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Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD

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ABSTRACT

BACKGROUND

The benefits of triple therapy for chronic obstructive pulmonary disease (COPD) with an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2 -agonist (LABA), as compared with dual therapy (either inhaled glucocorticoid–LABA or LAMA–LABA), are uncertain.

METHODS

In this randomized trial involving 10,355 patients with COPD, we compared 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 μg , umeclidinium (a LAMA) at a dose of 62.5 μg , and vilanterol (a LABA) at a dose of 25 μg (triple therapy) with fluticasone furoate–vilanterol (at doses of 100 μg and 25 μg , respectively) and umeclidinium–vilanterol (at doses of 62.5 μg and 25 μg , respectively). Each regimen was administered in a single Ellipta inhaler. The primary outcome was the annual rate of moderate or severe COPD exacerbations during treatment.

RESULTS

The rate of moderate or severe exacerbations in the triple-therapy group was 0.91 per year, as compared with 1.07 per year in the fluticasone furoate–vilanterol group (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; $P < 0.001$) and 1.21 per year in the umeclidinium–vilanterol group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; $P < 0.001$). The annual rate of severe exacerbations resulting in hospitalization in the triple-therapy group was 0.13, as compared with 0.19 in the umeclidinium–vilanterol group (rate ratio, 0.66; 95% CI, 0.56 to 0.78; 34% difference; $P < 0.001$). There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium–vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; $P < 0.001$).

CONCLUSIONS

Triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations than fluticasone furoate–vilanterol or umeclidinium–vilanterol in this population. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium–vilanterol. (Funded by GlaxoSmithKline; IMPACT ClinicalTrials.gov number, NCT02164513.)

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TRIPLE INHALED THERAPY FOR CHRONIC obstructive pulmonary disease (COPD) comprises an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β_2 -agonist (LABA). Such treatment is recommended in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy for COPD in patients who have clinically significant symptoms despite treatment with an inhaled glucocorticoid–LABA or LAMA–LABA and who are at increased risk for frequent or severe exacerbations.^{1,2} Although studies have shown that triple inhaled therapy has positive effects on lung function and COPD symptoms as compared with dual therapy,^{3–13} its use until recently has required patients to use multiple inhalers several times per day.^{14,15}

Recently, single inhalers containing an inhaled glucocorticoid, a LABA, and a LAMA have been developed; these inhalers offer potential advantages in practicality and adherence to therapy. However, the effectiveness of combination inhaled therapies has not been comprehensively evaluated in patients with COPD who have the highest symptom burden. Controversy exists regarding the use of inhaled glucocorticoids in COPD and the relative benefits of triple therapy as compared with dual therapy (inhaled glucocorticoid–LABA or LAMA–LABA) in patients with a history of previous exacerbations. The Informing the Pathway of COPD Treatment (IMPACT) trial evaluated the relative benefits and risks of these three regimens in patients with symptomatic COPD and a history of exacerbations.¹⁶ Here we report the primary, secondary, and other efficacy and safety outcomes.

METHODS

TRIAL DESIGN AND OVERSIGHT

The IMPACT trial was a phase 3, randomized, double-blind, parallel-group, multicenter trial.¹⁶ The primary objective was to evaluate the effects of 52 weeks of a once-daily combination of fluticasone furoate (an inhaled glucocorticoid) at a dose of 100 μg , umeclidinium (a LAMA) at a dose of 62.5 μg , and vilanterol (a LABA) at a dose of 25 μg (triple therapy), as compared with fluticasone furoate–vilanterol (at doses of 100 μg and 25 μg , respectively) or the dual bronchodilator umeclidinium–vilanterol (at doses of 62.5 μg and 25 μg , respectively), on the rate of moderate

or severe COPD exacerbations. Each regimen was administered in a single dry-powder inhaler (Ellipta, GlaxoSmithKline).

Patients enrolled were 40 years of age or older and had symptomatic COPD (COPD Assessment Test [CAT] score, ≥ 10 ; range, 0 to 40, with higher scores indicating more symptoms; minimal clinically important difference, 2 units). Patients had to have either a forced expiratory volume in 1 second (FEV_1) that was less than 50% of the predicted normal value and a history of at least one moderate or severe exacerbation in the previous year, or an FEV_1 of 50 to 80% of the predicted normal value and at least two moderate exacerbations or one severe exacerbation in the previous year. Patients continued to take their own medication, which could include a LAMA, a LABA, or an inhaled glucocorticoid alone or in combination, during a 2-week run-in period before randomization.

The trial was performed in 37 countries from June 2014 through July 2017. It was conducted in accordance with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki and received approval from local institutional review boards or independent ethics committees. All the patients provided written informed consent. The patients and treatment groups are described in Tables S1 through S3 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

All the patients underwent baseline chest radiography at trial entry, and all initial and subsequent chest images were overread centrally by radiologists who were unaware of the clinical information or trial treatment. The assignment of a diagnosis of pneumonia and the labeling of an event as an exacerbation were determined according to the clinical judgment of the investigator. The protocol required that all the patients with a suspected pneumonia, or moderate or severe exacerbation, have a chest radiograph obtained to help confirm the presence of a new infiltrate and better capture and understand these adverse events. When a diagnosis of pneumonia was made, the clinician also considered increased cough, sputum purulence, dyspnea, and signs on physical examination or laboratory testing.

The trial was designed by academic partners and the sponsor (GlaxoSmithKline), which also paid for editorial support; the lead author is an employee of the sponsor. All the authors dis-



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cussed and interpreted the results, agree with the completeness and accuracy of the data and analyses, and vouch for the adherence of the trial to the protocol, available at NEJM.org. All the authors contributed to the data analyses and writing of the manuscript.

PRIMARY EFFICACY OUTCOME

The primary efficacy outcome was the annual rate of moderate or severe exacerbations during treatment (including 1 day after the last dose was administered). The two coprimary treatment comparisons were triple therapy versus umeclidinium–vilanterol, and triple therapy versus fluticasone furoate–vilanterol.

Patients completed an electronic diary each morning to record their symptoms and were alerted to contact their trial investigator if symptoms suggestive of an exacerbation worsened over the course of 2 consecutive days. The investigator confirmed the presence or absence of an exacerbation. The severity of an exacerbation was defined according to the treatment. A mild exacerbation was worsening of symptoms treated with increased albuterol. A moderate exacerbation was defined as an exacerbation leading to treatment with antibiotics or systemic glucocorticoids. A severe exacerbation was one resulting in hospitalization or death.

SECONDARY AND OTHER EFFICACY OUTCOMES

Secondary outcomes in the statistical hierarchy were grouped sequentially according to lung function and symptoms and the time to the first exacerbation. The first analysis block included spirometry to assess trough FEV₁ and the change in the St. George's Respiratory Questionnaire (SGRQ) total score, as measured by the COPD-specific version, to assess health-related quality of life (scores range from 0 to 100, with lower scores indicating better health-related quality of life; minimal clinically important difference, 4 points). The second block in the hierarchy assessed the time to the first moderate or severe COPD exacerbation during treatment (Fig. S2 in the Supplementary Appendix).

Prespecified protocol-defined secondary outcomes that were not in the hierarchy included the annual rate of moderate or severe exacerbations and the time to the first moderate or severe exacerbation among patients with a blood eosinophil count of at least 150 cells per microliter at

baseline, and the annual rate of severe exacerbations. Protocol-defined other outcomes included analyses of lung function, time to death from any cause, health-related quality of life, and all exacerbations (mild, moderate, or severe) in the entire patient population and dyspnea in a subset of patients as assessed according to the Baseline Dyspnea Index and Transition Dyspnea Index (TDI; values range from –9 to 9, with lower values indicating worsening severity of dyspnea; minimal clinically important difference, 1 unit). (For details, see the section on additional statistical information in the Supplementary Appendix or see the protocol and statistical analysis plan, available with the protocol.)

SAFETY ASSESSMENTS

Incidences of adverse events, serious adverse events, pneumonia, cardiovascular events, bone fractures, and other adverse events of special interest (prespecified adverse events associated with the use of inhaled glucocorticoids, LAMAs, or LABAs) were documented at each clinic visit. Supporting radiography was used to document incidences of pneumonia.

Electrocardiographic (ECG) measurements and vital signs were assessed at screening and after 4, 28, and 52 weeks of treatment. Clinical (chemical and hematologic) assessments were performed at screening and at 16, 28, and 52 weeks. All reports of serious adverse events and all trial deaths were adjudicated by an independent adjudication committee whose members were unaware of the treatment assignments.

STATISTICAL ANALYSIS

It was estimated a priori that the annual rate of moderate or severe exacerbations would be 0.80 among patients treated with triple therapy, 0.91 among those treated with fluticasone furoate–vilanterol, and 0.94 among those treated with umeclidinium–vilanterol. On the basis of a two-sided 1% significance level and 90% power and assuming a negative binomial model with a dispersion parameter of 0.75, we calculated that approximately 4000 patients would be needed in the triple-therapy group, 4000 in the fluticasone furoate–vilanterol group, and 2000 in the umeclidinium–vilanterol group. The truncated Hochberg method was used in a closed testing hierarchy across the coprimary and key secondary treatment comparisons to control type I error at

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

Characteristic	Triple Therapy (N=4151)	Fluticasone Furoate– Vilanterol (N=4134)	Umeclidinium– Vilanterol (N=2070)	Total (N=10,355)
Age — yr	65.3±8.2	65.3±8.3	65.2±8.3	65.3±8.3
Female sex — no. (%)	1385 (33)	1386 (34)	714 (34)	3485 (34)
Body-mass index†	26.6	26.7	26.6	26.6
Former smokers — no. (%)‡	2715 (65)	2711 (66)	1342 (65)	6768 (65)
Moderate or severe COPD exacerbations in the previous yr — no. (%)				
0	2 (<1)	5 (<1)	2 (<1)	9 (<1)
1	1853 (45)	1907 (46)	931 (45)	4691 (45)
2	1829 (44)	1768 (43)	890 (43)	4487 (43)
≥3	467 (11)	454 (11)	247 (12)	1168 (11)
≥2 Moderate COPD exacerbations in the previous yr — no. (%)	1967 (47)	1921 (46)	989 (48)	4877 (47)
≥1 Severe COPD exacerbation in the previous yr — no. (%)	1087 (26)	1069 (26)	515 (25)	2671 (26)
≥2 Severe COPD exacerbations in the previous yr — no. (%)	147 (4)	148 (4)	76 (4)	371 (4)
Postbronchodilator FEV ₁ — % of predicted normal value	45.7±15.0	45.5±14.8	45.4±14.7	45.5±14.8
Mean score on the COPD Assessment Test at screening§	20.1±6.1	20.1±6.1	20.2±6.2	20.1±6.1

* Plus–minus values are means ±SD. Patients in the triple-therapy group received a once-daily inhaled combination of 100 µg of fluticasone furoate, 62.5 µg of umeclidinium, and 25 µg of vilanterol. Patients in the fluticasone furoate–vilanterol group received a once-daily inhaled combination of 100 µg of fluticasone furoate and 25 µg of vilanterol. Patients in the umeclidinium–vilanterol group received a once-daily inhaled combination of 62.5 µg of umeclidinium and 25 µg of vilanterol. A moderate exacerbation of chronic obstructive pulmonary disease (COPD) was defined as one leading to treatment with antibiotics or systemic glucocorticoids. A severe COPD exacerbation was defined as one resulting in hospitalization or death. FEV₁ denotes forced expiratory volume in 1 second.

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

‡ All the patients were required to have at least a 10 pack-year smoking history. Former smokers were defined as those who had stopped smoking at least 6 months before screening.

§ Scores on the COPD Assessment Test range from 0 to 40, with higher scores indicating more symptoms. The minimal clinically important difference is 2 units.

the 5% level. Efficacy and safety analyses were performed in the intention-to-treat population, except for the TDI, which was assessed in a subset of 5058 patients. Further details are provided in the section on additional statistical information and Figure S2 in the Supplementary Appendix.

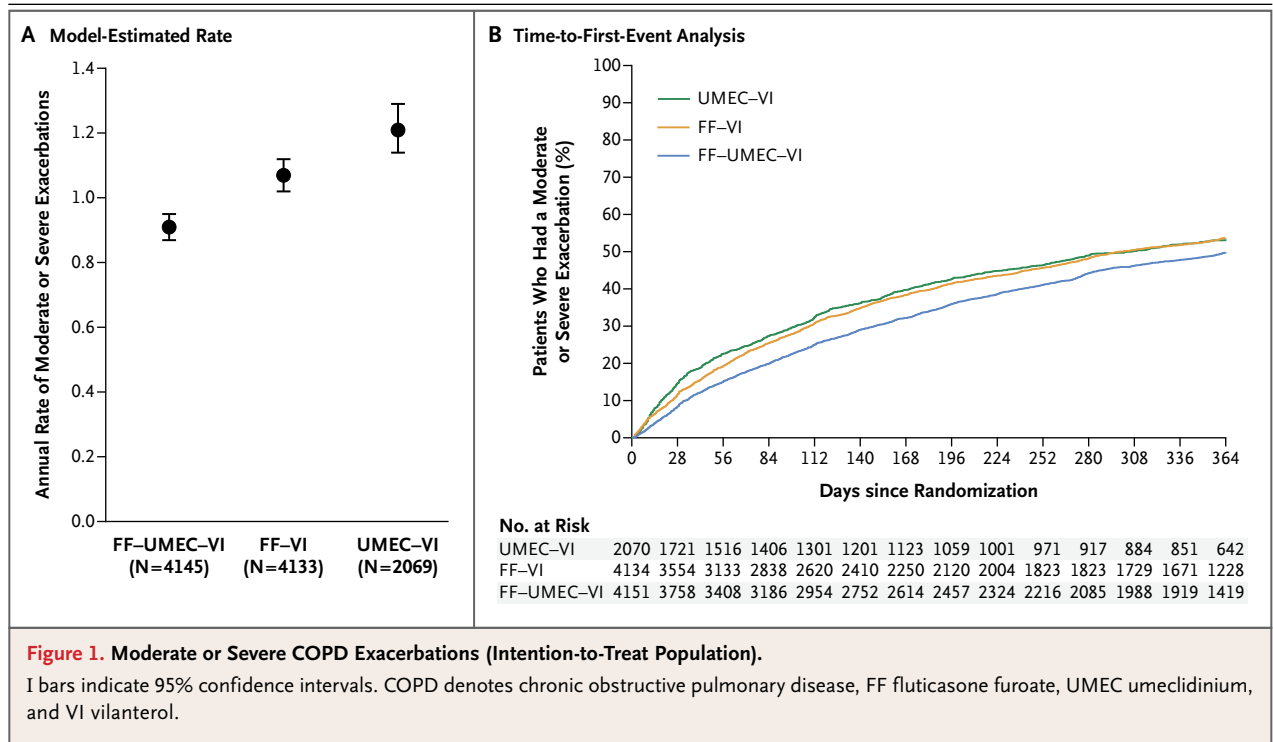
RESULTS

TRIAL POPULATION

The intention-to-treat population included 10,355 patients who underwent randomization and received investigational medication (4151 received triple therapy, 4134 received fluticasone furoate–vilanterol, and 2070 received umeclidinium–vilanterol). Overall, 9087 patients (88%) complet-

ed the trial, and 7991 (77%) completed the trial while receiving investigational medication (Fig. S1 in the Supplementary Appendix). In the intention-to-treat population, there were no clinically significant differences among the three treatment groups with regard to baseline demographic characteristics, COPD exacerbations, lung function, and CAT score (Table 1). The majority of patients (66%) were male, and the mean age was 65.3 years. A total of 18% of the patients had bronchodilator reversibility (defined as an increase in FEV₁ of ≥12% and ≥200 ml after administration of albuterol). A total of 43% had a baseline blood eosinophil level of less than 150 cells per microliter.

On trial entry, 38% of the patients were re-



ceiving triple therapy including an inhaled glucocorticoid, a LABA, and a LAMA; 29% were receiving an inhaled glucocorticoid and a LABA; and 8% were receiving a LAMA and a LABA. Details on medications at trial entry are provided in Table S4 in the Supplementary Appendix. After the initiation of investigational medication, the rate of premature discontinuation of treatment was lower in the triple-therapy group than in the dual-therapy groups; 758 patients (18%) withdrew from triple therapy, 1040 (25%) from fluticasone furoate–vilanterol, and 566 (27%) from umeclidinium–vilanterol.

PRIMARY EFFICACY ANALYSIS

The rate of moderate or severe exacerbations during treatment among patients assigned to triple therapy was 0.91 per year, as compared with 1.07 per year among those assigned to fluticasone furoate–vilanterol (rate ratio with triple therapy, 0.85; 95% confidence interval [CI], 0.80 to 0.90; 15% difference; $P < 0.001$) and 1.21 per year among those assigned to umeclidinium–vilanterol (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; 25% difference; $P < 0.001$). Thus, the rate of moderate or severe exacerbations was significantly lower with the combina-

tion of fluticasone furoate, umeclidinium, and vilanterol than with fluticasone furoate–vilanterol or umeclidinium–vilanterol (Fig. 1A).

SECONDARY EFFICACY ANALYSES

Triple therapy was associated with a lower risk of moderate or severe exacerbations during treatment than dual therapy, as assessed in a time-to-first-event analysis. The hazard ratio for triple therapy versus fluticasone furoate–vilanterol was 0.85 (95% CI, 0.80 to 0.91; 15% difference; $P < 0.001$), and the hazard ratio for triple therapy versus umeclidinium–vilanterol was 0.84 (95% CI, 0.78 to 0.91; 16% difference; $P < 0.001$) (Fig. 1B).

The annual rate of moderate or severe exacerbations was lower with triple therapy than with either dual-therapy combination, regardless of eosinophil level, although a greater reduction in the exacerbation rate was observed in patients with eosinophil levels of at least 150 cells per microliter. Among patients with eosinophil levels of less than 150 cells per microliter, the annual rate of moderate or severe exacerbations was 0.85 (95% CI, 0.80 to 0.91) with triple therapy, 1.06 (95% CI, 0.99 to 1.14) with fluticasone furoate–vilanterol, and 0.97 (95% CI, 0.88 to 1.07) with umeclidinium–vilanterol. Among patients with

Table 2. Trough FEV₁ and St. George's Respiratory Questionnaire (SGRQ) Total Score (Intention-to-Treat Population).*

Outcome	Triple Therapy (N=4151)	Fluticasone Furoate–Vilanterol (N=4134)	Umeclidinium–Vilanterol (N=2070)
Trough FEV₁			
No. of patients evaluated	3366	3060	1490
Mean at wk 52 (95% CI) — ml	1274 (1265 to 1282)	1177 (1168 to 1185)	1220 (1208 to 1232)
Mean change from baseline (95% CI) — ml	94 (86 to 102)	–3 (–12 to 6)	40 (28 to 52)
Difference between triple therapy and dual-therapy comparator (95% CI) — ml	—	97 (85 to 109)†	54 (39 to 69)†
SGRQ total score‡			
No. of patients evaluated	3318	3026	1470
Mean at wk 52 (95% CI)	45.0 (44.5 to 45.4)	46.8 (46.3 to 47.2)	46.8 (46.1 to 47.4)
Mean change from baseline (95% CI)	–5.5 (–5.9 to –5.0)	–3.7 (–4.2 to –3.2)	–3.7 (–4.4 to –3.0)
Difference between triple therapy and dual-therapy comparator (95% CI)	—	–1.8 (–2.4 to –1.1)†	–1.8 (–2.6 to –1.0)†
Response according to SGRQ total score at wk 52 — no. (%)§	1723 (42)	1390 (34)	696 (34)
Odds ratio for triple therapy vs. dual-therapy comparator (95% CI)	—	1.41 (1.29 to 1.55)†	1.41 (1.26 to 1.57)†

* The means presented are least-squares means.

† P<0.001.

‡ Total scores on the SGRQ range from 0 to 100, with lower scores indicating better health-related quality of life.

§ A response was defined as a decrease in the SGRQ total score of at least 4 units, as compared with the baseline value.

eosinophil levels of at least 150 cells per microliter, the annual rate was 0.95 (95% CI, 0.90 to 1.01) with triple therapy, 1.08 (95% CI, 1.02 to 1.14) with fluticasone furoate–vilanterol, and 1.39 (95% CI, 1.29 to 1.51) with umeclidinium–vilanterol.

The annual rate of severe exacerbations during treatment was 0.13 among patients assigned to triple therapy, 0.15 among those assigned to fluticasone furoate–vilanterol (rate ratio with triple therapy, 0.87; 95% CI, 0.76 to 1.01; 13% difference; P=0.06), and 0.19 among those assigned to umeclidinium–vilanterol (rate ratio with triple therapy, 0.66; 95% CI, 0.56 to 0.78; 34% difference; P<0.001). Thus, the rate was not significantly lower with triple therapy than with fluticasone furoate–vilanterol but was significantly lower with triple therapy than with umeclidinium–vilanterol.

For the spirometric outcome of the mean change from baseline in trough FEV₁, the difference between the triple-therapy and fluticasone furoate–vilanterol groups was 97 ml (95% CI, 85 to 109; P<0.001), and the difference between the triple-therapy and umeclidinium–vilanterol groups

was 54 ml (95% CI, 39 to 69; P<0.001). There were significant differences between the triple-therapy group and the fluticasone furoate–vilanterol and umeclidinium–vilanterol groups in the mean change from baseline in the SGRQ total score and in the percentage of patients who had a response as defined by a decrease in the SGRQ total score of at least 4 points (P<0.001 for both comparisons on both outcomes) (Table 2).

ANALYSES OF OTHER OUTCOMES

All tests within the predefined statistical testing hierarchy achieved statistical significance, with P<0.001. No adjustments for multiplicity were made for the other comparisons, and P values of less than 0.05 were considered to indicate statistical significance. Beyond the prespecified primary and secondary outcomes, there were multiple prespecified protocol-defined other outcomes, among which were death from any cause during treatment, all exacerbations (mild, moderate, or severe), and dyspnea according to the TDI. Results for these other outcomes provided support for the primary findings, although treatment comparisons were not corrected for multiplicity.

Death during treatment occurred in 50 patients (1%) in the triple-therapy group, 49 patients (1%) in the fluticasone furoate–vilanterol group, and 39 patients (2%) in the umeclidinium–vilanterol group. All-cause mortality was significantly lower with the regimens that included the inhaled glucocorticoid fluticasone furoate (triple therapy and fluticasone furoate–vilanterol) than with umeclidinium–vilanterol. The hazard ratio for triple therapy versus umeclidinium–vilanterol was 0.58 (95% CI, 0.38 to 0.88; 42% difference; unadjusted $P=0.01$), and the hazard ratio for fluticasone furoate–vilanterol versus umeclidinium–vilanterol was 0.61 (95% CI, 0.40 to 0.93; 39% difference; unadjusted $P=0.02$). The results of a prespecified analysis of the time to death from any cause including data from patients during treatment and not during treatment provided support for the findings during treatment. Further details are provided in the Supplementary Appendix.

An analysis of adjudicated cause-specific death during treatment showed a lower rate of deaths from both cardiovascular and respiratory causes in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group. There were 16 adjudicated cardiovascular deaths during treatment in the triple-therapy group, 21 in the fluticasone furoate–vilanterol group, and 15 in the umeclidinium–vilanterol group (rate per 1000 patient-years, 4.2, 6.0, and 8.7, respectively). There were 15 adjudicated deaths from respiratory causes during treatment in the triple-therapy group, 12 in the fluticasone furoate–vilanterol group, and 9 in the umeclidinium–vilanterol group (rate per 1000 patient-years, 4.0, 3.4, and 5.2, respectively). The rate of deaths that were associated with the patients' underlying COPD according to the independent adjudicators was lower in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group. There were 18 deaths during treatment that were determined to be associated with the patient's COPD in the triple-therapy group, 14 in the fluticasone furoate–vilanterol group, and 15 in the umeclidinium–vilanterol group (rate per 1000 patient-years, 4.8, 4.0, and 8.7, respectively). Similar results were observed in an analysis that included deaths that occurred in patients no longer receiving treatment. For a summary of adjudicated causes of death, see Tables S9 and S10 in the Supplementary Appendix.

Findings similar to those of the primary efficacy analysis were observed when mild exacerbations (those determined to require only increased albuterol) were included. The annual rate of mild, moderate, or severe exacerbations was 1.05 with triple therapy, 1.25 with fluticasone furoate–vilanterol, and 1.40 with umeclidinium–vilanterol. The rate was 16% lower with triple therapy than with fluticasone furoate–vilanterol (rate ratio, 0.84; 95% CI, 0.79 to 0.89; $P<0.001$) and 25% lower with triple therapy than with umeclidinium–vilanterol (rate ratio, 0.75; 95% CI, 0.70 to 0.81; $P<0.001$).

In a subset of 5058 patients, the percentage of patients who had a response as defined by an increase in the TDI of at least 1 unit was higher with triple therapy than with either dual therapy. The rate of response was 36% in the triple-therapy group, 29% in the fluticasone furoate–vilanterol group, and 30% in the umeclidinium–vilanterol group. The odds ratio for response was 1.36 for triple therapy versus fluticasone furoate–vilanterol (95% CI, 1.19 to 1.55; $P<0.001$) and 1.33 for triple therapy versus umeclidinium–vilanterol (95% CI, 1.13 to 1.57; $P<0.001$).

SAFETY AND ADVERSE-EVENT PROFILE

Overall, the adverse-event profile of triple therapy was similar to that of the dual-therapy comparators, and there were no new safety findings associated with the use of an inhaled glucocorticoid, a LAMA, or a LABA in combination (Table 3). There were no clinically relevant differences in ECG measurements, vital signs, or clinical laboratory values among the treatment groups.

The incidence of adverse events during treatment that led to discontinuation of trial treatment or withdrawal from the trial was 6% for triple therapy, 8% for fluticasone furoate–vilanterol, and 9% for umeclidinium–vilanterol; the incidence of discontinuation or withdrawal due to an adverse event of COPD was 2%, 2%, and 3%, respectively. Serious adverse events during treatment occurred in 895 patients (22%) receiving triple therapy, 850 (21%) receiving fluticasone furoate–vilanterol, and 470 (23%) receiving umeclidinium–vilanterol. A total of 14 patients (<1%) receiving triple therapy, 25 (<1%) receiving fluticasone furoate–vilanterol, and 14 (<1%) receiving umeclidinium–vilanterol were reported to have had a nonserious adverse event

Table 3. Adverse Events of Special Interest in the Intention-to-Treat Population.*

Event	Triple Therapy (N=4151)		Fluticasone Furoate–Vilanterol (N=4134)		Umeclidinium–Vilanterol (N=2070)	
	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)	No. of Patients (%)	Rate per 1000 Patient-Yr (No. of Events)
Anticholinergic syndrome	184 (4)	60.8 (226)	140 (3)	47.1 (163)	70 (3)	47.7 (81)
Asthma or bronchospasm	27 (<1)	7.5 (28)	34 (<1)	10.1 (35)	16 (<1)	9.4 (16)
Cardiovascular effects	450 (11)	167.2 (621)	430 (10)	157.0 (543)	224 (11)	166.6 (283)
Cardiac arrhythmia	153 (4)	50.9 (189)	161 (4)	51.5 (178)	81 (4)	51.2 (87)
Cardiac failure	138 (3)	42.5 (158)	126 (3)	42.8 (148)	68 (3)	44.8 (76)
CNS hemorrhages and cerebrovascular conditions	41 (<1)	12.1 (45)	28 (<1)	9.3 (32)	11 (<1)	6.5 (11)
Hypertension	113 (3)	35.5 (132)	115 (3)	35.0 (121)	54 (3)	34.2 (58)
Ischemic heart disease	80 (2)	26.1 (97)	57 (1)	18.5 (64)	47 (2)	30.6 (52)
Lower respiratory tract infection, excluding pneumonia	200 (5)	63.0 (234)	199 (5)	69.7 (241)	108 (5)	76.0 (129)
Pneumonia	317 (8)	95.8 (356)	292 (7)	96.6 (334)	97 (5)	61.2 (104)
Urinary retention	8 (<1)	2.7 (10)	12 (<1)	3.5 (12)	9 (<1)	5.3 (9)

* Adverse events of special interest are based on an analysis of a group of prespecified adverse events that are associated with the use of inhaled glucocorticoids, long-acting muscarinic antagonists, or long-acting β_2 -agonists. See Table S15 in the Supplementary Appendix for the full listing of adverse events of special interest. CNS denotes central nervous system.

of COPD worsening. A serious adverse event of pneumonia occurred in 184 patients (4%), 152 patients (4%), and 54 patients (3%), respectively. Further details are provided in Table S12 in the Supplementary Appendix.

There was a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium–vilanterol group, and the risk of clinician-diagnosed pneumonia was significantly higher with triple therapy than with umeclidinium–vilanterol, as assessed in a time-to-first-event analysis (hazard ratio, 1.53; 95% CI, 1.22 to 1.92; $P < 0.001$). There was no significant difference in the risk of pneumonia between triple therapy and fluticasone furoate–vilanterol (hazard ratio, 1.02; 95% CI, 0.87 to 1.19; $P = 0.85$).

DISCUSSION

In this trial, once-daily single-inhaler triple therapy with fluticasone furoate, umeclidinium, and vilanterol resulted in a significantly lower rate of moderate or severe COPD exacerbations and better lung function and health-related quality of life than dual therapy with fluticasone

furoate–vilanterol or the dual bronchodilator umeclidinium–vilanterol among patients with symptomatic COPD and a history of exacerbations. These benefits were observed regardless of the patients' blood eosinophil levels at randomization.

Our trial also showed that fluticasone furoate–vilanterol was superior to umeclidinium–vilanterol with respect to the rates of COPD exacerbations (moderate or severe exacerbations and all exacerbations). These findings are in contrast to those of the FLAME trial,¹⁷ which showed a benefit of LAMA–LABA over inhaled glucocorticoid–LABA for the prevention of exacerbations. This difference in findings between our trial and the FLAME trial is probably due to the differences in the patient populations and the design of the two trials. In the FLAME trial, all the patients were treated with tiotropium during a 1-month run-in period. Therefore, any patients who would require an inhaled glucocorticoid may have had an increase in exacerbations and a decrease in lung function during the run-in period and would have been forced to leave the trial. In addition, it is also possible that patients who could not

withdraw from an inhaled glucocorticoid were knowingly not enrolled, leading to a biased patient population. In contrast, patients in our trial who were assigned to the LAMA-LABA group and had been previously receiving an inhaled glucocorticoid would have had to abruptly stop the inhaled glucocorticoid, whereas patients in the inhaled-glucocorticoid groups would have continued to take an inhaled glucocorticoid. It is unknown whether the abrupt discontinuation of inhaled glucocorticoids could have contributed to our finding of a lower rate of exacerbations in the inhaled-glucocorticoid groups than in the LAMA-LABA group. In addition, the patients who were assigned to the triple-therapy group and had been previously receiving an inhaled glucocorticoid, a LABA, and a LAMA might not have been expected to have a benefit. Further research using different trial designs will be needed to resolve these issues.

Triple therapy and fluticasone furoate-vilanterol also showed a signal toward lower all-cause mortality during treatment than umeclidinium-vilanterol. However, the Study to Understand Mortality and Morbidity in COPD (SUMMIT),¹⁸ involving patients with moderate COPD and heightened cardiovascular risk, was powered to study all-cause mortality and did not show a significant effect for fluticasone furoate-vilanterol. It is possible that our finding is fragile; further investigation will be needed to understand the reasons for this finding.

The strengths of the IMPACT trial include the large number of patients enrolled and the comparison of triple therapy with dual therapies using the same molecules in the same delivery device. The trial used an electronic diary for rapid and reliable identification of symptoms suggestive of an exacerbation, and the measurement of health-related quality of life has been recognized as important to help physicians and patients achieve greater understanding of a treatment effect.¹⁹ A robust approach was taken for capture and evaluation of pneumonias to ensure that expected adverse events of pneumonia were appropriately understood.

Safety results showed a higher incidence of pneumonia in the inhaled-glucocorticoid groups than in the umeclidinium-vilanterol group, as would be expected. However, the rate of pneumonia was 95.8, 96.6, and 61.2 events per 1000

patient-years with triple therapy, fluticasone furoate-vilanterol, and umeclidinium-vilanterol, respectively, whereas the rate of moderate or severe COPD exacerbations was 922.8, 1051.5, and 1147.6 events per 1000 patient-years, respectively. No new safety signals emerged.^{11,18}

In summary, the results of the IMPACT trial show that a once-daily combination of fluticasone furoate, umeclidinium, and vilanterol resulted in a lower rate of moderate or severe COPD exacerbations and better lung function and health-related quality of life than dual therapy with fluticasone furoate-vilanterol or umeclidinium-vilanterol. Triple therapy also resulted in a lower rate of hospitalization due to COPD than umeclidinium-vilanterol in this symptomatic patient population.

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REFERENCES

- Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Am J Respir Crit Care Med* 2017;195:557-82.
- Pocket guide to COPD diagnosis, management, and prevention: a guide for health care professionals. Global Initiative for Obstructive Lung Disease, 2017 (<http://goldcopd.org/wp-content/uploads/2016/12/wms-GOLD-2017-Pocket-Guide.pdf>).
- Cazzola M, Andò F, Santus P, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulm Pharmacol Ther* 2007;20:556-61.
- Hanania NA, Crater GD, Morris AN, Emmett AH, O'Dell DM, Niewoehner DE. Benefits of adding fluticasone propionate/salmeterol to tiotropium in moderate to severe COPD. *Respir Med* 2012;106:91-101.
- Jung KS, Park HY, Park SY, et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. *Respir Med* 2012;106:382-9.
- Welte T, Miravitlles M, Hernandez P, et al. Efficacy and tolerability of budesonide/formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;180:741-50.
- Chatterjee A, Shah M, D'Souza AO, Bechtel B, Crater G, Dalal AA. Observational study on the impact of initiating tiotropium alone versus tiotropium with fluticasone propionate/salmeterol combination therapy on outcomes and costs in chronic obstructive pulmonary disease. *Respir Res* 2012;13:15.
- Short PM, Williamson PA, Elder DHJ, Lipworth SIW, Schembri S, Lipworth BJ. The impact of tiotropium on mortality and exacerbations when added to inhaled corticosteroids and long-acting β -agonist therapy in COPD. *Chest* 2012;141:81-6.
- Aaron SD, Vandemheen KL, Ferguson D, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 2007;146:545-55.
- Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β 2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016;388:963-73.
- Siler TM, Kerwin E, Sousa AR, Donald A, Ali R, Church A. Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: results of two randomized studies. *Respir Med* 2015;109:1155-63.
- Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017;389:1919-29.
- Lipson DA, Barnacle H, Birk R, et al. FULFIL trial: once-daily triple therapy in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017;196:438-46.
- Simeone JC, Luthra R, Kaila S, et al. Initiation of triple therapy maintenance treatment among patients with COPD in the US. *Int J Chron Obstruct Pulmon Dis* 2016;12:73-83.
- Wurst KE, Puneekar YS, Shukla A. Treatment evolution after COPD diagnosis in the UK primary care setting. *PLoS One* 2014;9(9):e105296.
- Pascoe SJ, Lipson DA, Locantore N, et al. A phase III randomised controlled trial of single-dose triple therapy in COPD: the IMPACT protocol. *Eur Respir J* 2016;48:320-30.
- Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016;374:2222-34.
- 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.
- Rotenstein LS, Huckman RS, Wagle NW. Making patients and doctors happier — the potential of patient-reported outcomes. *N Engl J Med* 2017;377:1309-12.

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