



Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2 -agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial

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Summary

Background Few data are available for the efficacy of “triple therapy” with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). We designed this study to assess efficacy of single-inhaler combination of an extra fine formulation of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) in COPD compared with beclomethasone dipropionate and formoterol fumarate (BDP/FF) treatment.

Methods TRILOGY was a randomised, parallel group, double-blind, active-controlled study done in 159 sites across 14 countries. The sites were a mixture of primary, secondary, and tertiary care providers, and specialist investigation units. Eligible patients with COPD had post-bronchodilator forced expiratory volume in 1 s (FEV_1) of lower than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score of 10 or more, and a Baseline Dyspnea Index focal score of 10 or less. Patients who met the inclusion and exclusion criteria at screening entered a 2-week open-label run-in period where they received beclomethasone dipropionate (100 μ g) and formoterol fumarate (6 μ g) in two actuations twice daily. Patients were then randomly assigned (1:1) with an interactive response technology system to either continue BDP (100 μ g) and FF (6 μ g) or step-up to BDP (100 μ g), FF (6 μ g), and GB (12.5 μ g) in two actuations twice daily for 52 weeks via pressurised metered-dose inhaler. The three co-primary endpoints were pre-dose FEV_1 , 2-h post-dose FEV_1 , and Transition Dyspnea Index (TDI) focal score, all measured at week 26 in the intention-to-treat population (all patients who were randomly assigned and received at least one dose of study drug and had at least one post-baseline efficacy assessment). Safety outcomes were measured in the safety population (all patients who were randomly assigned and received at least one dose of study drug). Secondary endpoints included moderate-to-severe COPD exacerbation rate over 52 weeks. This study is registered with ClinicalTrials.gov, number NCT01917331.

Findings Between March 21, 2014, and Jan 14, 2016, 1368 patients received either BDP/FF/GB (n=687) or BDP/FF (n=681). At week 26, BDP/FF/GB improved pre-dose FEV_1 by 0.081 L (95% CI 0.052–0.109; $p<0.001$) and 2-h post-dose FEV_1 by 0.117 L (0.086–0.147; $p<0.001$) compared with BDP/FF. Mean TDI focal scores at week 26 were 1.71 for BDP/FF/GB and 1.50 for BDP/FF, with a difference of 0.21 (95% CI –0.08 to 0.51; $p=0.160$). Adjusted annual moderate-to-severe exacerbation frequencies were 0.41 for BDP/FF/GB and 0.53 for BDP/FF (rate ratio 0.77 [95% CI 0.65–0.92]; $p=0.005$), corresponding to a 23% reduction in exacerbations with BDP/FF/GB compared with BDP/FF. Adverse events were reported by 368 (54%) patients with BDP/FF/GB and 379 (56%) with BDP/FF. One serious treatment-related adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group.

Interpretation We provide evidence for the clinical benefits of stepping up patients with COPD from an inhaled corticosteroid/long-acting β_2 -agonist combination treatment to triple therapy using a single inhaler.

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Introduction

The goals of pharmacological treatment of chronic obstructive pulmonary disease (COPD) are to reduce symptoms and the risk of future exacerbations.¹ Patients with COPD with a history of exacerbations are at an increased risk of future exacerbations,^{2,3} and are more likely to have a reduced quality of life,⁴ more rapid lung function decline,^{5,6} and increased mortality.⁷ To reduce the risk of future events, the Global Initiative for Chronic

Obstructive Lung Disease (GOLD) has specific recommendations for these patients; the first choice treatment is a long-acting muscarinic antagonist, or an inhaled corticosteroid plus a long-acting β_2 agonist.¹ Both of these options have been shown to improve lung function, alleviate symptoms, and reduce exacerbation rates.^{8,9}

Many patients with COPD continue to have exacerbations despite treatment with either a long-acting muscarinic

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Research in context

Evidence before this study

We searched PubMed for articles published before June 9, 2016, using the search term “Drug Therapy, Combination” [MeSH Terms] AND COPD limited to clinical trials with no language restrictions applied. Of the 312 results from this search, 13 presented data from clinical trials assessing the efficacy of triple therapy with an inhaled corticosteroid plus a long-acting β_2 agonist plus a long-acting muscarinic antagonist, with one further manuscript presenting data from a retrospective cohort analysis. Of these, four studies compared triple therapy with inhaled corticosteroid/long-acting β_2 -agonist therapy; three compared triple therapy with both a long-acting muscarinic antagonist and inhaled corticosteroid/long-acting β_2 -agonist therapy. Triple therapy consistently provided improved bronchodilation (assessed using forced expiratory volume in 1 s; FEV₁) compared with inhaled corticosteroid/long-acting β_2 -agonist therapy. However, results were more variable for the other endpoints, including health-related quality of life, breathlessness, and exacerbations. Most studies were of short duration and had insufficient sample size to assess exacerbations.

Added value of this study

To our knowledge, this is the first large, long-term study to compare a triple inhaled corticosteroid/long-acting β_2 -agonist/long-acting muscarinic antagonist combination in a single inhaler with an inhaled corticosteroid/long-acting β_2 -agonist combination. All patients received inhaled corticosteroid/long-acting β_2 -agonist therapy during the run-in period, and so the study provides an indication of the benefits of stepping up treatment in patients with COPD with both an exacerbation history and symptoms.

Implications of all the available evidence

Compared with inhaled corticosteroid/long-acting β_2 -agonist therapy, triple therapy with an inhaled corticosteroid/long-acting β_2 -agonist/long-acting muscarinic antagonist combination provides additive bronchodilation. This study also shows that a reduction in exacerbations can be achieved through this approach with the use of a single inhaler.

antagonist or an inhaled corticosteroid plus a long-acting β_2 -agonist combination. In clinical practice, treatment is often stepped up to “triple therapy” when this occurs, combining an inhaled corticosteroid, a long-acting β_2 agonist, and a long-acting muscarinic antagonist.¹⁰ Short-term clinical trials have shown that this step up improves lung function and reduces symptoms.^{11–16} However, GOLD recognises that there is little evidence for this approach regarding exacerbation reduction.¹

Patients with COPD receiving triple therapy currently use at least two inhalers, typically an inhaled corticosteroid plus a long-acting β_2 -agonist combination in one inhaler and a long-acting muscarinic antagonist in a second, and often these inhalers are of different types and designs. A single inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2 -agonist inhaler combining extra fine formulations of beclomethasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) has been developed to simplify this regimen. In the TRILOGY study, we aimed to compare the efficacy and safety of single inhaler triple therapy comprising BDP/FF/GB to that of beclomethasone dipropionate and formoterol fumarate (BDP/FF) in patients with COPD who have severe or very severe airflow limitation, symptoms, and an exacerbation history. The recruitment of this patient group allowed us to assess treatment effects on lung function, symptoms, and exacerbations.

secondary (n=99), and tertiary care (n=28) providers, and specialist investigation units (n=14). The main inclusion criteria were being aged 40 years or older; having a diagnosis of COPD, with a post-bronchodilator forced expiratory volume in 1 s (FEV₁) of less than 50% and a ratio of FEV₁ to forced vital capacity (FVC) of less than 0.7; at least one moderate or severe COPD exacerbation in the previous 12 months; and the use of an inhaled corticosteroid plus a long-acting β_2 agonist (as a free or fixed combination), or an inhaled corticosteroid plus a long-acting muscarinic antagonist, or a long-acting β_2 agonist plus a long-acting muscarinic antagonist (as a free or fixed combination), or long-acting muscarinic antagonist monotherapy for at least 2 months before screening (patients receiving triple therapy of an inhaled corticosteroid plus a long-acting β_2 agonist plus a long-acting muscarinic antagonist were not eligible). Additionally, all patients needed to be symptomatic for inclusion, classified as a COPD Assessment Test (CAT) total score of 10 or more and a Baseline Dyspnea Index (BDI) focal score of 10 or less at screening, with the BDI criterion also confirmed at the randomisation visit. The key criteria for exclusion were a diagnosis of asthma, or history of allergic rhinitis or atopy; a COPD exacerbation in the 4 weeks before screening or during the run-in period; clinically significant cardiovascular conditions or laboratory abnormalities; or unstable concurrent disease that might have affected efficacy or safety (as judged by the investigator). The full inclusion and exclusion criteria are listed in the appendix.

As rescue medication, patients were permitted to use salbutamol (100 µg per actuation by pressurised metered dose inhaler), although not within 6 h before a spirometry assessment. Other than study treatments

Methods

Study design and patients

TRILOGY was a randomised, parallel group, double-blind, active-controlled study done in 159 sites across 14 countries. The sites were a mixture of primary (n=18),

See Online for appendix

and rescue medication, for the duration of the study the following classes of medication were not permitted, from the indicated time before the screening visit: short-acting β_2 agonists (6 h); short-acting muscarinic antagonists (12 h); long-acting β_2 agonists (12 h; 72 h for ultra-long-acting β_2 agonists); long-acting muscarinic antagonists (72 h); inhaled corticosteroids (12 h); and xanthine derivatives (7 days). 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 Harmonisation Good Clinical Practice (ICH/CPMP/135/95). All patients provided written informed consent before any study-related procedure. There were no substantial protocol amendments.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either BDP/FF or BDP/FF/GB treatment by investigators contacting an interactive response technology system, which used a randomisation list generated by the interactive response technology provider. Randomisation was stratified by country and severity of airflow limitation (in the post-bronchodilator FEV₁ categories, <30% predicted or 30% to <50% predicted). The two study treatments were provided in matching inhalers, with patients, investigators, site staff, and sponsor personnel masked to treatment assignment for the duration of the study.

Procedures

Patients who met the inclusion and exclusion criteria at a screening visit (visit 1) entered a 2-week open-label run-in period during which they received an extra fine formulation of beclomethasone dipropionate (100 µg) and formoterol fumarate (6 µg), two actuations twice daily by pressurised metered dose inhaler. At the end of the run-in (visit 2), patients were randomly assigned to one of two treatment groups, to either continue to receive beclomethasone dipropionate (100 µg) and formoterol fumarate (6 µg), or to be stepped up to an extra fine formulation of BDP (100 µg), FF (6 µg), and GB (12.5 µg), both two actuations twice per day via pressurised metered dose inhaler for the 52-week treatment period. Over the treatment period, patients attended visits at weeks 4, 12, 26, 40, and 52.

At visit 2, baseline (pre-dose) data were collected for spirometry, BDI, and the St George's Respiratory Questionnaire (SGRQ); spirometry was also done at 2 h post-dose. At each subsequent visit, pre-dose and 2-h post-dose spirometry was done, and data were collected for the Transition Dyspnea Index (TDI; which measures change from the BDI at visit 2) and SGRQ. Centralised spirometry was used to improve the quality of FEV₁ data. For the duration of the study, patients recorded daily symptoms with the EXacerbations of Chronic pulmonary disease Tool Patient-Reported Outcome (EXACT-PRO) questionnaire, together with treatment compliance and

rescue medication use in an electronic diary; these data were reviewed by the investigator regularly, and at least at each visit.

Outcomes

We measured three co-primary endpoints to compare BDP/FF with BDP/FF/GB: change from baseline in pre-dose (morning) FEV₁, change from baseline in 2-h post-dose FEV₁, and TDI focal score, all assessed at week 26. The secondary efficacy variables were pre-dose FEV₁ at all the other clinic visits and averaged over the treatment period; FEV₁ response (change from baseline in pre-dose FEV₁ ≥100 mL) at weeks 26 and 52; 2-h post-dose FEV₁ at all the other clinic visits; TDI focal score at all the other clinic visits and TDI response (a focal score of one or more was deemed the minimum clinically important difference¹⁷) at weeks 26 and 52; SGRQ total score at all clinic visits, and SGRQ response (decrease from baseline in total score ≥4 was deemed the minimum clinically important difference¹⁷) at weeks 26 and 52; percentage of days without rescue medication use and average number of puffs per day; moderate-to-severe COPD exacerbation frequency over 52 weeks of treatment; and the time to first moderate-to-severe COPD exacerbation.

A COPD exacerbation was defined as a worsening of the patient's respiratory symptoms that in the view of the patient's health-care provider required treatment with systemic corticosteroids, antibiotics, or hospital admission, or a combination of these.¹⁸ Events were classified as moderate or severe according to European Medicines Agency/Committee for Medicinal Products for Human Use guidelines,¹⁸ with severe exacerbations being those requiring hospital admission or resulting in death. Data from the EXACT-PRO questionnaire were used to optimise the recognition of potential exacerbations by programming the electronic diary to alert physicians and to advise patients to contact their investigator in the event of worsening symptoms. EXACT-PRO data were also assessed for the exploratory Evaluating Respiratory Symptoms (E-RS) total score endpoint.¹⁹

Treatment-emergent adverse events were captured throughout the study, with all events judged by the investigator as having reasonable causal association to a medical product considered to be treatment-related adverse events. Blood pressure and electrocardiogram results were recorded pre-dose and at 10 min post-dose at each visit, and 24 h Holter recordings were captured for a subset of approximately 10% of the patients at baseline and at weeks 26 and 52. Major adverse cardiovascular events were adjudicated by an independent adjudication committee, comprising four cardiologists.

Statistical analysis

We estimated that 1304 randomly assigned patients (652 patients per group) would be required to reach a total of 1088 evaluable patients at week 26 (544 patients

per group), considering a non-assessable rate of approximately 16·5% at this timepoint. With the use of a two-sided significance level of 0·05, this sample size provided 97·7% power to detect a mean difference of 60 mL in pre-dose FEV₁, assuming an SD of 250 mL; 99·6% power to detect a mean difference of 70 mL in 2-h post-dose FEV₁, assuming an SD of 250 mL; and 87·1% power to detect a mean difference of 0·6 units in TDI focal score, assuming a SD of 3·2 units. An overall 85% study power for the primary efficacy analyses was therefore ensured.

The co-primary endpoints were all assessed with a linear mixed model for repeated measures, with data up to discontinuation included in the analysis for withdrawn patients. 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. Data are presented as the adjusted means (ie, least squares means) and adjusted mean differences between treatment groups, together with their 95% CIs. To deal with multiplicity, the primary efficacy variables

were tested in the following prespecified hierarchical order: (1) pre-dose FEV₁; (2) 2-h post-dose FEV₁; (3) TDI focal score. At each step of the procedure, no confirmatory claims were to be made unless the superiority of BDP/FF/GB over BDP/FF was shown in the preceding steps. Multiplicity was not adjusted for in the analyses of the secondary endpoints. Subgroup analyses of the co-primary endpoints were prespecified, with patients grouped according to severity of airflow limitation, smoking status, sex, reversibility to salbutamol, COPD phenotype (chronic bronchitis, emphysema, or mixed), blood eosinophil concentration at screening, and age, with TDI also analysed according to presence of cardiovascular comorbidities. Sensitivity analyses were done on the three co-primary endpoints to assess the potential effect of missing data, as described in the appendix.

Most secondary and exploratory endpoints were analysed with a similar mixed model for repeated measures to the co-primary endpoints. The responder analyses for FEV₁, TDI, and SGRQ were done with a logistic model, the number of moderate-to-severe COPD exacerbations was analysed using a negative binomial model, and the time to first moderate-to-severe COPD

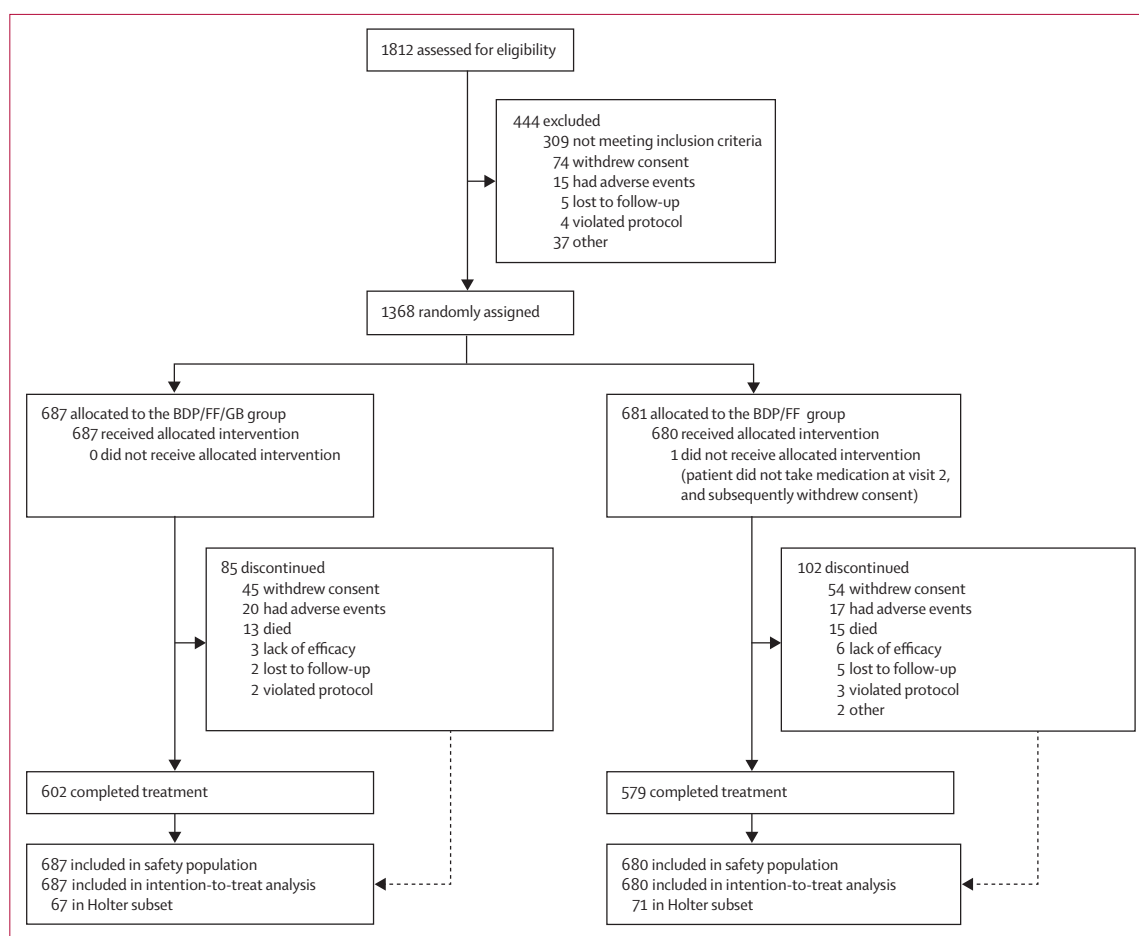


Figure 1: Trial profile

exacerbation was analysed with a Cox proportional hazards model. In these models, treatment, country, number of COPD exacerbations in the previous year, severity of airflow limitation, smoking status at screening, and the baseline value (where available) were included as fixed effects. Log-time on study was also accounted for as an offset in the negative binomial model. Post-hoc subgroup analyses of the rate of moderate-to-severe exacerbations were done, with patients grouped as for the TDI co-primary endpoint, and also according to number of exacerbations in the previous 12 months.

Primary and secondary endpoints were analysed in the intention-to-treat population classified as all randomly assigned patients who received at least one dose of study drug and had at least one post-baseline efficacy assessment. Safety outcomes were analysed in the safety population, which was classified as all randomly assigned patients who received at least one dose of study drug. An independent Data Safety Monitoring Board, composed of three independent clinicians and one independent biostatistician, provided a quarterly independent scrutiny of the study. All analyses presented in this manuscript were done with SAS software, version 9.2. The study is registered with ClinicalTrials.gov, number NCT01917331.

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 of the data in the study and DS had final responsibility for the decision to submit for publication.

Results

The study ran between March 21, 2014, and Jan 14, 2016. We recruited 1812 patients to this study, of whom, 1368 were randomly assigned to one of the treatment groups (687 to BDP/FF/GB and 681 to BDP/FF; figure 1), with 602 (87.6%) completing the study in the BDP/FF/GB group and 579 (85.0%) in the BDP/FF group. Compliance to treatment was high, with a median of 95.6% of doses taken in the BDP/FF/GB group and 95.0% of doses taken in the BDP/FF group. Median exposure in both groups was 365.0 days (range 6–395) in the BDP/FF/GB group and 365.0 days (3–409) in the BDP/FF group. Baseline characteristics of the recruited patients are shown in table 1. More than 80% of patients had at least one concomitant disease, with at least one cardiac disorder reported by 36% of patients in the BDP/FF/GB group and 35% in the BDP/FF group.

BDP/FF/GB was superior to BDP/FF for both pre-dose FEV₁ (adjusted mean difference 0.081 L [95% CI 0.052–0.109]; $p < 0.001$) and 2-h post-dose FEV₁ (adjusted mean difference 0.117 [0.086–0.147]; $p < 0.001$) at week 26 (table 2). TDI focal score improved at week 26 in both groups; the mean difference between treatments (0.21 units [95% CI –0.08 to 0.51]) was not statistically

	BDP/FF/GB (N=687)	BDP/FF (N=680)
Sex		
Male	509 (74%)	527 (77%)
Female	178 (26%)	153 (23%)
Race		
White	684 (100%)	679 (100%)
Other	3 (<1%)	1 (<1%)
Mean age (years)	63.3 (7.9)	63.8 (8.2)
Body-mass index (kg/m ²)	26.3 (5.4)	26.4 (5.3)
Blood leucocyte concentration (10 ⁹ /L)	8.02 (2.23)	8.13 (2.28)
Blood eosinophil concentration (10 ⁹ /L)	0.25 (0.17)	0.24 (0.19)
Blood eosinophil proportion (%)	3.12 (2.22)	3.06 (2.27)
Smoking status		
Current smoker	323 (47%)	318 (47%)
Ex-smoker	364 (53%)	362 (53%)
Time since first COPD diagnosis (years)	7.7 (5.8)	7.7 (6.0)
FEV ₁ (L)*	1.11 (0.32)	1.10 (0.33)
FEV ₁ percentage predicted*	36.9 (8.4)	36.2 (8.6)
30% to <50%	532 (77%)	525 (77%)
<30%	155 (23%)	155 (23%)
FVC (L)*	2.73 (0.76)	2.75 (0.76)
FEV ₁ /FVC ratio*	0.42 (0.11)	0.41 (0.11)
Reversibility	10.4 (14.2)	10.4 (14.1)
Chronic bronchitis†	450 (66%)	463 (68%)
Exacerbation rate in the previous year	1.2 (1.5)	1.2 (1.6)
CAT total score	20.8 (5.9)	20.8 (5.7)
COPD medication at study entry		
ICS/LABA	506 (74%)	487 (72%)
ICS/LAMA	10 (1%)	10 (1%)
LABA/LAMA	95 (14%)	107 (16%)
LAMA	76 (11%)	76 (11%)
Spacer use during the study	111 (16%)	129 (19%)
Patients with at least one concomitant disease‡	590 (86%)	563 (83%)
Hypertension	404 (59%)	382 (56%)
Ischaemic heart disease	172 (25%)	173 (25%)
Myocardial ischaemia	91 (13%)	92 (14%)
Coronary artery disease	66 (10%)	58 (9%)
Angina pectoris	44 (6%)	43 (6%)
Ischaemic cardiomyopathy	3 (<1%)	6 (1%)
Myocardial infarction	2 (<1%)	0
Diabetes	90 (13%)	89 (13%)
Cardiac failure	73 (11%)	86 (13%)
Hypercholesterolaemia	45 (7%)	41 (6%)
Respiratory failure	35 (5%)	45 (7%)
Gastritis	36 (5%)	30 (4%)
Benign prostatic hyperplasia	24 (3%)	42 (6%)
Cor pulmonale	39 (6%)	25 (4%)

Data are n (%), mean (SD), or n (range). BDP=beclomethasone dipropionate. FF=formoterol fumarate.

GB=glycopyrronium bromide. COPD=chronic obstructive pulmonary disease. FEV₁=forced expiratory volume in 1 s.

FVC=forced vital capacity. CAT=COPD Assessment Test. ICS=inhaled corticosteroid. LABA=long-acting β_2 -agonist.

LAMA=long-acting muscarinic antagonist. *Measured after salbutamol was administered. †Includes patients with a mixed chronic bronchitis and emphysema phenotype. ‡Only diseases where 5% of patients or more were affected in either group are included here.

Table 1: Baseline characteristics

significant. Subgroup analyses of the three co-primary endpoints (including by blood eosinophil concentration) were broadly consistent with the intention-to-treat analyses (appendix). An exception was for the subgroup with very severe airflow limitation; in these patients, pre-dose FEV₁ assessment did not differ significantly between treatment groups.

Compared with BDP/FF, BDP/FF/GB showed significantly greater improvements in both pre-dose and 2-h postdose FEV₁ at all visits (table 2; figure 2), with a significantly higher proportion of patients responding to BDP/FF/GB than BDP/FF (defined as ≥ 100 mL increase in pre-dose FEV₁) at weeks 26 and 52 (table 3). The average pre-dose FEV₁ mean difference between treatments over the duration of the study was 0.072 L (95% CI 0.048–0.096; $p < 0.001$).

Increases in TDI focal score were observed in both groups at all visits, with a statistically significant difference between treatments favouring BDP/FF/GB at the two earliest visits (weeks 4 and 12; figure 2). More than 50% of patients in each group reported clinically relevant improvements (≥ 1 unit) in TDI focal score at weeks 26 and 52; at week 26, patients were significantly more likely to respond to BDP/FF/GB than BDP/FF (table 3).

For SGRQ total score, clinically relevant improvements from baseline (decrease ≥ 4 units) occurred for the BDP/FF/GB group at all visits from week 12 onwards, with statistically significant differences between the two groups at weeks 4, 12, and 52 (mean treatment difference at week 52 of -1.69 [95% CI -3.20 to -0.17]; $p = 0.029$; figure 3). Patients were significantly more likely to have a

clinically relevant improvement in SGRQ total score with BDP/FF/GB than with BDP/FF at weeks 26 and 52 (table 3). The use of rescue medication in puffs per day was significantly lower with BDP/FF/GB than with BDP/FF up to week 26; patients in the BDP/FF/GB group had a significantly greater percentage of days with no rescue use than those in the BDP/FF group up to week 12 (appendix). Additionally, E-RS total scores (exploratory endpoint) were significantly lower with BDP/FF/GB than with BDP/FF up to week 26 (appendix).

The percentage of patients who had moderate-to-severe exacerbations was lower with BDP/FF/GB (31%) than with BDP/FF (35%). The adjusted annual rate of moderate-to-severe exacerbations was 0.41 for the BDP/FF/GB group and 0.53 for the BDP/FF group, with a rate ratio of 0.77 (95% CI 0.65–0.92; $p = 0.005$), indicating a significant 23% reduction in the rate with BDP/FF/GB. Subgroup analyses were broadly consistent with the intention-to-treat analysis, showing a reduction in the frequency of moderate-to-severe exacerbations for BDP/FF/GB compared with BDP/FF (appendix). Of note, there was a significant 33% reduction in the rate of moderate-to-severe exacerbations with BDP/FF/GB compared with BDP/FF in patients with a history of more than one exacerbation (rate ratio 0.67 [95% CI 0.48–0.94]; $p = 0.019$), whereas for patients with a history of one exacerbation, the treatment reduction appeared to be slightly lower (0.83 [0.67–1.02]; $p = 0.074$). The adjusted exacerbation frequency in patients was 0.37 and 0.44 in those with a history of one exacerbation and 0.65 and 0.97 in those with a history of more than one exacerbation in the BDP/FF/GB and BDP/FF groups, respectively. No association between blood eosinophil concentration and treatment effect was observed (appendix). The frequency of both moderate and severe exacerbations was lower in the BDP/FF/GB group than the BDP/FF group (figure 3). Furthermore, BDP/FF/GB significantly prolonged the time to first moderate-to-severe exacerbation compared with BDP/FF (hazard ratio 0.80 [95% CI 0.67–0.97]; $p = 0.020$; figure 3).

A similar proportion of patients had treatment-emergent adverse events in the two groups (table 4). Most events were mild or moderate in severity. One treatment-related serious adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group, and this event resolved in 15 days, and did not cause study drug discontinuation. Treatment-emergent adverse events resulted in death in a similar percentage of patients in the two groups. None of the deaths were assessed to be related to the study treatment.

Mean changes from baseline in blood pressure, heart rate, and Fridericia's corrected QT (QTcF) interval were small and similar in the two groups (appendix). The percentages of abnormal QTcF interval absolute values and changes were similar in both treatment groups (appendix). In the subgroup of patients with Holter

	BDP/FF/GB (N=687)	BDP/FF (N=680)	Adjusted mean difference between treatments	p value
FEV₁ (L)				
Baseline (pre-dose, week 0)	1.096 (0.381)	1.094 (0.393)	..	..
Week 26	0.082 (0.062 to 0.102)	0.001 (-0.019 to 0.021)	0.081 (0.052 to 0.109)	$p < 0.001$
Week 52	0.071 (0.050 to 0.093)	0.008 (-0.014 to 0.030)	0.063 (0.032 to 0.094)	$p < 0.001$
2-h post-dose FEV₁ (L)				
Week 26	0.261 (0.240 to 0.283)	0.145 (0.123 to 0.166)	0.117 (0.086 to 0.147)	$p < 0.001$
Week 52	0.249 (0.226 to 0.273)	0.146 (0.122 to 0.170)	0.103 (0.069 to 0.137)	$p < 0.001$
BDI and TDI focal score				
BDI focal score*	5.27 (1.81)	5.45 (1.82)	..	..
TDI focal score at week 26	1.71 (1.50 to 1.92)	1.50 (1.29 to 1.71)	0.21 (-0.08 to 0.51)	$p = 0.160$
TDI focal score at week 52	2.03 (1.81 to 2.25)	1.81 (1.59 to 2.04)	0.21 (-0.10 to 0.53)	$p = 0.186$

Data are mean (SD) or adjusted mean change (95% CI), unless otherwise stated. BDP=beclomethasone dipropionate. FF=formoterol fumarate. GB=glycopyrronium bromide. FEV₁=forced expiratory volume in 1 s. BDI=Baseline Dyspnea Index. TDI=Transition Dyspnea Index. *BDI focal score is the baseline value from which TDI focal score is assessed.

Table 2: FEV₁ and TDI at baseline, week 26, and week 52 in the intention-to-treat population

assessments, changes from baseline in 24 h average heart rate to weeks 26 and 52 were minimum and similar in both groups (appendix).

Discussion

This study shows that in patients with COPD who have severe or very severe airflow limitation, symptoms, and an exacerbation history, triple therapy with BDP/FF/GB had a greater effect on pre-dose and 2-h post-dose FEV₁ than BDP/FF. For the co-primary endpoint measuring breathlessness (TDI), superiority of BDP/FF/GB over BDP/FF was not shown. The rate of moderate-to-severe COPD exacerbations was 23% lower with BDP/FF/GB compared with BDP/FF, with the time to first exacerbation significantly longer with triple therapy. Thus, the greater improvement in lung function with BDP/FF/GB compared with BDP/FF was more clearly accompanied by a reduction in exacerbations than an improvement in breathlessness in this group of patients. Furthermore, BDP/FF/GB had a greater effect on health-related quality of life than BDP/FF.

Clinical trials have previously tested the effectiveness of triple therapy delivered by two separate devices. Active comparators in these studies have included long-acting muscarinic antagonist monotherapy, a long-acting muscarinic antagonist and a long-acting β_2 agonist using separate inhalers, and combined inhaled corticosteroid and long-acting β_2 agonist treatment. These studies show short-term superiority of triple therapy in terms of lung function and patient reported outcomes compared with long-acting muscarinic antagonist monotherapy^{15,20,21} or inhaled corticosteroid and long-acting β_2 agonist treatment.^{13,16,22} We chose inhaled corticosteroid and long-acting β_2 agonist treatment as the comparator group because of its widespread use in clinical practice in the target population we studied—namely, patients with COPD with severe to very severe airflow limitation and an exacerbation history. We showed that triple therapy had a greater effect on FEV₁ than inhaled corticosteroid and long-acting β_2 agonist treatment, with effect sizes similar to previous studies that were done with broader inclusion criteria.^{13,16,22}

TDI focal score had a clinically relevant improvement with both treatments, but the mean difference between treatments in TDI focal score at week 26 was not statistically significant. A practical issue for TDI measurements that might have affected this outcome is the requirement for patients to recall their previous symptoms, which can be a problem in longer studies, as

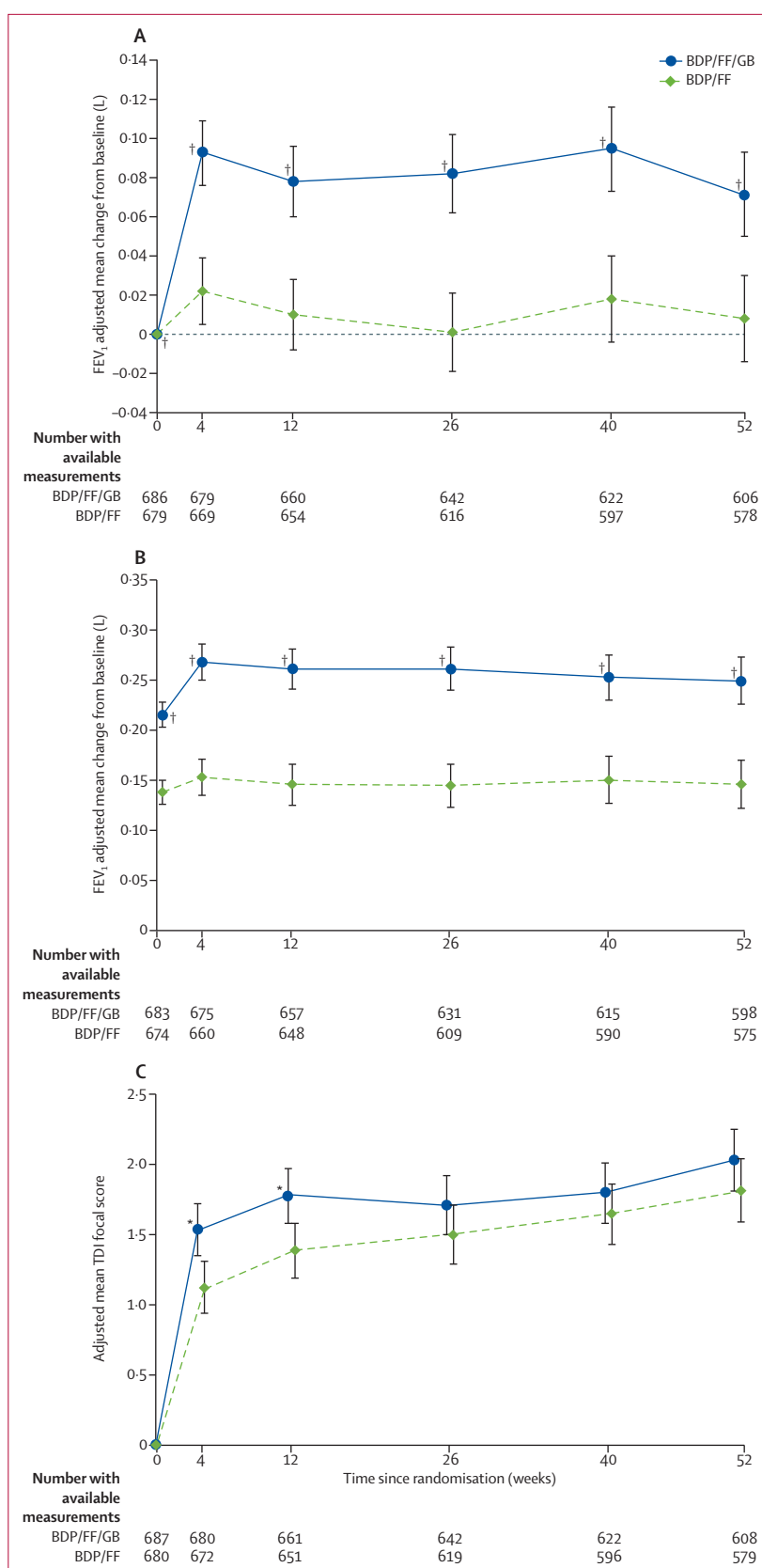


Figure 2: Adjusted mean change from baseline for pre-dose FEV₁ (A), 2-h post-dose FEV₁ (B), and TDI focal score (C) in the intention-to-treat population

Error bars show 95% CI. The first datapoints for 2-h post-dose FEV₁ are the week 0 post-baseline assessment. BDP=beclomethasone dipropionate. FF=formoterol fumarate. GB=glycopyrronium bromide. FEV₁=forced expiratory volume in 1 s. TDI=Transition Dyspnea Index. *p<0.01 for the difference between BDP/FF/GB and BDP/FF. †p<0.001 for the difference between BDP/FF/GB and BDP/FF.

	BDP/FF/GB (N=687)	BDP/FF (N=680)	Odds ratio	p value
Pre-dose FEV₁ (≥100 mL increase from baseline)				
Week 26	287 (42%)	165 (24%)	2.30 (1.82–2.91)	p<0.001
Week 52	259 (38%)	158 (23%)	2.06 (1.62–2.62)	p<0.001
TDI (focal score ≥1)				
Week 26	394 (57%)	352 (52%)	1.28 (1.03–1.59)	p=0.027
Week 52	370 (54%)	354 (52%)	1.09 (0.88–1.36)	p=0.430
SGRQ (≥4 unit decrease from baseline in total score)				
Week 26	321 (47%)	246 (36%)	1.52 (1.21–1.91)	p<0.001
Week 52	297 (43%)	244 (36%)	1.33 (1.06–1.66)	p=0.014

Data are n (%) or odds ratio (95% CI), unless otherwise stated.
BDP=beclomethasone dipropionate. FF=formoterol fumarate. GB=glycopyrronium bromide. FEV₁=forced expiratory volume in 1 s. TDI=Transition Dyspnea Index.
SGRQ=St George's Respiratory Questionnaire.

Table 3: Patients with a clinically relevant change from baseline for FEV₁, TDI, and SGRQ responder analyses at weeks 26 and 52 in the intention-to-treat population

discussed by the Food and Drug Administration (FDA).²³ TDI responder analysis has been suggested as an alternative way to assess differences between active treatments;¹⁷ this analysis showed a symptomatic benefit with BDP/FF/GB in a greater proportion of patients. Significant differences favouring BDP/FF/GB for SGRQ total score were also found at several timepoints (weeks 4, 12, and 52)—results that were supported by the SGRQ responder analysis. Overall, these responder analyses indicated that the lung function improvement with BDP/FF/GB compared with BDP/FF caused a clinically meaningful improvement in patient reported outcomes in a proportion of patients.

The evidence for an effect of triple therapy on exacerbations is scarce because studies have generally been of short duration and have not specifically recruited patients with COPD at risk of exacerbation events. In one of the few long-term studies, Aaron and colleagues assessed exacerbation frequency with a long-acting muscarinic antagonist alone or in combination with either a long-acting β_2 agonist or an inhaled corticosteroid and a long-acting β_2 agonist for 52 weeks;¹¹ although the exacerbation frequency was lower with triple therapy compared with long-acting muscarinic antagonist monotherapy, the difference was not statistically significant. This study had a small sample size and a high dropout rate, which reduced the number of events, thereby reducing statistical power. By contrast, a 12-week study²¹ showed a significant 62% reduction in the rate of severe exacerbations with triple therapy compared with long-acting muscarinic antagonist monotherapy ($p<0.001$), although the data for moderate-to-severe exacerbations were not reported.

The design of TRILOGY ensured that patients had at least one exacerbation in the past year despite treatment, most commonly with an inhaled corticosteroid/long-acting β_2 agonist combination (which accounted for

>70% of the study population). We specifically excluded patients who were previously on triple therapy, to avoid stepping down treatment in patients randomly assigned to inhaled corticosteroid/long-acting β_2 agonist therapy. The inclusion criteria of an FEV₁ lower than 50%, a CAT total score of 10 or more, and an exacerbation history means that all of the study population were in GOLD group D.¹ For these patients, the GOLD strategy document states that triple therapy is an option. However, in real life, triple therapy is not commonly prescribed as first-line treatment in such patients, but instead treatment is generally escalated from regimens of one or two long-acting bronchodilators or an inhaled corticosteroid/long-acting β_2 agonist combination,¹⁰ although the evidence supporting this approach was previously limited. Because we used a run-in period during which all patients received BDP/FF (with >70% also receiving inhaled corticosteroid/long-acting β_2 agonist therapy before entering the study), the study design therefore allows clinicians to better understand the consequences of escalation of maintenance therapy in patients with COPD already treated with inhaled corticosteroid/long-acting β_2 agonist therapy.

Combination treatment with a long-acting β_2 agonist and a long-acting muscarinic antagonist has been shown to have a greater effect on symptoms and exacerbations than long-acting muscarinic antagonist monotherapy.²⁴ Our study did not address the benefit of escalation to triple therapy from a long-acting β_2 agonist/long-acting muscarinic antagonist combination. This is an important point to examine in the future, especially given that a study²⁵ suggested that long-acting β_2 agonist/long-acting muscarinic antagonist treatment is more effective on a wide range of endpoints including exacerbations than an inhaled corticosteroid/long-acting β_2 agonist combination.

The 23% reduction in the exacerbation rate, which is above the suggested minimum clinically important difference,¹⁷ can be attributed to the long-acting muscarinic antagonist component of BDP/FF/GB. Most of this benefit was on moderate exacerbations—consistent with other studies that were mainly dominated by moderate events.^{11,20,26} Our results for exacerbations are broadly similar to a retrospective database review using UK National Health Service data to compare triple therapy with inhaled corticosteroid/long-acting β_2 agonist therapy in terms of exacerbations and mortality.²⁶ Over a mean follow-up of 4.65 years, triple therapy was associated with a significant 35% reduction in all-cause mortality ($p<0.001$), a 29% reduction in moderate exacerbations ($p<0.001$) and a 15% reduction in severe exacerbations ($p=0.04$). We now show a clinically relevant effect on moderate-to-severe exacerbations in GOLD group D patients of the long-acting muscarinic antagonist component after escalation to triple therapy from inhaled corticosteroid/long-acting β_2 agonist treatment.

The exacerbation rate was relatively low during the 1-year follow-up, despite the requirement for patients to have a history of at least one exacerbation in the year before study entry (the mean exacerbation rate over this period was 1.2). Most patients were receiving inhaled corticosteroid/long-acting β_2 -agonist therapy before study entry, so the exacerbation rate after randomisation to the inhaled corticosteroid/long-acting β_2 -agonist group was expected to be similar to the historic rate, rather than the observed rate of 0.53. We believe that this difference could be explained by the more regular care received in a clinical trial setting, plus potentially improved compliance during a clinical trial. The treatment difference between BDP/FF/GB and BDP/FF for exacerbations appeared to be even greater in patients with two or more exacerbations in the previous year. This is perhaps not surprising, showing a greater effect of triple therapy on exacerbations in patients who have more of these events.

Patients in the BDP/FF group had no change in therapy when progressing from the run-in period to the treatment period. This group was anticipated to have no change after randomisation (baseline) in patient-reported outcomes. However, we observed a mean improvement in TDI focal score that exceeded the minimum clinically important difference threshold,¹⁷ and an improvement in SGRQ total score being close to the threshold,¹⁷ despite no change in treatment. A trial effect on patient reported outcomes has been observed in previous COPD clinical trials.^{27,28} We attempted to minimise this by using a run-in period where patients were established on inhaled corticosteroid/long-acting β_2 -agonist therapy, and recruiting patients who previously were on background maintenance treatment; more than 70% of patients were previously taking inhaled corticosteroid/long-acting β_2 -agonist therapy. A longer run-in period might have reduced this effect. This apparent trial effect on patient-reported outcomes in the BDP/FF group possibly reduced the likelihood of observing an overall group mean difference compared with BDP/FF/GB. Nevertheless, the responder analysis indicates a benefit for triple therapy on symptoms and health-related quality of life for a greater proportion of individuals in this GOLD group D population.

There are a range of inhaler devices of various types (including by pressurised metered dose inhalers and dry powder systems) and of contrasting designs, which demand different patient manoeuvres to ensure correct

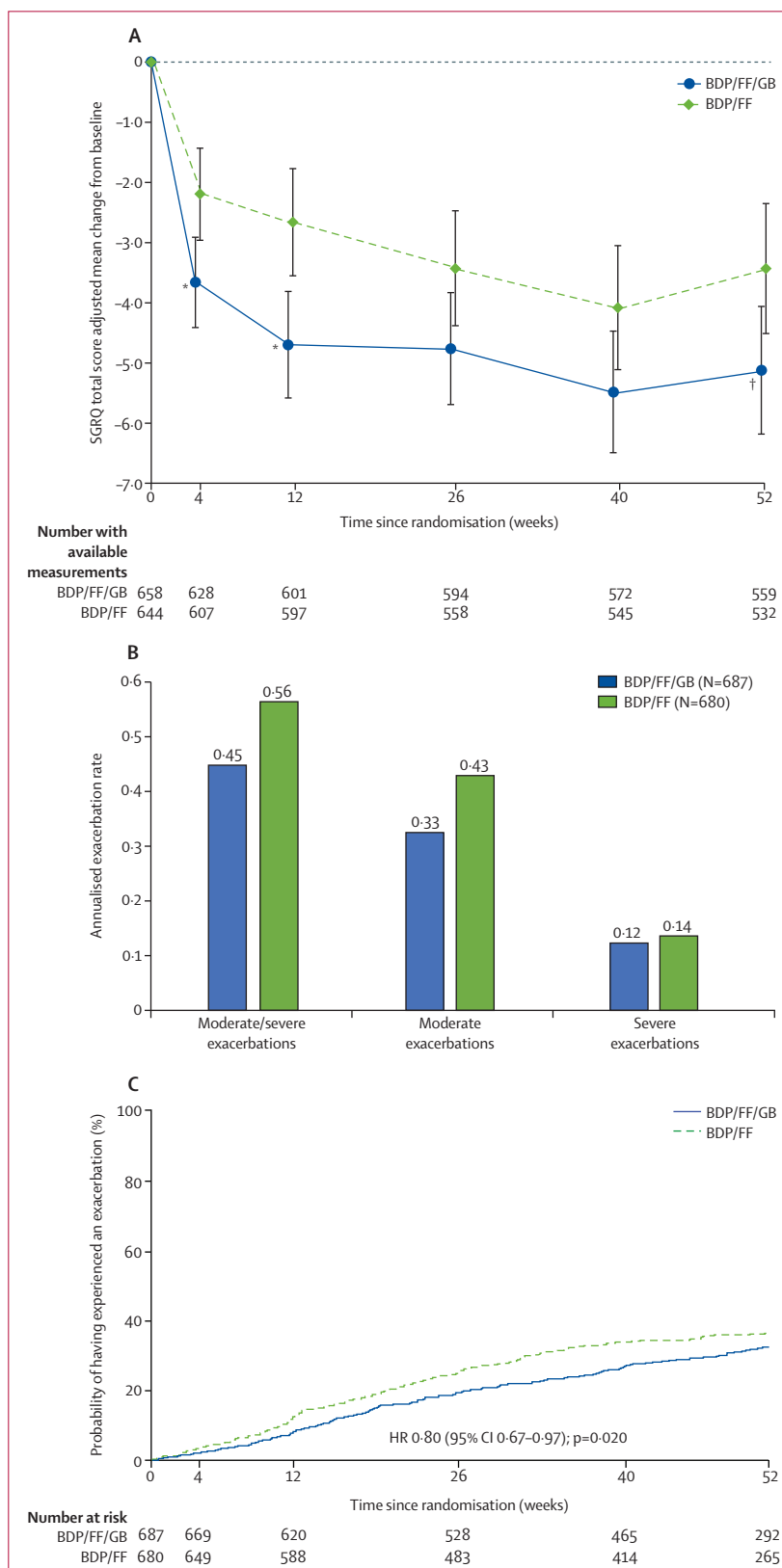


Figure 3: Adjusted mean change from baseline for SGRQ total score (A), unadjusted annual rate of COPD exacerbations of different severities (B), and time to first moderate-to-severe COPD exacerbation (C) in the intention-to-treat population

BDP=beclomethasone dipropionate. FF=formoterol fumarate.

GB=glycopyrronium bromide; SGRQ=St George's Respiratory Questionnaire.

COPD=chronic obstructive pulmonary disease. HR=hazard ratio. *p<0.01 for the difference between BDP/FF/GB and BDP/FF. †p<0.05 for the difference between BDP/FF/GB and BDP/FF.

	BDP/FF/GB (N=687)	BDP/FF (N=680)
Treatment-emergent adverse events	368 (54%)	379 (56%)
COPD	214 (31%)	240 (35%)
Nasopharyngitis	39 (6%)	38 (6%)
Pneumonia	23 (3%)	18 (3%)
Hypertension	21 (3%)	16 (2%)
Headache	12 (2%)	16 (2%)
Ischaemic heart disease	10 (1%)	16 (2%)
Angina pectoris	5 (1%)	3 (<1%)
Myocardial infarction	1 (<1%)	6 (1%)
Myocardial ischaemia	1 (<1%)	6 (1%)
Coronary artery disease	3 (<1%)	1 (<1%)
Respiratory tract infection viral	16 (2%)	10 (1%)
Oral candidosis	15 (2%)	4 (1%)
Serious treatment-emergent adverse events	106 (15%)	123 (18%)
COPD	66 (10%)	75 (11%)
Pneumonia	15 (2%)	7 (1%)
Ischaemic heart disease	2 (<1%)	11 (2%)
Myocardial infarction	1 (<1%)	6 (1%)
Myocardial ischaemia	0	4 (1%)
Angina pectoris	1 (<1%)	1 (<1%)
Cardiac failure	5 (1%)	5 (1%)
Treatment-related adverse events	26 (4%)	14 (2%)
Oral candidosis	10 (1%)	2 (<1%)
Muscle spasms	5 (1%)	3 (<1%)
Dry mouth	4 (1%)	2 (<1%)
Serious treatment-related adverse events	1 (<1%)	0
Severe treatment-emergent adverse events	77 (11%)	86 (13%)
Treatment-emergent adverse events leading to study drug discontinuation	35 (5%)	33 (5%)
Treatment-emergent adverse events leading to death	15 (2%)	16 (2%)
Major adverse cardiovascular events*	15 (2%)	15 (2%)

Only adverse events where 2% of patients or more were affected in either group for treatment-emergent adverse events and where 0.5% of patients or more were affected for serious adverse events and treatment-related adverse events are included here. BDP=beclometasone dipropionate. FF=formoterol fumarate. GB=glycopyrronium bromide. COPD=chronic obstructive pulmonary disease exacerbations. *Includes acute myocardial infarction, arrhythmias, cardiovascular death, heart failure, and stroke.

Table 4: Treatment-emergent adverse events and serious adverse events

dose delivery. This presents a particular challenge with triple therapy, since historically, in clinical practice its administration has required more than one inhaler device. The delivery of triple therapy with a single inhaler potentially has practical advantages in this respect, simplifying therapy in a patient population which includes elderly individuals.

This triple therapy approach did not result in any safety findings, with no relevant differences between treatments. Of particular note, few patients had pneumonia, an event that has been associated with

inhaled corticosteroid use in COPD.²⁹ The low incidence of pneumonia events was within the range reported in several previous inhaled corticosteroid/long-acting β_2 -agonist studies (as summarised by Singh and colleagues³⁰). Notably, the incidence of pneumonia in this study was similar to that observed in the FLAME trial,²⁵ where the incidence of treatment-emergent pneumonia was 3.2% in the group that received only dual bronchodilator treatment and 4.8% in those who received inhaled corticosteroid/long-acting β_2 -agonist therapy. Furthermore, the 24-h Holter assessment provided reassurance about the safety profile of GB when added to therapy with BDP/FF.

Overall, in this study, done in patients with symptomatic severe and very severe COPD at risk of exacerbations, extra fine BDP/FF/GB provided greater bronchodilation than BDP/FF, whereas superiority of BDP/FF/GB was not shown by the analysis of the co-primary endpoint of dyspnoea. Triple therapy had greater effects on health-related quality of life and the prevention of moderate-to-severe exacerbations. To our knowledge, this is the first study to provide evidence for the clinical benefits of stepping up patients with COPD from inhaled corticosteroid/long-acting β_2 -agonist combination treatment to triple therapy with the use of a single inhaler.

Contributors

JV and AP drafted the manuscript. DS, MC, IM, CF, GC, SV, and MS contributed to the conception and design of this study. DS, AP, IP, IM, CF, GC, SV, MS, and JV interpreted the data. AP and IP substantially contributed to the acquisition of data. AP, SV, and JV analysed the data. MC and IM contributed to the medical data integrity of this study. IM contributed to the data integrity of this study. CF and GC conducted the study. DS, AP, MC, IP, IM, CF, GC, SV, MS, and JV revised the manuscript critically for intellectual content. DS, AP, MC, IP, IM, CF, GC, SV, MS, and JV approved the version to be published.

Declaration of interests

DS received personal fees from Chiesi during the conduct of the study; grants and personal fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Glenmark, Johnson and Johnson, Merck, NAPP, Novartis, Pfizer, Takeda, Teva, Theravance, and Verona; and personal fees from Genentech and Skyepharma, outside of the submitted work. AP received grants from Chiesi Farmaceutici during the conduct of the study; reports grants, personal fees, and non-financial support from Chiesi Farmaceutici, AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Merck Sharp & Dohme, Pfizer, Takeda, Mundipharma, and Teva; and personal fees and non-financial support from Menarini, Novartis, and Zambon. MC received a research contract from Chiesi Farmaceutici SpA during the conduct of the study. IM is employed by Chiesi Farmaceutici SpA, the sponsor of the study. CF and GC are employed by Chiesi SAS, affiliate of the sponsor of the study. SV and MS are employed by Chiesi Farmaceutici SpA, the sponsor of the study. 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, outside of the submitted work. IP declares no competing interests.

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THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed.
We post it as supplied by the authors.

Supplement to: Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β_2 -agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; **388**: 963–73.

Supplementary material

Title: Triple therapy in a single inhaler for COPD: The TRILOGY randomised, double-blind study

Authors: Dave Singh, Alberto Papi, Massimo Corradi, Ilona Pavlišová, Isabella Montagna, Catherine Francisco, Géraldine Cohuet, Stefano Vezzoli, Mario Scuri, Jørgen Vestbo

Inclusion and exclusion criteria

Inclusion Criteria

For inclusion into the study, patients were required to fulfil all of the following criteria:

1. Male or female adults aged ≥ 40 years with written informed consent obtained prior to any study-related procedure;
2. Patients with a diagnosis of COPD (according to GOLD document, revised 2013) at least 12 months before screening;
3. Current smokers or ex-smokers who quit smoking at least 6 months prior to screening visit, with a smoking history of at least 10 pack-years (pack-years = [number of cigarettes per day x number of years]/20);
4. A post-bronchodilator $FEV_1 < 50\%$ of the predicted normal value **and** a post-bronchodilator $FEV_1/FVC < 0.7$, within 30 minutes after 4 puffs (4 x 100 μ g) of salbutamol pMDI. If this criterion was not met at screening, the test could be repeated once before randomisation visit;
5. A documented history of at least one exacerbation in the 12 months preceding screening. COPD exacerbation was defined according to the following: *“A sustained worsening of the patient’s condition (dyspnoea, cough and/or sputum production/purulence), from the stable state and beyond normal day-to-day variations, that is acute in onset and necessitates a change in regular medication in a patient with underlying COPD that includes prescriptions of systemic corticosteroids and/or antibiotics or need for hospitalisation”*. Also documented visits to an emergency department due to COPD exacerbation were considered acceptable to fulfil this criterion;
6. Patients under double therapy for at least 2 months prior to screening with either:
 - ICS/inhaled LABA or;
 - ICS/inhaled LAMA or;
 - Inhaled LABA and inhaled LAMA or;
 - Patients under monotherapy with LAMA for at least 2 months prior to screening;
7. Symptomatic patients at screening with a CAT score ≥ 10 ;
8. Symptomatic patients at screening with a BDI focal score ≤ 10 . This criterion had to be confirmed at randomisation (V2, Week 0);
9. A cooperative attitude and ability to be trained to use correctly the pMDI;
10. A cooperative attitude and ability to be trained to use correctly the spacer AeroChamber Plus™. The criterion on spacer applied only to patients who were using a spacer for the administration of their COPD medications at screening;
11. A cooperative attitude and ability to be trained to use correctly electronic devices with COPD questionnaire.

Exclusion Criteria

Patients were not enrolled if one or more of the following criteria were present:

1. Pregnant or lactating women and all women physiologically capable of becoming pregnant (i.e. women of childbearing potential) unless they were willing to use one or more of the following reliable methods of contraception:
 - a. Placement of an intrauterine device or intrauterine system;
 - b. Hormonal contraception (implantable, patch, oral);
 - c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical vaults/caps) with spermicidal foam/gel/film/cream/suppository;
 - d. Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

Reliable contraception should have been maintained throughout the study until the last study visit. “True abstinence” was acceptable only if it was in line with the preferred and usual lifestyle of the patient.

Pregnancy testing was carried out during the course of the study in all women of childbearing potential: serum pregnancy test was performed at screening and at V7 (Week 52) and urine pregnancy test was performed at all clinic visits except V7.

Any post-menopausal women (physiologic menopause was defined as “12 consecutive months of amenorrhea”) or women permanently sterilised (e.g. tubal occlusion, hysterectomy or bilateral salpingectomy) could be enrolled in the study;

2. Diagnosis of asthma or history of allergic rhinitis or atopy (atopy which may have risen contra-indications or impacted the efficacy of the study treatment according to Investigator's judgement);
3. Patients requiring use of the following medications:
 - a. Systemic steroids for COPD exacerbation in the 4 weeks prior to screening;
 - b. A course of antibiotics for COPD exacerbation longer than 7 days in the 4 weeks prior to screening;
 - c. Phosphodiesterase (PDE)-4 inhibitors in the 4 weeks prior to screening;
 - d. Use of antibiotics for a lower respiratory tract infection (e.g. pneumonia) in the 4 weeks prior to screening;
4. COPD exacerbation requiring prescriptions of systemic corticosteroids and/or antibiotics or hospitalisation during the run-in period;
5. Patients treated with non-cardio-selective β -blockers in the month preceding screening or during the run-in period;
6. Patients treated with long-acting anti-histamines unless taken at stable regimen at least 2 months prior to screening and to be maintained constant during the study or if taken as pro re nata (PRN, as needed);
7. Patients requiring long term (at least 12 hours daily) oxygen therapy for chronic hypoxaemia;
8. Known respiratory disorders other than COPD which may have impacted the efficacy of the study treatment according to Investigator's judgement. This could include but was not limited to α -1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease;
9. Patients who had clinically significant (CS) cardiovascular condition (such as but not limited to unstable ischaemic heart disease, NYHA Class III/IV, left ventricular failure, acute myocardial infarction);
10. Patients with AF:
 - a. Persistent defined as an AF episode either lasting more than 7 days or requiring termination by cardioversion, either with drugs or by direct current cardioversion within 6 months from screening;
 - b. Long standing persistent as defined by continuous AF diagnosed for less than 6 months and/or without a rhythm control strategy;
 - c. Permanent defined as lasting for at least 6 months with a resting ventricular rate ≥ 100 /minute controlled with a rate control strategy (i.e. selective β -blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy);
11. An abnormal and CS 12-lead ECG that resulted in active medical problem which may have impacted the safety of the patient according to Investigator's judgement.
Patients whose 12-lead ECG showed Fridericia's corrected QT interval (QTcF) >450 ms for males or >470 ms for females at screening or at randomisation were not eligible;
12. Medical diagnosis of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that in the opinion of the Investigator would have prevented use of anti-cholinergic agents;
13. History of hypersensitivity to M3 antagonists, β_2 -agonist, corticosteroids or any of the excipients contained in any of the formulations used in the study which may have raised contra-indications or impacted the efficacy of the study treatment according to the Investigator's judgement;
14. CS laboratory abnormalities indicating a significant or unstable concomitant disease which may have impacted the efficacy or the safety of the study treatment according to Investigator's judgement;
15. Patients with serum potassium levels <3.5 mEq/L (or 3.5 mmol/L);
16. Unstable concurrent disease: e.g. uncontrolled hyperthyroidism, uncontrolled diabetes mellitus or other endocrine disease; significant hepatic impairment; significant renal impairment; uncontrolled gastrointestinal disease (e.g. active peptic ulcer); uncontrolled neurological disease; uncontrolled haematological disease; uncontrolled autoimmune disorders, or other which may have impacted the efficacy or the safety of the study treatment according to Investigator's judgment;
17. History of alcohol abuse and/or substance/drug abuse within 12 months prior to screening;
18. Participation in another clinical study where investigational drug was received less than 8 weeks prior to screening.

Concomitant disease and safety methodology

- The dictionary used for coding concomitant disease and AEs was the Medical Dictionary for Regulatory Activities – MedDRA, Version 16.0. For this manuscript, preferred terms were grouped as follows:
 - ‘Angina pectoris’ includes the preferred terms angina pectoris, angina unstable and Prinzmetal angina.
 - ‘Cardiac failure’ includes the preferred terms cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, and cardiovascular insufficiency.
 - ‘Cor pulmonale’ includes the preferred terms cor pulmonale and cor pulmonale chronic.
 - ‘Diabetes mellitus’ includes the preferred terms diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, and pancreatogenous diabetes.
 - ‘Hypertension’ includes the preferred terms hypertension and essential hypertension.
 - ‘Myocardial infarction’ includes the preferred terms myocardial infarction and acute myocardial infarction.
 - ‘Oral candidiasis’ includes the preferred terms oral candidiasis, oral fungal infection, and oropharyngeal candidiasis.
 - ‘Pneumonia’ includes the preferred terms pneumonia, bronchopneumonia, and pneumonia aspiration.
 - ‘Respiratory failure’ includes the preferred terms respiratory failure and chronic respiratory failure.

Sensitivity analyses of the co-primary endpoints

In order to assess the potential impact of missing data on the results of the primary efficacy analyses, the following sensitivity analyses were performed on all randomised patients:

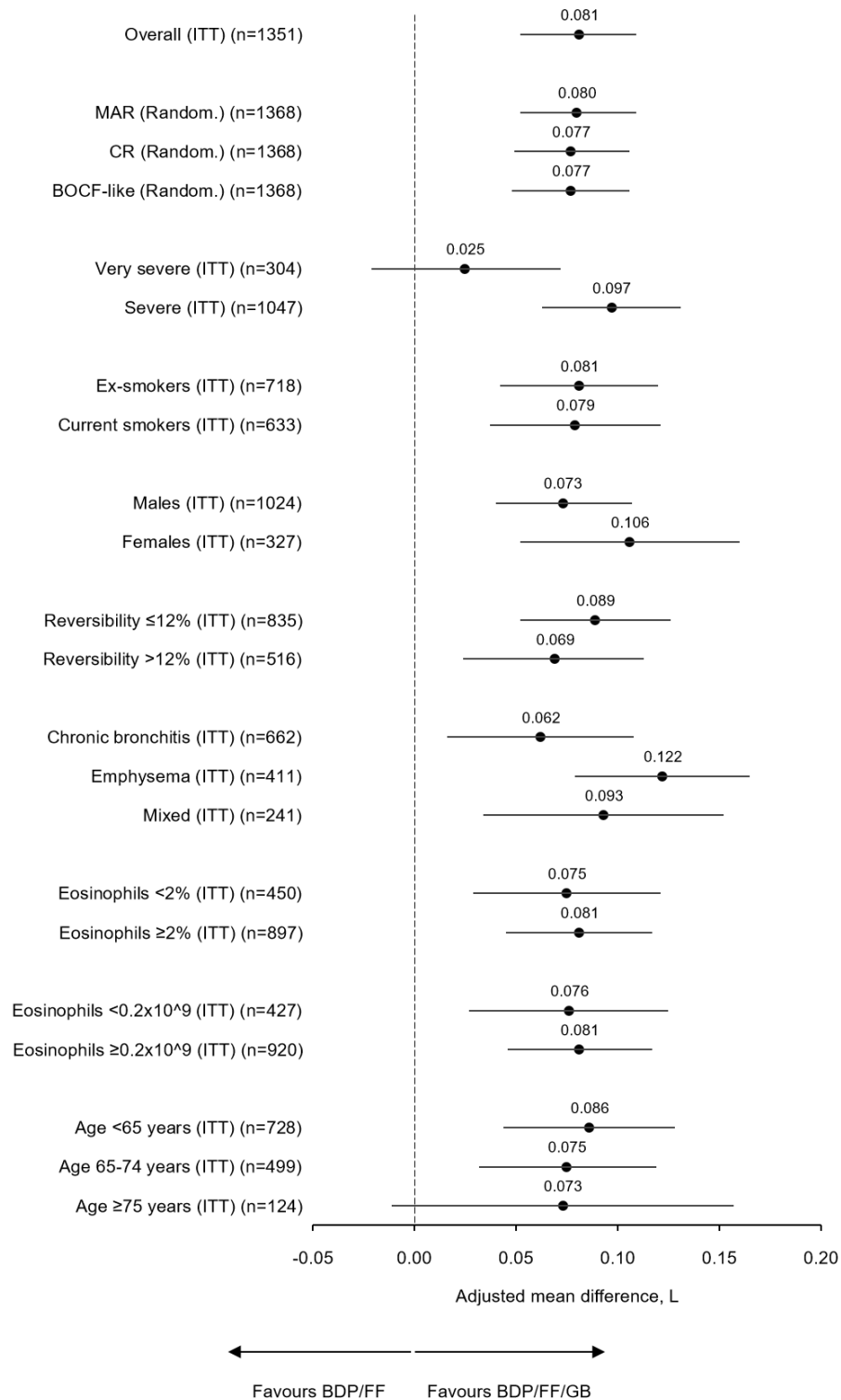
- change from baseline in pre-dose morning FEV₁: missing at random (MAR), copy reference (BDP/FF/GB) and baseline observation carried forward (BOCF) – like multiple imputation (MI);
- change from baseline in 2-hour post-dose FEV₁ and TDI focal score: MAR and copy reference MI, single imputation BOCF.

Of note, the analysis using MI under MAR is based on the same assumption behind the MMRM used for the primary efficacy analysis, however it allowed the inclusion in the analysis of all randomised patients (this is not always possible with the MMRM). Also, for 2-hour post-dose FEV₁ and TDI focal score it was not feasible to conduct a proper BOCF-like imputation since a real baseline value was not available. For this reason, this sensitivity analysis was based on a single imputation BOCF, even though the risk of biasing the standard error downwards by ignoring the uncertainty of imputed values is acknowledged.

Statistical Analysis System (SAS), Version 9.4 was used for the analyses based on MI.

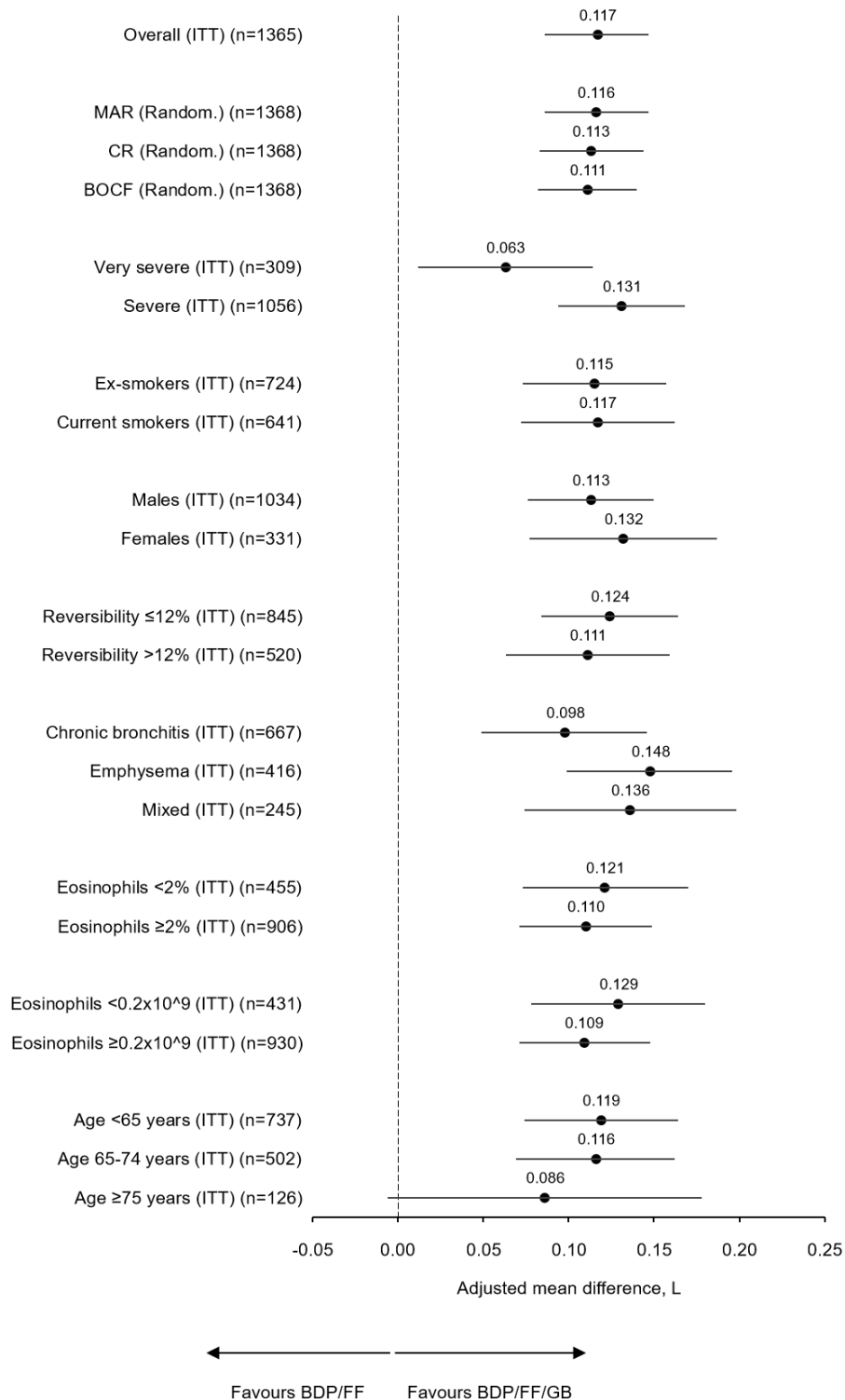
Supplementary results

Supplementary Figure 1. Adjusted mean differences (and 95% confidence intervals) between treatments in pre-dose FEV₁ at Week 26 (ITT or Randomised population)



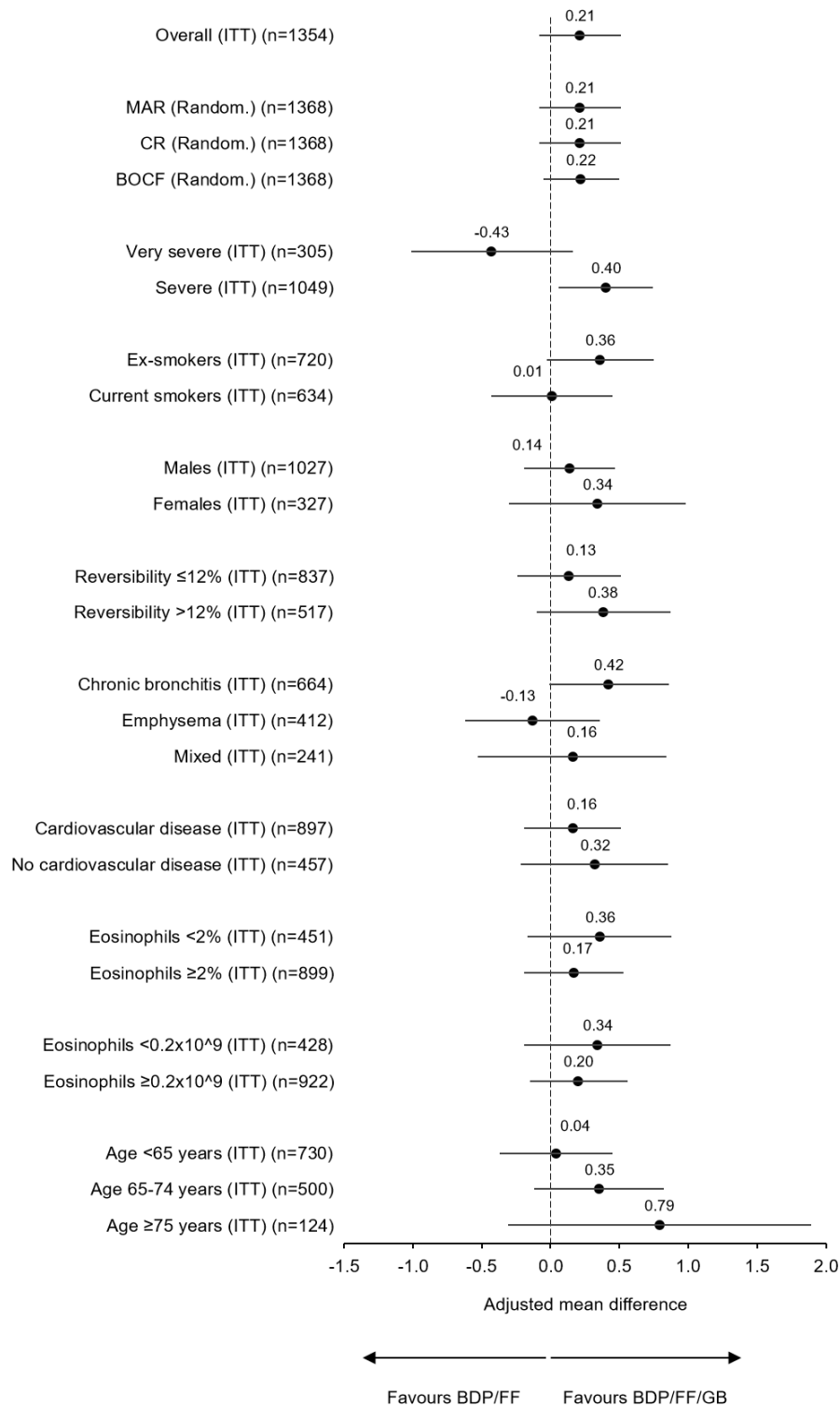
MAR = missing at random; CR = copy reference; BOCF = baseline observation carried forward; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide.

Supplementary Figure 2. Adjusted mean differences (and 95% confidence intervals) between treatments in 2-h post-dose FEV₁ at Week 26 (ITT or Randomised population)



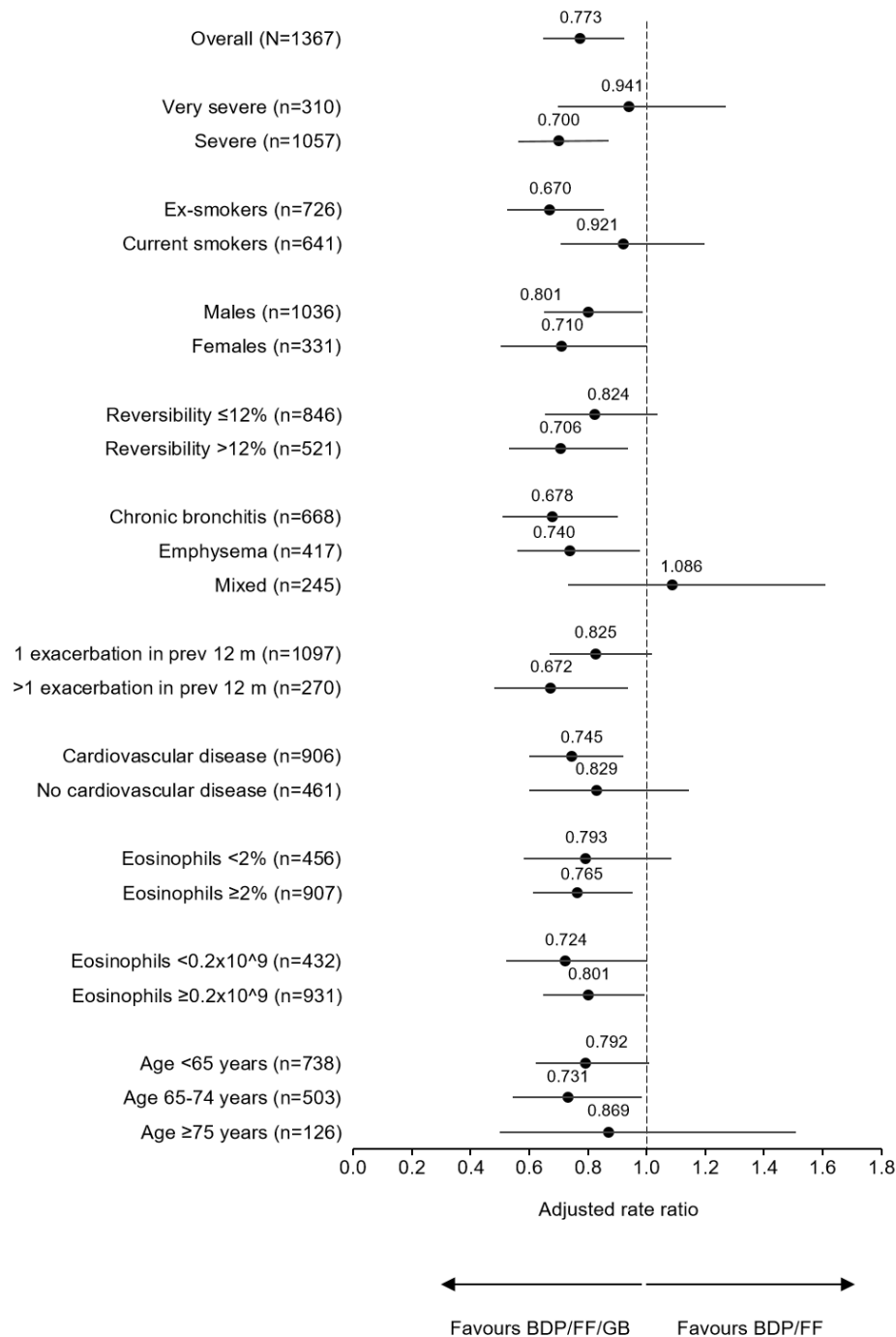
MAR = missing at random; CR = copy reference; BOCF = baseline observation carried forward; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide.

Supplementary Figure 3. Adjusted mean differences (and 95% confidence intervals) between treatments in Transition Dyspnea Index (TDI) focal score at Week 26 (ITT or Randomised population)



MAR = missing at random; CR = copy reference; BOCF = baseline observation carried forward; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide.

Supplementary Figure 4. Adjusted rate ratios (and 95% confidence intervals) for moderate/severe COPD exacerbations (ITT population)



BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide.

Supplementary table 1. Baseline and changes from baseline for rescue medication use (ITT population)

Endpoint	BDP/FF/GB (N=687)	BDP/FF (N=680)	Adjusted mean difference between treatments
Average number of puffs/day			
Baseline	2.32 (2.11)	2.38 (2.30)	
Weeks 1–4	–0.29 (–0.38, –0.20)	–0.07 (–0.17, 0.02)	–0.21 (–0.34, –0.08); p=0.001
Weeks 5–12	–0.25 (–0.36, –0.14)	–0.06 (–0.17, 0.05)	–0.19 (–0.35, –0.04); p=0.016
Weeks 13–26	–0.21 (–0.32, –0.09)	–0.02 (–0.14, 0.10)	–0.19 (–0.35, –0.02); p=0.029
Weeks 27–40	–0.09 (–0.22, 0.04)	0.02 (–0.11, 0.15)	–0.11 (–0.29, 0.07); p=0.225
Weeks 41–52	–0.04 (–0.17, 0.09)	0.07 (–0.07, 0.21)	–0.11 (–0.30, 0.08); p=0.262
Percentage of days without rescue medication use			
Baseline	33.22 (39.23)	33.88 (39.17)	
Weeks 1–4	6.67 (4.89, 8.44)	2.46 (0.67, 4.25)	4.21 (1.69, 6.73); p=0.001
Weeks 5–12	6.23 (4.19, 8.27)	3.18 (1.12, 5.24)	3.05 (0.15, 5.95); p=0.039
Weeks 13–26	5.49 (3.30, 7.67)	2.40 (0.19, 4.60)	3.09 (–0.02, 6.20); p=0.051
Weeks 27–40	4.39 (2.07, 6.72)	2.79 (0.43, 5.15)	1.60 (–1.71, 4.91); p=0.342
Weeks 41–52	3.82 (1.45, 6.19)	1.24 (–1.17, 3.65)	2.59 (–0.80, 5.97); p=0.134

Baseline data are mean (SD); post-baseline data are adjusted mean change from baseline (95% confidence interval). BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide.

Supplementary Table 2: Baseline and changes from baseline for average E-RS total score (ITT population)

	BDP/FF/GB (N=687)	BDP/FF (N=680)	Adjusted mean difference between treatments
Baseline	15.07 (5.95)	14.88 (5.60)	
Weeks 1–4	–1.19 (–1.41, –0.97)	–0.56 (–0.79, –0.34)	–0.62 (–0.94, –0.31); p<0.001
Weeks 5–12	–1.50 (–1.78, –1.23)	–0.85 (–1.12, –0.57)	–0.66 (–1.05, –0.27); p<0.001
Weeks 13–26	–1.65 (–1.95, –1.35)	–1.06 (–1.36, –0.75)	–0.60 (–1.02, –0.17); p=0.006
Weeks 27–40	–1.83 (–2.15, –1.51)	–1.41 (–1.73, –1.08)	–0.42 (–0.88, 0.03); p=0.070
Weeks 41–52	–1.77 (–2.10, –1.43)	–1.41 (–1.75, –1.08)	–0.35 (–0.82, 0.12); p=0.145

Baseline data are mean (SD); post-baseline data are adjusted mean change from baseline (95% confidence interval). BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide.

Supplementary Table 3. Treatment differences in changes from baseline in pre-dose and 10-minute post-dose HR (bpm) (Safety population)

BDP/FF/GB vs. BDP/FF	
Adjusted mean difference (90% CI); p-value	
Post-dose Week 0	0.41 (−0.07, 0.90); 0.158
Pre-dose Week 4	−0.08 (−0.89, 0.74); 0.878
Post-dose Week 4	−0.03 (−0.82, 0.76); 0.950
Pre-dose Week 12	−0.47 (−1.32, 0.38); 0.366
Post-dose Week 12	−0.07 (−0.90, 0.77); 0.895
Pre-dose Week 26	0.10 (−0.85, 1.04); 0.863
Post-dose Week 26	0.15 (−0.79, 1.10); 0.789
Pre-dose Week 40	−0.87 (−1.82, 0.09); 0.136
Post-dose Week 40	−0.24 (−1.15, 0.67); 0.661
Pre-dose Week 52	0.18 (−0.81, 1.16); 0.769
Post-dose Week 52	0.11 (−0.86, 1.08); 0.853

HR = heart rate; bpm = beats per minute; CI = confidence interval; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide. The analysis was based on mixed models for repeated measurements.

Supplementary Table 4. Treatment differences in changes from pre-dose in 10-minute post-dose HR (bpm)

(Safety population)

BDP/FF/GB vs. BDP/FF	
Adjusted mean difference (90% CI); p-value	
Week 4	–0.04 (–0.49, 0.41); 0.893
Week 12	0.34 (–0.12, 0.80); 0.230
Week 26	0.15 (–0.34, 0.63); 0.624
Week 40	0.53 (0.06, 1.01); 0.066
Week 52	0.02 (–0.48, 0.51); 0.959

HR = heart rate; bpm = beats per minute; CI = confidence interval; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide. The analysis was based on ANCOVA models at each visit.

Supplementary Table 5. Treatment differences in changes from baseline in pre-dose and 10-minute post-dose QTcF (ms) (Safety population)

	BDP/FF/GB vs. BDP/FF
	Adjusted mean difference (90% CI); p-value
Post-dose Week 0	-0.26 (-1.24, 0.72); 0.660
Pre-dose Week 4	0.55 (-0.64, 1.75); 0.443
Post-dose Week 4	-0.17 (-1.44, 1.10); 0.822
Pre-dose Week 12	-0.19 (-1.43, 1.05); 0.805
Post-dose Week 12	0.84 (-0.48, 2.15); 0.296
Pre-dose Week 26	-0.58 (-1.93, 0.76); 0.476
Post-dose Week 26	0.23 (-1.15, 1.62); 0.780
Pre-dose Week 40	-0.04 (-1.46, 1.38); 0.964
Post-dose Week 40	1.63 (0.18, 3.08); 0.065
Pre-dose Week 52	0.70 (-0.73, 2.13); 0.422
Post-dose Week 52	1.12 (-0.32, 2.56); 0.201

QTcF = Fridericia's corrected QT interval; ms = millisecond; CI = confidence interval; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide. The analysis was based on mixed models for repeated measurements.

Supplementary Table 6. Treatment differences in changes from pre-dose in 10-minute post-dose QTcF (ms)

(Safety population)

BDP/FF/GB vs. BDP/FF	
Adjusted mean difference (90% CI); p-value	
Week 4	-0.75 (-1.86, 0.37); 0.270
Week 12	0.71 (-0.40, 1.82); 0.290
Week 26	0.45 (-0.63, 1.54); 0.493
Week 40	1.39 (0.25, 2.52); 0.045
Week 52	0.38 (-0.74, 1.51); 0.575

QTcF = Fridericia's corrected QT interval; ms = millisecond; CI = confidence interval; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide. The analysis was based on ANCOVA models at each visit.

Supplementary Table 7. 12-lead ECG abnormalities in QTcF at any visit/timepoint after first study medication intake (Safety population)

	BDP/FF/GB	BDP/FF
Abnormalities in QTcF values, n (%)		
Males		
n	502	516
>450 ms	51 (10.2)	49 (9.5)
>480 ms	6 (1.2)	3 (0.6)
>500 ms	2 (0.4)	0 (0.0)
Females		
n	178	152
>470 ms	3 (1.7)	8 (5.3)
>480 ms	1 (0.6)	2 (1.3)
>500 ms	0 (0.0)	0 (0.0)
Abnormalities in change from baseline in QTcF, n (%)		
n	671	664
>30 ms	78 (11.6)	85 (12.8)
>60 ms	5 (0.7)	9 (1.4)
Abnormalities in change from pre-dose to 10-minute post-dose at the same visit in QTcF, n (%)		
n	678	667
>30 ms	35 (5.2)	26 (3.9)
>60 ms	1 (0.1)	2 (0.3)

QTcF = Fridericia's corrected QT interval; ECG = electrocardiogram; ms = millisecond; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide. n = Number of patients with available data.

Supplementary Table 8. Treatment differences in changes from baseline in Holter ECG 24-h average HR (bpm)
(Holter subset)

BDP/FF/GB vs. BDP/FF	
Adjusted mean difference (95% CI); p-value	
Week 26	0·30 (-2·77, 3·37); 0·846
Week 52	0·08 (-2·82, 2·99); 0·954

ECG = electrocardiogram; HR = heart rate; bpm = beats per minute; CI = confidence interval; BDP = beclometasone dipropionate; FF = formoterol fumarate; GB = glycopyrronium bromide. The analysis was based on mixed models for repeated measurements.

Supplementary Appendix 1

In the BDP/FF/GB group, the largest mean absolute change from baseline was observed at Week 40 (-1.4 mmHg [95% CI $-2.3, -0.4$]) for SBP and at Week 52 (-1.4 mmHg [95% CI $-2.1, -0.7$]) for DBP. In the BDP/FF group, the largest mean absolute change from baseline was observed at Weeks 40 and 52 (-2.0 mmHg [95% CI $-3.0, -1.0$]) for SBP and at Week 4 (-0.8 mmHg [95% CI $-1.4, -0.2$]) for DBP.

In the BDP/FF/GB group, the largest mean absolute change from pre-dose to 10-minute post-dose was observed at Week 26 (-1.3 mmHg [95% CI $-1.9, -0.7$]) for SBP and at Weeks 40 and 52 (-0.9 mmHg [95% CI $-1.3, -0.4$] and -0.9 mmHg [95% CI $-1.4, -0.5$], respectively) for DBP. In the BDP/FF group, the largest mean absolute change from pre-dose to 10-minute post-dose was observed at Week 26 (-1.4 mmHg [95% CI $-1.9, -0.8$]) for SBP and at Week 40 (-1.2 mmHg [95% CI $-1.7, -0.8$]) for DBP.