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Original article

Superiority of fluticasone propionate/formoterol fumarate versus fluticasone propionate alone in patients with moderate-to-severe asthma: a randomised controlled trial

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Abstract

Objective:

To demonstrate the efficacy and safety of fluticasone propionate/formoterol fumarate (flutiform*) in a pressurised metered-dose inhaler (pMDI) compared to two formulations of the fluticasone propionate component (Skyepharma fluticasone [SKP FP] or Flovent†, GlaxoSmithKline [GSK FP]) in adults and adolescents with moderate-to-severe asthma.

Methods:

Patients included in the study were ≥ 12 years, with symptomatic asthma for ≥ 1 year, steroid-requiring, had a forced expiratory volume in the first second (FEV₁) of 40% to 80% (inclusive) of predicted normal values, and documented reversibility within 12 months of the study. Albuterol/salbuterol was given as rescue medication. The primary efficacy endpoint was the change in FEV₁ from morning pre-dose at baseline (week 0) to 2 hours post-dose at week 12 for fluticasone/formoterol compared to SKP FP and, additionally, compared to GSK FP.

Results:

Fluticasone/formoterol was demonstrated to be statistically significantly superior to SKP FP. The least squares (LS) mean difference in FEV₁ from baseline pre-dose to 2 hours post-dose at week 12 was 0.161 L (95% CI: 0.078, 0.245, $p < 0.001$). Fluticasone/formoterol also demonstrated superior efficacy against GSK FP (LS mean difference = 0.185 L, 95% CI: 0.102, 0.268, $p < 0.001$). Results from multiple secondary and tertiary efficacy endpoints assessing lung function, asthma symptoms, exacerbations and rescue medication use supported a superior efficacy of the fluticasone/formoterol combination over both fluticasone formulations. Treatment-emergent adverse events were lowest in the fluticasone/formoterol group (32.9%) compared to SKP FP (39.7%) or GSK FP (40.4%).

Conclusions:

Results from this study demonstrate that fluticasone/formoterol 250/10 μ g b.i.d. provides superior efficacy compared to fluticasone alone for the management of moderate-to-severe asthma, with a safety profile similar to that of fluticasone monotherapy.

Trial registration:

ClinicalTrials.gov identifier: NCT00649025; EudraCT number: 2007-005653-37.

*These authors contributed equally to this work

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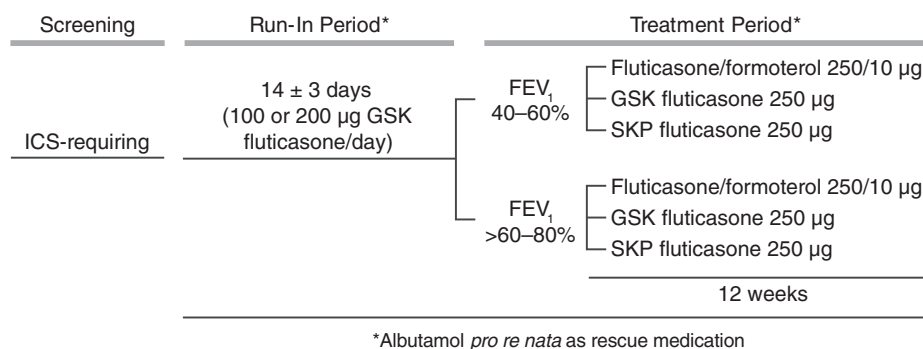


Figure 1. Study design.

Introduction

Asthma is one of the most common chronic diseases, affecting an estimated 300 million people worldwide. Its prevalence continues to rise in parallel with the increasing urbanisation of communities around the world, and an estimated 100 million more people may be affected by 2025¹. The Global Initiative for Asthma (GINA) guidelines recommends a step-wise approach to the treatment of asthma², with Step 3 recommending a medium or high-dose inhaled corticosteroid (ICS), plus a long-acting bronchodilator and an as-needed rapid-acting β_2 -agonist. ICS and long-acting β_2 -agonists (LABA) are often co-administered to treat moderate-to-severe asthma that is not adequately controlled by ICS therapy alone.

Combining an ICS and a LABA in a single inhaler has been shown to improve patient adherence compared to administering treatments separately^{3,4}. A new combination has recently been developed that combines the ICS fluticasone propionate (fluticasone) and the LABA formoterol fumarate (formoterol) together in a single inhaler for the treatment of patients with asthma that require Step 3 and 4 therapy. The anti-inflammatory effects of fluticasone are evident within 2 hours⁵, and are sustained for up to 26 hours⁶, and a single inhaler containing fluticasone and salmeterol has proven clinical effectiveness. Formoterol is a fast-acting LABA (within a few minutes), with a similar time to onset of action to salbutamol⁷, and has been shown to have a more rapid onset of action than fluticasone/salmeterol⁸.

The objective of this study was to compare the efficacy and safety of the combination of fluticasone and formoterol (250/10 µg, fluticasone/formoterol [flutiform*]) in a single hydrofluoroalkane pressurised metered-dose inhaler (HFA pMDI), administered twice daily over 12 weeks, to two formulations of the fluticasone component, in adolescent and adult patients with moderate-to-severe asthma who were previous ICS users.

Patients and methods

Study design and objectives

This study was a double-blind, randomised, active-controlled, parallel-group, stratified, multicentre study. Patients were stratified according to their percentage predicted forced expiratory volume in the first second (FEV₁; either 40% to 60% or >60% to 80%) (Figure 1).

Patients were recruited in primary care clinics and hospital clinics at 68 sites in Europe, South America and the United States between 18 March 2008 and 26 September 2008.

The study (ClinicalTrials.gov identifier: NCT00649025; EudraCT number: 2007-005653-37) was conducted in accordance with International Conference on Harmonisation Good Clinical Practice (GCP) guidelines, applicable regulations and guidelines governing clinical study conduct and ethical principles that have their origin in the Declaration of Helsinki. Depending on the country and region where the study site was located, the investigator ensured that the study was conducted in accordance with the European Union Clinical Trials Directive (2001/20/EC) and GCP Directive (2005/28/EC) or the provisions of the Food and Drug Administration regulations and complied with prevailing local laws and customs. Written informed consent was obtained from all patients before commencing the study. For patients less than 18 years of age, the study investigator thoroughly explained to both them and their respective parent/legal guardian the purpose of the study and the associated procedures. Each patient discussed and signed the informed consent form. In order to participate in this study, investigators had to obtain assent from adolescent patients, in addition to obtaining consent from their parent/legally authorised representative; their parent or legal guardian also signed and dated the consent form.

The primary efficacy endpoint was the change in FEV₁ from morning pre-dose at baseline (week 0) to 2 hours post-dose at 12 weeks; the primary comparison was that between fluticasone/formoterol and Skyepharma

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fluticasone (SKP FP). SKP FP is the identical fluticasone formulation used in the aerosol fluticasone/formoterol fixed combination manufactured by Skyepharma; Flovent[®] fluticasone, manufactured by GlaxoSmithKline (GSK), was included as a second fluticasone comparator for all primary, secondary and tertiary endpoints and is hereafter referred to as GSK FP.

Safety endpoints were the incidence of treatment-emergent adverse events, changes in laboratory tests, vital signs and 12-lead, single electrocardiogram (ECG) recordings.

Patients

Male and female patients aged 12 years and older, with a history of asthma for at least 12 months, as defined by the National Asthma Education and Prevention Program criteria⁹, were eligible to participate in the study. Patients had to have been using inhaled corticosteroids (fluticasone or equivalent) at a dose less than 500 µg per day for at least 4 weeks and be considered suitable for combination ICS/LABA therapy. In addition, patients' FEV₁ had to be 40% to 80% of predicted normal FEV₁ values following appropriate withholding of bronchodilator medication. Reversibility (as measured by FEV₁) after inhalation of a short-acting bronchodilator, such as albuterol via HFA pMDI or a nebuliser, had to be demonstrated within 12 months of the screening visit. During any seven consecutive days of the run-in period, eligible patients had to use two or more inhalations per day of rescue albuterol for at least 3 days, and the patient had to demonstrate one of the following asthma symptoms: at least one night with sleep disturbance or at least 3 days with asthma symptoms.

Interventions and randomisation

All treatment regimens were inhaled in the morning and evening. Patients received GSK FP (HFA pMDI 50 µg/inhalation) at one of the following two dosages during the run-in period, depending on their steroid usage prior to screening: 100 µg/day GSK FP for patients previously using ≤250 µg/day fluticasone or equivalent, and 200 µg/day GSK FP for patients previously using >250 µg/day fluticasone or equivalent. Patients were given training on the correct use of the inhaler by the study site staff. At randomisation, patients were allocated to receive either fluticasone/formoterol 250/10 µg, SKP FP 250 µg, or GSK FP 250 µg twice daily. To ensure that the blinding was maintained, all patients also received a placebo inhaler. The study site primed the pMDI canisters prior to baseline (week 0), week 4, and week 8 visits.

Albuterol/salbutamol (hereafter referred to as albuterol) pMDI was provided as rescue medication during both the run-in and treatment period.

Efficacy assessments

Pulmonary function testing was performed at the screening visit and at each study visit during the treatment period at the following time points: within 30 minutes prior to the morning dose of randomised study drug and at 30 minutes, 1, 2, and 4 hours after dosing.

In a subset of patients participating in the 12-hour serial spirometry sub-study, pulmonary function tests were also performed at 6, 8, 10, and 12 hours following the morning dose at week 0, 2, and 12 (or final visit, if the patient discontinued earlier).

At screening, pulmonary function testing was to be postponed until the following day if the patient used a short-acting bronchodilator within 6 hours or a LABA within 24 hours. All other pulmonary function tests were to be postponed to the next day if patients took rescue albuterol within 6 hours or study drug within 12 hours prior to the scheduled pulmonary function assessment.

Pulmonary function test procedures were carried out in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) Guidelines using a standardised spirometer (Micromedical, Model MicroLab 3500). Each patient was to use the same spirometer throughout the study. In addition, patients were issued with a peak flow meter (Micromedical, Model MicroPeak) to record their peak expiratory flow rate (PEFR) twice daily at home.

Asthma exacerbations were reviewed and recorded for each patient at baseline, weeks 2, 4, 8 and the final week. The severity of exacerbations was defined as follows: mild-moderate – pre-dose morning PEFR >30% below baseline on at least two consecutive days, or awakening at night due to asthma for at least two consecutive days, or use of three or more additional rescue albuterol pMDI inhalations per day with respect to baseline for at least two consecutive days; severe – deterioration in asthma requiring additional therapy (e.g. systemic steroid), or emergency visit or hospitalisation due to asthma. An exacerbation of asthma was to be considered as an adverse event if it did not resolve with study drug treatment, including albuterol, and if additional medication was required (e.g. systemic glucocorticosteroids).

On a daily basis throughout the run-in and treatment phase, patients entered the following information into a telephone diary system: number of inhalations for study drug, number of rescue albuterol inhalations, morning and evening PEFR, sleep disturbance scores and asthma symptom scores.

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Sleep disturbance was scored on a scale of zero to four (0 = slept through the night, no asthma; 1 = awoke once during the night because of asthma; 2 = two or more brief awakenings because of asthma; 3 = awake during most of the night because of asthma; 4 = could not sleep at all because of asthma).

Asthma symptoms were scored on a scale of zero to five (0 = no symptoms; 1 = asthma present for one short period during the day; 2 = asthma present for two or more short periods during the day; 3 = asthma present for most of the day but no effect on normal daily activities; 4 = asthma present for most of the day which adversely affects normal daily activities; 5 = asthma so severe that the patient is unable to go to work or school or carry out normal daily activities).

Following randomisation, early discontinuation criteria for patients who experienced worsening asthma ('lack of efficacy') were: severe asthma exacerbation requiring treatment intervention (emergency treatment, hospitalisation, or the use of asthma medication not allowed by study protocol), decrease in pre-dose FEV₁ of more than 20% of pre-dose FEV₁ at the baseline visit (week 0), decrease in morning pre-dose PEFR of more than 25% of mean morning pre-dose PEFR (from the entries in the telephone diary) at the baseline visit (week 0) on more than 3 of 7 days immediately preceding a study visit, excessive use of rescue albuterol pMDI (≥ 12 inhalations/day) on more than 3 of 7 days immediately preceding a study visit, or night awakenings caused by asthma that required rescue albuterol on more than 2 of 7 days immediately preceding a study visit.

Safety assessments

Safety assessments were conducted throughout the run-in and treatment phases and consisted of vital signs, ECGs, adverse event monitoring and clinical laboratory tests. Vital sign measurements and 12-lead ECGs were performed at the start of the run-in, at baseline, at weeks 2, 4, 8 and the final week. Adverse events were reviewed by the investigator at baseline, at weeks 2, 4, 8 and the final week. Samples for clinical laboratory tests (haematology, blood chemistry and urinalysis) were taken at the start of the run-in, baseline and the final week. Patients were followed up by telephone 14 days after the last dose of study drug to evaluate any new or on going adverse events.

Sample size

The study was designed to enrol 125 patients in each of the three treatment groups for a planned total of 375 patients. With 107 patients per treatment group, the study would have 90% power to detect a significant difference between two treatment groups using a two-sided *t*-test with alpha

= 0.05, assuming a difference of 0.2 L with respect to mean change in morning pre-dose FEV₁¹⁰, and a common standard deviation (SD) of 0.45. To account for an approximately 15% dropout rate, 125 patients were planned for each group.

Statistical methods

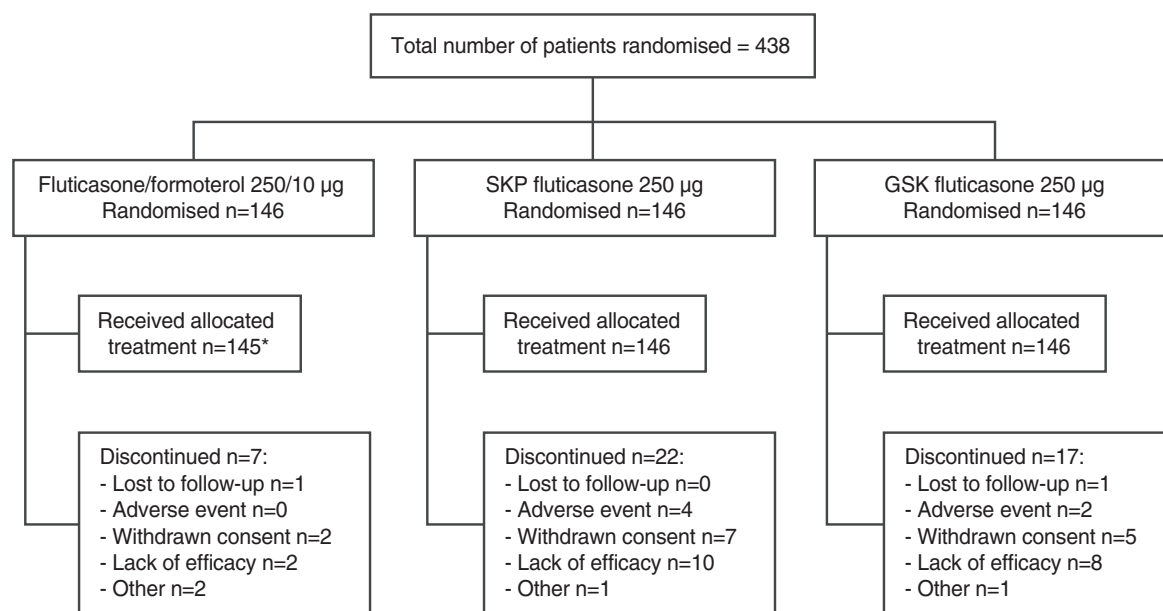
The change from pre-dose FEV₁ at baseline to 2 hours post-dose FEV₁ at week 12 was analysed using an analysis of covariance (ANCOVA) with all treatment groups, study site, and baseline FEV₁ % predicted category (40% to 60% and >60% to 80%) as main effects and baseline FEV₁ as a covariate. The primary analysis was based on the full analysis population, defined as all randomised patients who received at least one inhalation of study drug and who had a pre-dose baseline (week 0) FEV₁, at least one post-baseline pre-dose FEV₁, and at least one post-dose FEV₁. Missing post-dose 2 hour FEV₁ values were imputed using last observation carried forward (LOCF) for the comparison between fluticasone/formoterol versus SKP FP and GSK FP. Sensitivity analyses were performed using the per protocol (PP) population and a mixed model repeated measures analysis to assess the effect of missing data at 2 hours post-dose at week 12. The PP population was defined as patients who fulfilled the inclusion and exclusion criteria of the protocol and received the correct study drug according to the randomisation schedule.

If fluticasone/formoterol was statistically superior to SKP FP for the primary endpoint, the secondary efficacy endpoints were evaluated with a hierarchical testing scheme. The secondary endpoints for fluticasone/formoterol versus SKP FP or GSK FP were tested in the following order: change from baseline to final week in morning PEFR, evening PEFR, rescue medication use, asthma symptom scores, symptom-free days, rescue medication-free days, asthma control days, proportion of patients with asthma exacerbations, change from baseline to final week in sleep disturbance scores and awakening-free nights. If significance was not achieved for higher ranked endpoints, subsequent endpoints were tested in an exploratory manner.

Tertiary endpoints included asthma exacerbations, asthma symptom scores, sleep disturbance scores and rescue medication use from baseline to weeks 1 through 12. Tertiary endpoints were not included in the ranked endpoints for the hierarchical analysis.

Symptom based endpoints (asthma symptom scores, sleep disturbance scores and rescue medication) and other lung function parameters were analysed using a similar ANCOVA model to the primary endpoint.

The proportion of patients with asthma exacerbations was analysed using logistic regression. Differences between fluticasone/formoterol and each comparator for the



*Patient 1020001 was randomised to fluticasone/formoterol. From Week 0 to Week 8, the patient received fluticasone/formoterol. At Week 8, the treatment pack received was SKP fluticasone. This patient completed the study; therefore, the patient received SKP fluticasone instead of fluticasone/formoterol for the last 4 weeks of the study. The patient was analysed as randomised.

Figure 2. Patient flow diagram.

percentage of days with asthma exacerbations were assessed using van Elteren's method for combining Wilcoxon rank sum test results from independent strata, stratified by baseline FEV₁ % predicted (40% to 60% or >60% to 80%). Time to first asthma exacerbation was analysed using a log rank test. The annualised rate of asthma exacerbations was analysed *post hoc* using a negative binomial model. Time to first asthma exacerbation was also analysed using a proportional hazards model.

A sub-group analysis was performed to analyse the effect of the % predicted FEV₁ category (either 40% to 60%, or >60% to 80% at baseline) on the mean change in FEV₁ from morning pre-dose to 2 hours post-dose at week 12 using the same ANCOVA model as the primary endpoint, but without baseline FEV₁ % predicted category as a main effect. The full analysis population was used for the analysis. LOCF was used for missing values.

In a sub-set of patients, 12-hour serial spirometry was performed at 30 minutes, 1, 2, 4, 6, 8, 10 and 12 hours after dosing at week 0, 2 and 12 to analyse the area under the curve (AUC) for FEV₁. The trapezoidal method was used to calculate AUCs and actual measurements were used where possible. The AUCs were based upon the change from pre-dose baseline FEV₁ and were time-normalised.

Safety analyses were based on the patients included in the safety population, defined as all randomised patients who received at least one inhalation of study drug.

Patients received instructions and training with placebo-filled inhalers regarding the use of pMDI during the

screening visit; pMDI technique and dosing procedures were reviewed at each study visit. Patients were instructed to return all used and unused study drug to the site for drug accountability at each study visit. The amount of study drug dispensed to each patient was recorded. The patients were asked to indicate the number of inhalations for each of the pMDI devices and the dose indicators on the inhaler actuators were checked to confirm this. Patients who were less than 70% compliant with their fluticasone medication during the run-in period or study drug during the treatment period were to be withdrawn from the study. In the case of overdose, the treatment was stopped immediately and patients were treated symptomatically.

Results

A total of 438 patients were randomised to one of the three treatment groups, giving 146 patients in each treatment arm (Figure 2).

Demographic characteristics were similar across the treatment groups (Table 1). Mean age was 42 years old and the average duration of asthma was 16 to 17 years. Thirteen percent of patients were adolescents. Approximately two-thirds of patients in each treatment group reported baseline FEV₁ % predicted values between >60% and 80% and approximately one third reported values between 40% and 60%. All patients included in the study were required to be prior ICS users and 23% of

Table 1. Patient baseline characteristics – safety/full analysis population.

Characteristic	Description	Treatment group			Overall
		Fluticasone/formoterol 250/10 µg b.i.d.	SKP fluticasone 250 µg b.i.d.	GSK fluticasone 250 µg b.i.d.	
Sex, <i>n</i> (%)	Female	87 (59.6)	95 (65.1)	100 (68.5)	282 (64.4)
	Male	59 (40.4)	51 (34.9)	46 (31.5)	156 (35.6)
Ethnic origin, <i>n</i> (%)	White/Caucasian	114 (78.1)	110 (75.3)	114 (78.1)	338 (77.2)
	Black	3 (2.1)	4 (2.7)	1 (0.7)	8 (1.8)
	Asian	1 (0.7)	1 (0.7)	0 (0.0)	2 (0.5)
	Hispanic	23 (15.8)	29 (19.9)	25 (17.1)	77 (17.6)
	Other	5 (3.4)	2 (1.4)	6 (4.1)	13 (3.0)
Age, years	Mean (SD)	41.2 (16.99)	42.1 (16.83)	42.8 (16.88)	42.0 (16.87)
	Median	42.5	44.5	46.0	44.0
	Min–Max	12.0–81.0	12.0–73.0	12.0–75.0	12.0–81.0
FEV ₁ % predicted ^a at baseline	Mean (SD)	63.9 (11.28)	63.1 (11.32)	63.4 (11.14)	63.5 (11.23)
	Median	65.0	63.0	65.0	65.0
	Min–Max	40.0–92.0	39.0–84.0	39.0–83.0	39.0–92.0
FEV ₁ (L) at baseline ^b	Mean (SD)	1.999 (0.5227)	1.935 (0.5399)	1.934 (0.5636)	1.956 (0.5419)
	Median	1.935	1.885	1.860	1.895
	Min–Max	0.83–3.29	0.91–3.44	0.75–3.39	0.75–3.44
Duration of asthma ^c , years	Mean (SD)	16.3 (13.57)	15.9 (12.95)	17.1 (13.25)	16.5 (13.24)
	Median	11.4	12.3	14.4	12.4
	Min–Max	1.0–65.4	1.1–63.4	1.2–68.8	1.0–68.8

^aBased on standardised predicted FEV₁ values.^bBaseline was the last available value prior to dosing at the baseline/week 0 visit.^cDuration of asthma calculated as (date of screening visit from demographics case report form - asthma diagnosis date)/365.25 and rounded to one decimal place.

patients previously received ICS and LABA combination therapy for asthma.

Among the 438 patients, 52 were randomised at sites in the United States of America, 169 were randomised at European sites, and 217 were randomised at Latin American sites. Of the 438 randomised patients, 392 (89.5%) completed the study and 46 (10.5%) discontinued from the study. Fewer patients prematurely discontinued from the study in the fluticasone/formoterol group (seven patients; 4.8%) compared to the SKP FP (22 patients; 15.1%) and GSK FP (17 patients; 11.6%) groups. The main reason for premature discontinuation was loss of asthma control in 16 patients overall (one patient in the fluticasone/formoterol group, nine patients in the SKP FP group and six patients in the GSK FP group). One patient in the fluticasone/formoterol group and one patient in the GSK FP group were lost to follow up. Two patients were discontinued from the study after receiving concomitant medication; one after receiving prednisone and one after receiving Seretide*. Thirty-six patients had major protocol violations. Of these, 26 patients had met the pre-specified discontinuation criteria, but were not actually discontinued. These patients were evenly distributed across the treatment groups and none of the major protocol violations were expected to affect the conclusions of the study. All 438 patients were included in the full analysis population and the safety population.

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Lung function tests

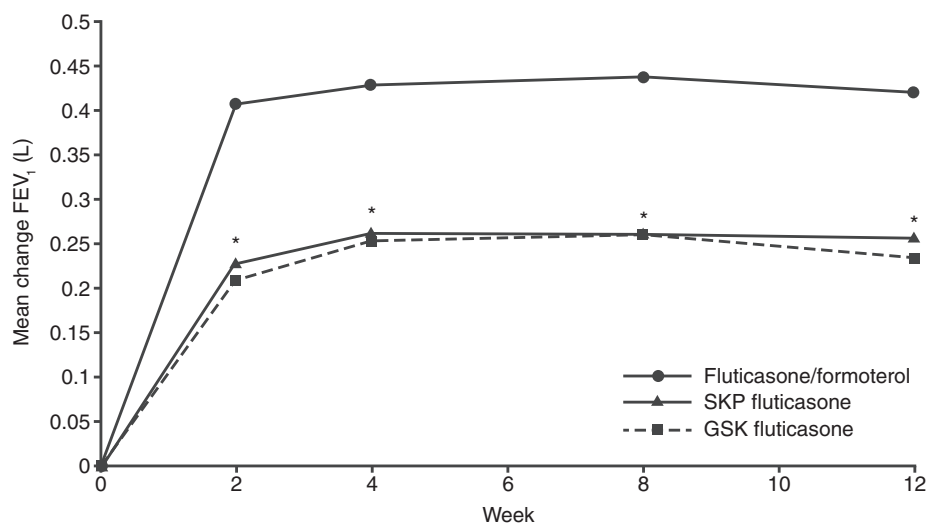
Fluticasone/formoterol was statistically significantly superior to SKP FP (least-squares [LS] mean difference = 0.161 L, 95% CI: 0.078, 0.245, $p < 0.001$, Figure 3) for the primary endpoint of the study: mean change in FEV₁ from baseline pre-dose to 2 hours post-dose at week 12 (baseline FEV₁ values were 2.0 L for fluticasone/formoterol and 1.9 L for SKP FP). This result was confirmed by the statistical sensitivity analyses.

Fluticasone/formoterol also demonstrated superior efficacy against GSK FP (LS mean difference = 0.185 L, 95% CI: 0.102, 0.268, $p < 0.001$) for mean change in FEV₁ from a pre-dose baseline value of 1.9 L to 2 hours post-dose at week 12 (Figure 3).

The differences between the fluticasone/formoterol treatment group and the SKP FP and GSK FP groups in the mean change in FEV₁ from baseline to 2 hours post-dose were also statistically significant at weeks 2, 4, and 8 (Figure 3).

Tertiary analyses showed that the fluticasone/formoterol combination provided numerically greater improvements in FEV₁ from pre-dose values at baseline to pre-dose values at week 12, indicating that the benefits of fluticasone/formoterol were evident over the dosing interval (Table 2).

The change between baseline and final week for morning PEFR was the first ranked secondary endpoint. Mean baseline values were 311 L/min for the



* $p \leq 0.05$ versus fluticasone/formoterol treatment group.
Doses were fluticasone/formoterol 250/10 µg b.i.d. or SKP fluticasone 250 µg b.i.d. or GSK fluticasone 250 µg b.i.d.

Figure 3. FEV₁ (L): mean change from pre-dose at baseline to 2 hours post-dose at weeks 2, 4, 8 and 12 – full analysis population using LOCF.

Table 2. Change in FEV₁ (litres) from pre-dose at baseline to pre-dose at week 12 – full analysis population using last observation carried forward (LOCF).

	Treatment Group		
	Fluticasone/formoterol 250/10 µg b.i.d. N = 146	SKP fluticasone 250 µg b.i.d. N = 146	GSK fluticasone FP 250 µg b.i.d. N = 146
n	145	145	144
Least squares mean	0.208	0.156	0.159
95% CI	(0.121, 0.294)	(0.071, 0.241)	(0.072, 0.246)
Difference (95% CI)		0.052 (–0.037, 0.141)	0.049 (–0.041, 0.138)
p-value		0.253	0.285

Analysis by ANCOVA with treatment, baseline pre-dose FEV₁ and baseline % predicted FEV₁ category as covariates and centre as a random effect.

fluticasone/formoterol group, and 307 L/min for the SKP FP and GSK FP groups. The effects of fluticasone/formoterol (44 L/min) exceeded those of SKP FP (33 L/min; LS mean difference = 11.6 L/min, 95% CI: –2.06, 25.17, $p = 0.096$) and GSK FP (23 L/min, LS mean difference = 21.2 L/min, 95% CI: 7.76, 34.64, $p = 0.002$; not considered significant as per gate-keeper approach). However, as the difference between fluticasone/formoterol and SKP FP was non-significant, all other endpoints were tested in an exploratory manner only.

Mean baseline values for evening PEFR were 318 L/min for the fluticasone/formoterol group, 314 L/min for the SKP FP group, and 312 L/min for the GSK FP group. The mean increase in evening PEFR from baseline to final week was numerically greater in the fluticasone/formoterol treatment group (43 L/min) compared to the SKP FP (35 L/min, LS mean difference = 8.0, 95% CI: –4.94, 21.04, $p = 0.224$) and GSK FP (21 L/min, LS mean difference = 22.2, 95% CI: 9.37, 35.08, $p < 0.001$; not considered significant as per gate-keeper approach) fluticasone alone groups.

Symptom based data

Asthma symptom scores

The mean asthma symptom scores reported at baseline were low (0.9 to 1.0) in patients with moderate-to-severe asthma. The mean decrease in asthma symptom scores from baseline to final week was numerically greater in the fluticasone/formoterol treatment group compared to the SKP FP and GSK FP treatment groups (Table 3).

Sleep disturbance scores

On a scale of zero to four, the mean baseline score averaged over the 7 days prior to the first dose of study drug was under one in all three treatment groups. The mean decrease from baseline to final week was significantly greater in the fluticasone/formoterol treatment group compared to the SKP FP ($p = 0.036$; not considered significant as per gate-keeper approach) or GSK FP groups ($p = 0.004$; not considered significant as per gate-keeper approach) (Table 3).

Table 3. Symptom-based efficacy results – full analysis population.

		Treatment Group		
	Statistic ^a	Fluticasone/formoterol 250/10 µg b.i.d. N= 146	SKP fluticasone 250 µg b.i.d. N= 146	GSK fluticasone 250 µg b.i.d. N= 146
Asthma symptom scores ^b : mean change from baseline to final week				
	<i>n</i>	144	143	144
Baseline ^b	Mean	1.0	0.9	1.0
Change from baseline to final week	LS mean (SE)	−0.683 (0.043)	−0.574 (0.043)	−0.631 (0.044)
Difference from FP/FORM	LS mean (SE)		−0.109 (0.059)	−0.052 (0.058)
	95% CI		−0.224, 0.007	−0.166, 0.063
	<i>p</i> -value		0.065	0.375
Sleep disturbance scores ^b : mean change from baseline to final week				
	<i>n</i>	145	141	144
Baseline ^b	Mean	0.611	0.668	0.713
Change from baseline to final week	LS mean (SE)	−0.583 (0.030)	−0.497 (0.030)	−0.465 (0.030)
Difference from FP/FORM	LS mean (SE)		−0.086 (0.041)	−0.118 (0.040)
	95% CI		−0.166, −0.006	−0.197, −0.039
	<i>p</i> -value		0.036*	0.004*
Use of rescue medication (inhalations/day): mean change from baseline to final week				
	<i>n</i>	145	143	145
Baseline ^b	Mean	2.5	2.5	2.7
Change from baseline to final week	LS mean (SE)	−1.845 (0.125)	−1.467 (0.125)	−1.535 (0.128)
Difference from FP/FORM	LS mean (SE)		−0.378 (0.170)	−0.310 (0.168)
	95% CI		−0.712, −0.045	−0.640, −0.021
	<i>p</i> -value		0.026*	0.066

LS = least squares; SE = standard error; CI = confidence interval; FP/FORM=Fluticasone/formoterol.

Final week is defined as the last 7 days on study drug.

^aLS mean, SE, CI, and *p*-value are from ANCOVA with factors for treatment group, site, and baseline FEV₁ % predicted category, with baseline asthma symptom scores as a continuous covariate.

^bBaseline was the average calculated in the last 7 days prior to the first dose of study drug.

*Not considered significant as per gatekeeper approach.

Rescue medication use and rescue medication-free days

Rescue medication use was significantly decreased in the fluticasone/formoterol treatment group compared to the SKP FP group ($p=0.026$; not considered significant as per gate-keeper approach) (Table 3) and numerically lower compared to the GSK FP group ($p=0.066$).

At baseline, the mean percentage of rescue-medication-free days was 32% in the fluticasone/formoterol and GSK FP groups and 31% in the SKP FP group. The mean increase in percentage of rescue medication-free days from baseline to final week was numerically greater in the fluticasone/formoterol treatment group (mean [SD] change from baseline = 48.8% [39.82]) compared to the SKP FP (40.0% [42.18], $p=0.246$) and GSK FP (42.0% [40.74], $p=0.116$) group.

Asthma control days

An asthma control day was defined as a day with no asthma symptoms, no awakening due to asthma, and no rescue medication use. At baseline, the mean percentage of asthma control days was 20% for the fluticasone/formoterol group, 18% for the SKP FP group and 16% for the

GSK FP group. The mean increase in percentage of asthma control days from baseline to final week was numerically greater in the fluticasone/formoterol treatment group (mean [SD] change from baseline = 54.9% [39.74]) compared to the SKP FP (44.6% [43.44], $p=0.294$) and GSK FP (51.5% [39.73], $p=0.771$) groups.

Symptom-free days

At baseline, the mean percentage of symptom-free days was 33% in the fluticasone/formoterol group and SKP FP groups, and 30% in the GSK FP group. The mean increase in percentage of symptom-free days from baseline to final week was numerically greater in the fluticasone/formoterol treatment group (mean [SD] change from baseline = 50.7% [38.20]) compared to the SKP FP (40.8% [40.87], $p=0.100$) and GSK (47.6% [40.99], $p=0.507$) groups.

Awakening-free nights

At baseline, the mean percentage of awakening-free nights was 50% in the fluticasone/formoterol group, 49% in the SKP FP group, and 47% in the GSK FP group. Overall, the

Table 4. Number (%) of patients with treatment-emergent adverse events reported for >2.0% of patients in any treatment group – safety population.

System organ class preferred term	Number (%) of patients		
	Fluticasone/formoterol 250/10 µg b.i.d. N= 146	SKP fluticasone 250 µg b.i.d. N= 146	GSK fluticasone 250 µg b.i.d. N= 146
Any event	48 (32.9)	58 (39.7)	59 (40.4)
Gastrointestinal disorders	2 (1.4)	10 (6.8)	6 (4.1)
Gastritis	0 (0.0)	4 (2.7)	0 (0.0)
Infections and infestations	29 (19.9)	31 (21.2)	41 (28.1)
Influenza	8 (5.5)	4 (2.7)	8 (5.5)
Nasopharyngitis	7 (4.8)	9 (6.2)	9 (6.2)
Pharyngitis	4 (2.7)	5 (3.4)	6 (4.1)
Rhinitis	4 (2.7)	6 (4.1)	4 (2.7)
Bronchitis acute	1 (0.7)	4 (2.7)	4 (2.7)
Urinary tract infection	1 (0.7)	3 (2.1)	1 (0.7)
Upper respiratory tract infection	0 (0.0)	1 (0.7)	3 (2.1)
Musculoskeletal and connective tissue disorders	7 (4.8)	6 (4.1)	2 (1.4)
Back pain	3 (2.1)	4 (2.7)	0 (0.0)
Nervous system disorders	4 (2.7)	6 (4.1)	8 (5.5)
Headache	3 (2.1)	4 (2.7)	3 (2.1)
Respiratory, thoracic and mediastinal disorders	12 (8.2)	10 (6.8)	14 (9.6)
Rhinitis allergic	8 (5.5)	1 (0.7)	7 (4.8)
Cough	2 (1.4)	2 (1.4)	3 (2.1)
Dysphonia	1 (0.7)	3 (2.1)	0 (0.0)

Adverse events were coded using MedDRA version 9.0. At each level of summation (preferred term, system organ class and overall), each patient was counted only once. Percentages are based on the number of patients in the population for each treatment group.

mean increase in percentage of awakening-free nights from baseline to final week was numerically greater in the fluticasone/formoterol treatment group (mean [SD] change from baseline = 45.3% [37.59]) compared to the SKP FP (39.0% [40.42], $p=0.863$) and GSK FP (38.8% [43.51], $p=0.607$) groups.

Asthma exacerbations

The proportion of patients with asthma exacerbations was numerically lower in the fluticasone/formoterol group ($n=54$, 37.0%) versus the SKP FP ($n=71$, 48.6%; odds ratio = 1.61, $p=0.367$) and GSK FP groups ($n=75$, 51.4%; odds ratio = 1.80, $p=0.087$). The mean percentage of days with an asthma exacerbation was also numerically smaller in the fluticasone/formoterol treatment group compared to the SKP FP and GSK FP treatment group (Figure 4). Compared with the fluticasone/formoterol group, annualised exacerbation rates were 67% higher in the SKP FP group (rate ratio 1.67, 95% CI: 1.087, 2.576, $p=0.019$) and 71% higher in the GSK FP group (rate ratio 1.71, 95% CI: 1.136, 2.570, $p=0.01$) (Figure 4).

Patients in the fluticasone/formoterol treatment group had a significantly longer time to first asthma exacerbation compared to GSK FP ($p=0.017$), whilst the time to first exacerbation was delayed but not significantly so compared to SKP FP ($p=0.057$) (Figure 5).

Sub-group analysis

FEV₁ % predicted category

A pre-specified sub-group analysis was performed to analyse mean change in FEV₁ from baseline pre-dose to 2 hours post-dose at endpoint (week 12) by baseline FEV₁ predicted category (40% to 60% and >60% to 80%).

The mean change in FEV₁ from morning pre-dose at baseline to 2 hours post-dose at week 12 was analysed for patients with a baseline FEV₁ predicted value of 40% to 60% and for patients with a baseline of >60% and up to 80%. In both categories, fluticasone/formoterol was demonstrated to be statistically significantly superior to SKP FP (LS mean: 0.222 L, 95% CI: 0.062, 0.382, $p=0.007$ for the 40% to 60% category and LS mean: 0.152 L, 95% CI: 0.047, 0.257, $p=0.005$ for the >60% to 80% category).

12-Hour serial FEV₁ AUC (AUC sub-population)

In a subset of 254 patients, 12-hour serial spirometry was performed at week 0 (after first dose), week 2 and week 12. The mean 12 hour FEV₁ AUC of the fluticasone/formoterol treatment group was numerically greater than the SKP FP and GSK FP treatment groups at week 0 (Figure 6a), week 2 and week 12 (Figure 6b). The mean FEV₁ AUC treatment differences (averaged over 12 hours) between the fluticasone/formoterol versus SKP FP groups at these visits ranged from 201 to 221 mL, whilst the

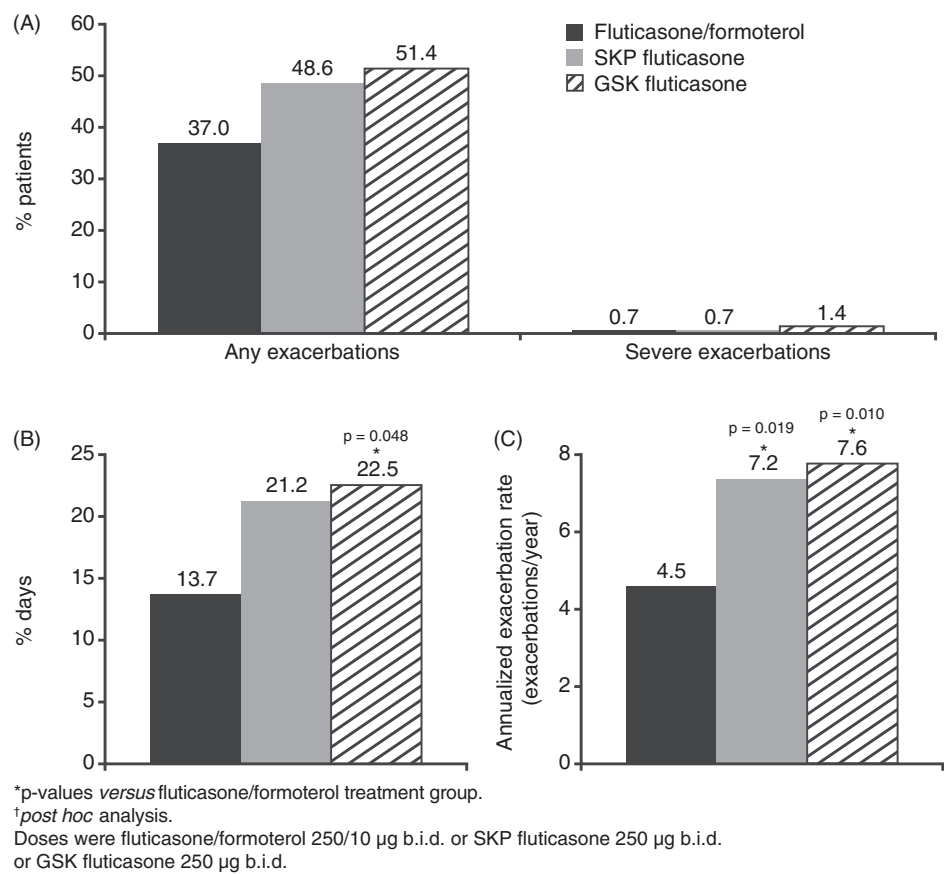


Figure 4. Asthma exacerbations. (a) Proportion of patients reporting exacerbations. (b) Proportion of days with exacerbations. (c) Annualised rate of any reported exacerbations[†] – full analysis population.

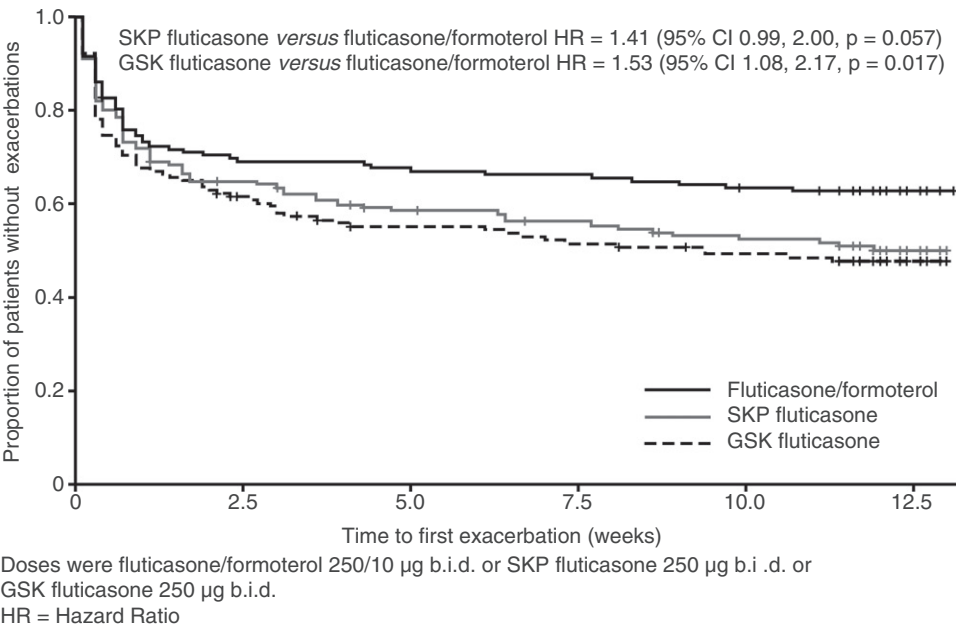
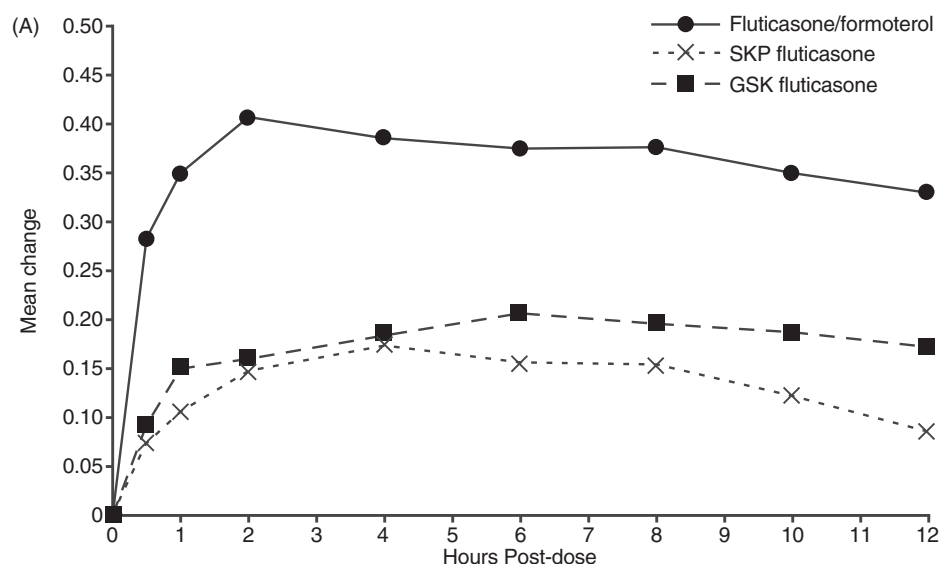
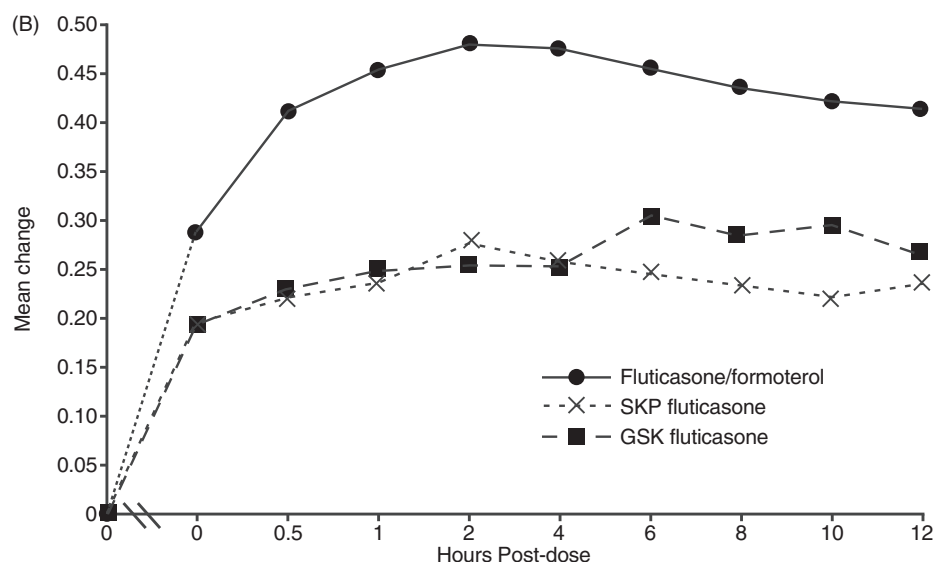


Figure 5. Kaplan-Meier plot: time to first exacerbation – full analysis population.



Note: At 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose, sample sizes were 89, 89, 90, 90, 88, 88, 88, and 88, respectively, in the fluticasone/formoterol group, 77, 76, 77, 77, 76, 76, 76, and 76, respectively, in the SKP fluticasone group, and 86, 87, 87, 87, 84, 83, 83, and 83, respectively, in the GSK fluticasone group.



Note: At 0.5, 1, 2, 4, 6, 8, 10, and 12 hours post-dose, sample sizes were 87, 87, 87, 86, 84, 84, 84, and 84, respectively, in the fluticasone/formoterol group, 73, 74, 74, 74, 69, 69, 69, and 69, respectively, in the SKP fluticasone group, and 80, 81, 81, 81, 76, 76, 76, and 75, respectively, in the GSK fluticasone group.

Figure 6. Twelve-hour serial FEV₁ (L). a. Mean change from baseline pre-dose at week 0 (post first dose); b. mean change from baseline pre-dose at week 12 – AUC population using observed data.

corresponding differences versus GSK FP were 173 to 182 mL. The greatest effect on lung function was observed 2 hours post-dosing with fluticasone/formoterol (Figure 6). Interestingly, there was a very strong correlation between the change from pre-dose FEV₁ at baseline to 2 hours post-dose FEV₁ and FEV₁ AUC₀₋₁₂ ($R = 0.97$). A very similar relationship has been noted in other fluticasone/formoterol studies^{11,12} indicating the utility of the 2 hours

post-dose FEV₁ endpoint as a surrogate for 12-hour treatment effect.

Comparison of fluticasone formulations

Although the main comparison of interest was fluticasone/formoterol versus SKP FP, the effect of GSK FP upon all

endpoints was also evaluated (as was the comparison between the fluticasone/formoterol combination and GSK FP). Results from the spirometric and symptom-based endpoints were generally clinically indistinguishable between SKP FP and GSK FP with respect to their respective comparisons with fluticasone/formoterol combination therapy.

Safety results

Fluticasone/formoterol was generally well tolerated, with a comparable safety profile to the two comparator treatments. The overall incidence of treatment-emergent adverse events ranged from 33% to 40% in all three treatment groups (Table 4). The most frequently reported adverse events were influenza, nasopharyngitis, and allergic rhinitis.

Adverse events were predominantly mild to moderate in severity. The only adverse event considered severe in more than one patient was asthma (one patient [0.7%] in the fluticasone/formoterol treatment group, one patient [0.7%] in the SKP FP treatment group, and two patients [1.4%] in the GSK FP treatment group). No deaths were reported. Serious adverse events were experienced by two GSK FP patients (spontaneous abortion and asthma), neither of which were considered by the investigator to be related to study drug.

Ten patients (one fluticasone/formoterol, five SKP FP, and four GSK FP) had adverse events that led to discontinuation. The only adverse events leading to discontinuation in more than one patient were asthma (one patient in the fluticasone/formoterol group, one in the SKP FP group, and two in the GSK FP group), insomnia (two patients in the SKP FP group), and anxiety (two patients in the SKP FP group). The discontinuations due to asthma adverse events could potentially indicate a lack of efficacy.

In addition, a number of patients in each group discontinued the study due to a pre-defined lack of efficacy, defined as a severe asthma exacerbation requiring treatment, a decrease in pre-dose FEV₁ of more than 20% of pre-dose FEV₁ at the baseline visit, a decrease in morning pre-dose PEFR of more than 25% of mean morning pre-dose PEFR at the baseline visit and excessive use of rescue albuterol (≥ 12 inhalations/day) on more than 3 days in the week before a study visit, and night awakenings caused by asthma that required rescue albuterol on more than two nights in the week before a study visit. Two patients in the fluticasone/formoterol group, ten in the SKP FP group and eight in the GSK FP group discontinued according to this definition of lack of efficacy.

No clinically meaningful differences in laboratory parameters, vital signs or ECG results were observed between treatment groups.

Discussion

This was a randomised, double-blind study, which provides support for the added benefit available from fluticasone/formoterol in those patients whose asthma is uncontrolled on ICS monotherapy alone. Fluticasone/formoterol 250/10 µg twice daily was superior to its ICS component, SKP FP 250 µg twice daily, for the primary endpoint, mean change in FEV₁ from the pre-dose value at baseline to the 2 hour post-dose value at week 12. Results for the 2 hour FEV₁ endpoint and FEV₁ AUC at week 12 (both measured as the change from baseline FEV₁ at week 0) correlated strongly, a finding previously noted in other fluticasone/formoterol studies. This indicates that the 2 hour post-dose endpoint is a useful surrogate for the more commonly used 12-hour serial measure, which is burdensome to both patients and investigators. Furthermore, fluticasone/formoterol was superior to GSK FP 250 µg twice daily, for the mean change in FEV₁ from the pre-dose value at baseline to the 2 hour post-dose value at week 12.

Due to the hierarchical testing scheme employed, confirmatory statistical testing ceased at the level of the first secondary endpoint, the change in morning PEFR, as the difference between fluticasone/formoterol and SKP fluticasone was not statistically significant. However, results from multiple other secondary and tertiary endpoints supported the primary endpoint findings and demonstrated greater effects with fluticasone/formoterol 250/10 µg twice daily compared to SKP FP: numerical benefits in favour of fluticasone/formoterol treatment over SKP FP were observed for asthma control days, sleep and symptom scores, rescue medication use, asthma exacerbations and PEFR.

Although the main comparison of interest was fluticasone/formoterol versus SKP FP, treatment effects for SKP FP and GSK FP were generally clinically indistinguishable.

From a safety perspective, fluticasone/formoterol was well tolerated in adolescent and adult patients with moderate-to-severe asthma and the adverse event profile was similar to that in patients treated with fluticasone monotherapy, and comparable to those previously reported with other ICS-LABA combination therapies^{13,14}. These data provide further support for the addition of LABA treatment to ICS in those patients whose asthma is uncontrolled on ICS monotherapy alone.

Conclusion

Results from this study demonstrate that fluticasone/formoterol 250/10 µg twice daily provides superior efficacy compared to fluticasone alone for the management of moderate-to-severe asthma. Effects with SKP FP and GSK FP formulations were similar to one another. The safety profile of the combination product was similar to that of fluticasone monotherapy.

Transparency

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Declaration of financial/other relationships

T.P. was an investigator for this study. S.D. is an employee of Mundipharma Research Limited. K.K. is an employee of Skyepharma, who sponsored this study.

CMRO peer reviewers may have received honoraria for their review work. The peer reviewers on this manuscript have disclosed any relevant financial relationships.

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References

- Masoli M, Fabian D, Holt S, Beasley R. Global burden of asthma, a report for the Global Initiative for Asthma. 2004. Available at: <http://www.ginasthma.org> [Last accessed June 2012]
- From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2011. Available at: <http://www.ginasthma.org> [Last accessed June 2012]
- Barnes PJ. Scientific rationale for using a single inhaler for asthma control. *Eur Respir J* 2007;29:587-95
- Stoloff SW, Stempel DA, Meyer J, et al. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004;113:245-51
- Ketchell RI, Jensen MW, Lumley P, et al. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5'-monophosphate in mild asthma. *J Allergy Clin Immunol* 2002;110:603-6
- Luijk B, Kempsford RD, Wright AM, et al. Duration of effect of single-dose inhaled fluticasone propionate on AMP-induced bronchoconstriction. *Eur Respir J* 2004;23:559-64
- Politiek MJ, Boersma M, Aalbers R. Comparison of formoterol, salbutamol and salmeterol in methacholine-induced severe bronchoconstriction. *Eur Respir J* 1999;13:988-92
- Bodzenta-Lukaszyk A, Dymek A, McAulay K, et al. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. *BMC Pulmonary Medicine* 2011;11:28
- National Asthma Education and Prevention Program, National Institute of Health, National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 2. 1997, Publication No. 97-4051
- Bodzenta-Lukaszyk A, Pulka G, Dymek A, et al. Efficacy and safety of fluticasone and formoterol in a single pressurized metered dose inhaler. *Respir Med* 2011;105:674-82
- Nathan RA, D'Urzo A, Blazhko V, et al. Safety and efficacy of fluticasone/formoterol combination therapy in adolescent and adult patients with mild-to-moderate asthma: a randomised controlled trial. *BMC Pulmonary Medicine* 2012;12:67
- Corren J, Mansfield LE, Pertseva T, et al. Efficacy and safety of fluticasone/formoterol combination therapy in patients with moderate-to-severe asthma. *Respir Med* 2013;107:180-95
- Drugs@FDA. Symbicort Summary Basis for Approval. Updated 25 June 2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021929s021lbl.pdf [Last accessed 5 November 2012]
- Drugs@FDA. Advair Diskus 250/50 Summary Basis for Approval. Updated 25 June 2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021077s042lbl.pdf [Last accessed 5 November 2012]