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Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: A superiority and therapeutic equivalence study

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Abstract

Aim: This paediatric asthma study evaluated the efficacy and safety of a novel hydrofluoroalkane pressurised metered-dose inhaler (pMDI) formulation of budesonide/formoterol versus budesonide pMDI and budesonide/formoterol dry-powder inhaler (DPI).

Methods: The study was a 12-week, multinational, double-blind trial involving children (aged 6–11 years) with symptomatic asthma on inhaled corticosteroids (375−1000 μg/day), with a history of exercise-induced bronchoconstriction and peak expiratory flow (PEF) ⩾50% of predicted. Patients were randomised (two inhalations twice daily) to budesonide pMDI 100 μg, budesonide/formoterol DPI 80/4.5 μg or budesonide/formoterol pMDI 80/4.5 μg. The primary endpoint was change from baseline in morning PEF.

Results: Overall, 622 patients were randomised. Increases in morning PEF with budesonide/formoterol pMDI and budesonide/formoterol DPI were therapeutically equivalent (29.5 versus 30.2 l/min, respectively; 95% confidence interval: −6.0 to 4.6; $P = 0.78$, also confirmed by per-protocol analysis). Improvements in secondary efficacy endpoints with both budesonide/formoterol formulations were not significantly different. Significantly greater improvement was achieved with budesonide/formoterol pMDI versus budesonide pMDI for morning PEF (+9.6 l/min; $P < 0.001$) and other lung function parameters. The safety profile of budesonide/formoterol pMDI was favourable and similar to that of budesonide/formoterol DPI and budesonide pMDI.

Conclusion: Budesonide/formoterol, administered via the therapeutically equivalent hydrofluoroalkane pMDI or DPI, is an effective and well-tolerated treatment for children with asthma.

Keywords: Asthma; Budesonide/formoterol; Dry-powder inhaler; Equivalence; Pressurised metered-dose inhaler

1. Introduction

Inhaled corticosteroids (ICS), such as budesonide, represent the basis of pharmacological therapy for children with moderate to severe persistent asthma [1–3]. Despite their proven efficacy, maintenance treatment with an ICS alone fails to provide adequate asthma control for many children. In these situations, inhaled long-acting β_2-agonists are recommended as first-line add-on therapy [1–3].

Studies in children, adolescents and adults with asthma have shown that the combination of budesonide and the long-acting β_2-agonist formoterol in the same dry-powder inhaler (DPI) (Symbicort® Turbuhaler®) is both effective and well tolerated [4–6]. In a study involving children and adolescents with asthma aged between 4 and 17 years, budesonide/formoterol DPI (used at fixed maintenance doses) provided greater improvements in lung function (morning and evening peak expiratory flow (PEF) and forced expiratory volume in 1 s (FEV_1)) than budesonide DPI alone [6].

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The choice of inhaler for school-age children is often driven by the patient's ability to use a particular device correctly and personal preference [7]. Both DPIs, such as the Turbuhaler®, and pressurised metered-dose inhalers (pMDIs) are effective and appropriate device options for patients in this age group [1,8,9]. To improve choice for patients and clinicians, budesonide/formoterol has been developed as a HFA pMDI formulation (Symbicort Rapihaler®). The aim of the present study was to compare the efficacy and safety of this novel pMDI formulation of budesonide/formoterol with that of budesonide/formoterol DPI and budesonide (Pulmicort®) pMDI in children with asthma.

2. Materials and methods

2.1. Patients

Paediatric outpatients (aged 6–11 years) with asthma [10] for $\geqslant$6 months and PEF $\geqslant$50% of predicted normal (pre-bronchodilator) were recruited. To be eligible for inclusion, all patients had to have a history of daily ICS use (stable dose of 375−1000 μg/day within the 30 days prior to enrolment) and clinically important exercise-induced bronchoconstriction ($\geqslant$1 episode/week) for $\geqslant$3 months before enrolment. Patients also had to demonstrate the ability to use a DPI, pMDI and peak flow meter (Mini-Wright® peak flow meter, Clement Clarke, Harlow, UK) correctly.

Prior to randomisation, all patients had to have a total asthma symptom score $\geqslant$1 on $\geqslant$4 of the last 7 days of run-in (scale: 0 = no symptoms; 1 = aware of symptoms but can tolerate them easily; 2 = asthma causing enough discomfort to interfere with normal activities or sleep; 3 = unable to perform normal activities or sleep because of asthma day- and night-time scores were summed) and a mean morning PEF 50–85% of their post-bronchodilatory PEF (measured at enrolment 15 min after inhalation of terbutaline 1 mg (Bricanyl®Turbuhaler®, AstraZeneca)) during the last 7 days of run-in.

2.2. Study design

This was a 12-week, Phase III, randomised, double-blind, double-dummy, parallel-group study (study code SD-039-0682) conducted in 53 centres across eight countries (Argentina, Brazil, Denmark, Hong Kong, Mexico, Poland, Slovakia and Taiwan). The study complied with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. The study protocol and patient consent form were approved by an independent ethics committee or institutional review board at each centre.

Following a 10- to 14-day run-in, during which they continued their pre-study ICS medication (stable dose of 375−1000 μg/day), patients were randomised to treatment (two inhalations twice daily) with one of the following: budesonide pMDI 100 μg (Pulmicort® pMDI, 3M Health Care); budesonide/formoterol DPI 80/4.5 μg (Symbicort® Turbuhaler®, AstraZeneca); or budesonide/formoterol pMDI 80/4.5 μg (Symbicort Rapihaler®, AstraZeneca). The doses of budesonide in each group were comparable. Differences in the labelling of the budesonide dose are due to different regulatory demands in different countries that require the delivered dose to be reported in some cases rather than the metered dose. For example, Symbicort® Turbuhaler® 80/4.5 μg is labelled as Symbicort® Turbuhaler® 100/6 μg in some countries, although it is the same product.

Patients were randomised sequentially in blocks of six using a computer-generated randomisation schedule. In order to maintain blinding, each patient also received a placebo device; to reduce inconvenience, each patient received only two of the three devices: one active and one placebo device. All patients were given the inhaled short-acting β_2-agonist, terbutaline 0.5 mg/inhalation, for symptom relief. If the subject preferred another short-acting β_2-agonist that was regarded as being equivalent in clinical practice, e.g. salbutamol, it was prescribed by the investigator. It was, however, important that the subject used the same brand and strength of rescue medication throughout the study.

2.3. Assessments

The primary efficacy endpoint was the change in morning PEF from baseline (mean of the last 10 days of run-in) to the mean value over the 12-week treatment period. Secondary efficacy endpoints included change from baseline (mean value over the last 10 days of run-in) to the mean value over the treatment period in evening PEF, reliever medication use, night-time awakenings caused by asthma, total asthma symptom score, symptom-free days (a night and day without asthma symptoms and no night-time awakenings caused by asthma) and asthma-control days (a night and day without asthma symptoms or reliever medication use and no night-time awakenings caused by asthma). All PEF measurements (taken prior to inhalation of study medication), reliever medication use, night-time awakenings caused by asthma and asthma symptom scores were recorded in a daily diary.

Change from baseline (randomisation) to the mean of the treatment period (Week 2 to Week 12) in FEV_1 and change from baseline (randomisation) to the end of treatment (Week 12) in Paediatric Asthma Quality of Life Questionnaire (standardised version) (PAQLQ(S)) scores [11] were also predefined secondary endpoints. FEV_1 was assessed during clinic visits at enrolment and randomisation, and at 2, 6 and 12 weeks after randomisation, according to European Respiratory Society guidelines [12,13]. The 23-item PAQLQ(S) was administered to patients aged 7–11 years during standardised interviews conducted at clinic visits at randomisation and at Weeks 2 and 12 (responses on a 7-point scale, where 1 = greatest possible impairment and 7 = least impairment) [11].