

ORIGINAL ARTICLE

Tezepelumab in Adults with Uncontrolled Asthma

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ABSTRACT

BACKGROUND

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In some patients with moderate-to-severe asthma, particularly those with non-eosinophilic inflammation, the disease remains uncontrolled. This trial evaluated the efficacy and safety of tezepelumab (AMG 157/MEDI9929), a human monoclonal antibody specific for the epithelial-cell–derived cytokine thymic stromal lymphopoietin (TSLP), in patients whose asthma remained uncontrolled despite treatment with long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids.

METHODS

In this phase 2, randomized, double-blind, placebo-controlled trial, we compared subcutaneous tezepelumab at three dose levels with placebo over a 52-week treatment period. The primary end point was the annualized rate of asthma exacerbations (events per patient-year) at week 52.

RESULTS

The use of tezepelumab at a dose of 70 mg every 4 weeks (low dose; 145 patients), 210 mg every 4 weeks (medium dose; 145 patients), or 280 mg every 2 weeks (high dose; 146 patients) resulted in annualized asthma exacerbation rates at week 52 of 0.26, 0.19, and 0.22, respectively, as compared with 0.67 in the placebo group (148 patients). Thus, exacerbation rates in the respective tezepelumab groups were lower by 61%, 71%, and 66% than the rate in the placebo group ($P < 0.001$ for all comparisons). Similar results were observed in patients regardless of blood eosinophil counts at enrollment. The prebronchodilator forced expiratory volume in 1 second at week 52 was higher in all tezepelumab groups than in the placebo group (difference, 0.12 liters with the low dose [$P = 0.01$], 0.11 liters with the medium dose [$P = 0.02$], and 0.15 liters with the high dose [$P = 0.002$]). A total of 2 patients in the medium-dose group, 3 in the high-dose group, and 1 in the placebo group discontinued the trial regimen because of adverse events.

CONCLUSIONS

Among patients treated with long-acting beta-agonists and medium-to-high doses of inhaled glucocorticoids, those who received tezepelumab had lower rates of clinically significant asthma exacerbations than those who received placebo, independent of baseline blood eosinophil counts. (Funded by MedImmune [a member of the AstraZeneca Group] and Amgen; PATHWAY ClinicalTrials.gov number, NCT02054130.)

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ASTHMA AFFECTS AN ESTIMATED 315 MILLION people worldwide,¹ of whom approximately 70% have moderate-to-severe disease (Global Initiative for Asthma [GINA] step 3 to 5).² In many of these patients, asthma can be controlled by increasing the dose of inhaled glucocorticoids. However, in some patients, asthma remains uncontrolled despite the use of available recommended therapies.³

The heterogeneous response to asthma treatment may be related to differences in patterns of airway inflammation, immune-cell activation, and responsiveness to glucocorticoids.^{4,7} Biologic therapies that inhibit specific molecular targets, including IgE and type 2 helper T (Th2) cytokines, such as interleukin-4, interleukin-5, interleukin-13, and their respective receptors, benefit some patients with asthma that is uncontrolled with inhaled glucocorticoids plus long-acting beta-agonist (LABA) therapy.⁸⁻¹⁴

Thymic stromal lymphopoietin (TSLP) is an epithelial-cell–derived cytokine produced in response to environmental and proinflammatory stimuli.¹⁵ TSLP is central to the regulation of type 2 immunity through its activity on dendritic cells, T and B cells, and innate immune cells,¹⁶⁻¹⁸ and it up-regulates production of cytokines by antigen-specific Th2 cells.¹⁹ TSLP expression is higher in the airways of patients with asthma than in those of healthy controls, and its levels correlate with Th2 cytokine and chemokine expression²⁰ and disease severity.^{21,22}

Tezepelumab (AMG 157/MEDI9929) is an investigational human IgG2 monoclonal antibody that binds to TSLP, preventing its interaction with the TSLP receptor complex. A proof-of-concept study involving patients with mild, atopic asthma showed that tezepelumab inhibited both early and late asthmatic responses and suppressed biomarkers of type 2 inflammation after inhaled allergen challenge.²³

To better define the biologic and clinical importance of TSLP in patients with moderate-to-severe asthma, we conducted PATHWAY, a randomized, placebo-controlled, dose-ranging trial of tezepelumab involving patients whose disease was uncontrolled with LABAs combined with medium-to-high doses of inhaled glucocorticoids.²⁴ Given the potentially broad effects of TSLP in asthma, we included patients with a wide range of blood eosinophil counts.

METHODS

TRIAL DESIGN AND PARTICIPANTS

This multicenter, placebo-controlled, parallel-group, double-blind, phase 2 trial was conducted at 108 sites across 12 countries (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All eligible patients were current nonsmokers (for ≥ 6 months and with a lifetime history of <10 pack-years) who were 18 to 75 years of age and who had asthma that was not well controlled despite treatment with LABAs combined with a medium dose (250 to 500 μg per day of fluticasone administered by means of a dry-powder inhaler or equivalent) or high dose (>500 μg per day of fluticasone administered by means of a dry-powder inhaler or equivalent) of inhaled glucocorticoids (as per GINA 2012 guidelines defining severe asthma²⁴) at least 6 months before enrollment. Patients were also required to have a history of at least two asthma exacerbations that led to systemic glucocorticoid treatment, or one severe exacerbation that led to hospitalization, in the 12 months before trial entry. Additional eligibility criteria included a prebronchodilator forced expiratory volume in 1 second (FEV₁) of at least 40% and no more than 80% of the predicted normal value, postbronchodilator reversibility of at least 12% and at least 200 ml, and a score on the six-item Asthma Control Questionnaire (ACQ-6)²⁵ of at least 1.5 during screening (range, 0 to 6, with lower scores indicating better disease control; minimal clinically important difference, 0.5 points).²⁶ Exclusion criteria included any clinically important pulmonary disease other than asthma. A full list of inclusion and exclusion criteria is provided in Table S2 in the Supplementary Appendix.

The sponsors, MedImmune and Amgen, developed the protocol and conducted the data analysis. The first draft of the manuscript was prepared by the MedImmune authors with input from all the authors. A professional medical writer (funded by MedImmune) assisted with revisions to early drafts of the manuscript. All the authors made the decision to submit the manuscript for publication. All the authors vouch for the accuracy and completeness of the data and the statistical analysis and for the adherence of the trial to the final protocol, available at NEJM.org.

This trial was performed in accordance with the ethical principles of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. Approvals from independent ethics committees were obtained, and all the patients provided written informed consent in accordance with local requirements.

RANDOMIZATION AND BLINDING

Patients were randomly assigned (in a 1:1:1:1 ratio), according to a central interactive voice-response or Web-response system, to receive one of three different doses of subcutaneous tezepelumab or placebo. Randomization was stratified according to location (Japan or the rest of the world), blood eosinophil count (≥ 250 or < 250 cells per microliter) as measured by a local laboratory, and dose level of inhaled glucocorticoids (medium or high, on the basis of GINA 2012 guidelines²⁴). Patients receiving a maintenance regimen of oral glucocorticoids were assigned to the high-dose inhaled glucocorticoid stratum. Tezepelumab and placebo were prepared by site staff who were aware of the trial-group assignments and who were not involved in trial assessments. The trial agents were similar in appearance and were administered by staff who were unaware of the trial-group assignments. Background asthma-control medications were maintained at a stable dose throughout the treatment period.

PROCEDURES

Patients were assigned to receive subcutaneous injections of tezepelumab at a dose of 70 mg every 4 weeks (low dose), 210 mg every 4 weeks (medium dose), or 280 mg every 2 weeks (high dose) or of placebo every 2 weeks for the duration of the trial. To maintain blinding, patients who were assigned to 4-week dosing regimens received placebo at the intermediate visits.

Baseline prebronchodilator and postbronchodilator spirometric assessments, measurements of the fraction of exhaled nitric oxide (F_{ENO}), blood eosinophil counts, the ACQ-6 score, and the score on the Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12 [hereafter referred to as AQLQ]²⁷; range, 1 to 7, with higher scores indicating better asthma-related quality of life;

minimal clinically important difference, 0.5 points)²⁸ were obtained throughout the 5-week screening period. The ACQ-6 score, AQLQ score, and asthma symptom score (reflecting daytime severity, daytime frequency, and nighttime severity; range, 0 [no symptoms] to 4 [worst possible symptoms]) were recorded with the use of an electronic device (further details are provided in the Supplementary Appendix). Safety was monitored at each trial site by asking participants whether they had had any adverse events from enrollment through follow-up at week 64.

END POINTS AND ASSESSMENTS

The primary efficacy end point was the annualized rate of asthma exacerbations (events per patient-year) at week 52. An asthma exacerbation was defined as a worsening of asthma symptoms that led to any of the following: the use of systemic glucocorticoids (oral or injectable) or, in the case of a stable maintenance regimen of oral glucocorticoids, a doubling of the dose for 3 or more days; an emergency department visit due to asthma that led to systemic glucocorticoid treatment; or an inpatient hospitalization due to asthma. Worsening of asthma was defined as new or increased symptoms or signs that were either worrisome to the patient or related to an asthma diary-driven alert.

Secondary end points included the changes from baseline in the prebronchodilator and postbronchodilator FEV₁ (an increase in values indicates improved lung function; minimal clinically important difference, 100 to 200 ml),²⁹ ACQ-6 score, AQLQ score, asthma symptom score, and forced vital capacity (FVC), as well as the annualized rate of severe asthma exacerbations at week 52, the time to the first asthma exacerbation, the time to the first severe asthma exacerbation, the percentage of patients with at least one asthma exacerbation, and the percentage of patients with at least one severe asthma exacerbation. Severe exacerbations were defined as exacerbations that led to hospital admission for more than 24 hours.

Primary and secondary end points (changes from baseline in prebronchodilator FEV₁, ACQ-6 score, AQLQ score, and asthma symptom score) were also assessed in prespecified subpopulations according to blood eosinophil count (≥ 250 or < 250 cells per microliter), Th2 status (high

[IgE level >100 IU per milliliter and blood eosinophil count \geq 140 cells per microliter] or low [IgE level \leq 100 IU per milliliter or blood eosinophil count <140 cells per microliter],³⁰ FENO level (on the basis of median baseline levels and the clinically meaningful cutoff of 24 ppb),³¹ serum periostin level (high or low, on the basis of median baseline levels), current (demonstrated during the screening period) postbronchodilator FEV₁ reversibility, and allergic status (defined by a positive or negative fluorescence enzyme immunoassay for IgE at baseline).

The primary end point was also stratified according to dose level of inhaled glucocorticoids (medium or high), use or nonuse of a maintenance regimen of oral glucocorticoids, and number of asthma exacerbations in the previous 12 months (prespecified subgroup analyses). Post hoc analyses included stratification of the primary end point according to baseline blood eosinophil count (<400 or \geq 400 cells per microliter) and patient smoking history.

STATISTICAL ANALYSIS

The efficacy analyses were based on the intention-to-treat population, which consisted of patients who underwent randomization and received at least one dose of tezepelumab or placebo; patients were evaluated according to the randomized trial group. The safety analyses were based on the as-treated population and included all the patients who received at least one dose of tezepelumab or placebo; patients were evaluated according to the trial agent received.

For the primary efficacy end point, 138 patients per trial group were required for 80% power to detect a 40% lower annualized rate of asthma exacerbations in each tezepelumab dose group than in the placebo group, with a two-sided alpha level of 0.1 and an expected 10% loss of information due to dropouts, under the assumption of an annualized asthma exacerbation rate of 0.7 in the placebo group and a negative binomial dispersion parameter of 0.7.

The primary efficacy end point of annualized rate of asthma exacerbations was analyzed with the use of a negative binomial model, with trial group, baseline blood eosinophil count (\geq 250 or <250 cells per microliter), and baseline dose level of inhaled glucocorticoids (medium or high) included in the model. Details of the statistical

analyses with respect to the secondary end points are provided in the Supplementary Appendix.

The primary end point was tested sequentially to control the overall type I error rate at 0.1. The hierarchy was high-dose tezepelumab versus placebo, medium-dose tezepelumab versus placebo, and low-dose tezepelumab versus placebo. No adjustments were made for multiplicity for the secondary end points. Nominal P values are presented. All analyses were carried out with the use of SAS software, version 9.3.

RESULTS

PATIENTS

Overall, 918 patients were screened and 584 underwent randomization: 145 were assigned to low-dose tezepelumab, 145 to medium-dose tezepelumab, 146 to high-dose tezepelumab, and 148 to placebo. Of the patients who received tezepelumab or placebo and were included in the intention-to-treat population, 391 (89.7%) and 139 (93.9%) completed the trial regimen, respectively (Fig. S1 in the Supplementary Appendix). Baseline and clinical characteristics were similar across the trial groups (Table 1, and Table S3 in the Supplementary Appendix).

The dose range of inhaled glucocorticoids for patients at baseline is shown in Figure S2 in the Supplementary Appendix. The median dose was 400 μ g per day of fluticasone administered by means of a dry-powder inhaler or equivalent in the medium-dose inhaled glucocorticoid stratum, with 73 patients in the placebo group, 71 in the low-dose tezepelumab group, 70 in the medium-dose group, and 72 in the high-dose group, and 1000 μ g per day of fluticasone administered by means of a dry-powder inhaler or equivalent in the high-dose inhaled glucocorticoid stratum, with 75, 74, 75, and 74 patients in the respective trial groups.

PRIMARY END POINT

Treatment with tezepelumab resulted in annualized rates of asthma exacerbations at week 52 of 0.26, 0.19, and 0.22 in the low-dose, medium-dose, and high-dose groups, respectively, as compared with 0.67 in the placebo group. Thus, exacerbation rates were lower in the tezepelumab groups than in the placebo group by 61% (90% confidence interval [CI], 39 to 75; $P < 0.001$), 71%

Table 1. Baseline Demographic and Clinical Characteristics in the Intention-to-Treat Population.*

Characteristic	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)	Total Tezepelumab (N=436)
Age — yr	52.2±11.5	50.6±12.4	52.6±12.5	50.1±12.2	51.1±12.4
Male sex — no. (%)	48 (32.4)	50 (34.5)	54 (37.2)	53 (36.3)	157 (36.0)
White race — no. (%)†	133 (89.9)	138 (95.2)	136 (93.8)	129 (88.4)	403 (92.4)
Body-mass index‡	28.5±5.5	28.3±5.1	28.4±4.9	27.7±5.0	28.1±5.0)
FEV ₁ before bronchodilation — liters	1.83±0.58	1.91±0.66	1.83±0.58	1.87±0.60	1.87±0.61
ACQ-6 score§	2.66±0.67	2.76±0.80	2.71±0.81	2.63±0.75	2.70±0.78
AQLQ(S)+12 score¶	4.06±0.86	4.14±0.94	4.19±0.90	4.09±0.90	4.14±0.91
Asthma symptom score	1.72±0.58	1.70±0.63	1.76±0.57	1.68±0.61	1.72±0.60
Dose level of inhaled gluco- corticoids — no. (%)					
Medium	73 (49.3)	71 (49.0)	70 (48.3)	72 (49.3)	213 (48.9)
High	75 (50.7)	74 (51.0)	75 (51.7)	74 (50.7)	223 (51.1)
Blood eosinophil count — cells/μl					
Mean	366±323	345±284	359±347	378±423	361±356
Median (range)	270 (0–1870)	270 (10–1600)	275 (0–3180)	255 (0–3990)	270 (0–3990)
Total serum IgE — IU/ml					
Mean	447±1232	314±870	464±1366	344±579	374±992
Median (range)	135 (4–11,860)	109 (2–7423)	135 (2–11,430)	138 (2–3814)	127 (2–11,430)
FENO					
No. of patients evaluated	146	144	143	141	428
Mean — ppb	36.3±38.9	34.5±46.9	30.4±29.4	32.6±33.9	32.5±37.5
Median (range) — ppb	21.5 (3.5–276.3)	22.0 (2.5–349.0)	20.5 (4.0–152.5)	19.7 (2.0–217.5)	21.0 (2.0–349.0)

* Plus-values are means ±SD. The low dose of tezepelumab was 70 mg every 4 weeks, the medium dose 210 mg every 4 weeks, and the high dose 280 mg every 2 weeks. FENO denotes fraction of exhaled nitric oxide, and FEV₁ forced expiratory volume in 1 second.

† Race was reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Scores on the six-item Asthma Control Questionnaire (ACQ-6) range from 0 to 6, with lower scores indicating better disease control. A score of 1.5 or more indicates uncontrolled asthma.

¶ Scores on the Asthma Quality of Life Questionnaire (standardized) for persons 12 years of age or older (AQLQ[S]+12) range from 1 to 7, with higher scores indicating better asthma-related quality of life.

|| Asthma symptom scores (reflecting daytime severity, daytime frequency, and nighttime severity) range from 0 (no symptoms) to 4 (worst possible symptoms).

(90% CI, 53 to 82; $P<0.001$), and 66% (90% CI, 47 to 79; $P<0.001$), respectively (Table 2, and Fig. S3A in the Supplementary Appendix). The types of asthma exacerbations that were used for the primary analysis are described in Table S4 in the Supplementary Appendix.

SECONDARY END POINTS

The annualized asthma exacerbation rate was lower in the tezepelumab groups than in the pla-

cebo group, irrespective of baseline blood eosinophil count or other assessed indicators of Th2 status (Fig. 1A, and Tables S5 through S8 in the Supplementary Appendix). Among patients in the medium-dose inhaled glucocorticoid stratum, low-dose, medium-dose, and high-dose tezepelumab resulted in annualized asthma exacerbation rates at week 52 of 0.19, 0.15, and 0.20, respectively, as compared with 0.38 with placebo. The rates in the tezepelumab groups were lower than

Table 2. Annualized Rate of Asthma Exacerbations and Change from Baseline in FEV₁, ACQ-6 Score, and AQLQ(S)+12 Score in the Intention-to-Treat Population.

Variable	Placebo (N=148)	Low-Dose Tezepelumab (N=145)	Medium-Dose Tezepelumab (N=145)	High-Dose Tezepelumab (N=146)
Annualized rate of asthma exacerbations through wk 52 — events per patient-yr (90% CI)	0.67 (0.57 to 0.80)	0.26 (0.19 to 0.34)	0.19 (0.13 to 0.27)	0.22 (0.16 to 0.30)
Relative reduction vs. placebo — % (90% CI)	—	61 (39 to 75)	71 (53 to 82)	66 (47 to 79)
P value	—	<0.001	<0.001	<0.001
FEV ₁ before bronchodilation				
No. of patients evaluated	141	137	128	125
Least-squares mean change from baseline at wk 52 — % of predicted value	-0.99	7.11	7.27	9.37
Difference vs. placebo (95% CI)	—	8.11 (2.39 to 13.82)	8.26 (2.50 to 14.03)	10.36 (4.60 to 16.13)
P value*	—	0.006	0.005	<0.001
Least-squares mean change from baseline at wk 52 — liters	-0.05	0.07	0.06	0.11
Difference vs. placebo (95% CI)	—	0.12 (0.02 to 0.21)	0.11 (0.02 to 0.20)	0.15 (0.06 to 0.25)
P value*	—	0.01	0.02	0.002
ACQ-6 score†				
No. of patients evaluated	53	53	44	49
Least-squares mean change from baseline at wk 52	-0.89	-1.13	-1.16	-1.22
Difference vs. placebo (95% CI)	—	-0.24 (-0.50 to 0.02)	-0.27 (-0.54 to 0.00)	-0.33 (-0.60 to -0.07)
P value*	—	0.07	0.046	0.01
AQLQ(S)+12 score‡				
No. of patients evaluated	47	52	41	49
Least-squares mean change from baseline at wk 52	0.95	1.07	1.13	1.33
Difference vs. placebo (95% CI)	—	0.12 (-0.15 to 0.39)	0.18 (-0.10 to 0.47)	0.38 (0.10 to 0.65)
P value*	—	0.39	0.21	0.008

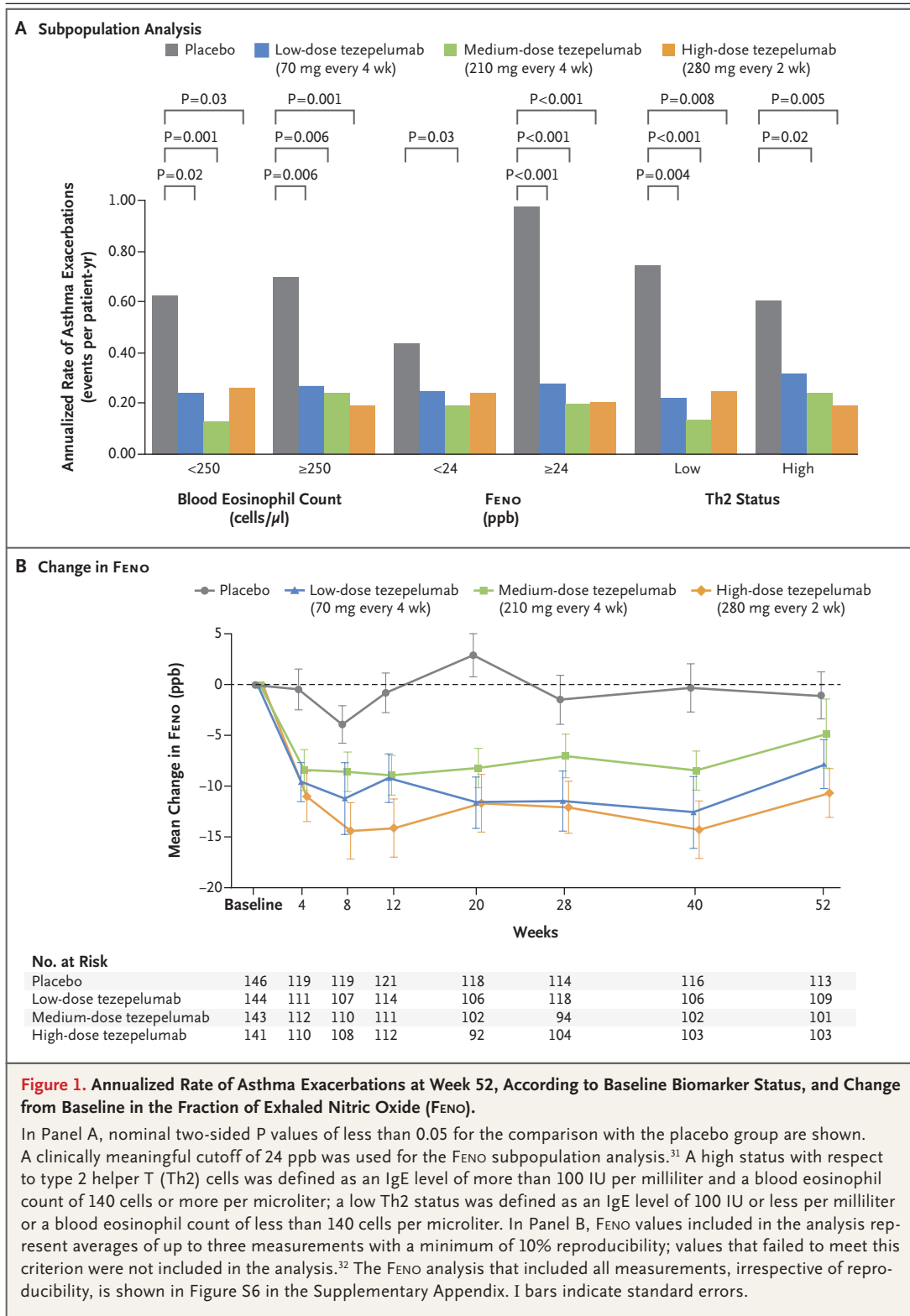
* P values are nominal and were not adjusted for multiplicity.

† ACQ-6 scores range from 0 to 6, with lower scores indicating better disease control. The minimal clinically important difference is 0.5 points.

‡ AQLQ(S)+12 scores range from 1 to 7, with higher scores indicating better asthma-related quality of life. The minimal clinically important difference is 0.5 points.

the rate in the placebo group by 51% (95% CI, -8 to 78; P=0.08), 60% (95% CI, 5 to 83; P=0.04), and 49% (95% CI, -13 to 77; P=0.10), respectively; thus, the between-group difference was nominally significant only at the medium dose level. Among patients in the high-dose inhaled glucocorticoid stratum, low-dose, medium-dose, and high-dose tezepelumab resulted in annualized asthma exacerbation rates at week 52 of 0.33, 0.23, and 0.24, respectively, as compared

with 0.96 with placebo. The rates in the tezepelumab groups were lower than the rate in the placebo group by 66% (95% CI, 33 to 83; P=0.002), 76% (95% CI, 49 to 89; P<0.001), and 75% (95% CI, 47 to 88; P<0.001), respectively (Table S9 in the Supplementary Appendix). The annualized asthma exacerbation rate was lower in some, but not all, tezepelumab groups than in the placebo group when patients were stratified according to the number of asthma exacerbations in the pre-



vious 12 months and, in post hoc analyses, according to smoking history (Table S10 in the Supplementary Appendix).

The time to the first asthma exacerbation was longer in the tezepelumab groups than in the placebo group. The risk of having any exacerbation was lower in the low-dose, medium-dose, and high-dose tezepelumab groups than in the placebo group by 34% (hazard ratio, 0.66; 95% CI, 0.41 to 1.05; $P=0.08$), 54% (hazard ratio, 0.46; 95% CI, 0.27 to 0.78; $P=0.003$), and 45% (hazard ratio, 0.55; 95% CI, 0.34 to 0.90; $P=0.02$), respectively; thus, the between-group difference was not nominally significant at the low dose level (Fig. S4 and Table S14 in the Supplementary Appendix).

In the overall population, the change from baseline at week 52 in the prebronchodilator FEV_1 was greater in the low-dose, medium-dose, and high-dose tezepelumab groups than in the placebo group by 0.12 liters (95% CI, 0.02 to 0.21; $P=0.01$), 0.11 liters (95% CI, 0.02 to 0.20; $P=0.02$), and 0.15 liters (95% CI, 0.06 to 0.25; $P=0.002$), respectively (Table 2, and Fig. S3B in the Supplementary Appendix). Similar differences were observed when the prebronchodilator FEV_1 was measured as the percent of the predicted value (Table 2). The treatment effect was observed as early as week 4 (the first time point assessed) and was sustained for the duration of the trial (Fig. S3B in the Supplementary Appendix).

The effects of tezepelumab on additional secondary end points — including the percentage of patients with at least one asthma exacerbation, the percentage of patients with at least one severe asthma exacerbation, the annualized rate of severe asthma exacerbations, the time to the first severe asthma exacerbation, and changes from baseline in the postbronchodilator FEV_1 , FVC, ACQ-6 score, AQLQ score, and asthma symptom score — are presented in Table 2, and in Figures S3C and S3D and Tables S11 through S14 in the Supplementary Appendix. The effects of tezepelumab on secondary end points according to subgroup (prebronchodilator FEV_1 , ACQ-6 score, AQLQ score, and asthma symptom score) are shown in Tables S5, S6, S7, and S12 in the Supplementary Appendix.

BIOMARKERS

Substantial and persistent decreases in blood eosinophil counts and F_{ENO} levels were observed in all tezepelumab groups, beginning at week 4 (the first time point assessed) after the initiation of treatment (Fig. 1B, and Fig. S5A in the Supplementary Appendix). Progressive decreases were also observed in total serum IgE in all tezepelumab groups (Fig. S5B in the Supplementary Appendix).

SAFETY AND SIDE-EFFECT PROFILE

The overall incidence of adverse events was similar across the trial groups (Table 3). In total, 62.2% of the patients in the placebo group, 66.2% of the patients in the low-dose tezepelumab group, 64.8% of the patients in the medium-dose group, and 61.6% of the patients in the high-dose group reported at least one adverse event, and 12.2%, 11.7%, 9.0%, and 12.3% reported at least one serious adverse event, respectively. When asthma-related adverse events were removed from the above analysis, the overall incidence of adverse events was similar across the trial groups (Table 3). A full list of serious adverse events is provided in Table S15 in the Supplementary Appendix. Three serious adverse events were deemed by the investigator to be related to the trial agent; two (pneumonia and stroke) occurred in the same patient in the low-dose tezepelumab group and one (the Guillain-Barré syndrome) in the medium-dose tezepelumab group. A detailed description of these events is included in the Supplementary Appendix. The rates of discontinuation due to adverse events were 1.1% among patients receiving tezepelumab (five patients, including two in the medium-dose group and three in the high-dose group) and 0.7% in the placebo group (one patient). One patient in the low-dose tezepelumab group died 8 weeks after the treatment period ended from a treatment-related serious adverse event (stroke in the same patient described above; additional details are provided in the Supplementary Appendix).

Injection-site reactions after 1-ml injections occurred in 3.4% of the patients in the placebo group, 2.8% of the patients in the low-dose tezepelumab group, 2.8% of the patients in the

Table 3. Summary of Adverse Events, with and without Inclusion of Asthma-Related Events.*

Event	Placebo (N = 148)		Low-Dose Tezepelumab (N = 145)		Medium-Dose Tezepelumab (N = 145)		High-Dose Tezepelumab (N = 146)		Total Tezepelumab (N = 436)	
	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded	All Events	Asthma-Related Events Excluded
≥1 Event	92 (62.2)	83 (56.1)	96 (66.2)	86 (59.3)	94 (64.8)	90 (62.1)	90 (61.6)	83 (56.8)	280 (64.2)	259 (59.4)
≥1 Event of grade 3–5 severity†	28 (18.9)	16 (10.8)	26 (17.9)	20 (13.8)	29 (20.0)	23 (15.9)	21 (14.4)	13 (8.9)	76 (17.4)	56 (12.8)
Death‡	0	0	1 (0.7)	1 (0.7)	0	0	0	0	1 (0.2)	1 (0.2)
≥1 Serious event‡	18 (12.2)	11 (7.4)	17 (11.7)	13 (9.0)	13 (9.0)	12 (8.3)	18 (12.3)	15 (10.3)	48 (11.0)	40 (9.2)
≥1 Serious event or event of grade 3–5 severity‡;§	34 (23.0)	21 (14.2)	32 (22.1)	24 (16.6)	31 (21.4)	26 (17.9)	29 (19.9)	20 (13.7)	92 (21.1)	70 (16.1)
≥1 Event leading to discontinuation of trial agent	1 (0.7)	1 (0.7)	0	0	2 (1.4)	2 (1.4)	3 (2.1)	3 (2.1)	5 (1.1)	5 (1.1)
Most common events of any grade§										
Bronchitis	7 (4.7)		8 (5.5)		5 (3.4)		9 (6.2)		22 (5.0)	
Nasopharyngitis	17 (11.5)		21 (14.5)		19 (13.1)		15 (10.3)		55 (12.6)	
Headache	7 (4.7)		8 (5.5)		11 (7.6)		5 (3.4)		24 (5.5)	
Asthma	50 (33.8)		35 (24.1)		27 (18.6)		38 (26.0)		100 (22.9)	

* Patients were counted once for each category regardless of the number of events.

† Grade 3 indicates a severe adverse event, grade 4 a life-threatening event, and grade 5 a fatal event.

‡ A serious adverse event was defined as an event that resulted in death, was life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or clinically significant disability or incapacity, was an important medical event, or resulted in a congenital anomaly or birth defect (in the offspring of the patient).

§ Shown are events that occurred in at least 5% of the total group of patients who received tezepelumab.

medium-dose group, and 1.4% of the patients in the high-dose group. The rates after 1.5-ml injections were 2.7%, 2.1%, 2.8%, and 3.4% in the respective groups (Table S16 in the Supplementary Appendix). No investigational product-related anaphylactic reactions were reported. After baseline, positive antidrug antibodies were noted in 13 of 148 patients (8.8%) in the placebo group, 7 of 144 patients (4.9%) in the low-dose tezepelumab group, 1 of 140 patients (0.7%) in the medium-dose group, and 3 of 142 patients (2.1%) in the high-dose group (Table S17 in the Supplementary Appendix). No neutralizing antibodies were detected.

DISCUSSION

Treatment with tezepelumab resulted in significantly lower annualized rates of asthma exacerbations than the rate with placebo among patients whose asthma remained uncontrolled despite treatment with LABAs and medium-to-high doses of inhaled glucocorticoids. Some, but not all, secondary outcomes were better with tezepelumab than with placebo. Treatment effects were observed shortly after the initiation of treatment and were maintained throughout the trial. The incidence of adverse events was similar in the tezepelumab and placebo groups, with similar levels of discontinuations, regardless of asthma-related adverse events.

Tezepelumab reduced blood eosinophil counts, FENO levels, and total serum IgE levels; changes in eosinophil counts and FENO levels occurred rapidly from week 4 and concurrently with changes in clinical end points. Our findings are consistent with those of a previous allergen-challenge study involving patients with mild asthma, in which tezepelumab inhibited post-allergen challenge increases in sputum and blood eosinophil counts and FENO levels.²³ These changes in biomarker levels indicate that tezepelumab has important effects on interleukin-4, interleukin-5, and interleukin-13 pathways and support the concept that inhibition of TSLP may have broader physiological effects than the targeting of individual Th2 cytokines.

The observed improvements in disease control in patients who received tezepelumab highlight the potential pathogenic role of TSLP across different asthma phenotypes. Nonallergic factors, including tobacco smoke, diesel particles, and

viruses, have been shown to trigger TSLP release and lead to activation of inflammatory responses in asthma.³³⁻³⁶ Although TSLP is central to the regulation of type 2 immunity, many cell types that are activated by or respond to TSLP, such as mast cells, basophils, natural killer T cells, innate lymphoid cells, and neutrophils, may play a role in inflammation in asthma beyond type 2 inflammation.^{17,35-40}

Our data provide clinical evidence that inhibition of TSLP with tezepelumab leads to a lower annualized rate of asthma exacerbations than placebo administration, independent of baseline eosinophil count or other Th2 biomarkers, and better results with respect to other clinical end points among patients with uncontrolled asthma who are receiving LABAs and medium-to-high doses of inhaled glucocorticoids. These findings highlight the potential advantages of targeting an upstream cytokine such as TSLP, which may affect disease activity more broadly than inhibition of a single downstream pathway. Future studies involving large, ethnically diverse populations of patients with uncontrolled asthma using the best available small-molecule therapies, including high-dose inhaled glucocorticoids plus LABAs, will be important to demonstrate the clinical importance of our findings.

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