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Budesonide/Formoterol
In Chronic Obstructive Pulmonary Disease

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Contents

Abstract

▲ Budesonide/formoterol is a fixed-dose combination of the corticosteroid budesonide and the long-acting β_2-agonist formoterol, and is inhaled via the Turbuhaler® device.

▲ In two large, randomised, double-blind, 12-month studies, patients with severe chronic obstructive pulmonary disease (COPD) receiving budesonide/formoterol 320/9μg twice daily had a significantly higher forced expiratory volume in 1 second (FEV_1) and significantly higher morning and evening peak expiratory flow at trial endpoint than recipients of budesonide or placebo; FEV_1 was significantly higher than with formoterol in the larger study.

▲ In both studies, the rate of COPD exacerbations and exacerbations requiring oral corticosteroids was significantly reduced with budesonide/formoterol versus formoterol and placebo. Moreover, the time to first exacerbation was significantly prolonged with budesonide/formoterol versus all other treatment arms in the larger study.

▲ At 12 months, significant improvements in health-related quality-of-life scores were seen with budesonide/formoterol versus placebo in both studies. The reduction in total and individual symptom scores was significantly greater with budesonide/formoterol than with budesonide or placebo in the smaller study.

▲ Budesonide/formoterol was generally well tolerated by patients with severe COPD. The tolerability profile of the combination was similar to that of the individual components with no increase in the incidence of adverse events.

Features and properties of budesonide/formoterol (Symbicort®)	
New indication	
Symptomatic treatment of severe chronic obstructive pulmonary disease	
Mechanism of action	
Budesonide	Corticosteroid: anti-inflammatory activity
Formoterol	Long-acting β_2-agonist: bronchodilation
Dosage and administration	
Recommended dosage	400/12μg budesonide/formoterol twice daily
Route of administration	Inhalation (via Turbuhaler® multidose dry powder inhaler)
Drug delivery	400/12μg budesonide/formoterol inhaler delivers 320/9μg per dose and 200/6μg inhaler delivers 160/4.5μg per dose
Pharmacokinetic profile	
Mean lung deposition of delivered dose via Turbuhaler®	Budesonide: 32–44% Formoterol: 28–49%
Time to peak plasma concentration	Budesonide: 17–30 minutes Formoterol: ≤10 minutes
Elimination	Budesonide: 85–90% first-pass metabolism, ≈60% of dose excreted in urine as metabolites Formoterol: metabolised to inactive metabolites, 8–13% excreted unchanged in urine
Elimination half-life	Budesonide: 2–3 hours Formoterol: 17 hours
Adverse events	
Most frequent (excluding respiratory events)	Rhinitis, back pain, chest pain, pharyngitis

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) programme has defined chronic obstructive pulmonary disease (COPD) as "a disease state characterised by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."[1] It is predicted that by the year 2020 COPD will be the fifth most common cause of disability worldwide, and will have risen from the sixth most important cause of death in the world (1990 data) to the third.[2] Smoking is by far the most important cause of COPD; other risk factors include occupational exposure to dust and chemicals, environmental pollution and α_1-antitrypsin deficiency.[1,3-5]

To date, the only interventions shown to prolong life in patients with COPD are smoking cessation and long-term oxygen therapy,[1,3-8] although recent data indicate an association between increased survival and the use of inhaled corticosteroids, alone or in combination with long-acting β_2-agonists.[9,10] The only measure generally accepted to slow the progressive decline in lung function is smoking cessation.[11] The current aims of pharmacological therapy in COPD are to prevent and control symptoms, reduce the frequency and severity of exacerbations, improve health status and improve exercise tolerance.[1,12] Bronchodilator therapy using β_2-agonists and/or anticholinergics has been shown to improve lung function,[3-6] symptoms,[4-6,8] exercise tolerance[3-5] and quality of life.[8,13] Recognition that inflammatory changes are central to the disease has resulted in the use of inhaled corticosteroids in COPD,[3,4] and they are recommended for patients who show an objective response to a trial of either inhaled or oral corticosteroids.[3,14,15] Long-term use of inhaled corticosteroids may improve symptoms[4] and lung function[3,5] and reduce exacerbations.[4,5]

The use of inhaled budesonide/formoterol (Symbicort®[1]) as a combination product for the treatment of asthma has been reviewed previously in *Drugs*.[16] In addition, inhaled formoterol has been reported to be effective and well tolerated in the treatment of COPD.[17] This profile focuses on the role of budesonide/formoterol inhaled via a Turbuhaler® (hereafter referred to as budesonide/formoterol) in the treatment of patients with COPD. The budesonide/formoterol 200/6μg inhaler delivers 160μg of budesonide and 4.5μg of formoterol per dose; the 400/12μg inhaler delivers 320μg of budesonide and 9μg of formoterol per dose.[18] This article refers to the delivered dose unless stated otherwise.

1. Pharmacodynamic Profile

The pharmacodynamic effects of budesonide and formoterol are well documented and reviewed in detail in previous publications.[16,17,19,20] Few data have been published on the pharmacodynamics of the combined product in patients with COPD. A small increase in cortisol suppression was seen after administration of budesonide/formoterol compared with the individual components, although this was not considered clinically relevant.[18] The following section provides a brief overview of the pharmacodynamic properties of budesonide and formoterol relevant to COPD.

Mechanisms of Action

- Budesonide is a topically active corticosteroid with potent glucocorticoid but low mineralocorticoid activity.[19] Corticosteroids act by binding to specific receptors in the cytoplasm of most cells to form a drug-receptor complex. This is translocated to the nucleus, where it influences gene transcription.[21] Corticosteroids exert their anti-inflammatory effects by reducing the activity and function of inflammatory cells (macrophages and T lymphocytes),[19,21,22] reducing synthesis and release of cytokines and other inflammatory mediators such as interleukin (IL)-8 and tissue necrosis factor-α,[21] and promoting the release of anti-inflammatory agents such as lipocortin-1, secretory leucocyte protease inhibitor and IL-10.[19,21,22]
- Formoterol is a long-acting selective β_2-agonist. β_2-Agonists exert their effects by activation of intra-

1 Use of tradenames is for product identification purposes only and does not imply endorsement.

cellular adenyl cyclase, which catalyses the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate and causes relaxation of bronchial smooth muscle.[17,23] Additional actions of β_2-agonists that may be beneficial in patients with COPD include reduced smooth muscle cell proliferation, improvement in airway muscle function, pulmonary artery vasodilation and increased mucus clearance.[7,23] In animal models, formoterol affected neutrophil function and reduced plasma exudation from postcapillary venules.[23,24] Salmeterol, another long-acting β_2-agonist, reduced damage to the respiratory epithelium induced by *Haemophilus influenzae*, suggesting that these agents may be of benefit in patients with infective COPD exacerbations.[25]

- *In vitro* studies have demonstrated a number of complementary interactions between long-acting β_2-agonists and corticosteroids, as reviewed by Barnes.[24] Long-acting β_2-agonists increase nuclear localisation of glucocorticoid receptors (resulting in increased gene transcription) and enhance the suppression of inflammatory mediators by corticosteroids. Furthermore, corticosteroids increase tissue β_2-receptor density, reverse β_2-receptor down regulation associated with long-term β_2-agonist use, reduce the pro-inflammatory effects of β_2-agonists and reverse β_2-receptor uncoupling associated with inflammation.[24,26]

Pulmonary Effects

- Single inhalations of budesonide/formoterol 400/12μg (metered dose) and fluticasone/salmeterol 250/50μg (metered dose) increased forced expiratory volume in 1 second (FEV_1) to a similar extent in a small, single-blind, randomised, crossover study in 16 patients with moderate-to-severe COPD.[27] Budesonide/formoterol was administered via a Turbuhaler® and fluticasone/salmeterol administered via a Diskus™ dry powder inhaler.[27] Budesonide/formoterol recipients showed a mean maximum improvement from baseline in FEV_1 earlier than fluticasone/salmeterol recipients (120 vs 300 minutes; mean maximum improvements of 0.29 vs 0.32L).[27] Significant ($p < 0.05$) between-group differences in FEV_1 occurred at 120 and 360 minutes (quantitative data not stated).[27] However, at 12 hours the mean increase from baseline in FEV_1 was the same for both combinations (0.10L).[27] There was no significant difference between budesonide/formoterol and fluticasone/salmeterol in the area under the curve of the change in FEV_1 between 0 and 12 hours (2.57 vs 2.83L).[27]
- The results of 12-month studies[28,29] demonstrating the beneficial effects of treatment with budesonide/formoterol on lung function in patients with severe COPD are presented in section 3.

2. Pharmacokinetic Profile

The pharmacokinetics of inhaled budesonide[30] and formoterol[17,20] have been reviewed in detail previously. Currently there is little published pharmacokinetic information on the budesonide/formoterol combination product inhaled via the Turbuhaler® device, and some is available only as abstracts and/or posters.[31,32] Data are also provided in the manufacturer's prescribing information.[18] The pharmacokinetics of the individual components are briefly described below.

Drug Delivery

- The mean lung deposition of budesonide after inhalation via a Turbuhaler® device is 32–44% of the delivered dose and the amount of formoterol that reaches the lungs from a Turbuhaler® is 28–49% of the delivered dose.[18] The delivery characteristics of budesonide/formoterol administered via a Turbuhaler® have been shown to be equivalent to the individual components administered separately using this device.[31]
- Approximately 50% of the nominal delivered dose of both budesonide and formoterol was delivered as fine particles (i.e. aerodynamic particle size ≤5μm), in an *in vitro* study in which budesonide/formoterol 160/4.5μg was delivered via a Turbuhaler® device.[32] The fine particle fraction reflects the proportion of the dose that reaches target areas of the lung.[32]

Absorption and Distribution

- Following inhalation, budesonide forms fatty acid esters in lung tissue, a process that is thought to prolong its anti-inflammatory activity at this site.[33] The systemic bioavailability of budesonide is approximately 49% of the delivered dose[18] and the drug reaches a maximum plasma concentration (C_{max}) at 17–30 minutes.[18,30,34]
- Although the pharmacokinetics of budesonide/formoterol are similar to those of the agents administered separately, for budesonide the area under the plasma concentration-time curve (AUC) was slightly higher, the rate of absorption more rapid and the C_{max} higher after administration of the combination product (values not reported).[18]
- The systemic bioavailability of formoterol is approximately 61% of the delivered dose, with C_{max} reached within 10 minutes of administration, which is similar to that seen with the single-component inhaler.[18]
- Plasma protein binding is approximately 90% for budesonide and 50% for formoterol.[18] Budesonide is widely distributed into tissues[19,30] and has a volume of distribution (Vd) of ≈3 L/kg;[18] the Vd of formoterol is ≈4 L/kg.[18]

Metabolism and Excretion

- Budesonide has high first-pass metabolism of approximately 85–90%.[19,30] The drug is metabolised by the cytochrome P450 (CYP) 3A4 isoenzyme[30] to metabolites that exhibit low glucocorticoid activity.[19,30] Approximately 60% of the administered dose is excreted in the urine as metabolites.[19] Budesonide has a plasma elimination half-life ($t_{1/2}\beta$) of 2–3 hours.[30,34]
- Formoterol is metabolised to inactive metabolites by four CYP isoenzymes (CYP2D6, CYP2C19, CYP2C9 and CYP2A6), which are not inhibited by formoterol at therapeutic levels.[35] The metabolites and approximately 8–13% of unchanged drug are excreted in the urine.[18] Formoterol has a $t_{1/2}\beta$ of 17 hours.[18]

Potential Drug Interactions

- The administration of budesonide/formoterol with drugs that inhibit the CYP3A4 isoenzyme is likely to markedly increase plasma concentrations of budesonide.[18] Concomitant administration of oral itraconazole caused a 4.2-fold increase in the AUC and a 1.6-fold increase in the C_{max} of a single inhaled dose of budesonide administered via a metered-dose inhaler attached to a large-volume spacer device in ten healthy volunteers in a randomised, double-blind, crossover study, probably due to the inhibition of its metabolism via the CYP3A4 isoenzyme by itraconazole.[36] Moreover, suppression of cortisol production has been reported in patients receiving both agents concomitantly.[36,37]
- There is no evidence of pharmacokinetic interaction between budesonide and formoterol.[18]

Special Patient Populations

- Systemic exposure to budesonide and formoterol may be increased in patients with liver disease (see section 5).[18] The pharmacokinetics of budesonide and formoterol in patients with renal failure are unknown.[18]

3. Therapeutic Efficacy

The efficacy of inhaled budesonide/formoterol compared with its individual components or placebo in the treatment of adult patients with severe COPD has been studied in two large, 12-month, randomised, double-blind, controlled trials.[28,29] Both trials compared the efficacy of budesonide/formoterol 320/9μg, budesonide 400μg (metered dose), formoterol 9μg and placebo, all administered twice daily via a Turbuhaler® device. The studies randomised 812[28] and 1022[29] patients.

In each trial, patients had an FEV_1 ≤50% predicted normal and an FEV_1/vital capacity (VC) ≤70%.[28,29] This equates to COPD stages III and IV according to GOLD classification (severe disease).[15] In both studies, patients had a history of at least one COPD exacerbation requiring medical intervention 2–12 months prior to trial entry.[28,29] Patients were eligible for enrolment into the trials if

they were outpatients aged ≥40 years with a history of COPD symptoms for ≥2 years and a smoking history of ≥10 pack-years; patients had documented use of short-acting inhaled bronchodilators as reliever medication.[28,29] In the trial reported by Szafranski et al.,[28] patients had a total symptom score ≥2 on at least 7 days during the run-in period.

Exclusion criteria were history of asthma and/or seasonal allergic rhinitis before the age of 40 years, any relevant cardiovascular disorders as judged by the investigator, use of β-blockers, a requirement for regular use of oxygen therapy, current respiratory tract disorders other than COPD and any other significant diseases or disorders which may have put them at risk or which may have influenced the results of the study.[28,29] Patients were also excluded if they had an exacerbation during run-in[28,29] or ≤4 weeks prior to enrolment,[29] or were individuals in whom it would have been unethical to withdraw inhaled corticosteroids.[28]

The run-in period for each trial differed markedly. In the study by Szafranski et al.,[28] preventative medication was withdrawn from all patients. Patients were allowed to use a terbutaline 0.5mg inhaler for relief of symptoms but no other therapy for a 2-week period before randomisation.[28] In the larger study, reported by Calverley et al.,[29] patients underwent a 2-week treatment-intensification period with oral prednisolone 30mg once daily and inhaled formoterol 9μg twice daily before randomisation.

Patients were allowed to use a terbutaline 0.5mg inhaler as a reliever throughout the run-in and study periods in both studies.[28,29]

Primary endpoints were the improvement in FEV_1,[28,29] reduction in the exacerbation rate[28] and increase in time to first exacerbation.[29] FEV_1 was assessed after administration of study medication and ≥6 hours after the last use of reliever medication.[28,29] In both studies, exacerbations were defined as episodes requiring oral corticosteroids and/or antibacterials and/or hospitalisation due to respiratory symptoms (exacerbations requiring medical intervention).[28,29]

Secondary endpoints included peak expiratory flow (PEF) [assessed before the morning and evening doses of study medication], VC, COPD symptoms (shortness of breath, cough, chest tightness and night-time awakenings) and health-related quality of life (HR-QOL).[28,29] COPD symptoms were scored on a scale of 0–4 (none/unaware of symptoms to severe/almost constant) and added together to give a total score of 0–16 (where 16 is the worst score).[28,29] HR-QOL was determined using the St. George's Respiratory Questionnaire (SGRQ).[28,29] SGRQ Total scores and scores from the three domains (Activity, Symptoms, Impact) were calculated to give a Total score (where 100 is the worst score). A clinically significant improvement in HR-QOL is defined as a reduction of at least 4 units in SGRQ Total score.[38] Analysis in both studies was on an intention-to-treat basis.[28,29]

Effect on Pulmonary Function

- At 12 months, patients receiving budesonide/formoterol had significantly higher FEV_1 values than those receiving placebo or budesonide in both studies,[28,29] and significantly higher FEV_1 values than formoterol recipients in the trial reported by Calverley et al.[29] In the study reported by Szafranski et al.,[28] at trial endpoint, patients receiving budesonide/formoterol had FEV_1 values 15% greater than those receiving placebo and 9% greater than budesonide recipients (both $p < 0.001$) [figure 1]. Mean FEV_1 values at baseline across treatment groups ranged from 0.96–1.01L.[28]
- In the trial reported by Calverley et al.,[29] treatment intensification with oral prednisolone and inhaled formoterol produced a mean improvement in FEV_1 values of 0.21L in all patients (baseline FEV_1 values ranged from 0.98–1.00L). At study endpoint, patients receiving budesonide/formoterol had FEV_1 values 14% greater than those receiving placebo, 11% greater than those receiving budesonide (both $p < 0.001$) and 5% greater than formoterol recipients ($p = 0.002$) [figure 1].[29]
- In both studies, at trial endpoint, patients receiving budesonide/formoterol had significantly greater morning PEF values than those receiving placebo, budesonide or formoterol, and greater evening PEF values than placebo and budesonide recipients.[28,29]

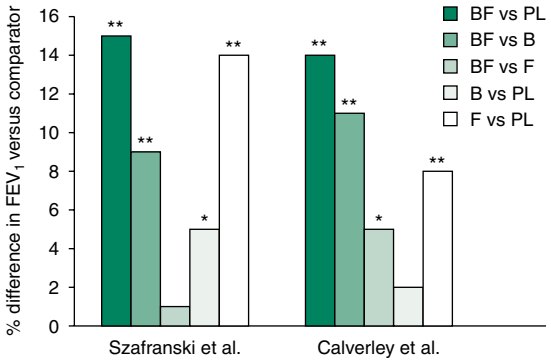

Fig. 1. Effect of inhaled budesonide/formoterol (BF) on lung function in patients with chronic obstructive pulmonary disease (COPD). Percentage difference between treatment arms in FEV_1 at study endpoint (12 months) with BF 320/9μg, budesonide 400μg (metered dose) [B], formoterol 9μg (F) and placebo (PL); all study treatments were administered twice daily via a Turbuhaler® device. Results are from two double-blind, randomised, 12-month trials in patients with severe COPD.[28,29] In the study reported by Szafranski et al.,[28] patients received BF (n = 208), B (n = 198), F (n = 201) or PL (n = 205). In the study reported by Calverley et al.,[29] patients received BF (n = 254), B (n = 257), F (n = 255) or PL (n = 256). **FEV_1** = forced expiratory volume in 1 second; * $p \leq 0.005$, ** $p < 0.001$ vs comparator.

At 12 months, budesonide/formoterol was associated with higher morning PEF values than placebo (between-group differences 24[28] and 18[29] L/min), budesonide (16[28] and 15[29] L/min) [all $p < 0.001$] and formoterol (12[28] and 7[29] L/min; both $p \leq 0.007$).

- Furthermore, patients receiving budesonide/formoterol recorded a higher evening PEF at 12 months than those receiving placebo (between-group differences 20[28] and 14[29] L/min) and budesonide (15[28] and 12[29] L/min) [all $p < 0.001$]. In the smaller trial,[28] budesonide/formoterol was associated with a higher evening PEF than formoterol (between-group difference 11 L/min; $p < 0.001$).

- In the study reported by Szafranski et al.,[28] VC increased from baseline by 9% in patients receiving budesonide/formoterol compared with those receiving placebo ($p < 0.001$); results of comparisons with other treatment arms were not reported. Recipients of budesonide/formoterol had significantly improved VC compared with patients who received budesonide or placebo (values not stated; both $p < 0.001$) in the trial reported by Calverley et al.[29]

Effect on COPD Exacerbations

- Budesonide/formoterol was significantly more effective than placebo and formoterol at reducing the rate of COPD exacerbations and exacerbations requiring oral corticosteroids in both trials at 12 months.[28,29] In the smaller trial,[28] budesonide/formoterol significantly reduced the rate of exacerbations by 24% compared with placebo ($p = 0.035$) and by 23% compared with formoterol ($p = 0.043$) [figure 2].

- Patients in the larger trial[29] receiving budesonide/formoterol had a significantly longer time to

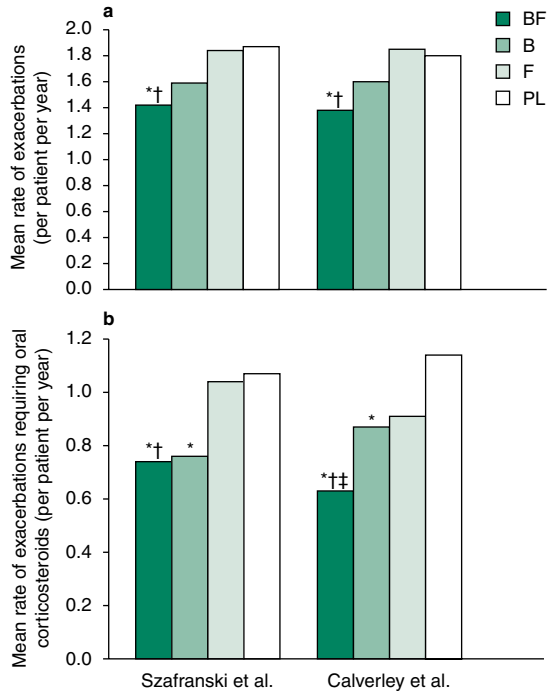

Fig. 2. Effect of inhaled budesonide/formoterol (BF) on exacerbations in patients with chronic obstructive pulmonary disease (COPD). Mean rate of (**a**) exacerbations (episodes requiring oral corticosteroids and/or antibacterials and/or hospitalisation due to respiratory symptoms) and (**b**) exacerbations requiring oral corticosteroids in patients receiving BF 320/9μg, budesonide 400μg (metered dose) [B], formoterol 9μg (F) and placebo (PL); all study treatments were administered twice daily via a Turbuhaler® device. Results are from two double-blind, randomised, 12-month trials in patients with severe COPD.[28,29] In the study reported by Szafranski et al.,[28] patients received BF (n = 208), B (n = 198), F (n = 201) or PL (n = 205). In the study reported by Calverley et al.,[29] patients received BF (n = 254), B (n = 257), F (n = 255) or PL (n = 256). * $p < 0.05$ vs PL; † $p < 0.05$ vs F; ‡ $p < 0.05$ vs B.

first exacerbation than recipients of placebo ($p = 0.006$), budesonide ($p < 0.05$) and formoterol ($p < 0.01$); the median time to first exacerbation was 254, 96, 178 and 154 days, respectively. Budesonide/formoterol reduced the rate of exacerbation by 23.6% versus placebo and by 25.5% versus formoterol (both $p < 0.05$) [figure 2].[29]

- Furthermore, budesonide/formoterol significantly reduced the rate of exacerbations requiring oral corticosteroid courses by 31%[28] and 44.7%[29] compared with placebo, and by 28%[28] and 30.5%[29] compared with formoterol (all $p < 0.05$) [figure 2]. In the larger trial[29] patients receiving budesonide/formoterol were treated with 28.2% fewer courses of oral corticosteroids compared with budesonide recipients ($p < 0.05$) [figure 2].

Effect on COPD Symptoms

- After 12 months' treatment, patients receiving budesonide/formoterol reported a significantly greater reduction in total symptom, awakening, shortness of breath and chest tightness scores than placebo recipients in both trials[28,29] and budesonide recipients in the trial reported by Szafranski et al.[28] (all $p < 0.05$) [figure 3]. In this trial,[28] the reduction in total symptom and awakening scores also significantly favoured budesonide/formoterol versus formoterol ($p = 0.043$ and $p = 0.019$) [figure 3]. In the other study,[29] the reduction in shortness of breath score was significantly greater in patients receiving budesonide/formoterol than in those receiving budesonide ($p = 0.04$) [figure 3].
- In both trials, patients receiving budesonide/formoterol used less reliever medication compared with those receiving placebo (mean difference 1.3[28] and 0.8[29] inhalations per 24 hours) or budesonide (0.7[28] and 0.8[29]) [all $p < 0.001$]; patients receiving budesonide/formoterol in the trial by Calverley et al.[29] reported a reduction in the use of reliever medication compared with formoterol recipients (between-group difference 0.3 inhalations per 24 hours; $p < 0.05$). In the trial reported by Szafranski et al.,[28] compared with placebo, budesonide/formoterol significantly increased the number of days free from shortness of breath by 12% and the number of awakening-free nights by 14% (both $p < 0.001$).

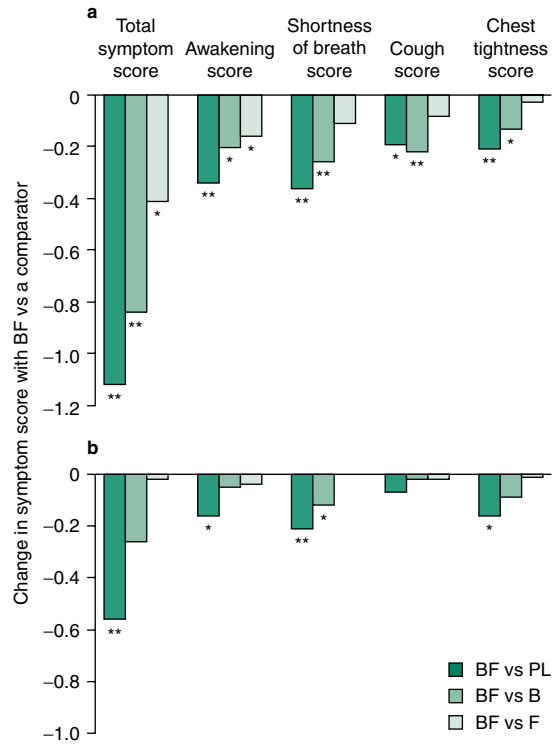

Fig. 3. Effect of inhaled budesonide/formoterol (BF) on symptoms in patients with chronic obstructive pulmonary disease (COPD). Change in symptom score at trial endpoint (12 months) with BF 320/9μg vs budesonide 400μg (metered dose) [B], formoterol 9μg (F) or placebo (PL); all study treatments were administered twice daily via a Turbuhaler® device. Results are from two double-blind, randomised, 12-month trials in patients with severe COPD.[28,29] In the study reported by Szafranski et al.[28] (**a**), patients received BF (n = 208), B (n = 198), F (n = 201) or PL (n = 205). In the trial reported by Calverley et al.[29] (**b**), patients received BF (n = 254), B (n = 257), F (n = 255) or PL (n = 256). * $p < 0.05$, ** $p < 0.001$ vs comparator.

Effect on Health-Related Quality of Life

- In both studies, patients receiving budesonide/formoterol experienced improvements in HR-QOL scores at trial endpoint.[28,29] In Szafranski et al.,[28] the reduction from baseline in mean SGRQ Total score was significantly greater in patients treated with budesonide/formoterol than in placebo recipients (−3.9 vs −0.03 units; $p = 0.009$). In patients receiving budesonide/formoterol, the SGRQ Symp-

tom and Impact scores were reduced by 5.9 and 4.7 units more than in placebo recipients ($p < 0.001$ and $p = 0.006$).[28] Mean reductions from baseline in the SGRQ Total score were −1.9 and −3.6 units in budesonide and formoterol recipients.[28] SGRQ Total scores at baseline, prior to which patients received rescue-medication only, ranged from 51 to 54 units.[28]

- In the second study,[29] in which patients received treatment intensification with oral prednisolone and inhaled formoterol, a mean reduction from baseline in SGRQ Total scores of 4.5 units was reported in all patients (baseline SGRQ Total scores ranged from 47 to 49 units). At 12 months, changes from baseline in SGRQ Total scores (versus placebo) were significant for budesonide/formoterol (−7.5 units; $p < 0.001$), budesonide (−3.0 units; $p < 0.05$) and formoterol (−4.1 units; $p < 0.01$).[29] Furthermore, the improvement in SGRQ Total scores in patients receiving budesonide/formoterol was significantly greater than in budesonide or formoterol recipients (values not stated; $p = 0.001$ and $p = 0.014$).[29]
- In this study, budesonide/formoterol improved SGRQ Symptom, Activity and Impact scores by ≥5.5 units compared with placebo ($p < 0.01$).[29] Moreover, patients receiving budesonide/formoterol showed significantly improved mean SGRQ Activity and Impact scores from baseline compared with those receiving budesonide (mean difference −3.6 and −5.7 units) and formoterol (−3.5 and −3.7 units) [all $p < 0.05$].[29]

4. Tolerability

The tolerability profile of budesonide/formoterol administered via a Turbuhaler® device is the same as that for the individual components and no increased incidence of adverse events has been seen following concurrent administration of the two drugs.[18] The adverse effects of inhaled budesonide[39,40] and formoterol[17,41] in patients with COPD have been described in detail elsewhere. Tolerability data are reported in the two studies presented in section 3;[28,29] further detailed information is published in the manufacturer's prescribing information.[18]

- The most commonly reported adverse effects associated with budesonide/formoterol are due to the pharmacological effect of the β_2-agonist component, and include tremor and palpitations (incidence >1%).[18] These tend to be mild and transient.[18] Other commonly reported adverse effects (incidence >1%) are headache, *Candida* infections in the oropharynx, coughing, mild throat irritation and hoarseness.[18]
- Budesonide/formoterol was generally well tolerated in patients with severe COPD in the two 12-month studies presented in section 3.[28,29] Statistical analysis of tolerability data was reported for withdrawal rates only.[28,29] The frequency of adverse events, reported in one study,[29] was 5, 5, 6 and 5 adverse events per 1000 treatment days for budesonide/formoterol, budesonide, formoterol and placebo, respectively (figure 4).
- Szafranski et al.[28] reported the withdrawal of 275 of 812 randomised patients (34%), 115 because of deterioration of COPD. Calverley et al.[29] reported the withdrawal of 393 of 1022 randomised patients (38%), 193 because of deterioration of COPD. In both trials, a significantly higher number of withdrawals due to deterioration of COPD occurred in the placebo groups (21%[28] and 23%[29]) compared with the budesonide/formoterol groups (10%[28] and 11%[29]) [both $p < 0.001$]. A significantly smaller proportion of patients withdrew from the budesonide/formoterol group due to deterioration of COPD than from the budesonide (18%; $p = 0.038$) or formoterol (23%; $p < 0.001$) groups in the larger study.[29]
- The rates of withdrawal due to adverse events other than deterioration of COPD were similar across treatment arms: 8%[28,29] for budesonide/formoterol, 7%[28] and 8%[29] for budesonide, 6%[28] and 8%[29] for formoterol, and 8%[28] and 4%[29] for placebo.
- The number of serious adverse events other than deaths was 43[28] and 65[29] with budesonide/formoterol, 35[28] and 88[29] with budesonide, 37[28] and 85[29] with formoterol, and 37[28] and 66[29] with placebo in 812[28] and 1022[29] patients, respectively. The number of deaths in the corresponding treat-

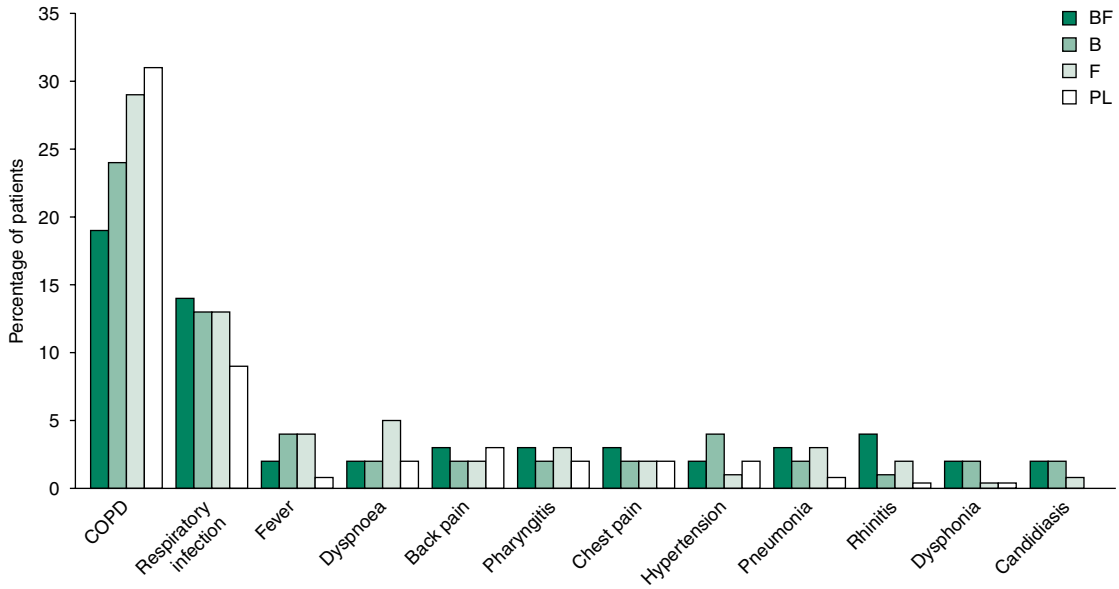

Fig. 4. Tolerability of inhaled budesonide/formoterol (BF). Incidence of adverse events in patients with chronic obstructive pulmonary disease (COPD). Tolerability of BF 320/9μg, budesonide 400μg (metered dose) [B] and formoterol 9μg (F); all study treatments were administered twice daily via a Turbuhaler® device. Results are from a double-blind, randomised, 12-month trial in patients with severe COPD.[29] Patients received BF (n = 254), B (n = 257), F (n = 255) or placebo (PL) [n = 256]. COPD was reported as an adverse event only if the COPD symptom was serious (resulted in death, was life-threatening, required hospitalisation or resulted in persistent or significant disability/incapacity) or resulted in withdrawal from the study.

ment groups were 6[28] and 5,[29] 5[28] and 6,[29] 6[28] and 13,[29] and 9[28] and 5.[29]

- No clinically important differences between groups were reported for clinical chemistry, haematology or ECG measurements, and no bruising was reported.[28]

5. Dosage and Administration

Inhaled budesonide/formoterol 200/6μg and 400/12μg (metered dose) via the Turbuhaler® device is approved in the EU for the symptomatic treatment of patients with severe COPD (FEV_1 <50% predicted normal) and a history of repeated exacerbations who have significant symptoms despite regular therapy with long-acting bronchodilators.[18] The budesonide/formoterol 200/6μg inhaler delivers 160μg of budesonide and 4.5μg of formoterol per dose; the 400/12μg inhaler delivers 320μg of budesonide and 9μg of formoterol per dose.[18] The recommended dosage for the treatment of COPD in adults is 320/9μg twice daily.[18] No dosage adjustment is required in elderly patients.[18] Systemic exposure to budesonide and formoterol may be increased in patients with liver disease (see section 2); however, no formal dosage recommendations are available for this patient group.[18]

6. Budesonide/Formoterol: Current Status

Budesonide/formoterol administered via the Turbuhaler® multidose dry powder inhaler is currently approved in the EU for the treatment of patients with severe COPD. At a dosage of 320/9μg inhaled twice daily, it showed clinical efficacy in two large, well designed studies in patients with severe COPD and was generally well tolerated, with an adverse event profile consistent with that of its individual components.

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