Beclomethasone/formoterol in the management of COPD: A randomised controlled trial

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Chronic obstructive airways disease; COPD; Inhaled corticosteroid; Long-acting β2-agonist; Lung function; Exacerbations

Summary
Objectives: To evaluate the effect of beclomethasone/formoterol versus budesonide/formoterol (non-inferiority) and versus formoterol (superiority) in patients with severe stable chronic obstructive pulmonary disease (COPD).
Methods: A double-blind, double-dummy, randomised, active-controlled, parallel-group study. After 4 weeks run-in with ipratropium/salbutamol (40/200 μg, three times daily) patients were randomised to receive beclomethasone/formoterol (200/12 μg pressurised metered dose inhaler), budesonide/formoterol (400/12 μg dry powder inhaler) or formoterol (12 μg dry powder inhaler) twice daily for 48 weeks. Co-primary efficacy variables were change from baseline to 48 weeks in pre-dose morning forced expiratory volume in 1 s (FEV1) and mean rate of COPD exacerbations.
Results: Of 718 patients randomised, 703 (232 beclomethasone/formoterol, 238 budesonide/formoterol, 233 formoterol) were in the ITT analysis. Improvement in pre-dose morning FEV1 was 0.077 L, 0.080 L and 0.026 L for beclomethasone/formoterol, budesonide/formoterol and formoterol respectively (LS mean from the ANCOVA model). Beclomethasone/formoterol was not inferior to budesonide/formoterol (95% CI of the difference −0.052, 0.048) and superior to formoterol (p = 0.046). The overall rate of COPD exacerbations/patient/year was similar and not statistically significantly different among treatments (beclomethasone/formoterol 0.414, budesonide/formoterol 0.423 and formoterol 0.431). Quality of life and COPD
Introduction

Chronic obstructive pulmonary disease (COPD) remains a highly prevalent condition, associated with episodic exacerbations that impair health status. Based on extensive clinical trials data treatment guidelines recommend that a combination of a long-acting β2-agonist (LABA) and an inhaled corticosteroid (ICS) should be used to improve symptoms and prevent exacerbations. This treatment is usually confined to patients with spirometrically severe disease (defined as forced expiratory volume in 1 s (FEV1) <50% predicted), although recent data suggest benefit in Global initiative in chronic Obstructive Lung Disease (GOLD) stage II patients. There is both a molecular and clinical rationale for combining LABAs and ICSS; LABAs increase nuclear uptake of the glucocorticoid receptor/ligand complex in vitro and corticosteroids up-regulate β-receptor numbers in the cell membrane processes. This may explain the greater improvement in lung function seen when these drugs are combined compared with that observed when LABAs or ICSS are used alone.

To date most studies in COPD patients have investigated combinations involving either fluticasone propionate or budesonide. Beclomethasone dipropionate (BDP) is a widely used ICS which has recently been combined with a LABA in a single inhaler. BDP (100 μg) plus formoterol fumarate (6 μg) is a fixed ICS/LABA combination delivered via a pressurised metered dose inhaler (pMDI) using a hydrofluoralkane propellant. This has been formulated with an extra-fine particle size which results in high lung deposition with less amount of drug deposited in the upper airways. The BDP component in the extra-fine formulation of beclomethasone/formoterol was able to achieve greater efficacy per μg of delivered steroid compared to conventional BDP. Therefore, the nominal dose of BDP per actuation from beclomethasone/formoterol in the extra-fine formulation is reduced from 250 μg (as in the conventional BDP formulation) to 100 μg per actuation, thus lowering the amount of inhaled ICS absorbed into the systemic circulation. This improved delivery of beclomethasone/formoterol extra-fine formulation has the potential to target inflammation and bronchoconstriction in the entire bronchial tree, including the smaller airways which is an anatomical site particularly involved in the progression of COPD. Moreover, the lung deposition pattern with extra-fine beclomethasone/formoterol in COPD patients was shown to be similar to that in asthmatics and normal subjects.

Beclomethasone/formoterol has been shown to be effective and well-tolerated in asthmatic patients. Comparative clinical studies in moderate-to-severe asthmatics have shown that the efficacy of beclomethasone/formoterol is at least comparable to that of other ICS/LABA combinations across a number of different asthma outcomes. The objective of this study was to investigate the efficacy and safety of the fixed combination of beclomethasone/formoterol (Foster®, Chiesi Farmaceutici) in COPD patients, and to compare it with the reference fixed combination of budesonide/formoterol (Symbicort®, AstraZeneca) and formoterol alone (Oxis®, AstraZeneca). The hypotheses that beclomethasone/formoterol was non-inferior to budesonide/formoterol in terms of the change in pre-dose morning FEV1 from baseline to 48 weeks and that beclomethasone/formoterol was superior to formoterol alone in terms of the mean rate of COPD exacerbations per patient per year were tested.

Methods

Patients

Hospital outpatients with severe stable COPD according to the GOLD guidelines were recruited. Patients were required to be aged ≥40 years with a diagnosis of symptomatic COPD for >2 years, at least a 20 pack-years smoking history, a post-bronchodilator FEV1 between 30% and 50% of the predicted normal and at least 0.7 L absolute value and a pre-dose FEV1/forced vital capacity (FVC) of ≤0.7. Moreover, patients needed to have experienced at least one exacerbation requiring medical intervention (oral corticosteroid and/or antibiotic treatment and/or need for a visit to an emergency department and/or hospitalisation) within 2–12 months before the screening visit and to be clinically stable for the 2 months before study entry. Finally, a change in FEV1 <12% of predicted normal value 30 min following inhalation of 200 μg of salbutamol pMDI was a prerequisite for inclusion. Patients were excluded if they had a history of asthma, allergic rhinitis or other atopic disease, variability of symptoms from day to day and frequent symptoms at night and early morning (suggestive of asthma). They were also excluded if they were receiving long term oxygen therapy or they had a lower respiratory tract infection or had been hospitalised for an acute COPD exacerbation within two months before screening or during the run-in period. Treatment with oral, injectable or depot corticosteroids and antibiotics, long-acting antihistamines or changes in the dose of an oral modified release theophylline in the two months preceding screening and during the run-in period were also exclusion criteria.

Study design

This was a 48-week, phase III, double-blind, double-dummy, randomised, active-controlled, 3-arm parallel-
group multicentre study (ClinicalTrials.gov identifier NCT476099) conducted in 76 centres in 8 countries across Europe. The study protocol was approved by the Institutional Review Board/Independent Ethics Committee of participating centres. The study was conducted in accordance with Good Clinical Practice, the Declaration of Helsinki and all applicable regulations. All patients gave written informed consent prior to study entry.

During the 4-week run-in period all non-permitted COPD treatments were discontinued and eligible patients were treated with combination ipratropium/salbutamol (20/100 µg, two inhalations three times daily). Rescue salbutamol was permitted throughout the study as required. This was the only treatment allowed in the 24 h preceding the randomisation visit (Week 0) but its use was avoided for 8 h before the visit. At Week 0, patients satisfying all the eligibility criteria were randomised in a 1:1:1 ratio to receive 48 weeks treatment with either: beclomethasone/formoterol pMDI 100/6 µg, two inhalations twice daily (total daily dose 400/24 µg), budesonide/formoterol dry powder inhaler (DPI) 200/6 µg, two inhalations twice daily (total daily dose 800/24 µg) or formoterol DPI 12 µg, one inhalation twice daily (total daily dose 24 µg). The randomisation scheme followed a balanced-block centre-stratified design and was prepared via a computerised system. Patients were centrally assigned, in one centre, to one of the three treatment arms at the end of the run-in period through an Interactive Voice/Web Response System (IXRS). Almac Clinical Technologies (UK) was in charge of the IXRS study drug management. The investigators at the sites called the IXRS to screen and randomise patients. The IXRS assigned the patient to a certain treatment group using a list-based randomisation algorithm and assigned the medication kit number corresponding to the treatment group. Study drug was kitted and uniquely numbered and the IXRS was used to assign both initial and subsequent kits in order to have an inventory control and patient dose tracking. The IXRS also maintained quantities, kit numbers, drug types, batch/code numbers, expiration dates and did not dispense after these dates. On each study day, patients took both active medications and matched placebo twice daily, in order to maintain blinding. In case of emergency, unblinding of the treatment code was done through IXRS. Clinic visits took place at the start and end of the run-in period, and at 4, 12, 24, 36 and 48 weeks after randomisation at Week 0.

Assessments

The co-primary efficacy variables were the change in pre-dose morning FEV₁ from baseline to 48 weeks and the mean rate of COPD exacerbations per patient per year. Pulmonary function tests (FEV₁, FVC, Peak expiratory flow [PEF]) and forced expiratory flow at 25–75% vital capacity [FEF₂⁵−₇⁵%]) were measured according to the American Thoracic Society/European Respiratory Society recommendation.¹⁶

Lung function parameters were measured pre-dose (time 0) at all visits, and 30, 60, 120 and 180 min post-dosing at weeks 0, 4, 24 and 48. COPD exacerbations were defined by the need for treatment with oral corticosteroids and/or antibiotics and/or the need to visit or be admitted to a hospital. Their occurrence was documented at all visits together with dyspnoea scores (using the Modified Medical Research Council questionnaire). At Weeks 0, 4 and 48, after the pulmonary function tests and before administration of study drug, health-related quality of life was assessed using the St. George’s Respiratory Questionnaire (SGRQ). A 6-min walking test (6-MWT) was performed according to standard methodologies¹⁷ and from these data the Body Mass Index, airflow Obstruction, Dyspnoea and Exercise capacity (BODE) index was calculated.¹⁸ Throughout the study, the pulmonary function assessments at the clinic visits started in the morning between 8.00 and 10.00 a.m. at approximately the same time for each patient. Patients recorded COPD symptoms daily each morning using a diary card. The use of study medication and rescue medication was also daily recorded.

Safety evaluation

Evaluation of the safety profile included adverse events and vital signs (heart rate and blood pressure) at every visit. A 12-lead electrocardiogram (ECG) was performed pre-dose and after the 60 min post-dose pulmonary function tests at Weeks 0, 24 and 48. ECG recordings were centralised for evaluation (including evaluation of QTc interval which was corrected using Bazett’s and Fridericia’s equations). Holter monitoring was also conducted in a subgroup of 10% of patients at baseline (week 0) and at week 48 and the 24-h recording was also collected and shipped to the central laboratory for evaluation. Blood samples for routine haematology and biochemistry were taken at Weeks 0, 4 and 48. Serum cortisol was assessed pre-dose and serum potassium and plasma glucose were assessed pre-dose and after the 30 min post-dose pulmonary function tests at Weeks 0, 24 and 48. An Independent Safety Monitoring Committee was established in order to ensure an independent scrutiny of the study and the ongoing safety of trial subjects.

Sample size

The aim of the study was to show both non-inferiority of beclomethasone/formoterol versus budesonide/formoterol (in terms of change in pre-dose morning FEV₁ from baseline to 48 weeks) and superiority of beclomethasone/formoterol versus formoterol (in terms of mean rate of COPD exacerbations per patient per year).

With a sample size of 192 patients per group, assuming exacerbations were experienced by 50% of patients in the beclomethasone/formoterol group and 66% in the formoterol group, the power for detecting a statistically significant difference, using a Poisson regression (assuming a homogeneous exponential distribution of exacerbations), was estimated at 97%.

For the change in pre-dose morning FEV₁ after 48 weeks of treatment, this sample size had more than 80% power to show non-inferiority of beclomethasone/formoterol versus budesonide/formoterol (one-sided significance level set at 2.5%) assuming a standard deviation of 340 mL with a non-inferiority margin of −100 mL. Therefore, assuming a 30%
drop-out rate, a total of 275 patients per group were to be randomised.

**Statistical methods**

Efficacy data were analysed for both the intention-to-treat (ITT) population and the per-protocol (PP) population. The ITT population included all randomised patients who received at least one inhalation of study drug and had at least one post-baseline efficacy evaluation. The PP population included all patients in the ITT analysis set who did not have any major protocol violations. The safety population included all randomised patients who received at least one inhalation of study medication. Missing values were accounted for using the last observation carried forward (LOCF) approach.

For the change in pre-dose morning FEV1 from baseline to 48 weeks, the non-inferiority of beclomethasone/formoterol versus budesonide/formoterol and its superiority versus formoterol were tested using an analysis of covariance (ANCOVA) model with treatment and centre as factors and baseline FEV1 as covariate. The number of COPD exacerbations (mean rate per patient per year) was analysed using Poisson regression with log-time on the study as an offset. Standard errors were estimated allowing for extra-Poisson variation. Superiority testing was conducted using a two-sided significance level set at 5% (i.e. $\alpha = 0.05$).

Within treatment comparisons for exacerbation rates before entering the study (as recorded within 2–12 months before the screening visit) and during the study period, were performed by using a generalised estimating equations (GEE) approach to Poisson regression accounting for within-patient correlation. The analysis was performed within each treatment group, separately.

All other pulmonary function tests and secondary efficacy variables were analysed using an ANCOVA model with treatment and centre as factors and baseline values as covariate. Adverse events were coded by system organ class (SOC) and preferred term (PT) using the MedDRA dictionary and were compared using the Chi-square test or Fisher’s exact test (the latter if at least one cell count was less than five). Laboratory parameters, vital signs and ECG QTc intervals were described using summary statistics and relevant parameters were compared using the ANCOVA model.

**Results**

**Patients**

Of the 828 patients screened, 718 patients were randomised to receive treatment and 621 patients completed the study (Fig. 1). Of these patients only 13 were older than 70 years and had an FEV1/FVC ratio $>0.65$ and so might not have been classified as having COPD using the lower limit of normal for this ratio. These patients were similarly distributed between the groups, and their data are reported here on an intention-to-treat basis. The first patient entered in December 2006, the last patient entered in July 2007 and the last patient’s last visit was in August 2008. The most common causes of early study discontinuation were withdrawn consent and adverse events. Consent withdrawal was less frequent with combination treatment than with formoterol (4.2%, 5.8% and 9.7%, in beclomethasone/formoterol, budesonide/formoterol and formoterol groups, respectively). Frequencies of withdrawals due to adverse events were similar among the treatments and ranged from 2.1% to 3.8%.

At baseline, the three treatment groups were well-matched in their demographic and functional characteristics (Table 1). The mean FEV1 % predicted at study entry ranged from 41.9% (beclomethasone/formoterol) to 42.5% (formoterol).

**Efficacy evaluation**

Of the 237 randomised patients in the beclomethasone/formoterol group, 232 and 223 were analysed in the ITT and PP populations respectively and were analysed for the primary outcome variables. The corresponding numbers for the budesonide/formoterol and formoterol groups respectively were 242 and 239 randomised, 238 and 233 in the ITT population and 231 and 225 in the PP population.

**Lung function**

The change in pre-dose morning FEV1 during the study is shown in Fig. 2. Although pre-dose morning FEV1 increased from baseline in all treatment arms, this improvement (calculated as LS mean from the ANCOVA model) was significantly greater in the beclomethasone/formoterol and budesonide/formoterol groups (0.077 L and 0.080 L respectively) compared to the formoterol group (0.026 L). Beclomethasone/formoterol was shown to be comparable to budesonide/formoterol (difference $-0.002$ L; lower limit of unilateral 97.5% CI $= -0.052$) and superior to formoterol (difference $0.051$ L; 95% CI 0.001 to 0.102; $p = 0.046$). Similar results were obtained in the PP population.

The peak post-dose FEV1 was significantly greater with beclomethasone/formoterol than with formoterol alone ($p = 0.033$) (Fig. 3), as was the post-dose 3 h average FEV1 ($p = 0.039$) (Fig. 7 online repository). The improvement in pre-dose FVC versus baseline was statistically significant for beclomethasone/formoterol ($p = 0.005$) but not for budesonide/formoterol ($p = 0.152$) or formoterol ($p = 0.582$) (Fig. 4). The results of the other pulmonary function parameters (FVC, PEF, $\text{FEF}_{25-75}$) showed no significant differences between treatments in pre-dose values, peak values and 3 h post-dose values (Table 3 online repository).

**Exacerbations**

The number of patients with at least one COPD exacerbation and the mean rate of COPD exacerbations per patient per year were similar and did not differ significantly between treatments. In the beclomethasone/formoterol group 64 (27.6%) patients experienced at least one exacerbation giving an exacerbation rate of 0.414 per patient per year. Corresponding figures for budesonide/formoterol were 64 (26.9%) patients with exacerbations giving a rate of 0.423 and for formoterol 66 (28.3%) patients giving a rate of 0.431 (Fig. 5). The number of patients with COPD exacerbations leading to hospitalisation was 13 (5.6%) for beclomethasone/formoterol, 7 (2.9%) for budesonide/formoterol.
(p < 0.001 versus beclomethasone/formoterol) and 8 (3.4%) for formoterol (p = 0.008 versus beclomethasone/formoterol). The mean rate per patient per year was 0.074 in the beclomethasone/formoterol, 0.033 in the budesonide/formoterol group and 0.040 in the formoterol group. The rate ratio (95% CI) between the beclomethasone/formoterol and the other two groups was 2.222 (1.384—3.567) versus the budesonide/formoterol group and 1.844 (1.173—2.901) versus the formoterol group.

The rate of hospitalisations in all the treatment groups was lower compared to a previous COPD trial.8 Also, differences between countries were observed in terms of rates of exacerbations requiring hospitalisations. This could reflect country-specific healthcare policies concerning admission to hospital of exacerbated patients. Therefore, a post-hoc analysis was carried out in patients with COPD exacerbations requiring oral corticosteroids and/or antibiotic who were managed in a hospital setting (either ER or unscheduled outpatient visit or hospitalisation). This analysis showed that the mean rate per patient per year was 0.162 in the beclomethasone/formoterol, 0.180 in the budesonide/formoterol group and 0.180 in the formoterol group. The comparison between the groups showed that the rate of COPD exacerbations leading to ER/unscheduled visits/hospitalisation in the beclomethasone/formoterol group was not statistically significantly different to that reported either in the budesonide/formoterol group (p = 0.597) or in the formoterol group (p = 0.607).

Other outcome measures

Dyspnoea score: The improvement (i.e. reduction) in dyspnoea score compared to baseline was similar for beclomethasone/formoterol (−0.19 ± 0.74) and budesonide/formoterol (−0.18 ± 0.78) and was greater than that observed for formoterol (−0.07 ± 0.76) (Fig. 8 online repository). The within group improvement was statistically significant for both the combination groups (p < 0.001) but not for the formoterol group. No statistically significant differences were found in the comparison between treatments.

Six minute walking test

The distance covered in 6 min at Week 48 was significantly greater versus baseline in all the three groups (p < 0.001), and did not significantly differ between treatments. The change in distance covered was higher, though not significantly so, in the beclomethasone/formoterol group (41 ± 85 m) than in the budesonide/formoterol group (35 ± 86 m) or the formoterol group (35 ± 79 m) (Fig. 6).

St. George’s Respiratory Questionnaire

The SGRQ mean total score decreased during the study indicating an improved quality of life (Table 2). Changes from baseline were statistically significant for all the three treatments, with no significant differences between the
groups. The percentage of patients with a change from baseline in the SGRQ \( \geq 4 \) units increased over time in all the groups (Fig. 9 online repository).

**BODE index**

A significant improvement in the BODE index was observed during the study in all treatment groups \((p < 0.001)\). The improvement (i.e. decrease) in the BODE index compared to baseline was similar for beclomethasone/formoterol \((-0.61 \pm 1.23)\) and budesonide/formoterol \((-0.64 \pm 1.36)\), and was greater than that observed for formoterol \((-0.44 \pm 1.26)\), although this difference was not statistically significant.

### Table 1  Demographics and baseline characteristics (ITT population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Beclomethasone/formoterol ((N = 232))</th>
<th>Budesonide/formoterol ((N = 238))</th>
<th>Formoterol ((N = 233))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0 ± 9.0 (range 41–83)</td>
<td>64.1 ± 9.1 (range 40–84)</td>
<td>63.7 ± 8.8 (range 41–84)</td>
</tr>
<tr>
<td>Males (n, %)</td>
<td>184 (79.3%)</td>
<td>194 (81.5%)</td>
<td>189 (81.1%)</td>
</tr>
<tr>
<td>Duration of the disease (years)</td>
<td>9.41 ± 7.0</td>
<td>9.89 ± 7.8</td>
<td>9.83 ± 6.7</td>
</tr>
<tr>
<td>No. exacerbations/patient (2–12 months of screening)</td>
<td>1.73 ± 1.0</td>
<td>1.67 ± 1.0</td>
<td>1.79 ± 1.0</td>
</tr>
</tbody>
</table>

**Smoking habits**

<table>
<thead>
<tr>
<th>Smoking habits</th>
<th>Beclomethasone (N = 232)</th>
<th>Budesonide (N = 238)</th>
<th>Formoterol (N = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers (n, %)</td>
<td>90 (38.8%)</td>
<td>86 (36.1%)</td>
<td>87 (37.3%)</td>
</tr>
<tr>
<td>Ex-smokers (n, %)</td>
<td>142 (61.2%)</td>
<td>152 (63.9%)</td>
<td>146 (62.7%)</td>
</tr>
<tr>
<td>Duration of smoking (years)</td>
<td>36.0 ± 10.3</td>
<td>36.0 ± 10.4</td>
<td>36.6 ± 10.9</td>
</tr>
<tr>
<td>Number of pack/year</td>
<td>37.3 ± 14.1</td>
<td>37.8 ± 14.6</td>
<td>39.7 ± 19.1</td>
</tr>
<tr>
<td>Previous Treatment (n, %)</td>
<td>103 (44.4%)</td>
<td>100 (43.2%)</td>
<td>100 (42.9%)</td>
</tr>
<tr>
<td>Long-acting anticholinergic</td>
<td>17 (7.33%)</td>
<td>12 (5.04%)</td>
<td>16 (6.87%)</td>
</tr>
<tr>
<td>ICS*</td>
<td>101 (43.53%)</td>
<td>87 (36.55%)</td>
<td>84 (36.05%)</td>
</tr>
<tr>
<td>ICS/LABA fixed combination</td>
<td>15 (6.47%)</td>
<td>25 (10.5%)</td>
<td>13 (5.58%)</td>
</tr>
<tr>
<td>FEV(_1) (L) pre-bronchodilator</td>
<td>1.14 ± 0.3</td>
<td>1.16 ± 0.3</td>
<td>1.14 ± 0.3</td>
</tr>
<tr>
<td>FEV(_1) % predicted normal pre-bronchodilator</td>
<td>41.9 ± 5.6</td>
<td>42.3 ± 6.0</td>
<td>42.5 ± 5.9</td>
</tr>
<tr>
<td>Reversibility test % (change in FEV(_1) % predicted)</td>
<td>2.94 ± 3.6</td>
<td>2.47 ± 4.0</td>
<td>2.97 ± 3.2</td>
</tr>
<tr>
<td>BODE index</td>
<td>3.99 ± 1.5</td>
<td>3.97 ± 1.5</td>
<td>4.00 ± 1.5</td>
</tr>
<tr>
<td>SGRQ score</td>
<td>60.4 ± 19.5</td>
<td>57.2 ± 18.6</td>
<td>59.5 ± 20.2</td>
</tr>
<tr>
<td>6 min walking test (metres)</td>
<td>334.7 ± 116.7</td>
<td>333.9 ± 119.1</td>
<td>332.0 ± 121.9</td>
</tr>
</tbody>
</table>

All values are presented as absolute numbers or mean ± standard deviation. ITT: intention-to-treat; LABA: long-acting \( \beta_2 \)-agonist; ICS: inhaled corticosteroid; FEV\(_1\): forced expiratory volume in 1 s; BODE: Body mass index, airflow Obstruction, Dyspnoea and Exercise capacity; SGRQ: St. George’s Respiratory Questionnaire.

* used alone or in combination.

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**Figure 2**  Change in pre-dose FEV\(_1\), (from baseline to 48 weeks) following 48 weeks treatment with beclomethasone dipropionate/formoterol (BDP/FF), budesonide/formoterol (BUD/FF) or formoterol (FF) in patients with severe stable COPD. FEV\(_1\): forced expiratory volume in 1 s \( \Delta \) Non significant difference BDP/FF versus BUD/FF \((p = 0.928)\); \^\(p = 0.046\) BDP/FF versus FF; \#\(p < 0.001\) for both combination treatments versus baseline.

**Figure 3**  Post-dose peak FEV\(_1\), following 48 weeks treatment with beclomethasone dipropionate/formoterol (BDP/FF), budesonide/formoterol (BUD/FF) or formoterol (FF) in patients with severe stable COPD. FEV\(_1\): forced expiratory volume in 1 s \( \Delta \) \(p < 0.05\) beclomethasone/formoterol versus formoterol; \*\(p < 0.05\) versus baseline.
There were no statistically significant differences among treatments regarding COPD symptom scores. In all groups there was statistically significant improvement versus baseline in breathlessness, and cough (Table 2). Statistically significant improvement versus baseline in breathlessness on rising and days without COPD symptoms was observed with both the combination groups but not with formoterol alone.

Use of rescue medication

The use of rescue salbutamol decreased in all treatment groups during the study, but was more evident in the beclomethasone/formoterol and budesonide/formoterol groups than in the formoterol group (Fig. 10 online repository), although no statistically significant difference was observed between treatments.

Safety evaluation

The mean extent of exposure was similar in all treatment groups and ranged between 304.99 days and 315.22 days. The incidence of adverse events (AEs), serious AEs, adverse drug reactions (ADRs) and withdrawals due to AEs was not significantly different among the three treatment groups (Table 4 online repository). The most commonly reported AE was exacerbation or worsening of COPD reported in 27–28% of patients. Pneumonia was reported by 5 (2.1%) patients in the beclomethasone/formoterol group, 7 (2.9%) in the budesonide/formoterol group and 1 (0.4%) in the formoterol group. A total of 20 patients withdrew from the study due AEs: 9 (3.8%) in the beclomethasone/formoterol group, 6 (2.5%) in the budesonide/formoterol group and 5 (2.1%) in the formoterol group.

Changes in vital signs, 12-lead ECG, QT interval and Holter assessments were rare, and did not raise any unexpected safety concern regarding the known profile of ICSs and LABAs in the treatment of COPD. Changes from baseline in serum cortisol were not statistically significant in any treatment group.

Six patients died during the treatment (two in the beclomethasone/formoterol group and four in the budesonide/formoterol group). None of deaths were considered to be related to the study medication.

Discussion

Many studies have considered whether the treatment with LABA/ICS is better than placebo or the individual treatment components. A clear statement on this came from the large TORCH study which demonstrated small but definite superiority in terms of lower exacerbation numbers when using combination treatment. That study was powered to demonstrate a difference in mortality, so it was thus significantly over-powered for an outcome of exacerbation. By contrast, the present study using beclomethasone/formoterol included a more modest number of patients, but should nonetheless have been sufficient to determine whether treatments were effective. This proved to be the case for one of the co-primary endpoints, pre-dose FEV1, but not for the exacerbation rate. The reason this occurred has implications for the interpretation of other studies and future clinical trial design.

Spirometry in general, and specifically the FEV1, is a robust assessment which is reproducible, is an accepted key marker for disease progression and has the ability to measure the different responses to interventions. These are the reasons why it is supported by regulatory agencies as a study endpoint. In the present study both combination treatments showed significant and sustained increases from baseline in FEV1 of similar magnitude, which were significantly greater than that observed with formoterol alone.
This finding reflects the additional contribution of the steroid component, and it can be linked to its anti-inflammatory effect. The extra-fine beclomethasone/formoterol combination was not inferior to the combination of budesonide/formoterol, despite the lower ICS dose included in the combination (400 μg/daily versus 800 μg/daily, respectively). The improvement from baseline observed with both beclomethasone/formoterol and budesonide/formoterol in peak FEV₁ was well above 200 mL (i.e. over the suggested minimal important difference considered to be clinically relevant). These enhanced bronchodilatory responses indicate an effective up-regulation of the b₂ receptors in the airways of COPD patients induced by the beclomethasone and budesonide components, respectively. Improvements in FVC occurred in all the groups, although only in the BDP/formoterol group did this achieve statistical significance. It has been suggested that improvement in FVC may indicate a reduction of air trapping associated with small airways patency.¹¹ For this reason the greater FVC improvement observed with beclomethasone/formoterol is consistent with a more efficient peripheral deposition in COPD patients due to the extra-fine aerosol that characterises this formulation and it is in line with the previous findings in asthma.¹⁴,²⁴,²⁵

Unlike previous studies using the budesonide/formoterol combination,¹⁹,²₀ the exacerbation rate did not differ between treatment arms. This study was powered on the basis of an earlier trial conducted by Calverley et al.²₀ some years earlier. Nevertheless, the patients recruited in the present study were more like those enrolled in the TRISTAN study²¹ in terms of their baseline lung function and reported exacerbation frequency. However, the observed exacerbation rates at the end of this study were less than half those reported in the TRISTAN study and many other trials.²⁶-²⁸ This low number of exacerbations cannot be due to different background therapy used before study entry, which was indeed similar to that in other studies of LABA/ICS combinations. The lower than expected exacerbation rate may have been due to the requirement for patients to be free from exacerbations for 2 months before study entry. This inclusion criterion may have inadvertently biased the recruitment of stable patients who were less likely to exacerbate thereafter. Indeed, recent data have shown exacerbations tend to cluster,²⁹ so the patients recruited in the present study may have been in a period

Table 2  Mean changes in St. George’s Respiratory Questionnaire (SGRQ) total score from baseline to 4 and 48 weeks and in COPD symptom scores from baseline to 48 weeks (ITT population).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Beclomethasone/formoterol (N = 232)</th>
<th>Budesonide/formoterol (N = 238)</th>
<th>Formoterol (N = 233)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGRQ Total score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>50.89 ± 15.35</td>
<td>49.66 ± 15.79</td>
<td>50.47 ± 16.21</td>
</tr>
<tr>
<td>4-week mean change</td>
<td>-4.09 ± 11.27*</td>
<td>-4.19 ± 10.07*</td>
<td>-2.72 ± 10.73*</td>
</tr>
<tr>
<td>48-week mean change</td>
<td>-3.75 ± 13.91*</td>
<td>-4.28 ± 11.92*</td>
<td>-2.90 ± 13.28*</td>
</tr>
<tr>
<td>Breathlessness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.11 ± 0.71</td>
<td>1.08 ± 0.72</td>
<td>1.09 ± 0.67</td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.13 ± 0.67*</td>
<td>-0.13 ± 0.62*</td>
<td>-0.09 ± 0.65**</td>
</tr>
<tr>
<td>Waking at night</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.38 ± 0.55</td>
<td>0.38 ± 0.57</td>
<td>0.38 ± 0.56</td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.04 ± 0.54</td>
<td>-0.04 ± 0.48</td>
<td>-0.04 ± 0.59</td>
</tr>
<tr>
<td>Breathlessness on rising</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.95 ± 0.74</td>
<td>0.88 ± 0.78</td>
<td>0.94 ± 0.80</td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.10 ± 0.64*</td>
<td>-0.11 ± 0.60***</td>
<td>-0.02 ± 0.62</td>
</tr>
<tr>
<td>Cough</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.01 ± 0.65</td>
<td>0.94 ± 0.66</td>
<td>0.93 ± 0.65</td>
</tr>
<tr>
<td>Mean change</td>
<td>-0.18 ± 0.67*</td>
<td>-0.10 ± 0.63***</td>
<td>-0.14 ± 0.61*</td>
</tr>
<tr>
<td>% Days without COPD symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.27 ± 18.98</td>
<td>7.11 ± 20.89</td>
<td>8.37 ± 23.24</td>
</tr>
<tr>
<td>Mean change</td>
<td>3.17 ± 23.80°</td>
<td>3.15 ± 24.13°</td>
<td>3.07 ± 27.78</td>
</tr>
</tbody>
</table>

All values are presented as mean ± standard deviation.
ITT: intention-to-treat; COPD: chronic obstructive pulmonary disease.
Statistically significant versus baseline value: *p < 0.01, **p = 0.03, ***p = 0.023, ****p = 0.021, °p = 0.046.
when they were no longer prone to exacerbate. A second consideration relates to the geographical distribution of recruited patients. Patients may not have experienced an exacerbation due to regular and close monitoring by the treating physician as part of the study protocol (the so-called “clinical trial effect”). As most patients came from Eastern Europe, this effect might have been particularly relevant in some of these countries. Adherence to treatment can have an important impact on exacerbations as was seen in the TORCH study. This possibility should be considered when planning future studies.

In this study, the rates of COPD exacerbations leading to hospitalisation were very low compared to a previous trial. Indeed, the rate of hospitalisations in patients treated with beclomethasone/formoterol combination was less than half the value observed in the TORCH trial in subjects receiving fluticasone/salmeterol combination. Again, there were large inter-countries differences in the rates of hospitalisation reported during the study. Although reliance on hospitalisation could work well in identifying severe exacerbations in a single country, it does not necessarily reflect what happens in different healthcare systems where hospital accessibility can differ. Therefore, under the assumption that the more severe episodes require a hospital-based assessment (either ER or unscheduled outpatient visit or hospitalisation), we performed a post-hoc analysis comparing COPD exacerbations that were managed in a hospital setting, and that required systemic corticosteroids and/or antibiotic treatment and, accordingly, to be considered as severe. No difference between the three study treatments was observed. Interestingly, when measured in this way, the annual rates of severe exacerbations per patient/year ranged from 0.16 to 0.18 among groups, a value which is similar to that reported in the TORCH trial.

Improvements in symptoms and patient reported outcomes were also observed during the study. The improvements in the dyspnoea score, COPD symptoms scores and BODE index were more marked with both ICS/LABA combinations compared with LABA alone, which is consistent with previous studies. There were significant improvements in the SGRQ scores which exceeded the clinically important difference of four units at four weeks of treatment, and remained close to this level over the subsequent 44 weeks. At the end of the study the change in the distance covered in the 6-min walking test was highest, although not statistically significant, in the patients receiving beclomethasone/formoterol followed by budesonide/formoterol and then formoterol alone. On average, the improvement with beclomethasone/formoterol in the 6-min walking test was above the threshold of 37 m, which has been recently described as clinically relevant. This ability to walk further after treatment with beclomethasone/formoterol may be linked to the improvement in air trapping experienced by the patients.

No unexpected or unusual safety signals of clinical concern were observed in this one year trial. In the three arms no cardiac safety concerns were raised by ECG and Holter evaluations. In addition there was a low dropout rate, but the study was not powered to completely exclude any very rare adverse event. The rate of reported pneumonia was similar to that reported in placebo-controlled trials using budesonide, where no pneumonia signals of concern have been observed over 1 year treatment.

In summary, the fixed combination of beclomethasone/ formoterol (total daily dose 400/24 μg) given for 48 weeks in patients with severe COPD improved pulmonary function and lessened disability. The increase in pre-dose FEV₁ with beclomethasone/formoterol, administered at a nominal dose of BDP two-fold lower than the equipotent daily dose of budesonide, was comparable to budesonide/formoterol (total daily dose 800/24 μg) and superior to formoterol alone (total daily dose 24 μg).

No difference was observed between treatments regarding the low exacerbation rate seen in this patient population. The use of beclomethasone/formoterol improved health-related quality of life, reduced rescue medication use and was safe and well-tolerated.

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Conflict of interest statement

This study was sponsored by Chiesi Farmaceutici S.p.A. The sponsor was involved in the study design and interpretation of the data.
Prof. Peter Calverley has received funding from several pharmaceutical companies to conduct clinical research trails in COPD, has led several large sponsored studies including those by GSK, Chiesi and Nycomed and has spoken at meetings supported by these companies and by AstraZeneca and Boehringer Ingelheim.

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**Supplementary material**

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.rmed.2010.09.008.

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