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Efficacy and safety of fluticasone propionate/salmeterol 250/50 mcg Diskus administered once daily ☆

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Summary
Background: The twice daily administration of an inhaled corticosteroid (ICS) and long-acting beta$_2$-agonist (LABA) has been shown to be effective in achieving asthma control. The once daily administration of an ICS/LABA may be a treatment option for some patients.
Objective: To assess the effectiveness of fluticasone propionate (FP)/salmeterol via a single inhaler (FSC) administered once daily compared with FP once daily, FSC twice daily, or placebo.
Methods: A 12-week, randomized, double-blind multicenter study conducted in 844 patients $\geqslant$12 years of age who were symptomatic while using a short-acting beta$_2$-agonist alone. Blinded treatments included: FSC 250/50 mcg once daily in the evening (FSC 250/50 QD), FP 250 mcg once daily in the evening (FP 250 QD), FSC 100/50 mcg twice daily (FSC 100/50 mcg BID), or placebo. All treatments were delivered via the Diskus® device.
Results: All treatments demonstrated greater improvements in efficacy measures compared with placebo. Overall, the greatest improvements were observed in the patients receiving FSC, either once or twice daily, compared with the FP 250 QD group. The two FSC treatments were similar except that QD dosing did not maintain improvements in lung function for 24 h compared with twice daily dosing. All treatments were well

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tolerated. No suppression of HPA axis, as assessed by 24-h urinary cortisol excretion, was observed in any of the active treatment groups.
Conclusion: In patients symptomatic on a short-acting beta$_2$-agonist alone, FSC 100/50 mcg BID was shown to provide better efficacy than a higher strength (FSC 250/50 mcg) administered once daily. However, a once daily regimen was effective and may be a valuable treatment option for some patients.
Registered at http://ctr.gsk.co.uk/welcome.asp (SAS30022)

Introduction

Current guidelines recommend the use of anti-inflammatory medications, including inhaled corticosteroids (ICS), and long-acting beta$_2$-agonists (LABA) for the treatment of persistent asthma. It is also recommended that the least amount of medication be used to maintain asthma control.[1,2]

Fluticasone propionate (FP), an ICS, is available in multiple strengths to aid the individualization of treatment and is approved for twice daily administration. However, data suggest that FP may be suitable for once daily administration in some patients. For example, clinical studies have shown FP to be effective when compared with placebo when given once-a-day.[3–6] Nonetheless, when the total daily dose of FP is given twice daily, it is generally more effective than once daily dosing.[7]

Salmeterol is also approved for use as a twice daily regimen. Clinical studies have shown that the effect of salmeterol on bronchodilation, protection against bronchial hyperresponsiveness, and other clinical measures exceed 12 h, suggesting that in some patients, salmeterol may exert therapeutic efficacy when given once daily.[8–12]

Given the results obtained in some studies with once daily dosing with FP and other ICS,[13–17] together with studies demonstrating a duration of action of salmeterol exceeding 12 h, this study was conducted to determine the efficacy and safety of FP/salmeterol 250/50 mcg administered once daily in the evening (FSC 250/50 QD) compared with FP 250 mcg administered once daily in the evening (FP 250 QD), FSC 100/50 mcg administered twice daily (FSC 100/50 BID), or placebo (PLA) in symptomatic adolescent and adult patients with asthma using short-acting beta$_2$-agonists alone. All treatments in this study were delivered via the Diskus®.

Methods

Patients

Male and female patients were eligible for the study if they were at least 12 years of age, had a medical history of asthma (as defined by the American Thoracic Society)[18] requiring physician prescribed asthma therapy for at least 3 months duration, and were using short-acting beta$_2$-agonists alone for at least 1 month prior to screening. At screening, patients were required to have a forced expiratory volume in 1 s (FEV_1) between 50% and 85% predicted value before administration of a bronchodilator and demonstrate a $\geqslant$12% increase in FEV_1 within 30 min following two puffs (180 mcg) of inhaled albuterol.

Exclusion criteria included: history of life-threatening asthma, smoking within the previous year or a history of $>$10 pack years, respiratory tract infection within 2 weeks of screening, history of significant concurrent disease, or the use of prophylactic short-acting beta$_2$-agonists of more than two puffs/day or use on more than 5 days/week. All patients (or parent/guardian if $<$18 years of age) provided written informed consent prior to entry into the study. The protocol was approved by the appropriate Institutional Review Board or Ethics Committee for each participating site.

Study design and interventions

This 12-week, randomized, double-blind, placebo-controlled, parallel-group study (SAS30022) was conducted at 103 sites in the United States and 18 sites in Canada. Eligible patients entered a 2-week placebo run-in period to assess compliance with therapy, obtain baseline data, confirm asthma stability, and evaluate eligibility for randomization to blinded treatment. All patients were supplied with albuterol inhalation aerosol for the relief of asthma symptoms as needed. Patients who met the entry criteria for the run-in period were provided two Diskus inhalers, each containing placebo to administer twice daily (one Diskus to be administered in the morning and the other in the evening, approximately 12 h apart). The morning and evening Diskus devices were differentiated by a different color label. Compliance with blinded study treatment was measured by the dose counter on the Diskus.

Patients were instructed on the use of a peak flow meter (MiniWright®, Clement Clark, Inc., London, United Kingdom) and completing a daily diary record of morning and evening peak flow measurements, albuterol use, and asthma symptoms. A nighttime asthma symptom score was recorded in the morning (scale 0–4 [0 = no symptoms; 4 = symptoms so severe patient did not sleep at all]) and every evening, a daytime asthma symptom score was recorded (scale 0–5 [0 = no symptoms; 5 = symptoms so severe that patient could not go to work/school or perform normal daily activities]). To be eligible for randomization patients had to have during the 7 days prior to the randomization visit: an asthma symptom score (combined daytime and nighttime) of $\geqslant$2 or used albuterol on $\geqslant$4 days, an evening PEF between 50% and 90% of predicted, and demonstrate an FEV_1 within $\pm$15% of the pre-bronchodilation screening FEV_1 at the randomization visit. Patients entering the double-blind phase were randomly assigned to receive one of the following four treatments for 12 weeks: FSC 250/50 mcg QD, FP 250 mcg QD, FSC 100/50 mcg BID, or placebo BID. Patients assigned to once daily treatment had