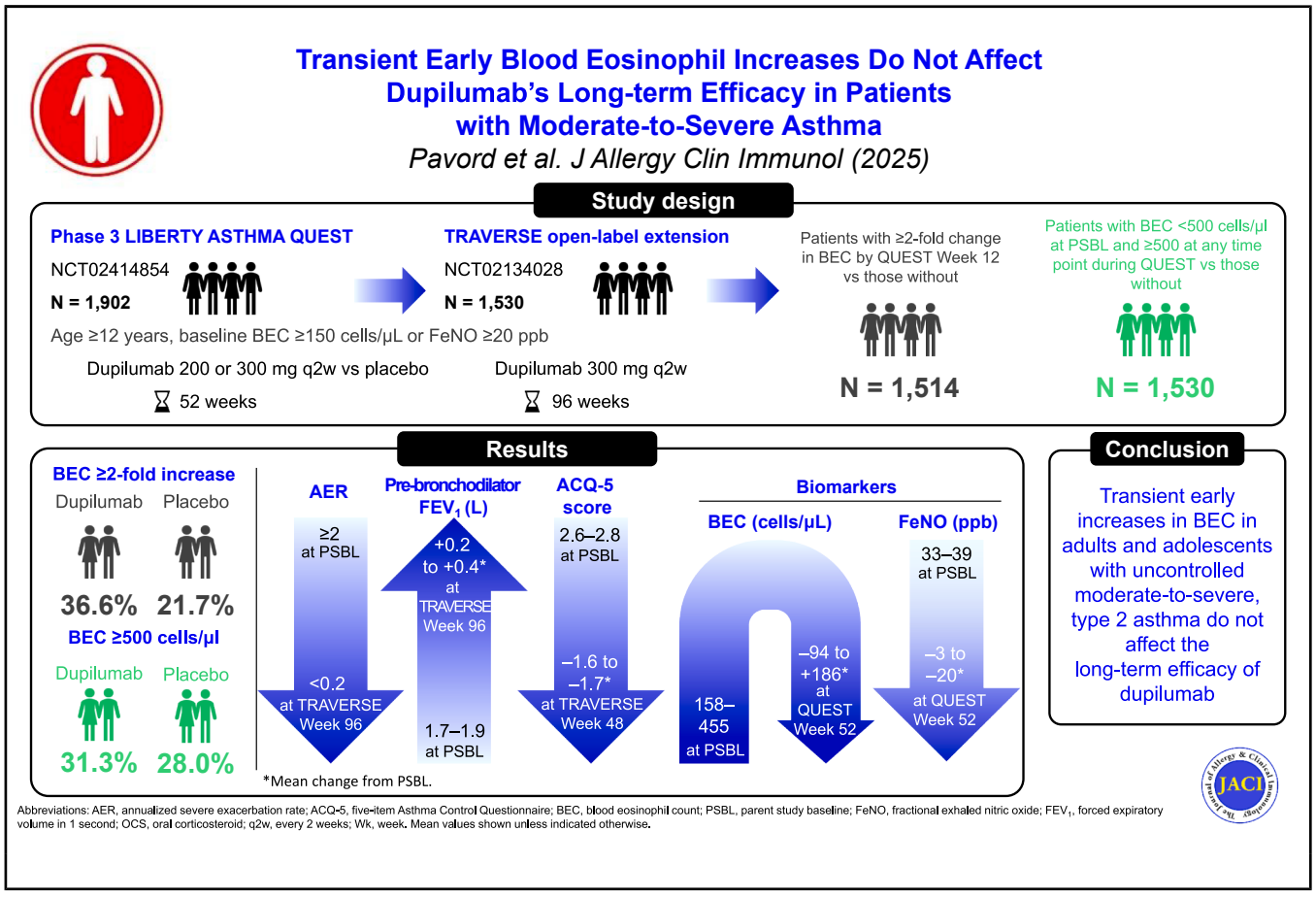
# Transient early blood eosinophil increases do not affect dupilumab's long-term efficacy in patients with moderate-to-severe asthma

**Ian D. Pavord, MD, Njira L. Lugogo, MD, Mario Castro, MD, Alberto Papi, MD, Arnaud Bourdin, MD, Michael E. Wechsler, MD, et al**

## GRAPHICAL ABSTRACT




**Capsule summary:** Early transient increases in blood eosinophil count are seen in some patients with uncontrolled moderate-to-severe type 2 asthma treated with dupilumab. This analysis confirms that such increases do not affect long-term dupilumab efficacy or safety.

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# Transient early blood eosinophil increases do not affect dupilumab's long-term efficacy in patients with moderate-to-severe asthma

Ian D. Pavord, MD,[a] Njira L. Lugogo, MD,[b] Mario Castro, MD,[c] Alberto Papi, MD,[d] Arnaud Bourdin, MD,[e] Michael E. Wechsler, MD,[f] Andréanne Côté, MD,[g] Kenneth R. Chapman, MD,[h] Changming Xia, PhD,[i] Mena Soliman, MD,[i] Nami Pandit-Abid, PharmD,[j] Juby A. Jacob-Nara, MD, DHSc,[j] and Harry Sacks, MD[i] *Ann Arbor, Mich; Bridgewater, NJ; Denver, Colo; Ferrara, Italy; Kansas City, Kan; Montpellier, France; Oxford, United Kingdom; Quebec, Quebec, and Toronto, Ontario, Canada; and Tarrytown, NY*

**Background: Transient increases in blood eosinophil count (BEC) have been observed in dupilumab clinical trials but are rarely associated with clinical symptoms.**
**Objective: We assessed the effect of early increases in BEC on long-term treatment outcomes.**
**Methods: Patients aged ≥12 years with moderate-to-severe type 2 asthma from the phase 3 QUEST study (NCT02414854; 52 weeks) who enrolled onto the TRAVERSE open-label extension study (NCT02134028; 96 weeks) were stratified by BEC: with or without ≥2-fold BEC increase any time by week 12 of QUEST, or presence or absence of increased BEC any time during QUEST (defined as <500 cells/μL at baseline but ≥500 cells/μL at any time during QUEST). End points included annualized severe exacerbation rate and change from parent study baseline in prebronchodilator forced expiratory volume in 1 second ($FEV_1$), 5-item Asthma Control Questionnaire, and type 2 inflammatory biomarkers.**
**Results: A total of 36.6% of dupilumab-treated patients versus 21.7% of placebo-receiving patients experienced a ≥2-fold BEC change by week 12, while 31.3% versus 28.0% experienced increased BEC any time during QUEST. Dupilumab versus placebo reduced annualized severe exacerbation rate, improved prebronchodilator $FEV_1$ and questionnaire scores, and reduced biomarkers across subgroups at week 52 of QUEST. Improvements were maintained in all subgroups through week 96 of TRAVERSE.**
**Conclusions: Dupilumab reduced asthma exacerbations and improved lung function and asthma control up to 148 weeks in patients with uncontrolled moderate-to-severe type 2 asthma irrespective of early transient increases in BEC. Overall safety was consistent with the known dupilumab safety profile. (J Allergy Clin Immunol 2026;157:363-73.)**

***Key words:*** *Asthma, type 2, blood eosinophil count, dupilumab, FENO, exacerbations, lung function, biomarkers, efficacy, safety*

Type 2 inflammation is identified as a key treatable trait in ~50% of patients with asthma.[1,2] It involves activation of type 2 $CD4^+$ T helper cells and type 2 innate lymphoid cells, with proinflammatory cytokine production (eg, IL-4, IL-5, and IL-13) and airway inflammatory cell accumulation (eg, eosinophils and basophils).[3] Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, inhibiting their signaling.[3-6] The phase 3 QUEST[7] (NCT02414854) and TRAVERSE[8] (NCT02134028) studies have demonstrated dupilumab's efficacy over 148 weeks in patients aged ≥12 years with moderate-to-severe asthma, showing benefits primarily in those with a type 2–high disease endotype while maintaining an acceptable safety profile.[7,9,10]

Transient increases in blood eosinophil count (BEC) have been observed in clinical trials of dupilumab in patients with some chronic type 2 inflammatory diseases, including asthma.[11,12] Increases generally occur in the first few weeks of treatment, and the BEC returns to around or below baseline by the study's end.[12] The mechanism for this transient increase may be related to sequestration of eosinophils in the blood due to the inhibition of eosinophil trafficking to tissues after IL-4/IL-13 blockade.[12,13] IL-4 regulates endothelial expression of vascular cell adhesion molecule 1, which supports adhesion of eosinophils to blood vessels and subsequent extravasation to tissues. In addition, inhibition of signal transducer and activator of transcription 6, or STAT6, which is activated by the binding of IL-4/IL-13 to their receptors, reduces the expression of thymus and activation-regulated chemokine (TARC) and eotaxins 1-3. These chemokines guide eosinophil migration to tissues.[12,13] IL-4/IL-13 blockade does not affect eosinophil production or maturation; therefore, continued release of eosinophils into blood together with decreasing tissue migration may explain the transient rise in BEC seen with dupilumab.[12,13] Type 2 inflammation biomarkers (eg, fractional exhaled nitric oxide [FENO]) are reduced

From [a]the NIHR Oxford Respiratory Biomedical Research Centre, Nuffield Department of Medicine, University of Oxford, Oxford; [b]the University of Michigan, Ann Arbor; [c]the Division of Pulmonary, Critical Care and Sleep Medicine, University of Kansas School of Medicine, Kansas City; [d]the Respiratory Medicine Unit, University of Ferrara, S. Anna University Hospital, Ferrara; [e]the Department of Respiratory Diseases, PhyMedExp INSERM CNRS, University of Montpellier, Montpellier; [f]the Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver; [g]the Quebec Heart and Lung Institute, Laval University, Quebec; [h]the University of Toronto, Toronto; [i]Regeneron Pharmaceuticals Inc, Tarrytown; and [j]Sanofi, Bridgewater.

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Corresponding author: Ian D. Pavord, MD, Respiratory Medicine Unit and Oxford Respiratory NIHR BRC, Nuffield Department of Medicine, University of Oxford, Room 7400, Level 7EF, John Radcliffe Hospital, Oxford OX3 9DU. E-mail: ian.pavord@ndm.ox.ac.uk.

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*Abbreviations used*
ACQ-5: 5-item Asthma Control Questionnaire
AER: Annualized severe exacerbation rate
BEC: Blood eosinophil count
CI: Confidence interval
EGPA: Eosinophilic granulomatosis with polyangiitis
FENO: Fractional exhaled nitric oxide
$FEV_1$: Forced expiratory volume in 1 second
PSBL: Parent study baseline
SD: Standard deviation
TARC: Thymus and activation-regulated chemokine
TEAE: Treatment-emergent adverse event

by dupilumab throughout this elevated BEC period.[7,14] BEC may not accurately reflect airway type 2 inflammation but can indicate clinical benefit: elevated BEC suggests successful blockade of eosinophil recruitment. Early transient BEC increases are rarely linked to clinical symptoms in dupilumab trials, and cases of eosinophilia or eosinophilic granulomatosis with polyangiitis (EGPA) in real-world practice are rare.[12,13] Information is limited on how early transient BEC increases relate to long-term treatment efficacy and safety and whether they predict outcome.

This *post hoc* analysis assessed the effect of early transient BEC increases on long-term treatment outcomes in patients from QUEST who subsequently enrolled onto TRAVERSE to determine whether there is clinical value in measuring eosinophil level changes shortly after starting dupilumab and what predictive value it may offer.

## METHODS

### Study design

Full details of QUEST (NCT02414854) and TRAVERSE (NCT02134028) have been published elsewhere.[7,8] Briefly, QUEST was a phase 3 study assessing efficacy and safety of dupilumab in patients aged ≥12 years with uncontrolled moderate-to-severe asthma despite treatment with high- or medium-dose inhaled corticosteroids and a second controller (eg, long-acting β-agonists, leukotriene receptor antagonists, methylxanthines).[7] Patients were randomized 2:2:1:1 to receive dupilumab 200 mg or 300 mg or matched-volume placebo every 2 weeks for up to 52 weeks. QUEST patients entered the open-label TRAVERSE extension study immediately after the end-of-treatment visit. All patients in TRAVERSE received dupilumab 300 mg every 2 weeks for up to an additional 96 weeks.[8] The treatment period was shortened to 48 weeks after a protocol amendment as a result of accumulating data demonstrating an acceptable safety profile for dupilumab across indications. Patients continued the background regimen established in the QUEST study throughout the TRAVERSE trial. QUEST and TRAVERSE had an exclusion criterion of BEC > 1,500 cells/mL at screening, and all patients with eosinophilia treatment-emergent adverse events (TEAEs) were medically reviewed.[7,8]

Both studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Study conduct and documentation were monitored by local institutional review boards or ethics committees. Written informed consent was obtained from all patients before enrollment. Patients aged <18 years provided assent according to the ethics committee–approved standard practice for pediatric patients at each participating center.

### Study population

This *post hoc* analysis included patients aged ≥12 years with uncontrolled moderate-to-severe type 2 (baseline BEC ≥ 150 cells/μL or FENO ≥ 20 ppb) asthma receiving dupilumab (200 mg or 300 mg) or matched-volume placebo every 2 weeks for 52 weeks in QUEST who enrolled onto TRAVERSE. Patients were stratified by those with or without a ≥2-fold change versus parent study baseline (PSBL) in BEC at any time point up to QUEST week 12; with or without a ≥2-fold change versus PSBL in BEC at specific QUEST timepoints of week 4 and separately, week 12; and presence or absence of increased BEC any time during QUEST, defined as <500 cells/μL at baseline but ≥500 cells/μL, considered eosinophilia, at any time point during QUEST.

### Outcomes

Clinical efficacy end points included unadjusted annualized severe exacerbation rates (AERs) and changes from PSBL in prebronchodilator forced expiratory volume in 1 second ($FEV_1$) during QUEST and TRAVERSE (up to week 96) and 5-item Asthma Control Questionnaire (ACQ-5) scores during QUEST and TRAVERSE (up to week 48).

Change from PSBL in BEC during QUEST and TRAVERSE and change from PSBL in FENO, total IgE, eotaxin-3, and TARC during QUEST were assessed. In addition, TEAEs, EGPA events, and treatment discontinuations were assessed.

### Statistical analysis

Statistical analyses were performed for QUEST study data only; TRAVERSE, an open-label extension study with no comparator arm, had only descriptive summaries using observed data only. The comparator value for efficacy end points was the PSBL.

Unadjusted AERs were computed as total number of events during the observation period divided by total exposure in patient-years in the observation period. Adjusted AERs were derived using a negative binomial model with total number of events onsets from randomization up to visit 18 or last contact date (whichever came earlier) as response variable, with 4 treatment groups (age, region [pooled country], baseline BEC, baseline inhaled corticosteroid dose) and number of severe exacerbation events within 1 year before study as covariates and log-transformed standardized observation duration as offset variable.

Efficacy end points (prebronchodilator $FEV_1$ and ACQ-5 score) are presented as mean change from PSBL during the treatment period. Least squares mean changes from PSBL, difference versus placebo, and *P* value analysis values were derived using a mixed-effect model with repeated measures, with treatment group, age, sex, baseline height, region (pooled country), baseline BEC, baseline inhaled corticosteroid dose level, visit, treatment-

**TABLE I.** Baseline demographics and disease characteristics

| Characteristic | Patients with ≥2-fold change in BEC by week 12 | | Patients without ≥2-fold change in BEC by week 12 | | Patients with increased BEC any time during QUEST* | | Patients without increased BEC any time during QUEST* | |
|---|---|---|---|---|---|---|---|---|
| | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab |
| No. of subjects | 111 | 367 | 400 | 636 | 145 | 317 | 372 | 696 |
| Age (years) | 46.6 (16.8) | 47.3 (15.7) | 48.5 (14.6) | 48.2 (15.0) | 46.1 (15.6) | 46.7 (15.4) | 49.0 (14.8) | 48.4 (15.1) |
| Female, no. (%) | 71 (64.0) | 225 (61.3) | 258 (64.5) | 386 (60.7) | 94 (64.8) | 194 (61.2) | 241 (64.8) | 424 (60.9) |
| Race, no. (%) | | | | | | | | |
| White | 93 (83.8) | 294 (80.1) | 347 (86.8) | 540 (84.9) | 127 (87.6) | 274 (86.4) | 318 (85.5) | 570 (81.9) |
| Black/of African descent | 4 (3.6) | 12 (3.3) | 13 (3.3) | 31 (4.9) | 4 (2.8) | 11 (3.5) | 13 (3.5) | 32 (4.6) |
| Asian | 13 (11.7) | 57 (15.5) | 37 (9.3) | 59 (9.3) | 11 (7.6) | 30 (9.5) | 40 (10.8) | 86 (12.4) |
| Native Hawaiian or other Pacific Islander | 0 (0.0) | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 1 (0.1) |
| Other | 1 (0.9) | 3 (0.8) | 3 (0.8) | 6 (0.9) | 3 (2.1) | 2 (0.6) | 1 (0.3) | 7 (1.0) |
| Ethnicity, no. (%) | | | | | | | | |
| Hispanic | 29 (26.1) | 95 (25.9) | 105 (26.3) | 169 (26.6) | 47 (32.4) | 99 (31.2) | 90 (24.2) | 170 (24.4) |
| Not Hispanic | 82 (73.9) | 272 (74.1) | 295 (73.8) | 467 (73.4) | 98 (67.6) | 218 (68.8) | 282 (75.8) | 526 (75.6) |
| Body mass index ($kg/m^2$) | 28.8 (6.8) | 27.6 (6.1) | 29.5 (6.4) | 29.6 (6.7) | 28.5 (6.0) | 28.4 (6.6) | 29.6 (6.7) | 29.1 (6.5) |
| High-dose inhaled corticosteroid treatment, no. (%) | 54 (48.6) | 170 (46.3) | 224 (56.0) | 336 (52.8) | 67 (46.2) | 145 (47.5) | 214 (57.5) | 370 (53.2) |
| Age at onset of asthma (years) | 25.2 (19.0) | 27.7 (18.5) | 27.9 (18.6) | 26.4 (19.5) | 26.7 (18.6) | 27.4 (19.0) | 27.6 (18.8) | 26.7 (19.2) |
| No. of severe asthma exacerbations‡ experienced in past year, no. (%) | | | | | | | | |
| 1 | 46 (41.4) | 173 (47.1) | 187 (46.8) | 342 (53.8) | 60 (41.4) | 156 (49.2) | 175 (47.0) | 364 (52.3) |
| 2 | 31 (27.9) | 95 (25.9) | 114 (28.5) | 162 (25.5) | 48 (33.1) | 86 (27.1) | 99 (26.6) | 174 (25.0) |
| 3 | 16 (14.4) | 53 (14.4) | 47 (11.8) | 65 (10.2) | 20 (13.8) | 38 (12.0) | 45 (12.1) | 81 (11.6) |
| ≥4 | 18 (16.2) | 46 (12.5) | 52 (13.0) | 67 (10.5) | 17 (11.7) | 37 (11.7) | 53 (14.2) | 77 (11.1) |
| Atopic medicalcondition,§ no. (%) | 97 (87.4) | 296 (80.7) | 325 (81.3) | 536 (84.3) | 118 (81.4) | 266 (83.9) | 308 (82.8) | 573 (82.3) |
| Prebronchodilator $FEV_1$ (L) | 1.85 (0.60) | 1.80 (0.60) | 1.75 (0.58) | 1.79 (0.63) | 1.89 (0.63) | 1.83 (0.62) | 1.72 (0.56) | 1.78 (0.62) |
| Predicted prebronchodilator $FEV_1$ (%) | 60.52 (11.94) | 58.67 (13.29) | 57.74 (13.57) | 58.47 (13.48) | 61.03 (12.10) | 58.97 (13.63) | 57.34 (13.56) | 58.25 (13.46) |
| $FEV_1$ reversibility (%) | 24.63 (16.35) | 26.17 (22.22) | 25.92 (18.62) | 26.48 (23.42) | 23.39 (14.89) | 28.37 (23.91) | 26.73 (19.22) | 25.42 (22.45) |
| Postbronchodilator $FEV_1$ (L) | 2.26 (0.73) | 2.19 (0.77) | 2.13 (0.69) | 2.18 (0.74) | 2.29 (0.74) | 2.24 (0.75) | 2.11 (0.67) | 2.15 (0.75) |
| ACQ-5 score | 2.64 (0.72) | 2.73 (0.75) | 2.75 (0.75) | 2.78 (0.80) | 2.73 (0.72) | 2.75 (0.73) | 2.73 (0.75) | 2.77 (0.81) |
| BEC (cells/μL) | | | | | | | | |
| Median (Q1-Q3) | 110 (50-200) | 190 (90-400) | 360 (190-580) | 280 (150-500) | 300 (170-410) | 290 (170-370) | 240 (120-620) | 220 (110-600) |
| Mean (SD) | 158 (184) | 292 (287) | 455 (409) | 389 (383) | 284 (138) | 272 (130) | 426 (447) | 386 (413) |
| BEC, no. (%) | | | | | | | | |
| <150 cells/μL | 75 (67.6) | 150 (40.9) | 64 (16.0) | 139 (21.9) | 34 (23.4) | 64 (20.2) | 110 (29.6) | 234 (33.6) |
| ≥150 to <300 cells/μL | 20 (18.0) | 85 (23.2) | 112 (28.0) | 191 (30.0) | 35 (24.1) | 96 (30.3) | 97 (26.1) | 180 (25.9) |
| ≥300 cells/μL | 16 (14.4) | 132 (36.0) | 224 (56.0) | 306 (48.1) | 76 (52.4) | 157 (49.5) | 164 (44.1) | 281 (40.4) |
| Total IgE (IU/mL) | | | | | | | | |
| Median (Q1-Q3) | 178.5 (79.0-440.0) | 196.0 (76.0- 558.0) | 187.0 (62.0-437.0) | 157.0 (58.0-420.0) | 199.0 (73.0-414.0) | 221.5 (99.0-579.0) | 176.5 (63.0-436.5) | 151.0 (54.0-417.0) |
| Mean (SD) | 418.1 (673.0) | 535.5 (922.7) | 408.4 (677.0) | 411.7 (716.3) | 415.1 (701.0) | 511.1 (791.3) | 404.0 (661.6) | 428.1 (797.7) |
| FENO (ppb) | | | | | | | | |
| Median (Q1-Q3) | 23.0 (14.0-41.0) | 26.0 (15.0-49.0) | 28.0 (16.0-49.0) | 24.0 (14.0-40.0) | 29.5 (16.0-49.0) | 29.0 (18.0-50.0) | 26.0 (15.0-46.5) | 23.0 (14.0-40.0) |
| Mean (SD) | 35.4 (41.9) | 36.5 (29.7) | 37.1 (32.5) | 33.6 (33.7) | 39.4 (39.7) | 38.6 (30.1) | 35.8 (32.6) | 33.0 (33.3) |
| TARC (pg/mL) | | | | | | | | |
| Median (Q1-Q3) | 264.0 (177.0-390.0) | 297.5 (206.5-425.0) | 303.5 (210.0 -488.0) | 307.5 (197.0 -445.0) | 280.0 (173.0-444.0) | 283.5 (204.0-403.0) | 298.0 (205.0-488.0) | 312.0 (199.0-444.0) |
| Mean (SD) | 336.6 (258.76) | 405.8 (558.6) | 390.4 (290.1) | 363.2 (282.8) | 351.6 (263.1) | 374.8 (344.4) | 387.3 (290.2) | 378.9 (429.5) |

Data are presented as means (SDs) unless otherwise specified.

*BEC of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.

†Pooled data for patients treated with 200 mg or 300 mg dupilumab every 2 weeks during QUEST followed by 300 mg every 2 weeks during TRAVERSE.

‡Severe asthma exacerbation before and study is defined as any treatment with 1 systemic (oral or parenteral) steroid burst or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma.

§Patients are considered to have ongoing atopic medical condition if they have any of these ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, or hives; or has baseline total IgE ≥ 100 IU/mL and at least 1 aeroantigen-specific IgE that is positive (≥0.35 IU/mL) at baseline.

by-visit interaction, baseline prebronchodilator $FEV_1$, and baseline-by-visit interaction as covariates.

Biomarker end points (BEC, FENO, TARC, and total IgE) are presented as mean change from PSBL during the treatment period. The association between changes from PSBL in FENO and prebronchodilator $FEV_1$ at week 52 of QUEST was assessed using linear regression analysis. Safety end points are presented as the absolute numbers of patients reporting TEAEs.

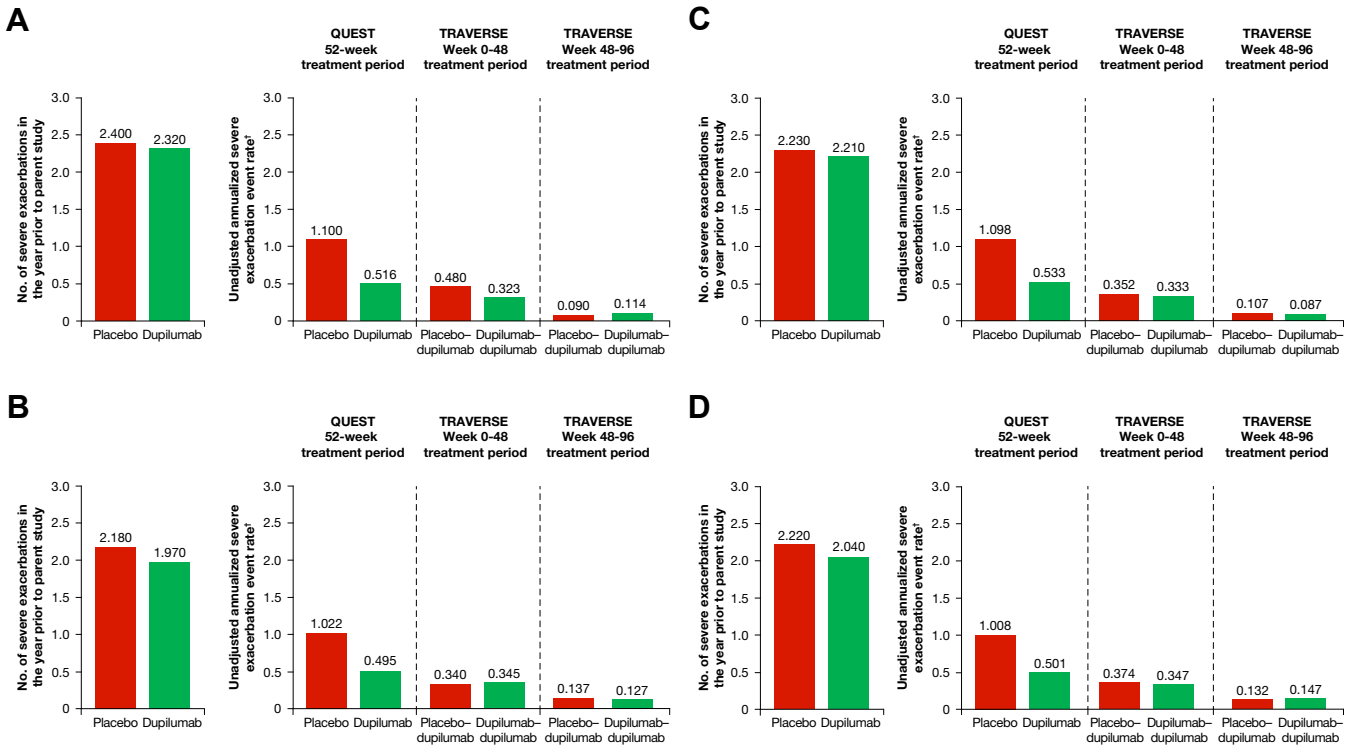


**FIG 1.** Unadjusted AER during QUEST and TRAVERSE in **(A)** patients with ≥2-fold change in BEC by week 12, **(B)** patients without ≥2-fold change in BEC by week 12, **(C)** patients with increased BEC any time during QUEST,* and **(D)** patients without increased BEC any time during QUEST.* *BEC of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST. †Total number of events that occurred during treatment period divided by total number of patient-years followed in treatment period.

## RESULTS

### Patients

Of dupilumab-treated patients, 36.6% experienced a ≥2-fold BEC change by week 12, compared with 21.7% of placebo recipients, while 31.3% of dupilumab and 28.0% of placebo recipients experienced an increased BEC, defined as <500 cells/μL at baseline but ≥500 cells/μL at any time point during QUEST. Demographics and disease characteristics at PSBL were similar across groups (Table I). Patients with ≥2-fold BEC change by week 12 or increased BEC any time during QUEST tended to have lower BEC and similar or higher FENO levels at PSBL than those without.

### AER

At PSBL, the mean number of exacerbations in the prior year was >2 for all patients (Fig 1). Dupilumab versus placebo reduced unadjusted AER during QUEST; these reductions were sustained during TRAVERSE regardless of a ≥2-fold BEC increase by week 12 or increased BEC any time during QUEST. Consistent AER reductions were also seen in placebo patients from QUEST on switching to dupilumab in TRAVERSE. Similar AER reductions were observed in patients with ≥2-fold BEC increase from PSBL at week 4 or week 12 (see Fig E1 in this article's Online Repository available at www.jacionline.org).

During QUEST, dupilumab reduced adjusted AER versus placebo across all treatment groups (relative risk vs placebo [95% confidence interval (CI)]: patients with ≥2-fold BEC change by week 12: 0.562 [0.379-0.832], $P = .0041$; patients without ≥2-fold BEC change by week 12: 0.527 [0.424-0.655, $P < .0001$; patients with increased BEC any time during QUEST: 0.511 [0.359-0.728], $P = .0002$; patients without increased BEC any time during QUEST: 0.537 [0.431-0.669], $P < .0001$).

During TRAVERSE, unadjusted AERs for weeks 0 to 48 for placebo/dupilumab and dupilumab/dupilumab arms were 0.480 and 0.323 for patients with ≥2-fold BEC change by week 12; 0.340 and 0.345 for patients without ≥2-fold BEC change by week 12; 0.352 and 0.333 for patients with increased BEC any time during QUEST; and 0.374 and 0.347 for patients without increased BEC any time during QUEST, respectively. Unadjusted AERs for weeks 48 to 96 were further reduced to 0.090 and 0.114 for patients with ≥2-fold BEC change by week 12; 0.137 and 0.127 for patients without ≥2-fold BEC change by week 12; 0.107 and 0.087 for patients with increased BEC any time during QUEST; and 0.132 and 0.147 for patients without, respectively.

### Prebronchodilator $FEV_1$

At PSBL, mean (standard deviation [SD]) prebronchodilator $FEV_1$ was comparable regardless of ≥2-fold BEC change by week 12 or increased BEC any time during QUEST, ranging from 1.72 (0.56) L to 1.89 (0.63) L (Table I).

During QUEST, dupilumab significantly improved prebronchodilator $FEV_1$ versus placebo across all subgroups from baseline to week 52 (least squares mean difference vs placebo [95% CI]: patients with ≥2-fold BEC by week 12: 0.18 L [0.08-0.28], $P = .0004$; patients without ≥2-fold BEC change by week 12:

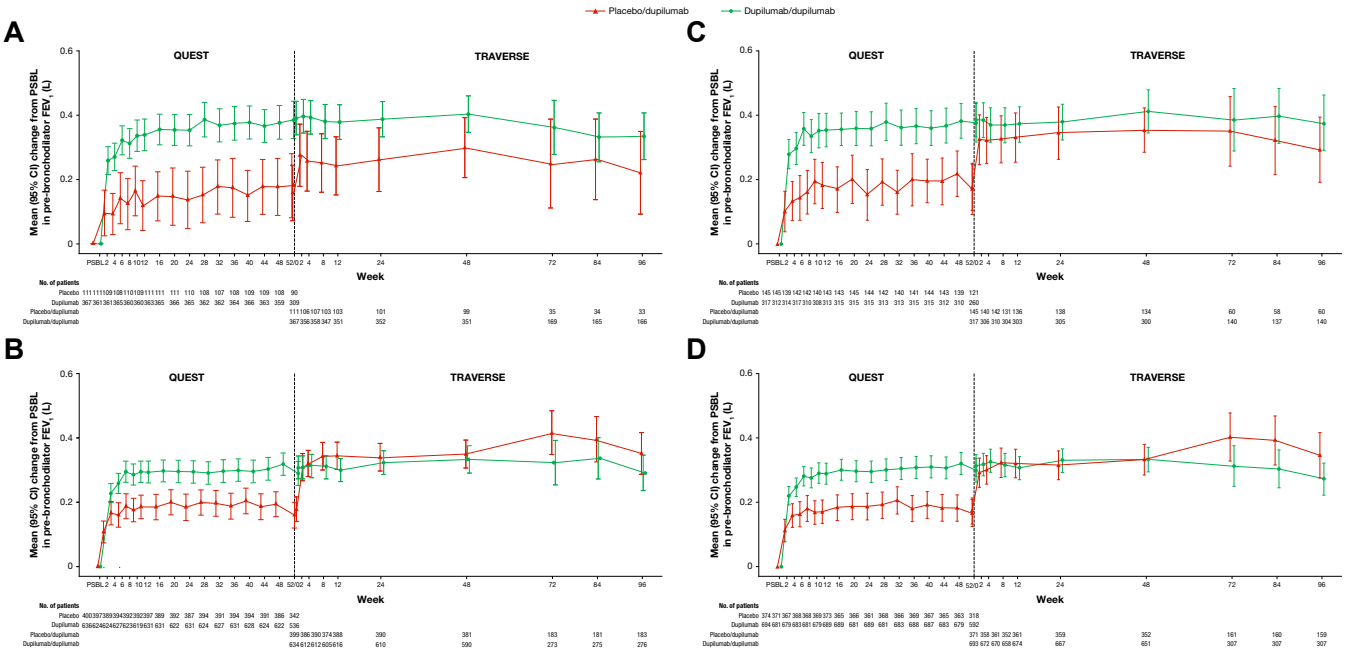


**FIG 2.** Mean change in prebronchodilator $FEV_1$ over QUEST and TRAVERSE in **(A)** patients with ≥2-fold change in BEC by week 12, **(B)** patients without ≥2-fold change in BEC by week 12, **(C)** patients with increased BEC any time during QUEST,* and **(D)** patients without increased BEC any time during QUEST.* *BEC of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.

0.15 L [0.11-0.20], $P < .0001$; patients with increased BEC any time during QUEST: 0.20 L [0.11-0.28], $P < .0001$; patients without: 0.15 L [0.01-0.20], $P < .0001$) (Fig 2). Numerically greater improvements were seen in dupilumab-treated patients with ≥2-fold BEC change by week 12 or increased BEC any time during QUEST than in those without them. These findings were echoed for patients with ≥2-fold change in BEC from PSBL at weeks 4 and 12 (see Table E1, *A,* in the Online Repository at www.jacionline.org).

Improvements in prebronchodilator $FEV_1$ were maintained through TRAVERSE in dupilumab-treated patients (mean [SD] change from PSBL at week 96 in dupilumab/dupilumab subgroups: patients with ≥2-fold BEC change by week 12: 0.34 [0.47] L; patients without: 0.29 [0.47] L; patients with increased BEC any time during QUEST: 0.38 [0.51] L; patients without: 0.27 [0.44] L). Similar results were observed for patients based on fold change in BEC from PSBL at week 4 and at week 12 (Table E1, *A*). Patients who received placebo in QUEST and switched to dupilumab during TRAVERSE saw similar improvements in prebronchodilator $FEV_1$ versus PSBL at TRAVERSE week 96 as the dupilumab/dupilumab patients, although improvement from PSBL was lower in the placebo/dupilumab versus dupilumab/dupilumab subgroups, with a ≥2-fold BEC change by week 12 (mean [SD] change from PSBL at week 96 in placebo/dupilumab: patients with ≥2-fold BEC change by week 12: 0.22 [0.36] L; patients without: 0.35 [0.44] L; patients with increased BEC any time during QUEST: 0.29 [0.39] L; patients without: 0.35 [0.45] L).

## ACQ-5 scores

At PSBL, mean (SD) ACQ-5 scores were comparable regardless of ≥2-fold BEC change by week 12 or increased BEC any time during QUEST and ranged from 2.64 (0.72) to 2.78 (0.80) (Table I).

Significantly greater improvements in ACQ-5 scores from PSBL were seen with dupilumab versus placebo through QUEST in all subgroups (least squares mean difference vs placebo at QUEST week 52 [95% CI]: patients with ≥2-fold change in BEC by week 12: −0.37 [−0.59 to −0.16], $P = .0007$; patients without: −0.30 [−0.43 to −0.17], $P < .0001$; patients with increased BEC any time during QUEST: −0.28 [−0.48 to 0.09], $P < .0043$; patients without: −0.32 [−0.45 to 0.20], $P < .0001$) (Fig 3).

Improvements were maintained through TRAVERSE week 48 in the dupilumab/dupilumab arm, and similar improvements were seen after patients switched to dupilumab in the placebo/dupilumab arm (mean change from PSBL [SD]: patients with ≥2-fold BEC change by week 12: placebo/dupilumab −1.58 [1.06], dupilumab/dupilumab −1.71 [1.04]; patients without: placebo/dupilumab −1.64 [1.08], dupilumab/dupilumab −1.67 [1.11]; patients with increased BEC any time during QUEST: placebo/dupilumab −1.67 [1.036], dupilumab/dupilumab −1.64 [1.052]; patients without: placebo/dupilumab −1.63 [1.098], dupilumab/dupilumab −1.70 [1.096]) (Fig 3). Similar results were observed through QUEST and TRAVERSE when patients were stratified on the basis of fold change in BEC from PSBL at weeks 4 and 12 (Table E1, *B*).

## Blood eosinophil levels

At PSBL, patients with a ≥2-fold change in BEC by week 12 had lower BECs than did those without such a change (see Table E2 in the Online Repository at www.jacionline.org): mean (SD) and median (Q1-Q3) BECs at PSBL were 158 (184) and 110 (50-200) cells/μL in the placebo group and 292 (287) and 190

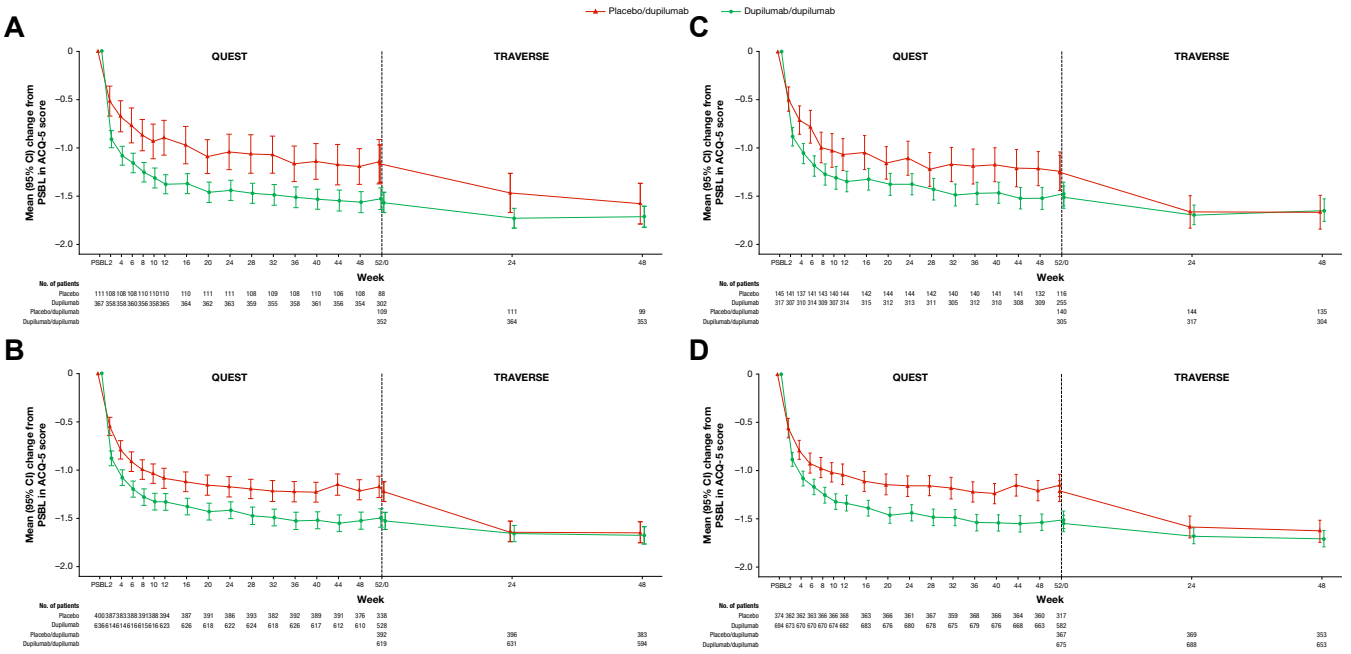


**FIG 3.** Mean change in ACQ-5 total score over QUEST and TRAVERSE in **(A)** patients with ≥2-fold change in BEC by week 12, **(B)** patients without ≥2-fold change in BEC by week 12, **(C)** patients with increased BEC any time during QUEST,* and **(D)** patients without increased BEC any time during QUEST.* *Eosinophil count of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.

(90-400) cells/μL in the dupilumab group. The respective values in patients without such a change were 455 (409) and 360 (190-580) cells/μL in the placebo group and 389 (383) and 280 (150-500) cells/μL in the dupilumab group. A similar pattern was observed in patients with and without an increased BEC any time during QUEST, in whom median (SD) and median (Q1-Q3) BECs at PSBL were, in those with an increase, 284 (138) and 300 (170-410) cells/μL in the placebo group and 272 (130) and 290 (170-370) cells/μL in the dupilumab group; in those without an increase, the respective values were 426 (447) and 240 (120-620) cells/μL in the placebo group and 386 (413) and 220 (110-600) cells/μL in the dupilumab group. In patients with or without a ≥2-fold change by week 12, BECs were significantly different at PSBL in the placebo and dupilumab groups (Table E2).

Early increases in BEC were seen during QUEST in all dupilumab-treated patients except those without a ≥2-fold change in BEC by week 12 (Fig 4). Peak increases (Fig 4, Table E2) occurred at week 8 for patients with a ≥2-fold change by week 12, in whom the mean (SD) and median (Q1-Q3) changes from PSBL were 475 (682) and 220 (70-670) cells/μL; at weeks 8 and 20 for patients with increased BEC any time during QUEST, in whom the respective values were 311 (533) and 160 (0-425) cells/μL at week 8 and 323 (723) and 140 (−20 to 450) cells/μL at week 20; and at week 4 for patients without increased BEC any time during QUEST, in whom the respective values were 61 (468) and 0 (−70 to 70) cells/μL). All increases in dupilumab-treated patients were transient and followed by a decline to near PSBL values by week 52 of QUEST (Table E2). The mean (SD) and median (Q1-Q3) changes from PSBL to week 52 were, in patients with a ≥2-fold change in BEC by week 12, 186 (337) and 90 (10-230) cells/μL in the placebo group and 177 (433) and 60 (−30 to 240) cells/μL in the dupilumab group; in patients without a ≥2-fold change by week 12, −87 (318) and −40 (−150 to 50) cells/μL in the placebo group and −94 (347) and −60 (−170 to 10) cells/μL in the dupilumab group; in patients with increased BEC any time during QUEST, 127 (298) and 60 (−50 to 240) cells/μL in the placebo group and 143 (376) and 50 (−80 to 250) cells/μL in the dupilumab group; and in patients without increased BEC any time during QUEST, −87 (336) and −30 (−135 to 50) cells/μL in the placebo group and −50 (409) and −30 (−150 to 30) cells/μL in the dupilumab group. In all 4 groups, BECs remained near to or fell below PSBL concentrations up to week 96 of TRAVERSE (Fig 4).

Comparison of BEC changes in the placebo and dupilumab groups (Table E2) shows that, in patients with a ≥2-fold change from PSBL in BEC by week 12, the early BEC elevation (to week 36) was significantly greater ($P < .0001$) in those who received dupilumab than in those who received placebo. Similarly, in patients with a BEC elevation at any time during the study, the BEC elevation was more often significantly greater in those who received dupilumab than in those who received placebo, with $P < .0001$ at weeks 4 to 12 and 20 and 28, $P \leq .001$ at weeks 16 and 32, and $P \leq .01$ at weeks 24 and 40 (at weeks 36, 44, 48, and 52, $P \geq .05$). For patients without a ≥2-fold change in BEC by week 12, in contrast, any difference between the placebo and dupilumab groups in the BEC change from PSBL was not often statistically significant, with $P < .05$ only at weeks 4, 8, and 20. In patients without a BEC elevation at any time during QUEST, any change in BEC was significantly different in the placebo and dupilumab groups at weeks 4 to 20 ($P \leq .0001$) and weeks 24 to 32 ($P < .01$).

## FeNO

At PSBL, mean (SD) FeNO levels were similar across patient groups (Table I).

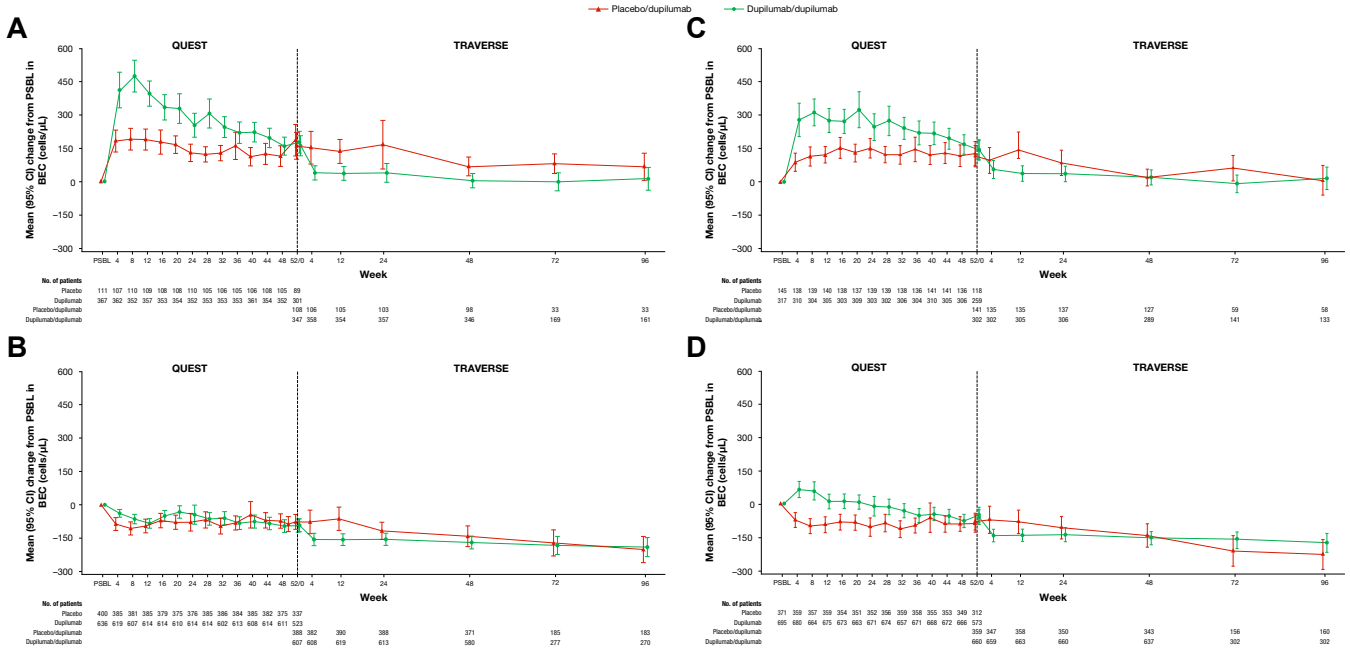


**FIG 4.** Mean change in BEC over QUEST and TRAVERSE in **(A)** patients with ≥2-fold change in BEC by week 12, **(B)** patients without ≥2-fold change in BEC by week 12, **(C)** patients with increased BEC any time during QUEST,* and **(D)** patients without increased BEC any time during QUEST.* *Eosinophil count of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.

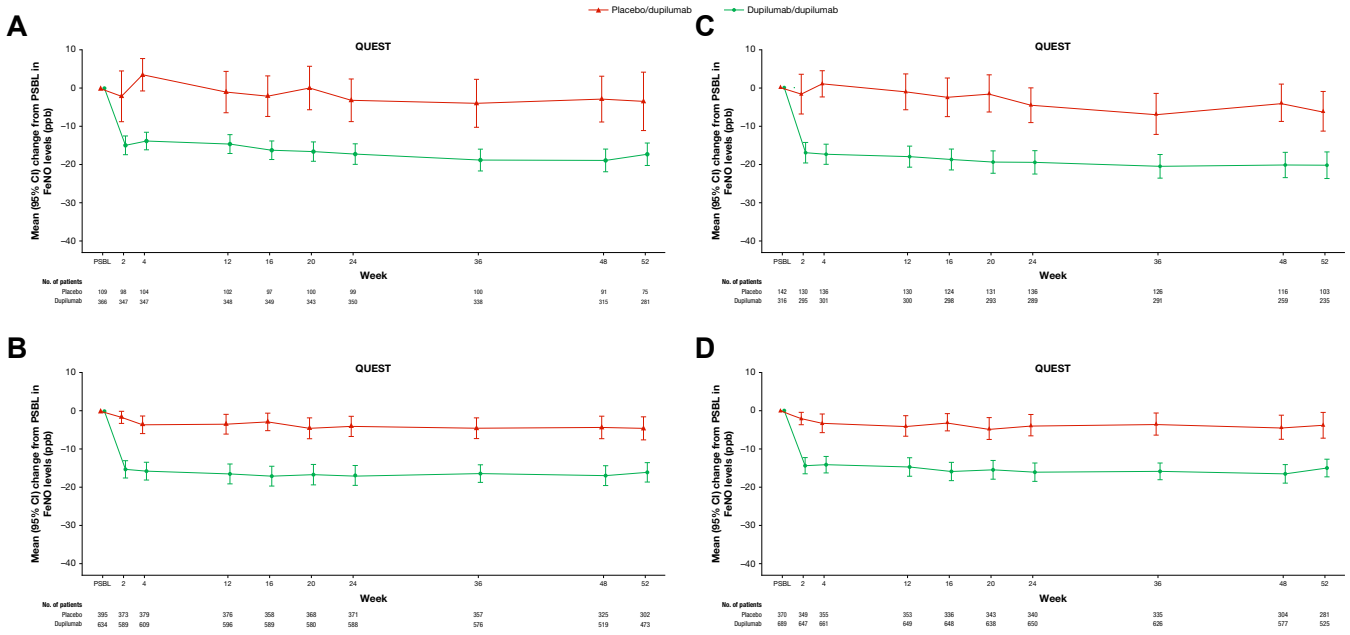


**FIG 5.** Mean change in FeNO levels over QUEST in **(A)** patients with ≥2-fold change in BEC by week 12, **(B)** patients without ≥2-fold change in BEC by week 12, **(C)** patients with increased BEC any time during QUEST,* and **(D)** patients without increased BEC any time during QUEST.* *Eosinophil count of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.

Dupilumab treatment versus placebo resulted in rapid reductions in FeNO levels in all subgroups by week 2 of QUEST and sustained them to week 52 (Fig 5). Most reductions were observed in patients with ≥2-fold BEC change by week 12 and those with increased BEC any time during QUEST (mean change from PSBL [SD]: patients with ≥2-fold BEC change by week 12: placebo −3.48 [33.19] ppb, dupilumab −17.31 [25.02] ppb; patients without: placebo −4.61 [26.62] ppb, dupilumab −16.12 [28.09] ppb; patients with increased BEC any time during QUEST: placebo −6.18 [26.53] ppb, dupilumab −20.29 [27.06] ppb; patients without: placebo −3.83 [28.68] ppb, dupilumab −15.00 [26.91] ppb).

**TABLE II.** TEAEs and treatment discontinuations during QUEST

| Characteristic | Patients with ≥2-fold change in BEC by week 12 | | Patients without ≥2-fold change in BEC by week 12 | | Patients with increased BEC any time during QUEST* | | Patients without increased BEC any time during QUEST* | |
|---|---|---|---|---|---|---|---|---|
| | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab |
| No. of subjects | 111 | 367 | 400 | 636 | 145 | 317 | 374 | 694 |
| TEAE | 95 (85.6) | 288 (78.5) | 322 (80.5) | 518 (81.4) | 109 (75.2) | 257 (81.1) | 316 (84.5) | 556 (80.1) |
| Treatment-related SAE | 10 (9.0) | 24 (6.5) | 21 (5.3) | 42 (6.6) | 6 (4.1) | 19 (6.0) | 26 (7.0) | 47 (6.8) |
| TEAE leading to death | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment-emergent EGPA‡ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatment discontinuations | 0 | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 1 (0.1) |
| Patient request | 0 | 1 (0.3) | 0 | 0 | 0 | 0 | 0 | 1 (0.1) |
| TEAE | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lack of efficacy | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Poor compliance | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Other | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Data are presented as nos. (%) unless otherwise indicated.
*SAE,* Serious adverse event.
*BEC of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.
†Pooled data for patients treated with 200 mg or 300 mg dupilumab every 2 weeks during QUEST followed by 300 mg every 2 weeks during TRAVERSE.
‡Dictionary-derived term or reported term for the adverse event is "eosinophilic granulomatosis with polyangiitis."

A low, negligible correlation between relative changes from PSBL to QUEST week 52 in FENO and prebronchodilator $FEV_1$ were observed across subgroups regardless of an increase in BEC (see Fig E2 in the Online Repository at www.jacionline.org).

## Other biomarkers of type 2 inflammation

At PSBL, total IgE, TARC, and eotaxin-3 levels were comparable regardless of increases in BEC.

Gradual reductions in total IgE (see Fig E3 in the Online Repository at www.jacionline.org) and rapid reductions in TARC (see Fig E4 in the Online Repository) were observed across all dupilumab-treated patients up to week 52 of QUEST.

Moderate and sustained reductions in eotaxin-3 levels were observed in all dupilumab-treated patients up to week 24 of QUEST (see Fig E5 in the Online Repository at www.jacionline.org). From week 24 to week 52, an increase to levels above PSBL was observed, albeit with wide CIs, in patients with ≥2-fold BEC change by week 12 and those with increased BEC any time during QUEST. In patients without ≥2-fold BEC change by week 12 and without increased BEC any time during QUEST, reduced eotaxin-3 levels were maintained to week 52. No correlation was observed between the relative change from PSBL in BEC and the relative change from PSBL in eotaxin-3 concentration (data not shown).

## Safety

Rates of TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation were similar across all patient groups during QUEST and TRAVERSE (Tables II and III). No patient discontinued treatment because of a TEAE during QUEST, and no incidences of treatment-emergent EGPA were reported. Between 1.5% and 6.3% of patients across subgroups withdrew from TRAVERSE as a result of TEAEs.

## DISCUSSION

In this analysis, dupilumab consistently reduced severe AERs and improved lung function and asthma control up to 148 weeks in patients with moderate-to-severe asthma, irrespective of transient increases in BEC.

36.6% of dupilumab-treated patients experienced a ≥2-fold BEC increase from PSBL at any time point up to week 12, and 31.3% experienced increased BEC at any time point during QUEST, versus 21.7% and 28.0% of placebo-receiving patients, respectively. Factors including the time of day the blood sample was collected, medication use, seasonality, infection, and natural variation may explain the BEC elevations observed in patients who received placebo.[15] In dupilumab-treated patients with ≥2-fold BEC change by week 12 and those with increased BEC any time during QUEST, BEC increases were early following treatment start, peaking between weeks 4 and 8 then decreasing to near PSBL levels by week 52, with these levels sustained to week 96. Although most efficacy outcomes were consistent across patients regardless of any transient increase in BEC, patients with an increased BEC had slightly greater improvement in prebronchodilator $FEV_1$ than did those without an increased BEC, despite having a lower BEC at PSBL.

These data and other evidence suggest that dupilumab efficacy in asthma is not directly linked to BEC changes.[12] Lung inflammation in asthma is heterogenous; peripheral BEC alone does not fully reflect this heterogeneity, and other markers, such as FENO, may inform on different but overlapping pathways.[16,17] Higher baseline FENO levels are associated with increased clinical benefit in patients treated with dupilumab, irrespective of baseline BECs and other clinical characteristics.[16] In this analysis, all patient subgroups had similar FENO levels at baseline. However, those with a ≥2-fold BEC increase or increases in BEC any time during QUEST on dupilumab showed greater FENO reductions by week 52 and improved prebronchodilator $FEV_1$ compared with those without transient BEC increases. In a recent real-world study of patients with severe type 2 asthma, baseline FENO levels significantly correlated with $FEV_1$ increases over 6 months of dupilumab treatment, although not with other measures of lung function or decreases in exacerbations; there was no significant correlation with baseline blood eosinophil or IgE levels with any FENO measure.[18] Taken together, these data may suggest that FENO levels may better predict dupilumab efficacy

**TABLE III.** TEAEs and treatment discontinuations during TRAVERSE

| Characteristic | Patients with ≥2-fold change in BEC by week 12 | | Patients without ≥2-fold change in BEC by week 12 | | Patients with increased BEC any time during QUEST* | | Patients without increased BEC any time during QUEST* | |
|---|---|---|---|---|---|---|---|---|
| | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab | Placebo/ dupilumab | Dupilumab†/ dupilumab |
| No. of subjects | 111 | 367 | 400 | 636 | 145 | 317 | 372 | 696 |
| TEAE | 88 (79.3) | 285 (77.7) | 320 (80.0) | 496 (78.0) | 109 (75.2) | 249 (78.5) | 305 (82.0) | 540 (77.6) |
| Treatment-related SAE | 15 (13.5) | 43 (11.7) | 38 (9.5) | 66 (10.4) | 13 (9.0) | 34 (10.7) | 40 (10.8) | 77 (11.1) |
| TEAE leading to death | 0 | 0 | 2 (0.5) | 1 (0.2) | 1 (0.7) | 0 | 1 (0.3) | 1 (0.1) |
| Treatment discontinuations | 19 (17.1) | 30 (8.2) | 32 (8.0) | 75 (11.8) | 18 (12.4) | 25 (7.9) | 34 (9.1) | 80 (11.5) |
| Patient request | 9 (8.1) | 11 (3.0) | 15 (3.8) | 39 (6.1) | 9 (6.2) | 10 (3.2) | 16 (4.3) | 40 (5.7) |
| TEAE | 7 (6.3) | 7 (1.9) | 6 (1.5) | 25 (3.9) | 6 (4.1) | 6 (1.9) | 7 (1.9) | 26 (3.7) |
| Lack of efficacy | 2 (1.8) | 0 | 1 (0.3) | 2 (0.3) | 1 (0.7) | 1 (0.3) | 2 (0.5) | 1 (0.1) |
| Poor compliance | 1 (0.9) | 2 (0.5) | 2 (0.5) | 5 (0.8) | 0 | 1 (0.3) | 3 (0.8) | 6 (0.9) |
| Other | 9 (8.1) | 21 (5.7) | 23 (5.8) | 43 (6.8) | 11 (7.6) | 17 (5.4) | 22 (5.9) | 47 (6.8) |

Data are presented as nos. (%) unless otherwise indicated.

*SAE,* Serious adverse event.

*BEC of <500 cells/μL at PSBL and ≥500 cells/μL at any time point during QUEST.

†Pooled data for patients treated with 200 mg or 300 mg dupilumab every 2 weeks during QUEST followed by 300 mg every 2 weeks during TRAVERSE.

as reflected by $FEV_1$ improvement than BECs and can help to identify patients with low BEC who may benefit from dupilumab treatment. Along with elevated FENO and allergen-specific IgEs, elevated BECs are now recognized as an indicator of type 2–high endotype in patients with asthma and, with other type 2 biomarkers, can guide asthma management because of inherent therapeutic and prognostic implications.[19,20]

Transient BEC elevation can identify type 2–high patients, especially those with low baseline BEC, revealing underlying inflammation.

In line with previous data,[21] we saw a rapid decline in TARC with dupilumab and a more gradual decline in total IgE with dupilumab during QUEST. TARC levels showed a small, gradual decline by week 12 of QUEST. The reasons for increased eotaxin-3 levels in dupilumab-treated subgroups around week 24 of QUEST are unclear, although CIs for these data points are very wide, so results should be treated with caution. Whether this increase can explain transient BEC increases seems unlikely since the trend in eotaxin-3 was most pronounced after peak eosinophil levels had been reached.

Overall safety was consistent with the known dupilumab safety profile and similar across all subgroups irrespective of early BEC increases. No patients discontinued treatment during QUEST because of a TEAE, and there were no reports of EGPA. TEAE rates and associated treatment discontinuations were similar across subgroups during TRAVERSE.

While data from this analysis come from large, randomized, controlled clinical trials, it has the usual limitations associated with its *post hoc* nature. TRAVERSE statistical analyses were descriptive only, and the treatment period was reduced from 96 to 48 weeks; therefore, for some analyses, only 48-week data in the extension study, beyond the 52-week QUEST data, are available. We considered BEC increases occurring anytime during the first 12 weeks, and anytime during the first 52 weeks, after treatment start to ensure that all potentially relevant BEC increases were captured in our analysis. We also analyzed patients by BEC increase at discrete time points (week 4 or week 12), since that could be more translatable to patient follow-up starting a new treatment in a real-world situation. We chose to dichotomize the increase in blood eosinophils to simplify interpretation and clinical translation.

These results confirm the long-term efficacy and safety of dupilumab and its mechanism of blocking IL-4/IL-13 signaling. While early BEC increases, especially ≥2-fold in the first 12 weeks, may predict better lung function improvement, FENO changes might be a superior biomarker. Additionally, higher baseline BEC doesn't correlate with the likelihood of early transient BEC increase, which may be clinically relevant for patients with high pretreatment BEC.

In conclusion, irrespective of transient BEC increases during the first 12 weeks of treatment, dupilumab consistently reduced severe AERs and improved prebronchodilator $FEV_1$ and asthma control up to 148 weeks in patients with uncontrolled moderate-to-severe type 2 asthma.

## DISCLOSURE STATEMENT

Sponsored by Sanofi and Regeneron Pharmaceuticals Inc.

Data sharing statement: Qualified researchers may request access (via vivli.org) to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and the statistical analysis plan) that support the methods and findings reported here. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (eg, FDA, EMA, or PMDA), if there is legal authority to share the data, and if there is not a reasonable likelihood of participant reidentification.

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**Clinical implication: Transient increases (≥2-fold) in BEC early in dupilumab treatment occurred in 36.6% of adults and adolescents with uncontrolled moderate-to-severe type 2 asthma but did not affect long-term efficacy or safety.**

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