ORIGINAL ARTICLE

Indacaterol–Glycopyrronium versus Salmeterol–Fluticasone for COPD

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ABSTRACT

BACKGROUND

Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA–LAMA regimen in these patients is unclear.

METHODS

We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 μg) plus the LAMA glycopyrronium (50 μg) once daily or the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) twice daily. The primary outcome was the annual rate of all COPD exacerbations.

RESULTS

A total of 1680 patients were assigned to the indacaterol–glycopyrronium group, and 1682 to the salmeterol–fluticasone group. Indacaterol–glycopyrronium showed not only noninferiority but also superiority to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol–glycopyrronium group had a longer time to the first exacerbation than did the salmeterol–fluticasone group (71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; P<0.001). The annual rate of moderate or severe exacerbations was lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (0.98 vs. 1.19; rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001), and the time to the first moderate or severe exacerbation was longer in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (hazard ratio, 0.78; 95% CI, 0.70 to 0.86; P<0.001), as was the time to the first severe exacerbation (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; P=0.046). The effect of indacaterol–glycopyrronium versus salmeterol–fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count. The incidence of adverse events and deaths was similar in the two groups. The incidence of pneumonia was 3.2% in the indacaterol–glycopyrronium group and 4.8% in the salmeterol–fluticasone group (P=0.02).

CONCLUSIONS

Indacaterol–glycopyrronium was more effective than salmeterol–fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.)

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Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with an accelerated decline in lung function,[1-3] impaired quality of life,[4] hospitalization,[5] and increased mortality.[6] COPD exacerbations are costly to health care systems.[7] Thus, prevention of exacerbations is a key goal in the management of COPD.[8]

Inhaled long-acting bronchodilators not only control symptoms but also prevent COPD exacerbations.[9-12] Inhaled glucocorticoids are also known to reduce the frequency of exacerbations and have been studied in combination with inhaled long-acting beta-agonists (LABAs).[11,13,14] In one trial, the combination of a LABA plus an inhaled glucocorticoid (salmeterol–fluticasone) in fixed doses and the inhaled long-acting muscarinic antagonist (LAMA) tiotropium had similar effects on the rate of COPD exacerbations among patients with a history of exacerbation.[15] Consequently, treatment guidelines have recommended that either a LABA plus an inhaled glucocorticoid or a LAMA can be used to prevent COPD exacerbations in high-risk patients.[8]

Long-term use of glucocorticoids is associated with a small but important risk of pneumonia[16,17] and other adverse effects.[18] An alternative to the combination of a LABA and an inhaled glucocorticoid for the prevention of COPD exacerbations in patients with a history of exacerbation is a dual bronchodilator regimen of a LABA and a LAMA.[19]

In the FLAME trial, we investigated whether the LABA indacaterol (110 μg) plus the LAMA glycopyrronium (50 μg) once daily would be at least as effective as the LABA salmeterol (50 μg) plus the inhaled glucocorticoid fluticasone (500 μg) twice daily in preventing COPD exacerbations. Because recent studies have indicated that prevention of COPD exacerbations with inhaled glucocorticoids may be related to the blood eosinophil count,[20-22] the relationship between the baseline blood eosinophil count and the rate of exacerbations associated with each intervention was examined prospectively.

Methods

Trial Design and Oversight

The FLAME trial was a multicenter, randomized, double-blind, double-dummy, parallel-group, noninferiority trial (see Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). From July 2013 through September 2015, patients were enrolled at 356 centers in 43 countries. A 1-week screening period was followed by a 4-week run-in period, during which all patients were treated with inhaled tiotropium at a dose of 18 μg once daily. After the run-in period, tiotropium was discontinued, and the patients were randomly assigned, in a 1:1 ratio, to receive either indacaterol (110 μg) plus glycopyrronium (50 μg) once daily or salmeterol (50 μg) plus fluticasone (500 μg) twice daily for 52 weeks; patients were followed for an additional 30 days after discontinuation of the study regimen. Open-label salbutamol (100 μg) was provided as rescue medication. Additional details are provided in Section 3 in the Supplementary Appendix.

The sponsor (Novartis) developed the protocol, with guidance from the first author and advice from the other academic authors. The first draft of the manuscript was written by the first and second authors. Editorial and technical support in the preparation of the manuscript was provided by a professional medical writer at CircleScience (an Ashfield company, part of UDG Healthcare); the medical writing support was funded by Novartis. All the authors reviewed and edited the manuscript and made the decision to submit the manuscript for publication. All the authors contributed to the interpretation of the data and had access to the full data (nondisclosure agreements were in place). The trial was approved by the ethics committee at each trial center, and all the patients provided written informed consent. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol (available at NEJM.org). Statistical analyses were performed by a statistician at DataMap. Novartis funded the trial and its analyses, performed trial monitoring and reporting, provided oversight, verified key results provided by DataMap, and had no other role in the trial.

Patients

We enrolled patients 40 years of age or older who had COPD with a grade of 2 or higher on the modified Medical Research Council scale (which ranges from 0 to 4, with higher grades indicating more severe dyspnea; a minimum clinically important difference has not been determined[23]), a post-bronchodilator forced expiratory volume in 1 second (FEV_1) of at least 25% to less than

60% of the predicted value, and a post-bronchodilator ratio of FEV_1 to forced vital capacity (FVC) of less than 0.70. Patients were required to have a documented history of at least one COPD exacerbation during the previous year for which they received treatment with systemic glucocorticoids, antibiotic agents, or both. Additional details are provided in Section 2 and Table S1 in the Supplementary Appendix.

OUTCOME MEASURES

The primary objective of this trial was to show whether indacaterol–glycopyrronium would be noninferior to salmeterol–fluticasone in reducing the rate of COPD exacerbations. The primary outcome was the annual rate of all COPD exacerbations (mild, moderate, or severe). An important secondary objective, if noninferiority could be established, was to show whether indacaterol–glycopyrronium would be superior to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations.

The protocol includes a list of 27 secondary outcome measures; we report data for 19 of these outcomes here and in Sections 4 and 5 in the Supplementary Appendix. The outcomes for which data are not reported herein can be found at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/results/NCT01782326). Secondary outcomes included the times to the first COPD exacerbation of any severity, the first moderate or severe COPD exacerbation, and the first severe COPD exacerbation and the annual rates of moderate or severe exacerbations and of severe exacerbations. We also assessed trough FEV_1, the standardized area under the curve for FEV_1 from 0 to 12 hours (in a subgroup of patients), health status (measured by the total score on the St. George's Respiratory Questionnaire for COPD [SGRQ-C], on which scores range from 0 to 100, with higher scores indicating worse health status, and the minimum clinically important difference is 4 points, as compared with the score with placebo[24]), and the use of rescue medication.

COPD exacerbations, which were defined according to the criteria of Anthonisen et al.,[25] were categorized as mild (involving worsening of symptoms for >2 consecutive days but not leading to treatment with systemic glucocorticoids or antibiotics), moderate (leading to treatment with systemic glucocorticoids, antibiotics, or both), or severe (leading to hospital admission or a visit to the emergency department that lasted >24 hours in addition to treatment with systemic glucocorticoids, antibiotics, or both). Patients recorded daily symptoms and the use of rescue medication in an electronic diary (Fig. S2 in the Supplementary Appendix). When worsening of symptoms met the prespecified criteria for exacerbation, alerts were triggered in the electronic diary, and patients were advised to contact their trial site.

The safety of indacaterol–glycopyrronium and salmeterol–fluticasone was also assessed. An independent adjudication committee assessed blinded safety data. Radiographic imaging was required to confirm the presence of pneumonia. Additional details are provided in Section 3 in the Supplementary Appendix.

STATISTICAL ANALYSIS

The noninferiority margin of 15% (corresponding to a rate ratio for exacerbations with indacaterol–glycopyrronium versus salmeterol–fluticasone of 1.15) was based on a previous study,[11] in which the rate ratio for moderate or severe exacerbations with salmeterol–fluticasone versus placebo was 0.75. If the FLAME trial could rule out a 15% higher rate of exacerbations with indacaterol–glycopyrronium than with salmeterol–fluticasone, the rate ratio for exacerbations with indacaterol–glycopyrronium versus placebo would be 0.8625, thus leading to a meaningfully lower rate of exacerbations with indacaterol–glycopyrronium than with placebo of more than 13.75%.

We calculated that a sample of approximately 3332 patients would be required to give the trial more than 95% power to rule out a 15% higher rate of COPD exacerbations of any severity with indacaterol–glycopyrronium than with salmeterol–fluticasone, at a one-sided error rate of 0.025, assuming a rate of dropouts or major protocol deviations of 30%. The modified intention-to-treat population included all patients who underwent randomization, received at least one dose of a drug during the treatment period, and did not have major violations of compliance with Good Clinical Practice guidelines before unblinding occurred. The per-protocol population included all patients in the modified intention-to-treat population who did not have any major protocol deviations (definitions of major protocol deviations were specified before unblinding occurred). The main analysis of the primary outcome was performed in the per-protocol population; a support-

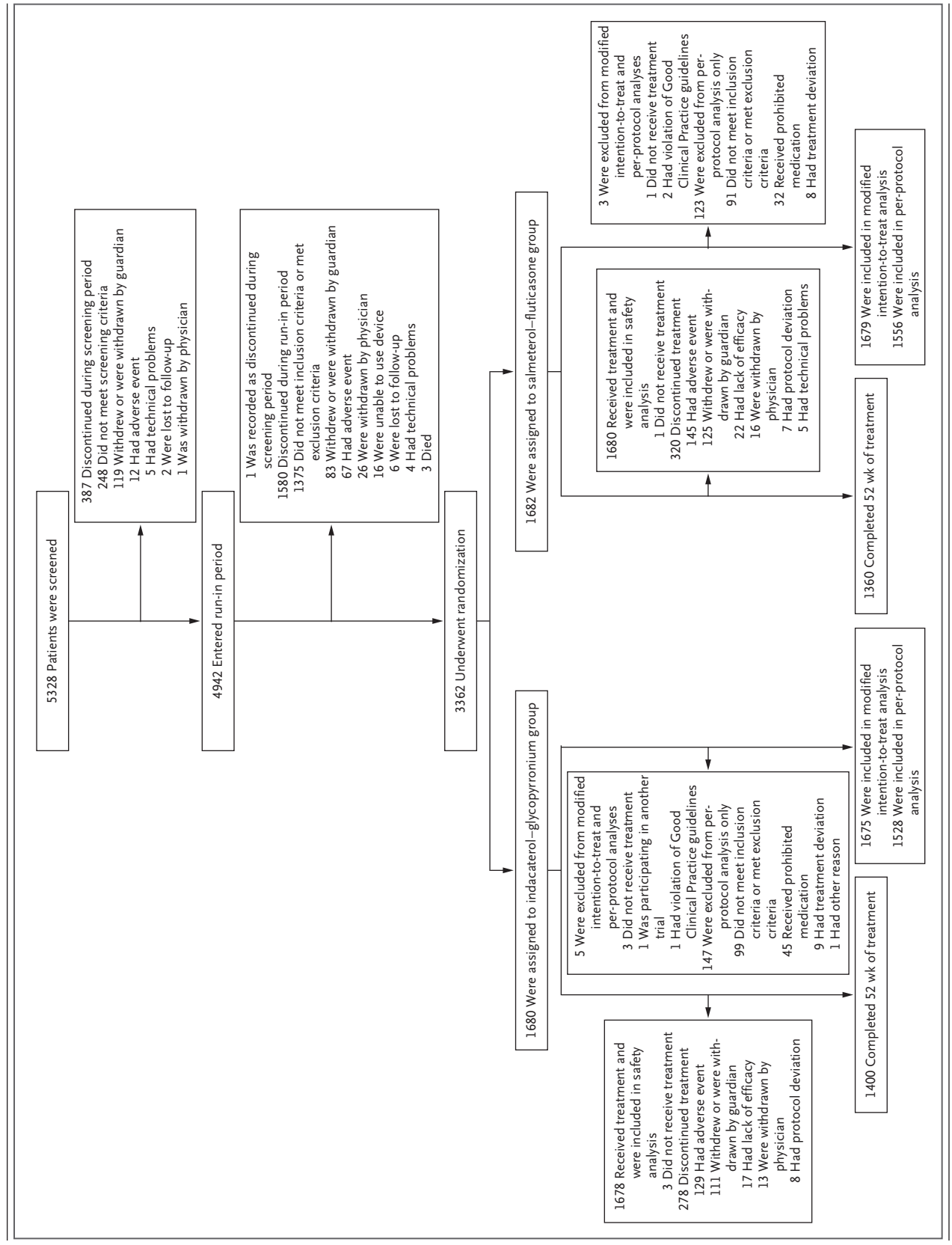


Figure 1 (facing page). Screening, Randomization, Treatment, and Analysis.

Of the patients who entered the run-in period, 179 (3.6%) discontinued because of an exacerbation; this number is derived from the case report forms for exacerbation and inclusion and exclusion, because there was no option for exacerbation as a reason for discontinuation on the case report forms. Patients were included in the safety analysis for the treatment they received; one patient who had been assigned to the salmeterol–fluticasone group had mistakenly received indacaterol–glycopyrronium before discontinuing treatment. Patients who discontinued during the treatment period because of technical problems were from one site that was closed prematurely. Patients who were excluded from the per-protocol analysis may be counted for more than one reason for exclusion.

ive analysis of that outcome was performed in the modified intention-to-treat population. Analyses of all other efficacy outcomes were performed in the modified intention-to-treat population. All efficacy analyses, unless stated otherwise, were based on on-treatment data (i.e., for participants who discontinued treatment early, only the data obtained while they were receiving treatment were used).

The number of exacerbations that occurred during the treatment period was analyzed with the use of a negative binomial model that included terms for treatment, baseline smoking status, use of inhaled glucocorticoids at the time of screening, severity of airflow limitation, and geographic region as fixed effects and baseline total symptom score (on a scale ranging from 0 to 18, with higher total scores indicating worse symptoms) and 1-year history of COPD exacerbations as covariates. The overall two-sided type I error rate for the noninferiority and subsequent superiority analyses was controlled at 0.05. Noninferiority of indacaterol–glycopyrronium to salmeterol–fluticasone in reducing the annual rate of COPD exacerbations could be claimed if the upper limit of the 95% confidence interval of the rate ratio for exacerbations with indacaterol–glycopyrronium versus salmeterol–fluticasone was less than 1.15; if noninferiority was established, superiority of indacaterol–glycopyrronium to salmeterol–fluticasone in reducing the annual rate of COPD exacerbations could be claimed if the upper limit of the same 95% confidence interval was less than 1.

Although the per-protocol analysis was prespecified as the main analysis of the primary outcome and the modified intention-to-treat analysis as the supportive analysis, it was important to achieve consistent results in the two analyses in order to draw convincing conclusions regarding noninferiority and superiority.[26,27] No adjustments for multiple testing were performed for the other outcomes.

Rates of exacerbations were also analyzed in 19 prespecified subgroup analyses, defined according to 15 baseline characteristics, including baseline blood eosinophil count, to assess the consistency of the treatment effect. All exacerbation outcomes were analyzed with the use of the negative binomial model. The outcomes for the time to the first event were analyzed with the use of a Cox regression model, which included the same terms as the negative binomial model. Additional details are provided in Section 3 in the Supplementary Appendix.

RESULTS

PATIENTS

During the run-in period, 3.6% of the patients discontinued treatment because of an exacerbation. A total of 3362 patients underwent randomization; 1680 were assigned to the indacaterol–glycopyrronium group, and 1682 to the salmeterol–fluticasone group. Of the 3362 patients, 4 were excluded from all analyses because they did not receive any trial drugs (additional details are provided in Section 4 in the Supplementary Appendix). The per-protocol population included 3084 patients, and the modified intention-to-treat population included 3354 (Fig. 1). The rates of treatment discontinuation were 16.6% in the indacaterol–glycopyrronium group and 19.0% in the salmeterol–fluticasone group (Fig. 1, and Fig. S4 in the Supplementary Appendix). The reasons for discontinuation during the screening, run-in, and treatment periods are shown in Figure 1, and in Figure S3 in the Supplementary Appendix.

The demographic characteristics and disease history were well balanced between the two treatment groups (Table 1). A total of 19.3% of the patients had a history of two or more moderate or severe exacerbations during the previous year, and 56.3% were using inhaled glucocorticoids at the time of screening. The rate of adherence to the treatment regimens was higher than

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Indacaterol–Glycopyrronium Group (N=1680)	Salmeterol–Fluticasone Group (N=1682)	All Patients (N=3362)
Age — yr	64.6±7.9	64.5±7.7	64.6±7.8
Male sex — no. (%)	1299 (77.3)	1258 (74.8)	2557 (76.1)
Duration of COPD — yr	7.2±5.3	7.3±5.5	7.3±5.4
Use of inhaled glucocorticoids at screening — no. (%)	954 (56.8)	939 (55.8)	1893 (56.3)
Current smoker — no. (%)	664 (39.5)	669 (39.8)	1333 (39.6)
Severity of COPD — no. (%)†			
Group A	2 (0.1)	0	2 (0.1)
Group B	400 (23.8)	422 (25.1)	822 (24.4)
Group C	1 (0.1)	2 (0.1)	3 (0.1)
Group D	1265 (75.3)	1249 (74.3)	2514 (74.8)
Post-bronchodilator FEV_1 — liters	1.2±0.3	1.2±0.4	1.2±0.3
Post-bronchodilator FEV_1 — % of predicted value	44.0±9.5	44.1±9.4	44.1±9.5
Post-bronchodilator ratio of FEV_1 to FVC — %	41.7±9.8	41.5±9.9	41.6±9.9
Total score on the SGRQ-C‡	47.3±15.8	47.2±15.9	47.3±15.8

* Plus–minus values are means ±SD. There were no significant differences between treatment groups, on the basis of Student's t-tests for continuous variables and chi-square tests (or Fisher's exact tests, as appropriate) for categorical variables. COPD denotes chronic obstructive pulmonary disease, FEV_1 forced expiratory volume in 1 second, and FVC forced vital capacity.

† The severity of COPD was determined on the basis of the 2015 Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system, in which group A indicates low risk and low symptom burden, group B low risk and high symptom burden, group C high risk and low symptom burden, and group D high risk and high symptom burden.

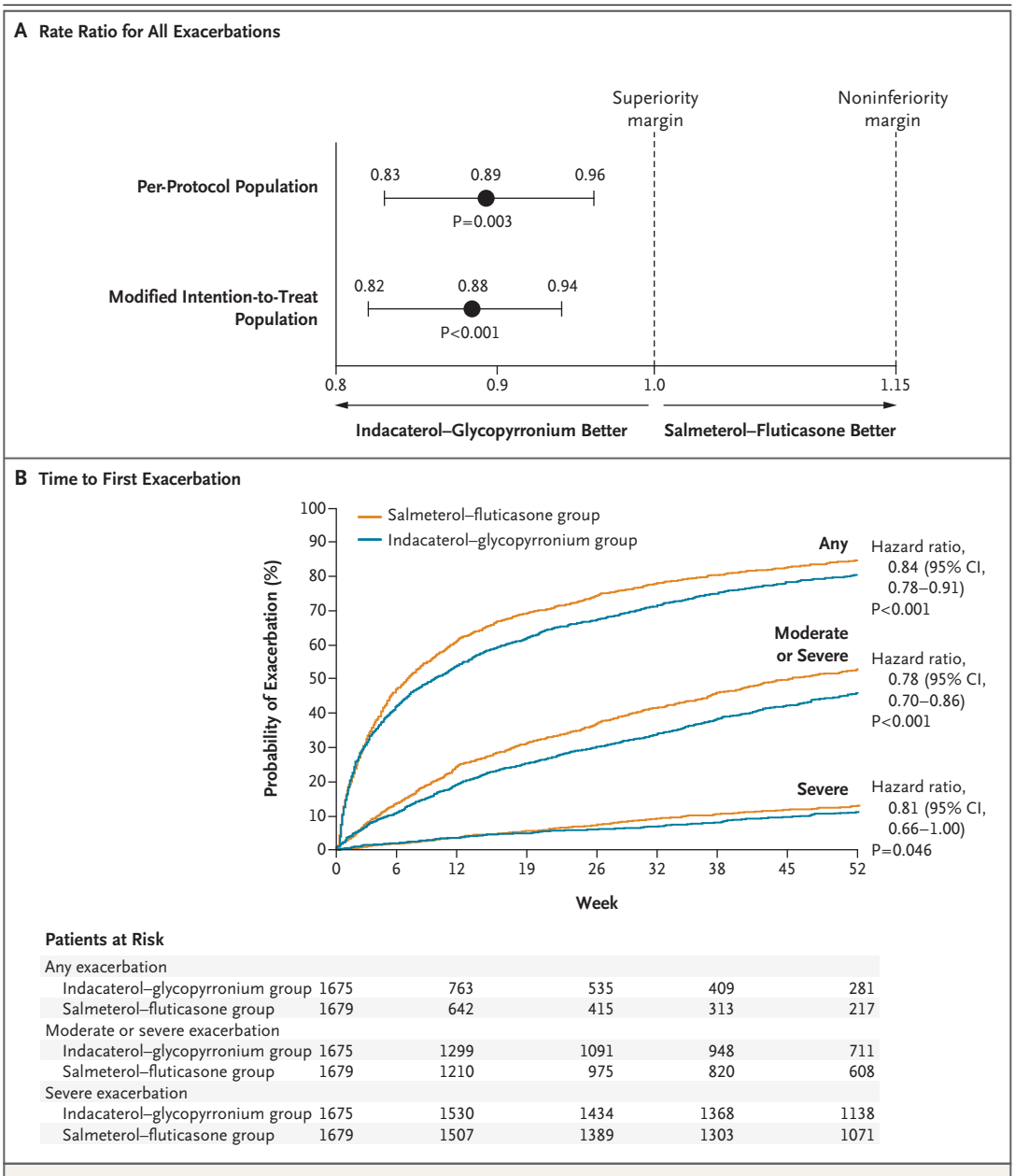
‡ Scores on the St. George's Respiratory Questionnaire for COPD (SGRQ-C) range from 0 to 100, with higher scores indicating worse health status; the minimum clinically important difference is 4 points, as compared with the score with placebo.[24]

99%. Additional details are provided in Tables S2 and S3 and Section 4 in the Supplementary Appendix.

PRIMARY OUTCOME

In the per-protocol population, the annual rate of all COPD exacerbations was 3.59 (95% confidence interval [CI], 3.28 to 3.94) in the indacaterol–glycopyrronium group and 4.03 (95% CI, 3.68 to 4.41) in the salmeterol–fluticasone group (rate ratio, 0.89 [95% CI, 0.83 to 0.96], representing an 11% lower rate; P=0.003) (Fig. 2A, and Fig. S5A in the Supplementary Appendix). The upper limit of the 95% confidence interval for the rate ratio was less than the noninferiority margin of 1.15, and therefore, indacaterol–glycopyrronium showed noninferiority to salmeterol–fluticasone with regard to the annual rate of all COPD exacerbations. Noninferiority was also established in the modified intention-to-treat population (rate of all COPD exacerbations, 3.59 [95% CI, 3.29 to 3.92] in the indacaterol–glycopyrronium group vs. 4.09 [95% CI, 3.75 to 4.46] in the salmeterol–fluticasone group; rate ratio, 0.88; 95% CI, 0.82 to 0.94; P<0.001) (Fig. 2A). Similar results were observed in additional sensitivity analyses performed with the addition of data on exacerbations and follow-up time from patients who discontinued treatment early (further details are provided in Table S4 and Section 4 in the Supplementary Appendix).

In a secondary analysis of the primary outcome that was adjusted for multiple testing, indacaterol–glycopyrronium showed superiority to salmeterol–fluticasone in reducing the annual rate of all COPD exacerbations. In both the per-protocol and modified intention-to-treat populations, the upper limits of the same 95% confidence intervals for the rate ratio were less than 1 (Fig. 2A).



Patients at Risk

Any exacerbation					
Indacaterol–glycopyrronium group	1675	763	535	409	281
Salmeterol–fluticasone group	1679	642	415	313	217
Moderate or severe exacerbation					
Indacaterol–glycopyrronium group	1675	1299	1091	948	711
Salmeterol–fluticasone group	1679	1210	975	820	608
Severe exacerbation					
Indacaterol–glycopyrronium group	1675	1530	1434	1368	1138
Salmeterol–fluticasone group	1679	1507	1389	1303	1071

Figure 2. Trial Outcomes.

Panel A shows the rate ratio for all exacerbations (mild, moderate, and severe) in the indacaterol–glycopyrronium group versus the salmeterol–fluticasone group. The bars indicate 95% confidence intervals. The modified intention-to-treat population included all patients who underwent randomization, received at least one dose of a trial drug during the treatment period, and did not have major violations of compliance with Good Clinical Practice guidelines before unblinding occurred. The per-protocol population included all patients in the modified intention-to-treat population who did not have any major protocol deviations (definitions of major protocol deviations were specified before unblinding occurred). Panel B shows the time to the first exacerbation of any severity, the time to the first moderate or severe exacerbation, and the time to the first severe exacerbation in the indacaterol–glycopyrronium group and the salmeterol–fluticasone group. The analyses were performed in the modified intention-to-treat population. Patients at risk are patients who were still receiving treatment and had not had an event.

SECONDARY OUTCOMES

Analyses of all other efficacy outcomes were performed in the modified intention-to-treat population. The indacaterol–glycopyrronium group had a longer time to first exacerbation than did the salmeterol–fluticasone group (median, 71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; P<0.001) (Fig. 2B). The annual rate of moderate or severe COPD exacerbations (i.e., exacerbations that required the use of health care services) was 17% lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (0.98 [95% CI, 0.88 to 1.10] vs. 1.19 [95% CI, 1.07 to 1.32]; rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001) (Fig. S5B in the Supplementary Appendix). The indacaterol–glycopyrronium group had a longer time to the first moderate or severe exacerbation than did the salmeterol–fluticasone group (127 days [95% CI, 107 to 149] vs. 87 days [95% CI, 81 to 103]; hazard ratio, 0.78 [95% CI, 0.70 to 0.86], representing a 22% lower risk; P<0.001) (Fig. 2B); because less than 50% of patients in the indacaterol–glycopyrronium group had an exacerbation, the time by which at least 25% of patients had a first moderate or severe exacerbation was calculated instead of the median time. In addition, the indacaterol–glycopyrronium group had a significantly longer time to the first severe exacerbation than did the salmeterol–fluticasone group, with a 19% lower risk (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; P=0.046) (Fig. 2B). The annual rate of severe COPD exacerbations was 0.15 (95% CI, 0.11 to 0.19) in the indacaterol–glycopyrronium group and 0.17 (95% CI, 0.13 to 0.22) in the salmeterol–fluticasone group (rate ratio, 0.87; 95% CI, 0.69 to 1.09; P=0.23). The number of exacerbation events according to severity is provided in Table S5 in the Supplementary Appendix.

The annual rate of moderate or severe COPD exacerbations was analyzed according to baseline blood eosinophil count (<2% vs. ≥2%). Among patients with baseline blood eosinophil counts lower than 2%, the rate was significantly lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (0.99 [95% CI, 0.86 to 1.14] vs. 1.24 [95% CI, 1.09 to 1.43]; rate ratio, 0.80; 95% CI, 0.68 to 0.93; P=0.004); among patients with baseline blood eosinophil counts of 2% or higher, the rate was also significantly lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (0.98 [95% CI, 0.87 to 1.11] vs. 1.15 [95% CI, 1.02 to 1.30]; rate ratio, 0.85; 95% CI, 0.75 to 0.96; P=0.01). Three other analyses in subgroups defined according to different cutoffs of baseline blood eosinophil counts provided similar results (data not shown). No meaningful interaction was seen between the rate of all COPD exacerbations or moderate or severe COPD exacerbations and previous therapy or other baseline characteristics (Fig. 3, and Fig. S6A and S6B in the Supplementary Appendix). Additional details are provided in Section 4 in the Supplementary Appendix.

The change from baseline in trough FEV_1 was significantly greater in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group, with a between-group difference of 62 ml at week 52 (P<0.001). The standardized area under the curve for FEV_1 from 0 to 12 hours was measured in a subgroup of 556 patients; the change from baseline was significantly greater in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group, with a between-group difference of 110 ml at week 52 (P<0.001). The improvement (decrease in score) over time in the total score on the SGRQ-C was greater in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group, with differences between the indacaterol–glycopyrronium group and the salmeterol–fluticasone group ranging from –1.2 points at week 12 to –1.8 points at week 52 (P<0.01 for both comparisons). At week 52, the percentage of patients who had a clinically important decrease of at least 4 points in the total score on the SGRQ-C was significantly higher in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group (49.2% vs. 43.7%; odds ratio, 1.30; P<0.001). The decrease over time in the use of rescue medication was also greater in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group. (For additional details on these secondary outcomes, see Fig. S7, Tables S6 and S7, and Section 4 in the Supplementary Appendix.)

SAFETY

The incidence of adverse events, including serious adverse events, was similar in the two treatment groups (Table 2). A total of 24 participants in each group (1.4%) died; the most common causes of death were respiratory and cardiovascular causes

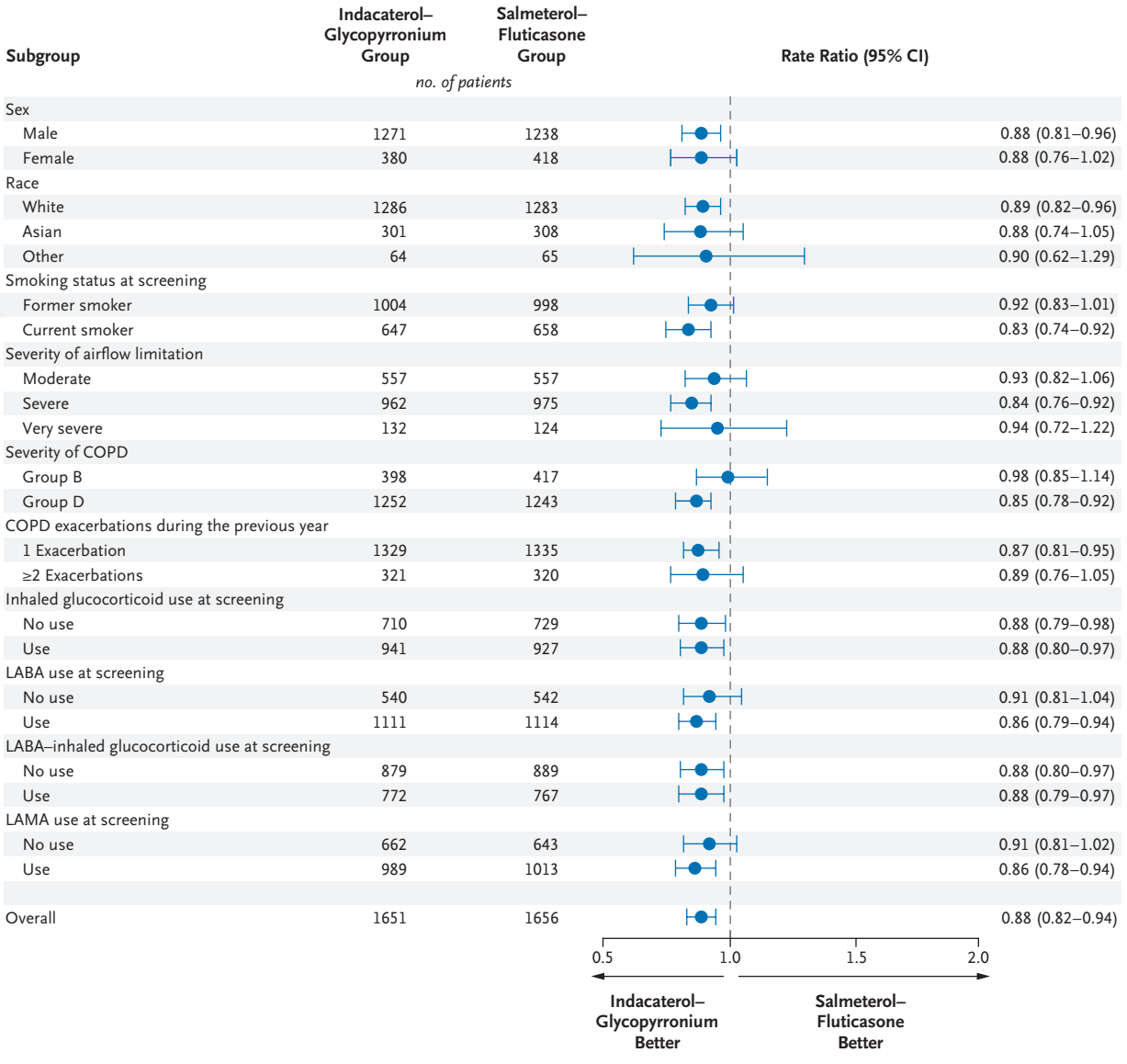


Figure 3. Subgroup Analysis of the Rate of All Exacerbations.

The analysis was performed in the modified intention-to-treat population. Race was self-reported. The severity of airflow limitation was determined on the basis of the 2011 Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system, in which moderate disease is indicated by a forced expiratory volume in 1 second (FEV_1) of 50 to 79% of the predicted value, severe disease by an FEV_1 of 30 to 49% of the predicted value, and very severe disease by an FEV_1 of less than 30% of the predicted value. The severity of chronic obstructive pulmonary disease (COPD) was determined on the basis of the 2015 GOLD staging system, in which group A indicates low risk and low symptom burden, group B low risk and high symptom burden, group C high risk and low symptom burden, and group D high risk and high symptom burden. COPD denotes chronic obstructive pulmonary disease, LABA long-acting beta-agonist, and LAMA long-acting muscarinic antagonist.

(Tables S8 and S9 in the Supplementary Appendix). The incidence of pneumonia was 3.2% in the indacaterol–glycopyrronium group and 4.8% in the salmeterol–fluticasone group (P=0.02). In a subgroup of 535 patients, the median percentage change over a period of 52 weeks in the ratio of 24-hour urinary cortisol to creatinine was 5.62% in the indacaterol–glycopyrronium group and –10.39% in the salmeterol–fluticasone group (Fig. S8 in the Supplementary Appendix).

Table 2. Adverse Events and Serious Adverse Events.*

Variable	Indacaterol–Glycopyrronium Group (N=1678)	Salmeterol–Fluticasone Group (N=1680)
	number (percent)	
Patients with ≥1 adverse event	1459 (86.9)	1498 (89.2)
Adverse events that occurred in ≥3% of either treatment group†		
Worsening of chronic obstructive pulmonary disease	1299 (77.4)	1374 (81.8)
Nasopharyngitis	197 (11.7)	195 (11.6)
Viral upper respiratory tract infection	132 (7.9)	138 (8.2)
Bacterial upper respiratory tract infection	125 (7.4)	168 (10.0)
Lower respiratory tract infection	82 (4.9)	98 (5.8)
Upper respiratory tract infection‡	81 (4.8)	83 (4.9)
Pneumonia	53 (3.2)	80 (4.8)
Cough	50 (3.0)	51 (3.0)
Dyspnea	49 (2.9)	51 (3.0)
Influenza	35 (2.1)	56 (3.3)
Oral candidiasis	20 (1.2)	71 (4.2)
Serious adverse event§	308 (18.4)	334 (19.9)
Death	24 (1.4)	24 (1.4)
Patients who discontinued because of adverse event	126 (7.5)	143 (8.5)
Patients who discontinued because of serious adverse event	85 (5.1)	87 (5.2)
Patients who discontinued because of nonserious adverse event	49 (2.9)	70 (4.2)

* The safety analysis included patients who received a drug during the treatment period. Patients were included in the analysis for the treatment they received; one patient who had been assigned to the salmeterol–fluticasone group had mistakenly received indacaterol–glycopyrronium.
† These events were coded according to preferred terms in the *Medical Dictionary for Regulatory Activities*, a standardized dictionary for clinical trials.
‡ This category includes upper respiratory tract infections not otherwise specified as viral or bacterial.
§ A definition of serious adverse events is provided in Section 3 in the Supplementary Appendix.

DISCUSSION

This clinical trial was powered for a noninferiority analysis to determine whether the combination of a LABA (indacaterol) and a LAMA (glycopyrronium) would be as effective as the combination of a LABA (salmeterol) and an inhaled glucocorticoid (fluticasone) for the prevention of COPD exacerbations. The LABA–LAMA regimen showed not only noninferiority but also, on a subsequent superiority analysis, consistent superiority to the LABA–inhaled glucocorticoid regimen for all outcomes related to exacerbations, lung function, and health status.

Clinical guidelines and strategy documents for COPD[8,28] have recommended that, in patients at risk for exacerbations, first-line therapy should be either a LABA plus an inhaled glucocorticoid or a LAMA. One previous trial showed no difference between the use of a LABA–inhaled glucocorticoid regimen and the use of LAMA monotherapy with regard to exacerbation rates.[15] However, a recent study showed that combined bronchodilator therapy with a LABA and a LAMA had greater efficacy in the reduction of exacerbation rates than did LAMA monotherapy.[19] Among patients who had been receiving combined treatment with a LABA, an inhaled glucocorticoid, and a LAMA, withdrawal from the inhaled glucocorticoid did not increase the exacerbation rate significantly,[29] a finding that further supports the hypothesis that inhaled glucocorticoids may not be essential for the prevention of COPD exacerbations in patients receiving therapy with a LABA and a LAMA.

The LABA–LAMA regimen had superior and

consistent effects with regard to COPD exacerbations of all severities, including exacerbations requiring the use of health care services. Exacerbations were carefully monitored with daily symptom recordings in electronic diaries,[4] which allowed us to document all exacerbations, including those requiring the use of health care services. Studies have shown underreporting of exacerbation events (mild exacerbations), yet these unreported events have an effect on patients' health status.[30-32] Therefore, in this trial, exacerbations of all severities were assessed for the primary outcome to reflect the importance of preventing every exacerbation. Capturing all exacerbations is a major strength of this trial, and we have found a very consistent benefit of dual bronchodilation therapy in reducing exacerbations of all severities.

Post hoc analyses of data from trials of LABA–inhaled glucocorticoid regimens for COPD have suggested that these regimens are more beneficial in reducing the rate of exacerbations among patients with elevated blood eosinophil counts (e.g., ≥2%) than among patients with lower eosinophil counts.[20-22] This suggests that a higher eosinophil count may be associated with a greater response to inhaled glucocorticoids. Therefore, the FLAME trial prospectively examined the relationship between blood eosinophil counts and exacerbation outcomes. In both the subgroup of patients with blood eosinophil counts lower than 2% and the subgroup of patients with counts of 2% or higher, the rates of moderate or severe exacerbations and of all exacerbations were significantly lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group, a finding that suggests that the LABA–LAMA regimen is more effective in reducing the rate of exacerbations than the LABA–inhaled glucocorticoid regimen in both eosinophil subgroups.

The superiority of indacaterol–glycopyrronium with respect to lung function was expected, since a combination of two bronchodilators improves lung function to a greater degree than does a combination of a LABA and an inhaled glucocorticoid.[33-35] Further evidence of a benefit with respect to symptoms was seen with the greater decrease in the use of rescue medication and the greater improvement in health status (decrease in SGRQ-C score) in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group.

A potential limitation of the study is that some patients who were treated with a LABA–inhaled glucocorticoid regimen before enrollment and were then assigned to the indacaterol–glycopyrronium group may have had withdrawal effects from the long-term use of their previous regimen, which could have resulted in an increase in exacerbations. There was no evidence that patients who had been receiving inhaled glucocorticoids before the trial withdrew from the trial during the run-in period at higher rates than did patients who had not been receiving inhaled glucocorticoids, and exacerbation rates during the run-in period were low. In addition, analyses of exacerbation rates according to previous therapy showed no meaningful interaction between the treatment and the type of maintenance therapy the patient had previously received.

It may also be argued that our trial design favored LABA–LAMA therapy over LABA–inhaled glucocorticoid therapy because the LABA–LAMA regimen was administered once daily, whereas the LABA–inhaled glucocorticoid regimen was administered twice daily. However, there is evidence that once-daily administration of a LABA–inhaled glucocorticoid regimen is no more effective than twice-daily administration with respect to lung function.[36] The once-daily dose of indacaterol–glycopyrronium is approved worldwide, except in the United States, where a lower, twice-daily dose of indacaterol–glycopyrronium is approved. Trials have shown that the twice-daily regimen has effects on lung function that are similar to those observed with a once-daily dosing regimen, but no direct comparison has been performed.[37,38]

Our trial used electronic diaries to flag exacerbations, and thus higher rates of all exacerbations were reported in this trial than in most trials assessing exacerbations, although this difference is unlikely to bias treatment comparisons. Because mild exacerbations were the most common events seen in this trial, it is possible that inclusion of such events could have made it more likely for us to conclude noninferiority, assuming a lack of difference between treatments with respect to the mild exacerbations; however, the fact that the rates of mild exacerbations and of moderate and severe exacerbations combined were lower in the indacaterol–glycopyrronium group than in the salmeterol–fluticasone group is reassuring.

The consistent exacerbation outcomes have major implications for COPD management, especially among patients with a history of exacerbation. Confirmation of these findings with the use of other combinations of long-acting bronchodilators would provide additional evidence to support the first-line use of a LABA–LAMA regimen in this patient population. However, we cannot exclude the possibility that some patients may benefit from the addition of inhaled glucocorticoids.

In conclusion, we found that among patients with COPD who had a history of exacerbation during the previous year, indacaterol–glycopyrronium was consistently more effective than salmeterol–fluticasone in preventing exacerbations and was associated with no detectable increase in adverse events.

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REFERENCES

1. Vestbo J, Edwards LD, Scanlon PD, et al. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med 2011;365:1184-92.

2. Donaldson GC, Law M, Kowlessar B, et al. Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015;192:943-50.

3. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847-52.

4. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418-22.

5. Müllerova H, Maselli DJ, Locantore N, et al. Hospitalized exacerbations of COPD: risk factors and outcomes in the ECLIPSE cohort. Chest 2015;147:999-1007.

6. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. Thorax 2005;60:925-31.

7. Toy EL, Gallagher KF, Stanley EL, Swensen AR, Duh MS. The economic impact of exacerbations of chronic obstructive pulmonary disease and exacerbation definition: a review. COPD 2010;7:214-28.

8. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. December 2015, updated 2016 (http://goldcopd.org).

9. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.

10. Kerwin E, Hébert J, Gallagher N, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J 2012;40:1106-14.

11. Calverley PM, 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.

12. Wedzicha JA, Buhl R, Lawrence D, Young D. Monotherapy with indacaterol once daily reduces the rate of exacerbations in patients with moderate-to-severe COPD: post-hoc pooled analysis of 6 months data from three large phase III trials. Respir Med 2015;109:105-11.

13. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74-81.

14. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003;22:912-9.

15. Wedzicha JA, Calverley PM, Seemungal TA, Hagan G, Ansari Z, Stockley RA. The prevention of chronic obstructive pulmonary disease exacerbations by salmeterol/fluticasone propionate or tiotropium bromide. Am J Respir Crit Care Med 2008;177:19-26.

16. 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.

17. Calverley PM, Stockley RA, Seemungal TA, et al. Reported pneumonia in patients with COPD: findings from the INSPIRE study. Chest 2011;139:505-12.

18. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. Prim Care Respir J 2013;22:92-100.

19. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med 2013;1:199-209.

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. 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.

22. 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.

23. de Torres JP, Pinto-Plata V, Ingenito E, et al. Power of outcome measurements to detect clinically significant changes in pulmonary rehabilitation of patients with COPD. Chest 2002;121:1092-8.

24. Jones PW. St. George's Respiratory Questionnaire: MCID. COPD 2005;2:75-9.

25. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.

26. Committee for Proprietary Medicinal Products. Points to consider on switching between superiority and non-inferiority. London: European Agency for the Evalua-

tion of Medicinal Products, July 2000 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003658.pdf).
27. Food and Drug Administration. Guidance for industry: non-inferiority clinical trials. March 2010 (http://www.fda.gov/downloads/Drugs/.../Guidances/UCM202140.pdf).
28. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. June 2010 (https://www.nice.org.uk/guidance/cg101).
29. Magnussen H, Disse B, Rodriguez-Roisin R, et al. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. N Engl J Med 2014;371:1285-94.
30. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2004;169:1298-303.
31. Langsetmo L, Platt RW, Ernst P, Bourbeau J. Underreporting exacerbation of chronic obstructive pulmonary disease in a longitudinal cohort. Am J Respir Crit Care Med 2008;177:396-401.
32. Jones PW, Lamarca R, Chuecos F, et al. Characterisation and impact of reported and unreported exacerbations: results from ATTAIN. Eur Respir J 2014;44:1156-65.
33. Zhong N, Wang C, Zhou X, et al. LANTERN: a randomized study of QVA149 versus salmeterol/fluticasone combination in patients with COPD. Int J Chron Obstruct Pulmon Dis 2015;10:1015-26.
34. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. Lancet Respir Med 2013;1:51-60.
35. Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umeclidinium/vilanterol versus fluticasone propionate/salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. Respir Med 2015;109:870-81.
36. Dransfield MT, Feldman G, Korenblat P, et al. Efficacy and safety of once-daily fluticasone furoate/vilanterol (100/25 mcg) versus twice-daily fluticasone propionate/salmeterol (250/50 mcg) in COPD patients. Respir Med 2014;108:1171-9.
37. Mahler DA, Kerwin E, Ayers T, et al. FLIGHT1 and FLIGHT2: efficacy and safety of QVA149 (indacaterol/glycopyrrolate) versus its monocomponents and placebo in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2015;192:1068-79.
38. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. Eur Respir J 2013;42:1484-94.