Brief report

Dupilumab efficacy in patients with type 2 asthma and early FENO level reductions

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Background: The QUEST (ClinicalTrials.gov identifier NCT02414854) and TRAVERSE (NCT02134028) studies demonstrated the efficacy of dupilumab, 200 or 300 mg, versus placebo every 2 weeks for 52 weeks (QUEST) and dupilumab, 300 mg, for an additional 96 weeks (TRAVERSE) in patients with uncontrolled, moderate-to-severe asthma.

Objective: This analysis assessed dupilumab efficacy in patients from QUEST who enrolled in TRAVERSE and were stratified by a reduction in fractional exhaled nitric oxide (FENO) level by week 2 of QUEST.

Methods: Patients with an FENO level of at least 25 ppb at parent study baseline (PSBL) were defined as those with or without a minimally important FENO level reduction/response (a ≥20% reduction in patients with an FENO level of ≥50 ppb and a reduction of >10 ppb in those with an FENO level of <50 ppb at PSBL) by week 2 of QUEST. We assessed annualized severe exacerbation rates (AERs) and changes from PSBL in prebronchodilator FEV_1 value, 5-item Asthma Control Questionnaire score, and Asthma Quality of Life Questionnaire score.

Results: During QUEST, dupilumab (compared with placebo) reduced AER by 58% to 59% across FENO response subgroups (unadjusted AER = 0.392-0.523 for dupilumab vs 1.052-1.280 for placebo) and improved prebronchodilator FEV_1 value regardless of FENO response. These improvements were sustained during TRAVERSE, with a slightly greater magnitude in FENO responders. Dupilumab also improved 5-item Asthma Control Questionnaire and Asthma Quality of Life Questionnaire scores independently of FENO responses.

Conclusion: Dupilumab sustained efficacy for up to 3 years in patients with and without a minimally important early reduction in FENO level. Greater improvements were seen in patients with an early reduction in FENO level, but patients without such a reduction also showed favorable outcomes during their treatment with dupilumab. (J Allergy Clin Immunol Global 2025;4:100474.)

Key words: *Dupilumab, asthma, FENO, asthma exacerbation, lung function, asthma control, asthma-related quality of life, early response*

INTRODUCTION

Up to 80% of patients with severe asthma have a type 2 inflammatory phenotype characterized by increased blood eosinophil counts and/or elevated fractional exhaled nitric oxide (FENO) levels.[1] FENO is a clinically useful biomarker for predicting treatment response to inhaled corticosteroids (ICS), asthma exacerbations, and lung function decline, as well as for monitoring airway inflammation in patients with asthma.[2,3] Data on its value during treatment with biologic therapies are limited.[4]

Dupilumab, a human mAb, blocks the shared receptor component for IL-4 and IL-13, which are key drivers of type 2 inflammation.[5] In the phase 3 QUEST study (ClinicalTrials.gov identifier NCT02414854), add-on dupilumab, 200 or 300 mg every 2 weeks, reduced severe asthma exacerbations and improved prebronchodilator FEV_1 values in patients with uncontrolled, moderate-to-severe asthma, with greater effects noted in patients with type 2 inflammation (blood eosinophil counts ≥ 150 cells/μL or FENO levels ≥25 ppb).[6] In TRAVERSE, the open-label extension study (NCT02134028), dupilumab sustained efficacy for up to 3 years.[7] As clinical trial safety data accumulated, the TRAVERSE treatment period reduced from 96 to 48 weeks, resulting in fewer patients completing to week 96.[7] Dupilumab was well tolerated, with a similar adverse event incidence in both studies; the full details have been reported.[6,7] In QUEST, higher baseline FENO levels are associated with better clinical outcomes in dupilumab-treated patients irrespective of eosinophil levels, and FENO level changes predict lung function improvement, supporting the utility of FENO level as an independent biomarker for dupilumab response.[8,9]

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Received for publication June 4, 2024; revised January 31, 2025; accepted for publication February 20, 2025.

Available online April 15, 2025.

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2772-8293

https://doi.org/10.1016/j.jacig.2025.100474

Abbreviations used
ACQ-5: 5-item Asthma Control Questionnaire
AER: Annualized severe exacerbation rate
AQLQ: Asthma Quality of Life Questionnaire
FENO: Fractional exhaled nitric oxide
ICS: Inhaled corticosteroid
PSBL: Parent study baseline

This *post hoc* analysis assessed dupilumab's efficacy in patients with an elevated FENO level (≥25 ppb) at parent study (QUEST) baseline (PSBL) who enrolled in TRAVERSE. Of relevance, current smokers, those who ceased smoking within 6 months, and those with a smoking history of more than 10 pack years were excluded from enrollment. We classified those who achieved a minimally important FENO level reduction by QUEST week 2 as FENO responders (a ≥20% reduction in patients with FENO level of ≥50 ppb and a >10-ppb reduction in those with an FENO level of <50 ppb)[2] and those who did not as FENO nonresponders. The dupilumab/dupilumab group received dupilumab during QUEST and TRAVERSE. FENO responder status was determined during QUEST for those receiving dupilumab; thus, patients receiving placebo during QUEST (placebo/dupilumab group) are excluded from the TRAVERSE efficacy results. End points include annualized severe exacerbation rates (AERs), changes from PSBL baseline in prebronchodilator FEV_1 value, 5-item Asthma Control Questionnaire (ACQ-5) score, and Asthma Quality of Life Questionnaire (AQLQ) score. In QUEST, patients received a background therapy regimen of a medium- or high-dose ICS and at least 1 other controller medication; they were encouraged to continue this regimen throughout TRAVERSE. The interaction *P* value for AERs in QUEST was derived by using a negative binomial model with the total number of events onset from randomization up to week 52 or last contact date (whichever came earlier) as the response variable, and the 4 treatment groups, age, region (pooled country), baseline eosinophil count, baseline ICS dose level, number of severe exacerbation events within 1 year before the study, subgroup (if different from the aforementioned covariates) and treatment-by-subgroup interaction as covariates. Adjusted AERs were used to derive the *P* value for interaction. The remaining interaction *P* values were derived from a mixed-effect model with repeated measures (using method type 3), with change from baseline in prebronchodilator FEV_1 value, ACQ-5 score, AQLQ score, and FENO value (as appropriate) over time in QUEST as the response variable and the following as covariates: sex and PSBL baseline height (prebronchodilator FEV_1 value only); treatment; age; region (pooled country); baseline eosinophil count; baseline ICS dose level; visit; treatment-by-visit interaction; baseline prebronchodilator FEV_1 value, ACQ-5 score, AQLQ score, and FENO value; PSBL-by-visit interaction; FENO responder status; FENO responder-by-treatment interaction; and FENO responder-by-treatment-by-visit interaction. The statistical analyses for TRAVERSE are descriptive summaries generated by using observed data only owing to the open-label, single-group nature, with no comparator group.[7]

RESULTS AND DISCUSSION

We included 727 patients from QUEST who enrolled in TRAVERSE and had an FENO level of 25 ppb or higher at PSBL (469 patients in the dupilumab/dupilumab group and 258 in the placebo/dupilumab group) (Fig 1).

The baseline demographics were generally similar between treatment arms in week 2 (in the case of FENO responders: n = 82 in the placebo/dupilumab and n = 367 in the dupilumab/dupilumab group; in the case of FENO nonresponders, n = 176 in the placebo/dupilumab group and n = 102 in the dupilumab/dupilumab group [Table I]). Compared with the nonresponders, the FENO responders had higher FENO levels and were more likely to be former smokers or have an atopic medical condition at PSBL (Table I).

Dupilumab versus placebo reduced AERs by 58% to 59% across subgroups (unadjusted AER during QUEST = 0.392-0.523 vs 1.052-1.280, respectively [Fig 2, *A*]). Compared with the nonresponders, the FENO responders who received dupilumab during QUEST and TRAVERSE (dupilumab/dupilumab group) had greater reductions in AER and higher proportions were exacerbation-free (93.8% vs 88.6%, respectively) during TRAVERSE weeks 48 to 96 (Fig 2, *A*).

Dupilumab improved prebronchodilator FEV_1 values during QUEST independent of early FENO response, sustaining these improvements throughout TRAVERSE in the dupilumab/dupilumab group. The maximum change from PSBL was seen at TRAVERSE week 48 (mean change ± SD: 0.50 ± 0.53 L and 0.44 ± 0.65 L in the FENO responders and nonresponders, respectively). Overall, the FENO responders showed numerically greater improvements during QUEST than the nonresponders did, sustaining the improvements during TRAVERSE (Fig 2, *B*).

Similarly, dupilumab improved ACQ-5 and AQLQ scores by QUEST week 52 independent of FENO response, and these improvements were maintained in the dupilumab/dupilumab group through to TRAVERSE week 48 (Fig 3).

By QUEST week 52, the reductions in FENO levels were greater in the FENO responders (mean change from PSBL ± SD at QUEST week 52: 38.7 ± 32.0 ppb with dupilumab vs 20.7 ± 32.9 ppb with placebo) than in the nonresponders (mean change from PSBL ± SD at QUEST week 52: 10.8 ± 10.4 ppb with dupilumab vs 2.8 ± 25.9 ppb with placebo [Fig 4]).

Our findings support the long-term efficacy of dupilumab in patients with moderate-to-severe asthma and elevated FENO levels at baseline, often with rapid and robust minimally important FENO reductions seen at 2 weeks after initiation of dupilumab administration in QUEST. FENO responders receiving dupilumab maintained early robust declines in FENO level through QUEST, whereas the FENO levels in nonresponders declined more gradually. Regardless of FENO response, the clinical outcomes seen by QUEST week 52 persisted or improved further. Overall, the reductions in AER and improvements in prebronchodilator FEV_1 value were greater in the FENO responders. However, patients not showing this early FENO response also demonstrated favorable outcomes during QUEST. Importantly, the improvements in AER, prebronchodilator FEV_1 value, ACQ-5 score, and AQLQ score seen by the end of QUEST persisted or improved further up to week 96 during TRAVERSE, occurring regardless of FENO response.

Clinically, FENO levels can be used to assess treatment response and adherence to inhaled ICS use and may predict efficacy, with FENO level changes, rather than absolute values, considered more valuable when assessing treatment response.[2] FENO levels respond rapidly to ICS treatment, and reductions within 2 to 6 weeks may indicate successful treatment and inflammation reduction.[2] As

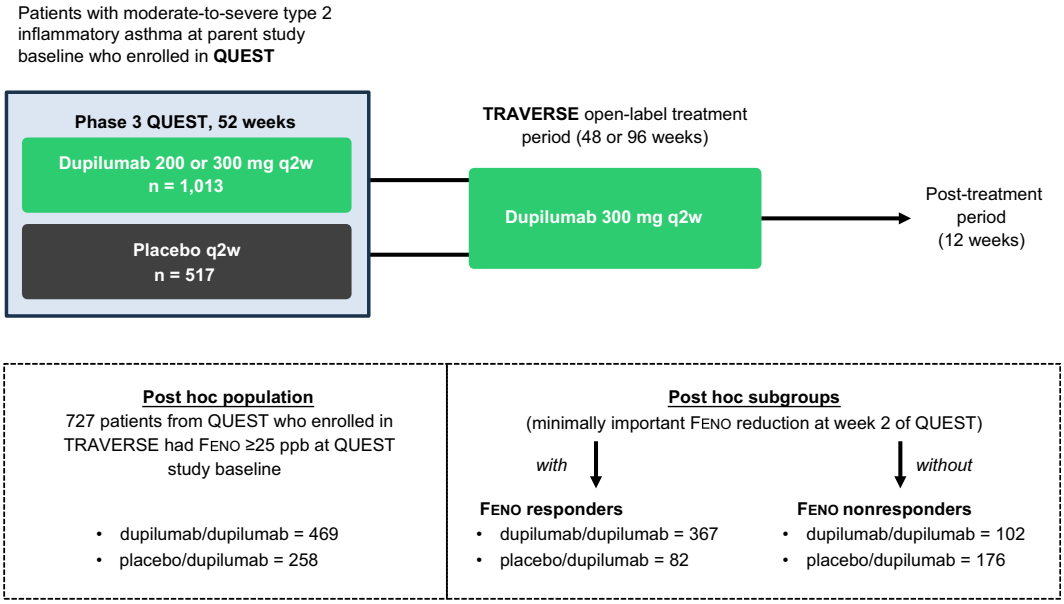

FIG 1. Study design for the TRAVERSE open-label extension study (adapted from Wechsler et al[7]) showing only patients from QUEST who enrolled in TRAVERSE plus patient subgroups included in this *post hoc* analysis. QUEST patient numbers represent the numbers of patients enrolled in and exposed to treatment in TRAVERSE. Patients from QUEST enrolled in TRAVERSE the same day as the end-of-treatment visit. *q2w,* Every 2 weeks.

demonstrated previously, higher baseline FENO levels are associated with greater risk of asthma exacerbations and can predict response to dupilumab independent of eosinophil levels.[4,6,8] This study adds to these data by exploring the effect of early reductions in FENO level on dupilumab treatment outcomes. Taken together, these findings suggest that FENO levels may be useful both as a pretreatment (baseline FENO levels) and during-treatment (early FENO level reductions) biomarker of response to dupilumab. Notably, long-term outcomes in dupilumab-treated patients not achieving early reductions in FENO level were still favorable. Patients in both response groups achieved clinically relevant improvements in AER[9] and prebronchodilator FEV_1 value,[10] with no apparent difference between the 2 groups in terms of improvements in asthma control or asthma-related quality of life. These observations are supported by the nonsignificance of the overall interaction *P* values between the responder groups and treatment arms for all outcomes at week 52 of QUEST. Although we noted some baseline differences between subgroups in characteristics known to affect FENO levels, such as smoking and atopy,[11] the long time since smoking cessation and the small numeric difference in those with atopic conditions suggest a negligible impact on clinical outcomes. Therefore, from a clinical practice perspective, our findings suggest that an absence of minimally important FENO reduction after dupilumab treatment initiation should not be interpreted as a reason to stop treatment in patients who would otherwise benefit from it, because these patients still show improvements in relevant clinical outcomes.

The prognostic value of FENO level in the treatment effect of other biologics is unclear, and different FENO responses between biologics likely reflect differences in immunologic targets[12-18]; FENO levels in asthma may be driven by primarily IL-13, which is blocked by dupilumab,[5] and our data support this, as FENO levels decline over time with dupilumab treatment.

The limitations of this study are inherent to its *post hoc* nature, including making inferences from assessments not part of the initial study design. Only patients who completed the parent study were eligible to participate in TRAVERSE, potentially introducing treatment bias toward patients receiving active treatment over those receiving placebo. The patient population was primarily White, and data relating to social determinants of health were not collected, which could limit the generalizability of the results. In this analysis, higher baseline FENO levels were observed in FENO responders than in nonresponders, and although classifying responders according to percentage change instead of absolute change may mitigate a ceiling effect (which could mask a true response), it is possible that this effect affected our findings. Lastly, we dichotomized FENO levels at 1 time point; in light of recent analyses in patients from QUEST showing a clear independent relationship between change in FENO levels and lung function improvement with dupilumab treatment (and not with exacerbations),[19] it may be more informative to assess long-term continuous changes in FENO level.

In conclusion, in patients aged 12 years or older with uncontrolled moderate-to-severe asthma and baseline FENO levels of 25 ppb or higher, dupilumab provides sustained, long-term reductions in exacerbation rates as well as improvements in lung function, asthma control, and quality of life for up to 3 years, regardless of whether patients did or did not achieve minimally important FENO level reductions 2 weeks after initiation of dupilumab treatment. In FENO responders, improvements in clinical outcomes were generally of greater magnitude than in nonresponders, but FENO nonresponders still showed favorable outcomes after treatment with dupilumab. These results add to the data supporting increased FENO levels at baseline as a biomarker to predict clinical response to dupilumab therapy while also showing that lack of an early minimally important FENO level

TABLE I. Demographic and disease characteristics of patients with FENO levels of 25 ppb or higher at QUEST baseline with and without a minimally important FENO level reduction at week 2 of QUEST

	FENO responders*		FENO nonresponders	
Characteristic	**Placebo/ dupilumab (n = 82)**	**Dupilumab/ dupilumab (n = 367)**	**Placebo/ dupilumab (n = 176)**	**Dupilumab/ dupilumab (n = 102)**
Age (y), mean (SD)	45.4 (15.1)	46.5 (14.6)	47.7 (15.7)	50.4 (14.2)
P value vs FENO responder			.262	.016
Female sex, no. (%)	42 (51.2)	223 (60.8)	107 (60.8)	55 (53.9)
P value vs FENO responder			.147	.214
Race, no. (%)				
Asian	5 (6.1)	55 (15.0)	24 (13.6)	15 (14.7)
Black/of African descent	4 (4.9)	13 (3.5)	4 (2.3)	4 (3.9)
White	73 (89.0)	297 (80.9)	146 (83.0)	82 (80.4)
Other	0	2 (0.5)	2 (1.1)	1 (1.0)
P value vs FENO responder			.156	.381
Ethnicity, no. (%)				
Hispanic	24 (29.3)	95 (25.9)	48 (27.3)	33 (32.4)
Non-Hispanic	58 (70.7)	272 (74.1)	128 (72.7)	69 (67.6)
P value vs FENO responder			.739	.195
Weight kg, mean (SD)	81.5 (18.4)	76.1 (18.0)	77.5 (17.6)	79.7 (16.8)
P value vs FENO responder			.100	.065
Body mass index (kg/m^2), mean (SD)	29.2 (6.1)	27.8 (5.9)	28.3 (5.8)	28.7 (5.1)
P value vs FENO responder			.274	.144
Use of a high-dose ICS, no. (%)	49 (59.8)	185 (50.4)	84 (47.7)	54 (52.9)
P value vs FENO responder			.072	.786
Age at onset of asthma (y), mean (SD)	28.0 (18.6)	27.9 (18.9)	27.3 (19.0)	28.9 (19.5)
P value vs FENO responder			.762	.660
Smoking history, no. (%)				
Never	63 (76.8)	302 (82.3)	149 (84.7)	93 (91.2)
Former	19 (23.2)	65 (17.7)	27 (15.3)	9 (8.8)
P value vs FENO responder			.126	.029
Time since smoking cessation (y), mean (SD)	14.6 (14.1)	17.8 (14.5)	19.5 (13.6)	25.4 (15.6)
P value vs FENO responder			.243	.199
No. of severe asthma exacerbations† experienced in the year prior, mean (SD)	2.29 (2.13)	2.20 (2.17)	2.26 (1.89)	1.99 (1.60)
P value vs FENO responder			.910	.272
With an ongoing atopic medical condition, no. (%)‡	74 (90.2)	322 (87.7)	147 (83.5)	79 (77.5)
P value vs FENO responder			.152	.009
Prebronchodilator FEV_1 value (L), mean (SD)	1.93 (0.58)	1.80 (0.62)	1.79 (0.61)	1.79 (0.64)
P value vs FENO responder			.068	.881
Prebronchodilator percent predicted FEV_1 value (%), mean (SD)	59.91 (12.74)	58.08 (13.49)	58.82 (12.51)	57.80 (13.83)
P value vs FENO responder			.518	.859
FEV_1 value reversibility (%), mean (SD)	26.86 (19.39)	27.78 (22.45)	25.51 (18.88)	24.44 (18.35)
P value vs FENO responder			.601	.124
Postbronchodilator FEV_1 value (L), mean (SD)	2.37 (0.69)	2.21 (0.75)	2.20 (0.74)	2.14 (0.79)
P value vs FENO responder			.076	.397
ACQ-5 score, mean (SD)	2.79 (0.80)	2.73 (0.81)	2.67 (0.72)	2.75 (0.75)
P value vs FENO responder			.256	.844
AQLQ score, mean (SD)	4.17 (1.02)	4.36 (1.10)	4.32 (1.01)	4.29 (1.03)
P value vs FENO responder			.288	.522
Blood eosinophil count (cells/μL), median (Q1-Q3)	370.0 (180.0-690.0)	370.0 (190.0-620.0)	390.0 (200.0-675.0)	300.0 (140.0-530.0)
P value vs FENO responder			.897	.0007
FENO level (ppb), median (Q1-Q3)	55.5 (38.0-77.0)	49.0 (36.0-72.0)	41.0 (31.0-56.0)	29.0 (26.0-38.0)
P value vs FENO responder			.009	<.0001
FENO level (ppb), no. (%)				
≤25 to <50 ppb	32 (39.0)	185 (50.4)	114 (64.8)	95 (93.1)
≥50 ppb	50 (61.0)	182 (49.6)	62 (35.2)	7 (6.9)
P value vs FENO responder			.0001	<.0001

P values for continuous variables were derived by using a *t* test, assuming unequal variance with the Satterthwaite method. *P* values for categoric variables were derived by using a chi-square test.

Q, Quartile.

*FENO responders are defined as patients achieving minimally important reductions in FENO level at QUEST week 2.

†Defined as any treatment with 1 or more systemic (oral or parenteral) steroid bursts for worsening asthma, hospitalization, or an emergency/urgent medical care visit for worsening asthma.

‡An ongoing atopic disease is considered present if the patient had or has any of the following diseases: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, eosinophilic esophagitis, food allergy, or hives, or a total IgE level of 100 IU/mL or higher and the result of at least 1 aeroallergen-specific IgE is positive (≥0.35 IU/mL) at baseline.

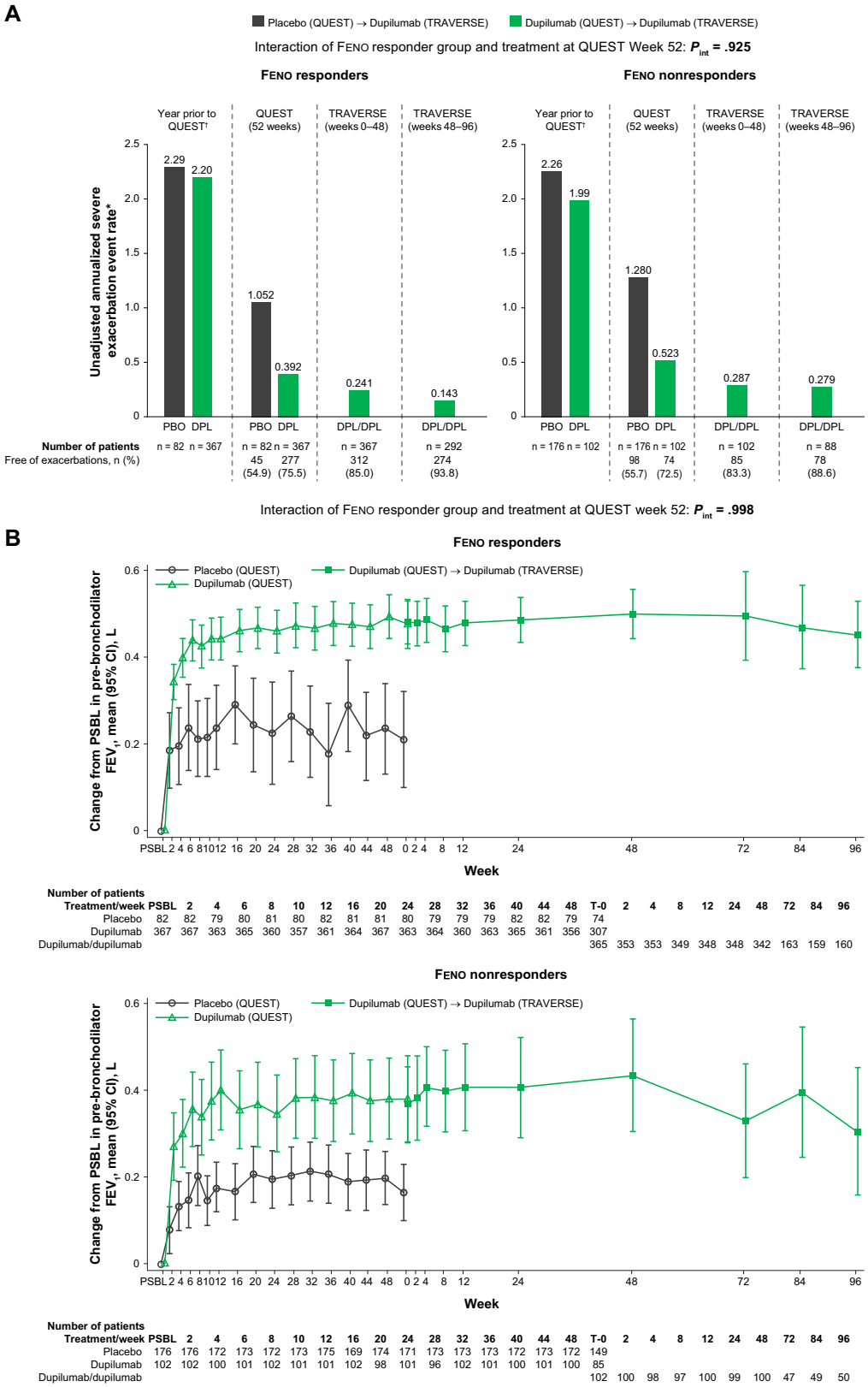

FIG 2. Unadjusted AERs* (**A**) and change from PSBL in prebronchodilator FEV_1 values over time (**B**) in patients with QUEST baseline FENO levels of 25 ppb or higher who enrolled in TRAVERSE. *Total events during the observational period/total patient years followed. †Mean (SD). Severe asthma exacerbation events are defined as systemic corticosteroid (SCS) use for at least days or hospitalization/emergency room visit for asthma, requiring an SCS. PSBL = QUEST baseline; week 0 = TRAVERSE start. FENO responders are defined as patients achieving minimally important FENO level reductions at QUEST week 2. *DPL*, Dupilumab; *PBO*, placebo.

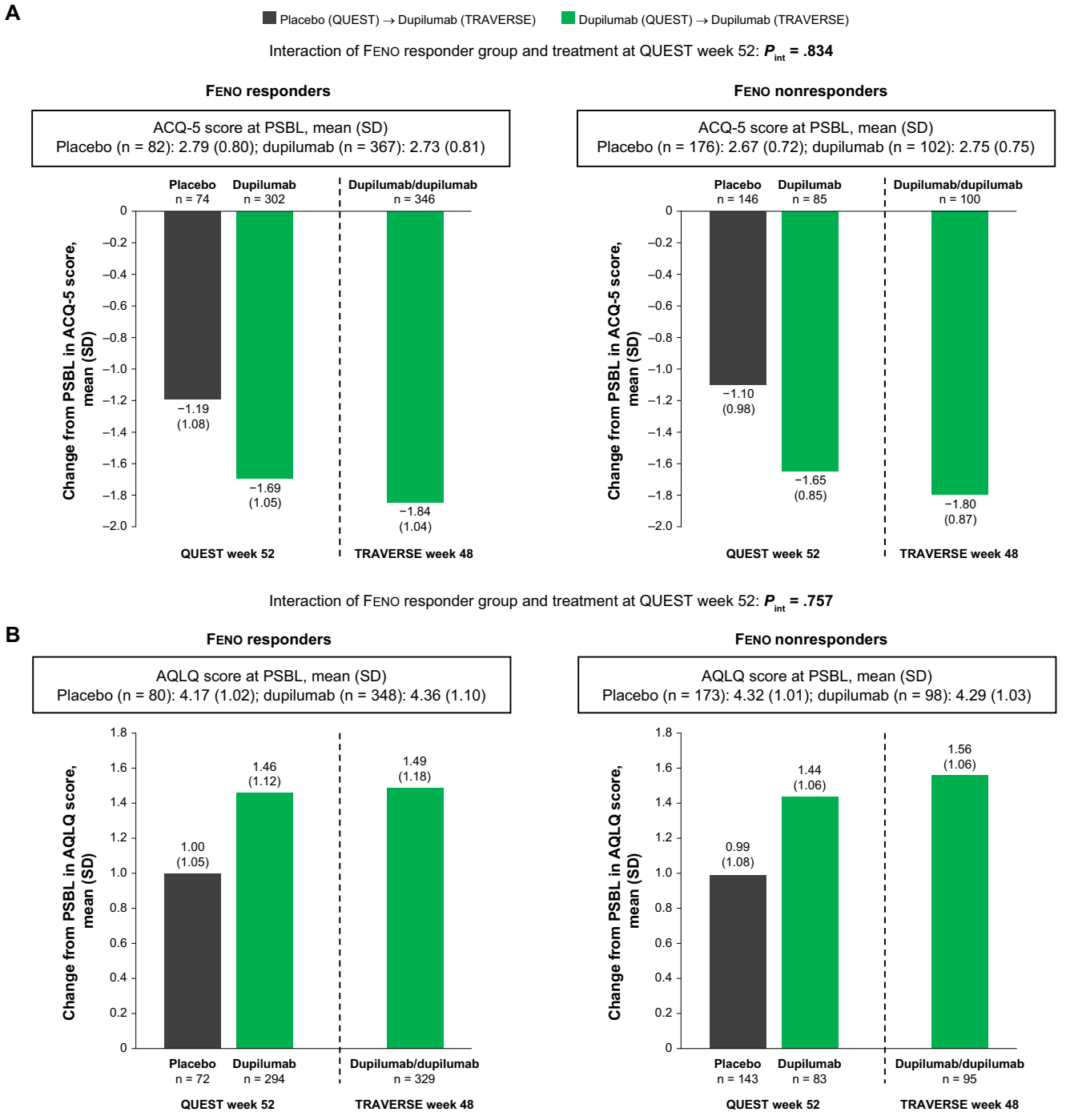

FIG 3. Change from PSBL in mean ACQ-5 (**A**) and AQLQ (**B**) scores in patients with QUEST baseline FENO levels of 25 ppb or higher who enrolled in TRAVERSE. PSBL = QUEST baseline. FENO responders are defined as patients achieving minimally important FENO level reductions at QUEST week 2.

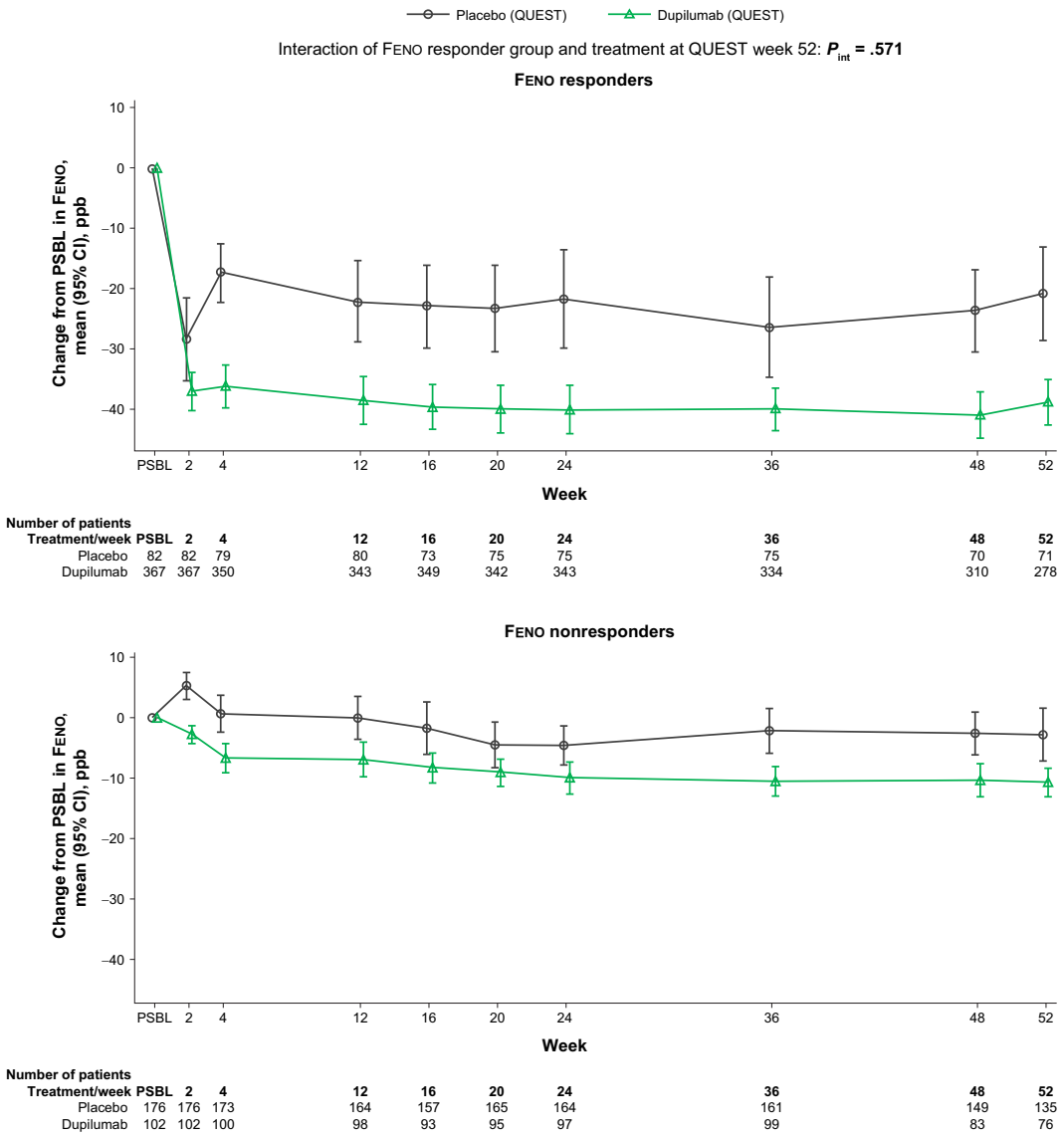

FIG 4. Change from baseline in FENO level (ppb) in patients with QUEST baseline FENO levels of 25 ppb or higher who enrolled in TRAVERSE. FENO levels collected only during QUEST and not during TRAVERSE. PSBL is QUEST baseline. FENO responders are defined as patients achieving minimally important FENO level reductions at QUEST week 2.

reduction after dupilumab treatment initiation should not deter clinicians from continuing treatment in patients who would otherwise benefit from it.

DISCLOSURE STATEMENT

This research (registered under ClinicalTrials.gov identifiers NCT02414854 and NCT02134028) was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. The study sponsor was involved in the study design, conduct, analysis, and interpretation of the data. This article was written with assistance from an independent medical writing company funded by the study sponsors.

Disclosure of potential conflict of interest: I. D. Pavord has received speaker fees from Aerocrine AB, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron Pharmaceuticals Inc, Sanofi, and Teva Pharmaceuticals; payments for organizing educational events from AstraZeneca, GSK, Regeneron Pharmaceuticals Inc, Sanofi, and Teva Pharmaceuticals; acted as a consultant for Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck, MSD, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals Inc, RespiVert, Sanofi, Schering-Plough, and Teva Pharmaceuticals; received international scientific meeting sponsorship from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp Pharmaceuticals, Regeneron Pharmaceuticals Inc, Sanofi, and Teva Pharmaceuticals; and received a research grant from Chiesi. M. E. Wechsler has received personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, CytoReason, Equillium, Genentech, Genzyme, Novartis, PULMATRIX, Regeneron Pharmaceuticals Inc, resTORbio, Sentien Biotechnologies, and Teva and received grants and personal fees from GSK, and Sanofi. W. W. Busse has received

consultant and speaker fees from AstraZeneca, Genentech, GSK, Novartis, Regeneron Pharmaceuticals Inc, and Sanofi. C. Domingo has received travel and speaker fees from ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, HAL Allergy, ImmunoTek, Menarini, Novartis, Sanofi, and Stallergenes Greer. C. Xia, R. Gall, A. Radwan, and Y. Deniz are employees and shareholders of Regeneron Pharmaceuticals Inc. N. Pandit-Abid and P .J. Rowe are employees of Sanofi and may hold stock and/or stock options in the company. J. A. Jacob-Nara is a former employee of Sanofi and may hold stock and/or stock options in the company.

We thank Éilis Sutton, PhD, of Excerpta Medica, for medical writing and editorial assistance that was funded by Sanofi and Regeneron Pharmaceuticals Inc, according to the Good Publication Practice guidelines.

Clinical implications: Dupilumab sustains long-term efficacy in patients with uncontrolled moderate-to-severe asthma irrespective of minimally important early reductions in FENO level. This finding strengthens the value of FENO level as a predictive biomarker of response to dupilumab.

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