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Effect of budesonide/formoterol pMDI on COPD exacerbations: A double-blind, randomized study

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Summary
Background: Treatment with an inhaled corticosteroid (ICS) and long-acting bronchodilator is recommended for severe/very severe chronic obstructive pulmonary disease (COPD) patients with repeated exacerbations. This randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study evaluated the effect of budesonide/formoterol pressurized metered-dose inhaler (pMDI) on COPD exacerbations.
Methods: Following a 2-week run-in during which COPD patients aged ≥40 years with an exacerbation history discontinued medications except ICSs, 1219 patients were randomized 1:1:1 to twice-daily budesonide/formoterol pMDI 320/9 μg, budesonide/formoterol pMDI 160/9 μg, or formoterol dry powder inhaler 9 μg. An exacerbation was defined as COPD worsening requiring oral corticosteroids and/or hospitalization. A post hoc analysis, with antibiotic treatment added to the exacerbation definition, was also performed.
Results: Budesonide/formoterol 320/9 and 160/9 reduced exacerbation rates (number per patient-treatment year) by 34.6% and 25.9%, respectively, versus formoterol ($p \leq 0.002$).

Budesonide/formoterol 320/9 prolonged time to first exacerbation versus formoterol, corresponding to a 21.2% reduction in hazard ratio (0.788 [95% CI: 0.639, 0.972]; $p = 0.026$). Exacerbation rates (number per patient-treatment year) including antibiotic treatment (post hoc analysis) were reduced by 25.9% and 18.7% with budesonide/formoterol 320/9 and 160/9, respectively, versus formoterol ($p \leq 0.023$). Both budesonide/formoterol doses were well tolerated with safety profiles similar to formoterol. Pneumonia adverse events occurred in 6.4%, 4.7%, and 2.7% of patients in the budesonide/formoterol 320/9, 160/9, and formoterol groups.

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Conclusions: Over 12 months, both budesonide/formoterol doses reduced the exacerbation rate (defined with or without antibiotic treatment) versus formoterol. Budesonide/formoterol pMDI is an appropriate treatment for reducing exacerbations in COPD patients with a history of exacerbations. (NCT00419744).
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Introduction

Although a standard definition has not been established,[1] the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define an exacerbation of chronic obstructive pulmonary disease (COPD) as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.[2] Increasing frequency of COPD exacerbations are an indication of increased disease severity[2] and have been associated with pulmonary function decline,[3,4] reduced quality of life,[5] and increased mortality.[6] Moreover, severe exacerbations of COPD are associated with increased health care utilization[7] and costs compared with mild or moderate exacerbations.[7,8]

Preventing and treating exacerbations of COPD is an important goal of disease management.[2] In patients with severe or very severe COPD who have repeated exacerbations, adding an inhaled corticosteroid (ICS) to a long-acting bronchodilator treatment is recommended.[2] Studies have shown benefits of regular ICS therapy relative to placebo in improving COPD symptoms,[9] reducing exacerbation frequency,[10,11] and improving quality of life.[10]

Treatment with budesonide/formoterol administered via a pressurized metered-dose inhaler (pMDI) has shown greater clinical benefits with regard to reducing COPD symptoms and improving pulmonary function and quality of life versus each monocomponent in a 6-month study[12] and versus formoterol in a 12-month study[13] in patients with moderate to very severe COPD. The effect of budesonide/formoterol pMDI treatment on COPD exacerbations, defined as a worsening of COPD requiring oral corticosteroid treatment, hospitalization, or both, also was assessed in these studies.[12,13] In the 12-month study, a significant prolongation of the time to first COPD exacerbation and reduction in exacerbation rate were observed with budesonide/formoterol pMDI compared with formoterol treatment. Exacerbations were assessed as a prespecified secondary end point controlling for multiplicity of testing in that study.[13] In the 6-month study, a numerical reduction in exacerbation rate was shown for treatment with budesonide/formoterol pMDI compared with formoterol.[12] However, the 6-month study was not powered a priori for evaluating exacerbations.[12]

The present randomized, double-blind, double-dummy, 12-month clinical study was specifically designed to compare the efficacy of 2 dosages of budesonide/formoterol pMDI (320/9 μg twice daily and 160/9 μg twice daily) with formoterol DPI 9 μg twice daily in preventing exacerbations in patients with COPD. Secondary efficacy, safety, and health economic outcomes also were assessed.

Methods

Patients

The inclusion and exclusion criteria were designed to enroll patients with COPD who were appropriate candidates for ICS/long-acting β_2-adrenergic agonist (LABA) combination therapy. Patients were current smokers or ex-smokers with a smoking history of $\geq$10 pack-years, aged $\geq$40 years, with a clinical diagnosis of COPD with symptoms for $>$2 years. Patients were required to have a history of $\geq$1 COPD exacerbation requiring treatment with a course of systemic corticosteroids, antibiotics, or both, within 1–12 months before screening (visit 1) and documented use of an inhaled short-acting bronchodilator as rescue medication. At screening, a prebronchodilator forced expiratory volume in 1 s (FEV_1) of $\leq$50% of predicted normal and a prebronchodilator FEV_1/forced vital capacity (FVC) of $<$70% also were required. Exclusion criteria included current, previous (within past 60 days), or planned enrollment in a COPD pulmonary rehabilitation program, treatment with oral corticosteroids, and incidence of a COPD exacerbation or any other significant medical diagnosis between the screening and randomization visits (visit 1–3). Additional inclusion and exclusion criteria are the same as those described in a previous study by Tashkin et al.[12]

Study design and treatments

This was a randomized, double-blind, double-dummy, parallel-group, 12-month multicenter study (NCT00419744; AstraZeneca LP D589CC00003) conducted between January 2007 and August 2009 at 180 study sites in the United States (106 sites), Central and South America (53 sites), and South Africa (21 sites). The study consisted of an initial screening visit (visit 1), a 2-week run-in period (beginning at visit 2), a 12-month randomized treatment period (visits 3–9), and telephone follow-up 2 weeks after study treatment cessation.

Before the run-in period, current COPD medications except ICSs, including LABAs, short-acting β_2-adrenergic agonists (SABAs), short- or long-acting anticholinergics, short-acting and slow-release oral β_2-agonists, xanthine derivatives (eg, theophylline), leukotriene antagonists or synthase inhibitors, and ephedrine-containing medications, were discontinued. Patients previously receiving ICS/LABA combination treatment were switched to a comparable dose of an ICS alone. Rescue medication (albuterol pMDI 90 μg $\times$ 2 inhalations) was provided for as-needed use during screening and run-in, and throughout the study. After the run-in period (at visit 3), ICS therapies were discontinued and eligible patients who met inclusion, exclusion, and randomization criteria were randomly assigned