Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial

Alberto Papi, Jørgen Vestbo, Leonardo Fabbri, Massimo Corradi, Hélène Prunier, Géraldine Cohuet, Alessandro Guasconi, Isabella Montagna, Stefano Vezzoli, Stefano Petruzzelli, Mario Scuri, Nicolas Roche, Dave Singh**

Lancet 2018; 391: 1076–84

Published Online February 8, 2018 http://dx.doi.org/10.1016/S0140-6736(18)30206-X

This online publication has been corrected. The corrected version first appeared at thelancet.com on February 26, 2018

See **Comment** page 1004

*Contributed equally

Research Centre on Asthma and COPD, University of Ferrara, Ferrara, Italy (Prof A Papi MD); **Division of Infection, Immunity and Respiratory Medicine and Manchester University NHS Foundation Trust, University of Manchester, Manchester, UK** (Prof J Vestbo DrMedSci, Prof D Singh MD); **Department of Medicine, University of Ferrara, Ferrara, Italy** (Prof L Fabbri MD); **COPD Center, Sahlgrenska University Hospital, Gothenburg, Sweden** (Prof L Fabbri); **Department of Medicine and Surgery, University of Parma, Italy** (Prof M Corradi MD); **Global Clinical Development, Chiesi Farmaceutici SpA, Parma, Italy** (H Prunier MSc, G Cohuet MSc, A Guasconi MSc, I Montagna MSc, S Vezzoli MSc, S Petruzzelli MD, M Scuri MD); **Hôpital Cochin (APHP), Université Paris-Descartes (EA2511), Service de Pneumologie et Soins Intensifs Respiratoires, Paris, France** (Prof N Roche MD); **and Medicines Evaluation Unit, Manchester, UK** (Prof D Singh)

Correspondence to: Prof Alberto Papi, Research Centre on Asthma and COPD, University of Ferrara, Ferrara 44121, Italy **ppa@unife.it**

Summary

Background **Evidence is scarce on the relative risk-benefit of inhaled triple therapy, consisting of inhaled corticosteroid, long-acting muscarinic antagonist, and long-acting β_2-agonist, versus dual bronchodilation for chronic obstructive pulmonary disease (COPD). We aimed to compare a single-inhaler triple combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium (BDP/FF/G) versus a single-inhaler dual bronchodilator combination of indacaterol plus glycopyrronium (IND/GLY) in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.**

Methods **This randomised, parallel-group, double-blind, double-dummy study was done at 187 sites across 17 countries. Eligible patients had symptomatic COPD, severe or very severe airflow limitation, at least one moderate or severe exacerbation in the previous year, and were receiving inhaled maintenance medication. After a 2 week run-in period with one inhalation per day of IND/GLY (85 µg/43 µg), patients were randomly assigned (1:1), via an interactive response technology system, to receive 52 weeks of treatment with two inhalations of extrafine BDP/FF/G (87 µg/5 µg/9 µg) twice per day or one inhalation of IND/GLY (85 µg/43 µg) per day. Randomisation was stratified by country and severity of airflow limitation. The primary endpoint was the rate of moderate-to-severe COPD exacerbations across 52 weeks of treatment in all randomised patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02579850.**

Findings **Between May, 29 2015, and July 10, 2017, 1532 patients received BDP/FF/G (n=764) or IND/GLY (n=768). Moderate-to-severe exacerbation rates were 0·50 per patient per year (95% CI 0·45–0·57) for BDP/FF/G and 0·59 per patient per year (0·53–0·67) for IND/GLY, giving a rate ratio of 0·848 (0·723–0·995, p=0·043) in favour of BDP/FF/G. Adverse events were reported by 490 (64%) of 764 patients receiving BDP/FF/G and 516 (67%) of 768 patients receiving IND/GLY. Pneumonia occurred in 28 (4%) patients receiving BDP/FF/G versus 27 (4%) patients receiving IND/GLY. One treatment-related serious adverse event occurred in each group: dysuria in a patient receiving BDP/FF/G and atrial fibrillation in a patient receiving IND/GLY.**

Interpretation **In patients with symptomatic COPD, severe or very severe airflow limitation, and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G significantly reduced the rate of moderate-to-severe exacerbations compared with IND/GLY, without increasing the risk of pneumonia.**

Funding **Chiesi Farmaceutici.**

Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent respiratory symptoms and airflow limitation that is usually caused by significant exposure to noxious particles or gases.[1] Chronic inflammation causes structural changes, narrowing of small airways, and destruction of the lung parenchyma, resulting in persistent airflow limitation, chronic respiratory symptoms, and exacerbations.[1] Inhaled triple therapy, consisting of a corticosteroid, a long-acting β_2-agonist, and a long-acting muscarinic antagonist, is recommended by the Global Initiative for Obstructive Lung Disease for patients who have further exacerbations despite dual bronchodilation with a long-acting β_2-agonist plus a long-acting muscarinic antagonist or a long-acting β_2-agonist plus an inhaled corticosteroid.[1] Triple therapy is commonly used in clinical practice,[2,3] but there is little evidence to support the risk-benefit of triple therapy versus dual bronchodilation. In particular, no studies have directly compared single-inhaler triple therapy with single-inhaler dual bronchodilator therapy for reducing exacerbations.

A single-inhaler triple therapy is available consisting of an extrafine formulation (ie, with mass median aerodynamic diameter <2 µm) of the inhaled corticosteroid beclometasone dipropionate (BDP), the long-acting β_2-agonist formoterol fumarate (FF), and the long-acting muscarinic antagonist glycopyrronium (G). Two previous 52 week studies have already assessed the efficacy and safety of this combination: in the TRILOGY

Research in context

Evidence before this study

We searched PubMed for articles published before Jan 4, 2018, using the search term *"Drug Therapy, Combination"[MeSH Terms] OR triple AND COPD AND trial*, with no limits applied. Of the 565 search results, 30 presented data from clinical trials investigating the efficacy of triple therapy consisting of an inhaled corticosteroid plus a long-acting β_2-agonist plus a long-acting muscarinic antagonist. Only two of these studies included a group receiving a long-acting β_2-agonist plus a long-acting muscarinic antagonist. One study compared the efficacy of triple therapy or dual bronchodilation with that of long-acting muscarinic antagonist monotherapy; although there were no formal statistical comparisons between triple therapy and dual bronchodilation, compared with patients receiving dual bronchodilation fewer patients receiving triple therapy had an exacerbation during the 1 year follow-up. The second study recruited patients who were newly diagnosed with COPD following referral for a surgical intervention for lung cancer, and who were then randomised to 1 week of treatment with triple therapy or dual bronchodilation.

Added value of this study

TRIBUTE is, to our knowledge, the first long-term study to specifically compare the effects of triple therapy in a single inhaler with those of dual bronchodilation on the rate of exacerbations.

Implications of all the available evidence

Compared with dual bronchodilator therapy, triple therapy with an inhaled corticosteroid, a long-acting β_2-agonist, and a long-acting muscarinic antagonist in a single inhaler reduces the rate of COPD exacerbations in patients with symptomatic COPD, an FEV_1 of less than 50%, and an exacerbation history, despite maintenance therapy.

study,[4] BDP/FF/G reduced the rate of COPD exacerbations by 23% compared with BDP/FF, whereas in TRINITY,[5] BDP/FF/G reduced the rate of COPD exacerbations by 20% compared with the long-acting muscarinic antagonist tiotropium.[5] In the present study, TRIBUTE, we compared the effects of BDP/FF/G with those of a single-inhaler combination of the long-acting β_2-agonist indacaterol plus glycopyrronium (IND/GLY). We chose IND/GLY as the comparator in this study because this combination has shown greater efficacy than both long-acting muscarinic antagonist monotherapy and the combination of an inhaled corticosteroid plus long-acting β_2-agonist in terms of the rate of moderate-to-severe exacerbations.[6,7] We aimed to compare BDP/FF/G with IND/GLY in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.

Methods

Study design

TRIBUTE was a randomised, parallel-group, double-blind, double-dummy, active-controlled phase 3b study, done at 187 sites across 17 countries (appendix). The sites were a mixture of primary (n=37), secondary (n=104) and tertiary care centres (n=1), and specialised investigation units (n=45).

Patients who met the inclusion and exclusion criteria at screening (visit 1) had their COPD maintenance therapy switched to one inhalation of IND/GLY per day for a 2 week open-label run-in period (appendix). At the end of the run-in (visit 2), patients were randomised 1:1 to either continue with IND/GLY or to receive BDP/FF/G.

The study was approved by the ethics committee or institutional review board at each site, and was done in accordance with the declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice (ICH/CPMP/135/95). No substantial protocol amendments were made that affected any randomised patients.

Patients

Eligible patients were aged 40 years or older; current or ex-smokers; had a diagnosis of COPD, with a ratio of post-bronchodilator (salbutamol 400 µg) forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 0·7, and severe or very severe airflow limitation (FEV_1 <50%); had at least one documented moderate or severe COPD exacerbation in the previous 12 months; were symptomatic at screening, with a COPD Assessment Test total score of at least 10; and, for at least 2 months before screening had used an inhaled corticosteroid plus a long-acting β_2-agonist, an inhaled corticosteroid plus a long-acting muscarinic antagonist, a long-acting β_2-agonist plus a long-acting muscarinic antagonist, or long-acting muscarinic antagonist monotherapy, but not triple therapy. All patients provided written informed consent prior to any study-related procedure.

Key exclusion criteria were a current diagnosis of asthma with a physician-judged need for inhaled or oral corticosteroid therapy for this disorder; clinically significant cardiovascular disorders or laboratory abnormalities; and unstable concurrent disease that could have affected efficacy or safety (as judged by the investigator). The full list of inclusion and exclusion criteria is available in the appendix.

See Online for appendix

Randomisation and masking

Patients were randomly assigned to treatment groups by central randomisation stratified by country and severity of airflow limitation (post-bronchodilator FEV_1 categories <30% predicted or 30% to <50% predicted) in accordance with a randomisation list generated by the interactive response technology provider. Patients, investigators, site

staff, and sponsor personnel were masked to treatment assignment for the duration of the study by use of a double-dummy approach, with each patient using both a pressurised metered-dose inhaler (containing BDP/FF/G or placebo) and a single-dose dry-powder inhaler (placebo or IND/GLY).

Procedures

During the run-in phase (starting at visit 1), all patients received one inhalation of IND 85 µg/GLY 43 µg per day via a single-dose dry-powder inhaler (Ultibro Breezhaler, Novartis Europharm, Camberley, UK). After randomisation, patients received 52 weeks of either one inhalation of IND 85 µg/GLY 43 µg per day or two actuations of extrafine BDP 87 µg/FF 5 µg/G 9 µg (corresponding to a nominal dose of 100/6/10 µg) twice per day via a pressurised metered-dose inhaler. Placebo was delivered with a pressurised metered-dose inhaler or a single-dose dry-power inhaler, depending on which treatment the patient had been assigned. During the 52 week treatment period, patients attended visits at weeks 4, 12, 26, 40, and 52. As rescue medication, patients were permitted to use either salbutamol via a pressurised metered-dose inhaler or terbutaline via a dry-powder inhaler, but not within 6 h before any spirometric assessment. Other non-permitted COPD medications are listed in the appendix.

On the morning of the randomisation visit (visit 2), baseline (pre-dose) data were collected for spirometry (FEV_1 and FVC, with centralised spirometry), St George's Respiratory Questionnaire (SGRQ), a measure of health-related quality of life, and the COPD Assessment Test. At each subsequent visit, pre-dose (morning) spirometry was done, and SGRQ data were collected. Patients recorded daily symptoms in an electronic diary using the EXAcerbations of Chronic pulmonary disease Tool Patient-Reported Outcome (EXACT-PRO) questionnaire, together with study and rescue medication use. Data from the COPD Assessment Test were collected at the end of the treatment period.

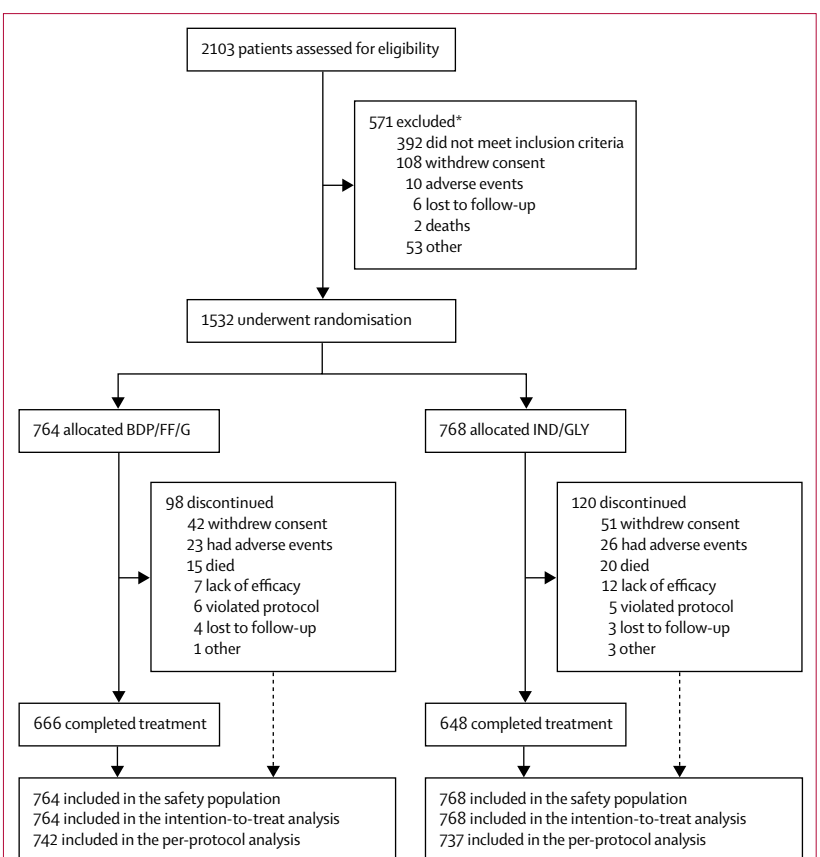

Figure 1: **Trial profile**
BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium. *320 were excluded after receiving at least one dose of run-in medication (IND/GLY) and 251 were excluded before receiving run-in medication.

Outcomes

The primary outcome was the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment. The secondary efficacy variables were time to first moderate or severe exacerbation and time to first severe COPD exacerbation; rate of severe and of moderate COPD exacerbations; pre-dose FEV_1, pre-dose FVC, and SGRQ total score at all clinic visits and averaged over the treatment period; FEV_1 response (change from baseline in pre-dose FEV_1 ≥100 mL) and SGRQ response (decrease from baseline in total score ≥4[8]) at weeks 26 and 52; use of rescue medication; EXACT-Respiratory Symptoms total score (weighted sum of 11 questions from the EXACT-PRO questionnaire);[9–11] and COPD Assessment Test total score at the end of treatment.

A COPD exacerbation was defined as a sustained worsening of respiratory symptoms that required treatment with systemic corticosteroids, antibiotics, or hospital admission, or any combination thereof.[12] Events were classified as moderate or severe according to European Medicines Agency Committee for Medicinal Products for Human Use guidelines,[12] with severe exacerbations defined as those requiring hospital admission or resulting in death. Data from the EXACT-PRO questionnaire were used by the investigators to enhance the recognition of potential exacerbations (in the event of worsening symptoms, the e-diary was programmed to encourage patients to contact their investigator).

Treatment-emergent adverse events (defined as events starting on or after first intake of randomised study medication) were captured throughout the study. In case of clinical features suggesting a diagnosis of pneumonia, investigators were asked to undertake, whenever possible, further investigations based on their clinical experience and judgement. Blood pressure was recorded pre-dose and at 10 min post-dose at each visit, with electrocardiogram (ECG) data captured pre-dose at baseline and weeks 26 and 52.

	BDP/FF/G (n=764)	IND/GLY (n=768)
Sex		
Male	548 (72%)	552 (72%)
Female	216 (28%)	216 (28%)
Race*		
White	705 (92%)	708 (92%)
Other	51 (7%)	52 (7%)
Age (years)	64·4 (7·7)	64·5 (7·7)
Body-mass index (kg/m²)†	25·7 (5·1)	26·6 (5·4)
Blood leukocyte count (10^9 cells per L)	8·05 (2·38)	8·00 (2·04)
Blood eosinophil count (10^9 cells per L)	0·24 (0·20)	0·23 (0·20)
Blood eosinophil	3·14% (2·47)	2·97% (2·30)
Smoking status		
Ex-smoker	413 (54%)	436 (57%)
Current smoker	351 (46%)	332 (43%)
Time since first COPD diagnosis (years)	8·16 (5·76)	7·99 (5·64)
FEV_1 (L)‡	1·07 (0·31)	1·07 (0·31)
Proportion of predicted normal FEV_1 value‡,§	36·4 (8·0)	36·4 (8·1)
<30%	154 (20%)	160 (21%)
≥30% to <50%	609 (80%)	608 (79%)
FVC (L)‡	2·70 (0·78)	2·64 (0·77)
FEV_1:FVC ratio‡	0·41 (0·10)	0·42 (0·10)
Reversibility (%)	8·4% (13·5)	8·8% (13·5)
Clinical COPD phenotype¶		
Chronic bronchitis	434 (57%)	421 (55%)
Emphysema	227 (30%)	235 (31%)
Mixed chronic bronchitis and emphysema	103 (13%)	112 (15%)
Moderate or severe exacerbations in the previous year (range)	1·2 (1–6)	1·2 (1–4)
1	612 (80%)	626 (82%)
≥2	152 (20%)	142 (18%)
COPD medication taken for at least 2 months before study entry		
ICS/LABA	467 (61%)	465 (61%)
ICS/LAMA	36 (5%)	24 (3%)
LABA/LAMA	183 (24%)	199 (26%)
LAMA	77 (10%)	80 (10%)
(Table 1 continues in next column)		
(Continued from previous column)		
Patients with at least one concomitant disease‖	644 (84%)	657 (86%)
Hypertension	437 (57%)	460 (60%)
Ischaemic heart disease	134 (18%)	156 (20%)
Myocardial ischaemia	69 (9%)	75 (10%)
Coronary artery disease	42 (5%)	63 (8%)
Angina pectoris	32 (4%)	27 (4%)
Myocardial infarction	3 (<1%)	0
Ischaemic cardiomyopathy	1 (<1%)	1 (<1%)
Diabetes	99 (13%)	108 (14%)
Cardiac failure	75 (10%)	75 (10%)
Hypercholesterolaemia	58 (8%)	65 (8%)
Dyslipidaemia	64 (8%)	56 (7%)
Benign prostatic hyperplasia	49 (6%)	35 (5%)
Obesity	33 (4%)	49 (6%)
Gastroesophageal reflux disease	35 (5%)	45 (6%)
Hyperlipidaemia	23 (3%)	47 (6%)

Data are n (%) or mean (SD) unless specified otherwise. BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium. COPD=chronic obstructive pulmonary disease. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. ICS=inhaled corticosteroid. LABA=long-acting β_2-agonist. LAMA=long-acting muscarinic antagonist. *Because of data collection restrictions, this information was not collected in Portuguese sites, and so data are missing from eight patients in each group. †At baseline (visit 2). ‡Measured at screening after salbutamol was given. §One patient in the BDP/FF/G group had an FEV_1 greater than 50% predicted—this patient was excluded from the per-protocol population. ¶Based on the clinical judgement of the investigator. ‖Most common concomitant diseases (≥5% in either group).

Table 1: **Baseline characteristics of the safety population**

Statistical analysis

To identify a difference between treatment groups in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment, we estimated that a total of 1534 patients (767 per group) would be necessary to have 85% power to detect a rate ratio of 0·80 between treatments using a negative binomial model, at a two sided significance level of 0·05. The sample size calculation assumed non-assessable rates for moderate-to-severe exacerbations to be about 13% at week 12, 16·5% at week 26, and 20% at Week 52, a rate of 0·9 exacerbations per patient per year in the IND/GLY group, and an overdispersion parameter of 0·56 for the negative binomial distribution.

The numbers of moderate-to-severe, moderate, and severe COPD exacerbations were analysed with a negative binomial model that included treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, and smoking status as fixed effects, and log-time in the study as an offset. Subgroup analyses of the primary endpoint were prespecified (appendix). Time to first exacerbation was analysed with a Cox proportional hazards model that included the same fixed effects as in the primary endpoint analysis; patients not experiencing exacerbations were censored at the end of the randomised treatment period. A Kaplan-Meier plot was also constructed to investigate this variable.

The changes from baseline in pre-dose FEV_1, pre-dose FVC, SGRQ total score, rescue medication use, and EXACT-Respiratory Symptoms total score endpoints were analysed with a linear mixed model for repeated measures. This model included treatment, visit, treatment by visit interaction, country, number of COPD

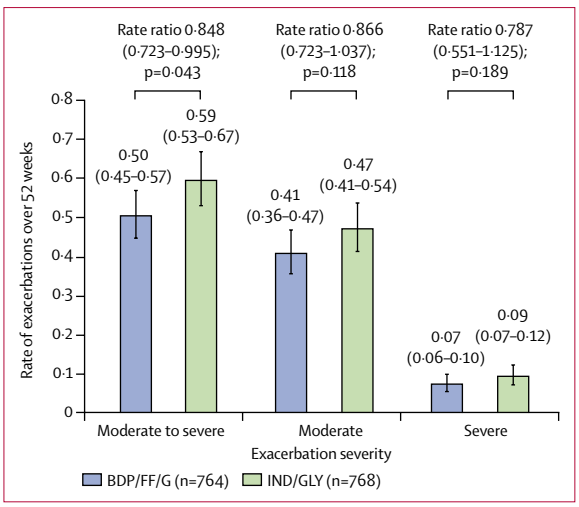

Figure 2: **Adjusted rate of moderate-to-severe, moderate, and severe COPD exacerbations**

Analysis was in the intention-to-treat population. Error bars and values in brackets with the exacerbation rates and rate ratios are 95% CIs. BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium.

exacerbations in the previous year, severity of airflow limitation, and smoking status at screening as fixed effects, and baseline value and baseline by visit interaction as covariates. The responder analyses for FEV_1 and SGRQ were done with a logistic regression model that included the same fixed effects as in the analysis of the primary endpoint, with the baseline value also considered as a covariate. Change from baseline in COPD Assessment Test total score was summarised descriptively only. No multiplicity adjustments were applied in the analyses of secondary endpoints, so the p values provided for these endpoints should be interpreted descriptively.

The efficacy endpoints were analysed in the intention-to-treat (ITT) population, which consisted of all patients who underwent randomisation and received at least one dose of study drug and had at least one post-baseline efficacy assessment. As a sensitivity analysis, the primary endpoint was also analysed in the per-protocol population, which contained all patients in the intention-to-treat population who had no major protocol deviations. Safety outcomes were analysed in all patients who received at least one dose of study drug.

All analyses were done with SAS software version 9.3, and all p values are two-sided. This study is registered with ClinicalTrials.gov, number NCT02579850.

Role of the funding source

The funder of the study was responsible for the design and analysis of the study, oversaw its conduct and was responsible for the study report preparation. All authors had full access to all the data in the study and AP had final responsibility for the decision to submit for publication.

Results

The study took place between May 29, 2015, and July 10, 2017. We recruited 2103 patients, of whom 1532 were eligible to be randomly assigned to one of the treatment groups. The study was completed by 666 (87%) of 764 patients assigned to the BDP/FF/G group and 648 (84%) of 768 patients in the IND/GLY group (figure 1). Compliance to treatment was high; the median of percentage of doses taken was 98·6% in the BDP/FF/G group and 98·4% in the IND/GLY group. Baseline characteristics of the recruited patients are shown in table 1.

The adjusted rates of moderate-to-severe COPD exacerbations were 0·50 per patient per year (95% CI 0·45–0·57) for patients receiving BDP/FF/G and 0·59 (0·53–0·67) per patient per year for those receiving IND/GLY (figure 2). The rate of moderate-to-severe COPD exacerbations was significantly lower with BDP/FF/G than with IND/GLY, with an adjusted rate ratio of 0·848 (95% CI 0·723–0·995; p=0·043), indicating a 15% reduction in the exacerbation rate (figure 2).

The per-protocol population results for the primary outcome were consistent with those of the ITT population, although the rate ratio was not significant (adjusted rate ratio 0·849, 0·721–1·000; p=0·050). Prespecified subgroup analyses of the primary endpoint are shown in the appendix. Among the COPD subgroups defined according to the clinical judgement of the investigator, patients with chronic bronchitis who received BDP/FF/G had a significantly reduced exacerbation rate compared with those receiving IND/GLY (0·752, 0·605–0·935, p=0·010), whereas the adjusted rate ratios were 0·995 (0·754–1·314, p=0·974) in patients with emphysema and 0·939 (0·605–1·459, p=0·781) in those with mixed bronchitis and emphysema. BDP/FF/G also significantly reduced the exacerbation rate compared with IND/GLY in patients with eosinophils of at least 2% (0·806, 0·664–0·978; p=0·029), with an adjusted rate ratio of 0·943 (0·711–1·251, p=0·685) in those with eosinophils less than 2%. In a second eosinophil subgroup analysis, the adjusted rate ratio was 0·806 (0·646–1·007; p=0·057) in patients with at least 200 cells per µL and 0·872 (0·692–1·098, p=0·244) for patients with <200 cells/µL.

The rates of moderate exacerbations and severe exacerbations analysed separately were not significantly different between BDP/FF/G and IND/GLY, with reductions of 13% and 21%, respectively (figure 2). The time to first moderate or severe exacerbation was similar between the two treatment groups (hazard ratio 0·901, 95% CI 0·763–1·064, p=0·219) (appendix), as was the time to the first severe exacerbation (0·864, 0·613–1·219, p=0·405).

Adjusted mean change in FEV_1 from baseline was significantly larger with BDP/FF/G than with IND/GLY at weeks 12 and 40 and when averaged over the treatment period (figure 3A). Improvement in mean SGRQ total score was significantly better with BDP/FF/G than with

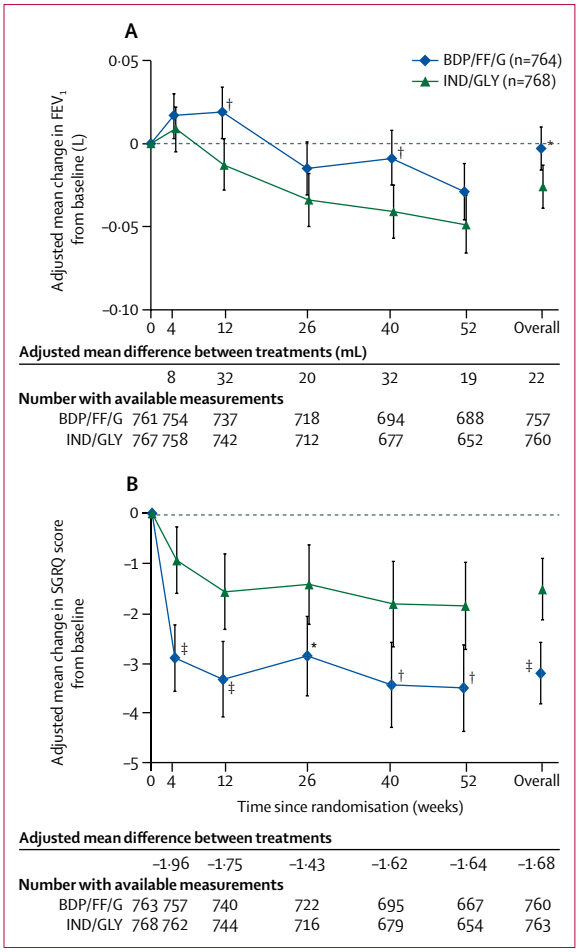

Figure 3: **Adjusted mean change from baseline in predose FEV_1 (A) SGRQ total score (B)**

Analysis was in the intention-to-treat population. Error bars are 95% confidence intervals. BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium. *p<0·05 *vs* IND/GLY. †p<0·01 *vs* IND/GLY. ‡p≤0·001 *vs* IND/GLY.

	Patients with a response		Odds ratio (95% CI)	p value
	BDP/FF/G (n=764)	IND/GLY (n=768)		
Pre-dose FEV_1*				
Week 26	176 (23%)	156 (20%)	1·18 (0·92–1·50)	0·194
Week 52	145 (19%)	125 (16%)	1·19 (0·91–1·55)	0·198
SGRQ total score†				
Week 26	310 (41%)	292 (38%)	1·13 (0·92–1·40)	0·255
Week 52	311 (41%)	279 (36%)	1·22 (0·99–1·51)	0·068

BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium. FEV_1=forced expiratory volume in 1 s. SGRQ=St George's Respiratory Questionnaire. *Response defined as ≥100 mL increase from baseline. †Response defined as ≥4 units decrease from baseline.

Table 2: **FEV_1 and SGRQ responder analysis**

IND/GLY both overall and at all visits (figure 3B). In the responder analyses, a numerically higher proportion of patients responded to BDP/FF/G than to IND/GLY in terms of FEV_1 and SGRQ total score change from baseline at both Week 26 and 52, although the odds ratios were not statistically significant (table 2). The adjusted mean changes from baseline in pre-dose FVC were similar between the two treatments, although BDP/FF/G was superior to IND/GLY at week 40 (appendix). The mean changes from baseline in total COPD Assessment Test score at the end of treatment, which were summarised descriptively only, were –0·8 with BDP/FF/G and –0·6 with IND/GLY.

The use of rescue medication (in terms of puffs per day and percentage of days with no use) was not significantly different between the two treatment groups (appendix). Compared with patients in the IND/GLY group, those in the BDP/FF/G group reported a significantly greater improvement from baseline in EXACT-Respiratory Symptoms score over the first 12 weeks of the study, although the two groups were not significantly different at subsequent visits (appendix).

The proportion of patients who had adverse events was similar between the two groups (table 3), with most events being mild or moderate in severity. Pneumonia was reported by 28 (4%) patients in the BDP/FF/G group and 27 (4%) patients in the IND/GLY group; more than 80% of these cases were diagnosed on the basis of medical imaging (24 [75%] events in the BDP/FF/G group and 26 [90%] in the IND/GLY group). Similarly, the incidence of cardiac adverse events (44 [6%] patients receiving BDP/FF/G and 51 [7%] receiving IND/GLY) and serious adverse events (11 [1%] patients receiving BDP/FF/G and 29 [4%] receiving IND/GLY) was low and similar between the two groups. One treatment-related serious adverse event occurred in each group: dysuria in a patient receiving BDP/FF/G and atrial fibrillation in a patient receiving IND/GLY. Fewer patients in the BDP/FF/G group had adverse events that led to discontinuation of study drug than in the IND/GLY group. The most common event leading to study drug discontinuation was a COPD exacerbation (five patients in the BDP/FF/G group and ten patients in the IND/GLY group). Adverse events resulted in 37 deaths, none of which were judged to be related to study medication. Changes from baseline in blood pressure, heart rate, and other ECG parameters were small, and did not differ between treatments (appendix).

Discussion

Our results showed that the inhaled corticosteroid-containing triple combination of extrafine BDP/FF/G in a single inhaler was associated with a significantly larger reduction in rate of moderate-to-severe COPD exacerbations than the dual bronchodilator combination of IND/GLY over 52 weeks of treatment, without differences in adverse effects, particularly pneumonia.

This study is, to our knowledge, the first to specifically compare single-inhaler triple therapy with a fixed

	BDP/FF/G (n=764)	IND/GLY (n=768)
Adverse events	490 (64%)	516 (67%)
COPD	273 (36%)	288 (38%)
Nasopharyngitis	43 (6%)	37 (5%)
Headache	44 (6%)	35 (5%)
Pneumonia	28 (4%)	27 (4%)
Respiratory tract infection	22 (3%)	28 (4%)
Dyspnoea	23 (3%)	24 (3%)
Back pain	21 (3%)	23 (3%)
Hypertension	15 (2%)	26 (3%)
Cough	13 (2%)	25 (3%)
Cardiac failure	15 (2%)	16 (2%)
Ischaemic heart disease	8 (1%)	16 (2%)
Myocardial infarction	1 (<1%)	8 (1%)
Angina pectoris	5 (1%)	1 (<1%)
Coronary artery disease	2 (<1%)	4 (1%)
Myocardial ischaemia	2 (<1%)	4 (1%)
Serious adverse events	117 (15%)	130 (17%)
COPD	61 (8%)	69 (9%)
Pneumonia	18 (2%)	17 (2%)
Cardiac failure	6 (1%)	7 (1%)
Death	3 (<1%)	8 (1%)
Ischaemic heart disease	2 (<1%)	11 (1%)
Myocardial infarction	1 (<1%)	8 (1%)
Coronary artery disease	1 (<1%)	2 (<1%)
Myocardial ischaemia	0	1 (<1%)
Atrial fibrillation	0	7 (1%)
Respiratory failure	3 (<1%)	4 (1%)
Lung neoplasm	4 (1%)	2 (<1%)
Treatment-related adverse events	43 (6%)	37 (5%)
Oral candidiasis	12 (2%)	6 (1%)
Dry mouth	3 (<1%)	6 (1%)
Cough	1 (<1%)	7 (1%)
Treatment-related serious adverse events	1 (<1%)	1 (<1%)
Severe adverse events	86 (11%)	87 (11%)
Adverse events leading to study drug discontinuation	37 (5%)	47 (6%)
Adverse events leading to death	16 (2%)	21 (3%)

Data are n (%). Adverse events are reported if they occurred in ≥2% of patients in either group. Serious adverse events and treatment-related adverse are reported if they occurred in ≥0·5% of patients in either group. BDP/FF/G=beclometasone dipropionate, formoterol fumarate, and glycopyrronium. IND/GLY=indacaterol and glycopyrronium. COPD=chronic obstructive pulmonary disease exacerbations.

Table 3: **Adverse events and serious adverse events (safety population)**

single-inhaler dual bronchodilator combination in terms of reduction in exacerbations. We recruited patients with severe or very severe airflow limitation who remained symptomatic despite treatment with one or more long-acting bronchodilators (with or without inhaled corticosteroid, but no triple therapy) and who had at least one moderate-to-severe exacerbation in the previous year. TRIBUTE met the primary endpoint, showing a significant 15% reduction in the rate of moderate-to-severe exacerbations with BDP/FF/G compared with IND/GLY. Reductions in both moderate and severe exacerbations contributed to the overall result, although these reductions were not significant when considered separately. However, the study was not powered to examine the effect of the treatments on these individual endpoints. The relative effect of BDP/FF/G versus IND/GLY on moderate-to-severe exacerbations was greater in patients with a clinical diagnosis of chronic bronchitis and in patients with eosinophils greater than 2%; the latter finding is consistent with results from several published prespecified and post-hoc subgroup analyses, in which the effect of inhaled corticosteroid (in combination with one or more bronchodilators) on exacerbations was more consistent in patients with higher blood eosinophil levels.[4,5,13,14] Although the effect of the two treatments was not significantly different when we used an eosinophil threshold of 200 cells per µL, the optimum cutoff for blood eosinophils is unclear.[15] However, the results from these subgroups should be interpreted with caution since the study was not powered around these analyses. Overall, therefore, this study helps to fill some of the evidence gaps in the management of COPD regarding the relative efficacy of triple therapy versus a dual combination of a long-acting β_2-agonist and a long-acting muscarinic antagonist,[16] by showing the benefit of adding an inhaled corticosteroid for patients who still report exacerbations despite dual bronchodilation.

We selected IND/GLY as the comparator, because it is the only combination of a long-acting β_2-agonist and a long-acting muscarinic antagonist to have previously been shown to reduce the rate of COPD exacerbations compared with once-daily glycopyrronium and twice-daily fluticasone plus salmeterol.[6,7] The results of the study by Wedzicha and colleagues,[7] in which there was a 17% reduction in the rate of moderate-to-severe COPD exacerbations with IND/GLY compared with fluticasone plus salmeterol,[6] supported the recommendation by Global Initiative for Obstructive Lung Disease that combinations of a long-acting β_2-agonist plus a long-acting muscarinic antagonist should be the first choice treatment for patients with COPD who are symptomatic and at risk of exacerbations.[1] In this context, the further 15% reduction in exacerbations in TRIBUTE is likely to be clinically relevant. Notably, even though all patients were receiving two bronchodilators during the study, BDP/FF/G was superior to IND/GLY for FEV_1 averaged over the whole treatment period, although not consistently at all individual visits, and patients in the BDP/FF/G group had significantly greater improvements in health-related quality of life at all visits, together with an early improvement in symptoms.

The rate of exacerbations during TRIBUTE was lower than the rate reported in the year before the study, a pattern that is similar to those seen in previous studies of BDP/FF/G with similar inclusion criteria.[4,5] This pattern

could be a clinical trial effect, either because of increased compliance (both in terms of the study, with more than 85% of randomised patients completing the study, and to treatment, with median compliance in excess of 98%) or to more accurate identification of COPD exacerbations by expert investigators.

Furthermore, the exclusion from the study of patients already on triple therapy means that there was no step down in treatment, unlike in other clinical trials,[6,7] which might increase the risk of exacerbations. Indeed, all patients in the triple therapy group (and several in the dual bronchodilation group) had a step up in therapy. However, although an exacerbation history is associated with an increased risk of future exacerbations at a population level,[17] this association is far from systematic at an individual patient level.[18,19] As a consequence, patients with a history of frequent exacerbations are not necessarily all at substantially increased risk of future exacerbations, suggesting that the observations in TRIBUTE correspond to what can be expected in many real-life COPD populations.[18,19] Importantly, the high proportion of patients with comorbidities in TRIBUTE suggests that the exclusion criteria (which are typical for this type of study) did not substantially narrow the recruited population, although as in most randomised controlled trials, a bias towards less severe comorbid diseases might be present. In view of the high level of incorrect inhaler technique seen in clinical practice (and the impaired outcomes associated with poor technique),[20] the availability of a single inhaler product could be especially useful for patients who require triple therapy to manage their COPD, especially if it avoids the use of two devices of different design.

Finally, the overall adverse event and safety profile of BDP/FF/G in TRIBUTE is reassuring, given its consistency with the profile of IND/GLY. The low rate of cardiac adverse events in both groups, particularly in the triple therapy group, provides further reassurance given reports of increased risk of such events in patients with COPD who are receiving long-acting bronchodilators,[21,22] especially older patients.[23] Results from several studies, including the TORCH trial, have shown that the use of inhaled corticosteroids by patients with COPD increases the risk of pneumonia.[24] That a similar proportion of patients in the two groups had pneumonia events (more than 80% of which were diagnosed on the basis of medical imaging) is therefore of interest, since this could suggest that the addition of extrafine BDP to a long-acting muscarinic antagonist plus long-acting β_2-agonist combination does not increase the risk of pneumonia.

We acknowledge that the study has some limitations. First we recruited fewer patients than did similar studies that examined the effect of pharmacological interventions on COPD exacerbations.[6,25] However, TRIBUTE was designed and powered specifically to address the first and most important question—ie, the effect on moderate-to-severe exacerbations—for which we showed a significant reduction with BDP/FF/G. Second, we have considered the reasons for a lower observed rate of moderate-to-severe exacerbations than in the year before study entry, and we believe that this lower rate does not diminish the importance of the positive results obtained. Finally, since we selected IND/GLY as the comparator, the two groups received different long-acting β_2-agonists, and different long-acting muscarinic antagonists, from different devices and in different dosing regimens; some of the improvements observed could therefore be due to differences in molecules, devices or the twice-daily versus once-daily dosing regimens.

TRIBUTE addresses an important evidence gap in the management of COPD. In patients with symptomatic COPD, an FEV_1 of less than 50%, and an exacerbation history despite maintenance therapy, treatment with the extrafine inhaled corticosteroid-containing triple therapy regimen of BDP/FF/G was more effective in reducing the rate of moderate-to-severe COPD exacerbations than the dual bronchodilator combination of IND/GLY, without increasing the risk of pneumonia.

Contributors

The study was conceived and designed by MC, HP, GC, IM, SV, SP, and DS. The data were acquired by AP and NR, analysed by AP, JV, LF, AG, SV, and NR, and interpreted by AP, JV, LF, MC, HP, GC, AG, IM, SV, SP, MS, NR, and DS. MC and IM contributed to the medical data integrity of this study. HP and GC contributed to the conduct of this study and GC oversaw the study. HP and GC were Chiesi clinical operation project managers, AG was Chiesi statistician, IM was Chiesi lead data manager, SV was Chiesi lead statistician, SP was head of Chiesi global clinical development, and MS was the Clinical Program Leader. NR was the study coordinator. The manuscript was drafted by AP, JV, LF, NR and revised for intellectual content and approved for publication by AP, JV, LF, MC, HP, GC, AG, IM, SV, SP, MS, NR, and DS.

Declaration of interests

AP reports grants, personal fees, non-financial support, and other support from Chiesi Farmaceutici, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Mundipharma, and Teva, personal fees and non-financial support from Menarini, Novartis, and Zambon, and grants from Sanofi. JV reports personal fees from Chiesi Farmaceutici during the conduct of the study, and personal fees from GlaxoSmithKline, Chiesi Farmaceutici, Boehringer Ingelheim, Novartis, and AstraZeneca. LF reports grants, personal fees and non-financial support from Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Takeda, AstraZeneca, Novartis, Menarini, Laboratori Guidotti, and Almirall, personal fees and non-financial support from Pearl Therapeutics, Mundipharma, and Boston Scientific, personal fees from Kyorin, Bayer, and Zambon, and grants from Pfizer, Dompè, Malesci, Biofutura Italia, and Vree Health Italia. MC has received grants and honoraria for lectures from Chiesi Farmaceutici. HP, GC, AG, IM, SV, SP, and MS are employed by Chiesi, the sponsor of the study. NR reports personal fees from Chiesi during the conduct of the study, and grants and personal fees from Boehringer Ingelheim, Pfizer, Novartis, personal fees from Teva, GlaxoSmithKline, AstraZeneca, Chiesi Farmaceutici, Mundipharma, Cipla, Sanofi, Sandoz, 3M, and Zambon. DS received personal fees from Chiesi Farmaceutici during the conduct of the study, and grants and personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Glenmark, Johnson & Johnson, Merck, NAPP, Novartis, Pfizer, Takeda, Teva, Theravance, and Verona, and personal fees from Genentech and Skyepharma.

Acknowledgments

This study was funded by Chiesi Farmaceutici. We thank the investigators and patients at the investigative sites for their support of this study. Writing support was provided by David Young of Young Medical Communications and Consulting, funded by Chiesi Farmaceutici.

References

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. http://goldcopd.org/gold-reports/ (accessed Dec 12, 2017).

2 Worth H, Buhl R, Criée C-P, Kardos P, Lossi NS, Vogelmeier CF. GOLD 2017 treatment pathways in 'real life': an analysis of the DACCORD observational study. *Respir Med* 2017; **131:** 77–84.

3 Vestbo J, Vogelmeier C, Small M, Higgins V. Understanding the GOLD 2011 Strategy as applied to a real-world COPD population. *Respir Med* 2014; **108:** 729–36.

4 Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; **388:** 963–73.

5 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.

6 Wedzicha JA, Banerji D, Chapman KR, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. *N Engl J Med* 2016; **374:** 2222–34.

7 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.

8 Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. *Am J Respir Crit Care Med* 2014; **189:** 250–55.

9 Leidy NK, Murray LT. Patient-reported outcome (PRO) measures for clinical trials of COPD: the EXACT and E-RS. *COPD* 2013; **10:** 393–98.

10 Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD: performance of the EXACT-Respiratory Symptoms Tool (E-RS) in three clinical trials. *Respir Res* 2014; **15:** 124.

11 EMA. Draft qualification opinion of qualification of Exacerbations of Chronic Pulmonary Disease Tool (EXACT), and EXACT-Respiratory Symptoms measure (E-RS) for evaluating treatment outcomes in clinical trials in COPD. EMA/CHMP/SAWP/178465/2015. London: European Medicines Agency, 2015.

12 EMA. Guideline on clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD). EMA/CHMP/483572/2012. London: European Medicines Agency, 2012.

13 Roche N, Chapman KR, Vogelmeier CF, et al. Blood eosinophils and response to maintenance chronic obstructive pulmonary disease treatment. Data from the FLAME trial. *Am J Respir Crit Care Med* 2017; **195:** 1189–97.

14 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.

15 Rabe KF, Beghé B, Fabbri LM. Peripheral eosinophil count as a biomarker for the management of COPD: not there yet. *Eur Respir J* 2017; **50:** 1702165.

16 Cazzola M, Rogliani P, Matera MG. Escalation and de-escalation of therapy in COPD: myths, realities and perspectives. *Drugs* 2015; **75:** 1575–85.

17 Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; **363:** 1128–38.

18 Han MK, Quibrera PM, Carretta EE, et al. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017; **5:** 619–26.

19 Kardos P, Vogelmeier C, Worth H, et al. A two-year evaluation of the 'real life' impact of COPD on patients in Germany: the DACCORD observational study. *Respir Med* 2017; **124:** 57–64.

20 Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; **105:** 930–38.

21 Suissa S, Dell'Aniello S, Ernst P. Concurrent use of long-acting bronchodilators in COPD and the risk of adverse cardiovascular events. *Eur Respir J* 2017; **49:** 1602245.

22 Wang M-T, Liou J-T, Lin CW, et al. Association of cardiovascular risk with inhaled long-acting bronchodilators in patients with chronic obstructive pulmonary disease: A nested case-control study. *JAMA Intern Med* 2018; published online Jan 2. DOI:10.1001/jamainternmed.2017.7720.

23 Gershon A, Croxford R, Calzavara A, et al. Cardiovascular safety of inhaled long-acting bronchodilators in individuals with chronic obstructive pulmonary disease. *JAMA Intern Med* 2013; **173:** 1175–85.

24 Crim C, Calverley PMA, Anderson JA, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *Eur Respir J* 2009; **34:** 641–47.

25 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.