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Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease

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ABSTRACT

BACKGROUND

Patients with chronic obstructive pulmonary disease (COPD) with an eosinophilic phenotype may benefit from treatment with mepolizumab, a monoclonal antibody directed against interleukin-5.

METHODS

We performed two phase 3, randomized, placebo-controlled, double-blind, parallel-group trials comparing mepolizumab (100 mg in METREX, 100 or 300 mg in METREO) with placebo, given as a subcutaneous injection every 4 weeks for 52 weeks in patients with COPD who had a history of moderate or severe exacerbations while taking inhaled glucocorticoid-based triple maintenance therapy. In METREX, unselected patients in the modified intention-to-treat population with an eosinophilic phenotype were stratified according to blood eosinophil count (≥ 150 per cubic millimeter at screening or ≥ 300 per cubic millimeter during the previous year). In METREO, all patients had a blood eosinophil count of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter during the previous year. The primary end point was the annual rate of moderate or severe exacerbations. Safety was also assessed.

RESULTS

In METREX, the mean annual rate of moderate or severe exacerbations in the modified intention-to-treat population with an eosinophilic phenotype (462 patients) was 1.40 per year in the mepolizumab group versus 1.71 per year in the placebo group (rate ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.98; adjusted $P=0.04$); no significant between-group differences were found in the overall modified intention-to-treat population (836 patients) (rate ratio, 0.98; 95% CI, 0.85 to 1.12; adjusted $P>0.99$). In METREO, the mean annual rate of moderate or severe exacerbations was 1.19 per year in the 100-mg mepolizumab group, 1.27 per year in the 300-mg mepolizumab group, and 1.49 per year in the placebo group. The rate ratios for exacerbations in the 100-mg and 300-mg mepolizumab groups versus the placebo group were 0.80 (95% CI, 0.65 to 0.98; adjusted $P=0.07$) and 0.86 (95% CI, 0.70 to 1.05; adjusted $P=0.14$), respectively. A greater effect of mepolizumab, as compared with placebo, on the annual rate of moderate or severe exacerbations was found among patients with higher blood eosinophil counts at screening. The safety profile of mepolizumab was similar to that of placebo.

CONCLUSIONS

Mepolizumab at a dose of 100 mg was associated with a lower annual rate of moderate or severe exacerbations than placebo among patients with COPD and an eosinophilic phenotype. This finding suggests that eosinophilic airway inflammation contributes to COPD exacerbations. (Funded by GlaxoSmithKline; METREX and METREO ClinicalTrials.gov numbers, NCT02105948 and NCT02105961.)

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CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is a common disease characterized by progressive airflow obstruction, chronic inflammation in the lungs, and the occurrence of persistent symptoms and acute exacerbations.¹ Up to 40% of patients with COPD have an eosinophilic phenotype, defined as a peripheral-blood differential eosinophil count of 2% or more, which equates to approximately 150 to 200 eosinophils per cubic millimeter.^{2,3} Blood eosinophil counts of this level are associated with an increased risk of COPD exacerbations; the risk can be partially mitigated by long-term treatment with inhaled glucocorticoids.^{4,5} Moreover, these patients have a good response to treatment of acute exacerbations with oral glucocorticoids.^{6,7} These findings are consistent with a pathogenic role for eosinophils in exacerbations of COPD and provide a strong rationale for therapies that specifically inhibit eosinophilic inflammation.

Current Global Initiative for Chronic Obstructive Lung Disease (GOLD) treatment guidelines for COPD recommend maintenance use of triple inhaled therapy that includes a combination of inhaled glucocorticoids, long-acting β_2 -agonists, and long-acting muscarinic-receptor antagonists in patients with frequent exacerbations who do not have adequate outcomes with other treatments.¹ However, approximately 30 to 40% of patients are reported to continue to have moderate or severe exacerbations despite receiving triple inhaled therapy.^{8,9}

Mepolizumab, a humanized monoclonal antibody, reduces eosinophil counts in blood and tissues by blocking interleukin-5, a key eosinophil cytokine, through binding to eosinophil surface receptors.^{10,11} In patients with severe eosinophilic asthma, mepolizumab treatment has been found to be associated with lower rates of exacerbations and symptoms and with greater improvements in health-related quality of life than placebo and the existing standard of care.¹²⁻¹⁴ In post hoc analyses of data from the Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) and Dose Ranging Efficacy and Safety with Mepolizumab in Severe Asthma (DREAM) trials, mepolizumab was also associated with lower exacerbation rates than placebo among patients who had severe eosinophilic asthma with clinical features of COPD.^{12,13,15}

The objective of the Mepolizumab vs. Placebo

as Add-on Treatment for Frequently Exacerbating COPD Patients (METREX) and Mepolizumab vs. Placebo as Add-on Treatment for Frequently Exacerbating COPD Patients Characterized by Eosinophil Level (METREO) trials was to evaluate the efficacy and safety of subcutaneous mepolizumab, as compared with placebo, as an add-on to triple inhaled therapy in patients with COPD who had an eosinophilic phenotype and a history of moderate or severe exacerbations, as well as the phenotypes of patients who are likely to have a response to mepolizumab treatment.

METHODS

DESIGN OF THE TRIALS

METREX and METREO were phase 3, randomized, placebo-controlled, double-blind, parallel-group trials; METREX was conducted in 16 countries (117 investigative sites), and METREO was conducted in 15 countries (168 investigative sites). Information regarding the authors' contributions (including those of authors who are employees of GlaxoSmithKline) to the trial design, data collection and analysis, and manuscript development is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. All the authors had access to the data and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trials to the protocols, which, along with the statistical analysis plans, are available at NEJM.org (Protocol 1 [METREX] and Protocol 2 [METREO]). Editorial support was provided by medical writers; this support was funded by GlaxoSmithKline.

After screening, eligible patients in METREX were randomly assigned in a 1:1 ratio to receive subcutaneous injections of mepolizumab (100 mg) or placebo; in METREO, eligible patients were randomly assigned in a 1:1:1 ratio to receive subcutaneous injections of 100 mg of mepolizumab, 300 mg of mepolizumab, or placebo. During the treatment period, injections were administered every 4 weeks for 52 weeks (final dose at week 48), in addition to triple inhaled therapy (administered in accordance with the standard of care); the treatment period was followed by 8 weeks of follow-up (Fig. S1 in the Supplementary Appendix). For both trials, patients who prematurely discontinued the trial

regimen were not required to withdraw from the trial but were encouraged to attend all the trial visits as planned in order to complete the trial assessments.

Both trials were conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and the applicable country-specific regulatory requirements. All the patients provided written informed consent.

TRIAL POPULATION

In both trials, enrolled patients were 40 years of age or older and had a documented diagnosis of COPD for at least 1 year (based on the American Thoracic Society–European Respiratory Society 2004 definition¹⁶); had a ratio of the forced expiratory volume in 1 second (FEV₁) to the forced vital capacity (FVC) of less than 0.70 before and after bronchodilator use and a FEV₁ after bronchodilator use that was more than 20% and less than or equal to 80% of the predicted value; and had a documented history of two or more moderate exacerbations (i.e., treated with systemic glucocorticoids, antibiotic agents, or both in association with a worsening of COPD) or one or more severe exacerbations (i.e., leading to hospitalization) in the previous 12 months. For 12 months before screening, patients had to have been receiving background inhaled glucocorticoid–based therapy consisting of high-dose inhaled glucocorticoids (≥ 500 μg per day of fluticasone propionate or equivalent), a long-acting bronchodilator (either a long-acting β_2 -agonist or a long-acting muscarinic-receptor antagonist), and a third class of regularly prescribed COPD medication (e.g., a long-acting β_2 -agonist, long-acting muscarinic-receptor antagonist, phosphodiesterase-4 inhibitor, or methylxanthine). For a minimum of 3 months immediately before screening, patients had to have been receiving triple inhaled therapy consisting of a high-dose inhaled glucocorticoid, long-acting β_2 -agonist, and long-acting muscarinic-receptor antagonist. Current or former smokers (≥ 10 pack-years) and nonsmokers were included. Patients with a current diagnosis of asthma and nonsmokers with a history of asthma were excluded.

At randomization in METREX, patients were stratified on the basis of blood eosinophil

counts as having either an eosinophilic phenotype (eosinophil count, ≥ 150 per cubic millimeter at screening or ≥ 300 per cubic millimeter at any point in the previous year) or a noneosinophilic phenotype (eosinophil count, < 150 per cubic millimeter at screening and no evidence of ≥ 300 per cubic millimeter in the previous year). In METREO, only patients who had an eosinophilic phenotype were eligible for inclusion. Further details regarding the inclusion and exclusion criteria are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

In both trials, the primary end point was the annual rate of exacerbations classified as moderate (leading to systemic glucocorticoid treatment, antibiotic treatment, or both) or severe (leading to hospitalization or resulting in death). The secondary end points were the time to the first moderate or severe exacerbation; the annual rate of exacerbations leading to an emergency department visit, hospitalization, or both; the mean change from baseline at week 52 in the St. George's Respiratory Questionnaire total score (SGRQ, measured by the SGRQ-COPD questionnaire; scores range from 0 to 100 points, with higher scores indicating worse health status; minimal clinically important difference, 4-point decrease from baseline¹⁷⁻¹⁹) and in the COPD Assessment Test (CAT) score (scores range from 0 to 40 units, with higher scores indicating greater effect of disease; minimal clinically important difference, 2-point decrease from baseline^{20,21}). Other end points (all assessed at week 52) included the change from screening in blood eosinophil count; the change from baseline in FEV₁, FVC, and SGRQ domain (symptoms, activity, and impact domains) scores; the proportion of patients with an SGRQ response (i.e., a ≥ 4 -point decrease from baseline), and the proportion of patients with a CAT response (i.e., a ≥ 2 -point decrease from baseline); and the physician-rated and patient-rated response.

The efficacy end points were assessed in a modified intention-to-treat population comprising all patients who underwent randomization and received at least one dose of mepolizumab or placebo; the analysis was according to the randomly assigned trial groups. In METREX, the primary analysis populations were the modified

intention-to-treat population with an eosinophilic phenotype (patients with blood eosinophil counts ≥ 150 per cubic millimeter at screening or ≥ 300 per cubic millimeter within the previous year) and the overall modified intention-to-treat population (all patients, with no eosinophil criteria applied). In METREO, the primary analysis population was the modified intention-to-treat population. Within each respective patient population, comparisons were made between each mepolizumab dose and placebo.

A prespecified meta-analysis of the primary end point was performed in the combined population (i.e., the modified intention-to-treat population with an eosinophilic phenotype in METREX and the modified intention-to-treat population in METREO) according to blood eosinophil count category at screening (< 150 [history of ≥ 300 in the previous year], ≥ 150 to < 300 , ≥ 300 to < 500 , and ≥ 500 per cubic millimeter) and according to blood eosinophil count threshold at screening (< 150 [history of ≥ 300 in the previous year], ≥ 150 , ≥ 300 , and ≥ 500 per cubic millimeter). The prespecified meta-analysis plan also included an assessment of the primary end point according to region (Europe, United States, and the rest of the world).

Three post hoc analyses were performed. First, the primary end point was assessed in patients with blood eosinophil counts of less than 150 per cubic millimeter, regardless of historical blood eosinophil count (in a combined population that included the METREX overall modified intention-to-treat population and the METREO modified intention-to-treat population). Second, the primary end point was assessed in patients with blood eosinophil counts of 300 per cubic millimeter or higher at screening or during the previous year (in the METREX modified intention-to-treat population with an eosinophilic phenotype and the METREO modified intention-to-treat population). Third, the effect of mepolizumab, as compared with placebo, on the annual rate of moderate or severe exacerbations treated with glucocorticoids (alone or in addition to antibiotics), as well as those treated with antibiotics alone, was assessed (in a combined population that included the METREX overall modified intention-to-treat population and the METREO modified intention-to-treat population).

The safety end points included adverse events

and serious adverse events. Immunogenicity was also assessed.

STATISTICAL ANALYSIS

For the assessment of the effect of mepolizumab in patients with an eosinophilic phenotype in METREX, we estimated that 400 patients (200 patients in each group) would be required to provide the trial with 90% power to detect a 35% lower rate of moderate or severe exacerbations in the mepolizumab group (on the basis of an expected rate of 2.0 per year in the placebo group vs. 1.3 per year in the mepolizumab group) at a two-sided alpha level of 4%. An additional 400 patients (200 patients in each group) with noneosinophilic COPD were also included in the trial, which provided the trial with 90% power to detect a 30% between-group difference at a two-sided alpha level of 1% in the overall modified intention-to-treat population. In METREO, an estimated 660 patients (220 patients in each group) were expected to provide the trial with 90% power to detect a 35% between-group difference in the rate of moderate or severe exacerbations (on the basis of an expected rate of 2.0 per year in the placebo group vs. 1.3 per year in each mepolizumab group) at a two-sided alpha level of 5%.

The multiplicity of comparisons within each trial was addressed with the use of prespecified multiple-testing procedures. For METREX, the alpha was split between the primary comparison in the modified intention-to-treat population with an eosinophilic phenotype (alpha, 4%) and the overall modified intention-to-treat population (alpha, 1%). For METREO, a Hochberg testing procedure was specified to control for the multiple comparisons of each mepolizumab dose versus placebo. For both trials, a prespecified order of testing for the primary and secondary end points was applied (further details are provided in the Supplementary Appendix).

In both trials, the annual rates of moderate or severe exacerbations and of exacerbations that led to emergency department visits or hospitalization were compared between each dose group and the placebo group with the use of a negative binomial model with covariates of smoking status (current smoker vs. nonsmoker or former smoker), number of moderate or severe exacerbations in the previous year (≤ 2 , 3, or ≥ 4 , as an ordinal variable), baseline disease severity (as the percentage of the predicted FEV₁ after bron-

chodilator use), and geographic region. In addition, the natural log of time was included as an offset variable. The time to the first moderate or severe exacerbation was analyzed with the use of a Cox proportional-hazards model including the same covariates as for the primary end point. Continuous end points were analyzed with a mixed-model repeated-measures analysis with adjustment for baseline value, smoking status, and geographic region and including terms for an interaction between trial visit and baseline value and for an interaction between trial visit and trial group.

In both trials, safety was assessed in all patients who underwent randomization and received one or more doses of mepolizumab or placebo; the analysis was conducted according to the actual trial agent received for more than 50% of the injections administered. In METREX, safety was also assessed in the safety population with an eosinophilic phenotype (same eosinophil criteria as the modified intention-to-treat population with an eosinophilic phenotype) and the safety population without an eosinophilic phenotype (same eosinophil criteria as the modified intention-to-treat population without an eosinophilic phenotype; eosinophil count, <150 per cubic millimeter at screening and no evidence of ≥ 300 per cubic millimeter in the previous year).

For both trials, data provided by patients who continued in the trial after discontinuation of the randomly assigned trial regimen were included in the analyses of the efficacy end points to provide a treatment policy estimate (i.e., an estimate of the effect of mepolizumab both during and after treatment) in the intention-to-treat population. The analysis of the primary end point used a negative binomial model that assumes missing data to be missing at random; sensitivity analyses to assess departures from this assumption were performed. Missing data for patients who withdrew early from the trial were imputed for the period after withdrawal from the trial and up to expected trial completion with the use of a jump-to-reference approach,²² in which the rate of exacerbations among patients who received mepolizumab was shifted to that in the placebo group. In addition, we used an approach whereby the imputations of missing data were based on the data collected after discontinuation of the trial regimen in each trial group (see the Supplementary Appendix).

Further details regarding sample-size estimation and multiple-testing procedures are provided in the Supplementary Appendix. All analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENT POPULATION

In METREX, patients were recruited from April 2014 through November 2015, with follow-up continuing until mid-January 2017. In total, 1161 patients were enrolled, 837 of whom underwent randomization and 836 of whom received at least one dose of mepolizumab or placebo (1 patient who was randomly assigned to the placebo group did not receive any dose). The modified intention-to-treat population with an eosinophilic phenotype, modified intention-to-treat population without an eosinophilic phenotype, and overall modified intention-to-treat population included 462, 374, and 836 patients, respectively. The percentage of patients who discontinued the trial regimen was higher in the placebo group than in the mepolizumab group in both the modified intention-to-treat population with an eosinophilic phenotype (19% vs. 13%) and the modified intention-to-treat population without an eosinophilic phenotype (22% vs. 19%) (Fig. 1).

In METREO, patients were recruited from April 2014 through November 2015, with follow-up continuing until mid-January 2017. In total, 1071 patients were enrolled, 675 of whom underwent randomization and 674 of whom received at least one dose of mepolizumab or placebo (1 patient who was randomly assigned to the 300-mg mepolizumab group did not receive any dose). The modified intention-to-treat population included 674 patients. The percentage of patients who discontinued the trial regimen was higher in the placebo group than in either mepolizumab group in the modified intention-to-treat population (25% vs. 12% [100 mg] and 19% [300 mg]) (Fig. 2).

In both trials, the numbers of patients were balanced among the trial groups (Figs. 1 and 2). In both trials, 94% or more of patients had GOLD group D COPD (i.e., ≥ 2 exacerbations in total, or ≥ 1 exacerbation leading to hospitalization, in the previous year, plus either a modified Medical Research Council Dyspnea Scale score of ≥ 2 [scores range from 0 to 4, with higher scores indicating more severe dyspnea] or a CAT score

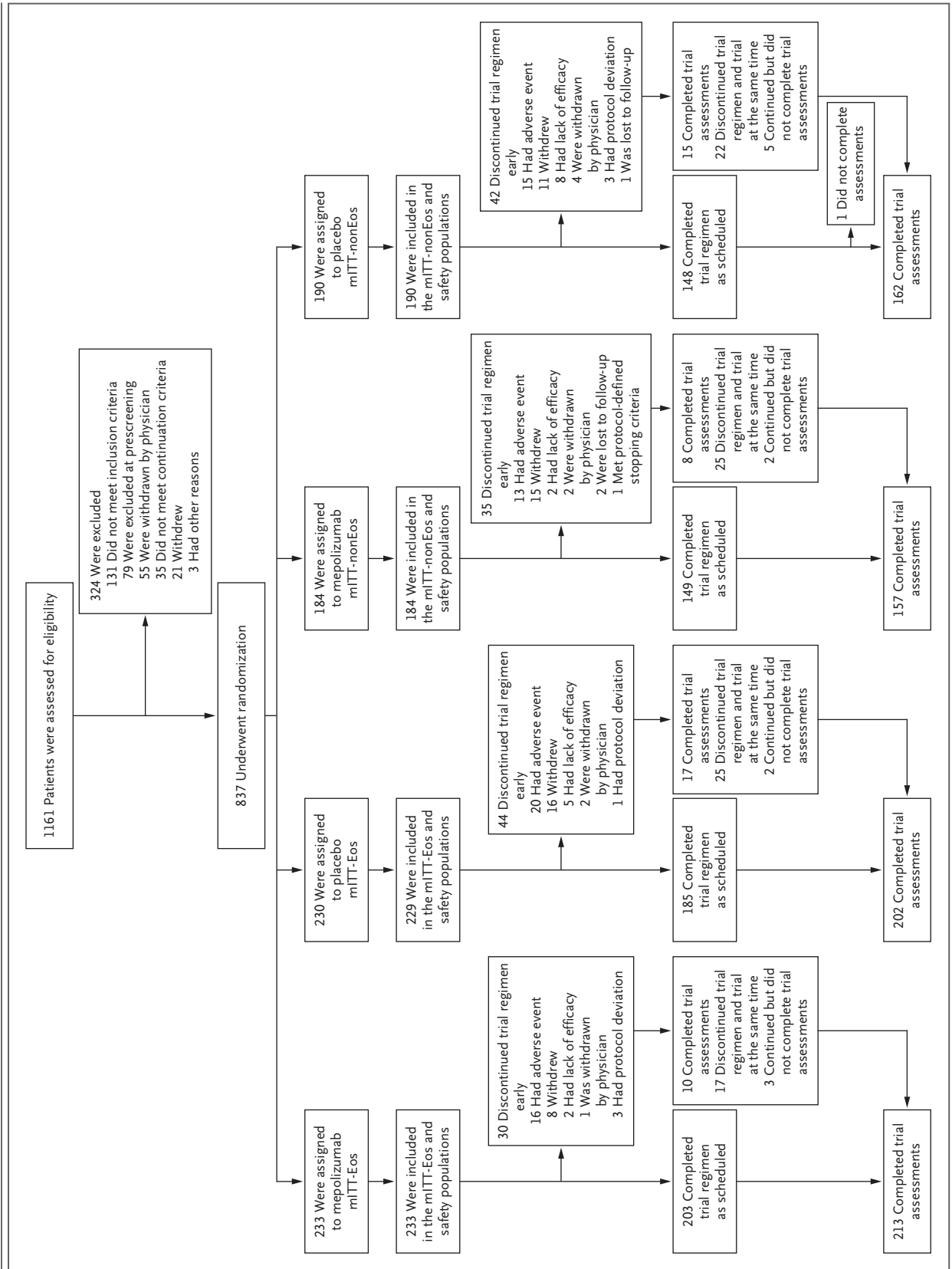


Figure 1 (facing page). Enrollment, Randomization, and Follow-up in METREX.

The METREX overall modified intention-to-treat population included patients who received at least one dose of mepolizumab or placebo; within this population, the METREX modified intention-to-treat population with an eosinophilic phenotype (mITT-Eos) included patients with an eosinophil count of at least 150 per cubic millimeter at screening or at least 300 per cubic millimeter within the previous year, and the modified intention-to-treat population without an eosinophilic phenotype (mITT-nonEos) included all other patients.

of ≥ 10). The characteristics of the patients are shown in Table 1, and in Table S1 in the Supplementary Appendix.

EXACERBATIONS*Primary End Point*

The difference between the trial groups with regard to the primary end point was significant in METREX but not in METREO. In the modified intention-to-treat population with an eosinophilic phenotype in METREX, the mean annual rate of moderate or severe exacerbations in the mepolizumab group was 1.40 per year, as compared with 1.71 per year in the placebo group (rate ratio, 0.82; 95% confidence interval [CI], 0.68 to 0.98; adjusted $P=0.04$) (Fig. 3A and Table 2). The corresponding rates in the overall modified intention-to-treat population did not differ significantly (1.49 and 1.52 per year, respectively) (Fig. 3B and Table 2). In METREO, the mean annual rate of moderate or severe exacerbations was 1.19 per year in the 100-mg mepolizumab group and 1.27 per year in the 300-mg mepolizumab group, as compared with 1.49 per year in the placebo group (rate ratio [100 mg vs. placebo], 0.80; 95% CI, 0.65 to 0.98; adjusted $P=0.07$; rate ratio [300 mg vs. placebo], 0.86; 95% CI, 0.70 to 1.05; adjusted $P=0.14$) (Fig. 3C and Table 2). Because the results in METREO with regard to the primary end point were not significant, none of the results for secondary end points were significant, in accordance with the prespecified multiple-testing strategy.

Secondary End Points

In METREX, the time to the first moderate or severe exacerbation was significantly longer with mepolizumab than with placebo in the modified intention-to-treat population with an eosinophilic

phenotype (Kaplan–Meier median time to first moderate or severe exacerbation, 192 vs. 141 days; hazard ratio, 0.75; 95% CI, 0.60 to 0.94; adjusted $P=0.04$) but not in the overall modified intention-to-treat population (Fig. 4 and Table 2, and Table S2 in the Supplementary Appendix). No significant differences between the mepolizumab group and the placebo group in the annual rate of exacerbations leading to an emergency department visit or hospitalization were found in either the intention-to-treat population with an eosinophilic phenotype or the overall intention-to-treat population (Table 2).

In METREO, after adjustment for multiplicity, no significant benefit of mepolizumab as compared with placebo was found with regard to any secondary end point (Table 2). The Kaplan–Meier median time to the first moderate or severe exacerbation in METREO was 267 days in the 100-mg mepolizumab group, 258 days in the 300-mg mepolizumab group, and 166 days in the placebo group (hazard ratio [100 mg mepolizumab vs. placebo], 0.82; 95% CI, 0.64 to 1.04; adjusted $P=0.14$; hazard ratio [300 mg mepolizumab vs. placebo], 0.77; 95% CI, 0.60 to 0.97; adjusted $P=0.14$) (Fig. 4C and Table 2). The mean annual rate of exacerbations leading to an emergency department visit or hospitalization in the 100-mg mepolizumab group, 0.17 per year, was not significantly lower than that in the placebo group, 0.28 per year; the rate in the 300-mg mepolizumab group, 0.23 per year, was also not significantly lower than that in the placebo group (rate ratio [100 mg mepolizumab vs. placebo], 0.59; 95% CI, 0.35 to 0.98; adjusted $P=0.14$; rate ratio [300 mg mepolizumab vs. placebo], 0.83; 95% CI, 0.51 to 1.34; adjusted $P=0.45$) (Table 2).

PATIENT-REPORTED OUTCOMES

In the METREX modified intention-to-treat population with an eosinophilic phenotype and overall modified intention-to-treat population, changes from baseline in measures of health-related quality of life (SGRQ total score and CAT scores) were similar between the trial groups at week 52, and there were no significant between-group differences in METREO (Table 2, and Fig. S2 in the Supplementary Appendix). The proportion of patients with SGRQ and CAT score responses did not differ significantly between the mepolizumab and placebo groups in METREX or METREO (Table S3 in the Supplementary Appendix).

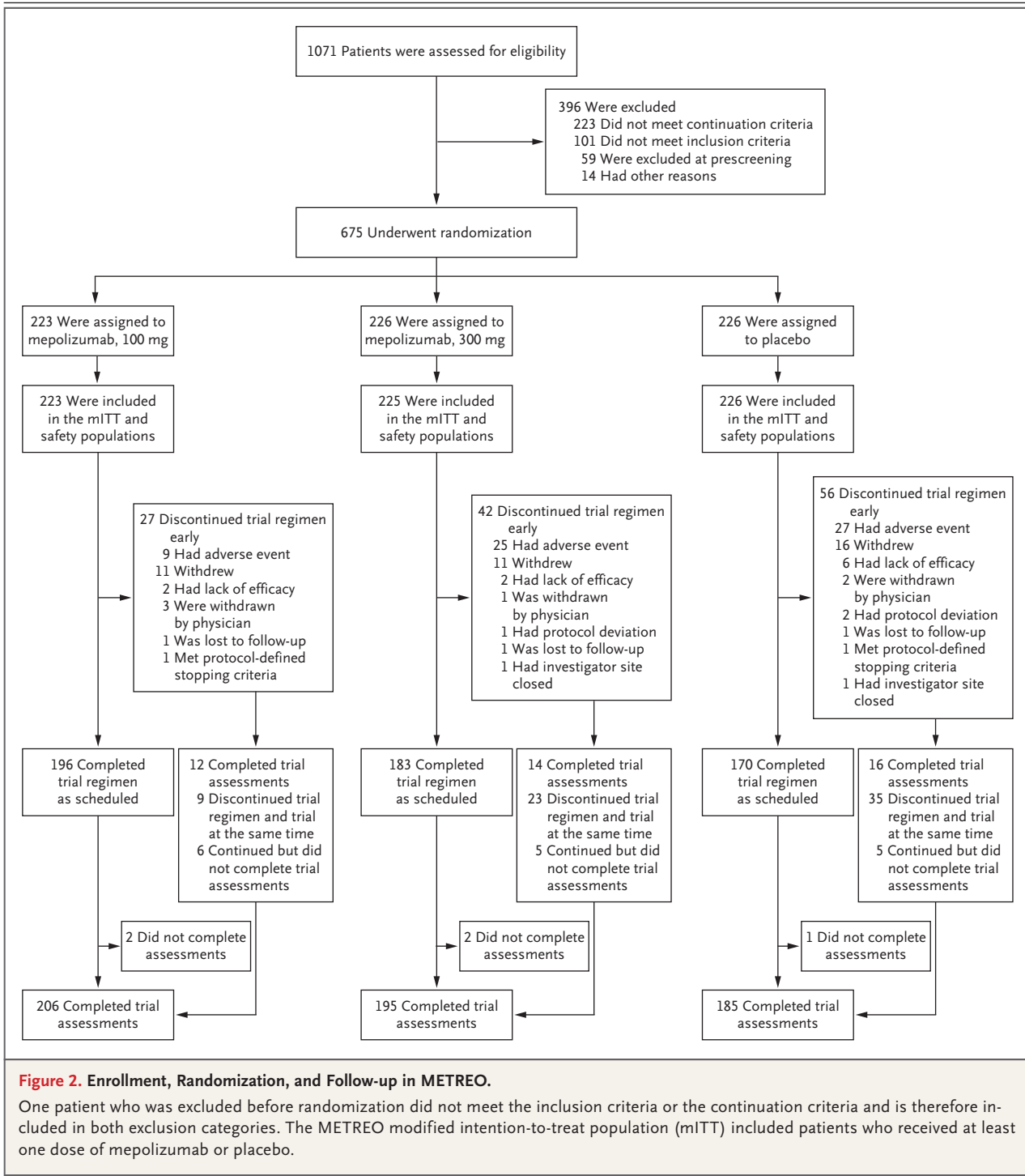


Figure 2. Enrollment, Randomization, and Follow-up in METREO.

One patient who was excluded before randomization did not meet the inclusion criteria or the continuation criteria and is therefore included in both exclusion categories. The METREO modified intention-to-treat population (mITT) included patients who received at least one dose of mepolizumab or placebo.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

| Characteristic | METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype† | | METREX Overall Modified Intention-to-Treat Population‡ | | METREO Modified Intention-to-Treat Population§ | |
|--|---|-------------------|--|-------------------|--|-------------------|
| | Mepolizumab, 100 mg (N = 233) | Placebo (N = 229) | Mepolizumab, 100 mg (N = 417) | Placebo (N = 419) | Mepolizumab, 100 mg (N = 223) | Placebo (N = 226) |
| Age — yr | 65±8 | 65±9 | 66±9 | 65±9 | 65±9 | 66±9 |
| Female sex — no. (%) | 84 (36) | 79 (34) | 160 (38) | 156 (37) | 91 (41) | 70 (31) |
| Smoking history — no. (%) | | | | | | |
| Current smoker | 62 (27) | 72 (31) | 106 (25) | 116 (28) | 55 (25) | 63 (28) |
| Former smoker | 164 (70) | 146 (64) | 295 (71) | 279 (67) | 163 (73) | 161 (71) |
| Duration of COPD — yr | 9.5±6.7 | 9.5±6.3 | 9.2±6.2 | 9.4±6.5 | 8.4±6.5 | 8.8±5.9 |
| Moderate or severe COPD exacerbations | | | | | | |
| No. in the 12 mo before screening | 2.6±1.3 | 2.5±1.2 | 2.5±1.2 | 2.5±1.2 | 2.7±1.4 | 2.6±1.4 |
| One or more requiring hospitalization in 12 mo before screening — no. (%)¶ | 81 (35) | 79 (34) | 137 (33) | 132 (32) | 76 (34) | 87 (38) |
| GOLD group D — no. (%) | 219 (94) | 218 (95) | 397 (95) | 399 (95) | 211 (95) | 216 (96) |
| Postbronchodilator lung function at screening | | | | | | |
| FEV ₁ — liters | 1.23±0.47 | 1.22±0.48 | 1.21±0.47 | 1.20±0.47 | 1.28±0.47 | 1.28±0.49 |
| Percent of predicted FEV ₁ | 45.0±15.0 | 43.4±14.5 | 44.9±15.3 | 43.7±14.5 | 47±15 | 46±15 |
| FVC — liters | 2.71±0.85 | 2.75±0.81 | 2.66±0.85 | 2.68±0.81 | 2.77±0.78 | 2.89±0.85 |
| FEV ₁ :FVC ratio | 0.5±0.1 | 0.4±0.1 | 0.5±0.1 | 0.5±0.1 | 0.5±0.1 | 0.4±0.1 |
| Blood eosinophil count ≥150/mm ³ at screening — no. (%) | 220 (94) | 228 (>99) | 220 (53) | 228 (54) | 182 (82) | 184 (81) |
| Geometric mean blood eosinophil count (SD on a log _e scale) — cells/mm ³ | 260 (0.438) | 290 (0.558) | 260 (0.438) | 290 (0.558) | 300 (0.520) | 310 (0.515) |
| Blood eosinophil count ≥300/mm ³ in 12 months before screening — no. (%) | 44 (19) | 38 (17) | 44 (11) | 38 (9) | 101 (45) | 108 (48) |
| Geometric mean blood eosinophil count (SD on a log _e scale) — cells/mm ³ | 200 (0.981) | 370 (0.699) | 200 (0.981) | 370 (0.699) | 170 (1.058) | 180 (1.108) |
| Health-related quality of life | | | | | | |
| SGRQ total score** | 54.1±17.5 | 56.5±15.8 | 54.5±17.3 | 55.3±16.6 | 51.9±17.3 | 52.9±15.9 |
| CAT score†† | 18.5±7.8 | 19.6±7.7 | 18.6±7.6 | 19.1±7.7 | 18.7±7.4 | 19.4±7.5 |

* Plus-minus values are means ±SD. None of the characteristics differed significantly among the trial groups, with the exception of sex (P=0.03) (analyses performed post hoc). COPD denotes chronic obstructive pulmonary disease, FEV₁ forced expiratory volume in 1 second, FVC forced vital capacity, and GOLD Global Initiative for Chronic Obstructive Lung Disease.

† The METREX modified intention-to-treat population with an eosinophilic phenotype included patients who received at least one dose of mepolizumab or placebo and had an eosinophil count of 150 per cubic millimeter or higher at screening or 300 per cubic millimeter or higher within the previous year.

‡ The METREX overall modified intention-to-treat population included patients who received at least one dose of mepolizumab or placebo.

§ The METREO modified intention-to-treat population included patients who received at least one dose of mepolizumab or placebo.

¶ Hospitalizations in the intensive care unit (ICU) and hospitalizations outside the ICU are included.

|| Patients with GOLD group D COPD have had at least two exacerbations in total, or at least one exacerbation leading to hospitalization, in the previous year and have either a modified Medical Research Council Dyspnea Scale score of 2 or higher (scores range from 0 to 4, with higher scores indicating more severe dyspnea) or a COPD Assessment Test (CAT) score of 10 or higher.

** St. George's Respiratory Questionnaire (SGRQ) total score is determined by the SGRQ-COPD questionnaire; scores range from 0 to 100 points, with higher scores indicating worse health status (minimum clinically important difference, 4-point decrease from baseline).

†† CAT scores range from 0 to 40 points, with higher scores indicating greater disease effects; minimum clinically important difference, 2-point decrease from baseline.

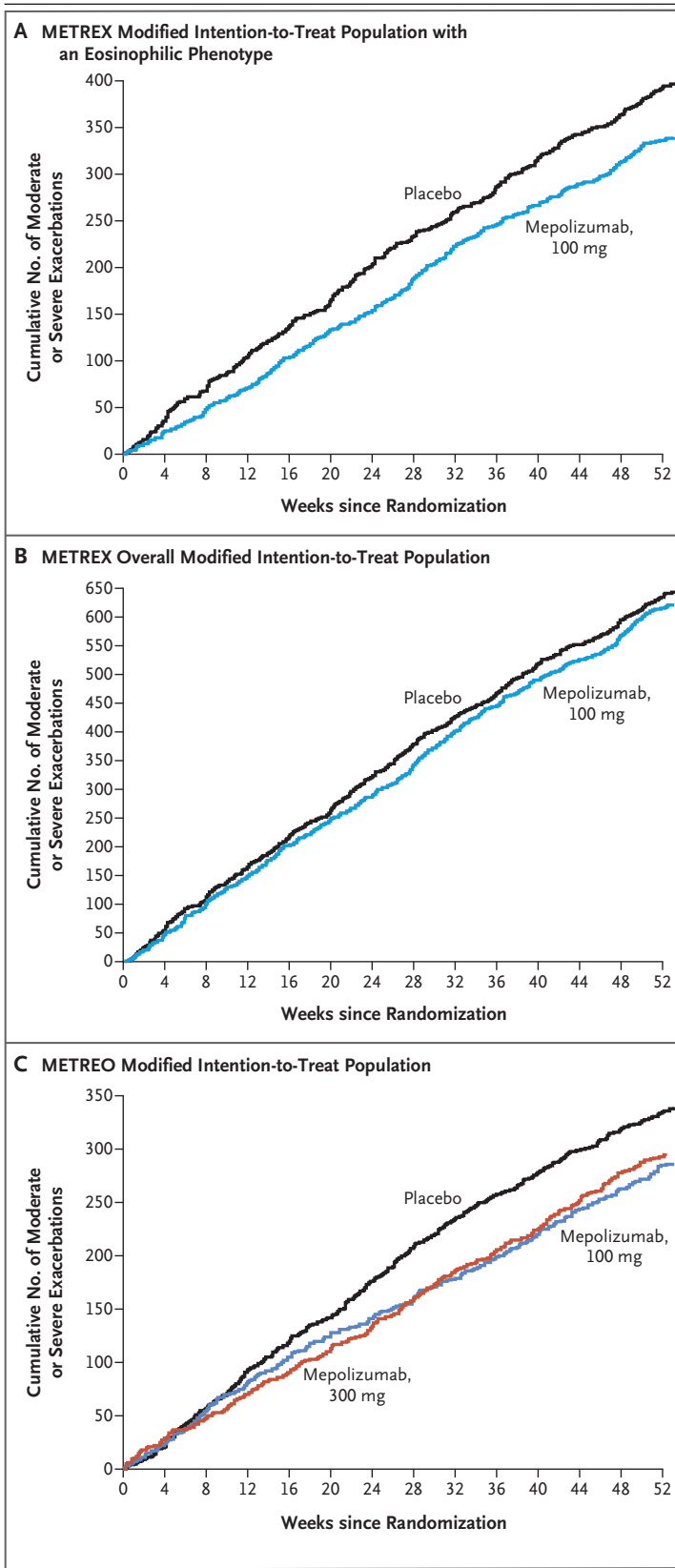


Figure 3. Cumulative Incidence of Moderate or Severe Exacerbations.

Numbers of moderate or severe exacerbations were tallied in each trial group during the 52-week trial period and plotted over time.

ADDITIONAL ANALYSES

A prespecified meta-analysis including data from the METREX modified intention-to-treat population with an eosinophilic phenotype and the METREO modified intention-to-treat population showed lower annual rates of moderate or severe exacerbations in association with mepolizumab than with placebo; these differences were greater among patients with higher blood eosinophil count categories and thresholds at screening (Fig. 5, and Fig. S3 in the Supplementary Appendix). This analysis also showed higher annual exacerbation rates in association with higher blood eosinophil count categories at screening in the placebo group (Fig. S4 in the Supplementary Appendix). A post hoc meta-analysis that included patients with blood eosinophil counts of 300 per cubic millimeter or higher at screening or during the previous 12 months showed that the mean annual rate of moderate or severe exacerbations was 23% lower in the 100-mg mepolizumab group than in the placebo group (rate ratio, 0.77; 95% CI, 0.63 to 0.94) (Fig. S5 in the Supplementary Appendix).

Sensitivity analyses were performed for the primary end point results. Missing data within these trials were limited, since patients were encouraged to provide data after discontinuation of the randomly assigned trial regimen (mepolizumab or placebo). For the primary end point, the amount of missing data was 8% or less (METREX modified intention-to-treat population with an eosinophilic phenotype: 3% of the scheduled years of follow-up missing in the mepolizumab group and 6% missing in the placebo group; METREO modified intention-to-treat population: 3% missing in the 100-mg mepolizumab group, 5% missing in the 300-mg mepolizumab group, and 8% missing in the placebo group). Missing-data sensitivity analyses showed little change in the differences in rates between mepolizumab and placebo that were seen with the primary analysis model, indicating a robustness of the primary efficacy results to departures from the assumptions regarding missing

Table 2. Primary and Secondary Efficacy End Points.*

| End Point | METREX Modified Intention-to-Treat Population with an Eosinophilic Phenotype | | METREX Overall Modified Intention-to-Treat Population | | METREO Modified Intention-to-Treat Population | |
|--|--|---------------------|---|---------------------|--|-----------------------------------|
| | Mepolizumab, 100 mg (N=233) | Placebo (N=229) | Mepolizumab, 100 mg (N=417) | Placebo (N=419) | Mepolizumab, 100 mg (N=223) | Mepolizumab, 300 mg (N=225) |
| Primary end point: moderate or severe exacerbations | | | | | | |
| Mean annual rate — events/yr† | 1.40 | 1.71 | 1.49 | 1.52 | 1.19 | 1.49 |
| Rate ratio vs. placebo (95% CI) | 0.82 (0.68 to 0.98) | — | 0.98 (0.85 to 1.12) | — | 0.80 (0.65 to 0.98) | 0.86 (0.70 to 1.05) |
| Adjusted P value | 0.04 | — | >0.99 | — | 0.07 | 0.14 |
| Secondary end points | | | | | | |
| Time to first moderate or severe exacerbation | | | | | | |
| Kaplan–Meier median time to first moderate or severe exacerbation — days | 192 | 141 | 194 | 176 | 267 | 258 |
| Estimated risk of a moderate or severe exacerbation by wk 52 — % (95% CI)‡ | 64.6 (58.3 to 70.8) | 75.2 (69.3 to 80.8) | 65.5 (60.7 to 70.1) | 71.2 (66.6 to 75.6) | 57.9 (51.5 to 64.5) | 58.8 (52.4 to 65.3) |
| Hazard ratio vs. placebo (95% CI) | 0.75 (0.60 to 0.94) | — | 0.89 (0.75 to 1.05) | — | 0.82 (0.64 to 1.04) | 0.77 (0.60 to 0.97) |
| Adjusted P value | 0.04 | — | >0.99 | — | 0.14§ | 0.14§ |
| Exacerbations leading to emergency department visit or hospitalization | | | | | | |
| Mean annual rate — events/yr† | 0.30 | 0.26 | 0.29 | 0.26 | 0.17 | 0.23 |
| Rate ratio vs. placebo (95% CI) | 1.16 (0.77 to 1.75) | — | 1.10 (0.81 to 1.49) | — | 0.59 (0.35 to 0.98) | 0.83 (0.51 to 1.34) |
| Adjusted P value | 0.60 | — | >0.99 | — | 0.14§ | 0.45§ |
| SGRQ total score at wk 52 | | | | | | |
| Change from baseline | -2.8±1.1 | -3.0±1.1 | -3.2±0.8 | -4.0±0.8 | -5.0±1.0 | -3.3±1.0 |
| Difference vs. placebo (95% CI) | 0.2 (-2.8 to 3.2) | — | 0.7 (-1.5 to 2.9) | — | -1.8 (-4.5 to 0.8) | -0.1 (-2.8 to 2.6) |
| Adjusted P value | >0.99 | — | >0.99 | — | 0.45§ | 0.93§ |
| CAT score at wk 52 | | | | | | |
| Change from baseline | -0.8±0.5 | 0.0±0.5 | -1.0±0.3 | -0.4±0.4 | -1.6±0.42 | -0.8±0.42 |
| Difference vs. placebo (95% CI) | -0.8 (-2.0 to 0.5) | — | -0.6 (-1.5 to 0.4) | — | -1.1 (-2.3 to 0.0) | -0.4 (-1.5 to 0.8) |
| Adjusted P value | >0.99 | — | >0.99 | — | 0.93§ | 0.93§ |

* Plus-minus values are least-squares means ±SE.

† The mean rate is an estimate from the analysis model.

‡ Values were determined with the use of Kaplan–Meier analysis.

§ The results were not significant, in accordance with the prespecified multiple-testing procedure.

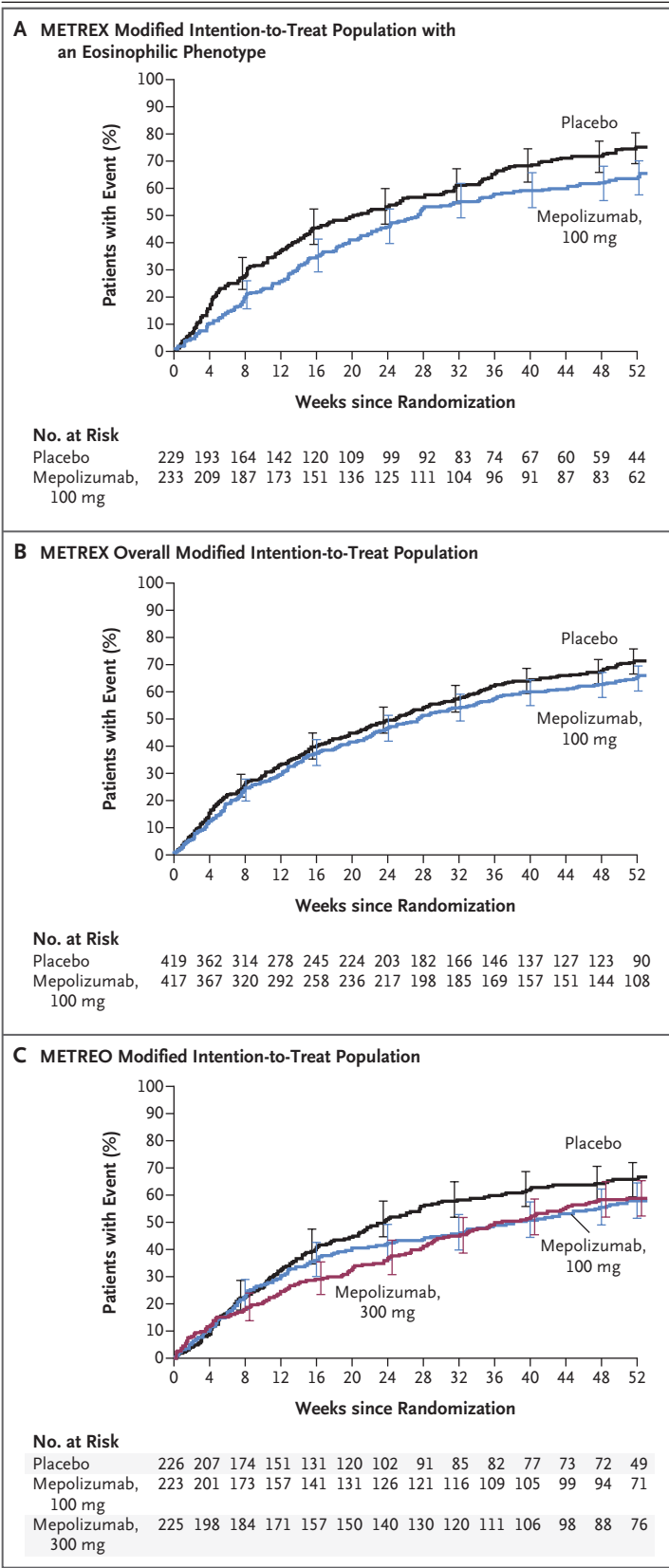


Figure 4. Time to First Moderate or Severe Exacerbation.

Estimates of the cumulative proportion of patients in each trial group with a moderate or severe exacerbation are shown, with a Kaplan–Meier cumulative incidence curve. I bars represent 95% confidence intervals.

data (see the Supplementary Appendix). Details of other prespecified and post hoc analyses are provided in Figures S6 through S10 and Tables S5 through S7 in the Supplementary Appendix.

SAFETY

In both trials, all patients who received at least one dose of mepolizumab or placebo were included in the respective trial safety populations. The incidence of adverse events and serious adverse events was similar between the trial groups in METREX and METREO (Table 3). Deaths occurred (either during the treatment period or after discontinuation of the trial regimen) in 4% of patients in METREX (16 of 417 patients in the mepolizumab group and 17 of 419 patients in the placebo group) and in 3% of patients in METREO (4 of 223 patients in the 100-mg mepolizumab group, 8 of 225 patients in the 300-mg mepolizumab group, and 9 of 226 patients in the placebo group) (Table 3). In both trials, the most commonly reported adverse events that occurred during the treatment period were exacerbations or worsening of COPD, nasopharyngitis, headache, and pneumonia (Table S4 in the Supplementary Appendix). In METREX, systemic reactions and injection-site reactions occurred during the treatment period in 2% and 3% of patients, respectively, in the 100-mg mepolizumab group; in METREO, systemic reactions and injection-site reactions occurred in 1% and 3% of patients, respectively, in the 100-mg mepolizumab group and in 2% and 5% of patients, respectively, in the 300-mg mepolizumab group (Table 3). Similar incidences of these events occurred in the placebo groups (2% and 3%, respectively, in METREX, and 2% and 4%, respectively, in METREO).

In METREX, antidrug antibodies were detected in 4% of patients (14 of 395) in the mepolizumab group and less than 1% of patients (2 of 395) in the placebo group. In METREO, antidrug antibodies were detected in 6% of patients (13 of 220) in the 100-mg mepolizumab group, 2% of patients (4 of 220) in the 300-mg mepolizumab group, and 1% of patients (3 of 217) in the pla-

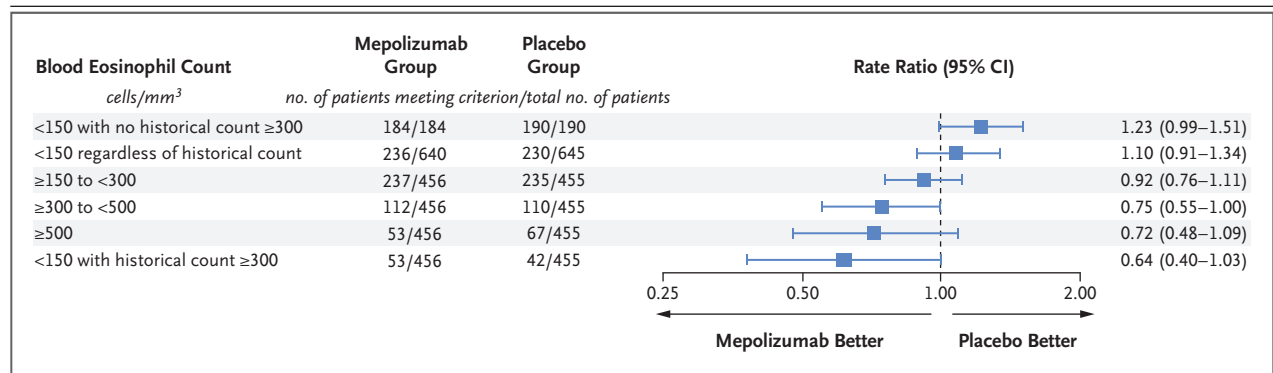


Figure 5. Moderate or Severe Exacerbations According to Blood Eosinophil Count Category at Screening.

Results shown are for the 100-mg mepolizumab group versus the placebo group and are from a meta-analysis of data from the METREX and METREO modified intention-to-treat populations. The eosinophil count category of less than 150 per cubic millimeter with no historical count of 300 per cubic millimeter or higher is from the METREX modified intention-to-treat population without an eosinophilic phenotype. The category of less than 150 per cubic millimeter regardless of historical count included patients from the post hoc analysis of the METREX overall modified intention-to-treat population and the METREO modified intention-to-treat population who had evidence of an eosinophil count of 300 per cubic millimeter or higher in the previous year. The remaining analyses are from a prespecified meta-analysis of data from the METREX modified intention-to-treat population with an eosinophilic phenotype and the METREO modified intention-to-treat population.

cebo group. No neutralizing antidrug antibodies were found in any patient who received mepolizumab in either trial. The safety profile of mepolizumab was similar to that of placebo in METREO and in both the safety population with an eosinophilic phenotype and the safety population without an eosinophilic phenotype in METREX.

DISCUSSION

In METREX and METREO, we investigated the efficacy of mepolizumab in patients with COPD and an eosinophilic phenotype who had a history of frequent exacerbations despite receiving maximal guideline-recommended inhaled glucocorticoid-based triple maintenance therapy. In METREX, mepolizumab was evaluated in patients who met our blood eosinophil criteria for eosinophilic COPD. In METREO, the effect of the higher, 300-mg dose of mepolizumab was assessed in patients with an eosinophilic phenotype. Overall, patients with an eosinophilic phenotype who were treated with 100 mg of mepolizumab had an annual rate of moderate or severe exacerbations (the primary end point) that was consistently 18% to 20% lower than that among patients who received placebo. There was no evidence of greater effects of mepolizumab at higher doses. With regard to the secondary end

points, the time to the first moderate or severe exacerbation was significantly longer in association with mepolizumab than with placebo in METREX but not in METREO. There were no significant differences between mepolizumab and placebo with regard to the remaining secondary end points of exacerbations leading to an emergency department visit or hospitalization, SGRQ total score, and CAT score in any patient population in either trial. In a prespecified meta-analysis involving patients from both trials, the effects of mepolizumab on the primary end point were greater among patients with higher blood eosinophil counts, similar to what has been found in severe eosinophilic asthma.^{12,23} The incidence of adverse events in association with mepolizumab was similar to that with placebo. These findings suggest that eosinophilic airway inflammation contributes to COPD exacerbations and that the use of mepolizumab directed by blood eosinophil counts might represent a precision-medicine approach to the management of COPD in selected patients who continue to have exacerbations despite inhaled glucocorticoid-based triple maintenance therapy.

These trials are important because we have identified a potential biomarker that may allow specific targeting of a subpopulation of patients with COPD in order to achieve a meaningful therapeutic effect. In METREX, we investigated the

Table 3. Adverse Events.

| Event | METREX Safety Population with an Eosinophilic Phenotype [‡] | | | METREX Overall Safety Population [†] | | METREO Safety Population [‡] | |
|---|--|-----------------|-----------------------------|---|-----------------------------|---------------------------------------|-----------------|
| | Mepolizumab, 100 mg (N=233) | Placebo (N=229) | Mepolizumab, 100 mg (N=417) | Placebo (N=419) | Mepolizumab, 100 mg (N=223) | Mepolizumab, 300 mg (N=225) | Placebo (N=226) |
| Adverse events [§] | <i>number of patients (percent)</i> | | | | | | |
| Any event | 190 (82) | 189 (83) | 332 (80) | 342 (82) | 191 (86) | 196 (87) | 185 (82) |
| Event leading to treatment discontinuation [¶] | 16 (7) | 20 (9) | 31 (7) | 35 (8) | 9 (4) | 25 (11) | 27 (12) |
| Event leading to withdrawal from trial | 7 (3) | 10 (4) | 18 (4) | 21 (5) | 7 (3) | 13 (6) | 18 (8) |
| Any serious adverse event [§] | 65 (28) | 80 (35) | 115 (28) | 131 (31) | 57 (26) | 60 (27) | 68 (30) |
| Any death | 6 (3) | 8 (3) | 16 (4) | 17 (4) | 4 (2) | 8 (4) | 9 (4) |
| Systemic or local site reaction during treatment period | | | | | | | |
| Systemic reaction | 3 (1) | 4 (2) | 7 (2) | 9 (2) | 3 (1) | 5 (2) | 4 (2) |
| Injection-site reaction | 7 (3) | 7 (3) | 12 (3) | 12 (3) | 6 (3) | 11 (5) | 10 (4) |

* The METREX safety population with an eosinophilic phenotype included patients with eosinophil counts of 150 per cubic millimeter or higher at screening or 300 per cubic millimeter or higher within the previous year.
[†] The METREX overall safety population included patients who received at least one dose of mepolizumab or placebo.
[‡] The METREO safety population included patients who received at least one dose of mepolizumab or placebo.
[§] Events (including fatal events) that occurred during the treatment period or after discontinuation of the trial regimen are shown.
[¶] P<0.05 for the between-group differences in METREO (analysis was performed post hoc).
^{||} Systemic or local site reactions were identified by means of an electronic case-report form that was designed for the collection of data on systemic reactions or local injection-site reactions. There were no reports of anaphylaxis that were considered by the investigator to represent a systemic reaction meeting Sampson's criteria for anaphylaxis. One patient in the METREO 300-mg mepolizumab group (modified intention-to-treat population) reported an anaphylactic reaction to diclofenac; the reaction resolved, and the patient continued the trial regimen.

effects of mepolizumab treatment in patients with blood eosinophil counts of 150 per cubic millimeter or higher at screening or of 300 per cubic millimeter or higher during the previous year, as well as in patients who did not meet those criteria. The availability of these data, together with the findings from METREO, provide considerable power for the investigation of variables associated with treatment efficacy. Our prespecified meta-analysis of the primary end point according to blood eosinophil count category and threshold at screening showed that the benefit of mepolizumab versus placebo with regard to exacerbation rates was greater when blood eosinophil counts at screening were higher. In the placebo group, exacerbation rates were lowest among patients in the METREX modified intention-to-treat population without an eosinophilic phenotype who had blood eosinophil counts of less than 150 per cubic millimeter and had no evidence of historical counts of 300 per cubic millimeter or higher. This suggests that both naturally and medically induced reductions in eosinophil counts are associated with lower rates of exacerbations, particularly exacerbations that are treated with systemic glucocorticoids. The progressively greater exacerbation-related treatment responses associated with mepolizumab versus placebo, particularly at screening eosinophil counts of 300 per cubic millimeter or higher, are similar to those in severe asthma and those found in a previous small study of benralizumab treatment in COPD.^{12,13,24} Beyond biologic therapy, the association of blood eosinophil counts of more than 150 to 200 per cubic millimeter with exacerbation frequency and responses to glucocorticoids suggests that eosinophil counts may be used as a stratifying tool for patients with COPD with respect to prognosis and treatment effect.²⁴⁻²⁸ Although we have not fully characterized the performance characteristics of blood eosinophil counts as a biomarker for identifying patients with COPD who continue to have exacerbations despite already receiving maximal treatment, METREX and METREO provide data sets for the evaluation of the relationship between screening blood eosinophil counts, exacerbation type, and response to mepolizumab.

There were no significant improvements from baseline in association with mepolizumab with regard to lung-function end points in either trial. This finding differs from those of a previous

phase 2 trial of benralizumab, which showed a significantly greater improvement from baseline in prebronchodilator FEV₁ (by approximately 200 ml) with benralizumab than with placebo.²⁴ It is unknown whether the difference in outcomes between the current trial and the benralizumab trial is due to differences in the pharmacologic characteristics of the drugs or in the respective trial populations.

The rate of adverse events associated with mepolizumab was similar to that with placebo. The incidence of pneumonia in both trials was higher (9 to 11%) than in previous trials involving patients with COPD and a history of moderate or severe exacerbations (2 to 7%),²⁹ although no significant differences were observed between mepolizumab and placebo among patients with or without an eosinophilic phenotype. Inhaled glucocorticoids have been shown to increase the risk of pneumonia in patients with COPD²⁹⁻³¹; therefore, the higher incidence of pneumonia may be due to the eligibility requirements in our trials, which included a population of patients who had frequent exacerbations while receiving high-dose inhaled glucocorticoids for 12 months or more before screening and for the duration of the trial.

The current trials were limited by several factors. There was the possibility of an unintended clinical-trial effect, as a result of increased adherence to inhaled medications; such an effect is suggested by the strikingly different rates of moderate or severe exacerbations in the year before the trial versus during the trial in the placebo group. A further limitation was that although patients with a current diagnosis of asthma and non-smokers with a history of asthma were excluded, information on certain baseline demographic characteristics that might potentially be valuable for identifying patients who are likely to have a response to the treatment — such as sinus or skin symptoms, a diagnosis of asthma-COPD overlap, or allergic history — was not available, nor was a detailed characterization of other systemic coexisting conditions, such as cardiac or renal disease, which may have been useful in determining which patients would be more or less likely to have a response to treatment. Whether these characteristics provide predictive information that could complement a blood eosinophil-based classification requires further study. In addition, the specific trigger factors of each exacerbation were

not captured within these trials, and previous treatment with oral glucocorticoids could have reduced the eosinophil count at trial entry, limiting the response to mepolizumab. Finally, because the number of events was small, we were unable to convincingly evaluate the effect of mepolizumab on severe exacerbations or mortality.

In conclusion, among patients with COPD who were already receiving maximal inhaled glucocorticoid–based triple inhaled maintenance therapy, mepolizumab resulted in lower rates of moderate or severe exacerbations than placebo and in

longer times to a first exacerbation, and the extent of these effects was related to blood eosinophil count. With the use of mepolizumab as a targeted treatment to reduce blood eosinophil counts, these trials show the importance of blood eosinophils in COPD exacerbations.

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APPENDIX

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REFERENCES

1. GOLD 2017: global strategy for the diagnosis, management and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease, 2017 (<http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/>).
2. Brightling CE, Monteiro W, Ward R, et al. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000;356:1480-5.
3. Singh D, Kolsum U, Brightling CE, Locantore N, Agusti A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014;44:1697-700.
4. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011;184:662-71.
5. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015;3:435-42.
6. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, Pavord ID. Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. *Eur Respir J* 2014;44:789-91.
7. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012;186:48-55.
8. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017;389:1919-29.
9. Mullerova H, Maskell J, Meeraus WH, Galkin D, Albers FC, Gait C. Characterization of COPD patients treated with inhaled triple therapy containing inhaled corticosteroids [ICS], long-acting beta2-agonists [LABA], and long-acting muscarinic antagonists [LAMA] in the UK. *Am J Respir Crit Care Med* 2017;195:A4986. abstract.
10. Hart TK, Cook RM, Zia-Amirhosseini P, et al. Preclinical efficacy and safety of mepolizumab (SB-240563), a humanized monoclonal antibody to IL-5, in cynomolgus monkeys. *J Allergy Clin Immunol* 2001;108:250-7.
11. Varricchi G, Bagnasco D, Borriello F, Heffler E, Canonica GW. Interleukin-5 pathway inhibition in the treatment of eosinophilic respiratory disorders: evidence and unmet needs. *Curr Opin Allergy Clin Immunol* 2016;16:186-200.
12. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
13. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
14. Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. *Lancet Respir Med* 2017;5:390-400.
15. Yancey S, Albers F, Gunsoy N, Harris S, Keene ON. Effect of mepolizumab on exacerbations in asthma patients with features common in COPD. *Am J Respir Crit Care Med* 2017;195:A4683. abstract.
16. Celli BR, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;23:932-46.
17. Jones PW. Interpreting thresholds for a clinically significant change in health

- status in asthma and COPD. *Eur Respir J* 2002;19:398-404.
18. Meguro M, Barley EA, Spencer S, Jones PW. Development and validation of an improved, COPD-specific version of the St. George Respiratory Questionnaire. *Chest* 2007;132:456-63.
19. Jones PW, Forde Y. St George's Respiratory Questionnaire for COPD Patients (SGRQ-C): manual. London: University of London, 2012 (http://www.healthstatus.sgu.ac.uk/SGRQ_download/sgrq-c-manual-april-2012.pdf).
20. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J* 2009;34:648-54.
21. Jones PW, Shahrour N, Nejjari C, et al. Psychometric evaluation of the COPD Assessment Test: data from the BREATHE study in the Middle East and North Africa region. *Respir Med* 2012;106:Suppl 2:S86-S99.
22. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. *Pharm Stat* 2014;13:258-64.
23. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med* 2016;4:549-56.
24. Brightling CE, Bleecker ER, Panettieri RA Jr, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. *Lancet Respir Med* 2014;2:891-901.
25. Pavord ID, Lettis S, Anzueto A, Barnes N. Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *Lancet Respir Med* 2016;4:731-41.
26. Siva R, Green RH, Brightling CE, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J* 2007;29:906-13.
27. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015;192:523-5.
28. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting β -2 agonist efficacy in COPD. *Thorax* 2016;71:118-25.
29. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med* 2013;1:210-23.
30. Calverley PMA, Stockley RA, Seemungal TAR, et al. Reported pneumonia in patients with COPD: findings from the INSPIRE study. *Chest* 2011;139:505-12.
31. Crim C, Calverley PM, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009;34:641-7.

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