

## ORIGINAL ARTICLE

## Triple Inhaled Therapy at Two Glucocorticoid Doses in Moderate-to-Very-Severe COPD

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## ABSTRACT

## BACKGROUND

Triple fixed-dose regimens of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting  $\beta_2$ -agonist (LABA) for chronic obstructive pulmonary disease (COPD) have been studied at single dose levels of inhaled glucocorticoid, but studies at two dose levels are lacking.

## METHODS

In a 52-week, phase 3, randomized trial to evaluate the efficacy and safety of triple therapy at two dose levels of inhaled glucocorticoid in patients with moderate-to-very-severe COPD and at least one exacerbation in the past year, we assigned patients in a 1:1:1:1 ratio to receive twice-daily inhaled doses of triple therapy (inhaled glucocorticoid [320  $\mu$ g or 160  $\mu$ g of budesonide], a LAMA [18  $\mu$ g of glycopyrrolate], and a LABA [9.6  $\mu$ g of formoterol]) or one of two dual therapies (18  $\mu$ g of glycopyrrolate plus 9.6  $\mu$ g of formoterol or 320  $\mu$ g of budesonide plus 9.6  $\mu$ g of formoterol). The primary end point was the annual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations, as analyzed in the modified intention-to-treat population with the use of on-treatment data only.

## RESULTS

The modified intention-to-treat population comprised 8509 patients. The annual rates of moderate or severe exacerbations were 1.08 in the 320- $\mu$ g-budesonide triple-therapy group (2137 patients), 1.07 in the 160- $\mu$ g-budesonide triple-therapy group (2121 patients), 1.42 in the glycopyrrolate-formoterol group (2120 patients), and 1.24 in the budesonide-formoterol group (2131 patients). The rate was significantly lower with 320- $\mu$ g-budesonide triple therapy than with glycopyrrolate-formoterol (24% lower: rate ratio, 0.76; 95% confidence interval [CI], 0.69 to 0.83;  $P < 0.001$ ) or budesonide-formoterol (13% lower: rate ratio, 0.87; 95% CI, 0.79 to 0.95;  $P = 0.003$ ). Similarly, the rate was significantly lower with 160- $\mu$ g-budesonide triple therapy than with glycopyrrolate-formoterol (25% lower: rate ratio, 0.75; 95% CI, 0.69 to 0.83;  $P < 0.001$ ) or budesonide-formoterol (14% lower: rate ratio, 0.86; 95% CI, 0.79 to 0.95;  $P = 0.002$ ). The incidence of any adverse event was similar across the treatment groups (range, 61.7 to 64.5%); the incidence of confirmed pneumonia ranged from 3.5 to 4.5% in the groups that included inhaled glucocorticoid use and was 2.3% in the glycopyrrolate-formoterol group.

## CONCLUSIONS

Triple therapy with twice-daily budesonide (at either the 160- $\mu$ g or 320- $\mu$ g dose), glycopyrrolate, and formoterol resulted in a lower rate of moderate or severe COPD exacerbations than glycopyrrolate-formoterol or budesonide-formoterol. (Funded by AstraZeneca, ETHOS ClinicalTrials.gov number, NCT02465567.)

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\*A complete list of the ETHOS trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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**T**REATMENT RECOMMENDATIONS FOR chronic obstructive pulmonary disease (COPD) involve a stepwise approach, in which treatments are added as necessary to control symptoms and reduce or eliminate exacerbations,<sup>1</sup> with an additional goal of reducing mortality from the disease. Triple therapy with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting  $\beta_2$ -agonist (LABA) was shown to lead to a lower risk of COPD exacerbations, a greater reduction in symptoms, and better lung function and health-related quality of life than dual therapies<sup>2-6</sup> and is recommended for patients who continue to have symptoms or exacerbations while receiving dual therapy with LAMA-LABA or inhaled glucocorticoid-LABA.<sup>1</sup>

Adverse events associated with inhaled glucocorticoids include pneumonia, bone fractures, and cataracts, for which the magnitude of risk may depend on the duration, dose, and type of inhaled glucocorticoid treatment.<sup>7-10</sup> Therefore, in a 52-week trial involving symptomatic patients with moderate-to-very-severe COPD and at least one exacerbation in the preceding year, we compared the efficacy and safety of two single-inhaler, triple fixed-dose combinations (i.e., budesonide at two different doses plus a LAMA and a LABA) with those of two dual therapies (LAMA-LABA and inhaled glucocorticoid-LABA).

## METHODS

### TRIAL DESIGN AND OVERSIGHT

The Efficacy and Safety of Triple Therapy in Obstructive Lung Disease (ETHOS) trial was a phase 3, randomized, double-blind, parallel-group trial conducted in 26 countries. The trial design has been published previously,<sup>11</sup> and the trial protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The protocol and informed consent form were approved by the appropriate institutional review board, independent ethics committee, or health authority; written informed consent was obtained from all patients before screening. An independent data monitoring committee and an independent clinical end-point committee reviewed safety data throughout the trial, including cardiovascular and cerebrovascular events, pneumonia, and cause-specific deaths.

The trial was designed by the sponsor (AstraZeneca) and the principal academic investigators. Data were collected by the clinical investigators and were analyzed by the employees of Everest Clinical Research Services and AstraZeneca. The first draft of the manuscript was written by a medical writer (funded by the sponsor) under the direction of the authors, in accordance with Good Publication Practice guidelines.<sup>12</sup> All the authors critically reviewed and provided feedback on all subsequent versions of the manuscript and, along with the sponsor, made the decision to submit the manuscript for publication. All the authors had access to the data, contributed to the interpretation of the data, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

### PATIENTS AND RANDOMIZATION

Eligible patients were 40 to 80 years of age and had symptomatic COPD (defined as a score of  $\geq 10$  on the COPD Assessment Test, on which scores range from 0 to 40, with higher scores indicating more symptoms; the minimum clinically important difference is 2 points); were receiving at least two inhaled maintenance therapies at the time of screening; had a postbronchodilator ratio of the forced expiratory volume in 1 second ( $FEV_1$ ) to the forced vital capacity of less than 0.7, with a postbronchodilator  $FEV_1$  of 25 to 65% of the predicted normal value; had a smoking history of at least 10 pack-years; and had a documented history of at least one moderate or severe COPD exacerbation (if their  $FEV_1$  was  $<50\%$  of the predicted normal value) or at least two moderate or at least one severe COPD exacerbation (if their  $FEV_1$  was  $\geq 50\%$  of the predicted normal value) in the year before screening. Patients who had a current diagnosis of asthma were excluded, but those who had had asthma in the past (e.g., as a child or adolescent) were eligible. Investigators were advised not to enroll patients who had received a diagnosis of active asthma within the past 5 to 10 years.

Eligible patients were randomly assigned in a 1:1:1:1 ratio to receive triple therapy (an inhaled glucocorticoid at one of two dose levels [budesonide, 160  $\mu\text{g}$  or 80  $\mu\text{g}$  per inhaler actuation], a LAMA [glycopyrrolate, 9  $\mu\text{g}$  per actuation], and a LABA [formoterol fumarate, 4.8  $\mu\text{g}$  per actuation]) or one of two dual therapies (LAMA-LABA

[glycopyrrolate, 9  $\mu$ g per actuation, and formoterol fumarate, 4.8  $\mu$ g per actuation] or inhaled glucocorticoid–LABA [budesonide, 160  $\mu$ g per actuation, and formoterol fumarate, 4.8  $\mu$ g per actuation]). All treatments were administered through identical metered-dose inhalers (Aerosphere, AstraZeneca) that were supplied by the sponsor. The patients received two doses per day over a 52-week period, and each dose consisted of two actuations (i.e., each dose of triple therapy delivered 320  $\mu$ g or 160  $\mu$ g of budesonide). Randomization was stratified according to exacerbation history (1 or  $\geq 2$  moderate or severe exacerbations), postbronchodilator FEV<sub>1</sub> (25 to <50% or 50 to <65% of the predicted normal value), blood eosinophil count (<150 or  $\geq 150$  cells per cubic millimeter), and country. Patients discontinued maintenance medications for COPD after the first screening visit (except for inhaled glucocorticoids if used before screening) and received scheduled treatment with ipratropium and as-needed treatment with albuterol during the screening period (1 to 4 weeks). Ipratropium and inhaled glucocorticoids were discontinued at the time of randomization.

#### END POINTS

The primary efficacy end point was the annual rate (the estimated mean number per patient per year) of moderate or severe COPD exacerbations. Moderate exacerbations were defined as those leading to treatment with systemic glucocorticoids, antibiotics, or both for at least 3 days; severe exacerbations were defined as those resulting in hospitalization or death. Secondary end points were defined according to the regional statistical approach used.<sup>11</sup> The secondary end points included in the statistical approach used in the United States were the time to the first moderate or severe COPD exacerbation, the change from baseline in average daily use of rescue medication over 24 weeks, the percentage of patients who had a St. George's Respiratory Questionnaire (SGRQ) response (defined as a decrease from baseline in the total score on the SGRQ of  $\geq 4$  points at week 24 [total scores range from 0 to 100, with lower scores indicating better health-related quality of life; the minimum clinically important difference is 4 points]), the annual rate of severe COPD exacerbations, and time to death from any cause. Details of the

secondary end points included in the statistical approach used outside the United States and of additional predefined end points are provided in Table S1 in the Supplementary Appendix, available at NEJM.org.

Subgroup analyses of the primary end point were also performed. Three subgroup analyses were prespecified for subgroups defined according to exacerbation history ( $\geq 2$  moderate or severe exacerbations in the preceding year), inhaled glucocorticoid use at the time of screening (using or not using inhaled glucocorticoids), and blood eosinophil count (<150 or  $\geq 150$  cells per cubic millimeter); the subgroup analysis according to blood eosinophil count was supplemented by a generalized additive model predicting exacerbation rates on the basis of eosinophil count as a continuous variable. One subgroup analysis was performed post hoc for a subgroup defined according to bronchodilator reversibility at the time of screening (with or without bronchodilator reversibility, defined as an increase in FEV<sub>1</sub> of  $\geq 12\%$  and  $\geq 200$  ml after administration of albuterol).

A comprehensive framework, as described in recent regulatory guidelines,<sup>13</sup> was used to provide clarity in the description of estimates of treatment effect, including the handling of potentially confounding events, such as treatment discontinuations. Each approach is denoted by a different “estimand” — a target of estimation that includes the analysis population and the end-point variable or variables and prespecifies the way in which these confounding events will be handled in the analysis. Although this terminology is relatively new, analyses that use an efficacy estimand are similar to those traditionally used in previous trials evaluating COPD exacerbations, as is the approach of using a treatment policy estimand to evaluate time to death. Most efficacy analyses were conducted in the modified intention-to-treat population (all patients who underwent randomization, received a trial treatment, and had postrandomization data obtained before discontinuation of treatment) with the use of an efficacy estimand, which included only data obtained from patients while they were receiving a trial treatment. There were two exceptions: the secondary analysis of the primary end point and the analysis of time to death. The secondary analysis of the primary

end point was conducted in the modified intention-to-treat population with the use of an attributable estimand, in which data obtained after treatment discontinuation due to lack of efficacy or adverse events were imputed as “poor responses.”<sup>14</sup> Time to death was assessed in the intention-to-treat population (all patients who underwent randomization and received any amount of trial treatment) with the use of a treatment policy estimand, which included all observed data obtained from patients regardless of whether they continued to receive their assigned treatment.

With respect to the primary end point, the treatment groups were compared in the following order: the 320- $\mu$ g-budesonide triple-therapy group versus the glycopyrrolate-formoterol group, the 320- $\mu$ g-budesonide triple-therapy group versus the budesonide-formoterol group, the 160- $\mu$ g-budesonide triple-therapy group versus the glycopyrrolate-formoterol group (all to assess superiority), and the 160- $\mu$ g-budesonide triple-therapy group versus the budesonide-formoterol group (to assess noninferiority and then superiority).

The safety population was similar to the modified intention-to-treat population, except that the patients were evaluated according to the treatment they received rather than to their assigned treatment; those with no postrandomization safety assessment were excluded. Safety assessments included physical examinations, vital signs, electrocardiograms, clinical laboratory tests, and monitoring of adverse events. Subgroups of patients also participated in substudies that included 4-hour pulmonary-function testing and 24-hour Holter monitoring, but the results are not reported in this article.

#### STATISTICAL ANALYSIS

A sample size of 8400 patients was estimated to provide the trial with 93% power to detect a 15% lower annual rate of moderate or severe exacerbations in the 320- $\mu$ g-budesonide triple-therapy group than in both the glycopyrrolate-formoterol group and the budesonide-formoterol group (96% power for each comparison), with type I error controlled at an equivalent of a two-sided alpha level of 0.05 (further details are provided in the Supplementary Appendix).

Rates of exacerbations were analyzed by means of negative binomial regression. Time-to-first-event analyses were performed with the use of Cox regression. The use of rescue medication

#### Figure 1 (facing page). Screening, Randomization, and Treatment.

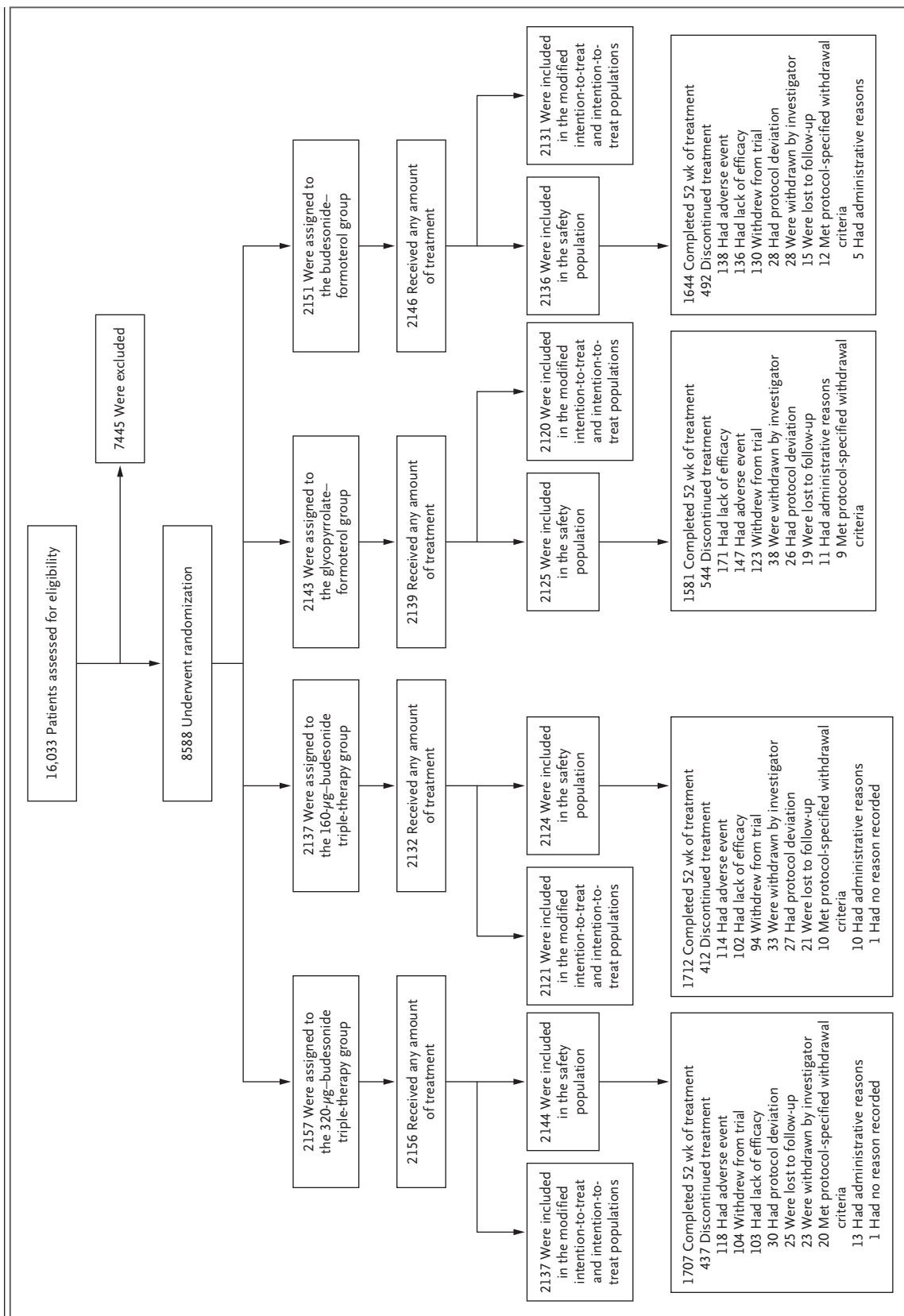
Shown is the distribution of patients during screening, randomization, and treatment. The patients in the 320- $\mu$ g-budesonide triple-therapy group received twice-daily doses of 320  $\mu$ g of budesonide, 18  $\mu$ g of glycopyrrolate, and 9.6  $\mu$ g of formoterol fumarate; those in the 160- $\mu$ g-budesonide triple-therapy group received twice-daily doses of 160  $\mu$ g of budesonide, 18  $\mu$ g of glycopyrrolate, and 9.6  $\mu$ g of formoterol fumarate; those in the glycopyrrolate-formoterol group received twice-daily doses of 18  $\mu$ g of glycopyrrolate and 9.6  $\mu$ g of formoterol fumarate; and those in the budesonide-formoterol group received twice-daily doses of 320  $\mu$ g of budesonide and 9.6  $\mu$ g of formoterol fumarate. The intention-to-treat population included all patients who underwent randomization and received any amount of trial treatment. The modified intention-to-treat population included all patients in the intention-to-treat population with post-randomization data obtained before discontinuation of treatment. Any data collected after completion of, or discontinuation of, the assigned trial regimen was excluded from the modified intention-to-treat analysis but included in the intention-to-treat analysis. The safety population included all patients who underwent randomization, received any amount of treatment, and had a postrandomization safety assessment. Forty-four patients were excluded from all analysis populations because of overlapping treatment exposure from participating multiple times in the same study or participating concurrently in another study. An additional 20 patients were not included in the modified intention-to-treat population (8509 patients) because they had multiple enrollments, although with nonoverlapping treatment exposure (19 patients) or because of administrative reasons (1 patient); these patients were included in the safety population (8529 patients).

was analyzed by means of a linear mixed model with repeated measures, and analysis of SGRQ response was performed with the use of logistic regression. For the comparison between the 160- $\mu$ g-budesonide triple-therapy group and the budesonide-formoterol group, the noninferiority margin for exacerbation end points was a rate ratio of 1.1 for the upper bound of the two-sided 95% confidence interval.

## RESULTS

### PATIENT POPULATION

A total of 8588 patients underwent randomization, and 8573 received a trial treatment (Fig. 1). The safety population comprised 8529 patients, and the intention-to-treat and modified intention-to-treat populations comprised 8509 patients each.





**Table 1. Demographic Characteristics of the Patients at Baseline (Modified Intention-to-Treat Population).\***

Characteristic	320- $\mu$ g–Budesonide Triple Therapy (N = 2137)	160- $\mu$ g–Budesonide Triple Therapy (N = 2121)	Glycopyrrolate–Formoterol (N = 2120)	Budesonide–Formoterol (N = 2131)
Age — yr	64.6 $\pm$ 7.6	64.6 $\pm$ 7.6	64.8 $\pm$ 7.6	64.6 $\pm$ 7.6
Male sex — no. (%)	1260 (59.0)	1298 (61.2)	1244 (58.7)	1279 (60.0)
Current smoker — no. (%)	910 (42.6)	865 (40.8)	856 (40.4)	864 (40.5)
Pack-years of smoking	47.0 $\pm$ 25.1	47.9 $\pm$ 25.8	48.4 $\pm$ 26.5	47.1 $\pm$ 26.3
COPD exacerbations in the past 12 mo — no.	1.7 $\pm$ 0.8	1.7 $\pm$ 0.9	1.7 $\pm$ 0.8	1.7 $\pm$ 0.9
0 Moderate or severe — no. (%)	2 (0.1)	2 (0.1)	2 (0.1)	2 (0.1)
1 Moderate or severe — no. (%)	940 (44.0)	932 (43.9)	907 (42.8)	912 (42.8)
$\geq 2$ Moderate or severe — no. (%)	1195 (55.9)	1187 (56.0)	1211 (57.1)	1217 (57.1)
$\geq 1$ Severe — no. (%)	451 (21.1)	463 (21.8)	429 (20.2)	458 (21.5)
Blood eosinophil count				
Median (range) — cells/mm <sup>3</sup>	165 (0–2510)	167 (5–1590)	170 (5–2305)	167 (0–2430)
$\geq 150$ cells/mm <sup>3</sup> — no. (%)	1277 (59.8)	1258 (59.3)	1272 (60.0)	1294 (60.7)
$\geq 300$ cells/mm <sup>3</sup> — no. (%)	310 (14.5)	318 (15.0)	293 (13.8)	333 (15.6)
FEV <sub>1</sub> after administration of albuterol — % of the predicted normal value	43.6 $\pm$ 10.3	43.1 $\pm$ 10.4	43.5 $\pm$ 10.2	43.4 $\pm$ 10.4
50 to <80% of the predicted normal value: moderate COPD — no. (%)	613 (28.7)	604 (28.5)	596 (28.1)	614 (28.8)
30 to <50% of the predicted normal value: severe COPD — no. (%)	1305 (61.1)	1270 (59.9)	1293 (61.0)	1283 (60.2)
<30% of the predicted normal value: very severe COPD — no. (%)	217 (10.2)	245 (11.6)	229 (10.8)	233 (10.9)
Change in FEV <sub>1</sub> from before to after administration of albuterol — ml	146.3 $\pm$ 158.0	144.4 $\pm$ 151.7	148.7 $\pm$ 151.1	142.3 $\pm$ 144.8
Bronchodilator reversibility — no. (%)†	657 (30.7)	631 (29.8)	669 (31.6)	654 (30.7)
Use of inhaled glucocorticoid at screening — no. (%)	1706 (79.8)	1729 (81.5)	1707 (80.5)	1704 (80.0)
COPD Assessment Test score‡	19.7 $\pm$ 6.5	19.6 $\pm$ 6.6	19.5 $\pm$ 6.6	19.5 $\pm$ 6.5

\* Plus-minus values are means  $\pm$ SD. The modified intention-to-treat population included all patients who underwent randomization, received any amount of trial treatment, and had postrandomization data obtained before discontinuation of treatment. The 320- $\mu$ g–budesonide triple-therapy group received twice daily doses of 320  $\mu$ g of budesonide, 18  $\mu$ g of glycopyrrolate, and 9.6  $\mu$ g of formoterol fumarate; the 160- $\mu$ g–budesonide triple-therapy group received twice-daily doses of 160  $\mu$ g of budesonide, 18  $\mu$ g of glycopyrrolate, and 9.6  $\mu$ g of formoterol fumarate; the glycopyrrolate–formoterol group received twice-daily doses of 18  $\mu$ g of glycopyrrolate and 9.6  $\mu$ g of formoterol fumarate; and the budesonide–formoterol group received twice-daily doses of 320  $\mu$ g of budesonide and 9.6  $\mu$ g of formoterol fumarate. The doses of glycopyrrolate and formoterol fumarate are equivalent to 14.4  $\mu$ g of glycopyrronium and 10  $\mu$ g of formoterol fumarate dihydrate, respectively. COPD denotes chronic obstructive pulmonary disease, and FEV<sub>1</sub> forced expiratory volume in 1 second.

† Bronchodilator reversibility was defined as an increase in FEV<sub>1</sub> of at least 12% and at least 200 ml after administration of albuterol.

‡ Scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating more symptoms; the minimum clinically important difference in score is 2 points.

A total of 7187 patients (83.8%) completed the trial, of whom 6654 (77.6%) completed 52 weeks of treatment (79.4% and 80.4% in the 320- $\mu$ g–budesonide and 160- $\mu$ g–budesonide triple-therapy groups, respectively, 74.1% in the glycopyrrolate–formoterol group, and 76.6% in the budesonide–formoterol group). The demographic characteristics of the patients in the modified intention-to-treat population were similar across treatment groups (Table 1).

Overall, 80.5% of the patients were using inhaled glucocorticoids at the time of screening; other previously used COPD medications are listed in Table S3.

#### PRIMARY EFFICACY ANALYSES

The model-estimated annual rates of moderate or severe exacerbations were 1.08 in the 320- $\mu$ g-budesonide triple-therapy group, 1.07 in the 160- $\mu$ g-budesonide triple-therapy group, 1.42 in the glycopyrrolate-formoterol group, and 1.24 in the budesonide-formoterol group. The annual rate of moderate or severe exacerbations was significantly lower with 320- $\mu$ g-budesonide triple therapy than with glycopyrrolate-formoterol (24% lower: rate ratio, 0.76; 95% confidence interval [CI], 0.69 to 0.83;  $P<0.001$ ) or budesonide-formoterol (13% lower: rate ratio, 0.87; 95% CI, 0.79 to 0.95;  $P=0.003$ ). Similarly, the annual rate of moderate or severe exacerbation was significantly lower with 160- $\mu$ g-budesonide triple therapy than with glycopyrrolate-formoterol (25% lower: rate ratio, 0.75; 95% CI, 0.69 to 0.83;  $P<0.001$ ) or budesonide-formoterol (14% lower: rate ratio, 0.86; 95% CI, 0.79 to 0.95;  $P=0.002$ ) (Table 2). No difference was observed between the two triple-therapy groups (rate ratio, 1.00; 95% CI, 0.91 to 1.10).

#### SECONDARY AND OTHER EFFICACY ANALYSES

In the secondary analysis of the primary end point, the rate ratios of moderate or severe exacerbations that were determined with the use of the attributable estimand were similar to the rate ratios in the primary analysis (Table 2). Both triple-therapy regimens significantly prolonged the time to the first moderate or severe exacerbation as compared with both dual therapies (Fig. 2A and Table 2).

The model-estimated annual rates of severe exacerbations were 0.13 in the 320- $\mu$ g-budesonide triple-therapy group, 0.14 in the 160- $\mu$ g-budesonide triple-therapy group, 0.15 in the glycopyrrolate-formoterol group, and 0.16 in the budesonide-formoterol group. The rate ratio of severe exacerbations over 52 weeks in the 320- $\mu$ g-budesonide triple-therapy group was 16% lower than in the glycopyrrolate-formoterol group (0.84; 95% CI, 0.69 to 1.03;  $P=0.09$ ) and 20% lower than in the budesonide-formoterol group (0.80; 95% CI, 0.66 to 0.97;  $P=0.02$ ). In the non-

inferiority analysis of the annual rate of severe exacerbations that was performed in the per-protocol population (all patients with postrandomization data obtained before any major protocol deviations), 160- $\mu$ g-budesonide triple therapy was shown to be noninferior to budesonide-formoterol (rate ratio, 0.82; 95% CI, 0.68 to 1.00); however, differences between the 160- $\mu$ g-budesonide triple-therapy group and either dual-therapy group were not significant (Table 2). The change from baseline in the use of rescue medication over 24 weeks and the proportion of patients with an SGRQ response at week 24 are shown in Table S4.

In time-to-first-event analyses performed with the use of the treatment policy estimand in the intention-to-treat population, the risk of death from any cause in the 320- $\mu$ g-budesonide triple-therapy group was 46% lower than that in the glycopyrrolate-formoterol group (28 vs. 49 deaths; hazard ratio, 0.54; 95% CI, 0.34 to 0.87) and 22% lower than that in the budesonide-formoterol group (28 vs. 34 deaths; hazard ratio, 0.78; 95% CI, 0.47 to 1.30). The risk of death from any cause in the 160- $\mu$ g-budesonide triple-therapy group was lower than that in the glycopyrrolate-formoterol group (39 vs. 49 deaths; hazard ratio, 0.79; 95% CI, 0.52 to 1.20) but higher than that in the budesonide-formoterol group (39 vs. 34 deaths; hazard ratio, 1.13; 95% CI, 0.72 to 1.80) (Fig. 2B and Table 2). Adjudicated causes of death are provided in Table S5.

Data on prespecified subgroup analyses of the rates of moderate or severe exacerbations according to baseline eosinophil counts, the use of inhaled glucocorticoids at the time of screening, and bronchodilator reversibility at the time of screening are provided in Figures S4 and S5 and Table S6. The triple-therapy regimens showed a benefit over the dual-therapy regimens with respect to the annual rate of moderate or severe exacerbations in both eosinophil subgroups ( $<150$  and  $\geq 150$  cells per cubic millimeter) and regardless of whether the patients were using inhaled glucocorticoids or had bronchodilator reversibility at the time of screening.

#### SAFETY AND ADVERSE-EVENT PROFILE

The percentage of patients who had at least one adverse event ranged from 61.7 to 64.5% across treatment groups. The percentage of patients

**Table 2. Efficacy End Points.\***

End Point	320- $\mu$ g–Budesonide Triple Therapy (N=2137)	160- $\mu$ g–Budesonide Triple Therapy (N=2121)	Glycopyrrolate–Formoterol (N=2120)	Budesonide–Formoterol (N=2131)
<b>Primary end point</b>				
Primary analysis: model-estimated annual rate of moderate or severe COPD exacerbations	1.08	1.07	1.42	1.24
320- $\mu$ g–Budesonide triple therapy vs. comparators				
Rate ratio for moderate or severe exacerbations (95% CI)	—	1.00 (0.91–1.10)	0.76 (0.69–0.83)	0.87 (0.79–0.95)
P value†		—	<0.001	0.003
160- $\mu$ g–Budesonide triple therapy vs. comparators				
Rate ratio for moderate or severe exacerbations (95% CI)	—	—	0.75 (0.69–0.83)	0.86 (0.79–0.95)
P value			<0.001	0.002
Secondary analysis: model-estimated annual rate of moderate or severe COPD exacerbations (attributable estimand)‡	1.25	1.23	1.63	1.47
320- $\mu$ g–Budesonide triple therapy vs. comparators				
Rate ratio for moderate or severe exacerbations (95% CI)	—	1.01 (0.94–1.10)	0.76 (0.71–0.83)	0.85 (0.78–0.92)
P value†		—	<0.001	<0.001
160- $\mu$ g–Budesonide triple therapy vs. comparators				
Rate ratio for moderate or severe exacerbations (95% CI)	—	—	0.75 (0.70–0.82)	0.84 (0.77–0.90)
P value			<0.001	<0.001
<b>Secondary exacerbation and mortality end points</b>				
Time to first moderate or severe COPD exacerbation over 52 wk				
Patients with exacerbations — no. (%)	1026 (48.0)	1013 (47.8)	1056 (49.8)	1085 (50.9)
320- $\mu$ g–Budesonide triple therapy vs. comparators				
Hazard ratio for moderate or severe exacerbation (95% CI)	—	1.02 (0.93–1.11)	0.88 (0.81–0.96)	0.89 (0.81–0.97)
P value†		—	0.004	0.006
160- $\mu$ g–Budesonide triple therapy vs. comparators				
Hazard ratio for moderate or severe exacerbation (95% CI)	—	—	0.87 (0.79–0.94)	0.87 (0.80–0.95)
P value			0.001	0.002
Model-estimated annual rate of severe COPD exacerbations	0.13	0.14	0.15	0.16
320- $\mu$ g–Budesonide triple therapy vs. comparators				
Rate ratio for severe exacerbations (95% CI)	—	0.96 (0.78–1.17)	0.84 (0.69–1.03)	0.80 (0.66–0.97)
P value†		—	0.09	0.02
160- $\mu$ g–Budesonide triple therapy vs. comparators				
Rate ratio for severe exacerbations (95% CI)	—	—	0.88 (0.72–1.08)	0.83 (0.69–1.01)
Time to death from any cause over 52 wk (treatment policy estimand)§				
Patient deaths — no. (%)	28 (1.3)	39 (1.8)	49 (2.3)	34 (1.6)



**Table 2. (Continued.)**

End Point	320- $\mu$ g-Budesonide Triple Therapy (N=2137)	160- $\mu$ g-Budesonide Triple Therapy (N=2121)	Glycopyrrolate-Formoterol (N=2120)	Budesonide-Formoterol (N=2131)
320- $\mu$ g-Budesonide triple therapy vs. comparators				
Hazard ratio for death (95% CI)	—	0.69 (0.42–1.13)	0.54 (0.34–0.87)	0.78 (0.47–1.30)
160- $\mu$ g-Budesonide triple therapy vs. comparators				
Hazard ratio for death (95% CI)	—	—	0.79 (0.52–1.20)	1.13 (0.72–1.80)

\* Efficacy analyses were performed in the modified intention-to-treat population with the use of an efficacy estimand, unless otherwise specified; the efficacy estimand included only data obtained from patients while they were receiving a trial treatment. The annual rate is the estimated mean number of exacerbations per patient per year. Additional secondary end points are reported in Table S4.

† Comparisons between the 320- $\mu$ g-budesonide triple-therapy group and the 160- $\mu$ g-budesonide triple-therapy group were not included in the testing hierarchy and thus no P values are provided.

‡ The secondary analysis of the primary end point was performed with an attributable estimand, where data obtained after treatment discontinuation due to lack of efficacy or adverse events were imputed as “poor responses.”

§ The analysis of time to death from any cause over 52 weeks was performed in the intention-to-treat population (all patients who underwent randomization and received any amount of trial treatment) with the use of a treatment policy estimand, which included all observed data from the patients regardless of whether they continued to receive their assigned treatment.

who had serious adverse events ranged from 19.9 to 21.0% across treatment groups. The most frequently reported adverse events overall were nasopharyngitis (10.5%), COPD (10.4%), and upper respiratory tract infection (5.6%) (Table 3).

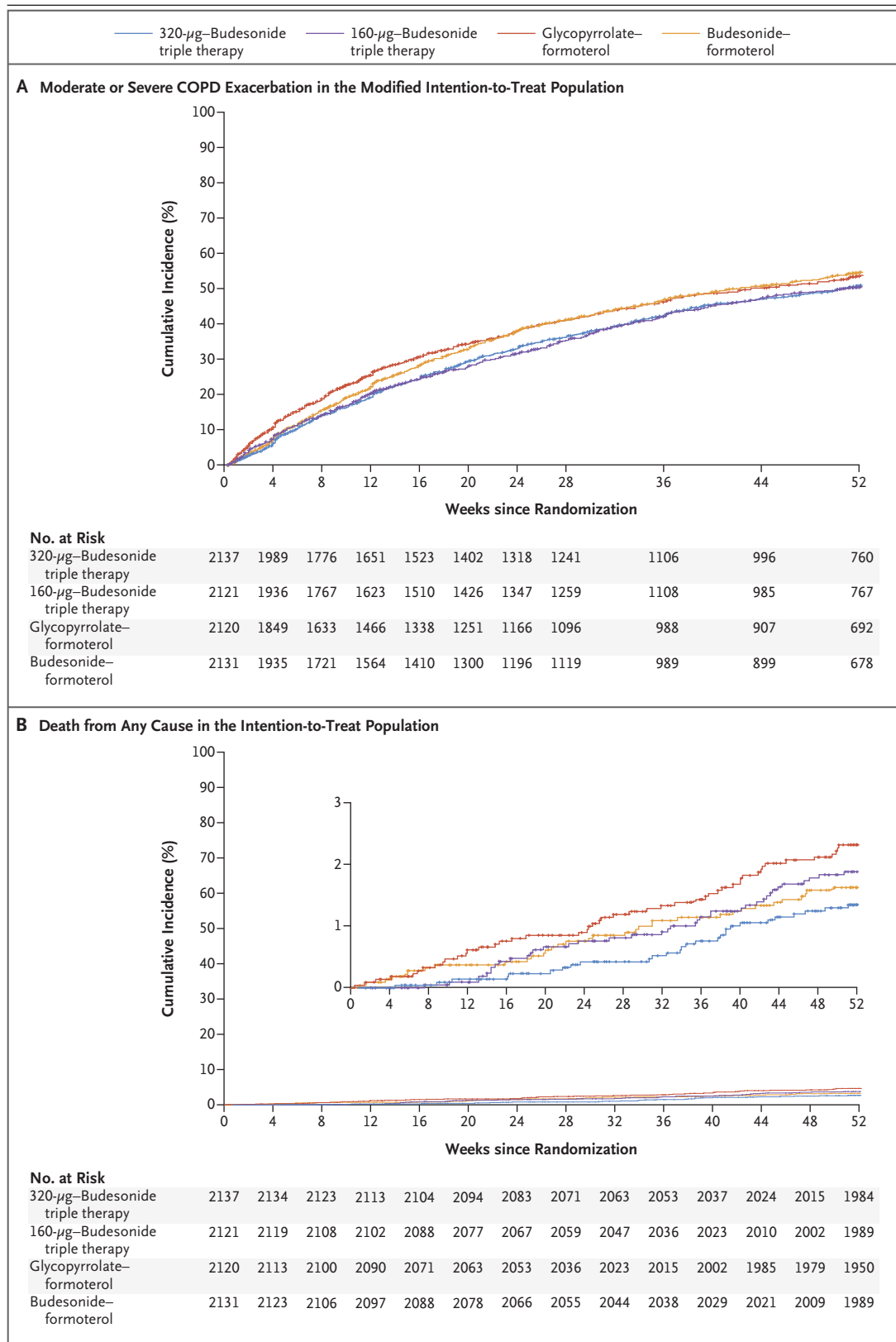
The incidence of confirmed pneumonia ranged from 3.5 to 4.5% in the treatment groups that received an inhaled glucocorticoid (41.3 to 57.8 events per 1000 patient-years) and was 2.3% in the glycopyrrolate-formoterol group (28.8 events per 1000 patient-years). The time to the first confirmed pneumonia event was longer in the glycopyrrolate-formoterol group than in the treatment groups that received an inhaled glucocorticoid ( $P<0.05$  for all comparisons) (Table S7). The incidence of serious confirmed pneumonia events was higher in the treatment groups that received an inhaled glucocorticoid (range, 2.4 to 3.0%) than in the glycopyrrolate-formoterol group (1.3%) ( $P<0.05$  for all comparisons) (Table 3 and Table S8). A similar pattern was observed for pharmacologically expected local effects of glucocorticoids (dysphonia and candidiasis), with a lower incidence in the glycopyrrolate-formoterol group than in the treatment groups that received an inhaled glucocorticoid ( $P<0.05$  for all comparisons), whereas the incidence of other systemic effects of glucocorticoids (diabetes mellitus, bone fracture, and ocular effects) were similar across treatment groups ( $P>0.05$  for all comparisons; Table S10). No clinically meaningful differences in vital signs, electrocardiogram

findings, or clinical laboratory test results were observed among the treatment groups.

## DISCUSSION

In this randomized trial involving more than 8500 patients with moderate-to-very-severe COPD, single-inhaler triple therapy with an inhaled glucocorticoid (budesonide, 320  $\mu$ g or 160  $\mu$ g twice daily) plus LAMA-LABA (glycopyrrolate-formoterol) resulted in significantly lower rates of moderate or severe exacerbations than dual therapy with LAMA-LABA or inhaled glucocorticoid-LABA. In addition, both triple-therapy regimens significantly improved patient-reported outcomes as compared with either dual-therapy regimen.

The ETHOS trial assessed two different doses of an inhaled glucocorticoid in fixed-dose triple therapy for COPD. Although a statistical evaluation of a dose-response relationship was not part of our testing hierarchy and the trial was not powered to detect a significant difference between the triple-therapy regimens, unadjusted comparisons between these regimens showed similar efficacy with respect to most exacerbation-related end points. These comparisons also showed trends in favor of 320- $\mu$ g-budesonide triple therapy with respect to severe exacerbations, SGRQ response, and use of rescue medication. Furthermore, despite a mortality of 1.8% overall, when the triple-therapy regimens were



**Figure 2 (facing page). Kaplan–Meier Estimates of the Cumulative Incidence of Moderate or Severe COPD Exacerbations and Death from Any Cause in Time-to-First-Event Analyses.**

Panel A shows the time to the first moderate or severe exacerbation of chronic obstructive pulmonary disease (COPD). The analysis was performed in the modified intention-to-treat population with the use of an efficacy estimand, which included only data obtained from patients while they were receiving a trial treatment. Panel B shows the time to death from any cause. The analysis was performed in the intention-to-treat population with the use of a treatment policy estimand, which included all observed data obtained from the patients regardless of whether they continued to receive their assigned treatment. The inset shows the same data on an enlarged y axis. Tick marks indicate the time of data censoring.

compared with glycopyrrolate–formoterol, a lower risk of death from any cause was observed only in the 320- $\mu$ g–budesonide triple-therapy group, as shown by the 95% confidence interval. The hazard ratio for death from any cause in the 320- $\mu$ g–budesonide triple-therapy group, as compared with the 160- $\mu$ g–budesonide triple-therapy group, was 0.69, but the 95% confidence interval was 0.42 to 1.13, which precluded any definitive conclusions regarding a dose–response relationship. This is the second trial to show a benefit of triple therapy over dual therapy with LAMA–LABA with respect to mortality among patients with COPD. In analyses including both on-treatment and off-treatment data, the risk of death from any cause was 46% lower in the ETHOS trial (for 320- $\mu$ g–budesonide triple therapy vs. glycopyrrolate–formoterol) and 29% lower in the Informing the Pathway of COPD Treatment (IMPACT) trial (for triple therapy with fluticasone furoate–umeclidinium–vilanterol vs. umeclidinium–vilanterol).<sup>4</sup> The difference observed between the 320- $\mu$ g–budesonide and the 160- $\mu$ g–budesonide triple-therapy groups with respect to mortality but not the other end points is unexplained but may reflect a beneficial effect on cardiovascular outcomes in this high-risk population. This possibility has been previously suggested by the findings from the Towards a Revolution in COPD Health (TORCH) trial,<sup>15,16</sup> but was not proven in a subsequent interventional study involving patients with cardiovascular risk factors but less severe respiratory disease (Study to Understand Mortality and Morbidity in COPD [SUMMIT]).<sup>17</sup>

The lower rates of moderate or severe exacerbations in the triple-therapy groups than in the dual-therapy groups in the ETHOS trial were similar to the findings from previous 52-week trials, including the IMPACT, TRILOGY, and TRIBUTE trials.<sup>4–6</sup> In addition, the results of the ETHOS trial further build on the findings from the KRONOS trial, a 24-week trial that showed benefits of triple therapy with a 320- $\mu$ g dose of budesonide plus glycopyrrolate and formoterol over dual therapies with respect to lung function, symptoms, and exacerbations for COPD in a population in which most patients (74%) had not had an exacerbation in the preceding year.<sup>2</sup> It has been proposed that the benefits of triple therapy over LAMA–LABA therapy in previous studies may have resulted from a short-term increase in the rates of exacerbations in the LAMA–LABA groups due to the discontinuation of inhaled glucocorticoids in patients who had been using inhaled glucocorticoids before trial entry.<sup>18</sup> However, in the ETHOS trial, the benefits of both triple-therapy regimens over the LAMA–LABA regimen were similar among the patients who were using inhaled glucocorticoids at the time of screening and those who were not; this finding indicates that the results were not driven by the immediate discontinuation of inhaled glucocorticoids.

Current recommendations from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggest that patients with elevated eosinophil levels who continue to have exacerbations while receiving a single bronchodilator regimen with either a LAMA or a LABA should initially step up to inhaled glucocorticoid–LABA therapy.<sup>1</sup> In the current trial, triple therapy with a 160- $\mu$ g dose of budesonide showed significant benefits over inhaled glucocorticoid–LABA therapy with a 320- $\mu$ g dose of budesonide with respect to exacerbations and symptoms, a finding that calls into question the role for inhaled glucocorticoid–LABA therapy in patients with moderate-to-very-severe COPD who are symptomatic and have a history of exacerbations. In the subgroups defined according to blood eosinophil counts, the benefits of triple therapy (with either dose of budesonide) over LAMA–LABA therapy with respect to exacerbations were greater among the patients with higher counts, a finding consistent with observations in previous studies of the re-

**Table 3. Adverse Events during the 52-Week Treatment Period (Safety Population).<sup>\*,‡</sup>**

Event	320- $\mu$ g–Budesonide Triple Therapy (N=2144)			160- $\mu$ g–Budesonide Triple Therapy (N=2124)			Glycopyrrolate–Formoterol (N=2125)			Budesonide–Formoterol (N=2136)		
	no. of patients (%)	no. of events (no. per 1000 patient-yr)		no. of patients (%)	no. of events (no. per 1000 patient-yr)		no. of patients (%)	no. of events (no. per 1000 patient-yr)		no. of patients (%)	no. of events (no. per 1000 patient-yr)	
Any adverse event	1368 (63.8)	4527 (2388.4)		1356 (63.8)	4382 (2318.7)		1312 (61.7)	4074 (2301.7)		1377 (64.5)	4746 (2587.0)	
Serious adverse events	426 (19.9)	664 (350.3)		445 (21.0)	681 (360.3)		433 (20.4)	639 (361.0)		440 (20.6)	653 (355.9)	
Adverse events that led to early discontinuation	119 (5.6)	150 (79.1)		112 (5.3)	146 (77.3)		146 (6.9)	187 (105.7)		140 (6.6)	160 (87.2)	
Confirmed major adverse cardiovascular event <sup>†</sup>	31 (1.4)	32 (16.9)		30 (1.4)	31 (16.4)		44 (2.1)	47 (26.6)		23 (1.1)	24 (13.1)	
Confirmed pneumonia <sup>†</sup>	90 (4.2)	93 (49.1)		75 (3.5)	78 (41.3)		48 (2.3)	51 (28.8)		96 (4.5)	106 (57.8)	
Deaths from any cause during treatment period	20 (0.9)	19 (10.0) <sup>‡</sup>		28 (1.3)	28 (14.8)		35 (1.6)	35 (19.8)		29 (1.4)	29 (15.8)	
Adverse events that occurred in $\geq 3\%$ of patients overall												
Nasopharyngitis	227 (10.6)	290 (153.0)		239 (11.3)	315 (166.7)		199 (9.4)	255 (144.1)		234 (11.0)	331 (180.4)	
COPD	203 (9.5)	256 (135.1)		221 (10.4)	263 (139.2)		219 (10.3)	268 (151.4)		242 (11.3)	300 (163.5)	
Upper respiratory tract infection	123 (5.7)	149 (78.6)		137 (6.5)	176 (93.1)		102 (4.8)	129 (72.9)		115 (5.4)	154 (83.9)	
Pneumonia	98 (4.6)	101 (53.3)		85 (4.0)	93 (49.2)		61 (2.9)	66 (37.3)		107 (5.0)	117 (63.8)	
Bronchitis	66 (3.1)	74 (39.0)		68 (3.2)	76 (40.2)		76 (3.6)	81 (45.8)		69 (3.2)	83 (45.2)	

\* The safety population included all patients who underwent randomization, received treatment, and had any postrandomization safety assessment.

<sup>†</sup> Confirmation was obtained from an independent clinical end-point committee.

<sup>‡</sup> A total of 20 patients in the 320- $\mu$ g–budesonide triple-therapy group had adverse events while they were receiving treatment that were linked to an outcome of death; however, death in 1 patient was adjudicated on the basis of a post-treatment adverse event and therefore was not included in the calculation of the event rate in the on-treatment analysis.

sponse to inhaled glucocorticoids,<sup>19,20</sup> as well as with the current GOLD recommendations.<sup>1</sup>

No unexpected safety signals were identified in the ETHOS trial. As previously shown in other 52-week trials involving patients with COPD,<sup>4,21</sup> the incidence of pneumonia was higher in the treatment groups that received an inhaled glucocorticoid than in those that received the LAMA–LABA combination. The incidence of confirmed pneumonia was higher in the 160- $\mu$ g–budesonide triple-therapy group (3.5%), the 320- $\mu$ g–budesonide triple-therapy group (4.2%), and the budesonide–formoterol group (4.5%) than in the glycopyrrolate–formoterol group (2.3%). Across treatment groups, the incidence of pneumonia was higher in the ETHOS trial than in the Key Assessment of Triple Therapy on Lung Function in Obstructive Lung Disease (KRONOS) trial (1.3 to 1.9%),<sup>2</sup> which may reflect the longer duration of the current trial as well as the differences in patient populations; the current trial involved patients with more severe airflow limitation and frequent exacerbations, which have been associated with a greater risk of pneumonia.<sup>22</sup>

In conclusion, our findings show the benefits of triple therapy with a budesonide–glycopyrrolate–formoterol combination over dual therapy

with a LAMA–LABA or an inhaled glucocorticoid–LABA combination with respect to the annual rate of moderate or severe COPD exacerbations, symptoms, and health-related quality of life in patients with moderate-to-very-severe COPD who are at risk of exacerbations. Triple therapy with a 320- $\mu$ g dose of budesonide also resulted in a lower all-cause mortality than LAMA–LABA therapy. We also showed that triple therapy with a 160- $\mu$ g dose of budesonide was an effective treatment option for COPD; this lower-dose inhaled glucocorticoid triple-therapy regimen showed greater efficacy than the higher-dose inhaled glucocorticoid–LABA regimen, with lower rates of exacerbations, greater reductions in symptoms, and greater improvement in health-related quality of life.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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## REFERENCES

- Global Initiative for Chronic Obstructive Lung Disease. 2020 Report: global strategy for prevention, diagnosis and management of COPD (<https://goldcopd.org/gold-reports/>).
- Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med* 2018;6:747-58.
- Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:438-46.
- Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018;378:1671-80.
- Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018;391:1076-84.
- Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting  $\beta_2$ -agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016;388:963-73.
- Kew KM, Seniukovich A. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014;3:CD010115.
- Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997;337:8-14.
- Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax* 2013;68:1029-36.
- Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax* 2011;66:699-708.
- Rabe KF, Martinez FJ, Ferguson GT, et al. A phase III study of triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler 320/18/9.6  $\mu$ g and 160/18/9.6  $\mu$ g using co-suspension delivery technology in moderate-to-very severe COPD: the ETHOS study protocol. *Respir Med* 2019;158:59-66.
- Battisti WP, Wager E, Baltzer L, et al. Good publication practice for communicating company-sponsored medical research: GPP3. *Ann Intern Med* 2015;163:461-4.
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). Guideline on statistical principles for clinical trials: addendum on estimands and sensitivity analysis in clinical trials. November 2019 ([https://database.ich.org/sites/default/files/E9-R1\\_Step4\\_Guideline\\_2019\\_1203.pdf](https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf)).
- Darken P, Nyberg J, Ballal S, Wright D. The attributable estimand: a new approach to account for intercurrent events. *Pharm Stat* 2020 March 21 (Epub ahead of print).
- Calverley PMA, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007;356:775-89.
- Calverley PMA, Anderson JA, Celli B, et al. Cardiovascular events in patients with COPD: TORCH study results. *Thorax* 2010;65:719-25.



17. Vestbo J, Anderson JA, Brook RD, et al. Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016;387:1817-26.
18. Suissa S, Ariel A. Triple therapy trials in COPD: a precision medicine opportunity. *Eur Respir J* 2018;52(6):1801848.
19. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018;6:117-26.
20. 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.
21. Chapman KR, Hurst JR, Frent SM, et al. Long-term triple therapy de-escalation to indacaterol/glycopyrronium in patients with chronic obstructive pulmonary disease (SUNSET): a randomized, double-blind, triple-dummy clinical trial. *Am J Respir Crit Care Med* 2018;198:329-39.
22. Williams NP, Coombs NA, Johnson MJ, et al. Seasonality, risk factors and burden of community-acquired pneumonia in COPD patients: a population database study using linked health care records. *Int J Chron Obstruct Pulmon Dis* 2017;12:313-22.

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