

ORIGINAL ARTICLE

Tozorakimab to Prevent COPD Exacerbations

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ABSTRACT

BACKGROUND

Many patients with chronic obstructive pulmonary disease (COPD) have exacerbations despite receiving standard-of-care inhaled maintenance therapy. Dysregulated interleukin-33 signaling is implicated in the pathogenesis of COPD. Tozorakimab is a monoclonal antibody that inhibits the activity of interleukin-33.

METHODS

In two replicate phase 3 trials (OBERON and TITANIA), we enrolled adults with COPD who were current or former smokers and had a history of exacerbations in the previous year despite receiving stable standard-of-care inhaled maintenance therapy. There were no eligibility criteria related to blood eosinophil count. Patients were randomly assigned to receive add-on subcutaneous tozorakimab (300 mg) or placebo every 4 weeks for 52 weeks. The primary end point was the annualized rate of moderate or severe exacerbations that occurred over a 52-week period among former smokers, and the first key secondary end point was the annualized rate of moderate or severe exacerbations in the overall population. Safety was also assessed.

RESULTS

The overall population in OBERON included 446 patients in the tozorakimab group and 431 in the placebo group, and in TITANIA included 438 in the tozorakimab group and 435 in the placebo group. The annualized rate of moderate or severe exacerbations among former smokers was 1.34 events in the tozorakimab group and 1.90 events in the placebo group (rate ratio, 0.71; 95% confidence interval [CI], 0.57 to 0.88; $P=0.002$) in OBERON, and 1.37 events and 2.07 events, respectively (rate ratio, 0.66; 95% CI, 0.55 to 0.80; $P<0.001$), in TITANIA. In the overall population, the annualized rate of moderate or severe exacerbations was 1.41 events in the tozorakimab group and 2.00 events in the placebo group (rate ratio, 0.70; 95% CI, 0.58 to 0.85; $P<0.001$) in OBERON, and 1.44 events and 2.03 events, respectively (rate ratio, 0.71; 95% CI, 0.59 to 0.84; $P<0.001$), in TITANIA. Adverse events occurred in 70.4% of the patients in the tozorakimab group and in 77.2% of those in the placebo group in OBERON, and in 80.1% and 79.8%, respectively, in TITANIA.

CONCLUSIONS

Among patients with COPD, treatment with tozorakimab resulted in a significantly lower rate of moderate or severe exacerbations than placebo in the cohort of former smokers and in the overall population of current and former smokers. (Funded by AstraZeneca; OBERON ClinicalTrials.gov number, NCT05166889; TITANIA ClinicalTrials.gov number, NCT05158387.)

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*A complete list of the OBERON and TITANIA Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a leading cause of death worldwide, and the prevalence is projected to reach approximately 600 million by 2050.^{1,2} COPD exacerbations are clinically important events that are associated with accelerated decline in lung function, impaired health-related quality of life, and increased risks of further exacerbations, cardiopulmonary events, and death.^{3,4} Exacerbations impose a substantial health care burden, especially when they result in hospitalization or emergency department (ED) visits.⁵

Many patients with COPD remain at high risk for exacerbations while receiving standard-of-care inhaled maintenance therapy.⁶ Dupilumab and mepolizumab are approved for patients with COPD and elevated blood eosinophil counts.⁷⁻⁹ There remains an unmet need for add-on therapy in a broader population of patients with COPD and a history of exacerbations.¹⁰

Interleukin-33 is an upstream orchestrator of multiple host-response mechanisms, including type 1, 2, and 3 inflammatory responses, tissue homeostasis, and repair functions.¹¹ Interleukin-33 levels are elevated in patients with COPD,^{12,13} including in current and former smokers,¹⁴ and this elevation is associated with an increased risk of exacerbations.¹⁵ The reduced form of interleukin-33 binds the serum stimulated-2 (ST2) receptor on inflammatory cells, promoting airway inflammation that may lead to tissue damage. The oxidized form of interleukin-33 binds the receptor for advanced glycation end products–epidermal growth factor receptor complex on epithelial cells, contributing to epithelial remodeling, disrupted repair function, and airway mucus hypersecretion.^{16,17} Both airway inflammation and mucus dysfunction are key drivers of COPD exacerbations.^{18,19}

Therapies targeting the interleukin-33–ST2 pathway are under development for the treatment of COPD.^{14,20} In one of two replicate phase 3 trials (AERIFY-1 and AERIFY-2), treatment with itepekimab, an anti-interleukin-33 monoclonal antibody, resulted in a significantly lower rate of moderate or severe exacerbations than placebo among former smokers.²¹ In the phase 2b ALIENTO trial (but not in the phase 3 ARNASA trial), the rate of moderate or severe exacerbations was significantly lower among current and former smokers who received the anti-ST2 mono-

clonal antibody astegolimab than among those who received placebo.²² In these trials, patients were enrolled irrespective of their blood eosinophil count. Together, these findings support further evaluation of the interleukin-33–ST2 pathway as a therapeutic target in COPD in current and former smokers.

Tozorakimab is a high-affinity human anti-interleukin-33 monoclonal antibody that inhibits the activity of both the reduced form and the oxidized form of interleukin-33.^{16,17} LUNA was a phase 3 clinical trial program designed to evaluate the efficacy and safety of tozorakimab added to standard-of-care therapy in patients with COPD.²³ The program comprised four trials: OBERON, TITANIA, PROSPERO, and MIRANDA. The dosing frequencies and treatment durations varied among these trials. Here, we report the results from OBERON and TITANIA.

METHODS

TRIAL DESIGN AND OVERSIGHT

OBERON and TITANIA were replicate phase 3, randomized, double-blind, placebo-controlled trials conducted to assess tozorakimab in patients with COPD and a history of exacerbations who were receiving stable inhaled standard-of-care maintenance therapy.²³ The trials followed identical protocols but were conducted at separate sites (Tables S1 and S2 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Originally, patients were randomly assigned, in a 1:1:1 ratio, to receive 300 mg of subcutaneous tozorakimab once every 4 weeks, 300 mg of tozorakimab once every 8 weeks, or matching placebo every 4 weeks for 52 weeks (Fig. S1). The protocols were amended to halt assignment to the group receiving tozorakimab every 8 weeks, and patients were subsequently assigned in a 1:1 ratio to receive either tozorakimab once every 4 weeks or placebo once every 4 weeks for 52 weeks (see the Supplementary Appendix). This amendment preceded all unblinded analyses and was made on the basis of findings from phase 2 trials in inflammatory diseases, including COPD, that showed lower trough systemic exposure than that in the first-in-human trial, with potentially therapeutically relevant reduced target engagement when tozorakimab was received every 8 weeks.^{24,25}

Table 1. Demographic and Clinical Characteristics at Baseline in the Overall Populations.*

Characteristic	OBERON		TITANIA	
	Tozorakimab (N=446)	Placebo (N=431)	Tozorakimab (N=438)	Placebo (N=435)
Age — yr	67.3±7.8	67.1±7.8	68.0±7.3	67.8±7.2
Sex — no. (%)				
Male	296 (66.4)	273 (63.3)	301 (68.7)	293 (67.4)
Female	150 (33.6)	158 (36.7)	137 (31.3)	142 (32.6)
Smoking status — no. (%)				
Former smoker	342 (76.7)	337 (78.2)	350 (79.9)	344 (79.1)
Current smoker	104 (23.3)	94 (21.8)	88 (20.1)	91 (20.9)
Smoking history — pack-yr	40.9±21.7	42.4±21.3	44.6±24.7	43.8±24.3
Inhaled therapy for COPD — no. (%)†				
Triple therapy	406 (91.0)	393 (91.2)	396 (90.4)	390 (89.7)
Dual therapy‡	40 (9.0)	38 (8.8)	42 (9.6)	45 (10.3)
Inhaled glucocorticoid	416 (93.3)	409 (94.9)	414 (94.5)	407 (93.6)
No. of moderate or severe exacerbations in the 12 mo before enrollment§	2.5±1.2	2.4±1.2	2.3±1.0	2.3±1.2
Blood eosinophil count at screening — no. (%)				
<150 cells/μl	165 (37.0)	166 (38.5)	178 (40.6)	184 (42.3)
150 to <300 cells/μl	160 (35.9)	152 (35.3)	162 (37.0)	151 (34.7)
≥300 cells/μl	121 (27.1)	113 (26.2)	98 (22.4)	100 (23.0)
Severity of airflow obstruction — no. (%)¶				
Mild	12 (2.7)	21 (4.9)	17 (3.9)	21 (4.8)
Moderate	154 (34.5)	134 (31.1)	137 (31.3)	152 (34.9)
Severe	198 (44.4)	185 (42.9)	193 (44.1)	182 (41.8)
Very severe	82 (18.4)	89 (20.6)	91 (20.8)	80 (18.4)
Missing data	0	2 (0.5)	0	0
Postbronchodilator FEV ₁ :FVC ratio — %	43.4±11.8	44.0±13.1	43.2±12.6	44.1±12.3
SGRQ total score	54.0±17.2	54.2±16.8	54.3±18.3	55.3±18.5
E-RS—COPD total score**	14.8±6.0	14.4±6.3	15.2±5.9	14.4±6.4
CAT total score††	21.7±5.8	21.5±5.6	21.7±5.5	22.0±5.7

* Plus-minus values are means ±SD. Data are shown for the patients who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. Percentages may not total 100 because of rounding. COPD denotes chronic obstructive pulmonary disease, FEV₁ forced expiratory volume in 1 second, and FVC forced vital capacity.

† Data regarding the inhaled therapy for COPD were obtained at the time of screening.

‡ The reasons for not receiving triple therapy were unacceptable adverse effects related to an individual component (6 patients [1.3%] in the tozorakimab group and 11 patients [2.6%] in the placebo group in OBERON; and 6 patients [1.4%] and 7 patients [1.6%], respectively, in TITANIA), triple therapy was not considered to be appropriate (25 patients [5.6%] and 15 patients [3.5%], respectively, in OBERON; and 27 patients [6.2%] and 27 patients [6.2%] in TITANIA), and other reasons (9 patients [2.0%] and 13 patients [3.0%], respectively, in OBERON; and 7 patients [1.6%] and 10 patients [2.3%] in TITANIA).

§ Moderate exacerbations were defined by worsening COPD symptoms resulting in treatment with systemic glucocorticoids for at least 3 days or antibiotics or both, or an emergency department visit lasting less than 24 hours with intensive treatment. Severe exacerbations were defined by worsening COPD symptoms resulting in hospitalization for at least 24 hours or death.

¶ Severity of airflow obstruction was classified according to Global Initiative for Chronic Obstructive Lung Disease criteria as grade 1 (mild, defined by an FEV₁ ≥80% of the predicted value), grade 2 (moderate, defined by an FEV₁ ≥50% and <80% of the predicted value), grade 3 (severe, defined by FEV₁ ≥30% and <50% of the predicted value), or grade 4 (very severe, defined by an FEV₁ <30% of the predicted value), determined with the use of Global Lung Function Initiative spirometry reference equations.²⁶

|| Total scores on the St. George's Respiratory Questionnaire (SGRQ) range from 0 to 100, with lower scores indicating a better health-related quality of life.

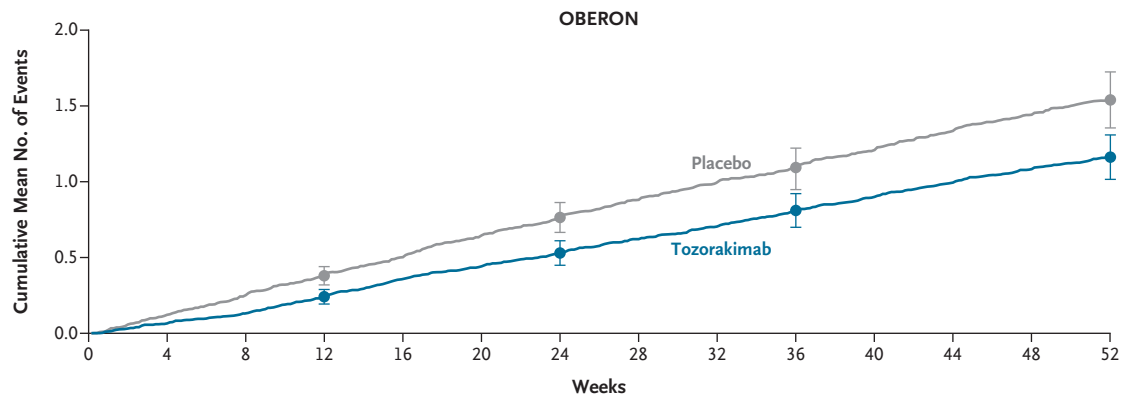
** Evaluating Respiratory Symptoms in COPD (E-RS—COPD) total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms.

†† Total scores on the COPD Assessment Test (CAT) range from 0 to 40, with higher scores indicating a greater effect of COPD on health status.

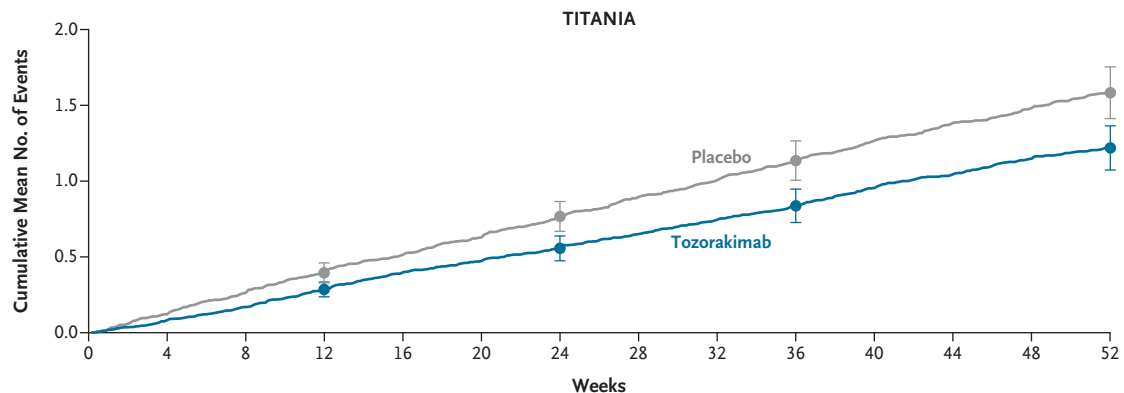
A Annualized Rate of Moderate or Severe Exacerbations

Population	Tozorakimab total no. of patients	Placebo total no. of patients	Tozorakimab adjusted annualized rate (95% CI)	Placebo adjusted annualized rate (95% CI)	Rate Ratio (95% CI)	P Value
OBERON						
Former smokers	342	337	1.34 (1.14–1.58)	1.90 (1.63–2.21)	0.71 (0.57–0.88)	0.002
Overall	446	431	1.41 (1.22–1.62)	2.00 (1.74–2.30)	0.70 (0.58–0.85)	<0.001
TITANIA						
Former smokers	350	344	1.37 (1.19–1.57)	2.07 (1.81–2.37)	0.66 (0.55–0.80)	<0.001
Overall	438	435	1.44 (1.27–1.63)	2.03 (1.80–2.30)	0.71 (0.59–0.84)	<0.001

0.1 1.0
Tozorakimab Better

B Cumulative Moderate or Severe Exacerbations**No. at Risk**

Placebo	431	429	424	423	418	417	414	412	407	403	399	396	390	349
Tozorakimab	446	445	443	440	436	431	429	423	422	417	417	417	415	371

**No. at Risk**

Placebo	435	434	429	428	426	422	419	417	412	404	400	397	392	352
Tozorakimab	438	437	437	434	434	431	427	423	418	415	408	407	401	369

Patients who had already been assigned to receive tozorakimab every 8 weeks continued with this regimen. Inferential testing was performed only for the comparison of tozorakimab administered every 4 weeks with placebo. Data among the patients who were assigned to receive tozorakimab

Figure 1 (facing page). Moderate or Severe Exacerbations.

Data are shown for the patients in the OBERON and TITANIA trials who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. Panel A shows the annualized rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations that had occurred over a 52-week period among former smokers (the primary end point) and in the overall population, which consisted of current and former smokers (the first key secondary end point). In the OBERON trial, two patients in the placebo group (one of whom was a former smoker) were excluded from the analyses because of missing lung-function data at screening. Panel B shows the cumulative mean number of moderate or severe exacerbations that occurred over a 52-week period in the overall population. The 95% confidence intervals (I bars) in Panel B have not been adjusted for multiplicity and should not be used to infer treatment effects.

every 8 weeks were used for dose-response characterization and were not included in the inferential analyses.

Patients had to continue treatment with inhaled maintenance therapy throughout both trials, with recommended adherence of at least 70%. They were encouraged to continue the same stable therapy, either triple therapy (inhaled glucocorticoid, long-acting beta-agonist, and long-acting muscarinic antagonist) or dual therapy (any two components of triple therapy, if triple therapy was not considered to be appropriate). Stable background maintenance therapy could include oral antibiotics, phosphodiesterase-4 inhibitors, or xanthines (see the Supplementary Appendix). After the 52-week treatment period, patients either entered the 8-week safety follow-up period of OBERON or TITANIA or were enrolled in the optional long-term extension trial (PROSPERO) (if they were eligible and had completed the 52-week treatment period).

Enrollment of current smokers was capped to ensure that at least 75% of the patients in each trial were former smokers, and we aimed for approximately 80% of the patients in each trial to be receiving triple therapy. Randomization was stratified according to geographic region, inhaled maintenance therapy (triple or dual), and smoking status (current or former smoker).

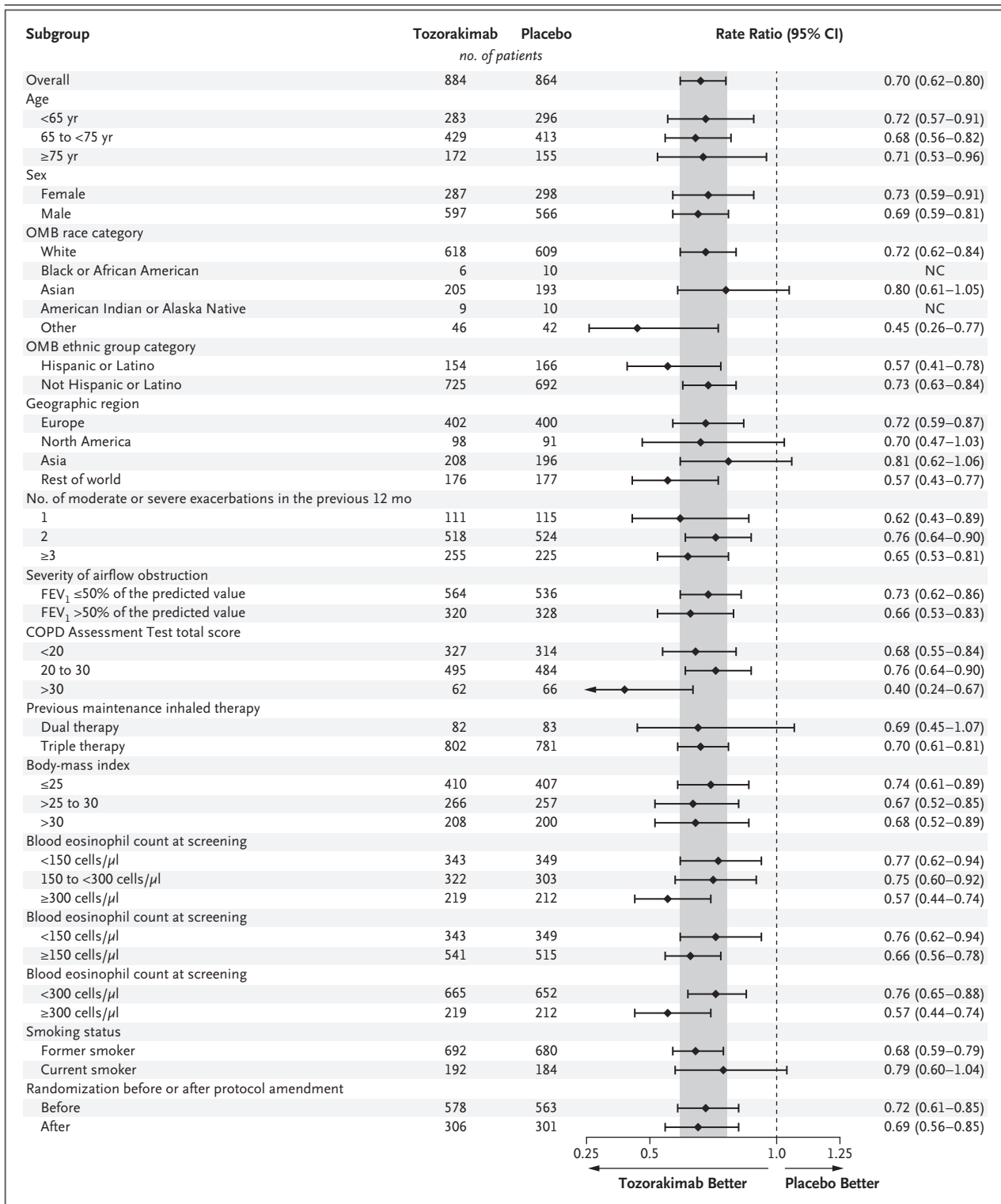
Both trials were conducted in accordance with the International Council for Harmonisa-

tion guidelines for Good Clinical Practice, the principles of the Declaration of Helsinki, and all applicable regulatory requirements. The protocols were approved by the institutional review board or independent ethics committee at each site. The protocols and statistical analysis plans are available at NEJM.org. All the patients provided written informed consent before entering the trials. All the authors contributed to the trial design, data interpretation, and drafting of the manuscript. The sponsor, AstraZeneca, designed the trials and collected and analyzed the data. Medical writing and editorial assistance, funded by the sponsor, was provided in accordance with Good Publication Practice guidelines. All the authors provided critical feedback and final approval for submission and vouch for the accuracy and completeness of the data and analyses and for the adherence of the trials to the protocols. All the authors had full access to and verified the data in the trials and had final responsibility for the decision to submit the manuscript for publication (see the Supplementary Appendix).

PATIENTS

Eligible patients were 40 years of age or older, had COPD diagnosed at least 12 months before enrollment, and had received stable standard-of-care inhaled maintenance therapy (triple or dual therapy) for the previous 3 months. Patients had to have had at least two moderate or at least one severe COPD exacerbation (as defined below) in the previous 12 months, including at least one resulting in treatment with systemic glucocorticoids and at least one while receiving their most recent stable maintenance therapy.

Current or former smokers with a smoking history of at least 10 pack-years were eligible. Former smokers were those who reported that they had stopped smoking for at least 6 months before screening (see the Supplementary Appendix). Eligible patients had to have a COPD Assessment Test total score of at least 10 (total scores range from 0 to 40, with higher scores indicating a greater effect of COPD on health status), with scores of at least 2 (on a scale of 0 [no effect] to 5 [severe effect]) for each of the phlegm (sputum) and cough items. Patients also had to have a postbronchodilator forced expira-



tory volume in 1 second (FEV₁) of more than 20% of the predicted normal value, with a ratio of postbronchodilator FEV₁ to forced vital capacity

of less than 0.70. The trials did not include any eligibility criteria related to blood eosinophil count. Patients with clinically significant or radiologically

Figure 2 (facing page). Subgroup Analysis of Moderate or Severe Exacerbations.

Shown is the annualized rate of moderate or severe COPD exacerbations in the pooled overall population from the OBERON and TITANIA trials, according to subgroup. Patients were originally assigned to receive tozorakimab once every 4 weeks or once every 8 weeks or placebo, but the protocol was later amended to stop assignment to the group receiving tozorakimab every 8 weeks. Data are shown for the patients who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. The gray shaded area indicates the 95% confidence interval for the pooled overall population. The 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects. All the subgroups were prespecified except for the subgroup defined according to a blood eosinophil count at screening of less than 150 cells per microliter or 150 cells or more per microliter, which combined the prespecified subgroups that were defined according to a blood eosinophil count of 150 to less than 300 cells per microliter or 300 cells or more per microliter; the modeled estimate among patients with a blood eosinophil count of less than 150 cells per microliter differs slightly between these analyses. Office of Management and Budget (OMB) race and ethnic group categories were reported by the patients. Total scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating a greater effect of COPD on health status. The body-mass index is the weight in kilograms divided by the square of the height in meters. FEV₁ denotes the forced expiratory volume in 1 second, and NC could not be calculated.

evident pulmonary disease other than COPD were ineligible, including those with asthma. Full eligibility criteria are listed in Table S3.

END POINTS

The primary end point was the annualized rate of moderate or severe exacerbations that occurred over a 52-week period in the prespecified cohort of former smokers. Moderate exacerbations were defined as worsening COPD symptoms resulting in treatment with systemic glucocorticoids for at least 3 days or antibiotics or both, or an ED visit lasting less than 24 hours with intensive treatment. Severe exacerbations were defined as worsening COPD symptoms resulting in hospitalization for at least 24 hours or death (see the Supplementary Appendix).

The key secondary end points were the annualized rate of moderate or severe exacerbations that occurred over a 52-week period in the overall population of current and former smokers,

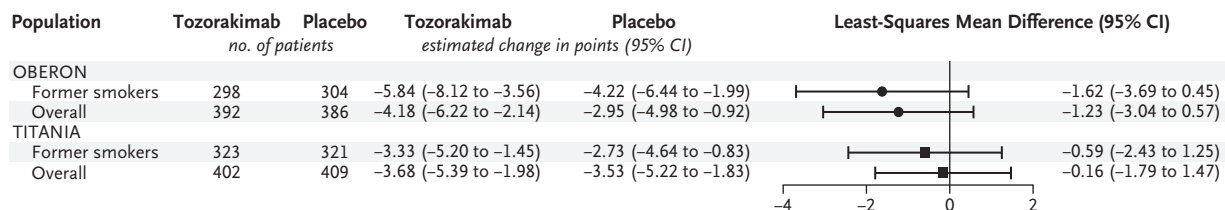
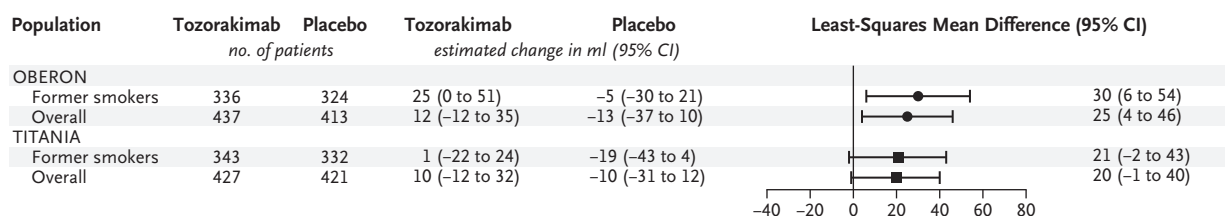
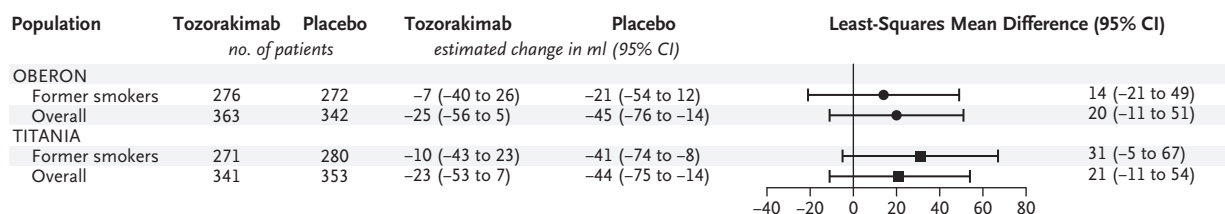
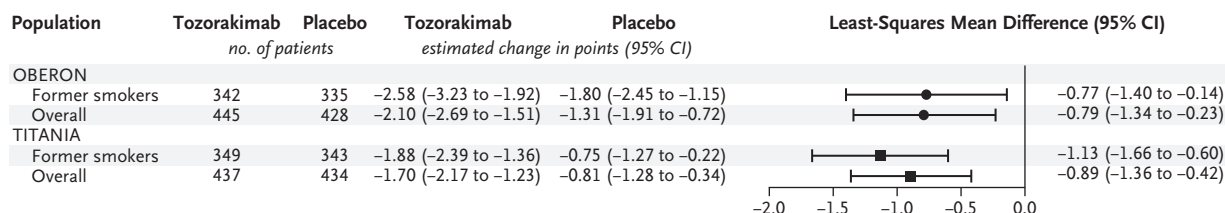
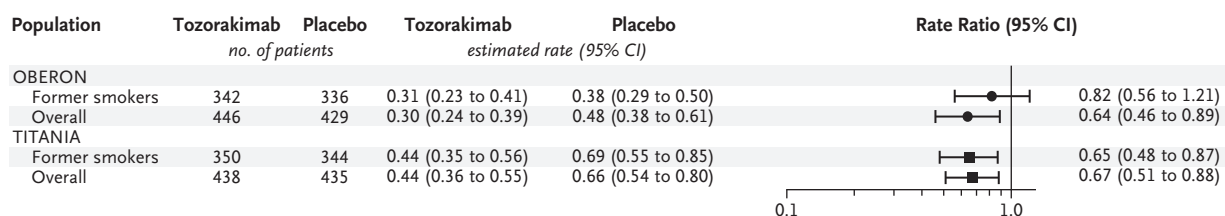
the change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score over a 52-week period, the change from baseline in the prebronchodilator FEV₁ over a 52-week period, the change from baseline in the postbronchodilator FEV₁ at week 52, the change from baseline in the Evaluating Respiratory Symptoms in COPD (E-RS-COPD) total score over a 52-week period, and the annualized rate of exacerbations resulting in hospitalization or ED visits (of any duration) or both that occurred over a 52-week period. The SGRQ total scores were assessed on the basis of guided patient reports at clinic visits; total scores range from 0 to 100, with lower scores indicating better health-related quality of life (minimum clinically important difference, 4 points).²⁶ The E-RS-COPD total scores were assessed on the basis of data from daily electronic diaries recorded by the patients; total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms (minimum clinically important difference, 2 points).²⁷⁻³⁰

Safety end points included adverse events, serious adverse events, and adverse events of special interest that occurred during the treatment period and the incidence of antidrug antibodies. For each trial, an independent data monitoring committee reviewed unblinded safety data. Separate independent adjudication committees reviewed heart-failure events, major adverse cardiovascular events, and fatal events.

STATISTICAL ANALYSIS

For both trials, we estimated that a sample of 318 former smokers per group would provide 90% power to detect a 30% lower annualized rate of moderate or severe exacerbations with tozorakimab (administered every 4 weeks) than with placebo at a two-sided significance level of 5%. We assumed an event rate of 1 moderate or severe exacerbation per patient per year in the placebo group. With the inclusion of current smokers (25% of the patients in each trial), the planned overall sample size was 424 patients per group in each trial. Efficacy was assessed according to the intention-to-treat principle. Safety was assessed, according to the agent that was received, in all the patients who had undergone randomization and had received at least one dose of tozorakimab or placebo.

The primary end point in each trial was analyzed with a negative binomial regression model

A Change in SGRQ Total Score**B Change in Prebronchodilator FEV₁****C Change in Postbronchodilator FEV₁****D Change in E-RS-COPD Total Score****E Annualized Rate of Exacerbations Resulting in Hospitalization, Emergency Department Visit, or Both**

with covariates of treatment group, geographic region, inhaled maintenance therapy (triple or dual), number of exacerbations in the previous year (1 or ≥ 2), smoking status (current or former smoker, in the overall population only), post-

bronchodilator percentage of the predicted FEV₁ at screening, and the log blood eosinophil count at screening.

A hierarchical testing procedure was applied separately to each trial to control type 1 error for

Figure 3 (facing page). Other Key Secondary End Points.

Data are shown for the patients who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. The estimated changes were calculated with the use of a linear model for repeated measures. The changes in Panels A, B, and D are the estimated least-squares mean changes from baseline over a 52-week period, and the change in Panel C is the estimated least-squares mean change from baseline at week 52. Negative least-squares mean differences in Panels A and D and positive least-squares mean differences in Panels B and C favor tozorakimab. The estimated rate in Panel E is the adjusted annualized rate, calculated with the use of a negative binomial regression model. In both trials, the key secondary end points were tested hierarchically in the order shown. The difference in the change from baseline in the St. George's Respiratory Questionnaire (SGRQ) total score over a 52-week period between tozorakimab and placebo among former smokers was not significant; therefore, no formal hypothesis testing was performed for subsequent end points in the testing hierarchy. SGRQ total scores range from 0 to 100, with lower scores indicating better health-related quality of life. Evaluating Respiratory Symptoms in COPD (E-RS-COPD) total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms. COPD exacerbations resulting in hospitalization, an emergency department visit, or both were defined as exacerbations that resulted in inpatient hospitalization, an emergency department visit of any duration, or death. The 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer treatment effects.

the primary and key secondary end points according to a prespecified sequence: each end point was assessed first in the cohort of former smokers and then in the overall population (Table S4). A treatment policy estimand was applied, which included all data regardless of discontinuation of the trial regimen. Prespecified subgroup analyses used pooled data from the overall populations in both trials. Additional statistical analysis methods are described in the Supplementary Appendix.

RESULTS

PATIENTS

From January 3, 2022, through December 20, 2024, we screened 1690 patients for enrollment in OBERON and 1896 patients for enrollment in

TITANIA (Fig. S2). In OBERON, 446 patients (342 of whom were former smokers) who had been assigned to receive tozorakimab every 4 weeks and 431 patients (337 former smokers) who had been assigned to receive placebo were included in the efficacy analyses (overall population); the safety population included 446 patients in the tozorakimab group and 430 in the placebo group. In TITANIA, the overall population and the safety population included 438 patients in the tozorakimab group (350 former smokers) and 435 in the placebo group (344 former smokers). A total of 241 patients in OBERON and 292 patients in TITANIA who had been assigned to receive tozorakimab every 8 weeks started treatment; results among these patients are reported in the Supplementary Appendix. Among the patients who started treatment, including those who had been assigned to receive tozorakimab every 8 weeks, 87.8% of the patients in OBERON and 86.2% in TITANIA completed the treatment period.

In both trials, the demographic and clinical characteristics of the patients at baseline were balanced between the groups in the cohort of former smokers and in the overall population, as well as among the patients who had been assigned to receive tozorakimab every 8 weeks (Table 1 and Tables S5 and S6). The mean age among all the patients in the trials was 67.1 years in OBERON and 68.0 years in TITANIA. The majority of the patients were men (65.8% in OBERON and 68.1% in TITANIA). Most of the patients were receiving triple inhaled maintenance therapy (91.0% and 90.0% in the two trials, respectively). The severity of airflow obstruction among the patients ranged from mild to very severe (grades 1 through 4 according to Global Initiative for Chronic Obstructive Lung Disease criteria), and the blood eosinophil counts at screening covered a broad range. The representativeness of the trial populations is shown in Table S7.

PRIMARY END POINT AND FIRST KEY SECONDARY END POINT

Among former smokers in OBERON, the annualized rate of moderate or severe exacerbations that had occurred over a 52-week period was 1.34 events (95% confidence interval [CI], 1.14 to 1.58) in the tozorakimab group and 1.90 events (95% CI, 1.63 to 2.21) in the placebo group (rate ratio,

Table 2. Adverse Events.*

Event	OBERON		TITANIA	
	Tozorakimab (N=446)	Placebo (N=430)	Tozorakimab (N=438)	Placebo (N=435)
	<i>number of patients (percent)</i>			
Any adverse event†	314 (70.4)	332 (77.2)	351 (80.1)	347 (79.8)
Leading to discontinuation of trial regimen	14 (3.1)	12 (2.8)	16 (3.7)	23 (5.3)
Any serious adverse event	104 (23.3)	116 (27.0)	136 (31.1)	141 (32.4)
Any adverse event leading to death	6 (1.3)	5 (1.2)	11 (2.5)	4 (0.9)
Adverse events occurring in ≥5% of patients‡				
COPD	56 (12.6)	76 (17.7)	89 (20.3)	108 (24.8)
Nasopharyngitis	45 (10.1)	46 (10.7)	37 (8.4)	35 (8.0)
Upper respiratory tract infection	27 (6.1)	22 (5.1)	38 (8.7)	38 (8.7)
Injection-site reaction	23 (5.2)	6 (1.4)	29 (6.6)	7 (1.6)
Fall	21 (4.7)	24 (5.6)	28 (6.4)	24 (5.5)
Coronavirus disease 2019	23 (5.2)	16 (3.7)	25 (5.7)	39 (9.0)
Pneumonia	17 (3.8)	17 (4.0)	24 (5.5)	36 (8.3)
Headache	23 (5.2)	19 (4.4)	18 (4.1)	22 (5.1)
Respiratory failure	9 (2.0)	19 (4.4)	24 (5.5)	25 (5.7)
Urinary tract infection	21 (4.7)	24 (5.6)	12 (2.7)	17 (3.9)
Lower respiratory tract infection	11 (2.5)	11 (2.6)	21 (4.8)	22 (5.1)
Acute respiratory failure	7 (1.6)	11 (2.6)	9 (2.1)	23 (5.3)

* Data are shown for the patients who were assigned to receive tozorakimab every 4 weeks and those who were assigned to receive placebo. Safety was assessed in all the patients who had undergone randomization and received at least one dose of tozorakimab or placebo.

† Data are shown for adverse events with an onset date on or after the date of the first dose of tozorakimab or placebo, up to and including the date of the last dose plus 84 days, or up to the date of withdrawal from the trial or enrollment in the long-term extension trial.

‡ Shown are the adverse events that occurred in at least 5% of the patients in either group in either trial. The adverse events were coded according to the preferred terms of the *Medical Dictionary for Regulatory Activities*, version 28.1, and ordered by decreasing frequency in the combined tozorakimab groups in both trials.

0.71; 95% CI, 0.57 to 0.88; $P=0.002$). In TITANIA, the annualized rate among former smokers was 1.37 events (95% CI, 1.19 to 1.57) in the tozorakimab group and 2.07 events (95% CI, 1.81 to 2.37) in the placebo group (rate ratio, 0.66; 95% CI, 0.55 to 0.80; $P<0.001$). In the overall population in OBERON, the annualized rate was 1.41 events (95% CI, 1.22 to 1.62) in the tozorakimab group and 2.00 events (95% CI, 1.74 to 2.30) in the placebo group (rate ratio, 0.70; 95% CI, 0.58 to 0.85;

$P<0.001$). In the overall population in TITANIA, the annualized rate was 1.44 events (95% CI, 1.27 to 1.63) and 2.03 events (95% CI, 1.80 to 2.30) in the two groups, respectively (rate ratio, 0.71; 95% CI, 0.59 to 0.84; $P<0.001$) (Fig. 1A and Table S8). Figure 1B shows the mean cumulative number of moderate or severe exacerbations that occurred during the 52-week treatment period in the overall population. The time to the first moderate or severe exacerbation is shown in Figure S3.

The results of prespecified sensitivity and prespecified supportive analyses were similar to those of the primary analyses (Fig. S4 and Table S9). The rates of moderate or severe exacerbations across prespecified subgroups in the pooled overall populations from the two trials are shown in Figure 2.

OTHER KEY SECONDARY END POINTS

Among former smokers, the least-squares mean change from baseline in the SGRQ total score over a 52-week period (the second key secondary end point) was -5.84 points (95% CI, -8.12 to -3.56) in the tozorakimab group and -4.22 points (95% CI, -6.44 to -1.99) in the placebo group in OBERON, and -3.33 points (95% CI, -5.20 to -1.45) and -2.73 points (95% CI, -4.64 to -0.83), respectively, in TITANIA (Fig. 3). There was no significant difference between the groups in the change in the SGRQ total score in either trial: the least-squares mean between-group difference was -1.62 points (95% CI, -3.69 to 0.45) in OBERON and -0.59 points (95% CI, -2.43 to 1.25) in TITANIA. Therefore, no further statistical testing of the key secondary end points was performed, according to the hierarchical testing procedure. The results for all other key secondary end points are reported in Figure 3. The changes in the SGRQ total score, the prebronchodilator FEV₁, the postbronchodilator FEV₁, and the E-RS-COPD total score in the overall population are shown in Figures S5 through S8. The results for all other secondary end points are reported in Table S11.

SAFETY

In the overall population, the percentage of patients who had adverse events appeared to be similar in the two groups in each trial (70.4% in the tozorakimab group and 77.2% in the placebo group in OBERON, and 80.1% and 79.8%, respectively, in TITANIA). The percentage of patients who had serious adverse events also appeared to be similar in the two groups in each trial (23.3% in the tozorakimab group and 27.0% in the placebo group in OBERON, and 31.1% and 32.4%, respectively, in TITANIA) (Table 2 and Tables S12 and S13). The incidence of adverse events of special interest was balanced between the two groups in all categories, with the exception of injection-

site reactions (which occurred in 6.5% of the patients in the tozorakimab group and in 3.3% of those in the placebo group in OBERON, and in 9.8% and 4.6%, respectively, in TITANIA) (Table S14). Serious adverse events that resulted in death occurred in 1.3% of the patients in the tozorakimab group and in 1.2% of those in the placebo group in OBERON, and in 2.5% and 0.9%, respectively, in TITANIA (Table S15). Events adjudicated as major adverse cardiovascular events occurred in 2 patients (0.4%) in the tozorakimab group and in no patients in the placebo group in OBERON, and in 11 (2.5%) and 5 (1.1%), respectively, in TITANIA (Table S16). In both trials, the prevalence and incidence of antidrug antibodies was approximately 2 to 4% in all the groups, including the placebo groups (Table S17).

DISCUSSION

Among patients with COPD and a history of exacerbations, tozorakimab as an add-on to inhaled maintenance therapy resulted in a significantly lower rate of moderate or severe exacerbations than inhaled maintenance therapy alone. Among former smokers, the annualized rate was 29% lower with tozorakimab than with placebo in OBERON and 34% lower with tozorakimab than with placebo in TITANIA. In the overall population, the rate was 30% lower with tozorakimab than with placebo in OBERON and 29% lower with tozorakimab than with placebo in TITANIA. The trial populations included patients with a broad range of blood eosinophil counts and severity of airflow obstruction, which reflects real-world presentation among patients. In the prespecified pooled analysis, the efficacy of tozorakimab appeared to be similar across most subgroups. Consistent findings across these replicate trials confirm the efficacy of tozorakimab in COPD.

Tozorakimab appeared to result in a lower annualized rate of moderate or severe exacerbations than placebo among patients across all blood eosinophil count thresholds in the pooled subgroup analysis. The efficacy of tozorakimab in this broad population aligns with the central role of the reduced form and the oxidized form of interleukin-33 in multiple COPD pathophysiological pathways, extending beyond type 2 in-

flammation and eosinophils.^{16,31,32} The efficacy of mepolizumab (anti-interleukin-5) and dupilumab (anti-interleukin-4 and anti-interleukin-13) is limited to patients with elevated blood eosinophil counts.⁷⁻⁹ Reductions in the rate of moderate or severe exacerbations with itepekimab and astegolimab have not been confirmed in replicate phase 3 trials, but the efficacy signals support the clinical value of interleukin-33 as a therapeutic target in COPD.^{21,22}

The proportions of patients who had adverse events and serious adverse events were similar in the tozorakimab group and the placebo group in each trial, apart from injection-site reactions, which were more common with tozorakimab (as previously observed for subcutaneously administered monoclonal antibodies).^{7-9,22,33} Major adverse cardiovascular events and serious adverse events that resulted in death occurred more frequently with tozorakimab than with placebo. Although these events were rare, the incidence was similar among patients who received tozorakimab every 4 weeks and those who received tozorakimab every 8 weeks. No patterns in adjudicated components of major adverse cardiovascular events, adjudicated causes of death, or in preferred terms for serious adverse events with the outcome of death were apparent.

A strength of the two trials was the broad inclusion criteria, which ensured that the trial populations were representative of patients with COPD and high unmet need.⁶ Former smokers were targeted a priori in the analysis of the primary end point to allow adequate assessment of efficacy in patient populations that were previously reported to be likely to benefit from anti-interleukin-33 therapy.²¹ Evaluating the overall population in the analysis of the first key secondary end point ensured that the unmet need among current smokers was not neglected. Tozorakimab inhibits activity of both the reduced form and oxidized form of interleukin-33 and was therefore hypothesized to benefit current and former smokers, as indicated by results of the phase 2 trial.^{16,24} The trials were adequately powered, although exacerbation rates in the placebo group were higher than in previous studies.^{7,9,22} The statistical testing hierarchy provided robust multiplicity-controlled assessment of the primary and key secondary end points. Safety monitoring

included independent adjudication of major adverse cardiovascular events and all deaths that occurred during the treatment period.

The trials had some limitations. Adherence to inhaled maintenance therapy was not monitored systematically (except during screening). Monitoring of rare safety events requires longer follow-up and larger sample sizes than in the present studies. The trials were initiated before the phase 2 trial was completed,²⁴ and assignment to tozorakimab every 8 weeks was halted. Some racial groups were underrepresented. The trials were not designed to assess efficacy among patients who had never smoked or to investigate the mechanism of action of tozorakimab.

By inhibiting interleukin-33, tozorakimab has downstream effects on airway inflammation and mucus dysfunction, which drive COPD exacerbations.^{11,16-19,24} Studies are ongoing to elucidate the mechanism of action of tozorakimab in preventing exacerbations. Phase 3 efficacy results for other add-on therapies in COPD are variable, with dupilumab affecting exacerbations, health-related quality of life, and lung function and mepolizumab affecting exacerbations but not symptoms or lung function.^{7,9} These findings may reflect differences in mechanism of action and in patient selection criteria among these studies.

In a broad population of patients with COPD who had a history of exacerbations and were receiving standard care, add-on tozorakimab therapy resulted in a lower rate of moderate or severe exacerbations than placebo. This result was observed among former smokers and in the overall population of current and former smokers.

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REFERENCES

- Boers E, Barrett M, Su JG, et al. Global burden of chronic obstructive pulmonary disease through 2050. *JAMA Netw Open* 2023;6(12):e2346598.
- Safiri S, Carson-Chahhoud K, Noori M, et al. Burden of chronic obstructive pulmonary disease and its attributable risk factors in 204 countries and territories, 1990-2019: results from the Global Burden of Disease Study 2019. *BMJ* 2022; 378:e069679.
- Donaldson GC, Seemungal TAR, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax* 2002;57:847-52.
- Daniels K, Lanes S, Tave A, et al. Risk of death and cardiovascular events following an exacerbation of COPD: the EXACOS-CV US study. *Int J Chron Obstruct Pulmon Dis* 2024;19:225-41.
- Halpin DM, Miravittles M, Metzendorf N, Celli B. Impact and prevention of severe exacerbations of COPD: a review of the evidence. *Int J Chron Obstruct Pulmon Dis* 2017;12:2891-908.
- De Soyza A, Nordon C, Coak E, et al. Clinical burden of people with symptomatic and exacerbating COPD while on triple inhaled therapy. *J Clin Med* 2025;14:6488.
- Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with blood eosinophil evidence of type 2 inflammation. *N Engl J Med* 2024;390:2274-83.
- Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for COPD with type 2 inflammation indicated by eosinophil counts. *N Engl J Med* 2023;389:205-14.
- Sciurba FC, Criner GJ, Christenson SA, et al. Mepolizumab to prevent exacerbations of COPD with an eosinophilic phenotype. *N Engl J Med* 2025;392:1710-20.
- Nordon C, Carstens D, Fagerås M, et al. Characteristics and outcomes of people with COPD who experience exacerbations while on inhaled triple therapy: results of the SIRIUS I cohort study in the US (2015-2019). *Int J Chron Obstruct Pulmon Dis* 2025;20:1851-64.
- Cayrol C, Girard J-P. Interleukin-33 (IL-33): a critical review of its biology and the mechanisms involved in its release as a potent extracellular cytokine. *Cytokine* 2022;156:155891.
- Xia J, Zhao J, Shang J, et al. Increased IL-33 expression in chronic obstructive pulmonary disease. *Am J Physiol Lung Cell Mol Physiol* 2015;308:L619-L627.
- Abdo M, Pedersen F, Kirsten A-M, et al. Association of airway inflammation and smoking status with IL-33 level in sputum of patients with asthma or COPD. *Eur Respir J* 2024;64:2400347.
- Faiz A, Mahbub RM, Boedijono FS, et al. IL-33 expression is lower in current smokers at both transcriptomic and protein levels. *Am J Respir Crit Care Med* 2023;208:1075-87.
- Rabe KF, Rennard S, Martinez FJ, et al. Targeting type 2 inflammation and epithelial alarmins in chronic obstructive pulmonary disease: a biologics outlook. *Am J Respir Crit Care Med* 2023;208:395-405.
- Strickson S, Houslay KF, Negri VA, et al. Oxidised IL-33 drives COPD epithelial pathogenesis via ST2-independent RAGE/EGFR signalling complex. *Eur Respir J* 2023;62:2202210.
- England E, Rees DG, Scott IC, et al. Tozorakimab (MEDI3506): an anti-IL-33 antibody that inhibits IL-33 signalling via ST2 and RAGE/EGFR to reduce inflammation and epithelial dysfunction. *Sci Rep* 2023;13:9825.
- Jin KN, Lee HJ, Park H, et al. Mucus plugs as precursors to exacerbation and lung function decline in COPD patients. *Arch Bronconeumol* 2025;61:138-46.
- Brightling C, Greening N. Airway inflammation in COPD: progress to precision medicine. *Eur Respir J* 2019;54: 1900651.
- Rabe KF, Celli BR, Wechsler ME, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. *Lancet Respir Med* 2021;9:1288-98.
- Rabe KF, Martinez FJ, Bhatt SP, et al. Efficacy and safety of itepekimab in former smokers with chronic obstructive pulmonary disease: AERIFY-1 and AERIFY-2 trials. *Am J Respir Crit Care Med* 2026; 212:Suppl 2:599. abstract (<https://doi.org/10.1093/ajrcrm/aamag286.124>).
- Papi A, Greening NJ, Bhatt SP, et al. Safety and efficacy of astegolimab for COPD with frequent exacerbations regardless of baseline blood eosinophil counts (ALIENTO and ARNASA): randomised, double-blind, placebo-controlled, phase 2b and 3 trials. *Lancet* 2026;407:2027-39.

23. Watz H, Sciurba FC, Bonini M, et al. Phase III LUNA clinical programme: design of four randomised, double-blind, placebo-controlled studies assessing the efficacy and safety of tozorakimab in patients with symptomatic COPD and a high risk of exacerbations. *BMJ Open Respir Res* 2026;13(1):e004145.
24. Singh D, Guller P, Reid F, et al. A phase 2a trial of the IL-33 monoclonal antibody tozorakimab in patients with COPD: FRONTIER-4. *Eur Respir J* 2025; 66:2402231.
25. Reid F, Singh D, Albayaty M, et al. A randomized phase I study of the anti-interleukin-33 antibody tozorakimab in healthy adults and patients with chronic obstructive pulmonary disease. *Clin Pharmacol Ther* 2024;115:565-75.
26. Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005;2:75-9.
27. Jones PW, Chen W-H, Wilcox TK, Sethi S, Leidy NK. Characterizing and quantifying the symptomatic features of COPD exacerbations. *Chest* 2011;139: 1388-94.
28. Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD: performance of the EXACT-Respiratory Symptoms tool (E-RS) in three clinical trials. *Respir Res* 2014;15:124.
29. Leidy NK, Sexton CC, Jones PW, et al. Measuring respiratory symptoms in clinical trials of COPD: reliability and validity of a daily diary. *Thorax* 2014;69:443-9.
30. Leidy NK, Wilcox TK, Jones PW, Roberts L, Powers JH, Sethi S. Standardizing measurement of chronic obstructive pulmonary disease exacerbations: reliability and validity of a patient-reported diary. *Am J Respir Crit Care Med* 2011;183:323-9.
31. Calderon AA, Dimond C, Choy DF, et al. Targeting interleukin-33 and thymic stromal lymphopoietin pathways for novel pulmonary therapeutics in asthma and COPD. *Eur Respir Rev* 2023;32(167):220144.
32. Zhou Y, Xu Z, Liu Z. Role of IL-33-ST2 pathway in regulating inflammation: current evidence and future perspectives. *J Transl Med* 2023;21:902.
33. Bhatt SP, Rabe KF, Hanania NA, et al. Dupilumab for chronic obstructive pulmonary disease with type 2 inflammation: a pooled analysis of two phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2025;13:234-43.

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