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Efficacy of fluticasone propionate/formoterol fumarate in the treatment of asthma: A pooled analysis

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Asthma;
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Summary
Background: Fluticasone propionate and formoterol fumarate have been combined in a single inhaler (fluticasone/formoterol; *flutiform*®) for the maintenance treatment of asthma. This pooled analysis assessed the efficacy of fluticasone/formoterol *versus* fluticasone in patients who previously received inhaled corticosteroids.
Methods: Data were pooled from five randomised studies in patients with asthma (aged ≥12 years) treated for 8 or 12 weeks with fluticasone/formoterol (100/10, 250/10 or 500/20 μg b.i.d.; $n = 528$ delivered via pMDI) or fluticasone alone (100, 250 or 500 μg b.i.d.; $n = 527$).
Results: Fluticasone/formoterol provided significantly greater increases than fluticasone alone in mean morning forced expiratory volume in 1 second (FEV_1) from pre-dose at baseline to 2 hours post-dose at study end (least-squares mean [LSM] treatment difference: 0.146 L; $p < 0.001$) and in pre-dose FEV_1 from baseline to study end (LSM treatment difference: 0.048 L; $p = 0.043$). Compared with fluticasone, fluticasone/formoterol provided greater increases in the percentage of asthma control days (no symptoms, no rescue medication use and no sleep disturbance due to asthma) from baseline to study end (LSM treatment difference: 8.6%; $p < 0.001$), and was associated with a lower annualised rate of exacerbations (rate ratio: 0.71; $p = 0.014$).

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Conclusions: In summary, fluticasone/formoterol provides clinically significant improvements in lung function and asthma control measures, with a lower incidence of exacerbations than fluticasone alone.

Introduction

The Global Initiative for Asthma (GINA) guidelines recommend adding a long-acting β_2-agonist (LABA) to an inhaled corticosteroid (ICS) for patients whose asthma is not controlled with low-to-medium dose ICS monotherapy [1]. Despite asthma control being attainable for most patients receiving ICS/LABA therapy in a clinical trial setting, the levels of asthma control in real life remain unsatisfactory [2]. In clinical practice, several factors can affect the ability of patients to achieve the clinical outcomes obtained in controlled conditions. The use of single-inhaler ICS/LABA combinations has been shown to increase patient adherence to treatment compared with the use of separate inhalers [3,4], which may help improve asthma outcomes.

An additional maintenance therapy for asthma, combining the ICS fluticasone propionate (fluticasone) and the LABA formoterol fumarate (formoterol) in a single pressurised metered-dose inhaler (fluticasone/formoterol; ***flutiform***®), has been approved for adolescents and adults who require ICS/LABA combination therapy. Fluticasone is a potent ICS [5] and formoterol is the fastest-acting inhaled LABA currently available for the treatment of asthma in a combination inhaler [6,7]. A rapid onset of action may be an important attribute of an ICS/LABA maintenance therapy for patients [4,8]; recent studies have suggested that therapies with a rapid onset of bronchodilation may encourage patient adherence to their treatment regimen [9,10]. Furthermore, fluticasone/formoterol has been shown *in vitro* to have a high fine particle fraction (FPF), to exhibit negligible flow-rate dependency [11], and has also demonstrated a slow, warm and prolonged aerosol plume [[12]; unpublished data] factors which may correlate with corresponding high levels of lung deposition *in vivo*.

The efficacy and safety profile of fluticasone/formoterol combination therapy has been demonstrated in a comprehensive programme of randomised, controlled clinical trials [13–20]. Here, we present the results of a pooled analysis of data from five studies [16–18,21,22] in the subgroup of patients with asthma who received prior ICS treatment, to assess the efficacy of fluticasone/formoterol combination therapy compared with that of fluticasone monotherapy; pooled safety data are presented for the overall patient population.

Methods

This was a pooled analysis of data from five randomised, double-blind, controlled clinical trials, to assess the efficacy and safety of fluticasone/formoterol compared with that of fluticasone monotherapy in adolescents and adults with a range of asthma severities. For consistency with the approved indication for fluticasone/formoterol, efficacy was assessed only in the subgroup of patients who had received ICS therapy prior to study enrolment; those patients who did not receive ICS before study entry (in two of the five studies) were excluded from the efficacy analyses; safety was evaluated for the overall population to provide as large a population as possible for the safety pool (Table 1). Asthma severity was defined based on the ICS dose and the level of symptoms and lung function during a run-in period. The studies included in this analysis represent all of the available randomised, double-blind trials comparing fluticasone/formoterol with fluticasone monotherapy at an equivalent nominal dose.

All studies were conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines, and were approved by the relevant independent ethics committees. All patients gave written informed consent. Where patients were aged <18 years (studies 1–4), written informed consent was given by both the patient and the parent or legal guardian.

Study design

The five studies included in this analysis were of similar design (Table 1). Patients underwent screening, followed by a 2–4-week run-in period, with fluticasone (50–250 μg twice daily [b.i.d.] via a pressurised metered-dose inhaler [pMDI]) for patients on prior ICS therapy. At the end of the run-in period, only patients who were symptomatic were randomised to study treatments for 12 weeks (studies 1–4) or 8 weeks (study 5). In all studies, patients could be withdrawn from the study due to worsening asthma (Text S1. Worsening Asthma Definitions).

Patients

All studies enrolled male and female adolescents (≥12 years) and adults (≥18 years), except for study 5, which only included adults (Table 1). Studies 1 and 2 enrolled patients with asthma who had been treated with ≤500 μg fluticasone-equivalents/day or who had not received ICS maintenance therapy prior to screening; however, ICS-naïve patients were excluded from this pooled analysis of the efficacy data. Studies 3–5 only included patients who had received prior ICS therapy (≤500 μg fluticasone-equivalents/day for studies 3 and 4, and ≥500 μg for study 5). Requirements for pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and FEV_1 reversibility at the