS mean (95% CI)	0.10 (0.02, 0.17)	0.25 (0.19, 0.30)	0.17 (0.06, 0.27)	0.33 (0.25, 0.40)	0.02 (−0.14, 0.19)	0.23 (0.06, 0.39)	0.01 (−0.09, 0.12)	0.23 (0.12, 0.35)
LS mean difference vs placebo (95% CI)	—	0.15 (0.06, 0.24)	—	0.16 (0.04, 0.28)	—	0.20 (−0.02, 0.43)	—	0.22 (0.07, 0.37)
P value vs placebo		.0011		.0104		.0710		.0046

BL, Baseline; *CI*, confidence interval; *FEV_1*, fractional exhaled volume in 1 second; ITT, intention-to-treat; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.

TABLE E4. Change from baseline in FEV_1/FVC at weeks 2 and 24 in patients meeting and not meeting criteria for allergic asthma

FEV1/FVC related outcomes	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 63)	Combined dupilumab (N = 131)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N=57)
FEV_1/FVC at BL (%), mean (SD)	64.07 (9.48)	65.20 (9.49)	64.12 (10.51)	63.33 (9.75)	58.26 (13.02)	61.43 (9.78)	58.91 (10.23)	56.71 (11.41)
Change from baseline in FEV_1 /FVC at week 2								
	n = 92	n = 173	n = 61	n = 128	n = 39	n = 46	n = 66	n = 55
LS mean (95% CI)	−0.19 (−1.41, 1.02)	2.16 (1.25, 3.06)	0.93 (−0.47, 2.33)	2.51 (1.49, 3.52)	−0.71 (−3.14, 1.73)	1.18 (−1.28,3.63)	−0.01 (−1.97, 1.95)	1.70 (−0.36, 3.75)
LS mean difference vs placebo (95% CI)	—	2.35 (0.88, 3.82)	—	1.58 (−0.06, 3.21)	—	1.88 (−1.39, 5.15)	—	1.71 (−0.95, 4.37)
P value vs placebo		.0018		.0588		.2559		.2059
Change from baseline in FEV_1/FVC at week 24								
	n = 90	n = 165	n = 56	n = 121	n = 39	n = 44	n = 65	n = 53
LS mean (95% CI)	0.93 (−0.34, 2.20)	2.82 (1.88, 3.77)	1.36 (−0.34, 3.06)	4.02 (2.80, 5.23)	0.29 (−2.30, 2.88)	2.33 (−0.29, 4.94)	0.54 (−1.57, 2.66)	2.21 (−0.03, 4.45)
LS mean difference vs placebo (95% CI)	—	1.89 (0.36, 3.43)	—	2.66 (0.64, 4.67)	—	2.04 (−1.47, 5.54)	—	1.67 (−1.25, 4.58)
P value vs placebo		.0159		.0101		.2509		.2599

BL, Baseline; *CI*, confidence interval; *FEV_1*, fractional exhaled volume in 1 second; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.

TABLE E5. Change from baseline in ACQ-5* and AQLQ† scores at weeks 2 and 24 in patients meeting and not meeting criteria for allergic asthma

	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
ACQ5 and AQLQ related outcomes	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 63)	Combined dupilumab (N = 131)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N = 57)
ACQ-5 at BL, mean (SD)	2.62 (0.80)	2.73 (0.82)	2.79 (0.78)	2.82 (0.83)	2.52 (1.13)	2.40 (1.22)	2.62 (1.07)	2.43 (1.26)
Change from baseline in ACQ-5 at week 2								
	n = 88	n = 166	n = 53	n = 124	n = 38	n = 43	n = 64	n = 52
LS mean (95% CI)	−0.71 (−0.89, −0.54)	−0.85 (−0.98, −0.72)	−0.71 (−0.94, −0.49)	−0.78 (−0.94, −0.62)	−0.03 (−0.26, 0.19)	−0.48 (−0.72, −0.25)	−0.37 (−0.56, −0.18)	−0.67 (−0.88, −0.46)
LS mean difference vs placebo (95% CI)	—	−0.14 (−0.35, 0.08)	—	−0.07 (−0.33, 0.20)	—	−0.45 (−0.76, −0.14)	—	−0.30 (−0.56, −0.04)
P value vs placebo		.2099		.6236		.0047		.0268
Change from baseline in ACQ-5 at week 24								
	n = 80	n = 158	n = 47	n = 121	n = 38	n = 44	n = 61	n = 52
LS mean (95% CI)	−1.14 (−1.35, −0.94)	−1.50 (−1.65, −1.35)	−1.15 (−1.42, −0.88)	−1.43 (−1.62, −1.25)	−0.49 (−0.78, −0.20)	−1.11 (−1.39, −0.82)	−0.62 (−0.91, −0.33)	−1.02 (−1.34, −0.70)
LS mean difference vs placebo (95% CI)	—	−0.35 (−0.60, −0.11)	—	−0.29 (−0.60, 0.03)	—	−0.61 (−1.01, −0.22)	—	−0.40 (−0.83, 0.02)
P value vs placebo		.0045		.0760		.0029		.0600
AQLQ at BL, mean (SD)	4.24 (1.11)	4.10 (1.13)	3.93 (1.07)	3.79 (1.12)	4.34 (1.16)	4.35 (1.21)	4.30 (1.10)	4.40 (1.26)
Change from baseline in AQLQ at week 12								
	n = 84	n = 163	n = 51	n = 118	n = 39	n = 44	n = 66	n = 54
LS mean (95% CI)	0.76 (0.56, 0.95)	1.13 (0.98, 1.27)	0.95 (0.67, 1.24)	1.13 (0.93, 1.32)	0.72 (0.43, 1.02)	0.78 (0.48, 1.09)	0.46 (0.21, 0.71)	0.76 (0.48, 1.03)
LS mean difference vs placebo (95% CI)	—	0.37 (0.14, 0.61)	—	0.17 (−0.15, 0.49)	—	0.06 (−0.34, 0.46)	—	0.30 (−0.05, 0.64)
P value vs placebo		.0021		.2850		.7626		.0909
Change from baseline in AQLQ at week 24								
	n = 80	n = 152	n = 47	n = 121	n = 39	n = 44	n = 61	n = 54
LS mean (SE)	0.91 (0.69, 1.13)	1.25 (1.09, 1.41)	0.83 (0.52, 1.14)	1.18 (0.97, 1.39)	0.52 (0.23, 0.80)	0.94 (0.65, 1.24)	0.54 (0.28, 0.80)	0.88 (0.59, 1.16)
LS mean difference vs placebo (95% CI)	—	0.34 (0.08, 0.61)	—	0.35 (−0.01, 0.71)	—	0.43 (0.04, 0.81)	—	0.34 (−0.03, 0.70)
P value vs placebo		.0112		.0548		.0315		.0706

ACQ-5, 5-Item Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *BL*, baseline; *CI*, confidence interval; *LS*, least squares; *q2w*, every 2 weeks; *SD*, standard deviation; *SE*, standard error.
*ACQ-5 scores range between 0 (totally controlled) and 6 (severely uncontrolled).
†AQLQ(S) scores are rated on a 7-point Likert-like scale (7 = not impaired at all − 1 = severely impaired).

TABLE E6. Change from baseline in serum IgE at weeks 4 and 24 in patients meeting and not meeting criteria for allergic asthma (exposed population)

	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
Serum IgE related outcomes	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 62)	Combined dupilumab (N = 128)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N = 57)
BL serum IgE (IU/mL), mean (SD)	569.73 (896.15)	552.11 (682.19)	188.82 (244.39)	166.70 (279.91)	876.58 (1296.01)	699.87 (875.08)	153.92 (215.71)	220.61 (246.14)
Baseline, median (95% CI)	302.00 (222.0, 367.0)	293.00 (249.0, 370.0)	94.50 (57.0, 147.0)	88.00 (57.0, 113.0)	340.00 (262.0, 662.0)	305.00 (195.0, 611.0)	68.00 (38.0, 106.0)	131.00 (94.0, 182.0)
Q1-Q3	138.0-523.0	129.5-646.0	31.0-216.0	25.5-174.5	187.0-820.0	150.0-941.0	23.0-164.0	48.0-244.0
Change from baseline in total IgE at week 4 (IU/mL)								
	n = 94	n = 173	n = 61	n = 126	n = 38	n = 44	n = 65	n = 54
Median change from BL (95% CI)	−2.00 (−8.00, 8.00)	−23.00 (−32.00, −16.00)	0.50 (−2.00, 4.00)	−10.50 (−17.00, −6.00)	−27.50 (−42.00, −2.00)	−50.00 (−117.00, −29.00)	−3.00 (−9.00, −1.00)	−21.50 (−47.00, −11.00)
Q1-Q3	−26.0 to 29.0	−85.0 to −3.0	−5.0 to 20.0	−32.0 to −2.0	−81.0 to 10.0	−162.0 to −15.5	−22.0 to 3.0	−72.0 to −3.0
P value vs placebo		<.0001		<.0001		.0213		.0009
Change from baseline in total IgE at week 24 (IU/mL)								
	n = 90	n = 164	n = 53	n = 121	n = 40	n = 44	n = 63	n = 56
Median change from BL (95% CI)	1.50 (−9.00, 27.00)	−152.00 (−178.00, −119.00)	0.00 (−3.00, 8.00)	−45.00 (−63.00, −29.00)	−35.50 (−93.00, −6.00)	−189.00 (−269.00, −111.00)	0.00 (−3.00, 3.00)	−67.50 (−100.00, −42.00)
Q1-Q3	−41.0 to 86.0	−327.5 to −64.0	−6.0 to 17.0	−101.0 to −11.0	−170.5 to 0.0	−544.0 to −76.0	−16.0 to 15.0	−161.0 to −21.0
P value vs placebo		<.0001		<.0001		<.0001		<.0001

BL, Baseline; *CI*, confidence interval; *Q*, quartile; *q2w*, every 2 weeks; *SD*, standard deviation.

TABLE E7. Change from baseline in FeNO at weeks 2 and 24 in patients meeting and not meeting criteria for allergic asthma (exposed population)

	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic asthma		Did not meet criteria for allergic asthma		Allergic asthma		Did not meet criteria for allergic asthma	
FeNO related outcomes	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 63)	Combined dupilumab (N = 128)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N = 57)
BL FeNO (ppb), mean (SD)	42.27 (38.56)	40.18 (37.62)	34.03 (27.89)	35.91 (26.29)	39.64 (27.56)	27.71 (18.95)	39.61 (37.76)	41.86 (32.89)
Baseline, median (95% CI)	32.00 (26.00, 37.00)	27.50 (23.00, 33.00)	24.50 (20.00, 30.00)	30.00 (25.00, 35.00)	30.00 (24.00, 44.00)	23.00 (16.00, 30.00)	23.50 (18.00, 41.00)	36.50 (25.00, 44.00)
Q1-Q3	16.0-49.0	16.0-53.0	16.0-42.0	16.0-47.0	21.0-55.0	13.0-39.0	14.5-57.5	17.5-54.5
Change from baseline in FeNO at week 2 (ppb)								
	n = 79	n = 140	n = 54	n = 108	n = 32	n = 42	n = 58	n = 48
Median change from BL (95% CI)	−2.00 (−6.00, 1.00)	−8.00 (−13.00, −5.00)	0.00 (−3.00, 3.00)	−11.00 (−15.00, −7.00)	−4.00 (−7.00, 1.00)	−5.50 (−10.00, −3.00)	−2.00 (−5.00, −1.00)	−10.50 (−16.00, −5.00)
Q1-Q3	−14.0 to 5.0	−29.0 to −1.0	−9.0 to 8.0	−25.0 to −1.0	−9.5 to 2.5	−23.0 to 0.0	−7.0 to 2.0	−31.0 to −3.5
P value vs placebo		<.0001		<.0001		.0032		.0004
Change from baseline in FeNO at week 24 (pbb)								
	n = 75	n = 137	n = 45	n = 101	n = 34	n = 41	n = 55	n = 47
Median change from BL (95% CI)	−2.00 (−8.00, 1.00)	−10.00 (−13.00, −6.00)	2.00 (−5.00, 6.00)	−10.00 (−16.00, −6.00)	0.00 (−7.00, 4.00)	−10.00 (−15.00, −3.00)	2.00 (−2.00, 6.00)	−13.00 (−25.00, −8.00)
Q1-Q3	−18.0 to 5.0	−26.0 to −2.0	−10.0 to 10.0	−29.0 to 0.0	−10.0 to 7.0	−21.0 to 0.0	−10.0 to 10.0	−35.0 to −3.00
P value vs placebo		<.0001		<.0001		.0002		<.0001

BL, Baseline; *CI*, confidence interval; *FeNO*, fractional exhaled nitric oxide; *Q*, quartile; *q2w*, every 2 weeks; *SD*, standard deviation.

TABLE E8. Change from baseline in serum TARC at weeks 4 and 24 in patients meeting and not meeting criteria for allergic asthma (exposed population)

	Phase 2B (24 wk)				Phase 3 VENTURE (24 wk)			
	Allergic phenotype		Did not meet criteria for allergic phenotype		Allergic phenotype		Did not meet criteria for allergic phenotype	
Serum TARC related outcomes	Placebo (N = 95)	Combined dupilumab (N = 176)	Placebo (N = 63)	Combined dupilumab (N = 128)	Placebo (N = 40)	Dupilumab 300 mg q2w (N = 46)	Placebo (N = 67)	Dupilumab 300 mg q2w (N = 57)
BL Serum TARC (pg/mL), mean (SD)	726.70 (1782.84)	493.96 (305.67)	414.64 (285.06)	607.74 (1158.21)	492.77 (884.42)	371.80 (365.48)	388.80 (486.58)	368.19 (233.51)
Baseline, median (95% CI)	377.28 (343.64, 439.89)	423.31 (383.28, 474.30)	330.58 (287.06, 457.90)	404.25 (373.88, 459.66)	291.00 (216.00, 356.00)	234.50 (173.00, 345.00)	281.50 (233.00, 313.00)	275.00 (257.00, 331.00)
Q1-Q3	267.87-577.82	305.64-641.77	228.79-502.92	285.60-596.63	161.00-550.00	134.00-475.00	170.00-402.00	232.00-448.00
Change from baseline in TARC at week 4 (pg/mL)								
	n = 95	n = 173	n = 62	n = 128	n = 38	n = 44	n = 65	n = 54
Median change from BL (95% CI)	−15.41 (−45.61, 13.64)	−129.31 (−149.60, −108.39)	−11.50 (−73.37, 8.39)	−144.18 (−171.94, −103.93)	−2.50 (−17.00, 42.00)	−60.50 (−100.20, −26.00)	−2.00 (−35.00, 28.00)	−115.50 (−151.00, −90.00)
Q1-Q3	−126.05 to 51.89	−225.43 to−61.24	−120-19 to 49.46	−227.73 to−48.77	−61.00 to 97.00	−180.60 to −13.90	−56.00 to 62.00	−216.00 to −61.00
P value vs placebo		<.0001		.0003		0.0010		<.0001
Change from baseline in TARC at week 24 (pg/mL)								
	n = 90	n = 166	n = 55	n = 119	n = 40	n = 45	n = 63	n = 56
Median change from BL (95% CI)	−17.65 (−32.70, 11.84)	−129.21 (−154.42, −91.76)	9.54 (0.84, 31.96)	−139.78 (−160.35, −109.58)	−2.50 (−63.00, 36.00)	−62.00 (−104.80, −29.50)	17.00 (−10.00, 56.10)	−107.50 (−155.00, −58.00)
Q1-Q3	−120.23 to 80.43	−224.96 to −48.78	−49.53 to 115.69	−226.33 to −49.69	−97.50 to 50.45	−137.00 to −20.50	−65.00 to 91.00	−193.75 to −25.50
P value vs placebo		<.0001		<.0001		.0007		<.0001

BL, Baseline; *CI*, confidence interval; *Q*, quartile; *q2w*, every 2 weeks; *SD*, standard deviation; *TARC*, thymus and activation-regulated chemokine.

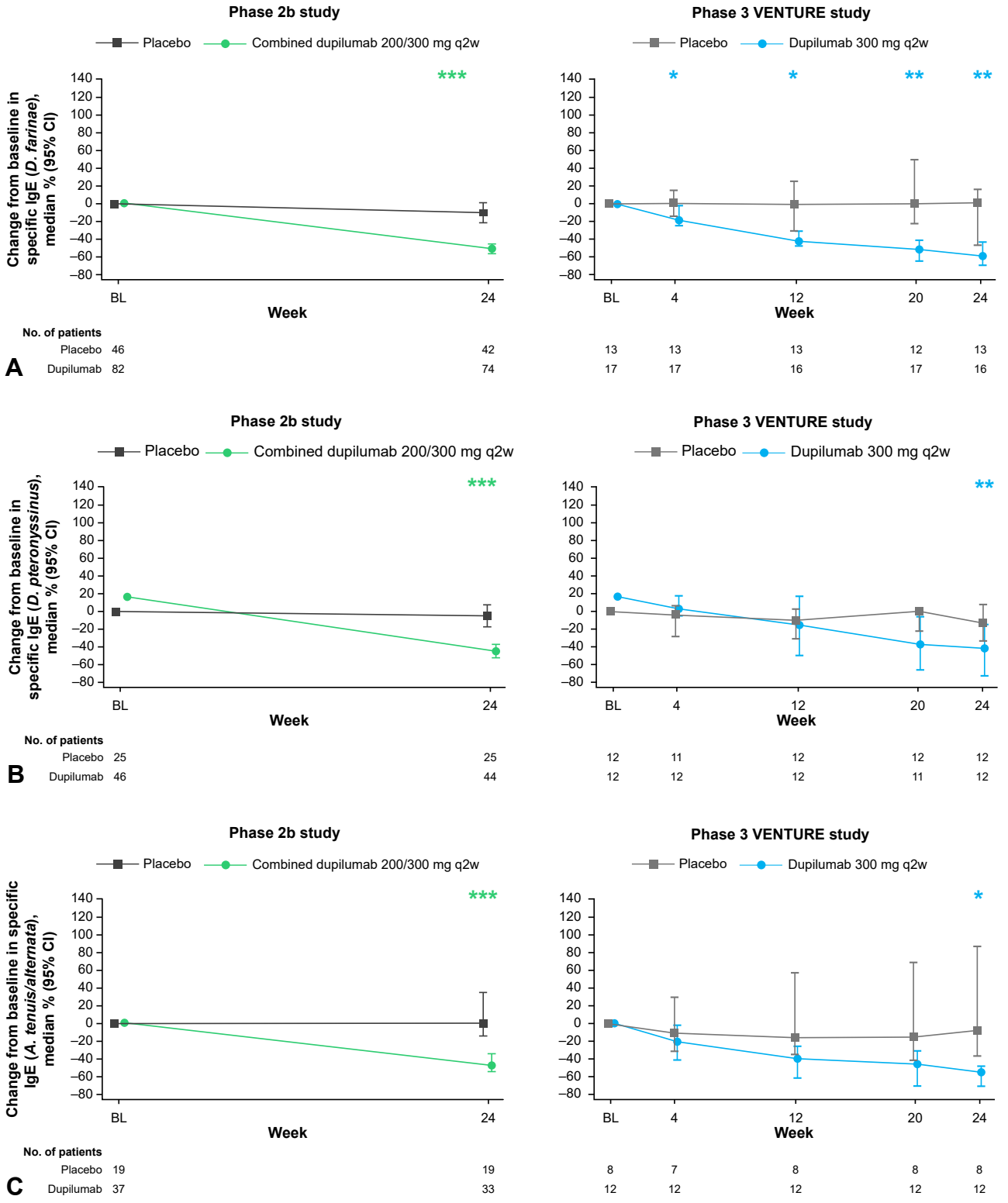

FIGURE E1. Percent change from baseline in specific IgE (95% CI) against (**A**) *Dermatophagoides farinae*, (**B**) *Dermatophagoides pteronyssinus*, (**C**) *Alternaria tenuis/alternata*, (**D**) cat dander, (**E**) dog dander, (**F**) German cockroach, (**G**) oriental cockroach, (**H**) *Cladosporium herbarum/hormodendrum*, and (**I**) *Aspergillus fumigatus* in exposed patients with baseline serum specific-IgE levels ≥0.35 kU/mL for each allergen and meeting criteria for allergic asthma. *BL*, Baseline; *CI*, confidence interval; *q2w*, every 2 weeks. **P* < .05, ***P* < .01, ****P* < .001, versus placebo.

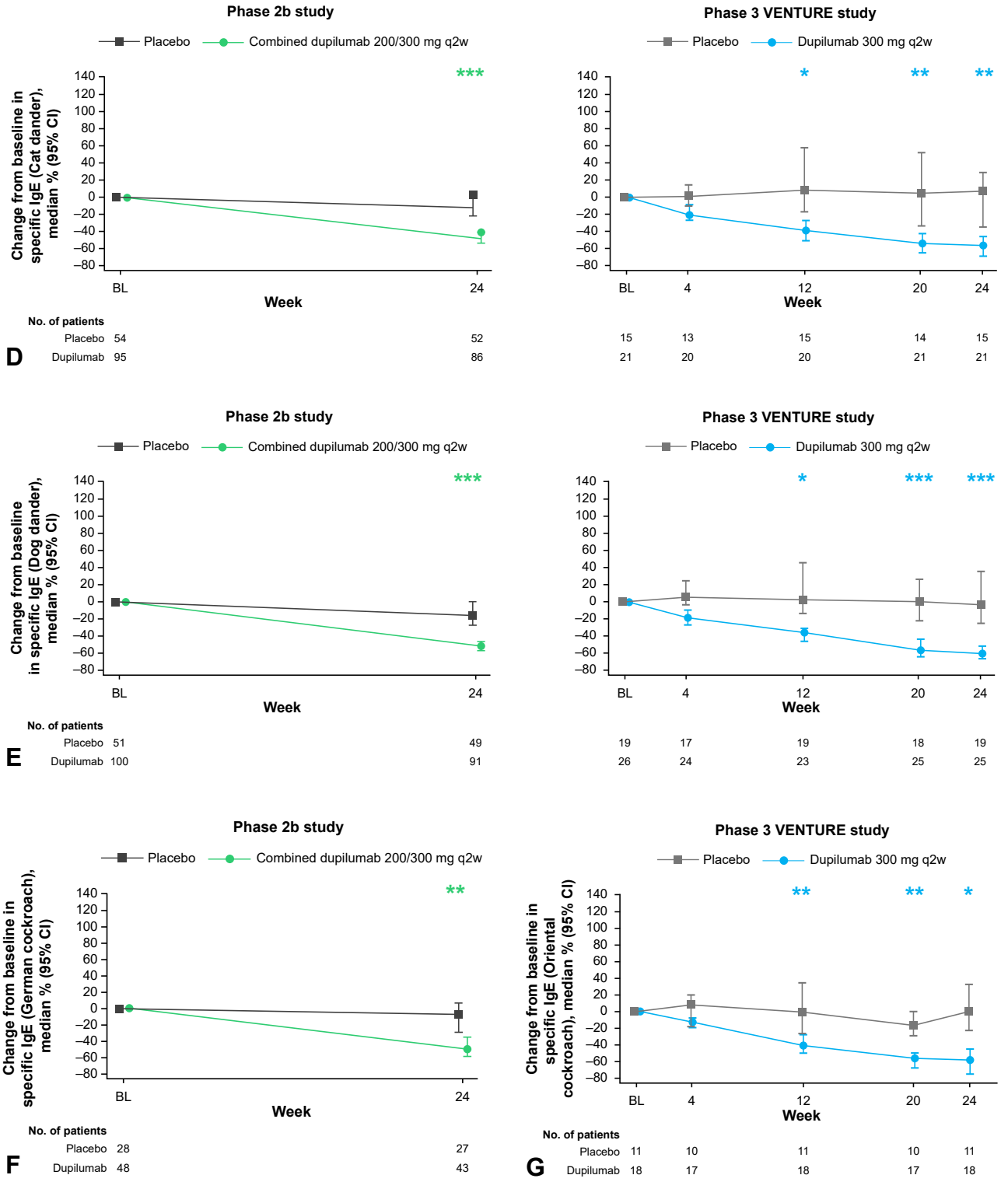

FIGURE E1. Continued

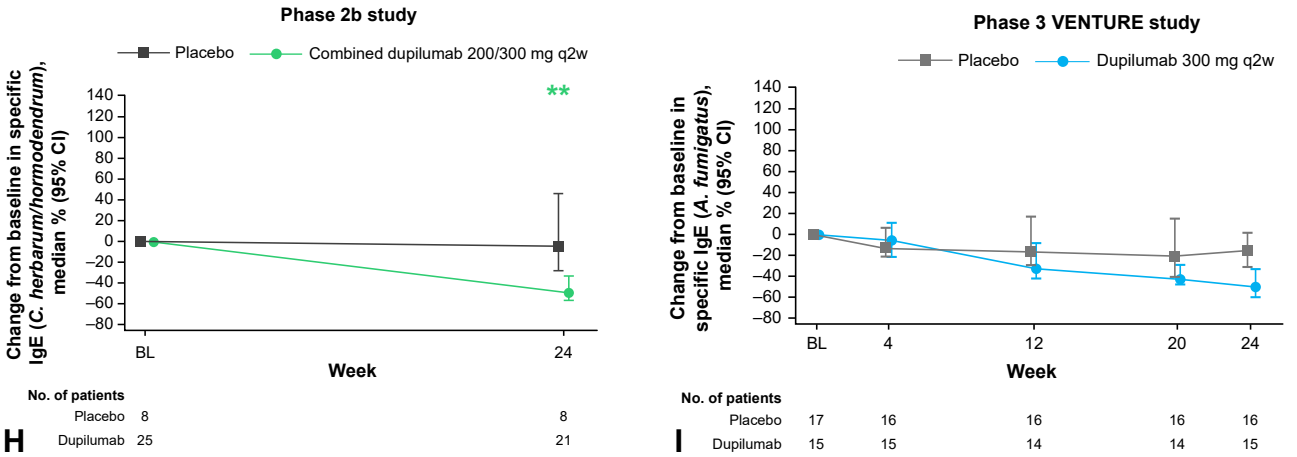

FIGURE E1. Continued