

Journal Pre-proof

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PII: S2213-2198(22)00507-4

DOI: <https://doi.org/10.1016/j.jaip.2022.05.019>

Reference: JAIP 4235

To appear in: *The Journal of Allergy and Clinical Immunology: In Practice*

Received Date: 12 November 2021

Revised Date: 4 May 2022

Accepted Date: 10 May 2022

Please cite this article as: Wechsler ME, Klion AD, Paggiaro P, Nair P, Staumont-Salle D, Radwan A, Johnson RR, Kapoor U, Khokhar FA, Daizadeh N, Chen Z, Laws E, Ortiz B, Jacob-Nara JA, Mannent LP, Rowe PJ, Deniz Y, Effect of Dupilumab on Blood Eosinophil Counts in Patients With Asthma, Chronic Rhinosinusitis With Nasal Polyps, Atopic Dermatitis, or Eosinophilic Esophagitis, *The Journal of Allergy and Clinical Immunology: In Practice* (2022), doi: <https://doi.org/10.1016/j.jaip.2022.05.019>.

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Support statement: The studies were sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifiers: NCT02414854, NCT01854047, NCT02528214, NCT02134028, NCT02912468, NCT02898454, NCT02277743, NCT02277769, NCT02260986, NCT01949311, NCT02379052.

24 **Disclosure of potential conflict of interest:**

25 **Wechsler ME:** AstraZeneca, Boehringer Ingelheim, Equillium, Gala Therapeutics, Genentech,
26 Genzyme, Mylan, Novartis, Pulmatrix, Regeneron Pharmaceuticals, Inc., resTORbio, Sentien
27 Biotechnologies, Teva – personal fees; GSK, Sanofi – grants and personal fees.

28 **Klion AD:** Nothing to disclose.

29 **Paggiaro P:** ALK-Abellò, AstraZeneca, Chiesi, GSK, Guidotti, Menarini, Mundipharma, Novartis, Sanofi
30 – institutional and personal grants for research activities and education.

31 **Nair P:** AstraZeneca, Boehringer Ingelheim, Cyclomedica, Foresee, Methapharm, Novartis, Roche,
32 Sanofi, Teva – grant support; AstraZeneca, Equillium, GSK, Merck, Sanofi, Teva – personal fees.

33 **Staumont-Salle D:** AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma,
34 LEO Pharma, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi – investigator, consultant, advisory
35 board member. AbbVie, AstraZeneca, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi –
36 consultant; AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, UCB – speaker.

37 **Radwan A, Khokhar FA, Chen Z, Deniz Y:** Regeneron Pharmaceuticals, Inc. – employees and
38 shareholders.

39 **Johnson R, Laws E, Jacob-Nara JA, Mannent LP, Rowe PJ:** Sanofi – employees, may hold stock
40 and/or stock options in the company.

41 **Daizadeh N, Kapoor U:** Sanofi – former employees, may hold stock and/or stock options in the
42 company.

43 **Ortiz B:** Regeneron Pharmaceuticals, Inc. – former employee and shareholder.

44

45 **Abstract:** 248/250 words

46 **Word count:** 3805/3500

47 **Tables and figures:** 5/8

48 **References:** 25

ABSTRACT

Background: Transient increases in blood eosinophil counts have been observed in dupilumab clinical trials.

Objective: Assessment of 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 (AD), and eosinophilic esophagitis (EoE).

Methods: Eosinophil counts, rates of eosinophilia-related TEAEs or treatment-emergent eosinophilia (>1500 cells/ μL), 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 AD (baseline: 434–600 cells/ μL ; week 4: 410–710 cells/ μL), followed by a decline starting by week 24 to baseline or below. No increases were seen in patients with EoE (baseline: 310 cells/ μL ; week 4: 230 cells/ μL). In dupilumab-treated patients across all studies, rates of eosinophilia TEAEs were 0%–13.6%. Clinical symptoms associated with increased eosinophils were rare (7/4666 dupilumab-treated patients, including 6 cases of eosinophilic granulomatosis with polyangiitis), and only occurred in patients with asthma or CRSwNP. Eosinophilia was not associated with reduced dupilumab efficacy.

Conclusion: Transient increases in eosinophil counts with dupilumab treatment did not impact efficacy and were rarely of clinical consequence. It remains important for physicians to base judgement on individual patient history and baseline eosinophil counts and be alert to hypereosinophilic symptoms.

Highlights box**What is already known about this topic?**

Transient increases in blood eosinophil counts have previously been reported in clinical trials with dupilumab in patients with asthma, CRSwNP, or AD.

What does this article add to our knowledge?

Transient increases in mean blood eosinophils in dupilumab-treated asthma, CRSwNP, or AD patients generally declined to below baseline and were not associated with decline in efficacy or clinical symptoms.

How does this study impact current management guidelines?

While the eosinophilia observed in these studies was temporary and only rarely associated with clinical symptoms, it remains important for clinicians to base judgement on individual patient history and baseline eosinophil counts.

Keywords

asthma; atopic dermatitis; chronic rhinosinusitis with nasal polyps; dupilumab; eosinophilia; eosinophilic esophagitis; eosinophils

87 Abbreviations

88 AD, atopic dermatitis

89 CRSwNP, chronic rhinosinusitis with nasal polyps

90 EGPA, eosinophilic granulomatosis with polyangiitis

91 EoE, eosinophilic esophagitis

92 FEV₁, forced expiratory volume in 1 second

93 ICS, inhaled corticosteroids

94 IgE, immunoglobulin E

95 IL, interleukin

96 IQR, interquartile range

97 ITT, intention-to-treat

98 NCS, nasal congestion/obstruction score

99 NPS, nasal polyp score

100 OCS, oral corticosteroids

101 OLE, open-label extension

102 POC, proof-of-concept

103 q2w, every 2 weeks

104 q4w, every 4 weeks

105 SAE, severe adverse event

106 TEAE, treatment-emergent adverse event

107 VCAM-1, vascular cell adhesion molecule 1

108 BACKGROUND

109 Chronic type 2 inflammatory diseases such as asthma, atopic dermatitis (AD), chronic rhinosinusitis
110 with nasal polyps (CRSwNP), and eosinophilic esophagitis (EoE) present a substantial and increasing
111 public health burden.¹ While there is variation in the underlying pathogenesis, type 2 inflammation
112 represents the dominant driver in these conditions.^{2,3} The type 2 inflammatory pathway is driven by
113 activation of type 2 CD4+ helper cells and innate lymphoid type 2 cells, resulting in tissue infiltration
114 of inflammatory cells such as eosinophils, mast cells, and basophils, and production of pro-
115 inflammatory cytokines including interleukin (IL)-4, IL-5, and IL-13.⁴ Dupilumab, a fully human
116 monoclonal antibody, blocks the shared receptor component for IL-4/IL-13, inhibiting their
117 signaling.⁵⁻⁷ Dupilumab is approved for patients with type 2 inflammatory diseases (AD, asthma, and
118 CRSwNP) and is currently under phase 3 investigation in EoE.⁸⁻¹⁸

119 Transient increases in eosinophil counts have been reported in dupilumab clinical trials.^{9-11,14,16} These
120 generally occurred in the first few weeks and returned to baseline or lower by the end of the
121 treatment period. The objective of this analysis was to aggregate data and compare the effect of
122 dupilumab on blood eosinophil counts over time across a broad range of type 2 diseases, and assess
123 its impact on eosinophilia-related treatment-emergent adverse events (TEAEs), clinical symptoms,
124 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], open-label extension [OLE] TRAVERSE [NCT02134028]); adults with severe CRSwNP (phase 3 LIBERTY NP SINUS-24 [SINUS-24; NCT02912468], 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], 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/consent was obtained from all participants prior to enrolment, and protocols and consent forms were reviewed by appropriate review boards/ethics committees prior to study commencement. Full study design details and patient characteristics have been published previously,^{9-11, 14-16, 18-21} a brief summary of each is provided in the **Online Repository and Table E1**.

Patients included in this analysis

Due to 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. Only data for biweekly dosing are included for SINUS-52 and the AD studies, for data consistency. 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 the studies. Mean, median, and median fold-change from baseline in eosinophil counts was assessed within each study at each of the timepoints when data were available. Numbers of patients reaching eosinophil counts >1500 or >3000 cells/ μL during the treatment period, commonly used measurements for eosinophilia and severe eosinophilia.^{22–24} were 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 (MedDRA) 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; EoE POC: 19.1). Eosinophilia TEAE was defined as 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 >3000 cells/ μL was also reported as an eosinophilia TEAE. Numbers of patients with TEAEs, severe adverse events (SAEs), discontinuing treatment due to eosinophilia, experiencing related clinical symptoms, reporting eosinophilic granulomatosis with polyangiitis (EGPA), requiring corrective treatment, and recovered were assessed.

Efficacy measures were assessed in patients with treatment-emergent eosinophilia (>1500 cells/ μL or eosinophilia TEAE) enrolled in the asthma and CRSwNP studies. For asthma, unadjusted annualized severe exacerbation rates (calculated as total number of events that occurred during the treatment period divided by total number of patient-years followed during the same treatment period) were assessed by treatment group. Unadjusted estimates were computed to enable comparison with estimates obtained in the subgroup of patients with at least one result >1500 eosinophils/ μL post-baseline or reporting an eosinophilia TEAE. Similarly, mean change from baseline in pre-bronchodilator forced expiratory volume in one second (FEV_1) at week 12 (QUEST,

DRI, VENTURE) or week 24 (TRAVERSE) was calculated. For CRSwNP, data post-systemic corticosteroid use or nasal polyp surgery were set to missing and imputed using the worst observation carried forward method. The mean changes from baseline in nasal polyp score (NPS) and nasal congestion/obstruction score (NCS) at week 24 were calculated.

Statistical analysis

Due to 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 the 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. All statistical analyses were performed using SAS version 9.4.

RESULTS

In total, 6642 patients were included in the analysis: 2876 with asthma (QUEST: 1897; VENTURE: 210; DRI: 769), 2249 of whom rolled over into TRAVERSE; 574 with CRSwNP (SINUS-24: 275; SINUS-52: 299); 3145 with AD (SOLO1&2: 921; CHRONOS: 425; AD-OLE: 2677, 878 of whom rolled over from assessed treatment arms of SOLO-1 & -2 and CHRONOS); and 47 with EoE. Full details of patient demographics and baseline characteristics have been published previously.^{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 **Fig 1A**, where it can be observed that median and interquartile ranges (IQRs) of blood eosinophil counts remained relatively unchanged throughout the treatment period for QUEST and DRI (**Fig 1A**). In DRI, median baseline eosinophil count was 260 cells/ μ L in both placebo (IQR: 160–430) and dupilumab (150–420) groups. Median values remained within the 240–270 cells/ μ L (placebo) and 230–260 cells/ μ L (dupilumab) ranges throughout the study. In QUEST, median values also remained within the ranges of 240–280 cells/ μ L (placebo) and 200–260 cells/ μ L (dupilumab). In VENTURE, median eosinophil counts were higher, and a clear elevation was seen in the dupilumab group (median 470 cells/ μ L by week 24, baseline count 280 cells/ μ L).

When examining mean eosinophil counts, transient increases were observed in QUEST, DRI and VENTURE in dupilumab but not placebo groups (**Fig 2A**). By week 4, mean eosinophil counts had risen from 348.9 cells/ μ L to 514.6 cells/ μ L in DRI, from 350.9 cells/ μ L to 481.0 cells/ μ L in QUEST, and from 369.5 cells/ μ L to 578.7 cells/ μ L in VENTURE (**Fig 2A**). 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/ μ L at week 52 in QUEST). The differences observed between median and mean eosinophil counts in QUEST and

DRI, with increases in mean eosinophil counts and no change in median counts, could be due to the spread of values that can be observed in the box plots in **Fig 1A**, which suggest that the rise in mean eosinophil levels is 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/ μ L, median 250 cells/ μ L; week 96: mean 243.5 cells/ μ L, median 165 cells/ μ L). 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/ μ L, median 270 cells/ μ L; week 4: mean 367.8 cells/ μ L, median 230 cells/ μ L). For patients enrolled in DRI who continued into both treatment arms of TRAVERSE following the 16-week gap in dupilumab dosing, a transient rise in mean eosinophil counts was observed from baseline (placebo/dupilumab: 328.7 cells/ μ L; dupilumab/dupilumab: 366.3 cells/ μ L), to week 4 (placebo/dupilumab: 486.1 cells/ μ L; dupilumab/dupilumab: 406.3 cells/ μ L), which resolved by week 24 (placebo/dupilumab: 351.5 cells/ μ L; dupilumab/dupilumab: 318.0 cells/ μ L). Median eosinophils remained relatively unchanged throughout (**Fig 1A, Fig 2A**).

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

CRSwNP

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

AD

In patients with AD, a slight rise in median eosinophils was observed at week 4 (baseline, 400 cells/ μ L; week 4, 500 cells/ μ L), which declined to baseline by week 8 (400 cells/ μ L) in dupilumab-treated patients enrolled in SOLO-1 and SOLO-2 (**Fig 1C**). Elevated mean eosinophil counts were observed from week 4 through week 12 (baseline, 600 cells/ μ L; week 4, 710 cells/ μ L; week 12, 620 cells/ μ L) versus placebo (baseline, 620 cells/ μ L; week 4, 590 cells/ μ L; week 12, 480 cells/ μ L) (**Fig 2C**). Similar trends were observed in CHRONOS, with an initial slight rise in mean eosinophils, from 580 cells/ μ L at baseline to 600 cells/ μ L by week 8, which dropped to similar or below baseline from week 12 (480 cells/ μ L); median eosinophil counts declined from week 16 (340 cells/ μ L) to week 52 (300 cells/ μ L). In AD-OLE, mean and median eosinophil counts increased slightly from baseline (mean 434 cells/ μ L, median 310 cells/ μ L) to week 24 (mean 452 cells/ μ L, median 330 cells/ μ L), but then gradually decreased to substantially lower than baseline as the study progressed (week 84: mean 318 cells/ μ L, median 220 cells/ μ L) (**Figs 1C and 2C**).

EoE

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/ μ L, median 300 cells/ μ L) to the first measurement at week 2 (mean 230 cells/ μ L, median 200 cells/ μ L) to week 12 (mean 170 cells/ μ L, median 200 cells/ μ L) (**Figs 1D and 2D**).

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, placebo 1.0), 8 (dupilumab 1.10, placebo 1), and 20 (dupilumab 1.09, placebo 0.96), with lower changes observed at week 52 (dupilumab 0.88, placebo 0.94) (**Fig 3A**). 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, dupilumab/dupilumab 0.77; week 72: placebo/dupilumab 0.73, 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, placebo 1.00; week 8: dupilumab 1.06, placebo 0.96); however, these returned to baseline or lower by week 12 (dupilumab 1.00, placebo 0.94). For dupilumab/dupilumab patients in TRAVERSE, minimal changes in median fold-change from 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, placebo 0.93; week 24: dupilumab 1.41, 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.

CRSwNP

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 (**Fig 3B**). By week 52, however, patients treated with dupilumab had a lower median fold-change from baseline than placebo.

AD

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) (**Fig 3C**).

EoE

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 timepoint (median fold-change from baseline 0.50 at week 12) (**Fig 3D**).

Eosinophilia

A total of 161 eosinophilia TEAEs and 22 eosinophilia SAEs were reported in the 6642 patients across all studies and diseases and were included in the analysis.

Excluding patients from VENTURE who were undergoing OCS reduction due to the association of OCS reduction with increased risk of severe eosinophilic events, rates of eosinophilia TEAEs during the treatment period, defined per each study protocol (with/without symptoms), ranged from 0–4.1% in the dupilumab groups and 0–1.5% in the placebo groups; most were of mild-to-moderate severity (**Table I**). Generally, rates of eosinophilia SAEs were higher in the dupilumab groups (0–1.9%) across studies (placebo: 0–0.8%). Percentages of dupilumab-treated patients discontinuing treatment or requiring corrective treatment were low across all studies (0–0.9% and 0–0.7%, 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

5.6–7.2%. 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 >1500 and >3000 cells/ μL during the treatment period were low across studies, and most patients returned to ≤ 1500 cells/ μL during the treatment period (**Table E2**). The proportions of patients reaching >1500 and >3000 cells/ μL during the treatment period were higher among patients with baseline eosinophils ≥ 500 cells/ μL (**Table E3**).

Cases of eosinophilia associated with clinical symptoms (defined as an investigator-reported MedDRA High-Level Term “Eosinophilic Disorder,” excluding the Preferred Term “Eosinophilia,” were rare in dupilumab-treated patients (7/4666 patients). Moreover, 2 cases occurred in placebo-treated patients with CRSwNP (**Table I**). Among patients with eosinophil counts >3000 cells/ μL , 6 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 studies treated with dupilumab and 2 treated with placebo developed EGPA (all of whom had asthma), and a majority of cases arose after at least 6 months of treatment (**Table E4**).

Efficacy endpoints in patients with eosinophilia

Asthma

Unadjusted rates of severe exacerbations varied between the asthma studies, in line with differences in enrolment criteria. Patients with eosinophil counts >1500 cells/ μL generally had higher exacerbation rates compared with those observed in the intention-to-treat (ITT) population, with lower rates 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) (**Fig 4A**). In TRAVERSE, unadjusted rates of severe exacerbations were similar between the ITT population and patients with eosinophil counts >1500 cells/ μL (**Fig 4A**). 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 very small, which limits robust interpretation of these trends (**Fig 4A**).

Change from baseline at week 12 in pre-bronchodilator FEV₁ was generally higher for dupilumab-treated patients with eosinophils >1500 cells/μL or eosinophilia TEAEs compared with the ITT populations (**Fig 4B**). Interpretation of results for patients with eosinophilia TEAEs were once 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 FEV₁ at week 48 were seen in TRAVERSE, irrespective of previous treatment in parent studies.

CRSwNP

Changes from baseline in NPS and NCS were similar in dupilumab-treated patients with eosinophilia as in the overall study population; however, interpretation of results is limited due to low sample sizes (**Fig 4C and 4D**).

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; very few patients experienced eosinophil counts >3000 cells/ μ L. Despite having raised eosinophil counts, most patients experienced no clinical symptoms or sequelae, and rates of eosinophilia-related TEAEs were low across all studies; most cases were of mild-to-moderate severity and very few required treatment discontinuation. Similarly, eosinophilia was only rarely observed in post-marketing 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 = 1 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 make 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, indicating that these increases were generally observed in patients with higher baseline eosinophil counts. Neither clinical symptoms nor EGPA were 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 to airway diseases, such as asthma and CRSwNP. One 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. VCAM-1 expression 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} As 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 has described 2 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. It should be noted that the number of cases of eosinophilic pneumonia and EGPA reported in dupilumab-treated patients in these trials was very 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

While the temporary eosinophilia observed in these studies was only rarely associated with clinical symptoms or sequelae, it remains important for clinicians to base judgement 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 the development of transient eosinophilia. The data from the VENTURE asthma study suggest that other factors, including the

effects of systemic corticosteroids on eosinophil regulation, may also play 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 and/or are associated with signs or symptoms raising clinical suspicion of an eosinophilic condition such as EGPA. General risk factors for the development of EGPA include steroid-resistant disease or steroid tapering, the presence of antineutrophil cytoplasmic antibodies, and neuropathy. As the asthma and CRSwNP clinical trial populations (except for DRI) were limited to patients with eosinophils <1500 cells/ μ L at screening, information on the potential effects of treatment on eosinophil counts in patients with higher baseline counts cannot be extrapolated from these data. The 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.

409 CONCLUSIONS

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

416 ACKNOWLEDGMENTS

417 Regeneron Pharmaceuticals, Inc.: Nora Crikelair; Sanofi: Colin Mitchell. This research was supported
418 in part by the Intramural Research Program of the NIH. Medical writing/editorial assistance was
419 provided by Grace Manley, PhD, of Excerpta Medica, funded by Sanofi and Regeneron
420 Pharmaceuticals, Inc., according to the Good Publication Practice guideline.

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FIGURE LEGENDS

FIG 1. Box-and-whisker plots of absolute blood eosinophil counts over time in each of the studies for patients with (A) asthma, (B) chronic rhinosinusitis with nasal polyps, (C) atopic dermatitis, and (D) eosinophilic esophagitis.

AD, atopic dermatitis; BL, baseline; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; POC, proof-of-concept; q2w, every 2 weeks; qw, weekly. From top to bottom, the box plots show maximum excluding outliers, Q3, median, Q1, and minimum excluding outliers. Outliers are plotted as individual points and the mean is represented by a red cross.

FIG 2. Mean blood eosinophil counts over time for individual studies in patients with (A) asthma, (B) chronic rhinosinusitis with nasal polyps, (C) atopic dermatitis, and (D) eosinophilic esophagitis.

AD, atopic dermatitis; BL, baseline; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; POC, proof-of-concept; q2w, every 2 weeks; qw, weekly, SD, standard deviation.

FIG 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, (C) atopic dermatitis, and (D) eosinophilic esophagitis.

AD, atopic dermatitis; BL, baseline; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; EoE, eosinophilic esophagitis; POC, proof-of-concept; q2w, every 2 weeks; qw, weekly.

FIG 4. Efficacy endpoints in the overall intention-to-treat populations, and in patients with >1500 eosinophils/ μ L or reporting an eosinophilia treatment-emergent adverse event. (A) Unadjusted

520 annualized exacerbation rates and (B) change from baseline in pre-bronchodilator FEV₁ in patients
521 with asthma; (C) change from baseline in nasal polyp score, and (D) change from baseline in nasal
522 congestion score at week 24 in patients with chronic rhinosinusitis with nasal polyps.

523 eos, eosinophils; FEV₁, forced expiratory volume in 1 second; ITT, intention-to-treat; NC, nasal
524 congestion; NPS, nasal polyp score; q2w, every 2 weeks; SD, standard deviation; TEAE, treatment-
525 emergent adverse event.

526 Only one patient in DRI experienced an eosinophilia TEAE, so this subgroup could not be assessed.

TABLES

Table I. Rates of eosinophilia treatment-emergent adverse events (TEAEs), severe adverse events, discontinuations due to eosinophilia, use of corrective treatment, and recovery rates for each of the studies

	Asthma										CRSwNP ^a				AD ^b				EoE ^b				
	QUEST ^a (52 weeks)		DRI ^b (24 weeks)		VENTURE ^a (24 weeks)		TRAVERSE ^a (rolled over from QUEST; 96-week OLE)		TRAVERSE ^a (rolled over from DRI; 96-week OLE)		TRAVERSE ^a (rolled over from VENTURE; 96-week OLE)		SINUS-24 (24 weeks)		SINUS-52 (52 weeks)		SOLO1&2 (16 weeks)		CHRONOS (52 weeks)		AD- OLE (188 week- OLE)	EoE POC (12 weeks)	
	PBO (N=634)	DPL (N=1263)	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)	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=2677)	PBO (N=24)	DPL (N=23)
Eosinophilia TEAE ^a																							
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)	2 (2.1)	2 (2.2)	0	1 (0.7)	0	1 (0.7)	0	1 (0.2)	1 (0.2)	1 (0.9)	4 (0.1)	0	0
SAE, n (%)	0	2 (0.2)	0	1 (0.2)	0	2 (1.9)	1 (0.2)	2 (0.2)	0	2 (0.5)	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
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)	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

Eosinophilia associated with clinical symptoms				Recovered by end of treatment	Require corrective treatment
Patients with EGPA, n (%)	Patients with a TEAE under HLT <i>eosinophilic disorders</i> excluding PT <i>eosinophilia</i> , n (%)				
0	0			3 (0.5)	1 (0.2)
0	1 (eosinophilic pneumonia)			41 (3.2)	5 (0.4)
0	0			0	0
0	0			1 (0.2)	1 (0.2)
0	0			1 (0.9)	1 (0.9)
0	0			11 (10.7)	3 (2.9)
0	0			5 (0.1)	2 (0.4)
2	2 (EGPA)			1 (< 0.1)	2 (0.2)
0	0			4 (3.6)	0
1	1 (EGPA)			10 (2.4)	3 (0.7)
1	1 (EGPA)			6 (6.2)	1 (1.0)
1	1 (EGPA)			3 (3.3)	2 (2.2)
1	1 (EGPA)			1 (0.8)	1 (0.8)
1	1 (EGPA)			2 (1.4)	1 (0.7)
1	1 (EGPA)			2 (1.3)	0
0	0			1 (0.7)	0
0	0			1 (0.2)	NA
0	0			8 (1.7)	NA
0	0			1 (0.3)	NA
0	0			2 (1.8)	NA
0	0			26 (1.0)	NA
0	0			0	NA
0	0			0	NA

AEs potentially related to eosinophilia concomitant with a rise in eosinophils >3000 cells/ μ L ^b , 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	0	0	0	0	0	1 (arthralgia and asthma exacerbation)	0	0	0	0	0	0	0
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AE, adverse event; DPL, dupilumab; EGPA, eosinophilic granulomatosis with polyangiitis; HLT; MedDRA High Level Term; NA, not available; PBO, placebo; PT, MedDRA Preferred

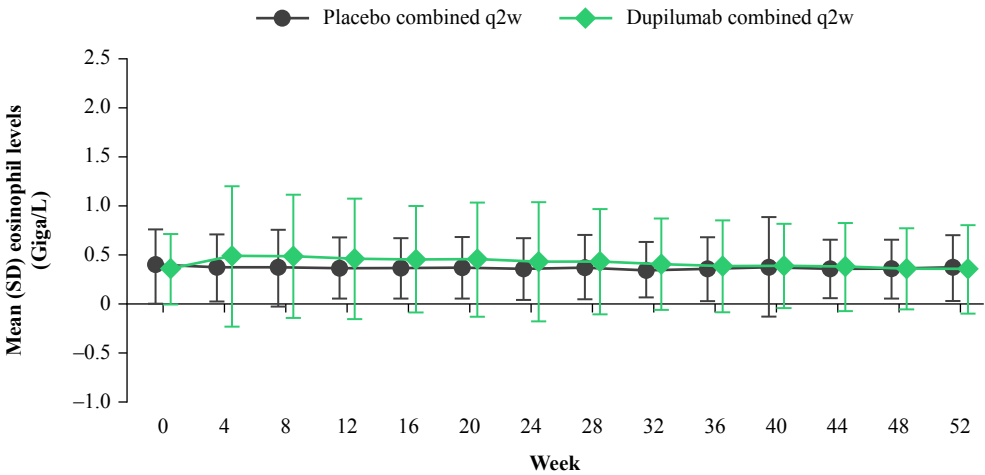
Term; SAE, severe adverse event; TEAE, treatment-emergent adverse event.

^aFor 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 >3000 cells/ μ L were reported as AEs. For DRI, AD, and EoE studies, "Eosinophilia TEAE" are defined per study protocol as HLT "Eosinophilic disorders" or PT "Eosinophil count increased."

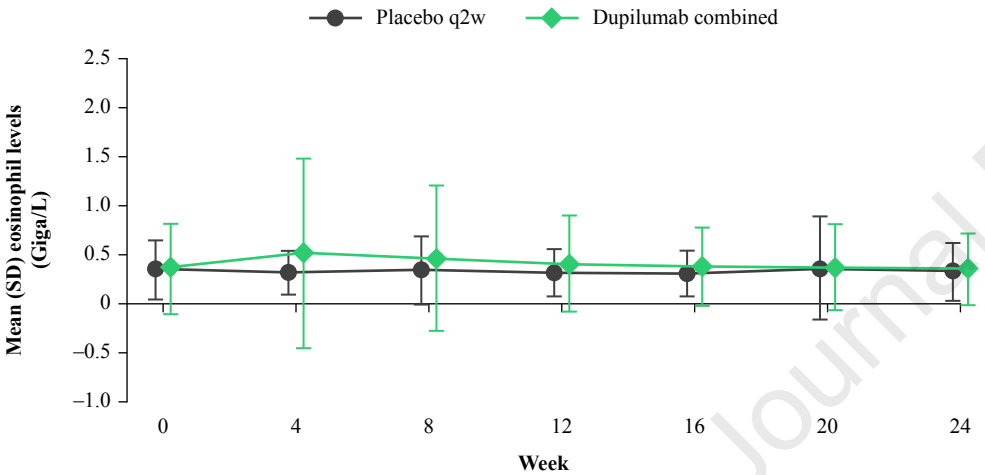
^bAs medically reviewed by the sponsor.

(A) Asthma
QUEST



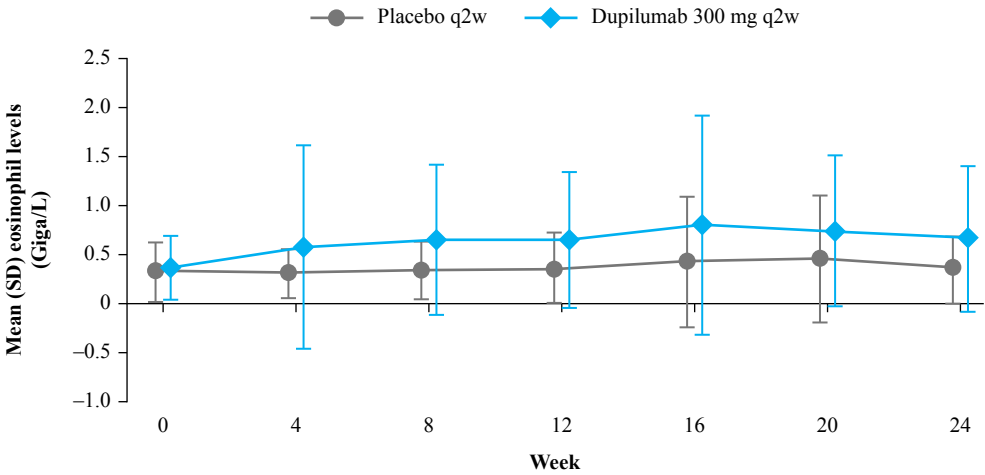
Placebo, n	633	607	604	600	593	579	580	576	575	573	568	558	548	480
Dupilumab, n	1262	1226	1186	1190	1185	1162	1155	1152	1127	1141	1126	1115	1090	941

DRI



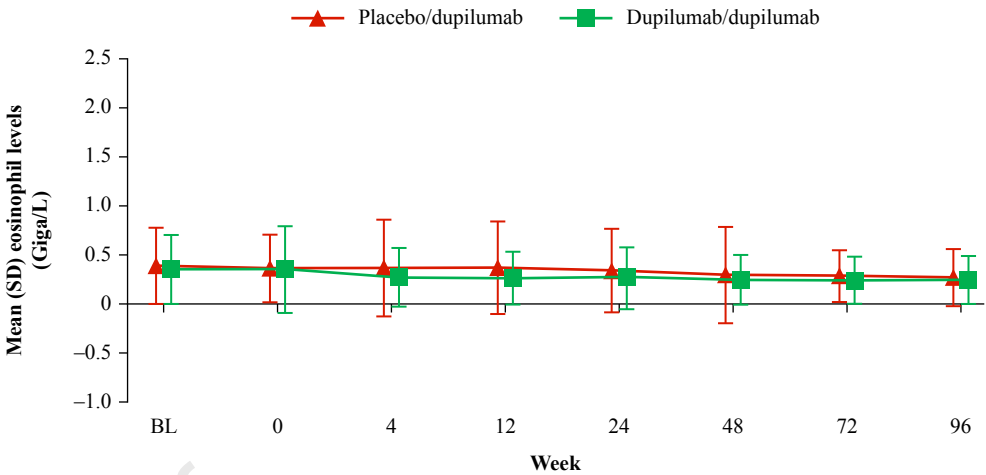
Placebo, n	158	153	149	146	144	145	137
Dupilumab, n	611	579	561	563	557	543	541

VENTURE



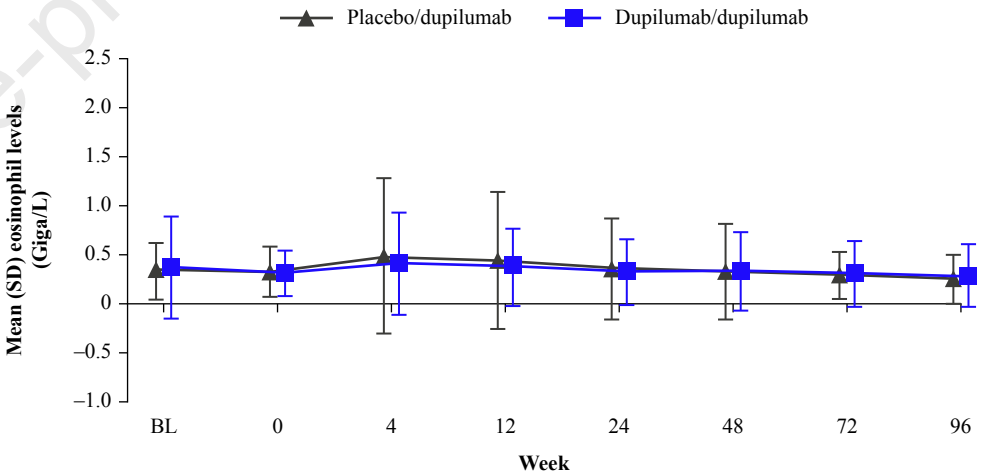
Placebo, n	107	104	105	98	103	105	101
Dupilumab, n	103	97	94	99	96	98	99

TRAVERSE – patients rolled over from QUEST



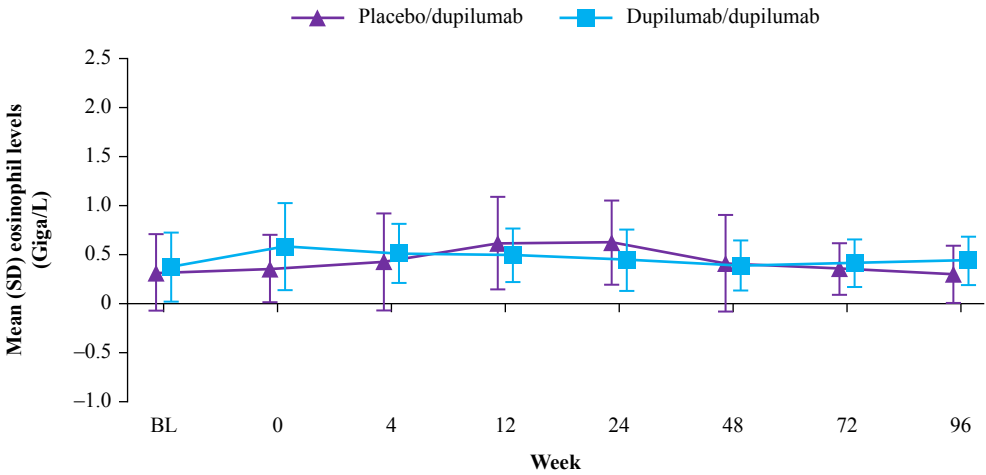
Placebo/dupilumab, n	516	501	494	501	497	475	221	219
Dupilumab/dupilumab, n	1012	962	975	983	980	936	451	436

TRAVERSE – patients rolled over from DRI

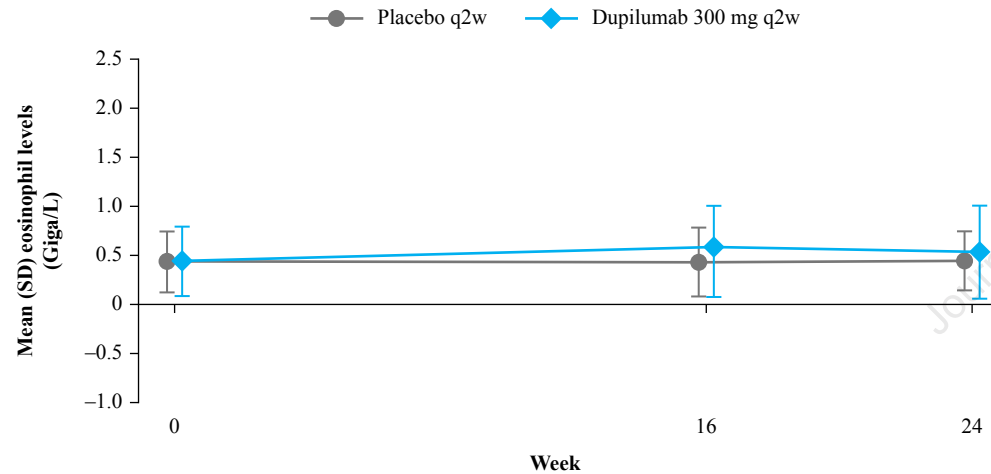


Placebo/dupilumab, n	111	109	103	110	110	103	106	102
Dupilumab/dupilumab, n	421	408	404	419	408	386	382	381

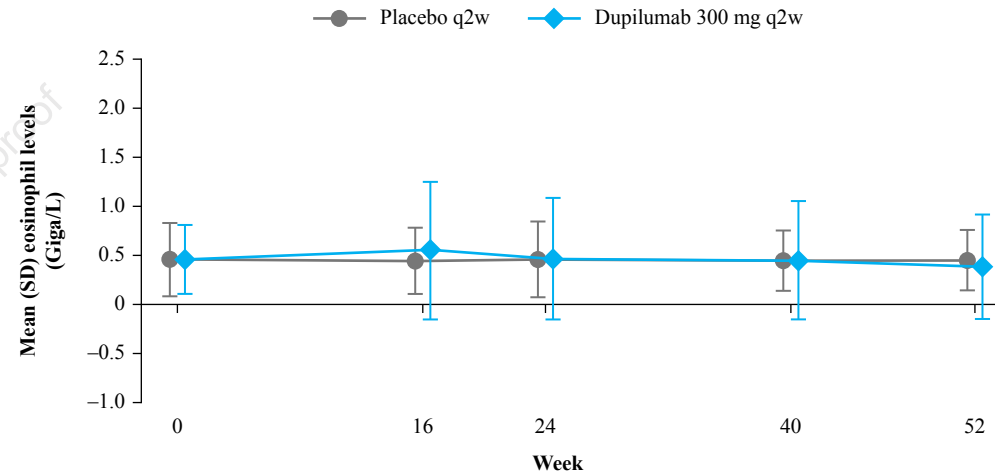
TRAVERSE – patients rolled over from VENTURE



Placebo/dupilumab, n	97	94	95	93	91	87	29	30
Dupilumab/dupilumab, n	90	88	83	85	82	82	26	29

(B) CRSwNP**SINUS-24**

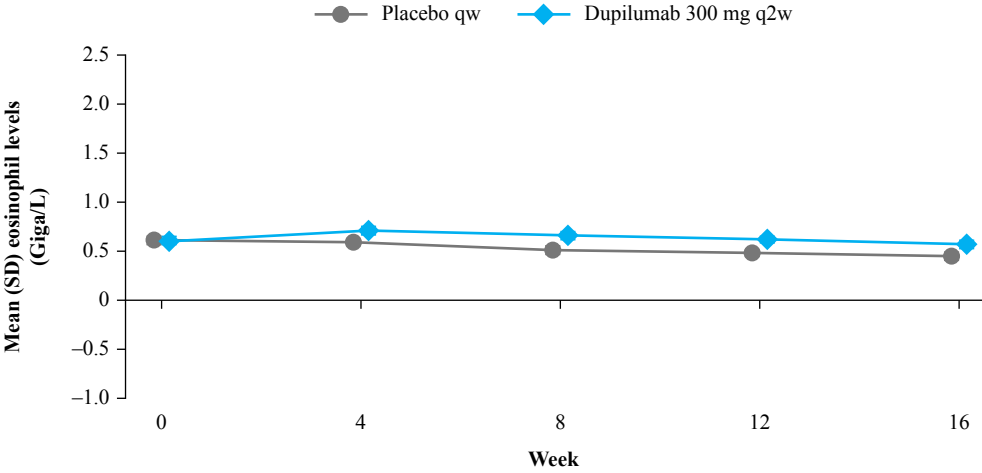
Placebo, n	132	129	123
Dupilumab, n	143	137	133

SINUS-52

Placebo, n	150	143	135	125	117
Dupilumab, n	148	141	141	136	134

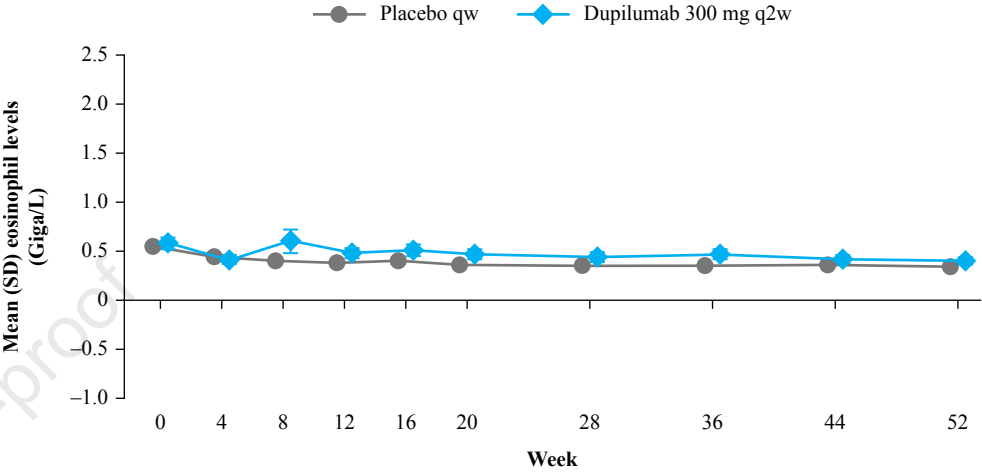
(C) AD

SOLO-1 & -2



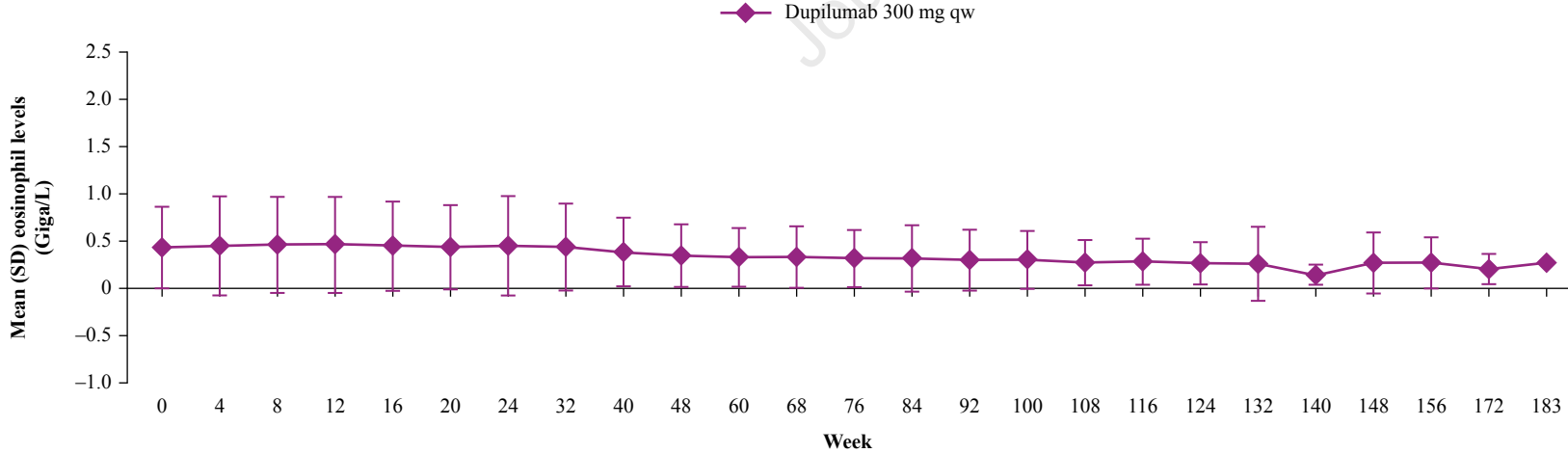
Placebo, n	454	324	235	208	195
Dupilumab, n	465	412	392	382	360

CHRONOS

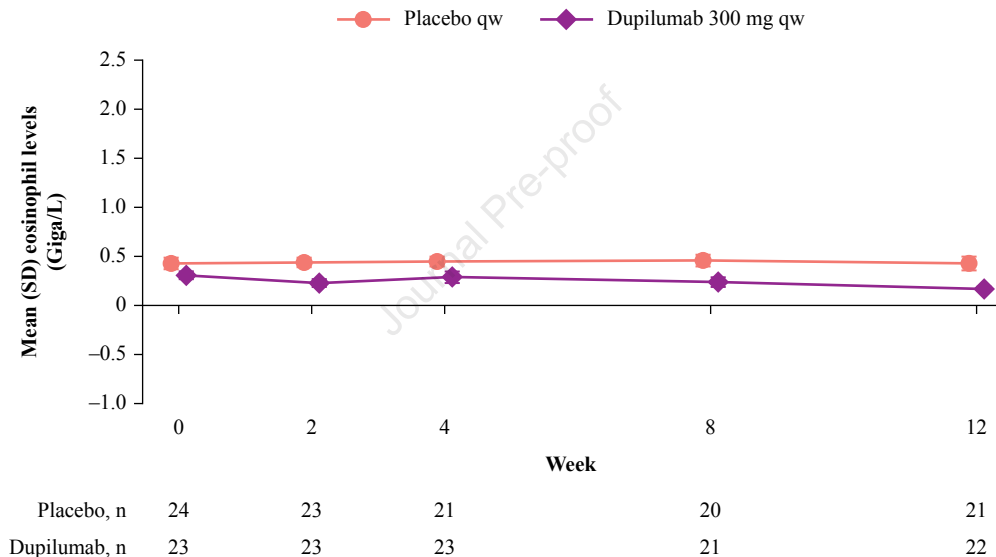


Placebo, n	314	269	240	207	187	172	151	135	125	120
Dupilumab, n	110	98	97	90	91	90	86	84	83	83

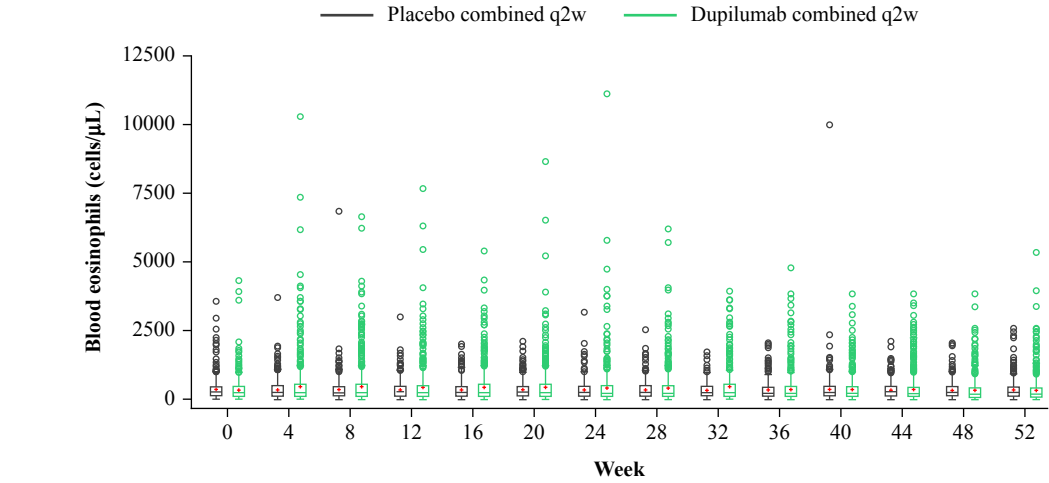
AD-OLE



Dupilumab, n	2638	2378	2315	2167	2535	1781	1592	1351	1261	2301	700	649	613	559	524	1023	566	375	171	95	49	331	175	7	1
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(D) EOE**POC**

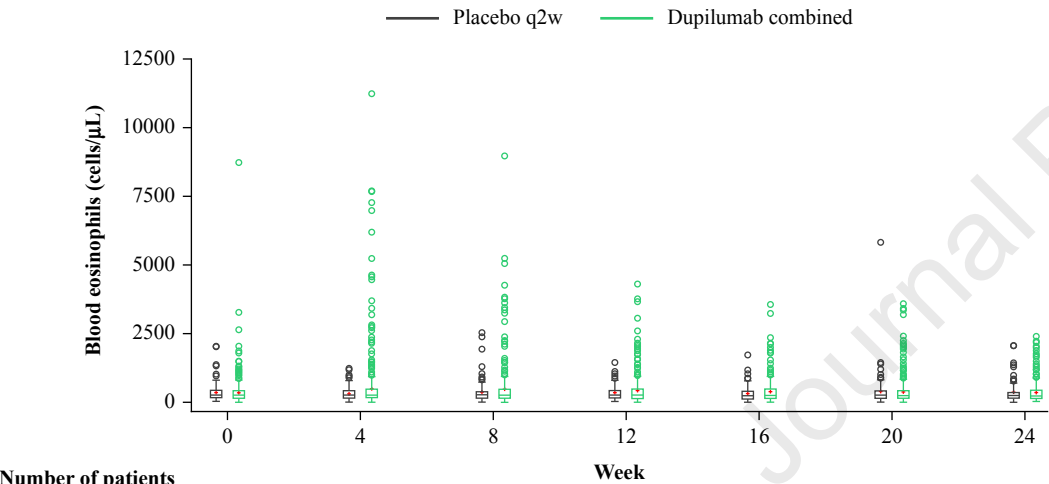
(A) Asthma
QUEST



Number of patients

Placebo, n	633	607	604	600	593	579	580	576	575	573	568	558	548	480
Dupilumab, n	1262	1226	1186	1190	1185	1162	1155	1152	1127	1141	1126	1115	1090	941

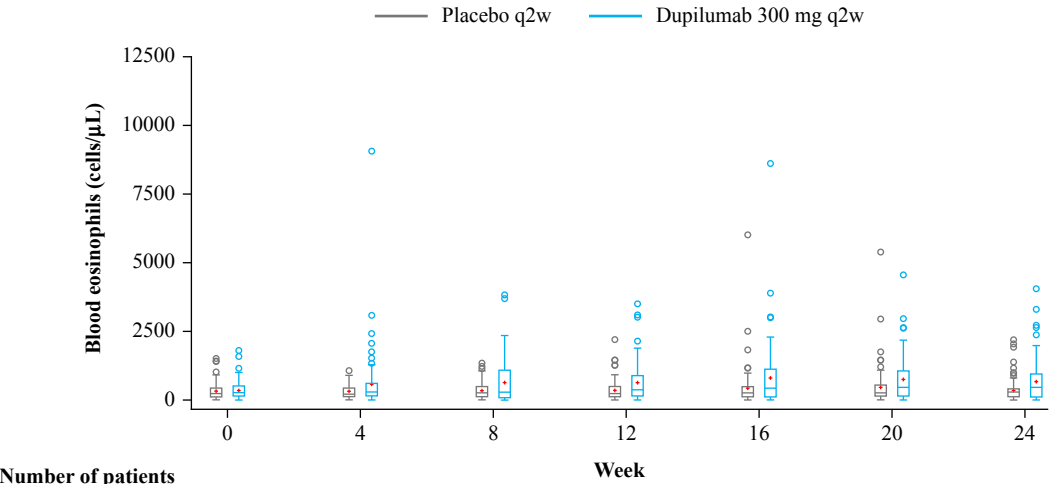
DRI



Number of patients

Placebo, n	158	153	149	146	144	145	137
Dupilumab, n	611	579	561	563	557	543	541

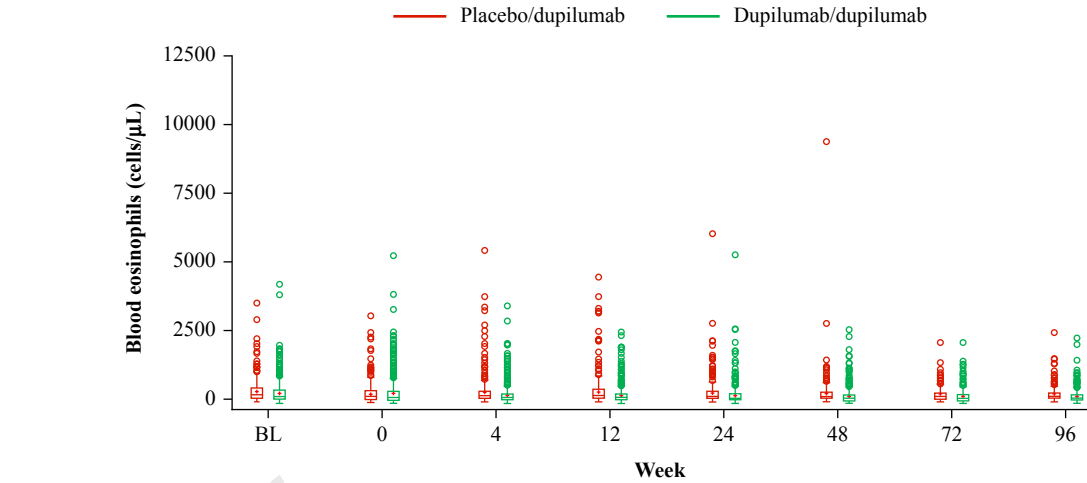
VENTURE



Number of patients

Placebo, n	107	104	105	98	103	105	101
Dupilumab, n	103	97	94	99	96	98	99

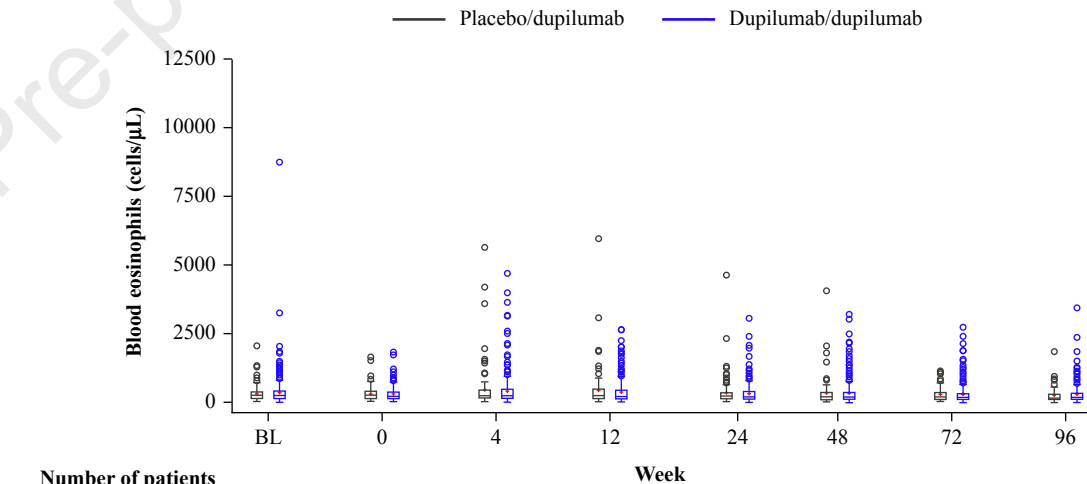
TRAVERSE – patients rolled over from QUEST



Number of patients

Placebo/dupilumab, n	516	501	494	501	497	475	221	219
Dupilumab/dupilumab, n	1012	962	975	983	980	936	451	436

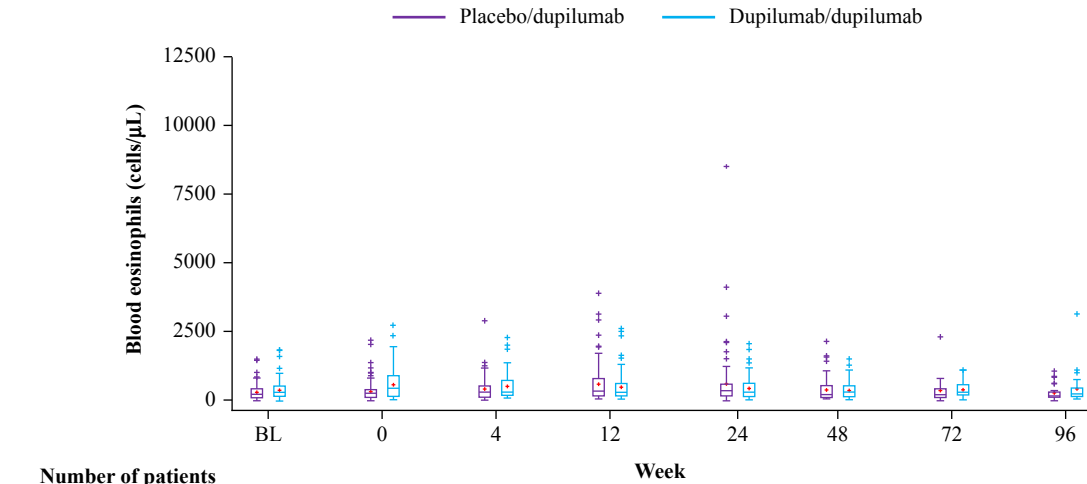
TRAVERSE – patients rolled over from DRI



Number of patients

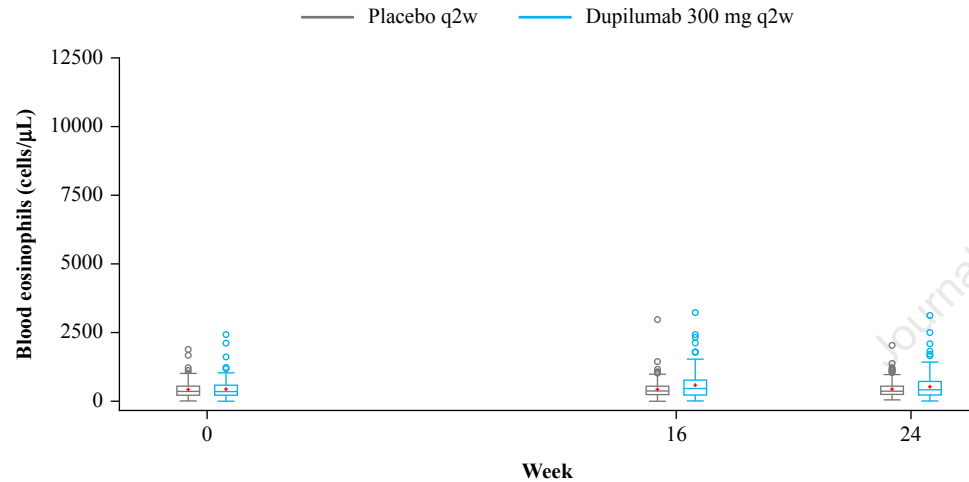
Placebo/dupilumab, n	111	109	103	110	110	103	106	102
Dupilumab/dupilumab, n	421	408	404	419	408	386	382	381

TRAVERSE – patients rolled over from VENTURE

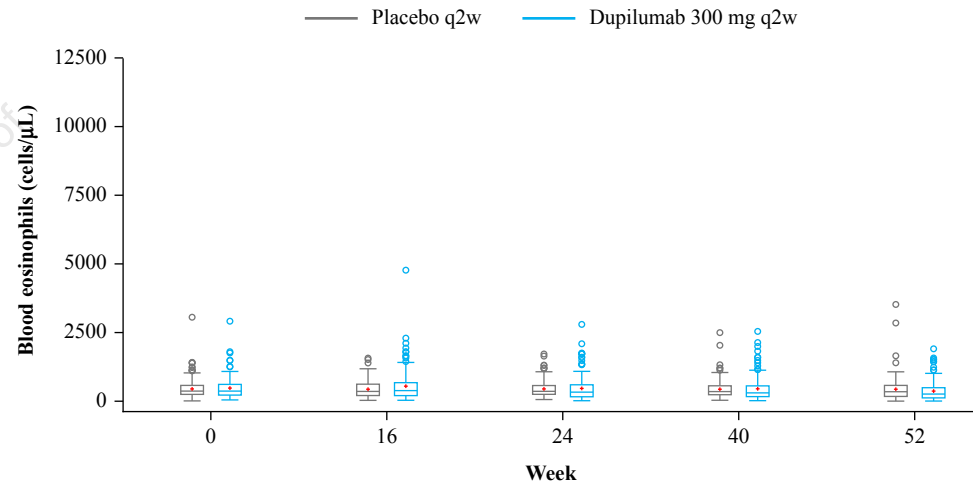


Number of patients

Placebo/dupilumab, n	97	94	95	93	91	87	29	30
Dupilumab/dupilumab, n	90	88	83	85	82	82	26	29

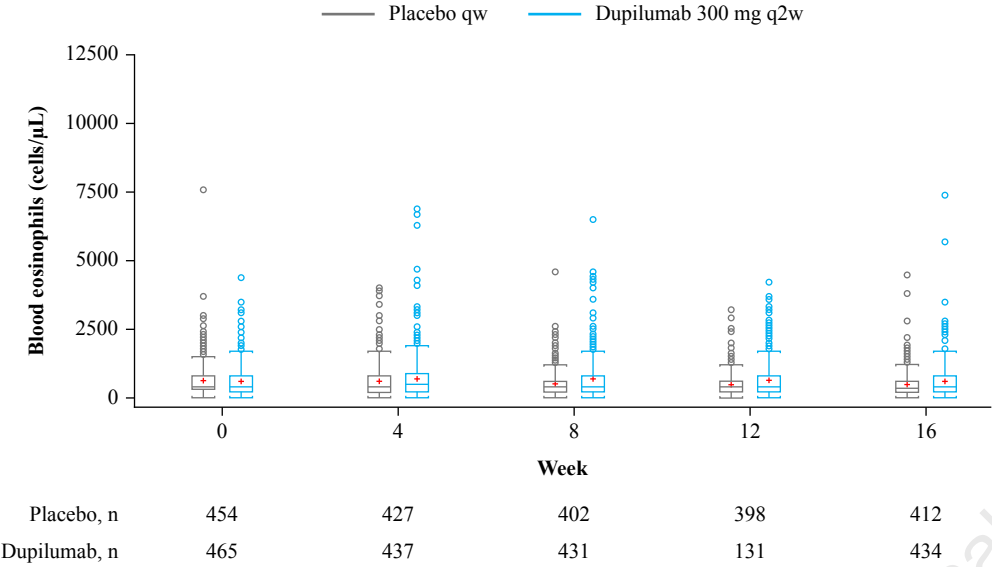
(B) CRSwNP**SINUS-24****Number of patients**

Placebo, n	132
Dupilumab, n	143

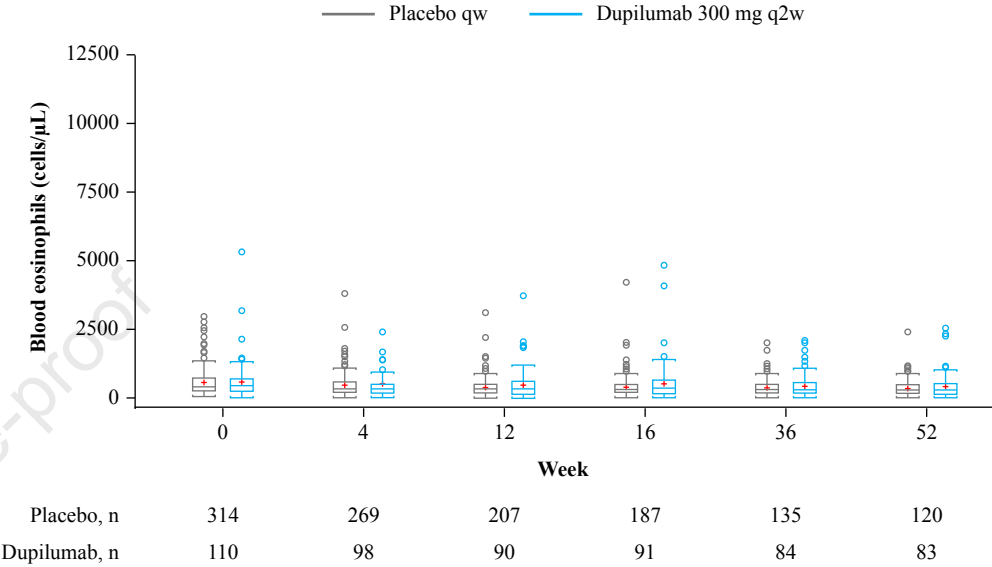
SINUS-52**Number of patients**

Placebo, n	150	143	137	131	130
Dupilumab, n	148	141	142	140	142

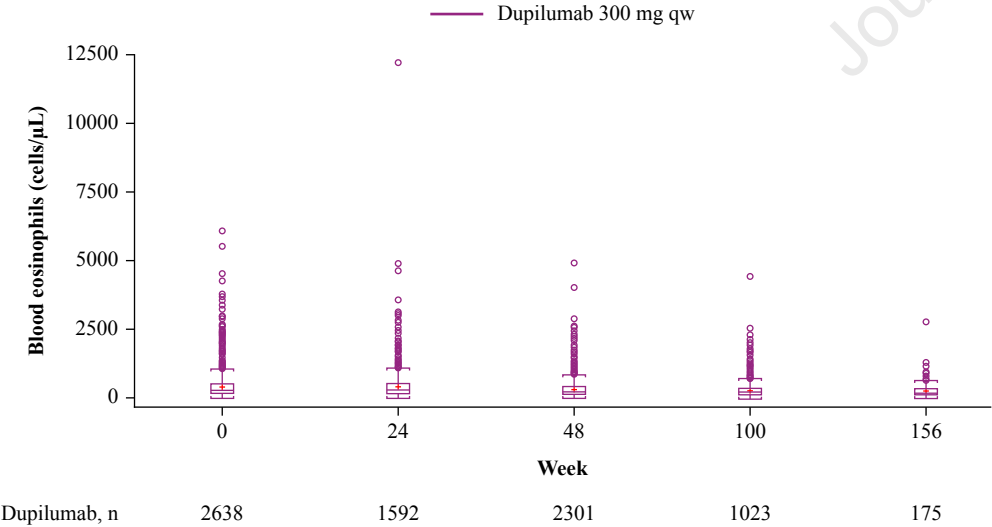
(C) AD
SOLO-1 & -2

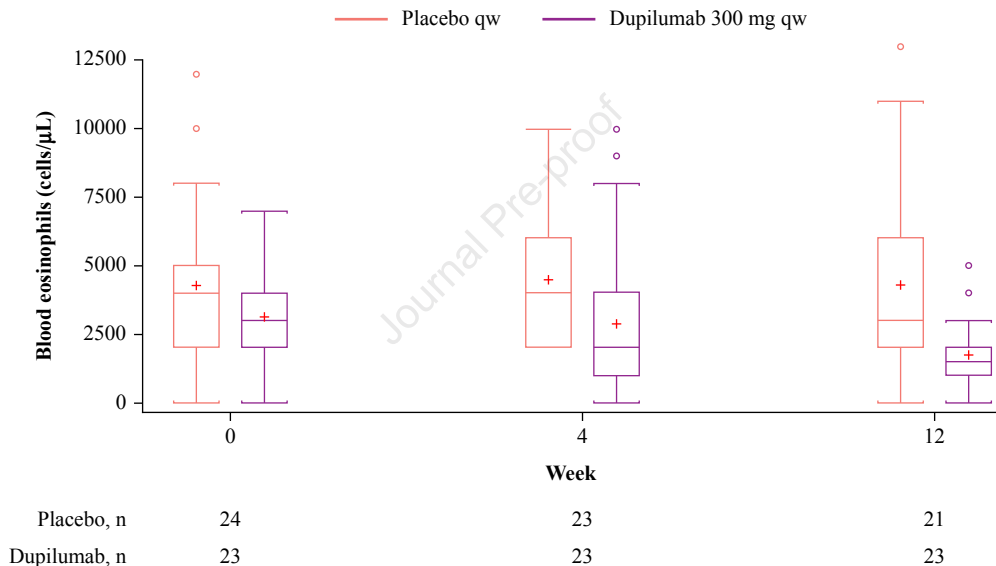


CHRONOS



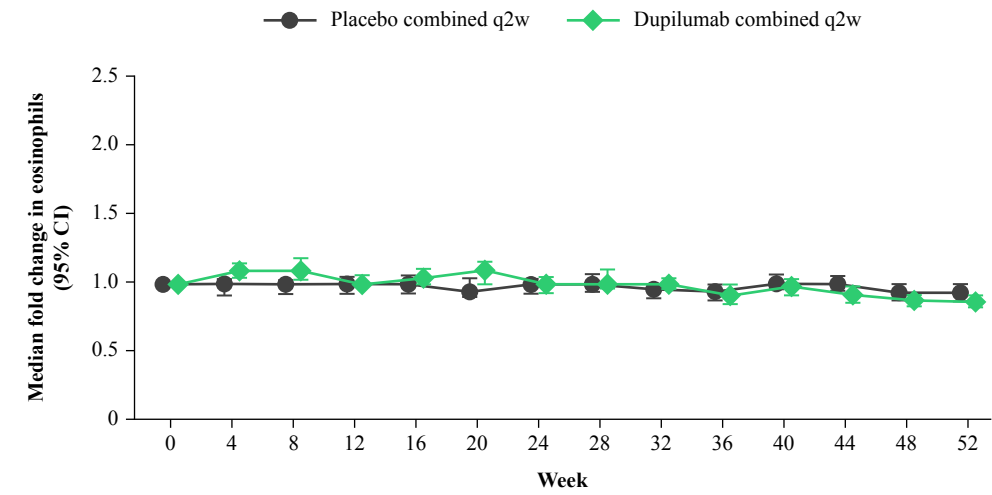
AD-OLE



(D) EOE**POC**

(A) Asthma

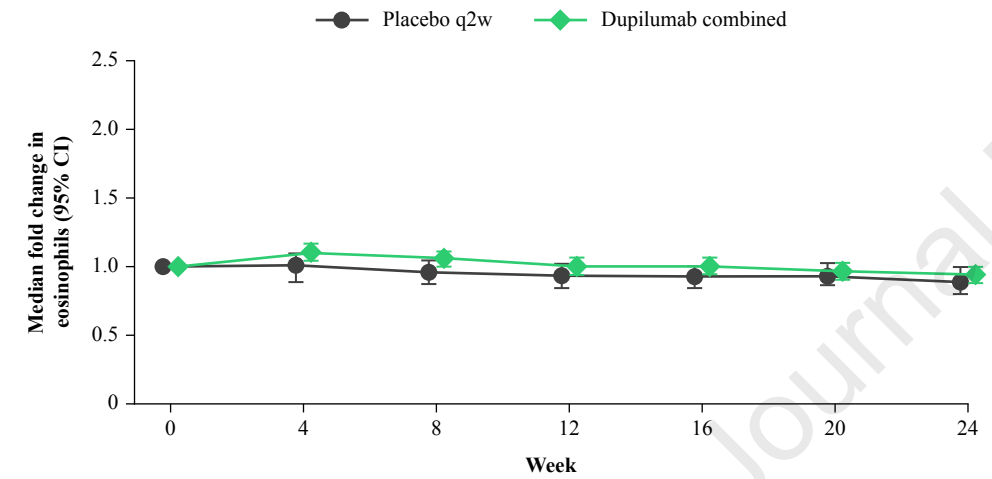
QUEST



Number of patients

Placebo, n	633	602	598	594	588	573	574	570	569	567	562	553	542	476
Dupilumab, n	1262	1214	1174	1178	1173	1152	1145	1141	1117	1130	1115	1104	1079	932

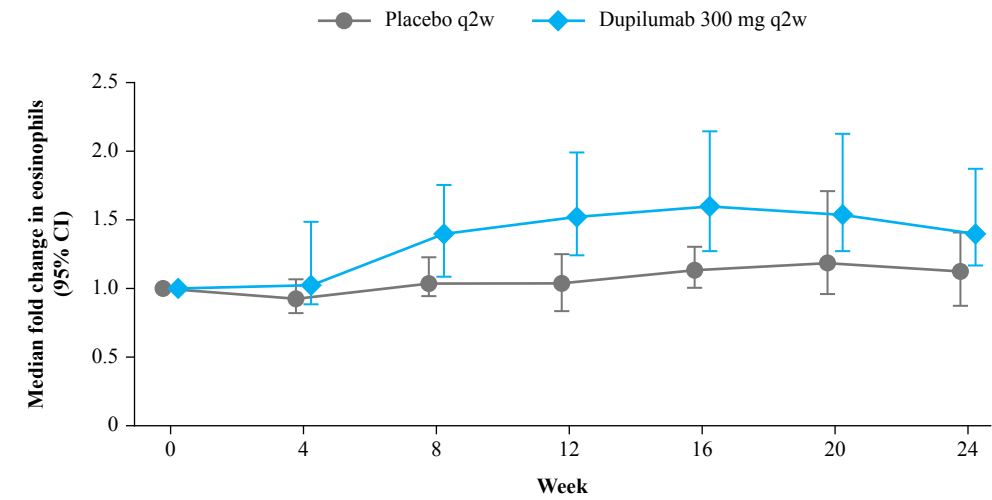
DRI



Number of patients

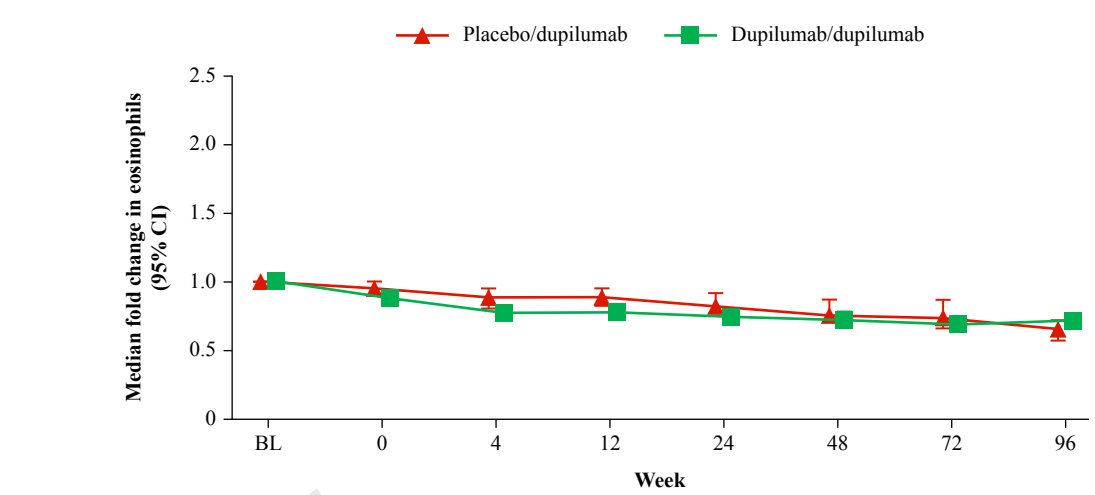
Placebo, n	158	153	149	146	144	145	137
Dupilumab, n	611	579	561	563	557	543	541

VENTURE



Placebo, n	107	103	104	97	102	104	100
Dupilumab, n	103	96	93	98	95	97	98

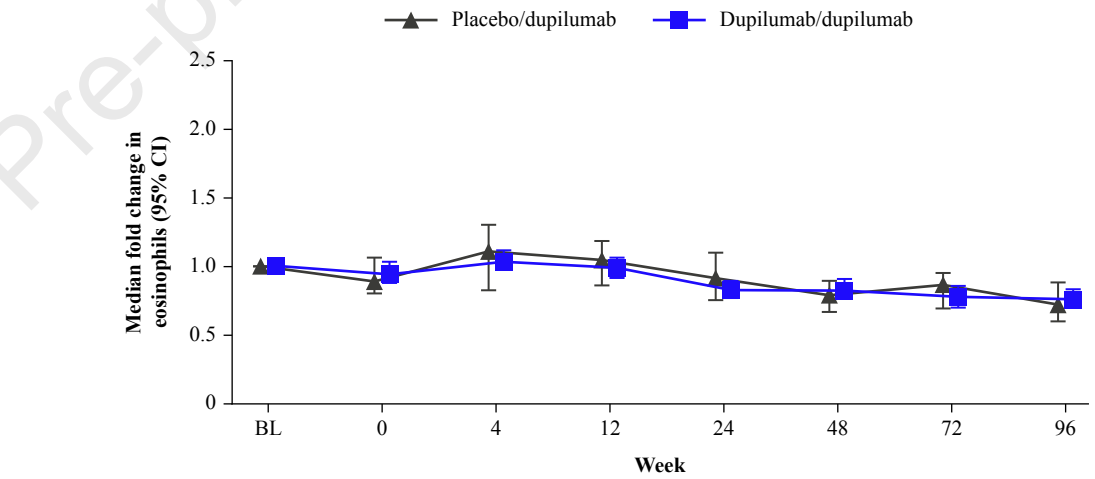
TRAVERSE – patients rolled over from QUEST



Number of patients

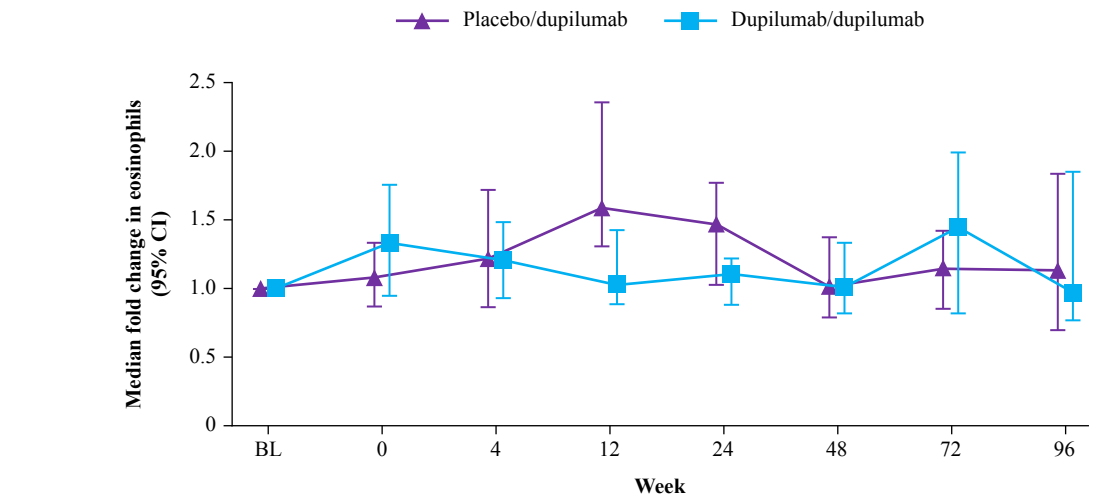
Placebo/dupilumab, n	516	496	488	495	491	469	218	216
Dupilumab/dupilumab, n	1012	954	966	973	970	926	446	431

TRAVERSE – patients rolled over from DRI

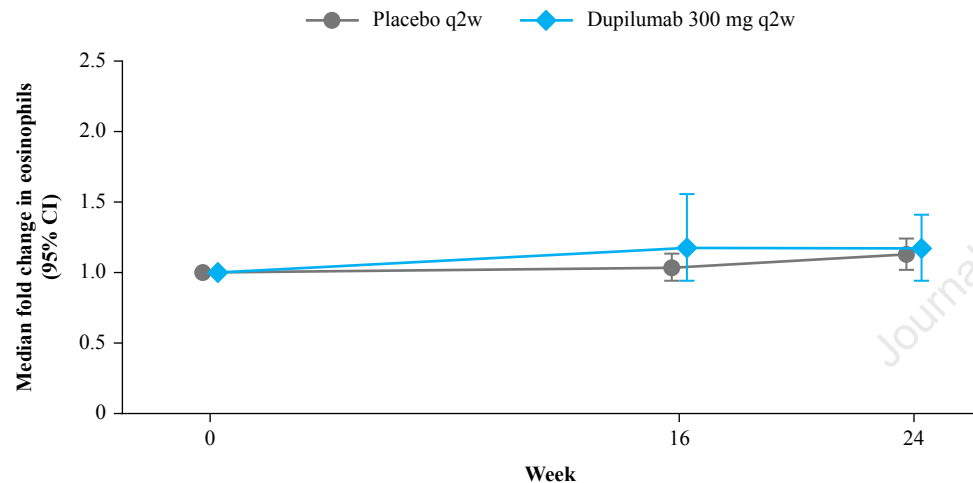


Placebo/dupilumab, n	111	109	103	110	110	103	106	102
Dupilumab/dupilumab, n	421	408	404	419	408	386	382	381

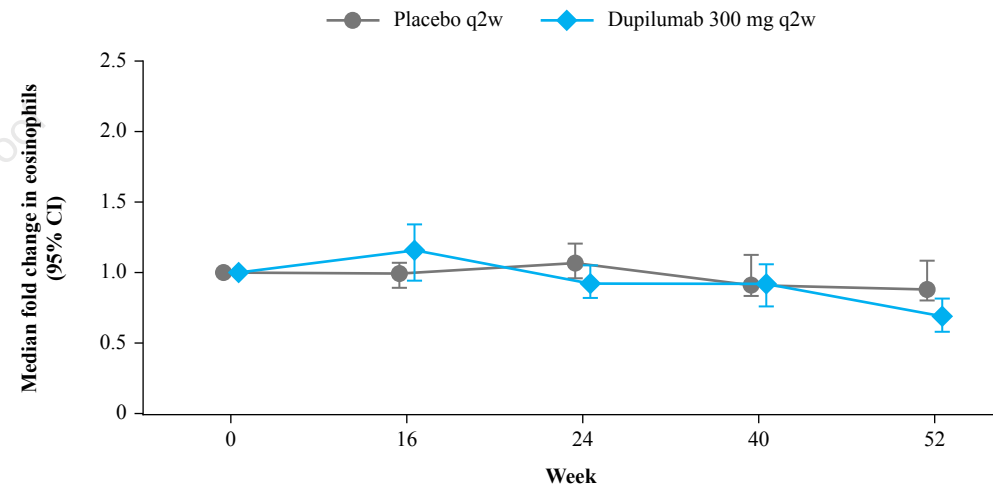
TRAVERSE – patients rolled over from VENTURE



Placebo/dupilumab, n	97	93	95	93	90	86	29	30
Dupilumab/dupilumab, n	90	87	82	84	81	81	26	29

(B) CRSwNP**SINUS-24****Number of patients**

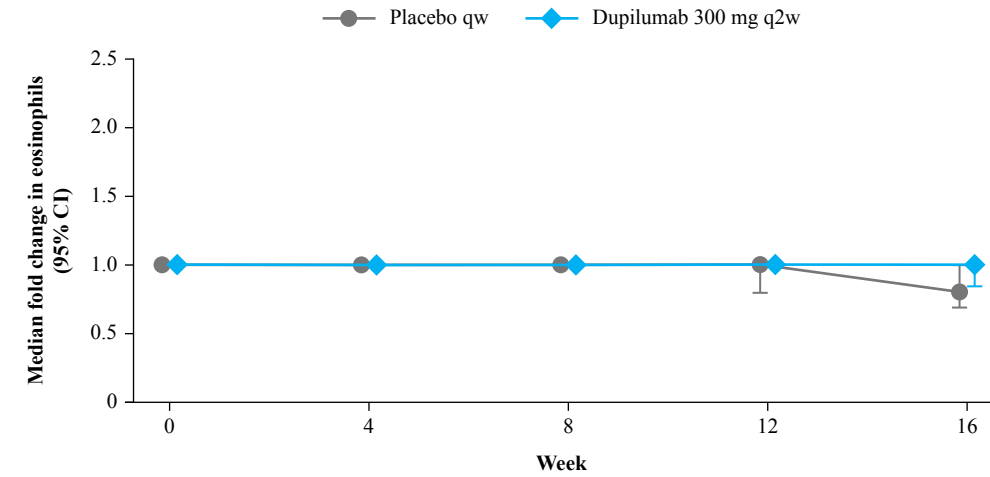
Placebo, n	132	129	123
Dupilumab, n	143	136	132

SINUS-52**Number of patients**

Placebo, n	150	142	134	124	116
Dupilumab, n	148	140	140	135	133

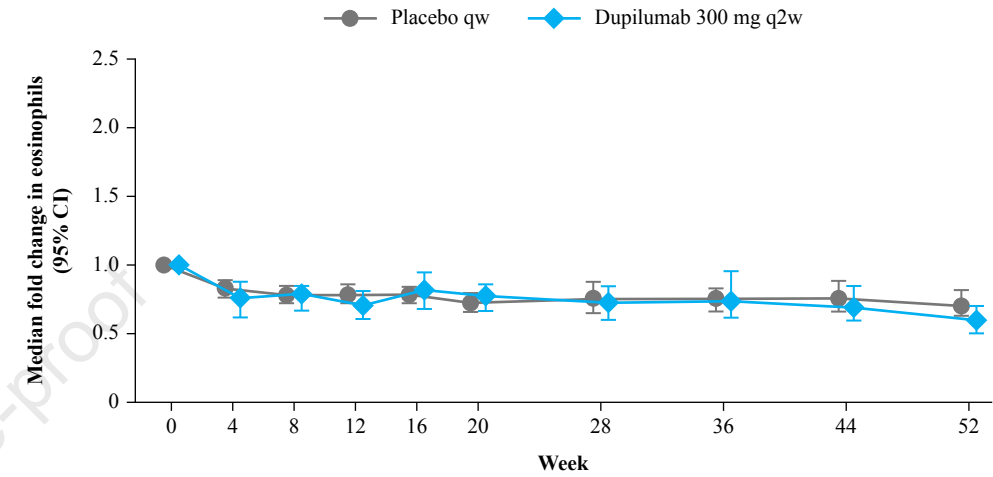
(C) AD

SOLO-1 & -2



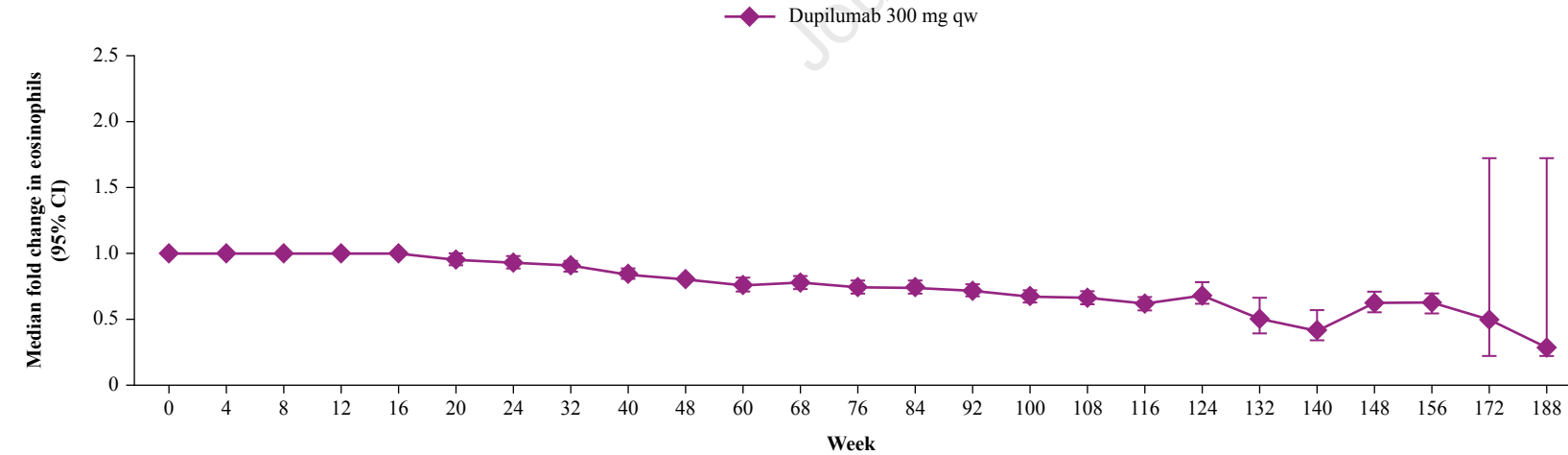
Placebo, n	454	317	230	204	190
Dupilumab, n	465	399	378	368	346

CHRONOS

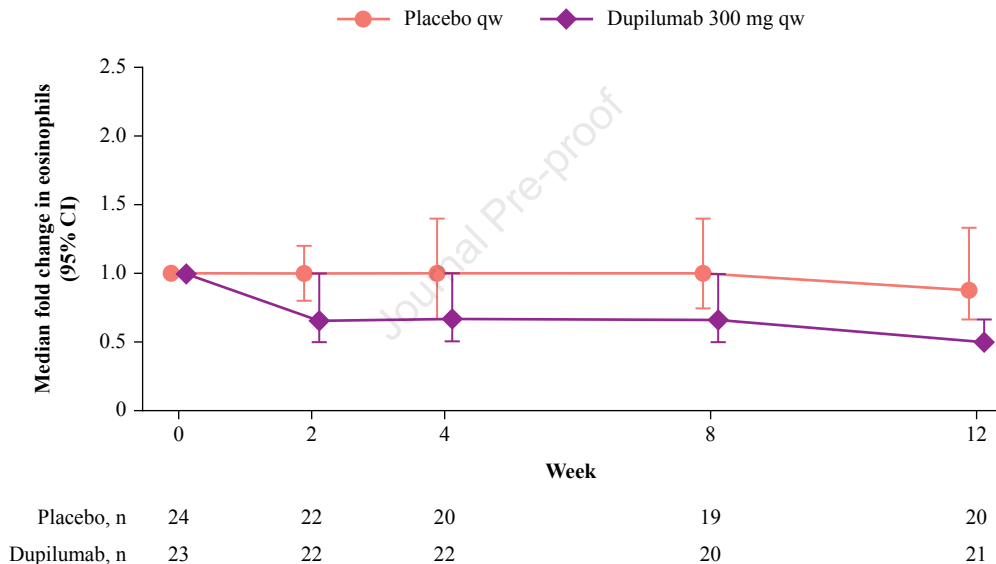


Placebo, n	315	268	239	206	186	171	150	134	124	119
Dupilumab, n	110	98	97	90	91	90	86	84	83	83

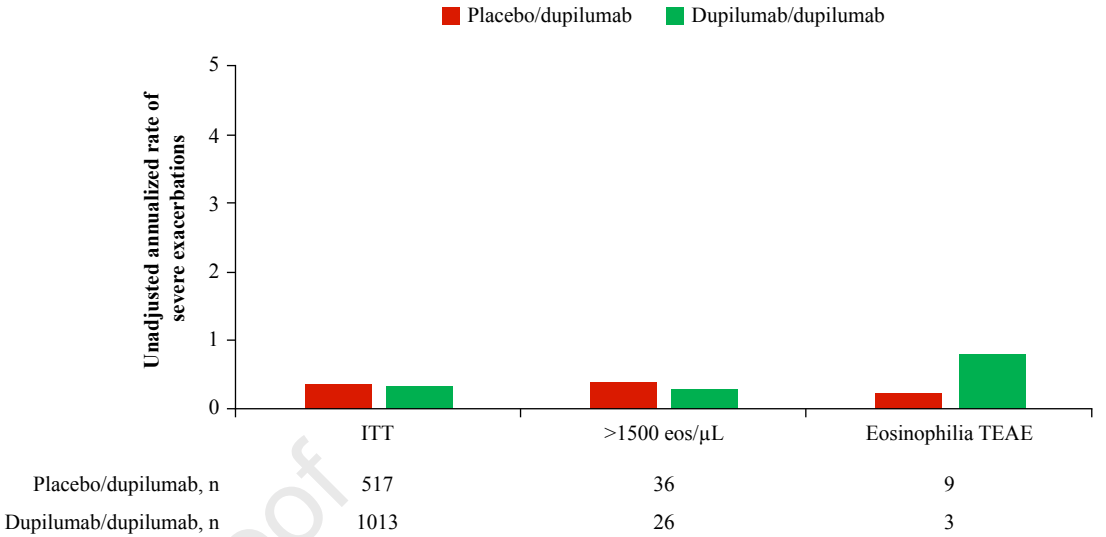
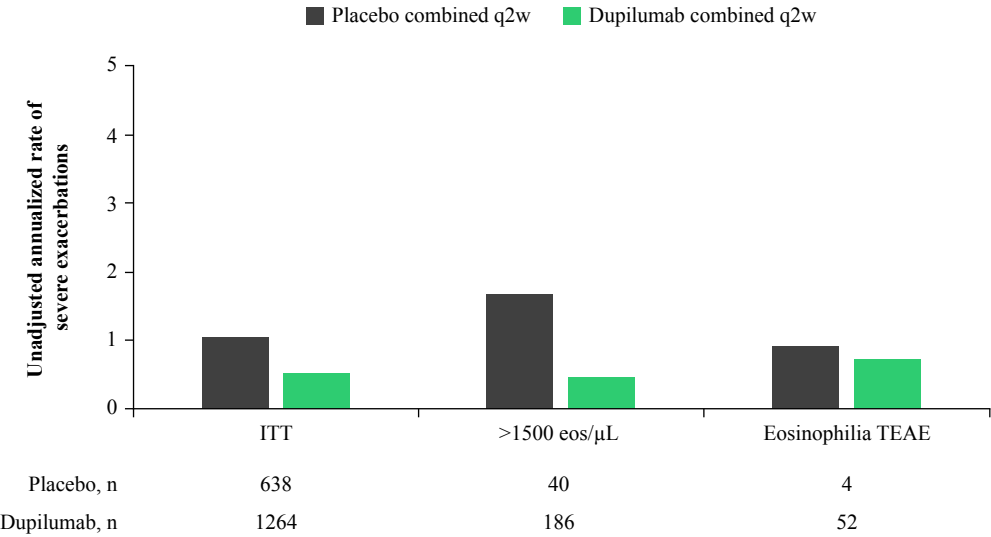
AD-OLE



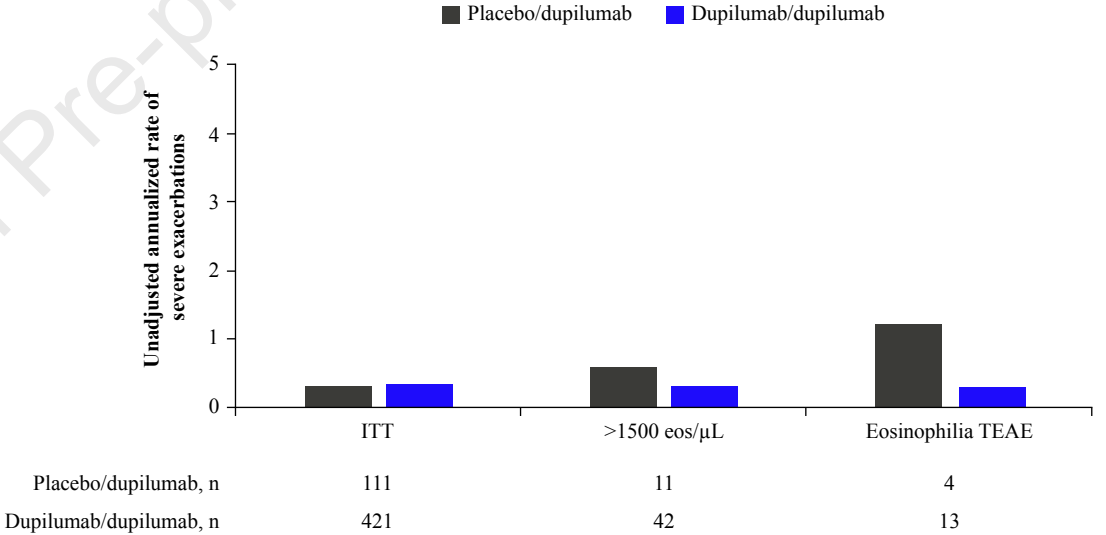
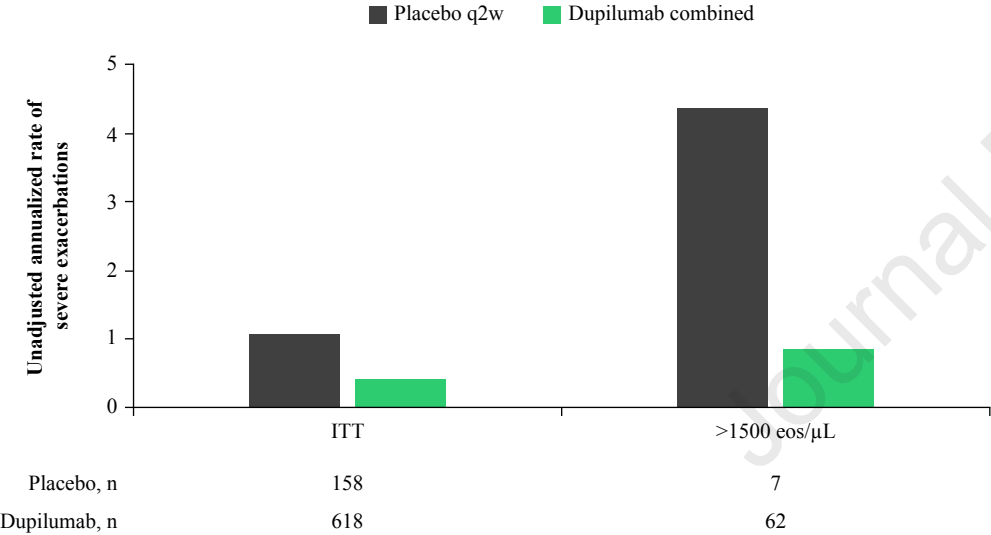
Dupilumab, n	2638	2378	2315	2167	2535	1781	1592	1351	1261	2301	700	649	613	559	524	1023	566	375	171	95	49	331	175	7	1
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(D) EOE**POC**

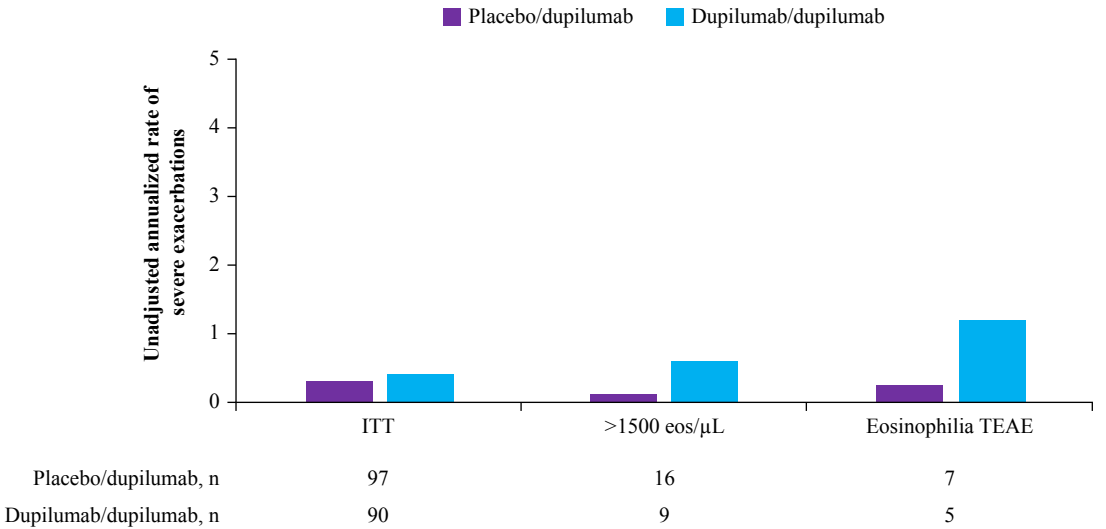
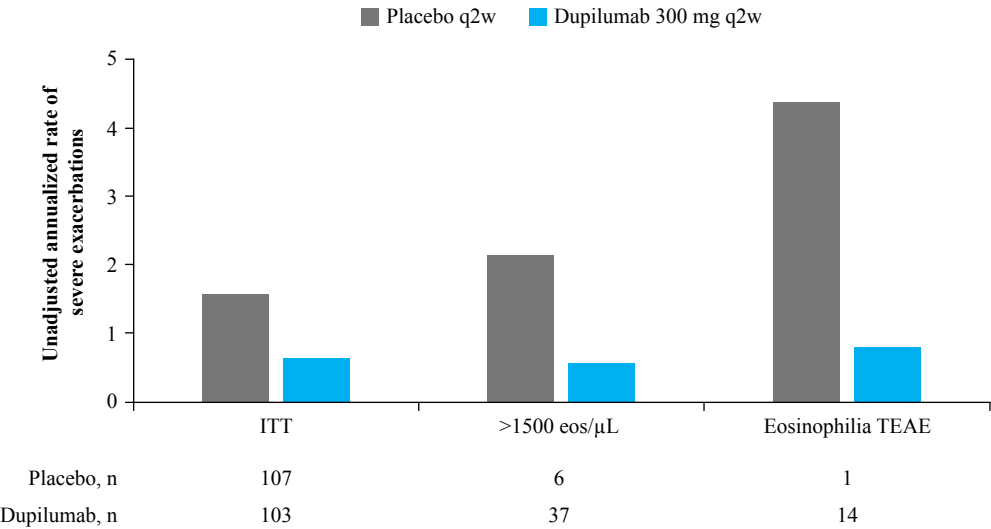
QUEST TRAVERSE – patients rolled over from QUEST



DRI TRAVERSE – patients rolled over from DRI



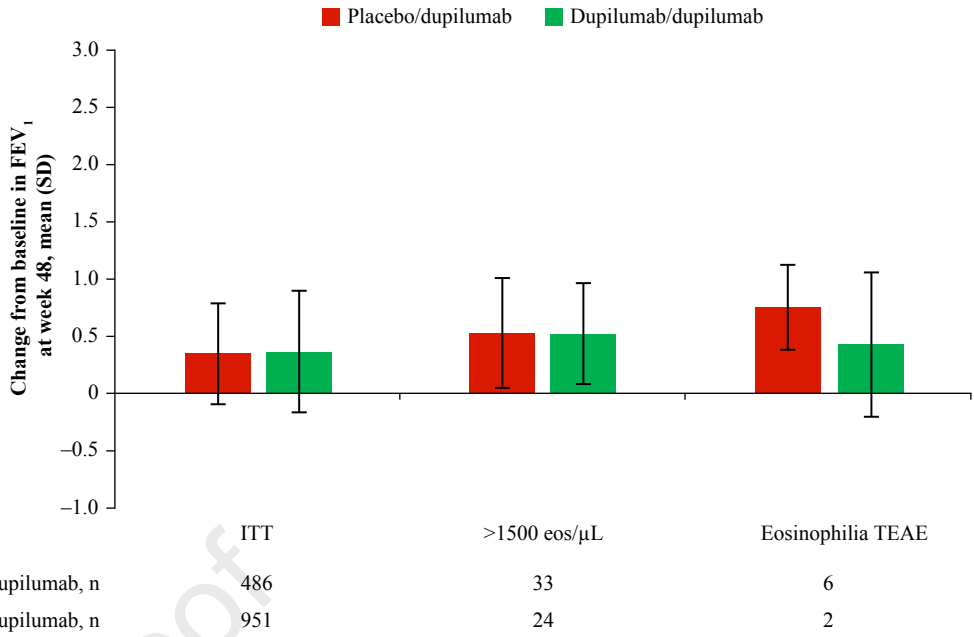
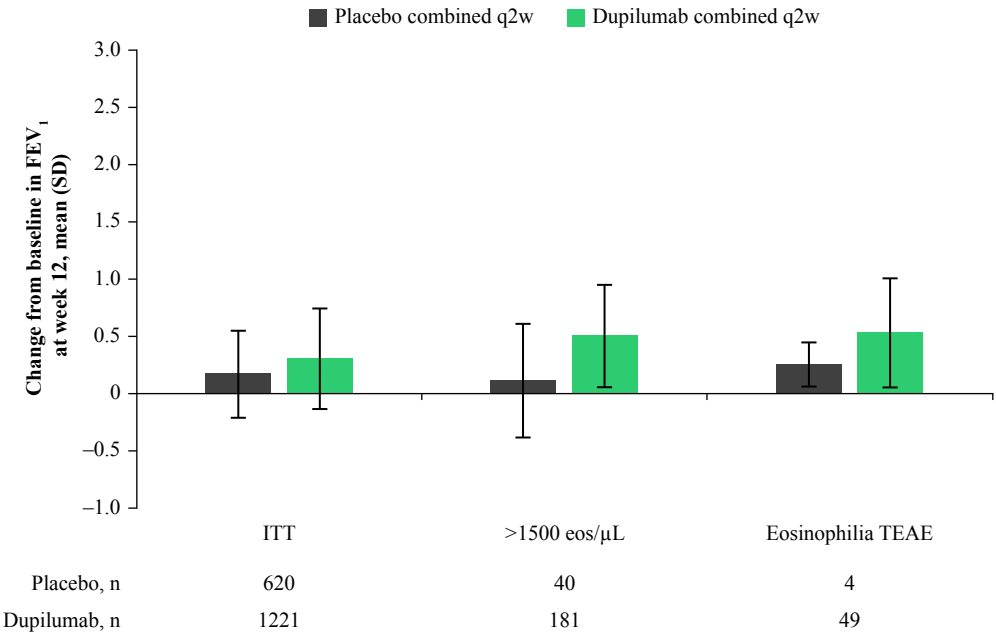
VENTURE TRAVERSE – patients rolled over from VENTURE



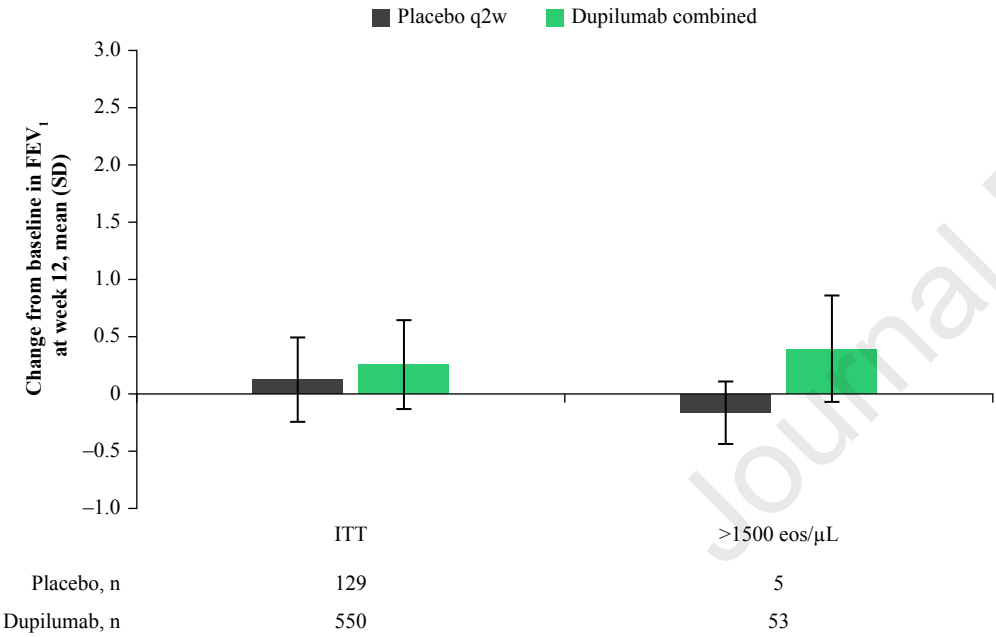
(B)

QUEST

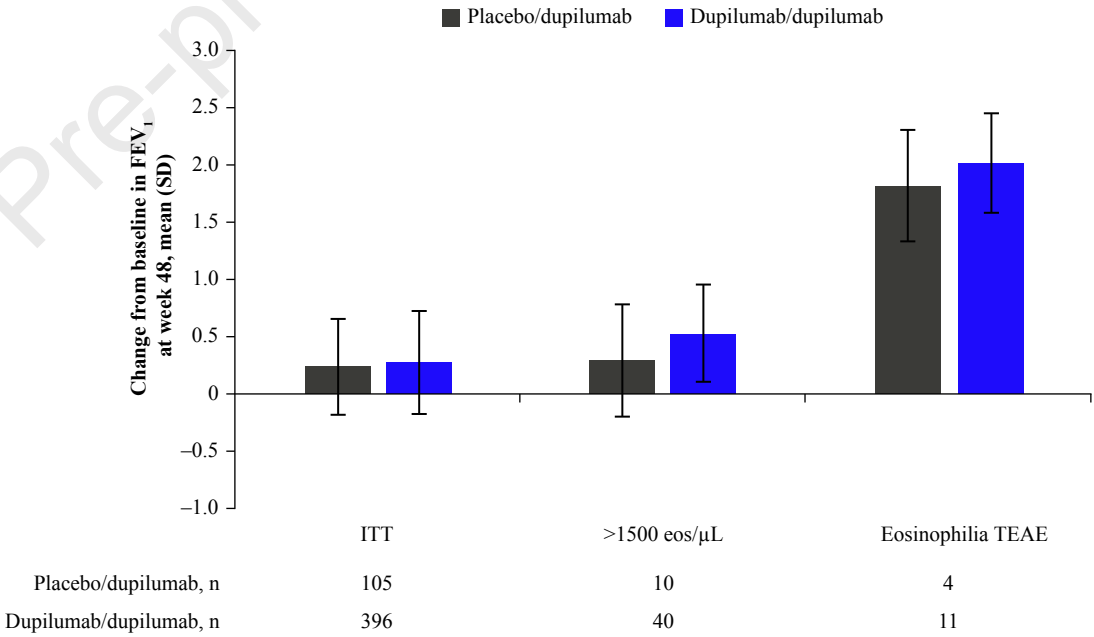
TRAVERSE – patients rolled over from QUEST



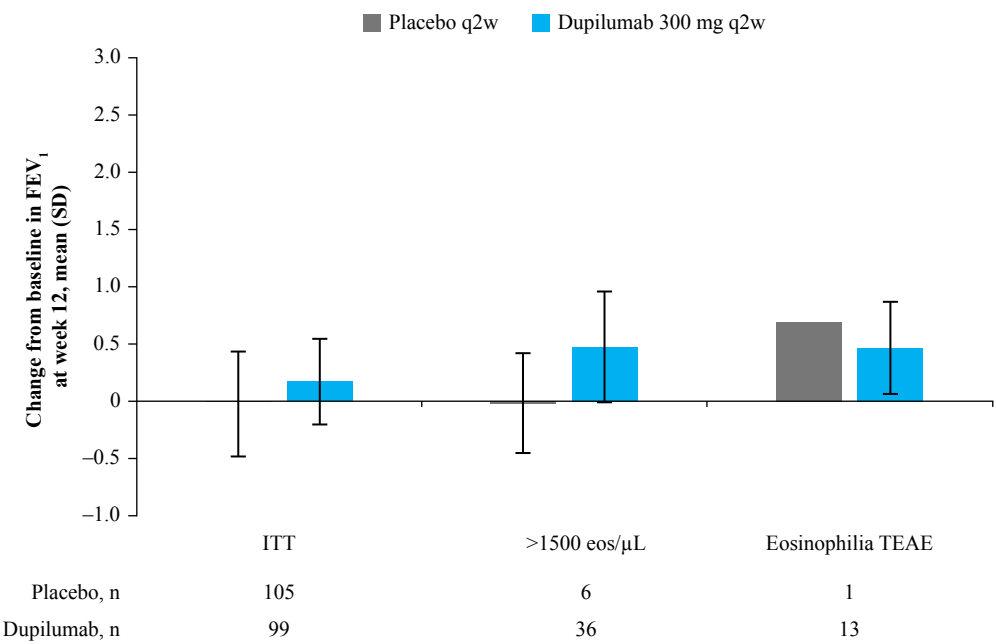
DRI



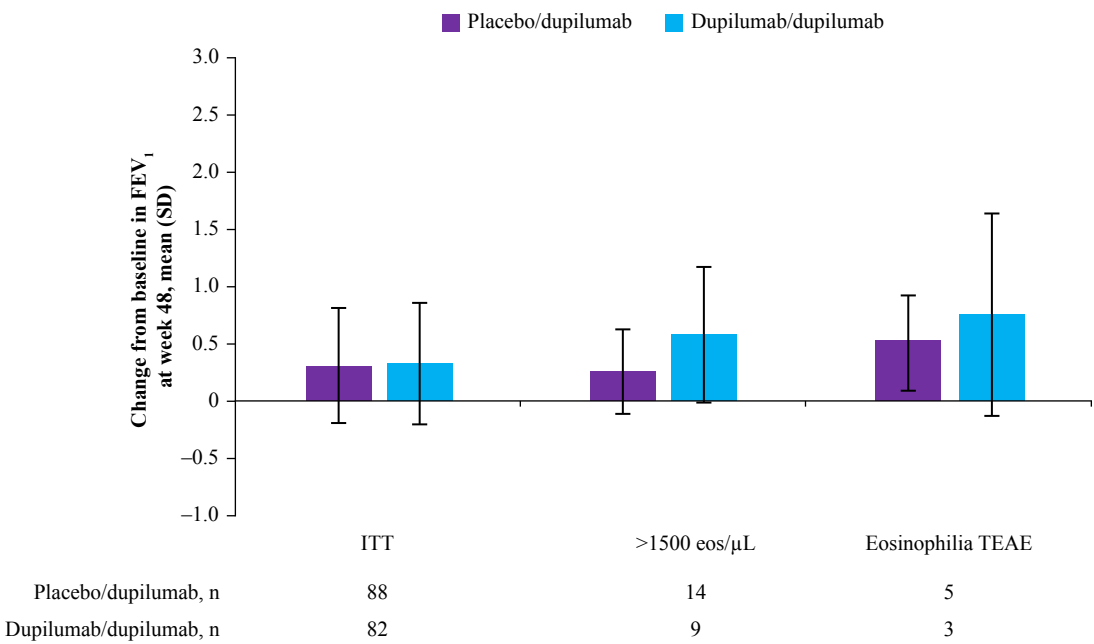
TRAVERSE – patients rolled over from DRI



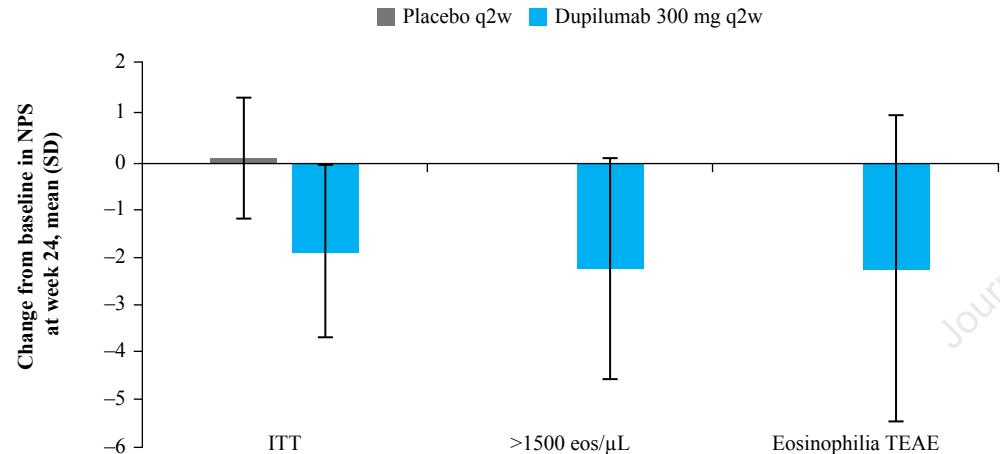
VENTURE



TRAVERSE – patients rolled over from VENTURE



(C)
SINUS-24

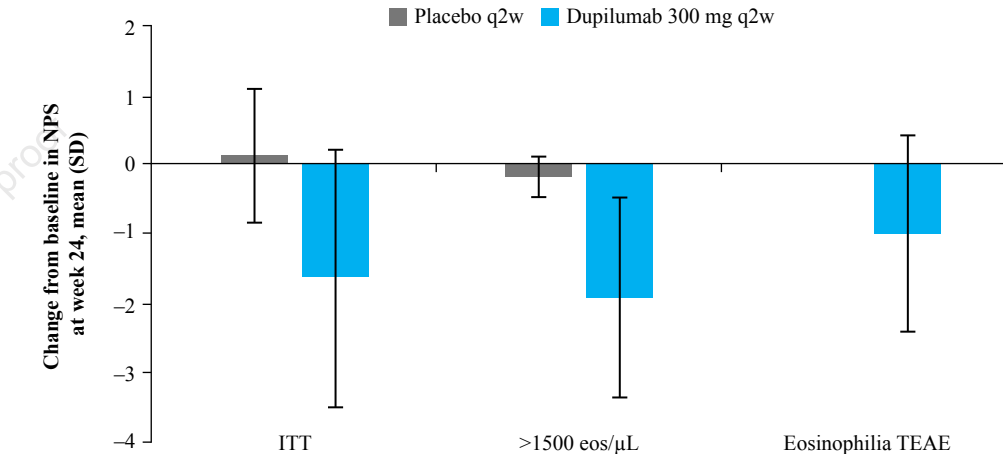


Placebo, n 128
Dupilumab, n 137

1
9

1
2

SINUS-52



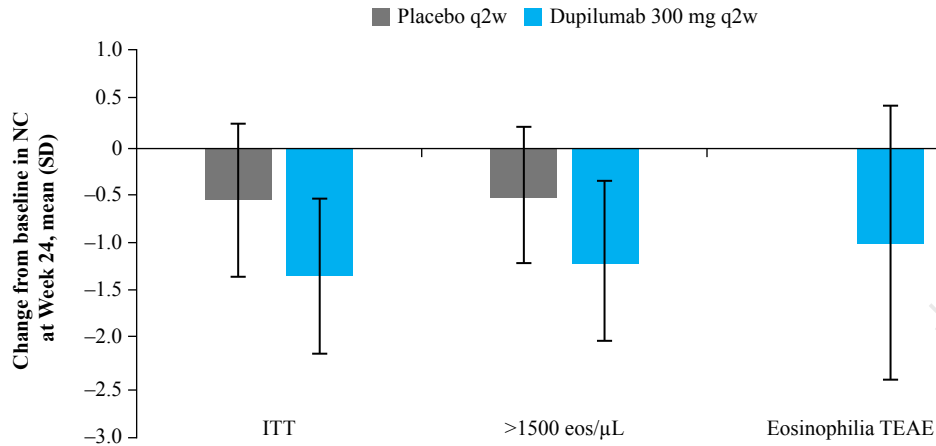
Placebo, n 145
Dupilumab, n 143

3
12

0
2

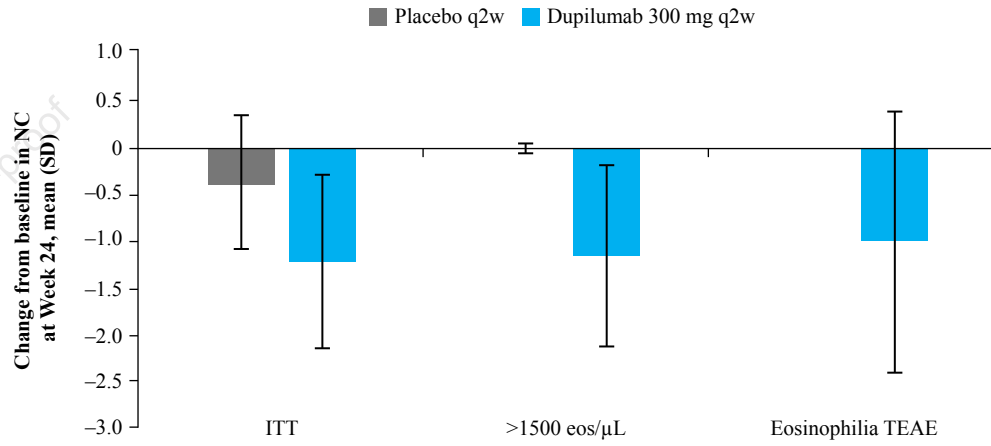
(D)

SINUS-24



Placebo, n	130	2	1
Dupilumab, n	141	9	2

SINUS-52



Placebo, n	147	3	0
Dupilumab, n	146	12	2