Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial

Jørgen Vestbo, Julie A Anderson, Robert D Brook, Peter M A Calverley, Bartolome R Celli, Courtney Crim, Fernando Martinez, Julie Yates, David E Newby, on behalf of the SUMMIT Investigators

Summary

Background Chronic obstructive pulmonary disease (COPD) often coexists with cardiovascular disease. Treatments for airflow limitation might improve survival and both respiratory and cardiovascular outcomes. The aim of this study was to assess whether inhaled treatment with a combined treatment of the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol could improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk.

Methods In this double-blind randomised controlled trial (SUMMIT) done in 1368 centres in 43 countries, eligible patients were aged 40–80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV_1) between 50% and 70% of the predicted value, a ratio of post-bronchodilator FEV_1 to forced vital capacity (FVC) of 0·70 or less, a smoking history of at least 10 pack-years, and a score of 2 or greater on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Enrolled patients were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive once daily inhaled placebo, fluticasone furoate (100 μg), vilanterol (25 μg), or the combination of fluticasone furoate (100 μg) and vilanterol (25 μg). The primary outcome was all-cause mortality, and secondary outcomes were on-treatment rate of decline in forced expiratory volume in 1 s (FEV_1) and a composite of cardiovascular events. Safety analyses were performed on the safety population (all patients who took at least one dose of study drug) and efficacy analyses were performed on the intention-to-treat population (safety population minus sites excluded with Good Clinical Practice violations). This study is registered with ClinicalTrials.gov, number NCT01313676.

Findings Between Jan 24, 2011, and March 12, 2014, 23 835 patients were screened, of whom 16 590 were randomised. 16 485 patients were included in the intention-to-treat efficacy population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group. Compared with placebo, all-cause mortality was unaffected by combination therapy (hazard ratio [HR] 0·88 [95% CI 0·74–1·04]; 12% relative reduction; p=0·137) or the components (fluticasone furoate, HR 0·91 [0·77–1·08]; p=0·284; vilanterol, 0·96 [0·81–1·14]; p=0·655), and therefore secondary outcomes should be interpreted with caution. Rate of decline in FEV_1 was reduced by combination therapy (38 mL per year [SE 2·4] *vs* 46 mL per year [2·5] for placebo, difference 8 mL per year [95% CI 1–15]) with similar findings for fluticasone furoate (difference 8 mL per year [95% CI 1–14]), but not vilanterol (difference –2 mL per year [95% CI –8 to 5]). Combination therapy had no effect on composite cardiovascular events (HR 0·93 [95% CI 0·75–1·14]) with similar findings for fluticasone furoate (0·90 [0·72–1·11]) and vilanterol (0·99 [0·80–1·22]). All treatments reduced the rate of moderate and severe exacerbation. No reported excess risks of pneumonia (5% in the placebo group, 6% in the combination group, 5% in the fluticasone furoate group, and 4% in the vilanterol group) or adverse cardiac events (17% in the placebo group, 18% in the combination group, and 17% in the fluticasone furoate group, and 17% in the vilanterol group) were noted in the treatment groups.

Interpretation In patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes, reduced exacerbations, and was well tolerated. Fluticasone furoate, alone or in combination with vilanterol, seemed to reduce FEV_1 decline.

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Centre for Respiratory Medicine and Allergy, Manchester Academic Health Sciences Centre, The University of Manchester and South Manchester University Hospital NHS Foundation Trust, Manchester, UK (Prof J Vestbo DMSc); Research & Development, GlaxoSmithKline, Stockley Park, Middlesex, UK (J A Anderson MA); University of Michigan Health System, Ann Arbor, MI, USA (R D Brook MD, F Martinez MD); University of Liverpool, Department of Medicine, Clinical Sciences Centre, University Hospital Aintree, Liverpool, UK (Prof P M A Calverley DSc); Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA (B R Celli MD); Research & Development, GlaxoSmithKline, Research Triangle Park, NC, USA (C Crim MD, J Yates BS); Division of Pulmonary and Critical Care Medicine, Weill Cornell Medicine, New York, NY, USA (F Martinez); and Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK (Prof D E Newby DSc)

Correspondence to: Prof Jørgen Vestbo, Centre for Respiratory Medicine and Allergy, University Hospital South Manchester, Manchester M23 9LT, UK **jorgen.vestbo@manchester.ac.uk**

Introduction

Chronic obstructive pulmonary disease (COPD) often coexists with other chronic diseases that can contribute to patients' health status and prognosis.[1–3] Impaired pulmonary function is particularly associated with cardiovascular morbidity and mortality, and patients with COPD are at greater risk of cardiovascular disease compared with age-matched and sex-matched individuals

Research in context

Evidence before this study

We searched PubMed and ClinicalTrials.gov up to Nov 18, 2015, for published or ongoing studies examining the treatment of patients with concomitant chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) with inhaled corticosteroids or long-acting β agonists with the following search terms: "COPD", "cardiovascular disease", "inhaled corticosteroids", "long-acting beta-agonists". The search was restricted to English language. The search also used our familiarity with the medical literature and research in progress within the specialty. There were no adequately powered trials, and only a few post-hoc or subgroup analyses of larger trials, to provide clinicians with evidence to make decisions about the treatment of patients with concomitant COPD and CVD.

Added value of this study

Our findings bridge a crucial gap by providing clinicians with evidence regarding inhaled treatments for patients with concomitant moderate COPD and CVD. In this patient group, combined inhaled corticosteroid and long-acting β-agonist treatment had no effect on overall mortality or cardiovascular events. By contrast with inhaled β-agonist therapy, inhaled corticosteroid treatment was associated with a reduction in the rate of decline of lung function. All treatments reduced the rate of moderate and severe exacerbations.

Implications of all of the available evidence

Treatment with a combination of an inhaled corticosteroid and long-acting β agonist has documented benefits in COPD. In patients with moderate COPD and CVD, these benefits do not extend to reductions in overall mortality or cardiovascular events. However, inhaled corticosteroid therapy does seem to inhibit the rate of decline in lung function.

without COPD.[4–7] Furthermore, more patients with moderate airflow limitation die from cardiovascular disease and lung cancer than from the respiratory consequences of COPD.[8,9] Several mechanisms have been proposed to link COPD with the increased risk of cardiovascular disease including shared risk factors (eg, smoking), systemic inflammation,[10] vascular dysfunction,[11] and sedentary activity secondary to the functional consequences of COPD.[12] Conversely, treatments that improve lung function and reduce exacerbations would be anticipated to reduce these factors thereby improving both respiratory and cardiovascular outcomes.[13]

The current Global Initiative for Chronic Obstructive Lung Diseases (GOLD) strategy document has highlighted the need to assess and treat comorbidities in COPD.[1] However, the evidence base is incomplete and most advice comes from expert statements or from secondary analyses of large studies. Indeed, there is disagreement on the potential effects of COPD treatment on cardiovascular outcomes. Some evidence suggests that in patients with COPD, inhaled β-agonist therapy might be associated with adverse cardiovascular outcomes.[14] On the other hand, in secondary analyses of the TOwards a Revolution in COPD Health (TORCH) trial,[15] there were apparent reductions in respiratory and cardiovascular mortality with inhaled salmeterol and fluticasone propionate. This was the rationale for this study where we address the hypothesis that inhaled corticosteroid and long-acting β-agonist therapy could improve mortality rates in patients with both COPD and cardiovascular disease.

In the Study to Understand Mortality and MorbidITy (SUMMIT), we prospectively assessed whether inhaled treatment with the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol, would improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk.

Methods

Study design and participants

This prospective double-blind parallel group placebo-controlled event-driven randomised trial was conducted at 1368 centres in 43 countries. Details of the study design and the analysis approach were published previously.[13] We recruited patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were aged 40–80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV_1) between 50% and 70% (inclusive) of the predicted value,[16] a ratio of post-bronchodilator FEV_1 to forced vital capacity (FVC) of 0·70 or less, and a score of 2 or greater on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Cardiovascular disease was defined as coronary artery disease, peripheral arterial disease, stroke, myocardial infarction, or diabetes mellitus with target organ disease. Increased cardiovascular risk was defined as aged 60 years or older and receiving medication for more than two of the following: hypercholesterolaemia, hypertension, diabetes mellitus, or peripheral arterial disease. Exclusion criteria included respiratory disorders other than COPD, lung reduction surgery, receiving long-term oxygen, or oral corticosteroid therapy, severe heart failure (New York Heart Association Class IV or ejection fraction <30%), life expectancy less than 3 years, and end-stage chronic renal disease.[13]

All patients provided written informed consent. The study was approved by local ethics committees and was

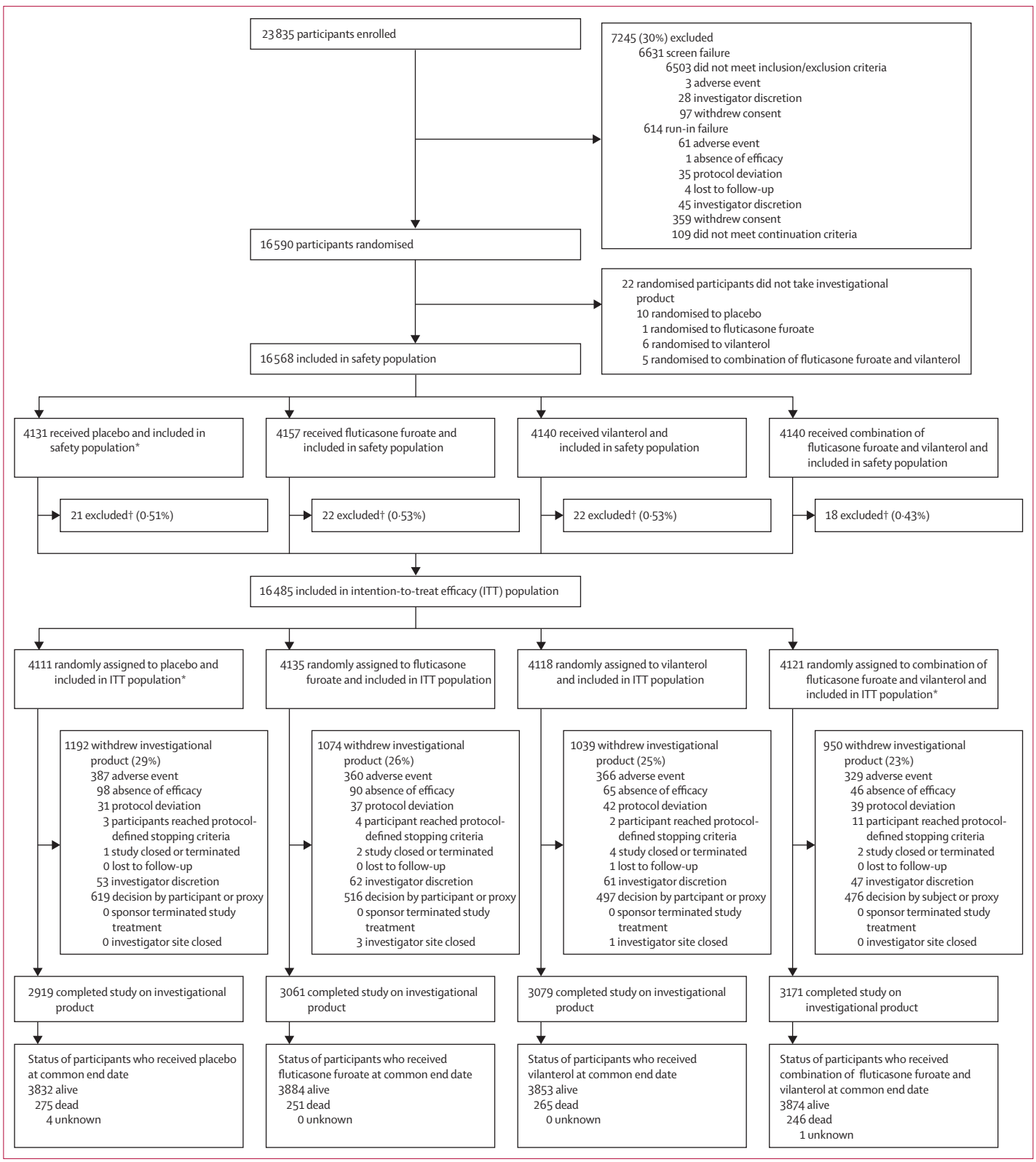


Figure 1: **Trial profile**

*One participant randomised to placebo in the intention-to-treat population was assigned to combined fluticasone furoate and vilanterol, the treatment the participant received, for most of the study, in the safety population. †Excluded participants were recruited at sites that were closed due to the result of audit findings or other information implying that the integrity of the data had been compromised.

	Placebo (n=4111)	Fluticasone furoate (n=4135)	Vilanterol (n=4118)	Combination therapy (n=4121)
Age (years)	65 (8)	65 (8)	65 (8)	65 (8)
Women	1040 (25%)	1082 (26%)	1065 (26%)	1009 (24%)
Race				
White	3328 (81%)	3358 (81%)	3339 (81%)	3332 (81%)
Asian	682 (17%)	683 (17%)	680 (17%)	679 (16%)
Other	101 (2%)	94 (2%)	99 (2%)	110 (3%)
Body-mass index (kg/m^2)	28 (6)	28 (6)	28 (6)	28 (6)
Current smokers	1936 (47%)	1945 (47%)	1929 (47%)	1868 (45%)
Smoking history (pack-years)	41 (25)	41 (24)	41 (24)	41 (24)
Post-bronchodilator FEV_1 (L)	1·70 (0·40)	1·70 (0·41)	1·70 (0·40)	1·70 (0·40)
Predicted post-bronchodilator FEV_1 (%)	59·7 (6·1)	59·6 (6·1)	59·7 (6·1)	59·7 (6·1)
FEV_1 reversibility (as a % of pre-bronchodilator FEV_1)	8·4% (12·1)	7·9% (11·7)	8·3% (12·2)	8·0% (11·8)
Pre-study COPD therapy				
Long-acting β agonist	1417 (34%)	1432 (35%)	1464 (36%)	1456 (35%)
Long-acting muscarinic agonist	659 (16%)	619 (15%)	634 (15%)	638 (15%)
Inhaled corticosteroid	1349 (33%)	1369 (33%)	1374 (33%)	1394 (34%)
Pre-study exacerbations in 12 months before study				
0	2447 (60%)	2546 (62%)	2500 (61%)	2528 (61%)
1	1044 (25%)	990 (24%)	988 (24%)	998 (24%)
2+	620 (15%)	599 (14%)	630 (15%)	595 (14%)
Cardiovascular inclusion criteria*				
Manifest disease				
Coronary artery disease	2103 (51%)	2119 (51%)	2044 (50%)	2113 (51%)
Peripheral arterial disease	766 (19%)	755 (18%)	817 (20%)	807 (20%)
Previous stroke	404 (10%)	418 (10%)	387 (9%)	386 (9%)
Previous myocardial infarction	658 (16%)	664 (16%)	722 (18%)	730 (18%)
Diabetes with target organ disease	374 (9%)	355 (9%)	377 (9%)	397 (10%)
At risk				
Hypercholesterolaemia	2112 (66%)	2051 (65%)	2191 (67%)	2125 (66%)
Hypertension	2861 (89%)	2835 (89%)	2900 (89%)	2882 (90%)
Diabetes mellitus	850 (27%)	870 (27%)	874 (27%)	886 (28%)
Peripheral arterial disease	279 (9%)	264 (8%)	301 (9%)	310 (10%)
Baseline cardiovascular therapy				
Any medication	3996 (97%)	4009 (97%)	3996 (97%)	4021 (98%)
Anti-thrombotic medication	2292 (56%)	2316 (56%)	2295 (56%)	2384 (58%)
Lipid-lowering medication	2751 (67%)	2746 (66%)	2797 (68%)	2829 (69%)
Renin-angiotensin aldosterone inhibitor therapy	2887 (70%)	2841 (69%)	2862 (69%)	2932 (71%)
β blockers	1389 (34%)	1458 (35%)	1376 (33%)	1444 (35%)
Calcium channel blockers	1551 (38%)	1606 (39%)	1569 (38%)	1593 (39%)
Nitrates	613 (15%)	556 (13%)	569 (14%)	556 (13%)
Diuretics	1508 (37%)	1541 (37%)	1549 (38%)	1550 (38%)

Data are mean (SD) or n (%). FEV_1=forced expiratory volume in 1 s. COPD=chronic obstructive pulmonary disease.
*Patients can have several cardiovascular diseases or risks at study entry.

Table 1: **Baseline characteristics of study participants**

conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Randomisation and masking

Participants were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive either placebo, fluticasone furoate, vilanterol, or the combination of fluticasone furoate and vilanterol. The randomisation schedule was generated using the GSK validated randomisation software RANDALL. A separate randomisation schedule was produced for each country. Treatment was double blind (masking was achieved with Ellipta inhalers of identical appearance) with only the database administrators having knowledge of treatment assignment.

Procedures

Participants received one of four treatments (placebo, fluticasone furoate [100 µg; GlaxoSmithKline], vilanterol [25 µg; GlaxoSmithKline], or the combination of fluticasone furoate and vilanterol [100/25 µg; Relvar/Breo, GlaxoSmithKline] given once daily as a dry powder with the use of an inhaler [Ellipta, GlaxoSmithKline]).

The use of all inhaled corticosteroids and inhaled long-acting bronchodilators was discontinued at least 48 h before study entry, although other COPD medications such as theophyllines were allowed.[13] Patients unable to tolerate withdrawal of therapy were excluded from study entry. After randomisation, patients were seen every 3 months to confirm vital status and record adverse events. Post-bronchodilator spirometry was done every 3 months and health status was assessed at 3 months then every 6 months. An independent data monitoring committee undertook safety reviews every 6 months, and one predefined interim efficacy analysis was done after about 500 deaths had occurred. The stopping guideline for efficacy was the Haybittle-Peto method (one-sided p=0·00005) in order to have a negligible effect on the final significance level.

Outcomes

The primary efficacy outcome was the time to death from any cause, regardless of maintenance of study medication. Categorisation of cause of death was done by a clinical endpoint committee using all available information including study data, death certificates, autopsy findings, and health records.[17] Secondary endpoints were on-treatment rates of decline in FEV_1 and the on-treatment composite cardiovascular endpoint of cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischaemic attack. Exacerbations were an additional outcome. Moderate exacerbations were defined as a symptomatic deterioration requiring treatment with antibiotic drugs or systemic corticosteroids, whereas severe exacerbations were defined as events leading to hospital admission.

Adverse events and medications were reviewed at each study visit. All terms that could relate to a specific adverse

event were compiled to provide a more comprehensive assessment of a specific safety term. The IDMC oversaw the ethical and safety interests of the patients by periodically reviewing cumulative data on serious adverse events in addition to the interim analysis.

Statistical analysis

This was an event-driven study in which follow-up continued until at least 1000 deaths had occurred. All data analysis decisions were determined before unblinding except for mortality by baseline therapy, which was done post hoc. To ensure no bias in the ascertainment of survival status, a "common end date" was determined several months in advance. This common end date was selected so that there would be at least 1000 deaths by this date. The common end date was set at Jan 25, 2015, and sites were required to ascertain the survival status of their patients on or after this date.

We assumed an annual placebo event rate of 3·0% per year[13,15] and the study was designed to have 90% power to detect a 30% reduction in all-cause mortality (hazard ratio=0·70) on combination therapy compared with placebo at the two-sided 1% significance level.[13] Statistical significance was taken as two-sided p<0·05. To control for multiplicity of testing of combination treatment versus placebo across endpoints, a closed testing procedure (gatekeeper) approach was planned. The hierarchy was the primary endpoint followed by the rate of decline in FEV_1 followed by the composite cardiovascular endpoint. If significance at the 5% level was not achieved for the primary endpoint for the comparison of combination treatment with placebo, then the tests for the secondary and other efficacy endpoints would be interpreted as descriptive only. The primary efficacy endpoint was analysed using a Cox proportional hazards regression model allowing for covariates of age and sex. A similar model was used for the time to the first on-treatment composite cardiovascular event, with the inclusion of two additional covariates: the presence of ischaemic heart disease (eg, previous myocardial infarction) or vascular disease (eg, previous stroke) at baseline. The rate of decline was analysed with a random coefficients model allowing for covariates of age, sex, and baseline FEV_1. The slope was calculated from 90 days, to ensure that any initial short-term increase in FEV_1 did not overestimate any treatment benefit on the slope. The frequency of exacerbations was analysed with the use of a generalised linear model (assuming a negative binomial distribution, which accounts for variability among patients in the number and frequency of exacerbations), with the number of exacerbations as the outcome and the logarithm of time during which treatment was received as an offset variable. The reduction in exacerbation rate was expressed as a percentage by dividing the rate of the treatment group by the rate of the placebo group then subtracting from one to convert to a percentage reduction. Adverse events of special interest were compared between treatment groups with Kaplan-Meier estimates.

Data were analysed with SAS (version 9.3).

Scientific oversight of the trial was provided by a scientific steering committee composed of six academic researchers and three employees from GlaxoSmithKline, who were collectively responsible for the study design and conduct, for approval of the statistical analysis plan, and for the review and interpretation of the data.

This study is registered with ClinicalTrials.gov, number NCT01313676.

Role of the funding source

The study was designed by the funder (GlaxoSmithKline) in collaboration with the academic members of the steering committee. The sponsor was responsible for the running of the trial, data collection, and statistical analysis. Statistical analyses were done by a contract

	Placebo (n=4131)	Fluticasone furoate (n=4157)	Vilanterol (n=4140)	Combination therapy (n=4140)
Any adverse event	2782 (67%)	2820 (68%)	2809 (68%)	2780 (67%)
Adverse event leading to discontinuation of study medication	397 (10%)	367 (9%)	370 (9%)	342 (8%)
Serious adverse event	918 (22%)	929 (22%)	972 (23%)	961 (23%)
Fatal adverse event	192 (5%)	183 (4%)	198 (5%)	182 (4%)
Total exposure to study medication (patient-years)	6614	6889	6955	7038
Adverse events of special interest*				
Local steroid events	146 (4%) [2·7, 2·3–3·1]	209 (5%) [3·9, 3·4–4·4]	152 (4%) [2·5, 2·1–2·9]	225 (5%) [4·2, 3·8–4·7]
All cardiovascular events	695 (17%) [16·4, 15·4–17·4]	699 (17%) [15·7, 14·8–16·7]	707 (17%) [15·7, 14·8–16·6]	735 (18%) [16·3, 15·4–17·3]
Cardiac arrhythmias	211 (5%) [4·1, 3·6–4·6]	229 (6%) [4·1, 3·6–4·6]	224 (5%) [3·9, 3·4–4·4]	209 (5%) [3·9, 3·4–4·3]
Lower respiratory tract infections excluding pneumonia	226 (5%) [4·7, 4·2–5·2]	238 (6%) [4·5, 4·0–5·0]	220 (5%) [4·2, 3·7– 4·7]	221 (5%) [4·2, 3·8–4·7]
Pneumonia	214 (5%) [3·8, 3·4–4·3]	228 (5%) [4·2, 3·8–4·8]	163 (4%) [2·8, 2·4–3·2]	237 (6%) [3·9, 3·5–4·4]
Hypersensitivity	143 (3%) [2·6, 2·2–3·0]	147 (4%) [2·7, 2·3–3·1]	160 (4%) [2·8, 2·5– 3·3]	175 (4%) [3·0, 2·6–3·4]
Bone disorders including fractures	78 (2%) [1·3, 1·1–1·6]	79 (2%) [1·5, 1·2–1·8]	88 (2%) [1·6, 1·3– 1·9]	96 (2%) [1·6, 1·3–1·9]
Hyperglycaemia/new onset diabetes mellitus	156 (4%) [2·7, 2·3–3·1]	153 (4%) [2·6, 2·2–3·0]	134 (3%) [2·3, 1·9– 2·7]	148 (4%) [2·3, 2·0–2·7]
Corticosteroid-associated eye disorder	43 (1%) [0·8, 0·6–1·0]	62 (1%) [1·0, 0·8–1·3]	59 (1%) [1·0, 0·8– 1·2]	57 (1%) [1·0, 0·8–1·3]
Hyperkalaemia or hypokalaemia	23 (<1%) [0·3, 0·2–0·5]	23 (<1%) [0·3, 0·2–0·5]	28 (<1%) [0·4, 0·3– 0·6]	31 (<1%) [0·5, 0·3–0·7]
Tremor	11 (<1%) [0·2, 0·1–0·3]	11 (<1%) [0·2, 0·1–0·3]	16 (<1%) [0·2, 0·1– 0·4]	12 (<1%) [0·2, 0·1–0·3]
Adrenal suppression	1 (<1%) [<0·1, 0·0–0·1]	3 (<1%) [<0·1, 0·0–0·1]	0	1 (<1%) [<0·1, 0·0–0·1]

Data are n (%), patient-years, or n (%) [rate per 100 patient-years, 95% CI]. *Defined as adverse events of interest associated with the known pharmacological action of inhaled corticosteroids or long-acting β-agonist therapy.

Table 2: **Reported adverse events among 16 568 patients in the safety population**

research organisation (Veramed Ltd, Twickenham, UK; funded by GSK) on behalf of, and with oversight from, employees of the funder. The first draft of the report was written by the primary academic author, and all the authors worked collaboratively to prepare the final content. All authors made the decision to submit the manuscript for publication. All the authors had full access to the data and vouch for the accuracy and completeness of all data and analyses, and for the fidelity of the study to the protocol. The corresponding author had access to all the data and had final responsibility for the decision to submit for publication.

Results

Between Jan 24, 2011, and March 12, 2014, 23 835 patients were screened at 1583 centres in 43 countries and 16 590 underwent randomisation (figure 1). Of these, 22 participants never took study medication and the safety population therefore consists of 16 568 patients. Data from five centres (83 patients) were excluded from the efficacy analysis because of failure to meet the standards of Good Clinical Practice and ethical practice, and were closed before the study ended. Thus, a total of 16 485 patients were included in the intention-to-treat efficacy (ITT) population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group (table 1).

About a third of patients stopped inhaled corticosteroids before study entry, with a similar proportion stopping long-acting β agonists. 6464 (39%) patients reported having had a COPD exacerbation in the year before entry.

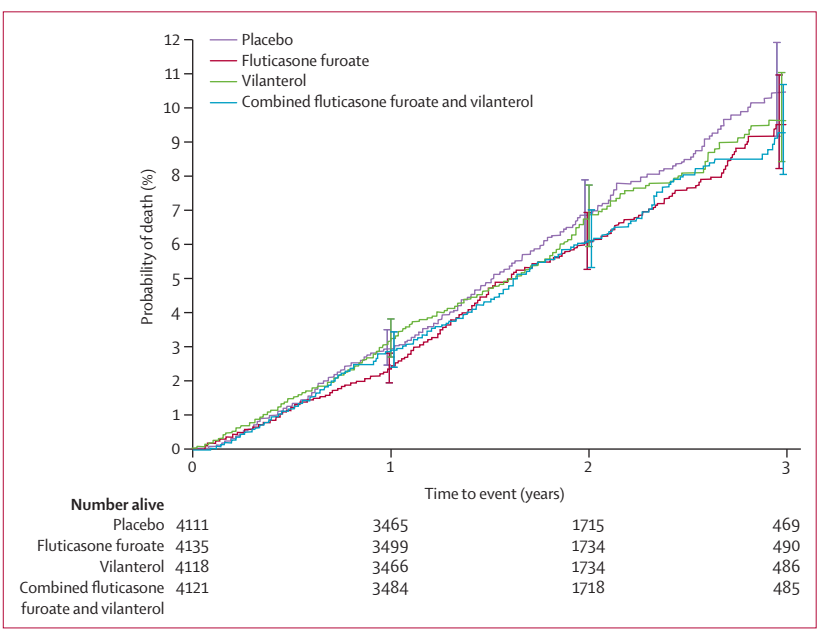


Figure 2: **Probability of death (primary endpoint)**
Error bars represent 95% CI.

Quality of life questionnaires were collected in a subset of patients (4443 [27%]). In this subset of patients, the mean baseline scores were 45–46 across all treatment groups on the St George's Respiratory Questionnaire (SGRQ) scale, and 18–19 on the COPD Assessment Test (CAT). Three-quarters of patients had established cardiovascular disease or diabetes mellitus with end-organ disease (n=11 662 [71%]), whereas a quarter (n=4641 [28%]) had an increased risk of cardiovascular disease only. Blood pressure at entry was on average about 135/80–81 mm Hg across all treatment groups. 182 patients failed to meet the cardiovascular entry criteria but were included in all analyses. More patients withdrew from study medication in the placebo group (29%) than in the three other groups: the lowest withdrawal rates were seen with combination therapy (23%). The maximum follow-up was 4 years; median study exposure was 1·8 years (IQR 1·2–2·6) and was similar across all treatment groups. Treatment exposure was highest with combination therapy followed by vilanterol, fluticasone furoate, and then placebo (table 2). The rate of adherence to treatment was similar in all groups with only 494 patients (3%) taking less than 80% of prescribed study medication doses.

Vital status was known for 16 480 (99·97%) of 16 485 patients in the ITT population. At the common end date, there were 1037 deaths: 24 deaths occurred after the common end date with ten still receiving study medication. The proportions of deaths from any cause were 6·7% (n=275) in the placebo group, 6·1% (n=251) in the fluticasone furoate group, 6·4% (n=265) in the vilanterol group, and 6·0% (n=246) in the combination therapy group. Compared with placebo, all-cause mortality was unaffected by combination therapy (absolute risk reduction for death with combination therapy 0·7%, hazard ratio [HR] 0·88 [95% CI 0·74–1·04]; 12% relative reduction [95% CI –4 to 26]; p=0·137) or the components (fluticasone furoate, HR 0·91 [0·77–1·08]; p=0·284; vilanterol, 0·96 [0·81–1·14]; p=0·655; figure 2). There was no significant heterogeneity according to age, sex, baseline therapy, or presence of cardiovascular disease. The risk of death in the fluticasone furoate group and the vilanterol group did not differ from the placebo group (table 3). Overall, 43% of deaths were adjudicated as due to cardiovascular causes, 23% to cancer, and 13% to pulmonary causes (table 3).

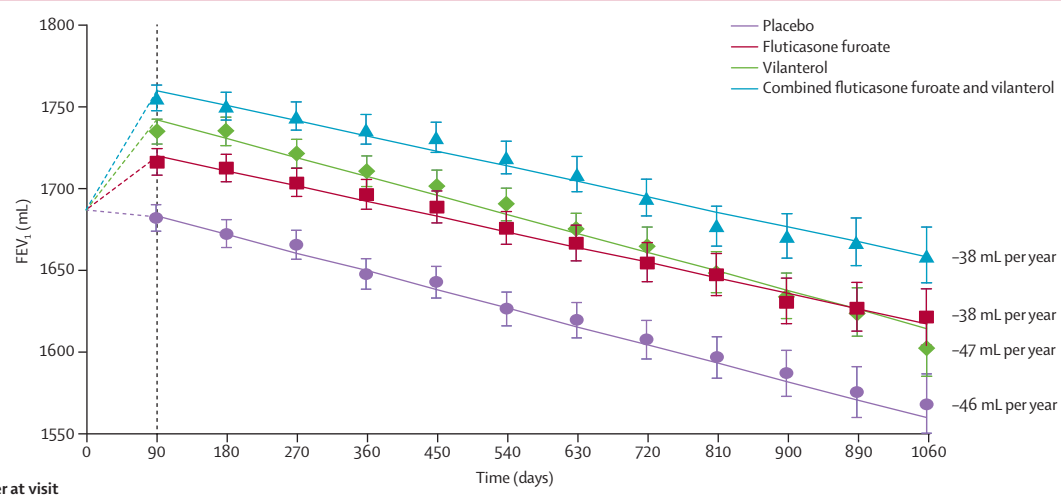
On-treatment rates of FEV_1 decline were 46 mL per year (SE 2·5) in the placebo group, 38 mL per year (2·4) in the fluticasone furoate group (difference from placebo 8 mL per year [95% CI 1–14]), 47 mL per year in the vilanterol group (2·4; difference from placebo –2 mL per year [95% CI –8 to 5]), and 38 mL per year (2·4) in the combination treatment group (difference from placebo 8 mL per year [1 to 15]; figure 3; table 2). Because combination treatment did not reduce overall mortality (the primary outcome), statistical inferences from these findings cannot be made.

The proportions of patients with an on-treatment composite cardiovascular endpoint were 4·2% (n=173) in the placebo group, 3·9% (n=161) in the fluticasone furoate group, 4·4% (n=180) in the vilanterol group, and 4·2% (n=174) in the combination therapy group (table 3). Compared with placebo, combination therapy had no effect on the composite cardiovascular endpoint (HR 0·93 [95% CI 0·75–1·14]). Similarly, the composite

	Placebo (n=4111)	Fluticasone furoate (n=4135)	p value *vs* placebo	Vilanterol (n=4118)	p value *vs* placebo	Combination therapy (n=4121)	p value *vs* placebo
All-cause mortality	275 (6·7%)	251 (6·1%)	0·284*	265 (6·4%)	0·655*	246 (6·0%)	0·137
Cause-specific mortality							
Cardiovascular	122 (3·0%)	97 (2·3%)	..	118 (2·9%)	..	108 (2·6%)	..
Pulmonary	35 (0·9%)	34 (0·8%)	..	33 (0·8%)	..	35 (0·8%)	..
Cancer	62 (1·5%)	59 (1·4%)	..	61 (1·5%)	..	56 (1·4%)	..
Other	20 (0·5%)	21 (0·5%)	..	25 (0·6%)	..	22 (0·5%)	..
Unknown	36 (0·9%)	40 (1·0%)	..	28 (0·7%)	..	25 (0·6%)	..
Decline in post-bronchodilator FEV_1 (mL per year)	46 (2·5)	38 (2·4)	0·026*	47 (2·4)	0·654*	38 (2·4)	0·019*
First composite cardiovascular event	173 (4·2%)	161 (3·9%)	0·317*	180 (4·4%)	0·908*	174 (4·2%)	0·478*
Myocardial infarction	38 (0·9%)	45 (1·1%)	..	44 (1·1%)	..	46 (1·1%)	..
Unstable angina	26 (0·6%)	16 (0·4%)	..	22 (0·5%)	..	19 (0·5%)	..
Stroke	33 (0·8%)	33 (0·8%)	..	30 (0·7%)	..	31 (0·8%)	..
Transient ischaemic attack	8 (0·2%)	7 (0·2%)	..	12 (0·3%)	..	7 (0·2%)	..
Sudden death	62 (1·5%)	53 (1·3%)	..	62 (1·5%)	..	63 (1·5%)	..
Procedural death	1 (<0·1%)	1 (<0·1%)	..	0	..	0	..
Other cardiovascular death	5 (0·1%)	6 (0·1%)	..	10 (0·2%)	..	8 (0·2%)	..
Annual rate of moderate and severe exacerbations	0·35	0·31	0·004*	0·31	0·017*	0·25	<0·0001*
Annual rate of severe exacerbations	0·07	0·06	0·023*	0·06	0·013*	0·05	0·0004*

Data are n (%) or mean (SE). FEV_1=forced expiratory volume in 1 sec *All p values are versus placebo and are nominal for descriptive purposes only.

***Table 3*: Primary and secondary outcomes and exacerbations of chronic obstructive pulmonary disease**



Number at visit

Placebo	3800	3782	3563	3396	3279	2678	2197	1858	1498	1171	949	736	486
Fluticasone furoate	3879	3858	3688	3580	3452	2777	2311	1936	1569	1246	1001	792	528
Vilanterol	3866	3830	3658	3554	3438	2813	2347	1971	1612	1300	1043	831	542
Combined fluticasone furoate and vilanterol	3912	3883	3731	3610	3505	2864	2391	1997	1633	1290	1035	827	545

***Figure 3*: On-treatment rate of decline in forced expiratory volume in 1 s (FEV_1; secondary endpoint)**
Error bars represent 95% CIs.

cardiovascular endpoint in the fluticasone furoate (HR 0·90 [95% CI 0·73–1·11]) and vilanterol (0·99 [0·80–1·22]) groups did not differ from placebo.

Compared with placebo, the percent reduction in moderate and severe exacerbations was 12% (95% CI 4–19) for the fluticasone furoate group, 10% (2–18) for the vilanterol group, and 29% (22–35) for the combination group (table 3). For exacerbations requiring hospital admissions the percent reduction was 18% (95% CI 3–31) for the fluticasone furoate group, 20% (5–32) for the vilanterol group, and 27% (13–39) for the combination group compared with placebo. As with FEV_1 decline, these findings can only be viewed descriptively as combination treatment did not reduce overall mortality (the primary outcome).

Adverse events were reported by 68% of patients in the study, and serious adverse events were reported by 23% of patients. In the placebo group, 2782 patients (67%) experienced an adverse event and 918 (22%) experienced a serious adverse event; in the fluticasone furoate, vilanterol, and combination therapy groups the numbers were 2820 (68%) and 929 (22%), 2809 (68%) and 972 (23%), and 2780 (67%) and 961 (23%), respectively. The most frequently reported adverse event was an exacerbation of COPD. There was no excess of pneumonia, cardiac disorders, or arrhythmias across all treatment groups. There were no differences in the incidence of fractures or eye disorders, whereas more patients allocated to fluticasone furoate experienced local steroid effects (oral candidiasis and hoarseness; table 2).

Discussion

To the best of our knowledge, SUMMIT is the largest survival study to date of an inhaled corticosteroid and long-acting β agonist in patients with COPD and heightened cardiovascular risk. In more than 16 000 patients, treatment with inhaled fluticasone furoate and vilanterol had no significant effect on all-cause mortality or cardiovascular outcomes. Inhaled therapy improved lung function and fluticasone furoate, alone or in combination with vilanterol, was associated with a reduction in the rate of decline in FEV_1. We conclude that inhaled combination fluticasone furoate and vilanterol does not affect overall survival or cardiovascular outcomes.

In the previous TORCH trial,[9] inhaled combination therapy with salmeterol and fluticasone propionate seemed to be associated with a 2·6% absolute reduction (17·5% relative risk reduction) in all-cause mortality in patients with moderate-to-severe COPD although this fell short of statistical significance (p=0·052). Many of these deaths were cardiovascular and a post-hoc analysis suggested that the combination treatment might reduce cardiovascular mortality.[15] In SUMMIT, we tested the hypothesis that greater mortality reductions might occur in populations with COPD that are enriched for cardiovascular disease. We report that the point estimate for all-cause mortality was 0·7% (12% relative reduction) lower with combined fluticasone furoate and vilanterol therapy than with placebo. This difference was not statistically significant and the trial did not reach its primary endpoint. However, it should be acknowledged that a clinically meaningful difference in mortality has not been entirely excluded because the 95% CI for the HR encompasses a 26% reduction in the risk of dying.

The absence of an effect on overall survival has several potential explanations including a failure to take sufficient active therapy, inadequate dosing, or an absence of effect on lung function in patients with less severe COPD. However, recorded adherence to treatment was high and patients receiving fluticasone furoate had the expected side-effects. As anticipated, we noted improvements in FEV_1 with both fluticasone furoate and vilanterol confirming the efficacy of the two interventions. We therefore do not believe that the failure to reach the primary endpoint was due to inadequate dosing or an absence of an effect on COPD. Finally, whether more prolonged follow-up would have been beneficial to increase the number of events, to extend drug exposure, and to acquire a more precise point estimate of a potential treatment effect is interesting to speculate.

We prespecified the first secondary endpoint as the rate of decline in FEV_1 to assess the efficacy of the trial intervention on respiratory pathophysiology and disease progression. Given the hierarchical analysis plan, these findings should not be viewed as conclusive because the primary endpoint was not met. We noted that the components seemed to have a differential treatment effect on the rate of decline in FEV_1. There was a consistent reduction in the rate of decline in FEV_1 associated with fluticasone furoate-containing groups that was not noted with vilanterol. In assessment of the effect of a decrease of 8 mL per year, it should be taken into account that in the general population FEV_1 normally declines at a rate of 25–30 mL per year and that this mean reduction could be viewed as between a third and half of the excess decline observed in this study population. Additionally, up to half of patients with COPD do not experience an accelerated decline suggesting that some patients might experience larger effects.[18] This observation suggests that treatments that include inhaled corticosteroids might inhibit lung inflammation and the decline in lung function attributable to COPD as noted in much smaller studies of patients with moderate COPD.[19] This also suggests that treatment of COPD at an earlier stage of the disease process has the potential for long-term benefits in preservation of lung function. The beneficial effect of inhaled corticosteroids on FEV_1 decline in this study as well as in the TORCH study[20] probably reflects the large sample size and power of these studies compared with earlier trials.[21–24] Inhaled corticosteroids could affect decline in lung function without having a notable effect on overall mortality in

view that we only followed study participants for slightly less than 2 years on average, a follow-up period too short to capture a mortality benefit in those with only moderate disease. There were fewer moderate and severe exacerbations in all treatment groups in SUMMIT supporting a beneficial effect for COPD drug treatment, even in patients with milder COPD.

For many clinicians and especially cardiologists, the use of inhaled β agonists in patients with cardiovascular disease has been of concern. Some have suggested that inhaled β agonists are proarrhythmic and could precipitate myocardial infarction or sudden death.[14] In our study, we have intentionally enriched our study population with patients who had established, or were at high risk of, cardiovascular disease. Despite this enrichment, we detected no evidence of adverse cardiovascular events either self-reported or as adjudicated cardiovascular endpoints. The point estimates for all trial interventions were favourable and there was no suggestion of an adverse cardiovascular safety signal. We believe that this study highlights the cardiovascular safety of use of long-acting β agonists and inhaled corticosteroids in patients with COPD and heightened cardiovascular risk. Despite the enrichment for patients with cardiovascular risk, we noted lower rates of cardiovascular events than anticipated. This difference could reflect the frequent use of highly effective preventive treatments, such as antiplatelet, lipid-lowering, and renin-angiotensin system inhibitor therapies, in our study population. These evidenced-based therapies will substantially reduce cardiovascular events and this might have hindered our ability to show a beneficial effect with the study intervention.

An increased risk of pneumonia was one of the main findings of the TORCH trial[9,25] and has been reported in other studies of inhaled corticosteroids in patients with COPD,[26] including fluticasone furoate.[27] Reassuringly, we noted no such effect in our study. There were no detectable differences in pneumonia rates between patients receiving placebo and those receiving fluticasone furoate alone or in combination with vilanterol. This probably reflects the lower rates of pneumonia and the lower rates of bacterial colonisation in the airways of patients with milder COPD.[28] The apparent lower risk of pneumonia in patients receiving vilanterol alone was unanticipated and we do not have a ready explanation for this unexpected finding.

In conclusion, in patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol does not affect mortality or cardiovascular outcomes, but is associated with fewer exacerbations of COPD and is well tolerated. Fluticasone furoate, alone or in combination with vilanterol, seems to reduce the rate of decline in FEV_1.

Contributors

JV and DEN wrote the draft report. All authors discussed the draft and provided comments and suggestions for change. All authors have approved the final report.

Members of the Steering Committee

Jørgen Vestbo (co-chair, UK), Robert D Brook (USA), Peter M A Calverley (UK), Bartolome R Celli (USA), Fernando Martinez (USA), David E Newby (UK), Courtney Crim, (co-chair, GlaxoSmithKline, USA), Julie A Anderson (GlaxoSmithKline, UK), Julie Yates (GlaxoSmithKline, USA).

Members of the Independent Data Monitoring Committee

Peter Lange (chair, Denmark), Richard Kay (UK), Mark Dransfield (USA), Sanjay Rajagopalan (USA).

Members of the Clinical Endpoint Committee

Robert Wise (chair, USA), Dennis Niewoehner (USA), Camilo Gomez (USA), Sheldon Madger (Canada), Martin Denvir (UK), Pierre Amarenco (France).

Declaration of interests

JV reports personal fees from GlaxoSmithKline during the conduct of the study as well as personal fees from GlaxoSmithKline, Chiesi Pharmaceuticals, Boehringer Ingelheim, Novartis, and AstraZeneca outside of the submitted work. JAA is an employee of GlaxoSmithKline and therefore reports personal fees from GlaxoSmithKline during the conduct of the study as well as outside of the submitted work. RDB reports personal fees from GlaxoSmithKline during the conduct of the study. PMAC reports personal fees from GlaxoSmithKline during the conduct of the study as well as personal fees from Boehringer Ingelheim, GlaxoSmithKline, AstraZeneca, and Takeda outside of the submitted work. BRC reports personal fees from GlaxoSmithKline during the conduct of the study as well as personal fees from Boehringer Ingelheim, AstraZeneca, Almirall, Rox Medical, and Novartis outside of the submitted work. CC is an employee of GlaxoSmithKline and therefore reports personal fees from GlaxoSmithKline during the conduct of the study as well as outside of the submitted work. FM reports non-financial support from GlaxoSmithKline during the conduct of the study as well as personal fees from Forest, Janssens, Nycomed/Takeda, Actelion, Amgen, AstraZeneca, Carden Jennings, CSA Medical, Ikaria, Genentech, Merck, Pearl, Pfizer, Roche, American College of Chest Physicians, CME Incite, Center for Healthcare Education, Inova Health System, MedScape, Miller Medical, National Association for Continuing Education, Paradigm, Peer Voice, Projects in Knowledge, St John's Hospital, St Mary's Hospital, University of Illinois Chicago, University of Virginia, UpToDate, Wayne State University, Boehringer Ingelheim, Bayer, Merion, Informa, GlaxoSmithKline, Western Society of Allergy and Clinical Immunology, Theravance, Novartis, Haymarket, Annenberg, Academic CME, Integritas, Unity, and Sunovion outside of the submitted work. JY is an employee of GlaxoSmithKline and therefore reports personal fees from GlaxoSmithKline during the conduct of the study as well as outside of the submitted work. DEN reports personal fees from GlaxoSmithKline during the conduct of the study.

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