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Original Article

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What is already known about this topic? Transient increases in blood eosinophil counts were reported in clinical trials with dupilumab in patients with asthma, chronic rhinosinusitis with nasal polyps, or atopic dermatitis.

What does this article add to our knowledge? Transient increases in mean blood eosinophils in dupilumab-treated asthma, chronic rhinosinusitis with nasal polyps, or atopic dermatitis patients generally declined to below baseline and were not associated with a decline in efficacy or clinical symptoms.

How does this study impact current management guidelines? Although the eosinophilia observed in these studies was temporary and only rarely associated with clinical symptoms, it remains important for clinicians to base judgment on individual patient history and baseline eosinophil counts.

BACKGROUND: Transient increases in blood eosinophil counts have been observed in dupilumab clinical trials.
OBJECTIVE: To assess eosinophil counts and eosinophilia-related treatment-emergent adverse events (TEAEs) across 11 dupilumab clinical trials, comparing adult and adolescent patients with asthma and adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP), atopic dermatitis, and eosinophilic esophagitis.
METHODS: Eosinophil counts, rates of eosinophilia-related TEAEs or treatment-emergent eosinophilia (>1,500 cells/μL),

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Conflicts of interest: M.E. Wechsler declares personal fees from AstraZeneca, Boehringer Ingelheim, Equillium, Gala Therapeutics, Genentech, Genzyme, Mylan, Novartis, Pulmatrix, Regeneron Pharmaceuticals, Inc, resTORbio, Sentien Biotechnologies, and Teva; and grants and personal fees from GSK and Sanofi. P. Paggiaro received institutional and personal grants for research activities and education from ALK-Abellò, AstraZeneca, Chiesi, GSK, Guidotti, Menarini, Mundipharma, Novartis, and Sanofi. P. Nair received grant support from AstraZeneca, Boehringer Ingelheim, Cyclomedica, Foresee, Methapharm, Novartis, Roche, Sanofi, and Teva; and personal fees from AstraZeneca, Equillium, GSK, Merck, Sanofi, and Teva. D. Staumont-Salle was an investigator, consultant, and advisory board member for AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc, and Sanofi; a consultant for AbbVie, AstraZeneca, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, and Sanofi; and a speaker for AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, and UCB. A. Radwan, F.A. Khokhar, Z. Chen, and Y. Deniz are employees and shareholders of Regeneron Pharmaceuticals, Inc. R.R. Johnson, E. Laws, J.A. Jacob-Nara, L.P. Mannent, and P.J. Rowe are employees of Sanofi who may hold stock and/or stock options in the company. N. Daizadeh and U. Kapoor are former employees of Sanofi who may hold stock and/or stock options in the company. B. Ortiz is a former employee and shareholder of Regeneron Pharmaceuticals, Inc. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
AD- Atopic dermatitis
CRSwNP- Chronic rhinosinusitis with nasal polyps
EGPA- Eosinophilic granulomatosis with polyangiitis
EoE- Eosinophilic esophagitis
ITT- Intention-to-treat
OLE- Open-label extension
POC- Proof-of-concept
q2w- Every 2 weeks
q4w- Every 4 weeks
SAE- Severe adverse event
TEAE- Treatment-emergent adverse event
VCAM-1- Vascular cell adhesion molecule 1

discontinuations, clinical symptoms, and efficacy in patients with asthma or CRSwNP with treatment-emergent eosinophilia are presented.
RESULTS: Transient increases in mean eosinophil counts were observed in dupilumab-treated patients with asthma (mean range across studies at baseline: 349-370 cells/μL; week 4: 515-578 cells/μL), CRSwNP (baseline: 440-448 cells/μL; week 16: 595 cells/μL), and atopic dermatitis (baseline: 434-600 cells/μL; week 4: 410-710 cells/μL), followed by a decline starting by week 24 to baseline or lower. No increases were seen in patients with eosinophilic esophagitis (baseline: 310 cells/μL; week 4: 230 cells/μL). In dupilumab-treated patients across all studies, rates of eosinophilia TEAEs were 0% to 13.6%. Clinical symptoms associated with increased eosinophils were rare (seven of 4,666 dupilumab-treated patients, including six cases of eosinophilic granulomatosis with polyangiitis) and occurred only in patients with asthma or CRSwNP. Eosinophilia was not associated with reduced dupilumab efficacy.
CONCLUSIONS: Transient increases in eosinophil counts with dupilumab treatment did not affect efficacy and were rarely of clinical consequence. It remains important for physicians to base judgment on individual patient history and baseline eosinophil counts and to be alert to hypereosinophilic symptoms. **(J Allergy Clin Immunol Pract 2022;10:2695-709)**

Key words: Asthma; Atopic dermatitis; Chronic rhinosinusitis with nasal polyps; Dupilumab; Eosinophilia; Eosinophilic esophagitis; Eosinophils

INTRODUCTION

Chronic type 2 inflammatory diseases such as asthma, atopic dermatitis (AD), chronic rhinosinusitis with nasal polyps (CRSwNP), and eosinophilic esophagitis (EoE) present a substantial and increasing public health burden.[1] Whereas there is variation in the underlying pathogenesis, type 2 inflammation represents the dominant driver in these conditions.[2,3] The type 2 inflammatory pathway is driven by activation of type 2 $CD4^+$ helper cells and innate lymphoid type 2 cells, resulting in tissue infiltration of inflammatory cells such as eosinophils, mast cells, and basophils, and production of proinflammatory cytokines, including IL-4, IL-5, and IL-13.[4] Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for IL-4/IL-13, inhibiting their signaling.[5-7] Dupilumab is approved for patients with type 2 inflammatory diseases (AD, asthma, and CRSwNP) and is currently under phase 3 investigation in EoE.[8-18]

Transient increases in eosinophil counts have been reported in dupilumab clinical trials.[9-11,14,16] These generally occurred in the first few weeks and returned to baseline or lower by the end of the treatment period. The objectives of this analysis were to aggregate data and compare the effect of dupilumab on blood eosinophil counts over time across a broad range of type 2 diseases and to assess its impact on eosinophilia-related treatment-emergent adverse events (TEAEs), clinical symptoms, and treatment efficacy.

METHODS

Study design

This is a post hoc analysis of 11 clinical trials of dupilumab in adult and adolescent patients with moderate to severe or severe corticosteroid-dependent asthma (phase 2b DRI [NCT01854047], phase 3 LIBERTY ASTHMA QUEST [QUEST; NCT02414854], phase 3 VENTURE [NCT02528214], and open-label extension [OLE] TRAVERSE [NCT02134028]); adults with severe CRSwNP (phase 3 LIBERTY NP SINUS-24 [SINUS-24; NCT02912468] and phase 3 LIBERTY NP SINUS-52 [SINUS-52; NCT02898454]); adults with moderate to severe AD (phase 3 LIBERTY AD SOLO-1 [SOLO-1; NCT02277743], SOLO-2 [SOLO-2; NCT02277769], phase 3 LIBERTY AD CHRONOS [CHRONOS; NCT02260986], and AD-OLE [NCT01949311]); and adults with active EoE (phase 2 proof-of-concept [POC] [NCT02379052]). All were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed assent or consent was obtained from all participants before enrolment, and protocols and consent forms were reviewed by appropriate review boards and ethics committees before study commencement. Full study design details and patient characteristics were published previously elsewhere.[9-11,14-16,18-21] A brief summary of each is provided in the Supplemental Methods and Table E1 (in this article's Online Repository at www.jaci-inpractice.org).

Patients included in this analysis

Because of differing study designs and diseases, data for each study population are presented separately and are comparative in nature. Exposed populations are included for all asthma and CRSwNP studies, with combined placebo and combined dupilumab data for studies in which more than one dose was evaluated (QUEST and DRI). Safety populations are included for all AD and EoE studies. For data consistency, only data for biweekly dosing are included for SINUS-52 and the AD studies. Weekly dosing is included for EoE POC; no biweekly data were available.

Assessments

Absolute blood eosinophil counts were assessed at baseline and throughout the treatment period. Testing frequency varied across studies. Mean, median, and median fold-change from baseline in eosinophil counts were assessed within each study at each time point when data were available. The number of patients reaching eosinophil counts of greater than 1,500 or 3,000 cells/μL during the treatment period, commonly used measurements for eosinophilia

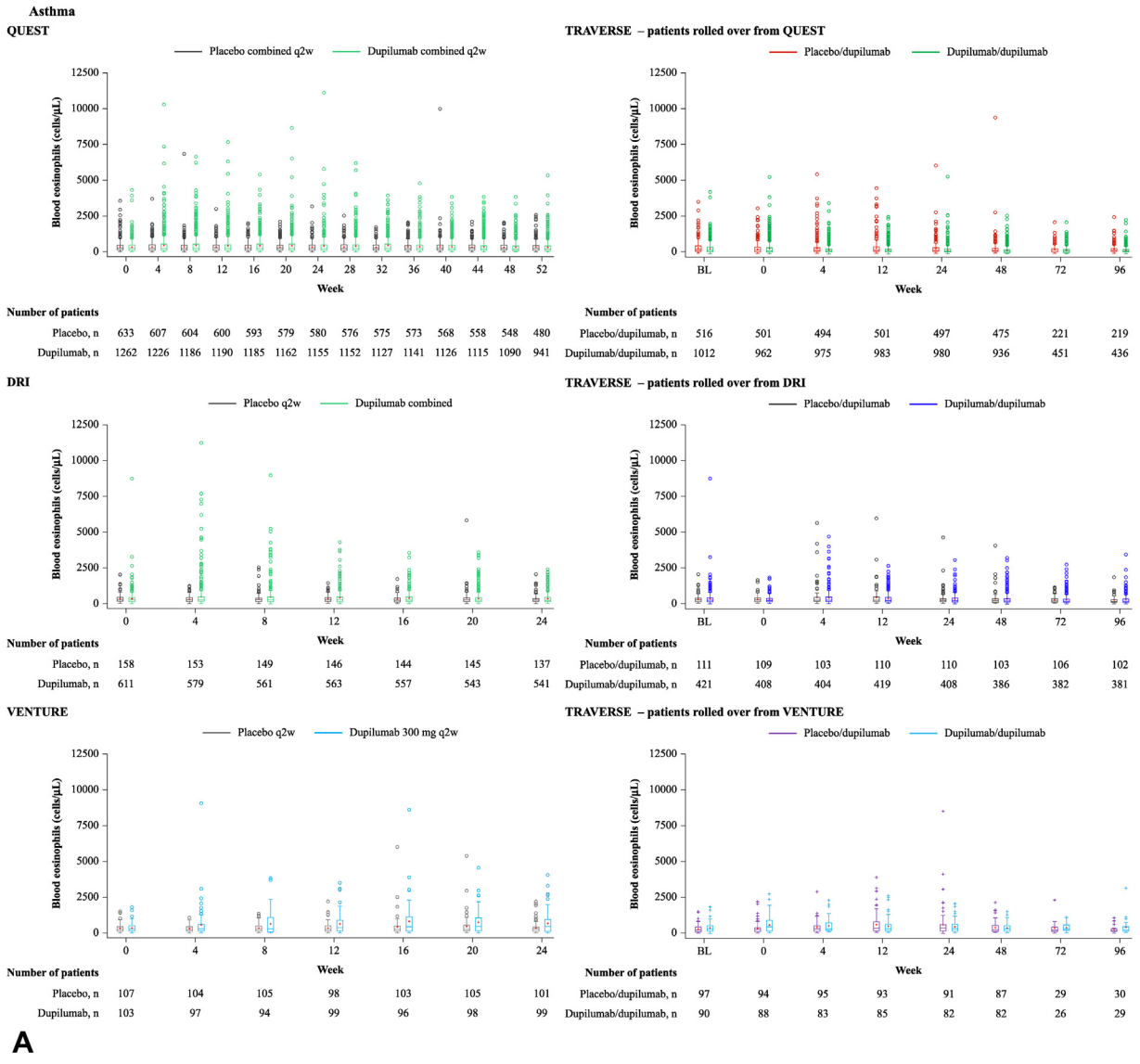


FIGURE 1. Box-and-whisker plots of absolute blood eosinophil counts over time in each study for patients with (**A**) asthma, (**B**) chronic rhinosinusitis with nasal polyps (CRSwNP), (**C**) atopic dermatitis (AD), and (**D**) eosinophilic esophagitis (EoE). From top to bottom, the box plots show maximum excluding outliers, quartile 3, median, quartile 1, and minimum excluding outliers. Outliers are plotted as individual points. The mean is represented by a red cross. *BL*, baseline; *OLE*, open-label extension; *POC*, proof-of-concept; *q2w*, every 2 weeks; *qw*, weekly.

and severe eosinophilia,[22-24] was assessed. Data from TRAVERSE were assessed for each parent study separately.

Eosinophilia TEAEs, reported per relevant study protocol by investigators at each site, were recorded using the Medical Dictionary for Regulatory Activities hierarchy version in effect at database lock for each study (DRI: 18.0; QUEST and VENTURE: 20.0; TRAVERSE: 22.0; SINUS-24 and SINUS-52: 21.0; SOLO-1 and -2, CHRONOS, AD-OLE: 18.0; and EoE POC: 19.1). Eosinophilia TEAE was defined as the high-level term "eosinophilic disorder" or preferred term "eosinophil count increased." For QUEST, VENTURE, TRAVERSE, SINUS-24, and SINUS-52, an on-treatment eosinophil count of greater than 3000 cells/µL was also reported as an eosinophilia TEAE. The number of patients with TEAEs, experiencing severe adverse events (SAEs), discontinuing treatment owing to eosinophilia, experiencing related clinical symptoms, reporting eosinophilic granulomatosis with polyangiitis (EGPA), requiring corrective treatment, and recovered was assessed.

Efficacy measures were assessed in patients with treatment-emergent eosinophilia (>1,500 cells/µL or eosinophilia TEAE) enrolled in the asthma and CRSwNP studies. For asthma, unadjusted annualized severe exacerbation rates (calculated as the total number of events that occurred during the treatment period divided by total number of patient-years observed during that treatment period) were assessed by treatment group. Unadjusted estimates were computed to enable a comparison with estimates obtained in the subgroup of patients with at least one result of greater than 1,500

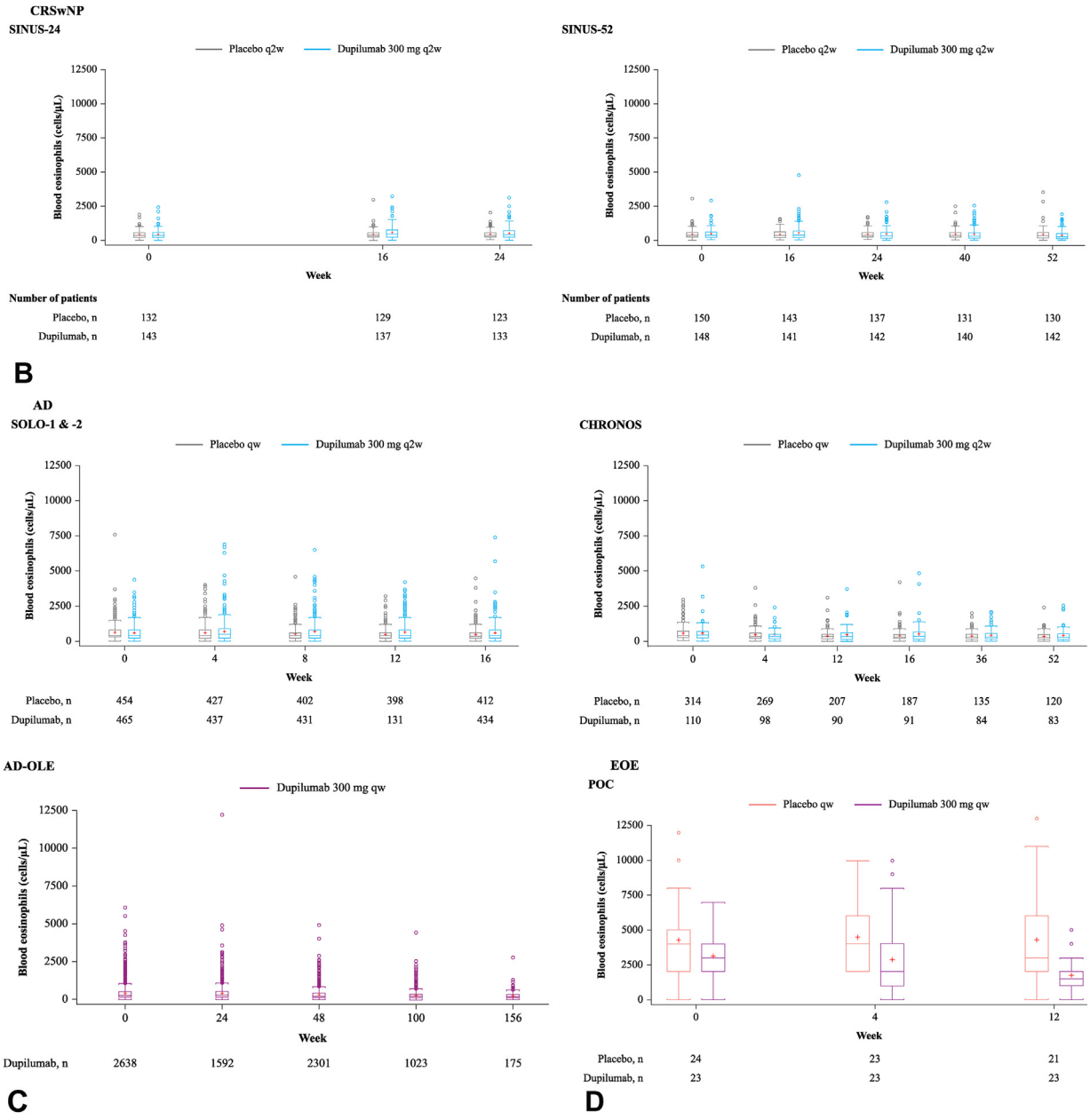


FIGURE 1. Continued.

eosinophils/µL after baseline or reporting an eosinophilia TEAE. Similarly, mean change from baseline in prebronchodilator FEV_1 at week 12 (QUEST, DRI, or VENTURE) or week 24 (TRAVERSE) was calculated. For CRSwNP, data from post-systemic corticosteroid use or nasal polyp surgery were set to missing and imputed using the worst observation carried forward method. Mean changes from baseline in nasal polyp score and nasal congestion/obstruction score at week 24 were calculated.

Statistical analysis

Because of differing study designs, no formal statistical comparisons were implemented across studies or diseases. Changes in eosinophil counts and safety data are summarized descriptively for each study. As such, the synthesis of data, comparisons across indications, and conclusions drawn are based on descriptive data presented from individual studies and not from a formal statistical analysis. Efficacy data were summarized using descriptive statistics for asthma and CRSwNP studies only.

We performed all statistical analyses using SAS software (version 9.4, SAS Institute Inc., Cary, NC).

RESULTS

In total, 6,642 patients were included in the analysis: 2,876 with asthma (QUEST: 1,897; VENTURE: 210; and DRI: 769), 2,249 of whom rolled over into TRAVERSE; 574 with CRSwNP (SINUS-24: 275; and SINUS-52: 299); 3,145 with AD (SOLO-1 and -2: 921; CHRONOS: 425; and AD-OLE: 2,677, 878 of whom rolled over from assessed treatment arms

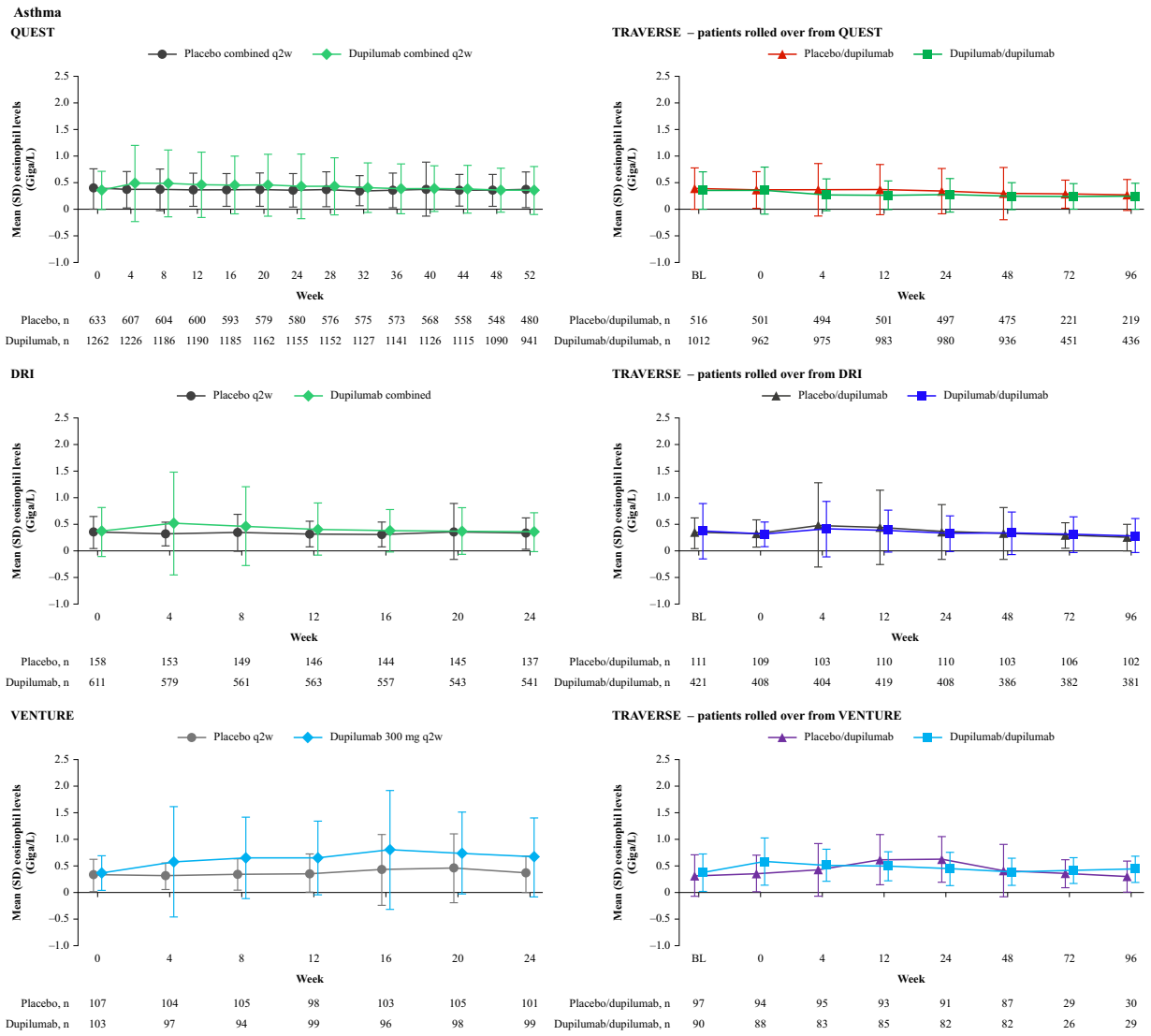


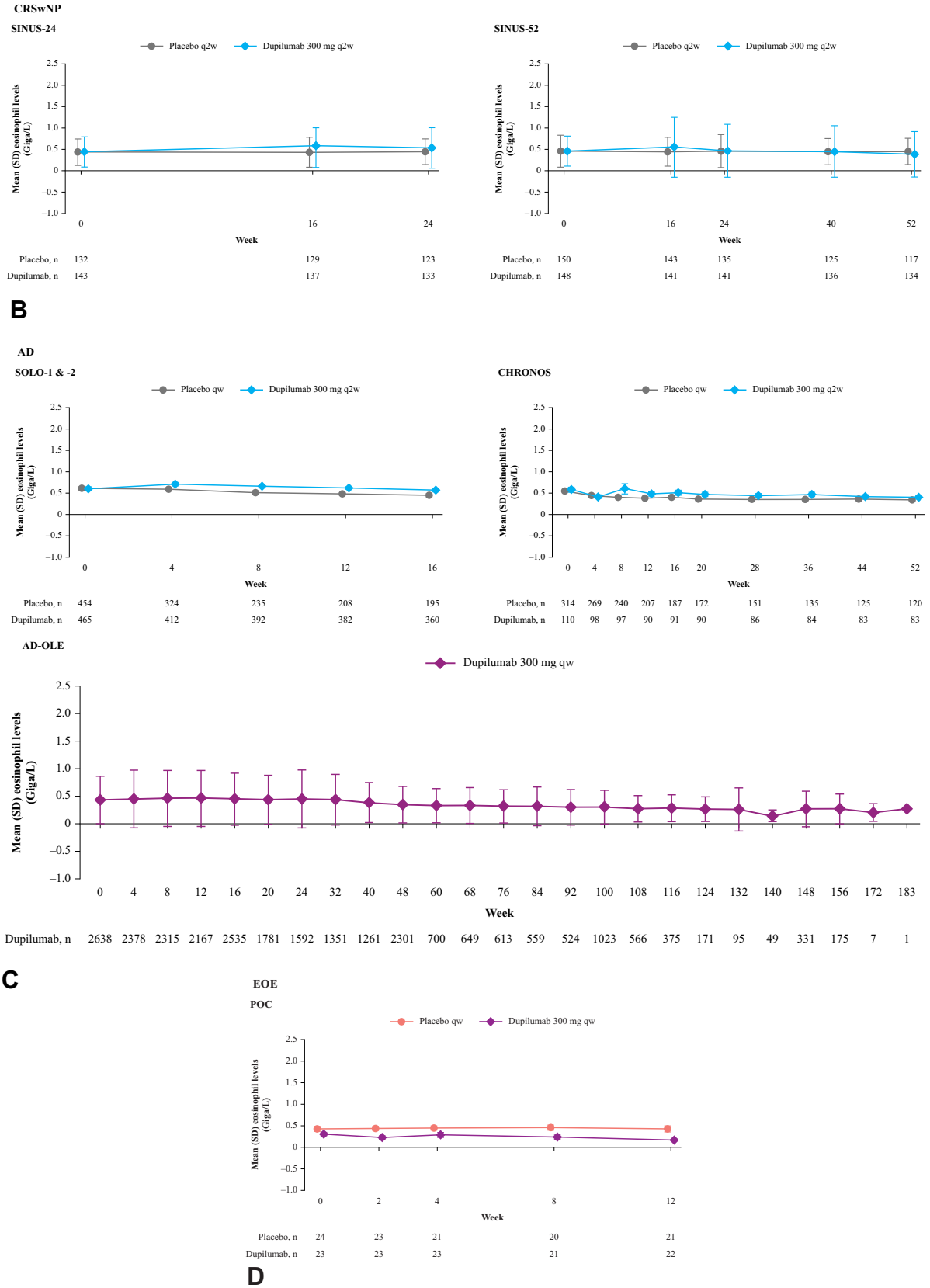
FIGURE 2. Mean blood eosinophil counts over time for individual studies in patients with (**A**) asthma, (**B**) chronic rhinosinusitis with nasal polyps (CRSwNP), (**C**) atopic dermatitis (AD), and (**D**) eosinophilic esophagitis (EoE). *BL*, baseline; *OLE*, open-label extension; *POC*, proof-of-concept; *q2w*, every 2 weeks; *qw*, weekly.

of SOLO-1 and -2 and CHRONOS); and 47 with EoE. Full details of patient demographics and baseline characteristics have been published elsewhere.[9-11,14-16,18-21]

Mean and median absolute eosinophil counts

Asthma. Absolute eosinophil levels in each patient with asthma included in the analysis are shown in the box plots presented in Figure 1, *A*, which illustrate that median and interquartile ranges of blood eosinophil counts remained relatively unchanged throughout the treatment period for QUEST and DRI. In DRI, median baseline eosinophil count was 260 cells/μL in both placebo (interquartile range: 160-430) and dupilumab (150-420) groups. Median values remained within 240 to 270 cells/μL (placebo) and 230 to 260 cells/μL (dupilumab) throughout the study. In QUEST, median values also remained within 240 to 280 cells/μL (placebo) and 200 to 260 cells/μL (dupilumab). In VENTURE, median eosinophil counts were higher, and a clear elevation was seen in the dupilumab group (median, 470 cells/μL by week 24; baseline count, 280 cells/μL).

For mean eosinophil counts, transient increases were observed in QUEST, DRI, and VENTURE in the dupilumab but not the placebo groups (Figure 2, *A*). By week 4, mean eosinophil counts had risen from 348.9 to 514.6 cells/μL in DRI, from 350.9 to 481.0 cells/μL in QUEST, and from 369.5 to 578.7 cells/μL in VENTURE (Figure 2, *A*). Eosinophil counts in the placebo group remained at baseline levels. Elevated mean eosinophil counts generally decreased from approximately week 24 onward in studies that continued past this point (eg, 351.4 cells/μL at week 52 in QUEST). Differences observed between median and



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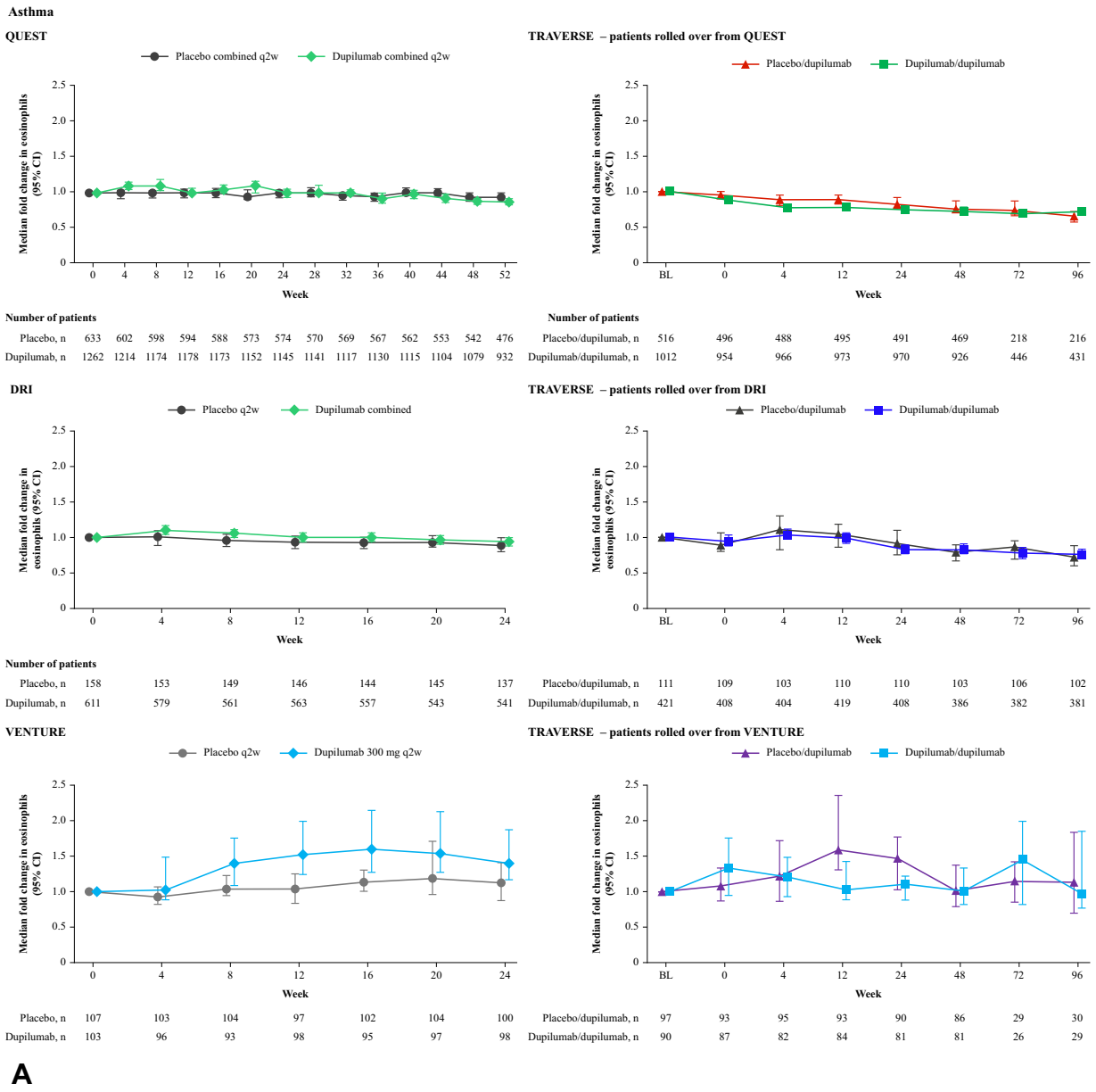
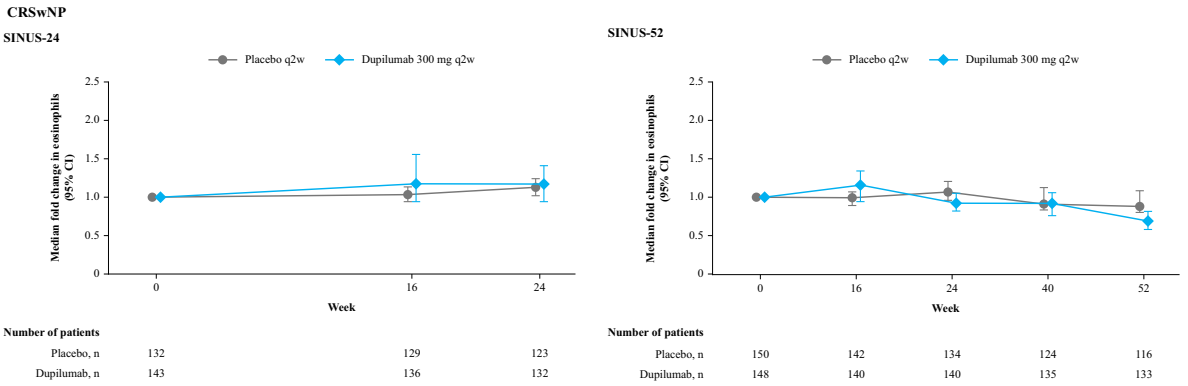


FIGURE 3. Median fold-change from baseline in blood eosinophil counts over time for individual studies in patients with (**A**) asthma, (**B**) chronic rhinosinusitis with nasal polyps (CRSwNP), (**C**) atopic dermatitis (AD), and (**D**) eosinophilic esophagitis (EoE). *BL*, baseline; *CI*, confidence interval; *OLE*, open-label extension; *POC*, proof-of-concept; *q2w*, every 2 weeks; *qw*, weekly.

mean eosinophil counts in QUEST and DRI, with increases in mean eosinophil counts and no change in median counts, may have resulted from the spread of patients seen in the box plots in Figure 1, *A*, which suggests that the rise in mean eosinophil levels was driven by outliers.

Asthma OLE. For patients who received dupilumab in QUEST and continued into TRAVERSE (dupilumab/dupilumab), mean and median eosinophil counts continued to decline over time (baseline: mean, 350.0 cells/μL and median, 250 cells/μL; week 96: mean, 243.5 cells/μL and median, 165 cells/μL). In patients who rolled over to TRAVERSE from the QUEST placebo arm (placebo/dupilumab), no rise in mean or median eosinophil counts was observed (baseline: mean, 386.5 cells/μL and median, 270 cells/μL; week 4: mean, 367.8 cells/μL and median, 230 cells/μL). For patients enrolled in DRI who continued into either treatment arm of TRAVERSE after the 16-week gap in dupilumab dosing, a transient rise in mean eosinophil counts was observed from baseline (placebo/dupilumab: 328.7 cells/μL; dupilumab/dupilumab: 366.3 cells/μL) to week 4 (placebo/dupilumab: 486.1 cells/μL; dupilumab/dupilumab: 406.3 cells/μL), which resolved by week 24 (placebo/dupilumab: 351.5 cells/μL; dupilumab/dupilumab: 318.0 cells/μL). Median eosinophils remained relatively unchanged throughout (Figures 1, *A* and 2, *A*).

For dupilumab/dupilumab patients who rolled over into TRAVERSE from VENTURE, mean and median eosinophil



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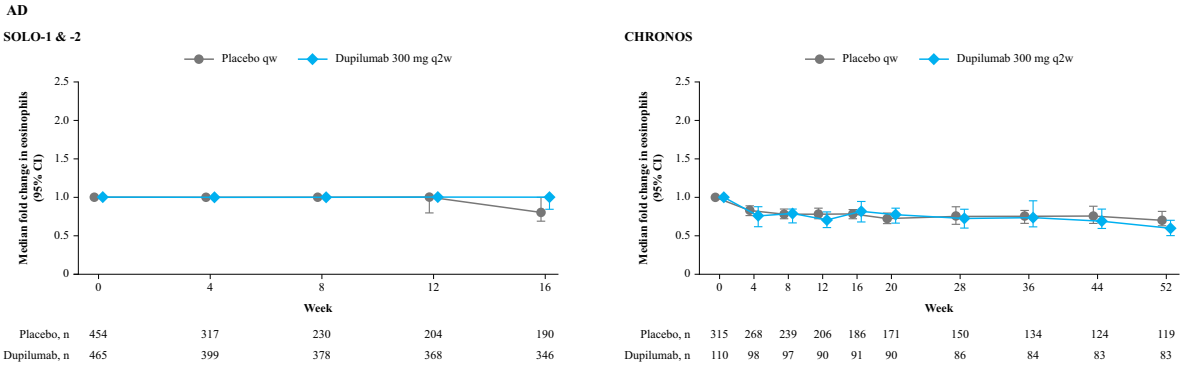

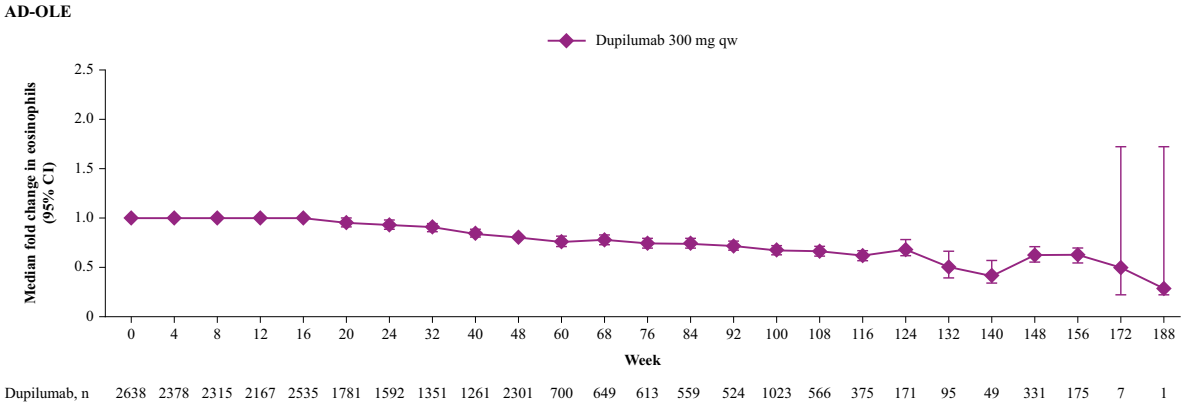

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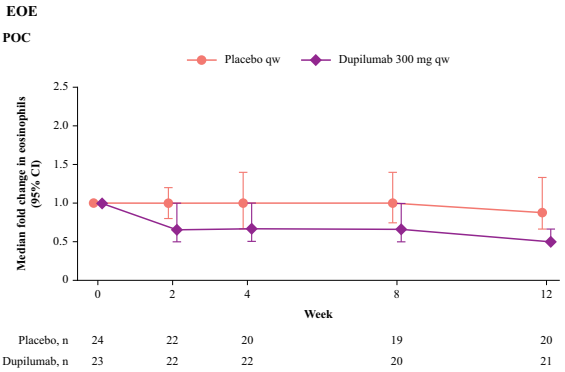

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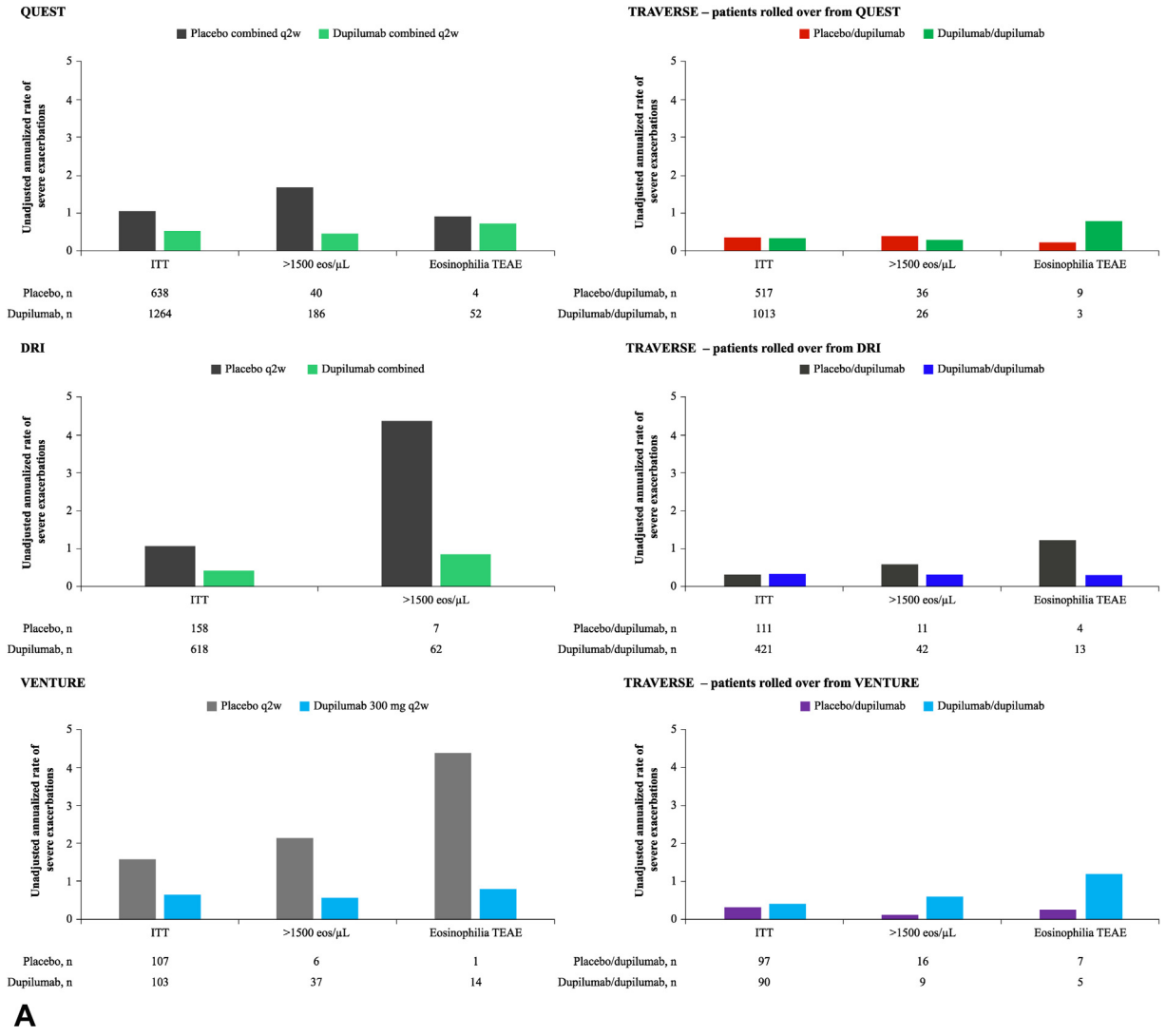

FIGURE 4. Efficacy end points in overall intention-to-treat (ITT) populations and in patients with greater than 1,500 eosinophils (eos)/μL or reporting an eosinophilia treatment-emergent adverse event (TEAE). (**A**) Unadjusted annualized exacerbation rates and (**B**) change from baseline in pre-bronchodilator FEV_1 in patients with asthma; (**C**) change from baseline in nasal polyp score (NPS), and (**D**) change from baseline in nasal congestion (NC) score at week 24 in patients with chronic rhinosinusitis with nasal polyps. Only one patient in DRI experienced an eosinophilia TEAE, so this subgroup could not be assessed. *q2w*, every 2 weeks.

counts declined over time from the first measurement at week 4 (mean, 517.5 cells/μL; and median, 320 cells/μL) to week 96 (mean, 441.0 cells/μL; and median, 250 cells/μL). For placebo/dupilumab patients from VENTURE, mean and median eosinophil counts rose from baseline (mean, 320.8 cells/μL; and median, 240 cells/μL) to week 24 (mean, 626.4 cells/μL; and median, 370 cells/μL) and then began to decline, reaching below baseline by week 96 (mean, 305.7 cells/μL; and median, 200 cells/μL).

Chronic rhinosinusitis with nasal polyps. Similar trends were seen for patients with CRSwNP, with median eosinophil count remaining relatively unchanged over time in both SINUS-24 and SINUS-52 (Figure 1, *B*). Higher mean eosinophil counts in dupilumab versus placebo were observed at week 16 in SINUS-24 (586 vs 434 cells/μL) and SINUS-52 (594.8 vs 434.5 cells/μL), which decreased from week 24 (SINUS-24: 534 vs 444 cells/μL; and SINUS-52: 457.1 vs 439.5 cells/μL) and reached below baseline by the end of 52 weeks of treatment in SINUS-52 (baseline, 447.6 cells/μL; and week 52, 374.6 cells/μL) (Figure 2, *B*).

Atopic dermatitis. In patients with AD, a slight rise in median eosinophils was observed at week 4 (baseline, 400 cells/μL; and week 4, 500 cells/μL), which declined to baseline by week 8 (400 cells/μL) in dupilumab-treated patients enrolled in SOLO-1 and SOLO-2 (Figure 1, *C*). Elevated mean eosinophil counts were observed from weeks 4 through 12 (baseline, 600 cells/μL; week 4, 710 cells/μL; and week 12, 620 cells/μL) versus placebo (baseline, 620 cells/μL; week 4, 590 cells/μL; and week 12, 480 cells/μL) (Figure 2, *C*). Similar trends were observed in CHRONOS, with an initial slight rise in mean eosinophils from

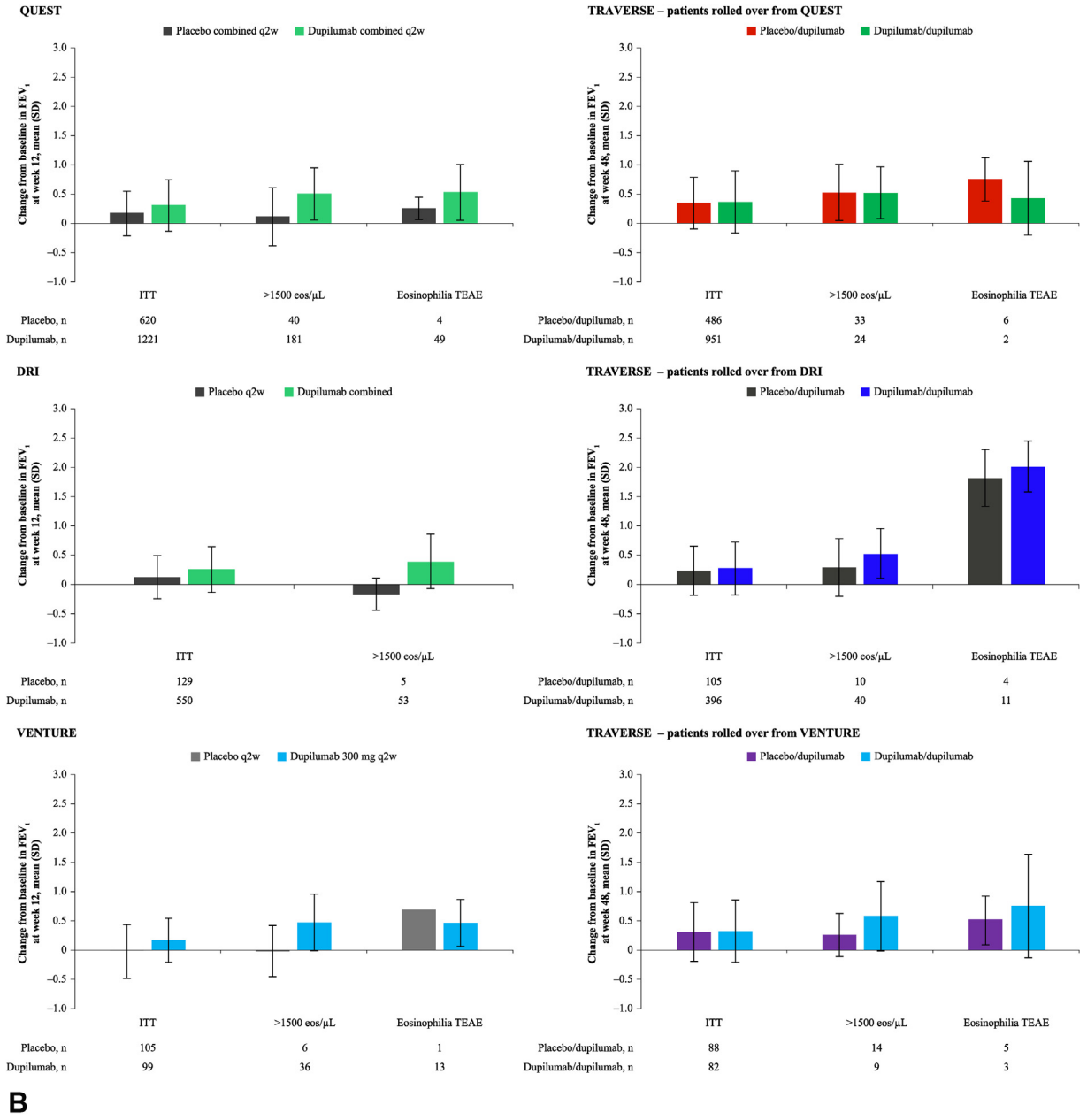

FIGURE 4. Continued.

580 cells/μL at baseline to 600 cells/μL by week 8, which dropped to similar or below baseline from week 12 (480 cells/μL); median eosinophil counts declined from week 16 (340 cells/μL) to week 52 (300 cells/μL). In AD-OLE, mean and median eosinophil counts increased slightly from baseline (mean, 434 cells/μL; and median, 310 cells/μL) to week 24 (mean, 452 cells/μL; and median, 330 cells/μL), but then gradually decreased to substantially lower than baseline as the study progressed (week 84: mean, 318 cells/μL; and median, 220 cells/μL) (Figures 1, *C* and 2, *C*).

Eosinophilic esophagitis. No increase in eosinophil counts was observed in patients with EoE. Median and mean eosinophil counts in the dupilumab group decreased over time from baseline (mean, 310 cells/μL; and median, 300 cells/μL) to the first measurement at week 2 (mean, 230 cells/μL; and median, 200 cells/μL) to week 12 (mean, 170 cells/μL; and median, 200 cells/μL) (Figures 1, *D* and 2, *D*).

Median fold-change from baseline in eosinophil counts

Asthma. In QUEST, higher median fold-changes from baseline were observed for dupilumab versus placebo at weeks 4 (dupilumab, 1.10; and placebo, 1.0), 8 (dupilumab, 1.10; and placebo, 1), and 20 (dupilumab, 1.09; and placebo, 0.96), with

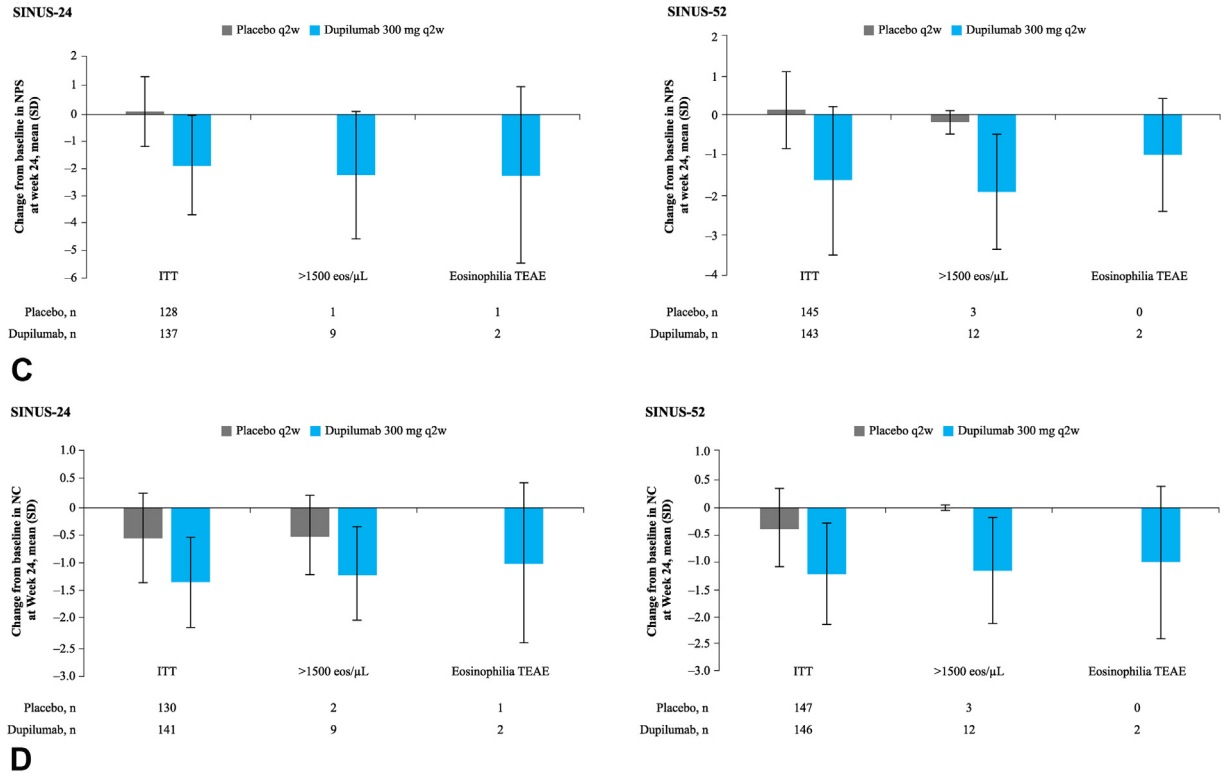

FIGURE 4. Continued.

lower changes observed at week 52 (dupilumab, 0.88; and placebo, 0.94) (Figure 3, *A*). In patients from QUEST rolled into TRAVERSE, eosinophil counts were generally lower throughout the OLE in dupilumab/dupilumab versus placebo/dupilumab patients (median fold-change from baseline at week 4: placebo/dupilumab 0.88, and dupilumab/dupilumab 0.77; week 72: placebo/dupilumab 0.73, and dupilumab/dupilumab 0.69). In DRI, higher median fold-changes were also observed with dupilumab versus placebo in the first few weeks of the study (week 4: dupilumab 1.10, and placebo 1.00; week 8: dupilumab 1.06, and placebo 0.96); however, these returned to baseline or lower by week 12 (dupilumab 1.00, and placebo 0.94). For dupilumab/dupilumab patients in TRAVERSE, minimal changes in median fold-change from the parent study baseline were observed. A transient increase in median fold-change eosinophils was observed for placebo/dupilumab patients, which resolved by week 24.

Asthma OLE. In patients from VENTURE, higher median fold-changes in dupilumab versus placebo were observed throughout the 24-week study (week 4: dupilumab 1.02, and placebo 0.93; week 24: dupilumab 1.41, and placebo 1.11). A transient increase in median fold-change from parent study baseline was observed for placebo/dupilumab patients from VENTURE rolled into TRAVERSE, which was resolved by week 48.

Chronic rhinosinusitis with nasal polyps. In patients with CRSwNP, no clear differences were seen in median fold-change from baseline in placebo versus dupilumab by week 24, although median fold-change was higher at week 16 in dupilumab in SINUS-52 (Figure 3, *B*). By week 52, however, patients treated with dupilumab had a lower median fold-change from baseline compared with placebo.

Atopic dermatitis. In patients with AD enrolled in SOLO-1 or -2, no median fold-change from baseline was observed in the dupilumab groups at any point in the studies, whereas a negative change was observed in placebo at week 16 (0.8). A gradual decline in median fold-change from baseline was observed in both placebo and dupilumab in CHRONOS (median fold-change declined from weeks 4 to 52: 0.83 to 0.70 for placebo and 0.76 to 0.59 for dupilumab) and AD-OLE (median fold-change 1.0 at week 4 and 0.26 at week 188) (Figure 3, *C*).

Eosinophilic esophagitis. In EoE, no change from baseline in eosinophil counts was observed in patients receiving placebo, whereas a reduction in median fold-change from baseline was observed in dupilumab at each time point (median fold-change from baseline 0.50 at week 12) (Figure 3, *D*).

Eosinophilia. A total of 161 eosinophilia TEAEs and 22 eosinophilia SAEs were reported in the 6,642 patients across all studies and diseases and were included in the analysis.

Excluding patients from VENTURE who were undergoing oral corticosteroid reduction owing to the association of oral corticosteroid reduction with an increased risk for severe eosinophilic events, rates of eosinophilia TEAEs during the treatment period, defined per each study protocol (with or without symptoms), ranged from 0% to 4.1% in the dupilumab groups and 0% to 1.5% in the placebo groups. Most were of mild to moderate severity (Table I). Generally, rates of eosinophilia SAEs were higher in the dupilumab groups (0% to 1.9%) across studies (placebo: 0% to 0.8%). Percentages of dupilumab-treated

TABLE I. Rates of eosinophilia TEAEs, severe AEs, discontinuations owing to eosinophilia, use of corrective treatment, and recovery rates for each study

	Asthma									
	QUEST* (52 wk)		DRI† (24 wk)		VENTURE* (24 wk)		TRAVERSE* (rolled over from QUEST; 96-wk OLE)		TRAVERSE* (rolled over from DRI; 96-wk OLE)	
Event	PBO (n = 634)	DPL (n = 1,263)	PBO (n = 158)	DPL (n = 611)	PBO (n = 107)	DPL (n = 103)	PBO/DPL (n = 517)	DPL/DPL (n = 1013)	PBO/DPL (n = 111)	DPL/DPL (n = 421)
Eosinophilia TEAE*										
n (%)	4 (0.6)	52 (4.1)	0	1 (0.2)	1 (0.9)	14 (13.6)	9 (1.7)	3 (0.3)	4 (3.6)	13 (3.1)
Severe AE, n (%)	0	2 (0.2)	0	1 (0.2)	0	2 (1.9)	1 (0.2)	2 (0.2)	0	2 (0.5)
Discontinuing treatment	1 (0.2)	7 (0.6)	0	1 (0.2)	1 (0.9)	0	1 (0.2)	2 (0.2)	0	2 (0.5)
Require corrective treatment	1 (0.2)	5 (0.4)	0	1 (0.2)	1 (0.9)	3 (2.9)	2 (0.4)	2 (0.2)	0	3 (0.7)
Recovered by end of treatment	3 (0.5)	41 (3.2)	0	1 (0.2)	1 (0.9)	11 (10.7)	5 (0.1)	1 (<0.1)	4 (3.6)	10 (2.4)
Eosinophilia associated with clinical symptoms										
Patients with a TEAE under HLT "eosinophilic disorders" excluding PT "eosinophilia," n (%)	0	1 (eosinophilic pneumonia)	0	0	0	0	0	2 (EGPA)	0	1 (EGPA)
Patients with EGPA, n (%)	0	0	0	0	0	0	0	2	0	1
AEs potentially related to eosinophilia concomitant with a rise in eosinophils >3,000 cells/μL,† n	0	2 (myalgia and arthralgia; myositis and radiculopathy)	0	1 (persistent dry cough and rhinitis)	0	0	2 (myalgia and arthralgia; arthralgia)	0	0	0

AD, atopic dermatitis; *AE*, adverse event; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *DPL*, dupilumab; *EGPA*, eosinophilic granulomatosis with polyangiitis; *EoE*, eosinophilic esophagitis; *HLT*; MedDRA high-level term; *NA*, not available; *OLE*, open-label extension; *PBO*, placebo; *PT*, MedDRA preferred term; *TEAE*, treatment-emergent adverse event.

*For QUEST, VENTURE, TRAVERSE, SINUS-24, and SINUS-52, "eosinophilia TEAEs" are defined per study protocol as HLT "eosinophilic disorders" or PT "eosinophil count increased." On-treatment eosinophil counts of greater than 3,000 cells/μL were reported as AEs. For DRI, AD, and EoE studies, "eosinophilia TEAEs" are defined per study protocol as HLT "eosinophilic disorders" or PT "eosinophil count increased."

†As medically reviewed by the sponsor.

patients discontinuing treatment or requiring corrective treatment were low across all studies (0% to 0.9% and 0% to 0.7%, respectively).

In VENTURE, incidences of eosinophilia TEAEs were 13.6% and 0.9% in dupilumab and placebo groups, respectively. For patients who rolled over into TRAVERSE, eosinophilia TEAEs occurred in 5.6% to 7.2%. Eosinophilia SAEs occurred in 1.0% and 1.9% of dupilumab-treated patients, of whom 0% and 2.2% discontinued treatment and 2.9% and 2.2% required corrective treatment for eosinophilia in VENTURE and patients rolled over from VENTURE into TRAVERSE, respectively.

Proportions of patients experiencing increases in eosinophil counts of greater than 1,500 and greater than 3,000 cells/μL during the treatment period were low across studies, and most patients returned to 1,500 cells/μL or less during the treatment period (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). The proportions of patients reaching greater than 1,500 and greater than 3,000 cells/μL during the treatment period were higher among patients with baseline eosinophils 500 cells/μL or higher (see Table E3 in this article's Online Repository at www.jaci-inpractice.org).

Cases of eosinophilia associated with clinical symptoms (defined as the investigator-reported Medical Dictionary for Regulatory Activities high-level term "eosinophilic disorder," excluding the preferred term "eosinophilia") were rare in dupilumab-treated patients (seven of 4,666 patients). Moreover, two cases occurred in placebo-treated patients with CRSwNP (Table I). Among patients with eosinophil counts of greater than 3,000 cells/μL, six adverse events possibly related to eosinophilia based on medical judgment were reported, all of which occurred in asthma or CRSwNP studies (Table I). Five patients in the asthma OLE and one in the CRSwNP study treated with dupilumab and two treated with placebo developed EGPA (all of whom had asthma), and most cases arose after at least 6 months of treatment (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Efficacy end points in patients with eosinophilia

Asthma. Unadjusted rates of severe exacerbations varied among asthma studies, in line with differences in enrolment criteria. Patients with eosinophil counts of greater than 1,500 cells/μL generally had higher exacerbation rates compared with those observed in the intention-to-treat (ITT) population. Lower rates were observed in dupilumab versus placebo in QUEST (0.45 vs 1.66), DRI (0.86 vs 4.38), and VENTURE (0.52 vs 2.14) (Figure 4, *A*). In TRAVERSE, unadjusted rates of severe exacerbations were similar between the ITT population and patients with eosinophil counts of greater than 1,500 cells/μL (Figure 4, *A*). In contrast, numerically higher exacerbation rates were observed in dupilumab/dupilumab patients rolled over from QUEST or VENTURE with eosinophilia TEAEs. However, subgroup population sizes for patients with an eosinophilia TEAE were small, which limits robust interpretation of these trends (Figure 4, *A*).

TABLE I. *(Continued)*

Asthma		CRSwNP*				AD†					EoE†	
TRAVERSE* (rolled over from VENTURE; 96-wk OLE)		SINUS-24 (24 wk)		SINUS-52 (52 wk)		SOLO-1 and -2 (16 wk)		CHRONOS (52 wk)		AD-OLE (188-wk OLE)	EoE POC (12 wk)	
PBO/DPL (n = 97)	DPL/DPL (n = 90)	PBO (n = 132)	DPL (n = 143)	PBO (n = 150)	DPL (n = 149)	PBO (n = 456)	DPL (n = 465)	PBO (n = 315)	DPL (n = 110)	Total (n = 2,677)	PBO (n = 24)	DPL (n = 23)
Eosinophilia TEAE*												
7 (7.2)	5 (5.6)	2 (1.5)	3 (2.1)	2 (1.3)	2 (1.3)	1 (0.2)	8 (1.7)	1 (0.3)	2 (1.8)	27 (1.0)	0	0
1 (1.0)	1 (1.1)	1 (0.8)	1 (0.7)	0	1 (0.7)	2 (0.4)	1 (0.2)	0	1 (0.9)	3 (0.1)	0	0
2 (2.1)	2 (2.2)	0	1 (0.7)	0	1 (0.7)	0	1 (0.2)	0	1 (0.9)	4 (0.1)	0	0
1 (1.0)	2 (2.2)	1 (0.8)	1 (0.7)	0	0	NA	NA	NA	NA	NA	NA	NA
6 (6.2)	3 (3.3)	1 (0.8)	2 (1.4)	2 (1.3)	1 (0.7)	1 (0.2)	8 (1.7)	1 (0.3)	2 (1.8)	26 (1.0)	0	0
Eosinophilia associated with clinical symptoms												
1 (EGPA)	1 (EGPA)	1 (EGPA)	1 (EGPA)	1 (EGPA)	0	0	0	0	0	0	0	0
1	1	1	1	1	0	0	0	0	0	0	0	0
0	0	0	0	0	1 (arthralgia and asthma exacerbation)	0	0	0	0	0	0	0

Change from baseline at week 12 in pre-bronchodilator FEV_1 was generally higher for dupilumab-treated patients with eosinophils of greater than 1,500 cells/μL or eosinophilia TEAEs compared with the ITT populations (Figure 4, *B*). Interpretation of results for patients with eosinophilia TEAEs were again limited by small sample sizes. One patient in DRI experienced an eosinophilia TEAE, so this subgroup could not be assessed. Similar changes from baseline in FEV_1 at week 48 were seen in TRAVERSE, irrespective of previous treatment in parent studies.

Chronic rhinosinusitis with nasal polyps. Changes from baseline in nasal polyp score and nasal congestion/obstruction score were similar in dupilumab-treated patients with eosinophilia to those in the overall study population; however, interpretation of results is limited owing to low sample sizes (Figure 4, *C* and *D*).

DISCUSSION

This analysis comparing 11 studies indicates that dupilumab treatment resulted in a transient increase in mean blood eosinophil counts in patients with asthma, CRSwNP, or AD, which typically declined to baseline or below baseline over time and was not generally associated with clinical symptoms or an impact on efficacy. Interestingly, no transient increases in blood eosinophil counts were observed in patients with EoE; however, this included a limited number of patients, and data from larger-scale phase 3 studies remain to be assessed.

In asthma and CRSwNP studies, eosinophil counts typically returned to baseline or lower after the first 24 weeks. Few patients experienced eosinophil counts of greater than 3,000 cells/μL. Despite having raised eosinophil counts, most patients experienced no clinical symptoms or sequalae, and rates of eosinophilia-related TEAEs were low across all studies. Most cases were of mild to moderate severity and few required treatment discontinuation. Similarly, eosinophilia was only rarely observed in postmarketing data: up to March 28, 2021, 571 cases of eosinophilia (not laboratory-defined) or related events were reported out of an estimated overall exposure of 360,748 patient-years (1 patient-year exposure = one patient exposed to dupilumab for 1 year; data not shown). The number of EGPA cases was also low, and all occurred in patients with asthma or CRSwNP with comorbid asthma. There was no meaningful evidence of reduced efficacy of dupilumab in patients with eosinophilia, although group sizes for eosinophilia TEAEs were too small to arrive at robust conclusions. In patients with AD, transient increases in absolute mean eosinophil counts were observed but were generally not reflected in median fold-change from baseline, which indicates that these increases were generally observed in patients with higher baseline eosinophil counts. Neither clinical symptoms nor EGPA was evident in patients with AD.

Further studies are needed to delineate the mechanisms behind the effect of dupilumab on eosinophil levels and why

these responses differ in AD compared with airway diseases such as asthma and CRSwNP. A potential mechanism is that dupilumab treatment inhibits eosinophil trafficking to the tissues, leading to a transient increase in blood eosinophils. Chemokines and adhesion molecules regulate adhesion of circulating eosinophils to blood vessels with receptors on the endothelium, such as vascular cell adhesion molecule (VCAM)-1. Expression of VCAM-1 is regulated by IL-4. Upon binding, eosinophils enter the tissue and migration is guided by chemokines, including thymus and activation-regulated chemokine, eotaxins, IL-5, and IL-13.[2] By blocking both IL-4 and IL-13 signaling, dupilumab may inhibit VCAM-1 expression and the eosinophil migration process.[7] This is also evidenced by reduced levels of serum eotaxin-3 and thymus and activation-regulated chemokine levels observed in dupilumab clinical trials.[10,14,25] Because IL-4 and IL-13 do not mediate eosinophil maturation and release into the blood, this reduced eosinophil migration into the tissue may lead to transient rises in blood eosinophil counts.

Few cases of eosinophilic pneumonia and EGPA were reported here, and a recent publication described two cases of eosinophilia adverse events in patients with asthma and CRSwNP treated with dupilumab.[26] This implies that the observed increase in blood eosinophils may not necessarily be limited to the periphery. The number of cases of eosinophilic pneumonia and EGPA reported in dupilumab-treated patients in these trials was low.

Given the observation from this analysis that the efficacy of dupilumab in asthma, CRSwNP, AD, and EoE is not directly linked to changes in blood eosinophil count, it is probable that the efficacy observed by blocking IL-4 and IL-13 signaling with dupilumab may be related to other known functions of IL-4 and IL-13, including effects on B-cell class-switching to IgE, mucus production, goblet cell hyperplasia, collagen production, and smooth muscle cell contractility.[4]

Although the temporary eosinophilia observed in these studies was only rarely associated with clinical symptoms or sequelae, it remains important for clinicians to base judgment on individual patient history and baseline eosinophil counts. The data presented here raise the possibility that patients with higher baseline eosinophil levels may be at greater risk for developing transient eosinophilia. Data from the VENTURE asthma study suggest that other factors, including the effects of systemic corticosteroids on eosinophil regulation, may also have a role in these responses. Whereas eosinophilic conditions have been reported in patients treated with dupilumab, the distribution of relatively rare symptomatic eosinophilia cases over time appears to be random.[8] Further monitoring and evaluation may be appropriate in cases in which elevated eosinophil counts persist or are associated with signs or symptoms raising clinical suspicion for an eosinophilic condition such as EGPA. General risk factors for developing EGPA include steroid-resistant disease or steroid tapering, the presence of antineutrophil cytoplasmic antibodies, and neuropathy. Because the asthma and CRSwNP clinical trial populations (except for DRI) were limited to patients with eosinophils of less than 1,500 cells/μL at screening, information on the potential effects of treatment on eosinophil counts in patients with higher baseline counts cannot be extrapolated from these data.

Strengths of this analysis are the inclusion of data from a large number of placebo-controlled clinical trials and the comparison of eosinophilia across a broad group of type 2 diseases. Unfortunately, the differences in study design and patient inclusion criteria precluded pooling of data across studies; therefore, the presented analyses are comparative in nature. Nonetheless, this analysis provides a broad overview of eosinophil count and eosinophilia events in dupilumab clinical studies to date.

CONCLUSIONS

In this analysis comparing eosinophil counts across 11 clinical trials in patients with a broad range of type 2 inflammatory diseases, dupilumab treatment resulted in transient increases in eosinophil counts in patients with asthma, CRSwNP, and AD. These were mostly not associated with clinical symptoms or sequalae and had no observable impact on treatment efficacy. Although these increases are mostly transient, clinician discretion should be used to monitor patients suspected of having an eosinophilic condition.

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