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Comparable long-term safety and efficacy of a novel budesonide/formoterol pressurized metered-dose inhaler versus budesonide/formoterol Turbuhaler® in adolescents and adults with asthma

Alyn H. Morice[a,*], Luděk Hochmuth[b], Jan Ekelund[c], Anders Thorén[c], Allan S. Puterman[d]

[a]*Respiratory Medicine, Academic Medicine, University of Hull, Castle Hill Hospital, Castle Road, Cottingham, East Yorkshire HU16 5JQ, UK*
[b]*FD Roosevelt Hospital, Namestie L Svobodu 1, 975 17 Banská Bystrica, Slovak Republic*
[c]*AstraZeneca R&D, Lund S-221 87, Sweden*
[d]*Syringa House, Kingsbury Hospital, Wilderness Road, Claremont, Cape Town, South Africa*

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Abstract

Budesonide/formoterol in one inhaler is an established therapy for asthma and chronic obstructive pulmonary disease. The long-term safety and efficacy profile of a novel hydrofluoroalkane (HFA) pressurized metered-dose inhaler (pMDI) formulation of budesonide/formoterol was compared with that of budesonide/formoterol in a dry powder inhaler (DPI; Turbuhaler®). This multinational, 52-week, randomized, open, parallel-group study included patients aged ⩾12 years with asthma who had a forced expiratory volume in 1 s (FEV_1)⩾50% of predicted normal; all patients used inhaled corticosteroids (400–1200 μg/day) and needed additional short-acting β_2-agonist therapy. Patients were randomized to receive budesonide/formoterol pMDI or DPI 160/4.5 μg, two inhalations twice daily. Safety endpoints included assessment of adverse events and laboratory parameters. Efficacy endpoints included change from baseline in FEV_1 and time to first severe asthma exacerbation. Overall, 673 patients (446 pMDI, 227 DPI) were included. There were no clinically significant differences between treatment groups in the nature, incidence or severity of adverse events or laboratory parameters. The number of patients experiencing adverse events was comparable in the pMDI (332/446 [74%]) and DPI (175/227 [77%]) groups; the most commonly reported adverse event was upper respiratory tract infection. The proportion of patients discontinuing as a result of adverse events was low in both groups (pMDI 12/446 [3%], DPI 2/227 [1%]). Lung function was improved to a similar extent in both groups and there was no detectable difference in time to first severe asthma exacerbation. The novel HFA pMDI formulation of budesonide/formoterol is an equally well tolerated and effective treatment for adults and adolescents with asthma as the budesonide/formoterol DPI.

Keywords: Asthma; Budesonide/formoterol; Dry-powder inhaler; Safety; Pressurized metered-dose inhaler

1. Introduction

International asthma management guidelines [1,2] recommend treatment with inhaled corticosteroids (ICS) for patients with persistent disease. For those whose symptoms are not adequately controlled by ICS alone, a second controller medication is recommended; the most commonly used add-on therapy is a long-acting β_2-agonist (LABA). Several studies have shown that treatment with an ICS/LABA combination is more effective than an ICS alone [3–7]. The combination of both agents in one inhaler has simplified treatment for asthma patients, in whom adherence declines as the complexity of treatment increases [8].

The combination of budesonide/formoterol in one dry-powder inhaler (DPI), Symbicort® Turbuhaler®, is an effective and well-tolerated therapy for both asthma [3,6,7,9,10] and chronic obstructive pulmonary disease [11,12]. In patients with asthma, fixed dosing with budesonide/formoterol is more effective than higher doses of ICS alone [6,9,13]. The pharmacological properties of budesonide/formoterol mean that this combination is suitable for both once-daily dosing [3] and adjustable

*Corresponding author. Tel.: +44 (0)1482 624066; fax: +44 (0)1482 624068.
E-mail address: a.h.morice@hull.ac.uk (A.H. Morice).

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maintenance dosing [14–17], in addition to use in the acute setting [18] and as maintenance and reliever therapy (Symbicort® Maintenance And Reliever Therapy [SMART]) [19–22].

In a chronic condition, such as asthma, where patients need to take regular doses of medication over long periods, adherence to treatment is very important. Ease and convenience of device use and overall confidence in the device may improve patient adherence to an inhaler [23]. Many studies have demonstrated comparable efficacy for drugs delivered via DPIs and pressurized metered-dose inhalers (pMDIs), and recent guidelines have concluded that devices used for the delivery of bronchodilators and steroids can be equally efficacious [24,25]. Indeed, two recent studies have shown that budesonide/formoterol has equivalent efficacy in adults, adolescents and children whether delivered via the DPI or the new hydrofluoroalkane (HFA) pMDI formulation [26,27].

The long-term safety of budesonide/formoterol DPI is well established [19,21,22,28]. The primary aim of the present study was to compare the long-term safety profile of budesonide/formoterol HFA pMDI with that of budesonide/formoterol DPI (reference inhaler) over 52 weeks in adults and adolescents with asthma. A secondary objective was to compare the efficacy of both devices.

2. Methods

2.1. Patients

Patients who met the following criteria were eligible for recruitment into this study: aged $\geqslant$12 year with asthma [29] of $\geqslant$6 months duration; forced expiratory volume in 1 s (FEV_1) $\geqslant$50% of predicted normal (prebronchodilator); reversibility of $\geqslant$12% (FEV_1) after inhalation of terbutaline 1 mg (Bricanyl Turbuhaler®, AstraZeneca). Patients were required to have used ICS with additional need for inhaled short-acting β_2-agonists (SABAs) or LABAs for $\geqslant$3 months prior to the start of the study, with a constant ICS dose of 400–1200 μg/day within the 30 days before starting the study. Patients were excluded if they had a smoking history of $>$10 pack-years.

2.2. Study design

This randomized, open-label, parallel-group study (study code SD-039-0715) was conducted in 60 centres across six countries (Australia, France, the Philippines, Slovakia, South Africa and Thailand). The study complied with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. Local ethics committees or institutional review boards at each centre approved the study protocol and patient consent form before study commencement.

Patients were randomized to treatment over 52 weeks with either budesonide/formoterol DPI (Symbicort® Turbuhaler®, AstraZeneca; 160/4.5 μg, two inhalations twice daily) or budesonide/formoterol pMDI (Symbicort Rapihaler®, AstraZeneca; 160/4.5 μg, two inhalations twice daily), plus a SABA (terbutaline 0.5 mg/inhalation) as needed for symptom relief. The doses of budesonide in each group were comparable; differences are explained by labelling changes for new inhaled drugs that require the delivered dose to be reported rather than the metered dose. Randomization was performed by allocating patients with a code assigned sequentially from a computer-generated list in balanced blocks. Investigators, but not patients, were blinded prior to dispensing study treatment.

Patients were provided with appropriate instructions and training on how to use their inhaler. Patients were also provided with a notebook in which they recorded their daily use of study medication and any adverse events.

2.3. Assessments

2.3.1. Safety

The primary objective of this study was to compare the long-term safety profiles of budesonide/formoterol DPI and budesonide/formoterol pMDI. No one variable was considered to be the primary endpoint. Adverse events (both spontaneously reported and reported in response to questioning) were assessed at each clinic visit, i.e. at randomization (baseline) and 2, 12, 26, 38 and 52 weeks after randomization. Deterioration in asthma and the signs or symptoms of asthma were only reported as adverse events if they were considered serious or if they resulted in discontinuation.

Changes in clinical laboratory parameters (haematology, clinical chemistry and urinalysis) were assessed in all patients at randomization and at weeks 2, 12, 26 and 52 after randomization. Morning plasma cortisol was also assessed in all patients at these visits using the standard method of Hsu et al. [30]; the lower limit of detection was 20 nmol/l. In a subgroup of all patients from preselected clinics in France and Slovakia, 24-h urinary cortisol was measured at randomization and at weeks 26 and 52 using the same methodology; the lower limit of detection was 10 nmol/l. Blood samples were collected between 8.00 and 9.00 a.m. to avoid diurnal variation.

Vital signs and electrocardiograms (ECGs) were recorded at randomization and 2, 12, 26 and 52 weeks after randomization. Physical examination was performed at enrolment and at weeks 26 and 52.

2.3.2. Efficacy

The secondary objective of this study was to compare the efficacy of budesonide/formoterol DPI and budesonide/formoterol pMDI. Spirometry was performed for measurement of FEV_1 in accordance with European Respiratory Society recommendations [31]. Time to first severe asthma exacerbation (defined as asthma symptoms requiring oral steroids and/or hospitalization/emergency room treatment for asthma) was defined as the number of days from visit 1