Original Article

Efficacy of Tezepelumab in Patients with Severe, Uncontrolled Asthma and Perennial Allergy

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What is already known about this topic? Allergic asthma is a common phenotype of severe asthma; tezepelumab is an anti−thymic stromal lymphopoietin biologic therapy in development for the treatment of severe asthma.

What does this article add to our knowledge? Our analysis of participants in the phase IIb PATHWAY study shows that tezepelumab reduced exacerbations, improved lung function, and reduced type 2 biomarkers versus placebo in patients with severe, uncontrolled asthma with or without perennial allergy.

How does this study impact current management guidelines? Tezepelumab may be a valuable treatment option for patients with severe allergic asthma, as well as for those without allergy.

BACKGROUND: Tezepelumab is an anti−thymic stromal lymphopoietin mAb. In the PATHWAY phase IIb study (NCT02054130), tezepelumab significantly reduced annualized asthma exacerbation rates (AAERs) versus placebo in adults with severe, uncontrolled asthma.

OBJECTIVE: This *post hoc* analysis assessed the efficacy of tezepelumab in PATHWAY participants with perennial allergy.
METHODS: Adults (N = 550) with severe, uncontrolled asthma were randomized to receive tezepelumab (70 mg or 210 mg every 4 weeks or 280 mg every 2 weeks) or placebo, for 52 weeks. The AAER over 52 weeks was analyzed in patients grouped by sensitivity to perennial aeroallergens and by eligibility for omalizumab treatment according to the US or European Union prescribing information. Change from baseline to week 52 in prebronchodilator FEV_1 and type 2 biomarkers was assessed in the perennial allergy subgroups.
RESULTS: Across doses, tezepelumab reduced the AAER versus placebo by 66% to 78% in patients with perennial allergy (n = 254) and 67% to 71% in patients without perennial allergy (n = 261). Tezepelumab improved prebronchodilator FEV_1 and reduced blood eosinophil counts and fractional exhaled nitric oxide levels over 52 weeks, irrespective of perennial allergy status. Tezepelumab reduced the AAER versus placebo by 61% to 82% in omalizumab-eligible patients (US, n = 159; European Union, n = 101) and 63% to 70% in omalizumab-ineligible patients (US, n = 372; European Union, n = 440), respectively.
CONCLUSIONS: Treatment with tezepelumab reduced exacerbations, improved lung function, and reduced type 2 biomarkers versus placebo in patients with severe, uncontrolled asthma with or without perennial allergy, further supporting its efficacy in a broad population of patients with severe, uncontrolled asthma. **(J Allergy Clin Immunol Pract 2021;■:■-■)**

Key words: *Allergens; Asthma; Eosinophil; IgE; Omalizumab; Tezepelumab; Thymic stromal lymphopoietin*

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Abbreviations used
AAER- Annualized asthma exacerbation rate
EU- European Union
FEIA- Fluorescence enzyme immunoassay
FENO- Fractional exhaled nitric oxide
ICS- Inhaled corticosteroid
LS- Least-squares
Q4W- Every 4 weeks
Q2W- Every 2 weeks
T2- Type 2
TSLP- Thymic stromal lymphopoietin

INTRODUCTION

Allergic asthma is a common phenotype of asthma[1] and accounts for approximately 60% of patients with severe asthma.[2,3] Exposure of the airway to allergens leads to a characteristic type 2 (T2) inflammatory response mediated by antigen-specific T_H2 cells, with secretion of IL-4, IL-5, and IL-13 from these and other cells, production of IgE leading to mast cell degranulation, and eosinophilia.[4] In addition, type 2 innate lymphoid cells have been found to contribute to the activity of immune effector cells, such as eosinophils, in allergic asthma.[5] Patients with moderate to severe allergic asthma that is uncontrolled by treatment with inhaled corticosteroids (ICSs) and long-acting β_2 agonists may be prescribed a biologic therapy as an additional controller medication.[6] Omalizumab, an mAb directed against IgE, is specifically indicated for allergic asthma, as defined by a positive skin test result or *in vitro* reactivity to a perennial aeroallergen.[6]

Thymic stromal lymphopoietin (TSLP) is an epithelial-derived cytokine produced in response to allergens and other irritants, such as viruses and cigarette smoke, and plays a key role in the initiation and persistence of airway inflammation in asthma.[7] TSLP activates many cell types and pathways involved in both T2 and non-T2 inflammation.[8] In allergic responses, activation of dendritic cells by TSLP facilitates antigen presentation to $CD4^+$ naive T cells, thereby accelerating the differentiation of $CD4^+$ naive T cells to T_H2 cells.[8,9] Type 2 innate lymphoid cells respond to TSLP by producing type 2 cytokines, IL-5 and IL-13, associated with the allergic response.[8,10] TSLP can also directly induce mast cells to produce T2 cytokines, and mast cells can produce TSLP following IgE cross-linking, to propagate eosinophilic inflammation, allergic inflammation, and airway smooth muscle pathology.[8,11-13]

Tezepelumab is a human mAb IgG2λ directed against TSLP, preventing its interaction with the heterodimeric TSLP receptor.[14,15] In a proof-of-concept study, intravenous treatment with tezepelumab attenuated asthmatic responses to allergen challenge in patients with mild asthma.[14] In the phase IIb PATHWAY study (ClinicalTrials.gov identifier NCT02054130), tezepelumab significantly reduced annualized asthma exacerbation rates (AAERs) by up to 71% versus placebo in adults with severe, uncontrolled asthma, irrespective of baseline disease characteristics, including the presence of any allergy (seasonal or perennial).[15] Tezepelumab also improved lung function, asthma control, and health-related quality of life[15] and reduced health care resource utilization.[16] Furthermore, tezepelumab reduced levels of biomarkers of inflammation, including blood eosinophils, fractional exhaled nitric oxide (FENO), and total serum IgE.[15] This *post hoc* analysis evaluated the effect of tezepelumab in PATHWAY study participants with or without a perennial allergic phenotype, defined by sensitivity to perennial aeroallergens and by eligibility for omalizumab treatment.

METHODS

Study design

PATHWAY was a phase IIb, multicenter, randomized, double-blind, placebo-controlled study, conducted between December 2013 and March 2017. The full design and inclusion and exclusion criteria of this study have been described previously.[15] Eligible patients were current nonsmokers, 18 to 75 years old, with severe, uncontrolled asthma despite treatment with medium-dose (250-500 μg/d fluticasone dry powder inhaler or equivalent) or high-dose (>500 μg/d fluticasone dry powder inhaler or equivalent) ICS plus a long-acting β_2 agonist. Patients were required to have a history of at least 2 asthma exacerbations that led to systemic corticosteroid treatment, or at least 1 severe exacerbation that resulted in hospitalization, in the 12 months before study entry. Patients with any clinically important pulmonary disease other than asthma were excluded. Before randomization, patients were stratified according to study site (Japanese or non-Japanese) and subsequently by blood eosinophil count (≥250 cells/μL or <250 cells/μL) and ICS dose level (medium or high). Patients were randomized to receive subcutaneous tezepelumab (70 mg every 4 weeks [Q4W], 210 mg Q4W, 280 mg every 2 weeks [Q2W]) or placebo Q2W for 52 weeks.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained, and all patients provided written informed consent in accordance with local requirements.

Assessments and statistical analyses

In this *post hoc* analysis, the primary patient population of interest was patients with at least 1 positive test result for a perennial aeroallergen. Allergen sensitivity was determined according to a positive (≥0.35 kUA/L) or negative fluorescence enzyme immunoassay (FEIA) test result for IgE against the following perennial aeroallergens: animal (cat dander, dog dander, and cockroach), dust mite (*Dermatophagoides farinae* and *D pteronyssinus*), and mold (*Alternaria alternata*, *Aspergillus fumigatus*, *Cladosporium herbarum*, and *Penicillium chrysogenum*). For additional context, baseline data are presented for patients with at least 1 positive test result for a perennial aeroallergen, a seasonal aeroallergen, and either a perennial or a seasonal aeroallergen. Seasonal aeroallergens tested included pollen of Bermuda grass, birch, common ragweed, Japanese cedar, Johnson grass, and timothy grass. Unknown allergen sensitivity was defined as patients with FEIA test results missing for at least 1 aeroallergen and negative FEIA test results for the remaining allergens.

The primary efficacy end point in PATHWAY was the AAER, defined as the total number of asthma exacerbations divided by the total person-year follow-up time. For this analysis, differences in AAERs between tezepelumab 210 mg (the dose being used in ongoing phase III trials) and placebo, and pooled tezepelumab doses and placebo, were analyzed in patients grouped by sensitivity to perennial aeroallergens. Among patients with a positive FEIA test result for at least 1 perennial aeroallergen, AAER over 52 weeks was assessed in patients who had 1 or 2 or 3 or more positive test results for different perennial aeroallergens.

The AAER analysis was also performed in patients grouped by eligibility for omalizumab treatment, according to either the US[17] or

TABLE I. Baseline demographic and clinical characteristics of patients by perennial allergen sensitivity and by eligibility for treatment with OMA (US or EU prescribing information)

	Perennial aeroallergen		OMA US prescribing information		OMA EU prescribing information	
Characteristic	**FEIA$^+$ (n = 254)***	**FEIA$^-$ (n = 261)***	**OMA-eligible (n = 159)***	**OMA-ineligible (n = 372)***	**OMA-eligible (n = 101)***	**OMA-ineligible (n = 440)***
Age (y), mean ± SD	48.9 ± 12.9	54.3 ± 11.0	49.4 ± 12.8	52.7 ± 11.8	50.3 ± 13.6	52.0 ± 11.9
Sex: female, n (%)	152 (59.8)	186 (71.3)	102 (64.2)	249 (66.9)	65 (64.4)	290 (65.9)
BMI (kg/m^2), mean ± SD	28.2 ± 5.1	28.3 ± 5.2	28.2 ± 5.2	28.3 ± 5.1	28.0 ± 5.1	28.3 ± 5.2
ICS dose (μg/d)†						
Mean ± SD	724 ± 383	693 ± 379	722 ± 387	696 ± 375	937 ± 366	646 ± 358
Medium, n (%)	127 (50.0)	134 (51.3)	80 (50.3)	191 (51.3)	0	281 (63.9)
High, n (%)	127 (50.0)	127 (48.7)	79 (49.7)	181 (48.7)	101 (100)	159 (36.1)
Maintenance oral corticosteroid use, n (%)	23 (9.1)	25 (9.6)	17 (10.7)	32 (8.6)	18 (17.8)	31 (7.0)
Prebronchodilator FEV_1 % predicted, mean ± SD	59.2 ± 12.5	60.3 ± 12.9	59.3 ± 12.5	59.9 ± 12.9	57.6 ± 13.0	60.1 ± 12.9
No. of exacerbations in previous 12 mo, n (%)						
1 or 2	211 (83.1)	203 (77.8)	131 (82.4)	297 (79.8)	78 (77.2)	357 (81.1)
≥3	43 (16.9)	58 (22.2)	28 (17.6)	75 (20.2)	23 (22.8)	83 (18.9)
Total serum IgE (IU/mL), median (range)	284.3 (8.7-11,859.6)	82.8 (2.0-1,551.3)	172.7 (30.7-638.1)	117.6 (2.0-11,859.6)	193.1 (37.1-907.6)	116.3 (2.0-11,859.6)
Blood eosinophil count (cells/μL)						
Mean ± SD	353 ± 269	392 ± 425	320 ± 246	389 ± 390	338 ± 268	374 ± 369
Median (range)	280 (0-1,510)	270 (0-3,990)	270 (0-1,510)	280 (0-3,990)	280 (0-1,510)	270 (0-3,990)
FENO (ppb)						
Mean ± SD	38.6 ± 41.7	30.0 ± 29.1	34.9 ± 31.7	33.9 ± 38.3	41.4 ± 45.2	32.2 ± 33.6
Median (range)	25.0 (4.0-312.5)	20.3 (2.0-181.5)	25.0 (4.0-155.5)	21.0 (2.0-312.5)	29.0 (5.5-312.5)	21.0 (2.0-276.3)

OMA, Omalizumab; *ppb*, parts per billion.

*Of the 550 randomized patients included in the analysis, FEIA result for perennial aeroallergen sensitivity was unknown for 35 patients, and OMA eligibility was unknown for 19 and 9 patients in the US and EU analyses, respectively.

†Fluticasone (dry powder inhaler) or equivalent; medium-dose ICS: 250-500 μg/d; high-dose ICS: >500 μg/d.

European Union (EU)[18] prescribing information. For the US analysis, omalizumab-eligible patients were receiving medium- to high-dose ICS and had a positive (≥0.35 kUA/L) FEIA test result for IgE against the perennial aeroallergens described above, a baseline total serum IgE level of greater than or equal to 30 to less than or equal to 700 IU/mL, and an IgE-bodyweight combination within the dosing range of the omalizumab US prescribing information. For the EU analysis, omalizumab-eligible patients were receiving high-dose ICS and had a positive (≥0.35 kUA/L) FEIA test result for IgE against the perennial aeroallergens described above, a baseline total serum IgE level of greater than or equal to 30 to less than or equal to 1500 IU/mL, and an IgE-bodyweight combination within the range of the omalizumab EU prescribing information.

AAERs with 95% CIs for tezepelumab 210 mg, pooled tezepelumab and placebo, and rate ratios with 95% CIs for the difference between tezepelumab and placebo were estimated within perennial allergen sensitivity and omalizumab eligibility subgroups using a negative binomial regression model, with treatment group, baseline blood eosinophil count (≥250 cells/μL or <250 cells/μL), baseline ICS dose level (medium or high), subgroup ($FEIA^+$/$FEIA^-$ for perennial aeroallergen, or eligible/ineligible for omalizumab), and treatment-by-subgroup interaction included as covariates. The 2 rate ratios (1 for each subgroup separately) were estimated simultaneously from 1 model. No adjustment for multiple comparisons was done, and all results should be considered exploratory.

Prebronchodilator FEV_1 was evaluated at baseline and at postbaseline time points up to week 52. The following T2 biomarkers were also assessed at baseline and at postbaseline time points up to week 52: blood eosinophil count, FENO, and total serum IgE. Blood eosinophil count was determined at a centralized laboratory using a standard clinical hematology analyzer with automated or manual differentials using Wright-Giemsa stains. FENO was measured using a NIOX MINO airway inflammation monitor (Circassia Pharmaceuticals, Inc, Morrisville, NC), as per American Thoracic Society recommendations.[19] Total serum IgE levels were assessed at a centralized laboratory by immunoassay (Phadia, Thermo Fisher, Waltham, Mass).

Changes from baseline in FEV_1 and T2 biomarkers were determined for tezepelumab 210 mg Q4W and placebo within the perennial aeroallergen sensitivity subgroups using a mixed model for repeated measures with the following covariates: treatment group, baseline blood eosinophil count (≥250 cells/μL or <250 cells/μL), baseline ICS dose level (medium or high), baseline FEV_1 or biomarker level, FEIA status subgroup, visit, treatment-by-visit, subgroup-by-visit, treatment-by-subgroup, and treatment-by-visit-by-subgroup interaction. Least-squares (LS) means with 95% CIs, and LS mean differences between tezepelumab 210 mg Q4W and placebo with 95% CIs, were generated for each parameter over time.

RESULTS

Baseline characteristics

After completion of PATHWAY, data from 1 study site were removed from the final analyses because of irregularities in the data collected at that site.[20] Accordingly, of 584 patients who were randomized to study treatment, 550 were included in the present analysis (tezepelumab 70 mg Q4W, n = 138; 210 mg Q4W, n = 137; 280 mg Q2W, n = 137; placebo, n = 138; see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). Patients with perennial aeroallergen sensitivity comprised 46.2% of the study population ($FEIA^+$, n = 254; $FEIA^-$, n = 261; unknown, n = 35; Table I; see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Patients who were eligible for omalizumab treatment according to the US and EU prescribing information comprised 28.9% of the study population (eligible, n = 159; ineligible, n = 372; unknown, n = 19) and 18.4% of the study population (eligible, n = 101; ineligible, n = 440; unknown, n = 9), respectively (Table I; Figures 1 and E1). Patients with seasonal aeroallergen sensitivity comprised 38.0% of the study population ($FEIA^+$, n = 209; $FEIA^-$, n = 290; unknown, n = 51; see Table E2 in this article's Online Repository at www.jaci-inpractice.org). One-third of patients were $FEIA^+$ for both perennial and seasonal aeroallergen classes (33.7%; n = 167), 44.0% (n = 218) did not exhibit sensitivity to either allergen class, and 13.9% and 8.3% were sensitive to perennial aeroallergens only and seasonal aeroallergens only, respectively (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

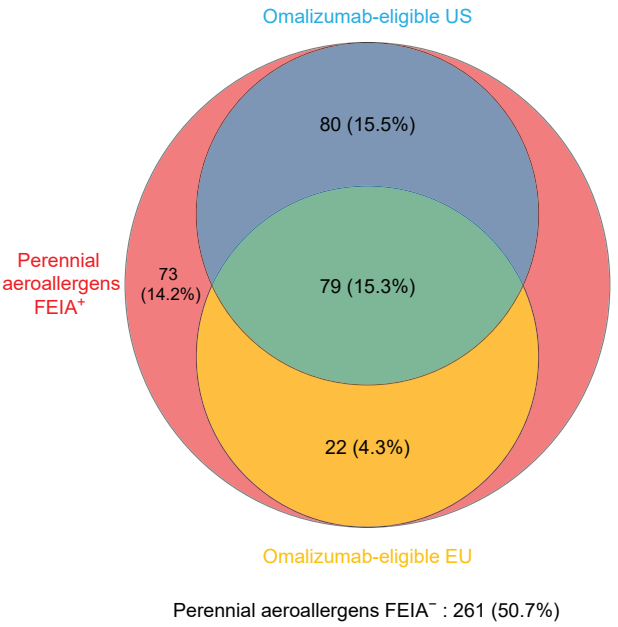

FIGURE 1. Overlap of patients with sensitivity to perennial aeroallergens and eligibility for omalizumab according to the US or EU prescribing information. Patients with unknown FEIA status for perennial aeroallergens or unknown omalizumab eligibility (US or EU prescribing information) (n = 35) are excluded from the figure.

Patients with perennial and/or seasonal aeroallergen sensitivity had higher total serum IgE and higher FENO at baseline than those without allergy and were younger and more likely to be men (Tables I, E1, and E2). Other characteristics, including baseline blood eosinophil counts, were generally similar between subgroups, including within the treatment groups (Tables I, E1, and E2). Among patients with perennial allergy, the proportion of women was slightly higher in the placebo group (66%) versus the tezepelumab 210 mg (55%) and pooled tezepelumab groups (58%). Rhinitis and eczema or atopic dermatitis were more common in patients who were $FEIA^+$ for perennial aeroallergens than in those who were $FEIA^-$ (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). Omalizumab-eligible patients (according to either the US or EU prescribing

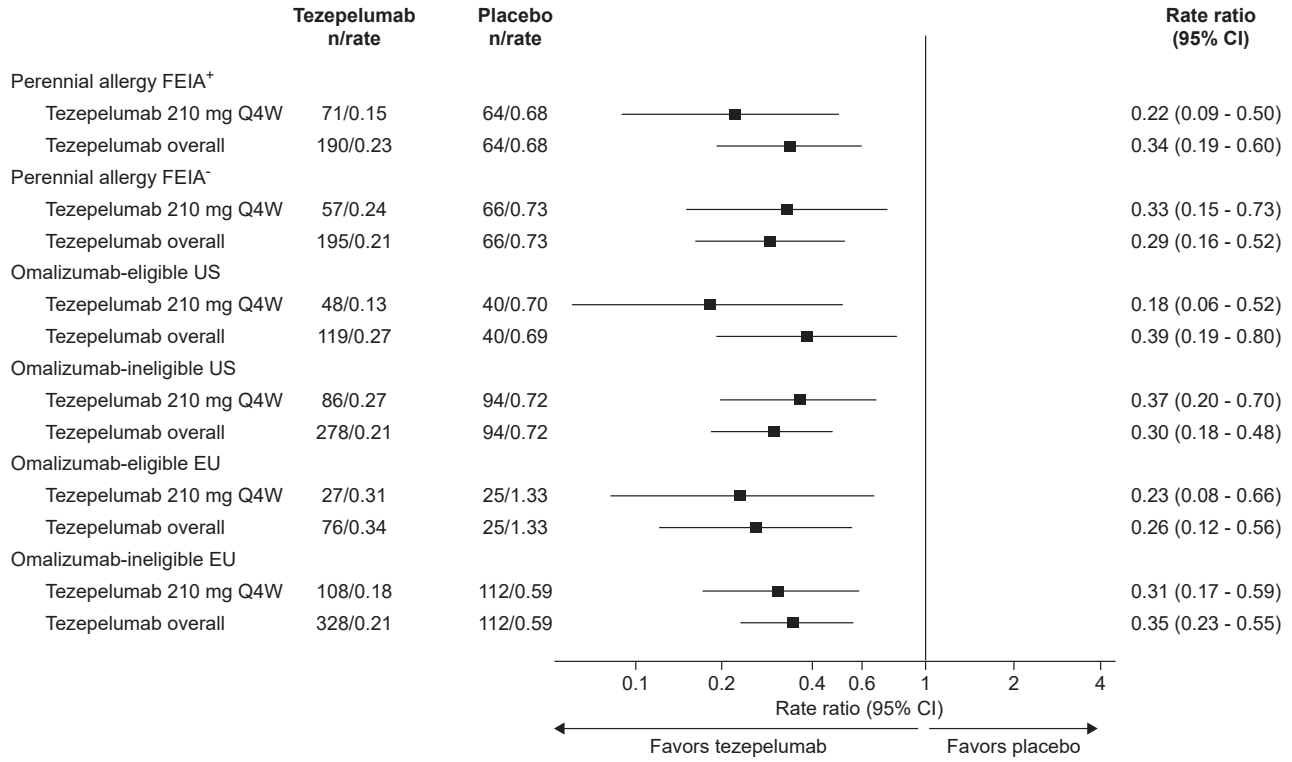

FIGURE 2. Reductions in AAER over 52 weeks in patients who were FEIA$^+$ or FEIA$^-$ for any perennial allergy and eligible or ineligible for treatment with omalizumab, according to the EU or US prescribing information. Marginal ratios are presented.

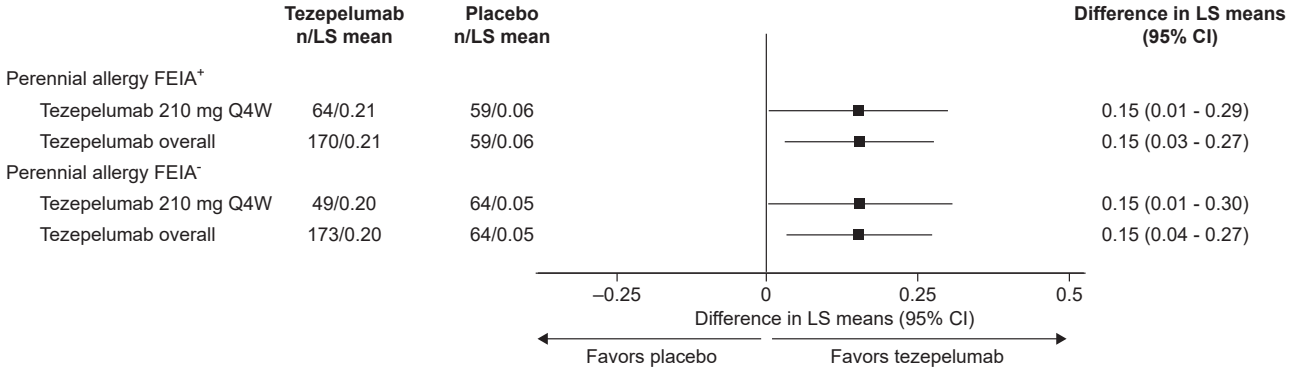

FIGURE 3. Improvements from baseline in prebronchodilator FEV_1 at week 52 in patients who were FEIA$^+$ or FEIA$^-$ for perennial allergy. Differences in LS mean values (L) for change from baseline to week 52 are presented.

information) had higher total serum IgE levels at baseline than omalizumab-ineligible patients (Table I). Patients eligible for omalizumab according to the EU prescribing information also had higher FENO than ineligible patients, and were more likely to be receiving maintenance oral corticosteroids.

Exacerbation rates

Among patients who received placebo, the AAER over 52 weeks was similar in those who were FEIA$^+$ for perennial aeroallergen and those who were FEIA$^-$ (FEIA$^+$, 0.68; FEIA$^-$, 0.73) (Figure 2). The AAER was reduced by tezepelumab treatment versus placebo in patients who were FEIA$^+$ or FEIA$^-$ for perennial aeroallergens. Reductions versus placebo were 78% (95% CI, 50-91) and 67% (95% CI, 27-85) in patients who were FEIA$^+$ and FEIA$^-$ for perennial aeroallergens in the tezepelumab 210 mg group, respectively, and 66% (95% CI, 40-81) and 71% (95% CI, 48-84) in the pooled tezepelumab dose groups, respectively. The distribution of the numbers of exacerbations experienced during the study period was similar in patients who were FEIA$^+$ or FEIA$^-$ for perennial aeroallergens, with a higher proportion of patients in the tezepelumab 210 mg and pooled tezepelumab groups having 0 exacerbations during the study period than those in the placebo group (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

In the omalizumab eligibility subgroup analysis, placebo recipients who were eligible for omalizumab according to the EU

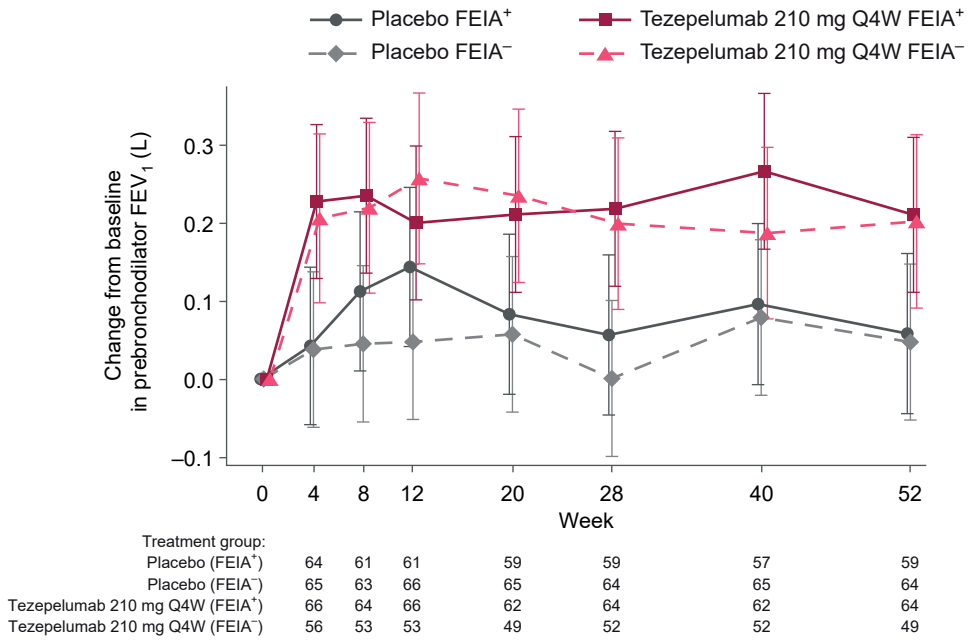

FIGURE 4. LS mean change from baseline in prebronchodilator FEV_1 over 52 weeks by FEIA status for perennial aeroallergens. Data are LS means with 95% CIs.

label had a considerably higher AAER than those who were ineligible (1.33 vs 0.59; Figure 2). Within the US omalizumab eligibility subgroups, the AAER among placebo recipients was similar among eligible and ineligible patients (0.70 vs 0.72). Tezepelumab reduced the AAER versus placebo in both omalizumab-eligible (tezepelumab 210 mg Q4W vs placebo, 82% [95% CI, 48-94], and 77% [95% CI, 34-92], for the US and EU analyses, respectively) and omalizumab-ineligible patients (tezepelumab 210 mg Q4W vs placebo, 63% [95% CI, 30-80], and 69% [95% CI, 41-83], respectively).

When data were analyzed by number of $FEIA^+$ perennial aeroallergens, there was a trend toward greater improvements in AAER in those with allergy to 3 or more versus 1 or 2 perennial aeroallergens. In patients who were $FEIA^+$ for only 1 or 2 perennial aeroallergens, the AAER was reduced versus placebo (n = 32) by 70% (95% CI, −4 to 91) and 58% (95% CI, −8 to 84) in the tezepelumab 210 mg group (n = 41) and pooled tezepelumab (n = 101) dose groups, respectively. In patients who were $FEIA^+$ for 3 or more perennial aeroallergens, the AAER versus placebo (n = 32) was reduced by 84% (95% CI, 31-96) and 69% (95% CI, 24-87) in the tezepelumab 210 mg group (n = 30) and pooled tezepelumab (n = 89) dose groups, respectively.

Lung function

Prebronchodilator FEV_1 at week 52 was improved from baseline in patients who received tezepelumab versus placebo, irrespective of FEIA status for perennial aeroallergens (LS mean difference between tezepelumab 210 mg Q4W and placebo: $FEIA^+$, 0.15 L; $FEIA^-$, 0.15 L) (Figure 3). Differences between tezepelumab and placebo were observed as early as week 4 (the first postbaseline time point assessed) and were sustained until week 52 (Figure 4).

Biomarkers

Blood eosinophil count and FENO level decreased in patients who received tezepelumab 210 mg Q4W versus placebo, irrespective of perennial aeroallergen FEIA status (Figure 5, *A* and *B*; see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Differences between tezepelumab and placebo were seen as early as week 4 and were sustained until week 52. Total serum IgE was reduced by treatment with tezepelumab in patients who were $FEIA^+$ for perennial aeroallergens but not among those who were $FEIA^-$. Differences between tezepelumab and placebo were observed by week 4 and were sustained until week 52 (Figure 5, *C*; Table E5).

DISCUSSION

This *post hoc* analysis of data from the phase IIb PATHWAY study demonstrated that treatment with tezepelumab reduced the rate of exacerbations, improved lung function, and reduced levels of inflammatory biomarkers in PATHWAY participants with allergy to perennial aeroallergens, including those who were eligible for omalizumab treatment. Exacerbations over 52 weeks were reduced with tezepelumab versus placebo in patients with and without perennial allergy. Furthermore, there were improvements in lung function and reductions in blood eosinophil count and FENO levels, irrespective of allergic status, which were observed by the first postbaseline time point evaluated and sustained throughout the 52-week treatment period.

The proportion of patients with allergy (perennial or seasonal) in PATHWAY (53.8%) was lower than that observed in adults with severe asthma in the Severe Asthma Research Program cohort (75.2%)[21] or the Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes (U-BIOPRED) cohort (78.3% of nonsmokers).[22] This may be a result of differences in study inclusion criteria: epidemiologic studies typically include all

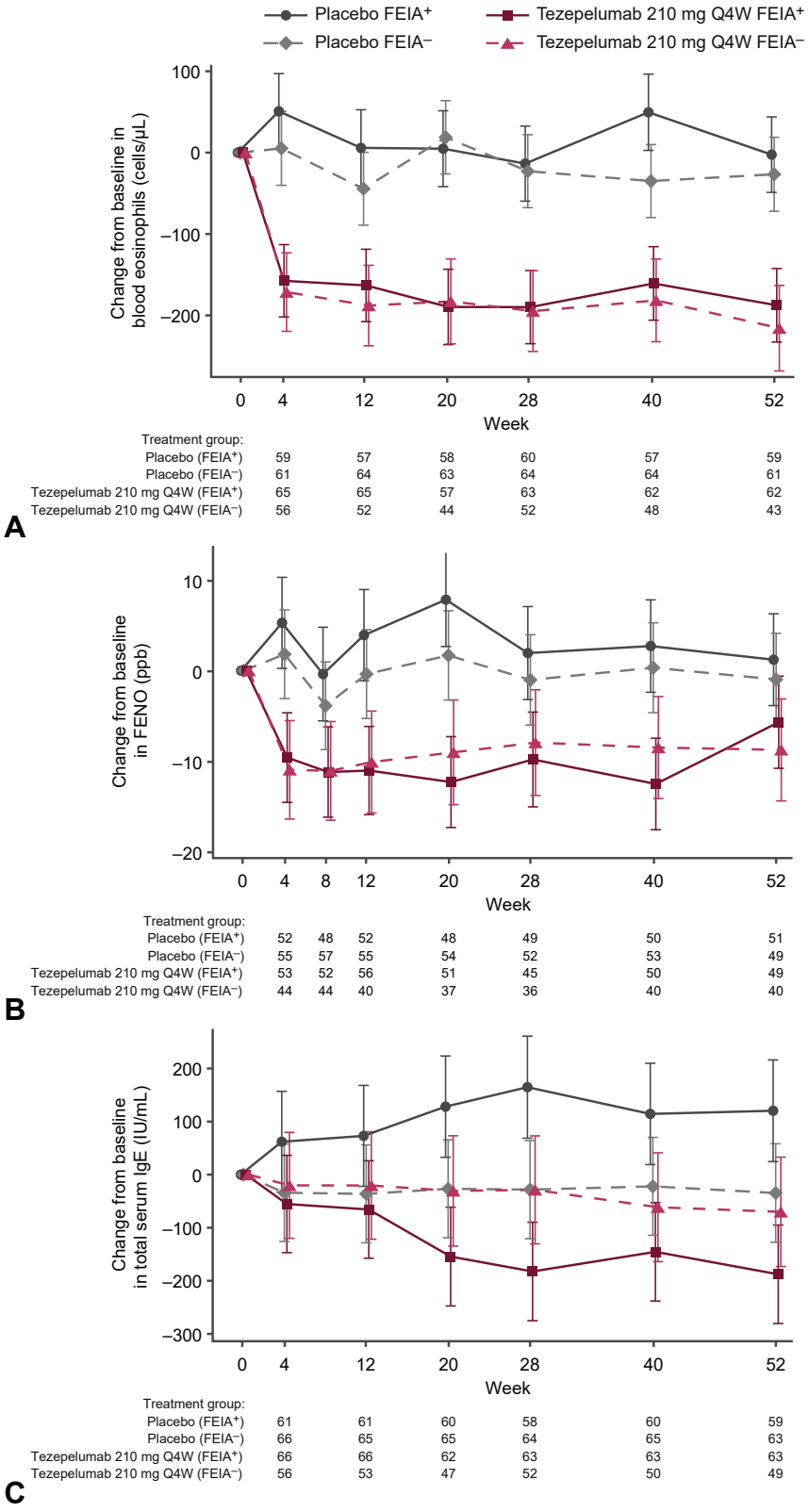

FIGURE 5. LS mean change from baseline in (**A**) blood eosinophil count, (**B**) FENO, and (**C**) total serum IgE, over 52 weeks by FEIA status for perennial aeroallergens. Data are LS means with 95% CIs. *ppb,* Parts per billion.

comers, whereas randomized controlled trials of therapies for severe asthma typically select frequently exacerbating patients, which enriches for eosinophilic (and often nonallergic) patients.[23] The proportion of patients with allergy in this study was toward the lower end of the rates of atopy recorded in phase III trials of other biologic therapies (48%-82%).[24-28] These trials enrolled adolescents as well as adults, which may have increased rates of atopy compared with PATHWAY (because allergic asthma is associated with younger age[21,29]).

Although there were no notable differences in most measures of asthma severity between patients with and without allergen sensitivity at baseline in this study, there were some apparent differences in biomarkers of inflammation: patients with allergy, including those eligible for omalizumab treatment, had higher total serum IgE (as expected) and a trend toward higher FENO at baseline, with no clear difference in blood eosinophil count. Patients with allergy were also more likely to be younger and have comorbid rhinitis and atopic dermatitis than those without allergy.

The AAER was reduced by tezepelumab treatment in patients who were $FEIA^+$ or $FEIA^-$ for perennial aeroallergens in this analysis, with a similar magnitude of reduction as seen in the overall PATHWAY population (71% with tezepelumab 210 mg Q4W).[15] Prebronchodilator FEV_1 at week 52 was improved from baseline in patients who received tezepelumab versus placebo, irrespective of FEIA status. The LS mean difference in FEV_1 between tezepelumab and placebo at week 52 was similar to the equivalent value for the overall PATHWAY population (0.13 L with tezepelumab 210 mg Q4W).[15] The efficacy of tezepelumab in both allergic and nonallergic asthma is likely due to the wide-ranging effects of blocking TSLP. Tezepelumab has been shown to reduce eosinophilic inflammation in the airway of patients with moderate to severe asthma,[30] as well as levels of cytokines such as IL-5 and IL-13,[31] elevated levels of which are characteristic of allergic asthma.[1] In addition, tezepelumab has been found to reduce airway hyperresponsiveness in these patients,[30,32] which may lead to improved clinical outcomes in both allergic and nonallergic patients. Blocking TSLP may also have suppressive effects on non-T2 inflammatory processes with particular relevance in nonallergic asthma.[8]

In the omalizumab eligibility analysis, among patients who received placebo during the study, the AAER was over twice as high in those who were EU omalizumab-eligible versus those who were EU omalizumab-ineligible, although no differences were observed between US omalizumab-eligible and US omalizumab-ineligible patients. These findings are most likely explained by the omalizumab EU label requirement for receipt of high-dose ICSs with additional controllers; patients receiving this treatment regimen during the PATHWAY study had a higher AAER while receiving placebo than those receiving medium-dose ICSs.[15] Tezepelumab reduced the AAER versus placebo in both omalizumab-eligible (82% and 77% with tezepelumab 210 mg Q4W for the US and EU analyses, respectively) and omalizumab-ineligible patients (63% and 69% with tezepelumab 210 mg Q4W for the US and EU analyses, respectively), albeit to a slightly higher extent in the omalizumab-eligible patients.

We found that tezepelumab reduced blood eosinophil count and FENO levels from baseline in patients with or without perennial allergy. The reductions in these 2 biomarkers are a known pharmacodynamic effect of tezepelumab[15,31] and are likely related to decreased IL-5 and IL-13 levels, respectively, caused by blocking TSLP activity and subsequent reduced activity of immune cells such as T_H2 cells and type 2 innate lymphoid cells.[8] In contrast, blocking IL-4 and IL-13, without IL-5, as seen with dupilumab, may lead to transient blood eosinophilia in patients with mild to moderate asthma.[24] Reductions in FENO levels were greater in patients who were $FEIA^+$ versus $FEIA^-$ for perennial aeroallergens, that is, in the subgroup with higher FENO levels at baseline. After treatment with tezepelumab 210 mg Q4W, mean FENO levels in the $FEIA^-$ subgroup were similar to published median values for healthy volunteers (16 parts per billion).[33] Mean total serum IgE was reduced by tezepelumab in patients who were $FEIA^+$ for perennial aeroallergens, but this was not evident in those without perennial allergy (ie, $FEIA^-$). In contrast, among placebo recipients, an increase in total serum IgE was observed among those $FEIA^+$ for perennial aeroallergens, as might occur in patients with allergic asthma who are uncontrolled and experience a year without additional treatment. There is considerable variability in total serum IgE levels among patients with severe asthma, which can be affected by oral and inhaled corticosteroid use and airborne allergen exposure[34,35]; there was no increase in median total IgE levels in placebo recipients $FEIA^+$ for perennial aeroallergens in the larger Liberty Asthma QUEST phase III study of dupilumab.[36] In the present study, no change in mean total IgE was observed among tezepelumab or placebo recipients $FEIA^-$ for perennial aeroallergens. As expected, the nonallergic population had lower baseline total IgE levels than the allergic population, and the mean total IgE levels among patients without allergy were similar to or below the normal range for healthy adults.[37] These observations suggest that, across a broad population of patients, the specific immunologic effects of TSLP blockade will vary depending on a patient's baseline inflammatory profile and biomarker status.

A strength of this *post hoc* analysis was that multiple definitions of perennial allergy were used ($FEIA^+$ for perennial aeroallergens and US and EU omalizumab eligibility). A limitation of this analysis was that the PATHWAY phase IIb study was not prospectively powered to specifically investigate differences between patients with or without an allergic phenotype. These analyses need to be repeated using larger data sets from phase 3 studies, which have recently been completed. In addition, complete evaluations of allergic status, such as the use of skin testing, were not performed. Furthermore, exposure to the relevant aeroallergens and any resulting symptoms were not taken into account. Despite these limitations, the current analyses suggest efficacy of tezepelumab regardless of the presence or absence of perennial allergy.

CONCLUSIONS

Treatment with tezepelumab reduced exacerbations versus placebo in patients with severe asthma and perennial allergy, defined by sensitivity to perennial aeroallergens or by eligibility for omalizumab treatment, and in those without perennial allergy. Compared with placebo, tezepelumab improved prebronchodilator FEV_1 and reduced blood eosinophil count and FENO in patients with or without perennial allergy. Tezepelumab also reduced total serum IgE among those with perennial allergy. This *post hoc* analysis provides further support for the efficacy of TSLP inhibition with tezepelumab in reducing asthma

exacerbations in a broad population of patients with severe, uncontrolled asthma.

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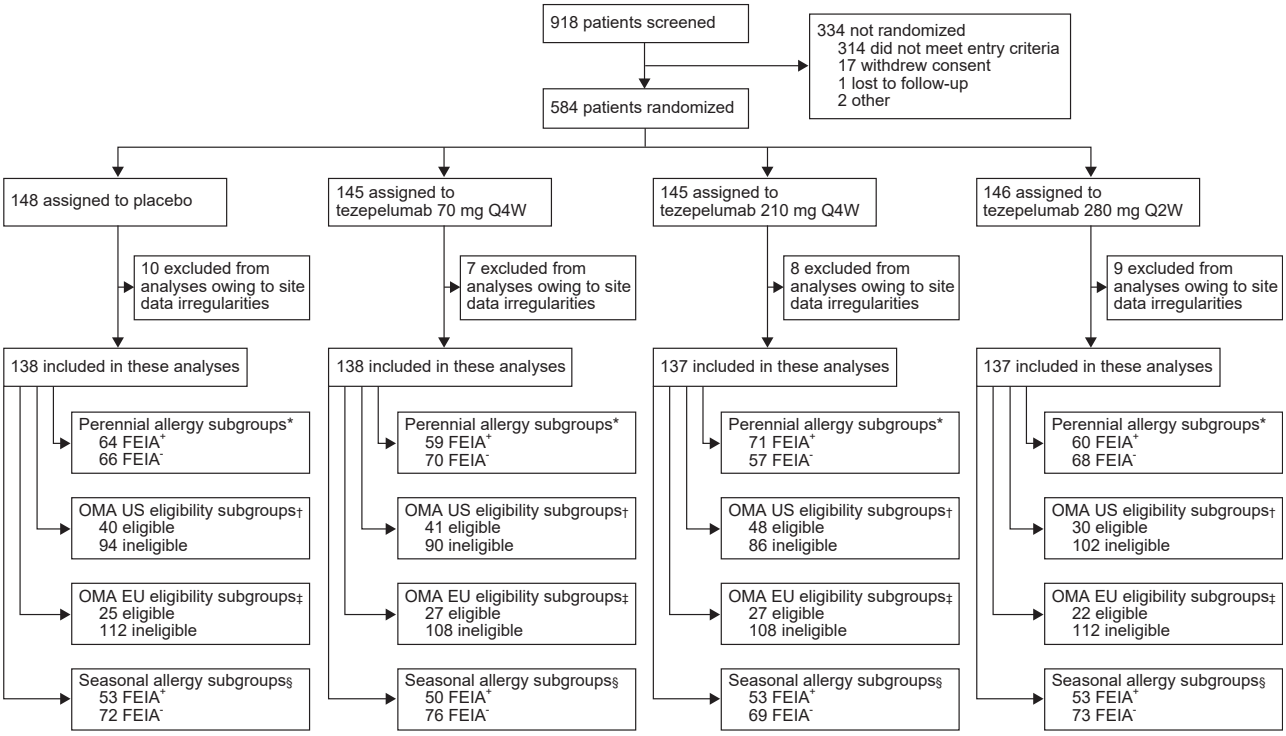

FIGURE E1. Flow diagram of PATHWAY participants' eligibility for the present subgroup analyses. *OMA*, Omalizumab. *FEIA result for perennial aeroallergen sensitivity was unknown for 35 patients included in the analyses overall. †OMA US eligibility was unknown for 19 patients included in the analyses overall. ‡OMA EU eligibility was unknown for 9 patients included in the analyses overall. §FEIA result for seasonal aeroallergen sensitivity was unknown for 51 patients included in the analyses overall.

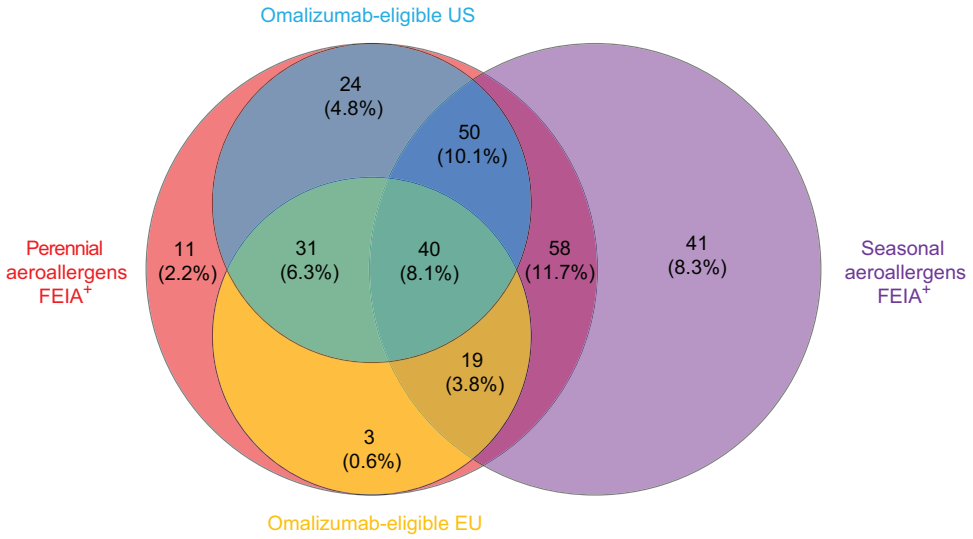

FIGURE E2. Overlap of patients with sensitivity to perennial and/or seasonal aeroallergens and/or eligibility for omalizumab according to the US or EU prescribing information. Patients with unknown FEIA status for either perennial or seasonal aeroallergens, or unknown omalizumab eligibility (US or EU prescribing information) (n = 55, total), are excluded from the figure.

TABLE E1. Baseline demographic and clinical characteristics of patients by perennial aeroallergen sensitivity by treatment group

	Placebo (n = 138)		Tezepelumab 210 mg Q4W (n = 137)		Pooled tezepelumab (n = 412)		Overall (N = 550)	
Characteristic	**FEIA$^+$ (n = 64)***	**FEIA$^-$ (n = 66)***	**FEIA$^+$ (n = 71)***	**FEIA$^-$ (n = 57)***	**FEIA$^+$ (n = 190)***	**FEIA$^-$ (n = 195)***	**FEIA$^+$ (n = 254)***	**FEIA$^-$ (n = 261)***
Age (y), mean ± SD	49.8 ± 12.6	54.5 ± 10.7	50.2 ± 12.9	55.2 ± 12.1	48.6 ± 13.0	54.2 ± 11.1	48.9 ± 12.9	54.3 ± 11.0
Sex: female, n (%)	42 (65.6)	46 (69.7)	39 (54.9)	42 (73.7)	110 (57.9)	140 (71.8)	152 (59.8)	186 (71.3)
BMI (kg/m^2), mean ± SD	28.7 ± 5.3	28.0 ± 5.7	28.1 ± 5.2	29.1 ± 4.6	28.0 ± 5.0	28.4 ± 5.1	28.2 ± 5.1	28.3 ± 5.2
ICS dose (μg/d)†								
Mean ± SD	739 ± 369	644 ± 359	700 ± 334	654 ± 406	718 ± 388	709 ± 385	724 ± 383	693 ± 379
Medium, n (%)	30 (46.9)	37 (56.1)	36 (50.7)	30 (52.6)	97 (51.1)	97 (49.7)	127 (50.0)	134 (51.3)
High, n (%)	34 (53.1)	29 (43.9)	35 (49.3)	27 (47.4)	93 (48.9)	98 (50.3)	127 (50.0)	127 (48.7)
Maintenance oral corticosteroid use, n (%)	8 (12.5)	6 (9.1)	5 (7.0)	4 (7.0)	15 (7.9)	19 (9.7)	23 (9.1)	25 (9.6)
Prebronchodilator FEV_1 % predicted, mean ± SD	58.4 ± 12.5	61.6 ± 14.6	57.7 ± 12.5	60.5 ± 12.9	59.4 ± 12.6	59.8 ± 12.3	59.2 ± 12.5	60.3 ± 12.9
No. of exacerbations in previous 12 mo, n (%)								
1 or 2	54 (84.4)	49 (74.2)	54 (76.1)	43 (75.4)	157 (82.6)	154 (79.0)	211 (83.1)	203 (77.8)
≥3	10 (15.6)	17 (25.8)	17 (23.9)	14 (24.6)	33 (17.4)	41 (21.0)	43 (16.9)	58 (22.2)
Total serum IgE (IU/mL), median (range)	325.3 (37.1-11,859.6)	104.9 (6.0-617.7)	285.5 (8.7-11,429.6)	82.0 (2.0-1,307.0)	277.0 (8.7-11,429.6)	75.6 (2.0-1,551.3)	284.3 (8.7-11,859.6)	82.8 (2.0-1,551.3)
Blood eosinophil count (cells/μL)								
Mean ± SD	396 ± 317	372 ± 334	353 ± 216	388 ± 477	339 ± 250	398 ± 453	353 ± 269	392 ± 425
Median (range)	285 (0-1,510)	280 (0-1,870)	300 (0-1,080)	240 (10- 3,180)	280 (0-1,340)	270 (0-3,990)	280 (0-1,510)	270 (0-3,990)
FENO (ppb)								
Mean ± SD	44.0 ± 48.2	31.9 ± 29.9	35.9 ± 30.5	27.8 ± 30.3	36.8 ± 39.2	29.4 ± 28.9	38.6 ± 41.7	30.0 ± 29.1
Median (range)	25.2 (6.0-276.3)	20.5 (3.5-136.5)	25.3 (4.0-152.5)	15.5 (5.0-136.0)	25.0 (4.0-312.5)	20.0 (2.0-181.5)	25.0 (4.0-312.5)	20.3 (2.0-181.5)

ppb, Parts per billion.

*Of the 550 randomized patients included in the analysis, FEIA result for perennial aeroallergen sensitivity was unknown for 35 patients (8 placebo and 27 pooled tezepelumab, including 9 tezepelumab 210 mg Q4W are part of the 27 pooled tezepelumab).

†Fluticasone (dry powder inhaler) or equivalent; medium-dose ICS: 250-500 μg/d; high-dose ICS: >500 μg/d.

TABLE E2. Baseline demographic and clinical characteristics of patients by allergen sensitivity

	Any allergen		Perennial aeroallergen		Seasonal aeroallergen	
Characteristic	**FEIA$^+$ (n = 296)***	**FEIA$^-$ (n = 218)***	**FEIA$^+$ (n = 254)***	**FEIA$^-$ (n = 261)***	**FEIA$^+$ (n = 209)***	**FEIA$^-$ (n = 290)***
Age (y), mean ± SD	49.6 ± 12.6	54.1 ± 11.3	48.9 ± 12.9	54.3 ± 11.0	49.7 ± 12.1	53.2 ± 11.8
Sex: female, n (%)	178 (60.1)	159 (72.9)	152 (59.8)	186 (71.3)	122 (58.4)	205 (70.7)
BMI (kg/m^2), mean ± SD	28.3 ± 5.1	28.3 ± 5.3	28.2 ± 5.1	28.3 ± 5.2	28.0 ± 4.9	28.4 ± 5.3
ICS dose (μg/day)†						
Mean ± SD	712 ± 373	701 ± 393	724 ± 383	693 ± 379	702 ± 340	707 ± 408
Medium, n (%)	153 (51.7)	107 (49.1)	127 (50.0)	134 (51.3)	110 (52.6)	143 (49.3)
High, n (%)	143 (48.3)	111 (50.9)	127 (50.0)	127 (48.7)	99 (47.4)	147 (50.7)
Maintenance oral corticosteroid use, n (%)	24 (8.1)	24 (11.0)	23 (9.1)	25 (9.6)	16 (7.7)	29 (10.0)
Prebronchodilator FEV_1 % predicted, mean ± SD	60.0 ± 12.9	59.3 ± 12.6	59.2 ± 12.5	60.3 ± 12.9	60.5 ± 12.6	59.4 ± 12.8
No. of exacerbations in previous 12 mo, n (%)						
1 or 2	241 (81.4)	172 (78.9)	211 (83.1)	203 (77.8)	173 (82.8)	231 (79.7)
≥3	55 (18.6)	46 (21.1)	43 (16.9)	58 (22.2)	36 (17.2)	59 (20.3)
Total serum IgE (IU/mL), median (range)	245.1 (8.7-11,859.6)	78.3 (2.0-1,551.3)	284.3 (8.7-11,859.6)	82.8 (2.0-1,551.3)	308.9 (8.7-11,859.6)	90.2 (2.0-1,551.3)
Blood eosinophil count (cells/μL)						
Mean ± SD	355 ± 272	399 ± 447	353 ± 269	392 ± 425	364 ± 274	378 ± 409
Median (range)	280 (0-1,520)	275 (0-3,990)	280 (0-1,510)	270 (0-3,990)	300 (0-1,520)	270 (0-3,990)
FENO (ppb)						
Mean ± SD	37.3 ± 40.1	30.1 ± 29.5	38.6 ± 41.7	30.0 ± 29.1	37.4 ± 41.6	30.8 ± 31.2
Median (range)	24.5 (4.0-312.5)	20.0 (2.0-181.5)	25.0 (4.0-312.5)	20.3 (2.0-181.5)	24.5 (4.0-312.5)	20.0 (2.0-216.5)

ppb, Parts per billion.

*Of the 550 randomized patients included in the analysis, FEIA results for any, perennial, and seasonal aeroallergen sensitivities were unknown for 36, 35, and 51 patients, respectively.

†Fluticasone (dry powder inhaler) or equivalent; medium-dose ICS: 250-500 μg/d; high-dose ICS: >500 μg/d.

TABLE E3. Allergic status by allergy history

	Any FEIA allergy*			FEIA perennial allergy*			FEIA seasonal allergy*		
Allergy history, n (%)	Positive (n = 296)	Negative (n = 218)	Unknown (n = 36)	Positive (n = 254)	Negative (n = 261)	Unknown (n = 35)	Positive (n = 209)	Negative (n = 290)	Unknown (n = 51)
Nasal polyps									
Yes	43 (14.5)	33 (15.1)	6 (16.7)	36 (14.2)	40 (15.3)	6 (17.1)	30 (14.4)	43 (14.8)	9 (17.6)
No	246 (83.1)	183 (83.9)	29 (80.6)	212 (83.5)	218 (83.5)	28 (80.0)	174 (83.3)	244 (84.1)	40 (78.4)
Unknown	7 (2.4)	2 (0.9)	1 (2.8)	6 (2.4)	3 (1.1)	1 (2.9)	5 (2.4)	3 (1.0)	2 (3.9)
Rhinitis									
Yes	161 (54.4)	101 (46.3)	17 (47.2)	139 (54.7)	123 (47.1)	17 (48.6)	118 (56.5)	138 (47.6)	23 (45.1)
No	128 (43.2)	116 (53.2)	18 (50.0)	109 (42.9)	136 (52.1)	17 (48.6)	86 (41.1)	150 (51.7)	26 (51.0)
Unknown	7 (2.4)	1 (0.5)	1 (2.8)	6 (2.4)	2 (0.8)	1 (2.9)	5 (2.4)	2 (0.7)	2 (3.9)
Eczema or atopic dermatitis									
Yes	36 (12.2)	11 (5.0)	2 (5.6)	34 (13.4)	13 (5.0)	2 (5.7)	26 (12.4)	18 (6.2)	5 (9.8)
No	252 (85.1)	207 (95.0)	33 (91.7)	213 (83.9)	247 (94.6)	32 (91.4)	177 (84.7)	271 (93.4)	44 (86.3)
Unknown	8 (2.7)	0 (0)	1 (2.8)	7 (2.8)	1 (0.4)	1 (2.9)	6 (2.9)	1 (0.3)	2 (3.9)

*Of the 550 randomized patients included in the analysis, FEIA results for any, perennial, and seasonal aeroallergen sensitivities were unknown for 36, 35, and 51 patients, respectively.

TABLE E4. Number of exacerbations through week 52 by perennial aeroallergen sensitivity within treatment group

	Placebo		Tezepelumab 210 mg Q4W		Pooled tezepelumab	
No. of exacerbations	**FEIA$^+$ (n = 64)**	**FEIA$^-$ (n = 66)**	**FEIA$^+$ (n = 71)**	**FEIA$^-$ (n = 57)**	**FEIA$^+$ (n = 190)**	**FEIA$^-$ (n = 195)**
0	48 (75.0)	43 (65.2)	63 (88.7)	46 (80.7)	158 (83.2)	160 (82.1)
1	6 (9.4)	10 (15.2)	6 (8.5)	10 (17.5)	25 (13.2)	31 (15.9)
2	4 (6.3)	5 (7.6)	2 (2.8)	1 (1.8)	5 (2.6)	4 (2.1)
3	1 (1.6)	4 (6.1)	0	0	2 (1.1)	0
4	1 (1.6)	4 (6.1)	0	0	0	0
5	3 (4.7)	0	0	0	0	0
6	0	0	0	0	0	0
7	1 (1.6)	0	0	0	0	0

Data are n (%).

TABLE E5. Change from baseline in inflammatory biomarkers following treatment with tezepelumab 210 mg Q4W over 52 wk by FEIA status for perennial aeroallergens

	Tezepelumab 210 mg Q4W		Placebo	
Biomarker	**FEIA$^+$ (n = 71)**	**FEIA$^-$ (n = 57)**	**FEIA$^+$ (n = 64)**	**FEIA$^-$ (n = 66)**
Blood eosinophil count (cells/μL)				
n	62	43	59	61
LS mean (SE)	−187 (23)	−215 (27)	−2 (24)	−27 (23)
FENO (ppb)				
n	49	40	51	49
LS mean (SE)	−5.7 (2.6)	−8.7 (2.9)	1.2 (2.6)	−1.0 (2.6)
Total serum IgE (IU/mL)				
n	63	49	59	63
LS mean (SE)	−187.2 (47.1)	−70.0 (52.3)	119.9 (48.6)	−34.6 (47.2)

ppb, Parts per billion.