# Extrafine inhaled triple therapy versus dual bronchodilator therapy in COPD (TRIBUTE): a double-blind, parallel group, randomised controlled trial

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# Summary

## Background

There is limited evidence on the relative risk/benefit in chronic obstructive pulmonary disease (COPD) of inhaled triple therapy, comprising inhaled corticosteroid, long-acting muscarinic antagonist and long-acting $\beta_2$-agonist, versus dual bronchodilation. The aim of this study was therefore to compare the single inhaler triple combination of the inhaled corticosteroid beclometasone dipropionate, the long-acting $\beta_2$-agonist formoterol fumarate, and the long-acting muscarinic antagonist glycopyrronium (BDP/FF/G), versus the single inhaler dual bronchodilator combination of the long-acting $\beta_2$-agonist indacaterol plus glycopyrronium (IND/GLY) in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment.

## Methods

For this randomised, parallel-group, double-blind, double-dummy study, 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, patients were randomised (1:1) using an interactive response technology system to 52 weeks treatment with extrafine BDP/FF/G 87/5/9µg, two inhalations twice daily, or to IND/GLY 85/43µg, one inhalation daily. Randomisation was stratified by country and severity of airflow limitation. The primary endpoint was the annual rate of moderate-to-severe COPD exacerbations. ClinicalTrials.gov NCT02579850.

## Findings

Between May 2015 and July 2017, 1532 patients received BDP/FF/G (n=764) or IND/GLY (n=768). Moderate-to-severe exacerbation rates were 0·50 (95% CI 0·45–0·57) for BDP/FF/G and 0·59 (0·53–0·67) for IND/GLY; rate ratio 0·848 (95% CI 0·723–0·995; p=0·043) in favour of BDP/FF/G. Adverse events were reported by 490 patients (64%) with

BDP/FF/G and 516 (67%) with IND/GLY; pneumonia occurred in 28 (3·7%) versus 27 (3·5%) patients.

**Interpretation**

In patients with symptomatic COPD, $FEV_1$ of less than 50% and an exacerbation history despite maintenance therapy, extrafine BDP/FF/G was more effective than IND/GLY in reducing the rate of moderate-to-severe exacerbations, without increasing the pneumonia risk.

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## Keywords

Combination drug therapy; pulmonary disease, chronic obstructive; bronchitis, chronic; pulmonary emphysema; lung; airway obstruction

# Introduction

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, small airways narrowing and destruction of the lung parenchyma, resulting in persistent airflow limitation, chronic respiratory symptoms and exacerbations.[1] Inhaled 'triple therapy' comprising an inhaled corticosteroid, a long-acting $\beta_2$-agonist and a long-acting muscarinic antagonist is recommended in the Global Initiative for Obstructive Lung Disease report for patients who have further exacerbations despite dual bronchodilation with a long-acting $\beta_2$-agonist plus a long-acting muscarinic antagonist or a combination of a long-acting $\beta_2$-agonist plus an inhaled corticosteroid,[1] and is commonly used in clinical practice.[2,3] However, there is limited evidence to support the risk/benefit of triple therapy versus dual bronchodilation. In particular, no direct comparisons of single inhaler triple therapy with single inhaler dual bronchodilator therapy in reducing exacerbations have been reported.

A single inhaler triple therapy is available combining in an extrafine formulation (i.e., with mass median aerodynamic diameter <2 μm) the inhaled corticosteroid beclometasone dipropionate (BDP), the long-acting $\beta_2$-agonist formoterol fumarate (FF) and the long-acting muscarinic antagonist glycopyrronium (G). Two prior 52-week studies have already assessed the efficacy and safety of this combination: in the TRILOGY study BDP/FF/G reduced the rate of COPD exacerbations by 23% compared with BDP/FF,[4] while in TRINITY BDP/FF/G reduced the rate of COPD exacerbations by 20% compared with the long-acting muscarinic antagonist tiotropium.[5] In the TRIBUTE study that we describe here, we compared the effects of BDP/FF/G with those of the single inhaler combination of the long-acting $\beta_2$-agonist indacaterol plus glycopyrronium (IND/GLY). IND/GLY was chosen as the comparator in this study since this combination has demonstrated greater efficacy than both long-acting muscarinic antagonist monotherapy and the combination of an inhaled corticosteroid plus long-acting $\beta_2$-agonist in terms of the rate of moderate-to-severe

exacerbations.[6,7] The aim was 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, conducted in 187 sites across 18 countries. 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 IND/GLY 85/43 µg, one inhalation once daily via single-dose dry-powder inhaler (Ultibro Breezhaler [Novartis Europharm Ltd, Camberley, United Kingdom]) for a 2-week open-label run-in period (Supplementary Figure 1). At the end of the run-in (Visit 2), patients were randomised 1:1 to either continue IND/GLY 85/43 µg, one inhalation once daily, or to receive extrafine BDP/FF/G 87/5/9 µg (corresponding to a nominal dose of 100/6/10 µg), two actuations twice daily via pressurised metered-dose inhaler. Over the 52-week treatment period, patients attended visits at Week 4, 12, 26, 40 and 52. As rescue medication, patients were permitted to use either salbutamol via pressurised metered-dose inhaler or terbutaline via dry-powder inhaler, but not within 6 hours prior to any spirometric assessment. Other non-permitted COPD medications are listed in the supplement.

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

## Patients

The main inclusion criteria were: ≥40 years of age; current or ex-smokers; COPD diagnosis, with post-bronchodilator (salbutamol 400 µg) forced expiratory volume in 1 second ($FEV_1$) to forced vital capacity (FVC) ratio <0·7 and severe or very severe airflow limitation ($FEV_1$ <50%); at least one documented moderate or severe COPD exacerbation in the previous 12

months; symptomatic at screening, with a COPD Assessment Test (CAT) total score ≥10; and the use for at least 2 months prior to screening of an inhaled corticosteroid plus a long-acting $\beta_2$-agonist, an inhaled corticosteroid plus a long-acting muscarinic antagonist, a long-acting $\beta_2$-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.

The key criteria for exclusion were: a current diagnosis of asthma with a physician-judged need for inhaled or oral corticosteroid therapy for this condition; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that may have impacted efficacy or safety (as judged by the investigator). The full inclusion and exclusion criteria are listed in the supplement.

## Randomisation and masking

Patients were allocated to treatment arms by central randomisation stratified by country and severity of airflow limitation (post-bronchodilator $FEV_1$ categories <30% predicted or 30% to <50% predicted) according to a randomisation list generated by the interactive response technology provider. Patients, investigators, site staff and sponsor personnel were blinded to treatment assignment for the duration of the study by use of a double-dummy approach, with all patients using a pressurised metered-dose inhaler twice daily (containing BDP/FF/G or placebo) and a single-dose dry-powder inhaler once daily (placebo or IND/GLY).

## Procedures

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 CAT. At each subsequent visit, pre-dose (morning) spirometry was conducted, and SGRQ data were collected. Patients recorded daily symptoms in an electronic diary using the EXACT-PRO questionnaire (EXAcerbations of Chronic pulmonary disease Tool Patient-Reported

Outcome), together with study and rescue medication use. Data from CAT were collected at the end of the treatment period.

## Outcomes

The primary objective was to demonstrate superiority of BDP/FF/G over IND/GLY in terms of the moderate-to-severe COPD exacerbation rate over 52 weeks of treatment. The secondary efficacy variables were: time to first moderate-or-severe, 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; rescue medication use; EXACT-Respiratory Symptoms (E-RS) total score (which is the weighted sum of 11 questions from the EXACT-PRO questionnaire);[9–11] and CAT 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 a combination of these.[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 being 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 perform, 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 Week 26 and 52.

## Statistical analysis

To demonstrate superiority of BDP/FF/G over IND/GLY in terms of the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment, a total of 1534 patients (767 per arm) was estimated to 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 of 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 over-dispersion parameter for the negative binomial distribution of 0·56.

The numbers of moderate-to-severe, moderate, and severe COPD exacerbations were analysed using a negative binomial model including treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation and smoking status as fixed effects, and log-time on study as an offset. Subgroup analyses of the primary endpoint were pre-specified, as listed in the supplement. Time to first exacerbation was analysed using a Cox proportional hazards model, including the same fixed effects as in the primary endpoint analysis, with the results presented as a Kaplan-Meier figure and hazard ratio.

The changes from baseline in pre-dose $FEV_1$, pre-dose FVC, SGRQ total score, rescue medication use and E-RS total score endpoints were analysed using a linear mixed model for repeated measures (MMRM). This model included treatment, visit, treatment by visit interaction, country, number of COPD 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 conducted using a logistic regression model that included the same fixed effects as in the analysis of the primary endpoint were included, with the baseline value also considered.

Change from baseline in CAT total score was summarised descriptively only. No multiplicity adjustments were applied in the analyses of secondary endpoints, and so the p values provided for these endpoints should be interpreted descriptively.

The efficacy endpoints were analysed in the intention-to-treat (ITT) population, classified as all randomised patients who 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 was all patients in the intention-to-treat population with no major protocol deviations. Safety outcomes were analysed in the safety population, which was all randomised patients who received at least one dose of study drug. All analyses were performed 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, Chiesi Farmaceutici SpA, 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 of the data, with the lead author (AP) responsible for the decision to submit for publication.

# Results

The study ran between May 2015 and July 2017. We recruited 2103 patients, of whom 1532 were randomly assigned to one of the treatment groups, with 666 (87·2%) of 764 completing the study in the BDP/FF/G group, and 648 (84·4%) of 768 in the IND/GLY group (Figure 1). Compliance to treatment was high, with a median of 98·6% and 98·4% of doses taken in the BDP/FF/G and IND/GLY groups, respectively. Baseline characteristics of the recruited patients are shown in Table 1.

*Table 1. Baseline characteristics (Safety population).*

| | **BDP/FF/G (N=764)** | **IND/GLY (N=768)** |
|---|---|---|
| Sex, n (%) | | |
| Male | 548 (71·7) | 552 (71·9) |
| Female | 216 (28·3) | 216 (28·1) |
| Race, n (%)[a] | | |
| White | 705 (92·3) | 708 (92·2) |
| Other | 51 (6·7) | 52 (6·8) |
| Age (years), mean (SD) | 64·4 (7·7) | 64·5 (7·7) |
| Body-mass index (kg/m²), mean (SD)[b] | 25·7 (5·1) | 26·6 (5·4) |
| Blood leukocyte count ($10^9$/L), mean (SD) | 8·05 (2·38) | 8·00 (2·04) |
| Blood eosinophil count ($10^9$/L), mean (SD) | 0·24 (0·20) | 0·23 (0·20) |
| Blood eosinophil (%), mean (SD) | 3·14 (2·47) | 2·97 (2·30) |
| Smoking status, n (%) | | |
| Ex-smoker | 413 (54·1) | 436 (56·8) |
| Current smoker | 351 (45·9) | 332 (43·2) |
| Time since first COPD diagnosis (years), mean (SD) | 8·16 (5·76) | 7·99 (5·64) |
| $FEV_1$ (L), mean (SD)[c] | 1·07 (0·31) | 1·07 (0·31) |
| $FEV_1$ % of predicted normal value, mean (SD)[c,d] | 36·4 (8·0) | 36·4 (8·1) |
| <30%, n (%) | 154 (20·2) | 160 (20·8) |
| ≥30% and <50%, n (%) | 609 (79·7) | 608 (79·2) |
| FVC (L), mean (SD)[c] | 2·70 (0·78) | 2·64 (0·77) |
| $FEV_1$/FVC ratio, mean (SD)[c] | 0·41 (0·10) | 0·42 (0·10) |
| Reversibility (%), mean (SD) | 8·4 (13·5) | 8·8 (13·5) |
| Clinical COPD phenotype, n (%)[e] | | |
| Chronic bronchitis | 434 (56·8) | 421 (54·8) |

| | BDP/FF/G (N=764) | IND/GLY (N=768) |
|---|---|---|
| Emphysema | 227 (29·7) | 235 (30·6) |
| Mixed chronic bronchitis and emphysema | 103 (13·5) | 112 (14·6) |
| Moderate or severe exacerbations in the previous year, rate (range) | 1·2 (1, 6) | 1·2 (1, 4) |
| 1, n (%) | 612 (80·1) | 626 (81·5) |
| ≥2, n (%) | 152 (19·9) | 142 (18·5) |
| COPD medication taken for at least 2 months prior to study entry, n (%) | | |
| ICS/LABA | 467 (61·1) | 465 (60·5) |
| ICS/LAMA | 36 (4·7) | 24 (3·1) |
| LABA/LAMA | 183 (24·0) | 199 (25·9) |
| LAMA | 77 (10·1) | 80 (10·4) |
| Patients with at least one concomitant disease, n (%)[f] | 644 (84·3) | 657 (85·5) |
| Hypertension | 437 (57·2) | 460 (59·9) |
| Ischaemic heart disease | 134 (17·5) | 156 (20·3) |
| Myocardial ischaemia | 69 (9·0) | 75 (9·8) |
| Coronary artery disease | 42 (5·5) | 63 (8·2) |
| Angina pectoris | 32 (4·2) | 27 (3·5) |
| Myocardial infarction | 3 (0·4) | 0 |
| Ischaemic cardiomyopathy | 1 (0·1) | 1 (0·1) |
| Diabetes mellitus | 99 (13·0) | 108 (14·1) |
| Cardiac failure | 75 (9·8) | 75 (9·8) |
| Hypercholesterolaemia | 58 (7·6) | 65 (8·5) |
| Dyslipidaemia | 64 (8·4) | 56 (7·3) |
| Benign prostatic hyperplasia | 49 (6·4) | 35 (4·6) |
| Obesity | 33 (4·3) | 49 (6·4) |
| Gastroesophageal reflux disease | 35 (4·6) | 45 (5·9) |
| Hyperlipidaemia | 23 (3·0) | 47 (6·1) |

BDP/FF/G = beclometasone dipropionate/formoterol fumarate/glycopyrronium; IND/GLY = indacaterol/glycopyrronium; SD = standard deviation; COPD = chronic obstructive pulmonary disease; $FEV_1$ = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting $\beta_2$-agonist; LAMA = long-acting muscarinic antagonist. [a]Due to data collection restrictions, this information was not collected in Portuguese sites, and so data are missing from 8 patients in each group. [b]At baseline (Visit 2). [c]Measured at screening after salbutamol was administered. [d]One patient in the BDP/FF/G group had an $FEV_1$ above 50% predicted; this patient was excluded from the per-protocol population. [e]Based on the clinical judgement of the investigator. [f]Most common concomitant diseases (≥5% in either group).

The adjusted rates of moderate-to-severe COPD exacerbations were 0·50 and 0·59 per patient per year for BDP/FF/G and IND/GLY, respectively (Figure 2). BDP/FF/G was

superior to IND/GLY, with an adjusted rate ratio of 0·848 (95% confidence interval [CI] 0·723–0·995; p=0·043), indicating a significant 15% reduction in the exacerbation rate (Figure 2). The per-protocol population results were consistent with the ITT population, although the rate reduction just missed the statistical significance (adjusted rate ratio 0·849 [0·721–1·000]; p=0·050). Pre-specified subgroup analyses of the primary endpoint are shown in the supplement (Supplementary Figure 2). Amongst the COPD subgroups (defined based on the clinical judgement of the investigator), in patients with chronic bronchitis BDP/FF/G significantly reduced the exacerbation rate vs IND/GLY by 25% (0·752 [0·605 to 0·935], p=0·010), whereas the adjusted rate ratios were 0·995 (0·754 to 1·314; p=0·974) in patients with emphysema and 0·939 (0·605 to 1·459; p=0·781) in those with mixed bronchitis and emphysema. BDP/FF/G also significantly reduced the exacerbation rate vs IND/GLY by 19% in patients with eosinophils ≥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 levels <2%. In the second eosinophil subgroup analysis, the adjusted rate ratios were 0·806 (0·646–1·007; 0·057) and 0·943 (0·711–1·251; 0·685) for ≥200 and <200 cells/μL, respectively.

The rates of moderate and severe exacerbations taken separately were lower with BDP/FF/G than IND/GLY, with reductions of 13 and 21%, respectively, although not reaching statistical significance (Figure 2). The time to first moderate-or-severe exacerbation was similar in the two treatment groups (hazard ratio 0·901 [95% CI 0·763–1·064]; p=0·219) (Supplementary Figure 3), as was the time to first severe exacerbation (0·864 [0·613–1·219]; p=0·405).

BDP/FF/G was superior to IND/GLY for adjusted mean change from baseline in pre-dose $FEV_1$ when averaged over the treatment period and at Weeks 12 and 40 (Figure 3A), and provided a significantly greater improvement in mean SGRQ total score 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 two treatments provided similar adjusted mean changes from baseline in pre-dose FVC, with BDP/FF/G superior to IND/GLY at Week 40 (Supplementary Figure 4). The mean changes from baseline in CAT total score at the end of treatment were –0·8 with BDP/FF/G and –0·6 with IND/GLY (this endpoint was summarised descriptively only).

*Table 2. $FEV_1$ and SGRQ responder analysis (intention-to-treat population)*

| | Responders, n (%) | | Odds ratio (95% CI); p value |
|---|---|---|---|
| | **BDP/FF/G (N=764)** | **IND/GLY (N=768)** | |
| Pre-dose $FEV_1$[a] | | | |
| Week 26 | 176 (23·0) | 156 (20·3) | 1·18 (0·92–1·50); p=0·194 |
| Week 52 | 145 (19·0) | 125 (16·3) | 1·19 (0·91–1·55); p=0·198 |
| SGRQ total score[b] | | | |
| Week 26 | 310 (40·6) | 292 (38·0) | 1·13 (0·92–1·40); p=0·255 |
| Week 52 | 311 (40·7) | 279 (36·3) | 1·22 (0·99–1·51); p=0·068 |

BDP/FF/G = beclometasone dipropionate/formoterol fumarate/glycopyrronium; IND/GLY = indacaterol/glycopyrronium; $FEV_1$ = forced expiratory volume in 1 second; SGRQ = St George's Respiratory Questionnaire; CI = confidence interval. a. Response defined as ≥100 mL increase from baseline; b. Response defined as ≥4 units decrease from baseline.

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 (Supplementary Table 1). Compared to those in the IND/GLY group, patients in the BDP/FF/G group reported a greater improvement from baseline in E-RS symptoms over the first 12 weeks of the study, with the two groups not significantly different at subsequent visits (Supplementary Figure 5).

A similar proportion of patients had adverse events in the two groups (Table 3), with most events being mild or moderate in severity. Pneumonia was reported in a small number of patients, with similar incidence in the two treatment groups (3·7% and 3·5% for BDP/FF/G and IND/GLY, respectively); more than 80% of these cases were diagnosed on the basis of

medical imaging (75% of the events in the BDP/FF/G group and 90% in the IND/GLY group). Similarly, the incidence of cardiac adverse events and serious adverse events was low and similar in the two groups (adverse events 5.8% and 6.6%, serious adverse events 1.4% and 3.8% for BDP/FF/G and IND/GLY, respectively). 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 experienced adverse events leading to discontinuation of study drug in the BDP/FF/G group than in the IND/GLY group, with the most common event leading to study drug discontinuation being a COPD exacerbation (in five patients in the BDP/FF/G group and ten in the IND/GLY group). Adverse events resulted in a total of 37 deaths, none considered related to study medication. Changes from baseline in blood pressure, heart rate and other ECG parameters were small, and not different between treatments (Supplementary Appendix and Supplementary Tables 2 and 3).

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

| Number (%) of patients | **BDP/FF/G (N=764)** | **IND/GLY (N=768)** |
|---|---|---|
| Adverse events | 490 (64·1) | 516 (67·2) |
| COPD | 273 (35·7) | 288 (37·5) |
| Nasopharyngitis | 43 (5·6) | 37 (4·8) |
| Headache | 44 (5·8) | 35 (4·6) |
| Pneumonia | 28 (3·7) | 27 (3·5) |
| Respiratory tract infection | 22 (2·9) | 28 (3·6) |
| Dyspnoea | 23 (3·0) | 24 (3·1) |
| Back pain | 21 (2·7) | 23 (3·0) |
| Hypertension | 15 (2·0) | 26 (3·4) |
| Cough | 13 (1·7) | 25 (3·3) |
| Cardiac failure | 15 (2·0) | 16 (2·1) |
| Ischaemic heart disease | 8 (1·0) | 16 (2·1) |
| Myocardial infarction | 1 (0·1) | 8 (1·0) |
| Angina pectoris | 5 (0·7) | 1 (0·1) |
| Coronary artery disease | 2 (0·3) | 4 (0·5) |
| Myocardial ischaemia | 2 (0·3) | 4 (0·5) |
| Serious adverse events | 117 (15·3) | 130 (16·9) |
| COPD | 61 (8·0) | 69 (9·0) |

| Number (%) of patients | **BDP/FF/G (N=764)** | **IND/GLY (N=768)** |
|---|---|---|
| Pneumonia | 18 (2·4) | 17 (2·2) |
| Cardiac failure | 6 (0·8) | 7 (0·9) |
| Death | 3 (0·4) | 8 (1·0) |
| Ischaemic heart disease | 2 (0·3) | 11 (1·4) |
| Myocardial infarction | 1 (0·1) | 8 (1·0) |
| Coronary artery disease | 1 (0·1) | 2 (0·3) |
| Myocardial ischaemia | 0 | 1 (0·1) |
| Atrial fibrillation | 0 | 7 (0·9) |
| Respiratory failure | 3 (0·4) | 4 (0·5) |
| Lung neoplasm | 4 (0·5) | 2 (0·3) |
| Treatment-related adverse events | 43 (5·6) | 37 (4·8) |
| Oral candidiasis | 12 (1·6) | 6 (0·8) |
| Dry mouth | 3 (0·4) | 6 (0·8) |
| Cough | 1 (0·1) | 7 (0·9) |
| Treatment-related serious adverse events | 1 (0·1) | 1 (0·1) |
| Severe adverse events | 86 (11·3) | 87 (11·3) |
| Adverse events leading to study drug discontinuation | 37 (4·8) | 47 (6·1) |
| Adverse events leading to death | 16 (2·1) | 21 (2·7) |

Data are n (%). ≥2% in either group for adverse events and ≥0.5% in either group for serious adverse events and treatment-related adverse events. BDP/FF/G = beclometasone dipropionate/formoterol fumarate/glycopyrronium; IND/GLY = indacaterol/glycopyrronium; COPD = chronic obstructive pulmonary disease exacerbations.

# Discussion

In this study, the inhaled corticosteroid-containing triple combination of extrafine BDP/FF/G in a single inhaler was shown to be superior to the dual bronchodilator combination of IND/GLY in reducing the rate of moderate-to-severe COPD exacerbations over 52 weeks of treatment, without differences in adverse effects, particularly pneumonia.

This study is the first to specifically compare triple therapy with a fixed dual bronchodilator combination both in a single inhaler in terms of reducing exacerbations. We recruited patients with severe or very severe airflow limitation, who despite treatment with one or more long-acting bronchodilators (with or without inhaled corticosteroid, but no triple therapy) were symptomatic, and who had at least one moderate-to-severe exacerbation in the previous year. TRIBUTE met the primary endpoint, with a significant 15% reduction in the rate of moderate-to-severe exacerbations with BDP/FF/G compared to IND/GLY. Both moderate and severe exacerbations contributed to the overall result, with reductions of 13 and 21%, respectively, although these reductions were not statistically significant. However, it should be noted that 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 higher (>2%) eosinophil levels; the latter finding is consistent with a number of published pre-specified 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] While this observation was not statistically significant using the 200 cell/µL cut-off, the optimum cut-off for blood eosinophils is unclear.[15] The results from these subgroups should be interpreted with caution, of course, 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 long-acting $\beta_2$-agonist/long-acting

muscarinic antagonist combination,[16] by demonstrating the benefit of adding an ICS in patients who still report exacerbations despite dual bronchodilation.

We selected IND/GLY as the comparator, as it is the only long-acting $\beta_2$-agonist/long-acting muscarinic antagonist combination to have previously demonstrated a reduction in the rate of COPD exacerbations compared with once-daily glycopyrronium and twice-daily fluticasone/salmeterol.[6,7] The latter study, in which there was a 17% reduction in the rate of moderate-to-severe COPD exacerbations with IND/GLY compared with fluticasone/salmeterol,[6] supported the recommendation in the Global Initiative for Obstructive Lung Disease report of long-acting $\beta_2$-agonist/long-acting muscarinic antagonist combinations as first choice treatment for patients with COPD who are symptomatic and at risk of exacerbations.[1] In this context, the further 15% reduction in TRIBUTE is likely to be clinically relevant. Of note, 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 treatment period (although not consistently at all individual visits) and patients in the BDP/FF/G group had a significantly greater improvement in health-related quality of life at all visits, together with an early improvement in symptoms.

The rate of exacerbations observed during TRIBUTE was lower than the rate reported in the year prior to the study, a pattern that is similar to previous BDP/FF/G studies conducted using very similar inclusion criteria.[4,5] This could be a clinical trial effect, either due to 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%) and/or more accurate identification of COPD exacerbations by expert investigators. Furthermore, the exclusion from the study of patients on triple therapy means that there was no ‘step down’ in treatment, unlike other clinical trials,[6,7] which may increase the risk of exacerbations. Indeed, all patients in the triple therapy group (and a number in the dual bronchodilation group) had a ‘step up’ in therapy. However, although at a population level a history of exacerbations is associated with an increased risk of future exacerbations,[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 that which can be expected in many real-life COPD populations.[18,19] Importantly, the high level of comorbidities amongst patients 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 may be present. In view of the high level of incorrect inhaler technique 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 the consistency with the profile of IND/GLY. The low rate of cardiac disorder adverse events in both groups, particularly in the triple therapy arm, is reassuring given reports of increased risk of such events in patients with COPD receiving long-acting bronchodilators,[21,22] especially older patients,[23] and is consistent with reports of the protective effects of inhaled corticosteroids added to long-acting bronchodilators in elderly COPD populations.[24] A number of studies, including the TORCH trial, have shown that the use of inhaled corticosteroids by patients with COPD increases the risk of pneumonia.[25] That a similar proportion of patients in the two groups experienced pneumonia (more than 80% of which were diagnosed on the basis of medical imaging) is therefore of interest, since this could indicate that adding extrafine BDP to a long-acting muscarinic antagonist plus long-acting $\beta_2$-agonist combination does not increase the risk of pneumonia in the given population.

We acknowledge that the study has some limitations. First we recruited fewer patients than similar studies that examine the effect of pharmacological interventions on COPD

exacerbations.[6,26] However, TRIBUTE was designed and powered specifically to address the first and most important question, i.e., the effect on moderate-to-severe exacerbations, with statistical significance achieved for this endpoint. Secondly, the reasons for a lower observed rate of moderate-to-severe exacerbations compared to the year prior to study entry have been discussed, and we believe that this lower rate does not diminish the importance of the positive results obtained. Finally, we selected IND/GLY as the comparator, the two groups received different long-acting $\beta_2$-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 vs once-daily dosing regimens.

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

# Research in context

## Evidence before this study

We searched PubMed for articles published before 4 January 2018, using the search term *"Drug Therapy, Combination"[MeSH Terms] OR triple AND COPD AND trial*, with no limits applied. Of the 565 hits, 30 presented data from clinical trials evaluating the efficacy of triple therapy comprising an inhaled corticosteroid plus a long-acting $\beta_2$-agonist plus a long-acting muscarinic antagonist. Only two of these included a group receiving a long-acting $\beta_2$-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 those receiving dual bronchodilation fewer patients receiving triple therapy experienced an exacerbation over 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 the first long-term study to specifically compare the effects of triple therapy with those of dual bronchodilation on the rate of exacerbations.

## Implications of all the available evidence

In comparison to dual bronchodilator therapy, triple therapy with an inhaled corticosteroid, a long-acting $\beta_2$-agonist and a long-acting muscarinic antagonist in a single inhaler reduces the rate of COPD exacerbations in patients with symptomatic COPD, $FEV_1$ of less than 50% and an exacerbation history despite maintenance therapy.

# Contributors

Alberto Papi substantially contributed to the acquisition, analysis, and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Jørgen Vestbo contributed to the analysis and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Leonardo Fabbri contributed to the analysis and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Massimo Corradi contributed to the conception, design and medical data integrity of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Hélène Prunier, in her Chiesi Clinical Operation Project Manager role, contributed to the conception, design and conduct of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Géraldine Cohuet, in her Chiesi Lead Clinical Project Manager role, contributed to the conception, design, oversight and conduct of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Alessandro Guasconi, in his Chiesi Statistician role, contributed to the analyses and interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Isabella Montagna, in her Chiesi Lead Data Manager role, contributed to the conception, design and data integrity of this study, to the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Stefano Vezzoli, in his Chiesi Lead Statistician role, contributed to the conception and design of this study, and to the analyses and interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Stefano Petruzzelli in his role as Head of Chiesi Global Clinical Development, contributed to the conception and design of the study, to the interpretation of the data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Mario Scuri, in his Chiesi Clinical Program Leader role, contributed to the interpretation of the data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

Nicolas Roche was the study coordinator and substantially contributed to the acquisition, analysis, and interpretation of data for the work. He contributed to drafting and revising the manuscript for intellectual content, and he provided approval of the version to be published.

Dave Singh contributed to the conception and design of this study, and the interpretation of its data, revised the manuscript critically for intellectual content, and provided approval of the version to be published.

## Declaration of interests

Alberto Papi reports grants, personal fees, non-financial support and other from Chiesi, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Mundipharma, and TEVA, personal fees and non-financial support from Menarini, Novartis, and Zambon, and grants from Sanofi, all outside the submitted work.

Jørgen Vestbo reports personal fees from Chiesi Farmaceutici during the conduct of the study. Outside the submitted work, Dr Vestbo reports personal fees from GlaxoSmithKline, Chiesi Farmaceutici, Boehringer-Ingelheim, Novartis, and AstraZeneca.

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Massimo Corradi received grants and honoraria for lectures from Chiesi Farmaceutici SpA, outside the submitted work.

Hélène Prunier is employed by Chiesi, the sponsor of the study.

Géraldine Cohuet is employed by Chiesi, the sponsor of the study.

Alessandro Guasconi is employed by Chiesi, the sponsor of the study.

Isabella Montagna is employed by Chiesi, the sponsor of the study.

Stefano Vezzoli is employed by Chiesi, the sponsor of the study.

Stefano Petruzzelli is employed by Chiesi, the sponsor of the study.

Mario Scuri is employed by Chiesi, the sponsor of the study.

Nicolas Roche reports personal fees from Chiesi during the conduct of the study. Outside the submitted work, Dr Roche reports grants and personal fees from Boehringer Ingelheim, Pfizer, Novartis, personal fees from Teva, GlaxoSmithKline, AstraZeneca, Chiesi, Mundipharma, Cipla, Sanofi, Sandoz, 3M, and Zambon.

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# Figure legends

*Figure 1. Patient disposition.*

*BDP/FF/G = beclometasone dipropionate/formoterol fumarate/glycopyrronium; IND/GLY = indacaterol/glycopyrronium. [a]320 were excluded after receiving at least one dose of run-in medication (IND/GLY), while 251 were excluded before receiving run-in medication.*

*Figure 2. Adjusted annual rate of moderate-to-severe, moderate, and severe COPD exacerbations. Analysis of intention-to-treat population.*

*Error bars and values in brackets under the exacerbation rates are 95% confidence intervals. BDP/FF/G = beclometasone dipropionate/formoterol fumarate/glycopyrronium; IND/GLY = indacaterol/glycopyrronium.*

*Figure 3: (A) Adjusted mean change from baseline in pre-dose $FEV_1$ and (B) adjusted mean change from baseline in SGRQ total score. Analysis of intention-to-treat population.*

*Error bars are 95% confidence intervals. BDP/FF/G = beclometasone dipropionate/formoterol fumarate/glycopyrronium; IND/GLY = indacaterol/glycopyrronium. *p<0·05, **p<0·01 vs IND/GLY, ***p≤0·001 vs IND/GLY.*