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# Combined Salmeterol/Fluticasone Propionate versus Fluticasone Propionate Alone in Mild Asthma

## A Placebo-Controlled Comparison

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### Abstract

**Background and objective:** Combined therapy with inhaled corticosteroids (ICSs) and long-acting  $\beta_2$ -adrenoceptor agonists (LABAs) is the recommended approach for the treatment of patients with asthma that is uncontrolled on ICSs alone. Additional studies are needed to assess the safety and efficacy of combination treatment with ICSs and LABAs in patients with mild asthma. The aim of this study was to compare the efficacy and tolerability of once-daily salmeterol/fluticasone propionate combination (SFC) with once-daily fluticasone propionate (FP) over a 12-week treatment period in patients with mild persistent asthma.

**Methods:** This was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study carried out in primary care or at a hospital outpatient department and included patients 12–79 years of age with mild persistent asthma ( $n = 458$ ). After a 2-week run-in period, patients were randomized to receive SFC 50  $\mu\text{g}/100 \mu\text{g}$  ( $n = 149$ ), FP 100  $\mu\text{g}$  ( $n = 154$ ) or placebo ( $n = 155$ ) once daily in the morning for 12 weeks. The primary efficacy endpoint was patient-recorded pre-dose mean morning peak expiratory flow (PEF). Other assessments included asthma symptom scores, use of rescue medication and investigator-recorded exacerbations. Lung function was measured and assessed during clinic visits.

**Results:** For the primary efficacy endpoint of mean change in morning PEF, SFC achieved significantly greater increases from baseline than both placebo (difference in adjusted means 23 L/min; 95% CI 15.0, 30.3;  $p < 0.001$ ) and FP (difference in adjusted means 14 L/min; 95% CI 6.3, 21.7;  $p < 0.001$ ). Compared with those who received FP, patients in the SFC group demonstrated significantly greater improvements in mean evening PEF (95% CI 11.7, 28.1;  $p < 0.001$ ), forced expiratory volume in 1 second (95% CI 0.093, 0.257;  $p < 0.001$ ), forced expiratory flow between 25% and 75% of forced vital capacity (95% CI 0.242,

0.617;  $p < 0.001$ ), the percentage of symptom-free days (95% CI 0.34, 0.87;  $p = 0.011$ ), and the percentage of rescue medication-free days (95% CI 0.34, 0.90;  $p = 0.018$ ). During weeks 5–12, 52% of patients in the SFC group achieved 'well controlled' asthma, compared with 42% and 26% of patients in the FP and placebo groups, respectively. Only one patient (receiving placebo) had a severe asthma exacerbation during the study; the frequency of adverse events was similar across the three treatment groups.

**Conclusion:** Once-daily SFC 50 µg/100 µg provided significantly greater improvements in lung function and in asthma symptoms than once-daily FP 100 µg alone in patients with mild persistent asthma. However, twice-daily treatment with either SFC or ICSs plus short acting  $\beta_2$ -adrenoceptor agonists could be required to achieve guideline-defined asthma control in some patients.

## Introduction

Asthma is a chronic inflammatory disease of the airways associated with recurrent symptoms and increased airway responsiveness. Bronchodilators such as inhaled  $\beta_2$ -adrenoceptor agonists reverse and/or inhibit bronchoconstriction and alleviate related symptoms of acute asthma. However, bronchodilators do not address the underlying inflammation, and anti-inflammatory agents such as inhaled corticosteroids (ICSs) are required to reduce airway inflammation and improve airway hyper-responsiveness.<sup>[1]</sup> The modes of action of ICSs and long-acting  $\beta_2$ -adrenoceptor agonists (LABAs) are complementary<sup>[2,3]</sup> and studies have demonstrated that the combination of LABAs and ICSs in patients with persistent asthma provides greater improvements in lung function and symptom control than ICSs alone.<sup>[4-6]</sup> Combined low-dose ICSs and LABAs is the recommended therapy for patients whose symptoms are uncontrolled on low-dose ICS alone (Step 3 of GINA [Global INitiative for Asthma]).<sup>[1]</sup>

The current GINA guidelines define mild persistent asthma as (i) symptoms that are experienced more than once a week but less than once a day; (ii) exacerbations that can affect activity and sleep;

(iii) nocturnal symptoms experienced more than twice a month; (iv) forced expiratory volume in 1 second (FEV<sub>1</sub>) or peak expiratory flow (PEF)  $\geq 80\%$  predicted; and (v) PEF or FEV<sub>1</sub> variability  $< 20\text{--}30\%$ .<sup>[1]</sup> GINA currently recommends assessing and treating patients according to the level of control; however, at the time this study was conducted, GINA recommended classification of patients with asthma according to severity and use of this as the basis for treatment decisions.<sup>[7]</sup> The 2004 GINA report recommended use of the ICS + LABA combination for long-term control and prevention of symptoms in both moderate and severe persistent asthma.<sup>[7]</sup> The current study was designed to assess the efficacy and safety of ICSs + LABAs in mild persistent asthma.

Following a single dose, salmeterol/fluticasone propionate combination (SFC) [Seretide<sup>®</sup>/Advair<sup>®</sup>, GlaxoSmithKline, Stockley Park, UK]<sup>1</sup> has been shown to induce sustained bronchodilation for 20–24 hours in patients with asthma.<sup>[8-10]</sup> Several studies have demonstrated the efficacy of once- or twice-daily fluticasone propionate (FP) [Flixotide<sup>®</sup>/Flovent<sup>®</sup>, GlaxoSmithKline] in patients with persistent asthma.<sup>[11-15]</sup> The current study compares the efficacy and safety of SFC 50 µg/100 µg once daily

1 The use of trade names is for product identification purposes only and does not imply endorsement.

with FP 100 µg once daily or placebo over a 12-week treatment period in patients with mild persistent asthma.

## Patients and Methods

### Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicentre study conducted in nine countries worldwide in a primary-care or hospital outpatient setting. The study was approved by ethics committees for each of the 69 centres and conducted in accordance with the Declaration of Helsinki. An initial 2-week run-in period was followed by a 12-week treatment period and a 2-week follow-up.

### Patients

Eligible patients had a documented history of asthma for at least 6 months, were aged 12–79 years, and had provided written informed consent. Patients were receiving inhaled short-acting  $\beta_2$ -adrenoceptor agonists (SABAs) only and were excluded if they had received ICSs or leukotriene antagonists within 12 weeks of the run-in period. Additional exclusion criteria were: treatment with LABAs, sodium cromoglicate, nedocromil, anticholinergic bronchodilators or methylxanthines within 2 weeks of the run-in period; upper or lower respiratory tract infection within 4 weeks of the run-in period; acute asthma exacerbation within 12 weeks of the run-in period; a smoking history of >10 pack-years; and pregnancy or lactation.

Following the run-in period, during which patients received salbutamol (Ventolin®, GlaxoSmith-Kline) as required, patients eligible for randomization met the following criteria: (i) pre-bronchodilator PEF  $\geq 80\%$  predicted; (ii) daytime asthma symptom score  $\geq 1$  on 3–6 days of the past 7 days; and (iii) either PEF reversibility  $\geq 15\%$  following

inhaled salbutamol 400 µg or mean morning PEF <85% post-salbutamol PEF value in the seven consecutive days prior to the run-in period. Patients excluded from randomization following the run-in period included those with daily symptoms, daily use of rescue salbutamol or emergency-room treatment for asthma.

### Treatments

Treatment with SABAs, other than the rescue medication provided (salbutamol), was discontinued for the duration of the study. Following the run-in period, patients were randomized to receive SFC 50 µg/100 µg, FP 100 µg or placebo once daily via a metered-dose inhaler (MDI) on arising each morning. No asthma medications, other than the study drugs, rescue salbutamol and oral prednisolone for treatment of exacerbations, were permitted.

### Assessments

Daily record cards (DRCs) were issued to each patient on study entry to record the best-of-three morning and evening PEF readings measured using a mini-Wright peak flow metre (Clement Clarke, Harlow, UK), rescue salbutamol use, and daytime and nocturnal symptom score. Daytime symptoms were rated on a scale from 0 (signifying no symptoms) to 5 (signifying severe symptoms). Nocturnal symptoms were rated on a scale from 0 (signifying no symptoms during the night) to 4 (signifying symptoms so severe that the patient did not sleep at all). PEF was measured each morning prior to taking study or rescue medication, and again each evening after salbutamol had been withheld for 6 hours if possible.

A moderate asthma exacerbation was defined as a deterioration in asthma requiring treatment with a short course of oral corticosteroids, based on a morning PEF >30% below the baseline value (defined as the mean of the values over the past 7 days prior to randomization) for  $\geq 2$  consecutive days, or

in the investigator's opinion. Individual courses of oral corticosteroids were classified as separate exacerbations only if they were administered more than 1 week apart. A severe asthma exacerbation was defined as a deterioration in asthma symptoms requiring hospital admission. Patients who experienced more than two asthma exacerbations requiring treatment with oral corticosteroids, or any exacerbation that required hospitalization, were withdrawn from the study.

FEV<sub>1</sub>, forced expiratory flow between 25% and 75% of forced vital capacity (FEF<sub>25-75</sub>), and PEF were assessed during clinic visits (arranged at the same time of day  $\pm$ 3 hours) at the end of the run-in period and after 4, 8 and 12 weeks of treatment. Spirometers (Masterscope® CT, Viasys, Hoechberg, Germany) were provided and regularly calibrated according to American Thoracic Society criteria.<sup>[16]</sup> Patients refrained from use of rescue salbutamol for 6 hours before each clinic visit, if possible.

Asthma control was assessed on a weekly basis from information recorded on the DRCs and data gathered at each clinic visit. 'Well controlled' asthma was defined as a composite measure derived from the treatment goals of GINA and the National Institute of Health guidelines,<sup>[17,18]</sup> as amended in the GOAL (Gaining Optimal Asthma control) study (table I).<sup>[19]</sup> The frequency, causal relationship and severity of adverse events were recorded at each clinic visit.

#### Statistical Analysis

The primary analysis was performed on the intent-to-treat (ITT) population using SAS version 8.0 or later (SAS Institute, Cary, NC, USA). The standard deviation of morning PEF was estimated at 40 L/min. With 150 subjects per group, the study had 90% power to detect a difference of 15 L/min between SFC 50  $\mu$ g/100  $\mu$ g and FP 100  $\mu$ g at a 2-sided 5% level of significance.

**Table I.** Definition of asthma control

Well controlled asthma <sup>a,b</sup>
<b>Two or more of the following three criteria:</b>
Symptom score >1 allowed on only $\leq$ 2 days/week
Rescue salbutamol use $\leq$ 2 days/week and up to a maximum of four occasions per week
Predicted morning PEF $\geq$ 80% every day
AND
<b>All of the following criteria:</b>
No night-time awakenings due to asthma
No exacerbations
No emergency visits
No treatment-related adverse events forcing a change in asthma therapy that led to withdrawal
a Assessed on a weekly basis.
b An individual week was evaluable if data were available for all criteria on at least 5 of the 7 days. Each week was classified as 'well controlled', 'uncontrolled' or 'unevaluable' according to the definitions. If there were fewer than 5 days' data available in 1 week, subjects were classified as 'unevaluable' for that week. A subject was considered to have 'well controlled' asthma if they achieved, during weeks 5–12: 4 controlled weeks out of 4 (in the case of only 4 evaluable weeks of data), 5/5 weeks, 6/6 weeks, 6/7 weeks, 7/7 weeks, 7/8 weeks or 8/8 weeks.
PEF= peak expiratory flow.

Comparisons of FEV<sub>1</sub>, FEF<sub>25-75</sub> and PEF were performed using analysis of covariance (ANCOVA), adjusting for country grouping, age, sex and baseline. Symptom control was categorized according to percentage of symptom-free days (0–25%, >25–50%, >50–75%, >75–<100% and 100%) and evaluated using logistic (proportional odds) regression, adjusting for age, sex and country grouping. Asthma symptom control and 24-hour rescue salbutamol use were compared using the van Elteren extension to the Wilcoxon rank sum test for pairwise comparisons (stratified by country grouping). Confidence intervals (CIs) were calculated using the Hodges-Lehman method.<sup>[20]</sup> For DRC analyses, baseline was defined as the average value in the 7 days prior to randomization. The study had a single primary endpoint; therefore, no adjustments for multiplicity were made.

## Results

### Patient Characteristics

Of 697 patients enrolled, 464 were randomized and 458 were included in the ITT population (figure 1). Baseline demographic characteristics, pulmonary function and DRC data were similar in the three treatment groups (table II). Lung function at baseline clinic visit was characteristic of a population with mild asthma, with percentage predicted PEF and FEV<sub>1</sub> between 94% and 97%.

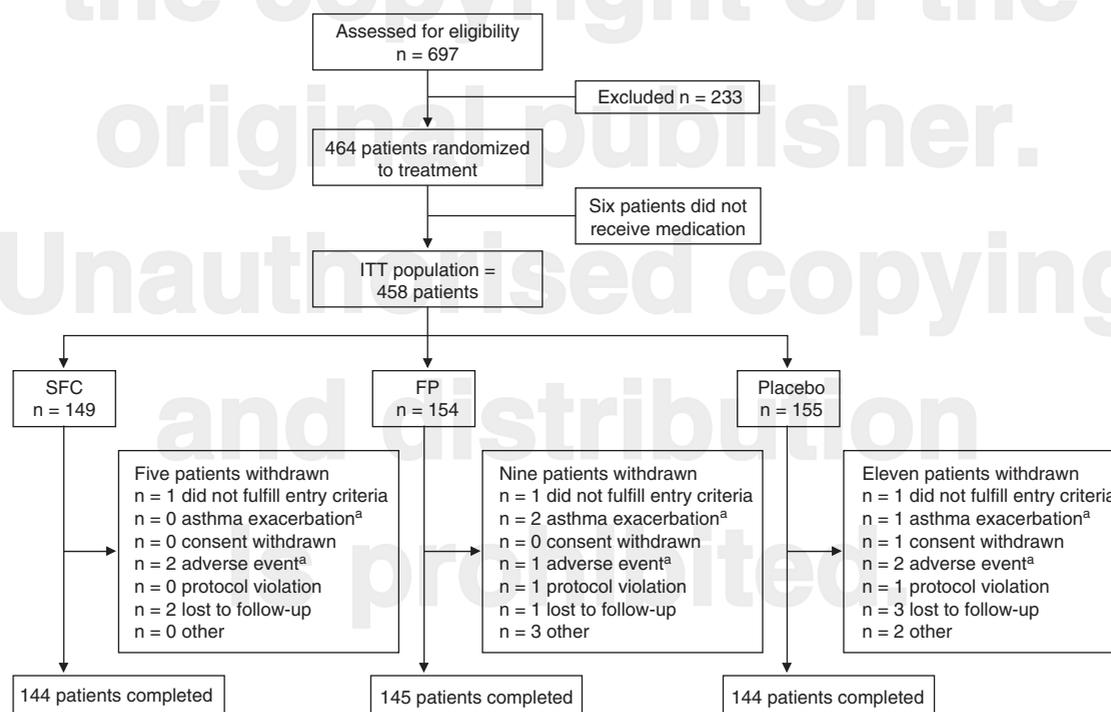
### Mean Morning Peak Expiratory Flow (PEF)

The adjusted mean changes from baseline for morning PEF over weeks 1–12 of the study were 36 L/min, 22 L/min and 13 L/min in the SFC, FP

and placebo groups, respectively (ITT population) [figure 2]. In comparison with FP, SFC also provided a significant increase of 14 L/min (95% CI 6.3, 21.7;  $p < 0.001$ ). Differences in morning PEF were also statistically significant for the SFC group compared with the other treatment groups at each of the other study time points (weeks 1, 2, 3, 4 and 5–12). Compared with placebo, FP and SFC were both associated with significant improvements in mean morning PEF of 9 L/min (95% CI 1.0, 16.2;  $p = 0.026$ ) and 23 L/min (95% CI 15.0, 30.3;  $p < 0.001$ ), respectively.

### Mean Evening PEF

The adjusted mean evening PEF values, derived from DRC recordings throughout the 12-week treatment period, increased from baseline by 38 L/min in



<sup>a</sup> Severe exacerbations were considered adverse events.

**Fig. 1.** Patient flow. **FP** = fluticasone propionate; **ITT** = intent-to-treat; **SFC** = salmeterol/fluticasone propionate combination.

**Table II.** Baseline patient characteristics

Characteristic	Treatment group		
	placebo	FP	SFC
Patients (n)	155	154	149
Sex [n (%)]			
male	83 (54)	67 (44)	69 (46)
female	72 (46)	87 (56)	80 (54)
Age (y) [mean (range)]	33.4 (12–73)	34.0 (12–68)	34.7 (13–73)
Clinic lung function [mean (SD)]			
pre-salbutamol FEV <sub>1</sub> (L)	3.343 (0.970)	3.223 (0.899)	3.185 (0.947)
predicted normal FEV <sub>1</sub> (%)	96.1 (15.3)	96.0 (15.2)	94.3 (14.5)
pre-salbutamol PEF (L/min)	458.7 (109.4)	448.6 (108.3)	441.1 (114.9)
predicted PEF (%)	95.6 (14.6)	96.4 (14.9)	94.1 (14.5)
pre-salbutamol FEF <sub>25–75</sub> (L/s)	2.878 (1.274)	2.838 (1.206)	2.783 (1.255)
Daily record card data			
am PEF (L/min) [mean (SD)]	413.8 (88.9)	409.3 (91.3)	393.6 (90.8)
pm PEF (L/min) [mean (SD)]	431.2 (94.5)	427.1 (99.9)	413.7 (95.4)
median symptom-free days [% (range)]	57.14 (0.0–100)	57.14 (14.3–100)	42.86 (14.3–100)
median rescue-free days [% (range)]	57.14 (0.0–100)	57.14 (0.0–100)	57.14 (14.3–100)

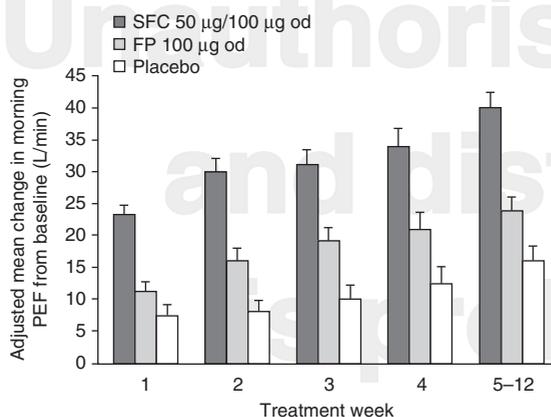
FEF<sub>25–75</sub> = forced expiratory flow at 25–75% forced vital capacity; FEV<sub>1</sub> = forced expiratory volume in 1 second; FP = fluticasone propionate; PEF = peak expiratory flow; SD = standard deviation; SFC = salmeterol/fluticasone propionate combination.

the SFC group, 18 L/min in the FP group and 11 L/min in the placebo group. SFC was associated with a statistically significant improvement compared with both placebo (adjusted mean treatment difference 27 L/min; 95% CI 18.7, 35.1;  $p < 0.001$ ) and FP (adjusted mean treatment difference 20 L/min; 95% CI 11.7, 28.1;  $p < 0.001$ ). There was no statistically

significant difference between the FP and placebo groups.

#### Forced Expiratory Flow between 25% and 75% of Forced Vital Capacity and Forced Expiratory Volume in 1 Second

Baseline FEF<sub>25–75</sub> was lower in the SFC group (2.78 L/s) than in the FP and placebo groups (2.84 and 2.88 L/s, respectively). However, significantly greater improvements at week 12 were observed in the SFC group compared with FP and placebo. The adjusted mean differences between SFC and placebo, and between SFC and FP, were 0.49 L/s (95% CI 0.301, 0.677;  $p < 0.001$ ) and 0.43 L/s (95% CI 0.242, 0.617;  $p < 0.001$ ), respectively. SFC provided similar improvements in FEV<sub>1</sub> at week 12 with significant improvements compared with FP (95% CI 0.093, 0.257;  $p < 0.001$ ) and placebo (95% CI 0.112, 0.276;  $p < 0.001$ ). The adjusted mean changes from baseline in FEV<sub>1</sub> at week 12 were 0.19 L, 0.01 L and –0.01 L in the SFC, FP and placebo groups, respectively.



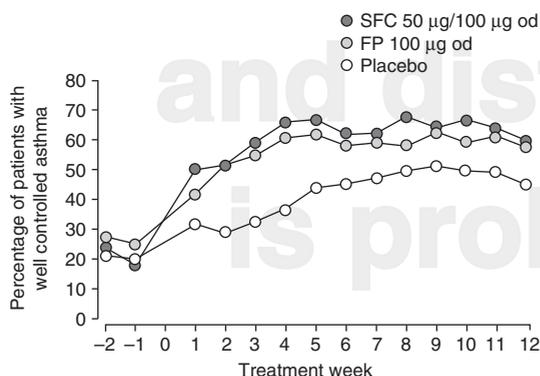
**Fig. 2.** Adjusted mean change from baseline in mean morning peak expiratory flow (PEF) in the intent-to-treat population for salmeterol/fluticasone propionate combination (SFC) once daily (od), fluticasone propionate (FP) od and placebo.

### Symptom Control and Exacerbations

At baseline, patients were free from symptoms on approximately half of all days assessed. During weeks 1–12, the median percentage of symptom-free days increased to 93%, 87% and 79% in the SFC, FP and placebo groups, respectively. The improvements provided by SFC attained significance compared with both placebo (odds ratio [OR] 0.24; 95% CI 0.15, 0.38;  $p < 0.001$ ) and FP (OR 0.55; 95% CI 0.34, 0.87;  $p = 0.011$ ). FP was also associated with a significant improvement compared with placebo (OR 0.44; 95% CI 0.28, 0.68;  $p < 0.001$ ).

Improvements were also observed with SFC for the percentage of rescue medication-free days (OR 0.19; 95% CI 0.12, 0.32;  $p < 0.001$  compared with placebo, and OR 0.56; 95% CI 0.34, 0.90;  $p = 0.018$  compared with FP) and mean 24-hour rescue salbutamol use, although this reduction was significant only when compared with placebo (median difference:  $-0.17$ ; 95% CI  $-0.23, -0.11$ ;  $p < 0.001$ ).

More patients in the SFC group achieved 'well controlled' asthma than patients receiving FP or placebo (figure 3). During weeks 5–12, 52% of patients in the SFC group achieved 'well controlled'



**Fig. 3.** Percentage of patients who achieved 'well controlled' asthma by treatment week for salmeterol/fluticasone propionate combination (SFC) once daily (od), fluticasone propionate (FP) od and placebo.

asthma, compared with 42% in the FP group and 26% in the placebo group (difference in percentage 15.8; 95% CI 5.3, 26.2;  $p = 0.004$  for SFC vs placebo; difference in percentage 25.2; 95% CI 14.6, 35.8;  $p < 0.001$  for FP vs placebo). The difference between the SFC- and FP-treatment groups was not statistically significant.

The proportion of patients with asthma exacerbations was lower in the SFC and FP groups than in the placebo group (both  $p < 0.001$  vs placebo). The incidence of asthma exacerbations requiring oral corticosteroids was low during the treatment period (three patients in the SFC group, eight patients in the FP group [one patient had two exacerbations] and 12 patients in the placebo group [three patients had two exacerbations]).

### Adverse Events

SFC and FP had similar safety profiles. Adverse events were reported in 33% and 37% of patients who received SFC and FP, respectively, and in 48% of patients who received placebo. The most frequently occurring adverse event was nasopharyngitis (7–13% of patients). There was little clinical evidence of oral candidiasis and no positive results were recorded following swab culture. The frequency of adverse events that were considered to be 'possibly related' to study medication was low across all treatment groups (3–5%). Five patients were withdrawn from the study because of adverse events. One patient in the placebo group was withdrawn from the study after 23 days because of a severe asthma exacerbation. The most commonly reported adverse events included one patient in each of the SFC and FP groups with cough and hoarseness; one in the SFC group with nasal and throat irritation, tracheal and chest pain, and cough and facial rash; and two in the placebo group, one with allergic reaction, and one with flushing, nausea, nervousness and tachycardia.

## Discussion

The current study demonstrates the benefit of once-daily SFC 50 µg/100 µg, compared with placebo or once-daily FP 100 µg, in terms of bronchodilation and symptom control in patients with mild persistent asthma, defined in accordance with the GINA guidelines.<sup>[7]</sup> Both SFC and FP provided significant improvements in symptom control compared with placebo but SFC demonstrated superiority over FP in daily symptom scores.

Although previous research has shown that improvements in airway obstruction do not correlate well with an improvement in asthma symptoms,<sup>[21]</sup> the improvements in PEF observed in the current study did parallel an improvement in asthma symptoms. During weeks 5–12 of the treatment period, the proportion of patients whose asthma was assessed as 'well controlled' was 10% higher in those receiving SFC than FP. However, it should be noted that the study was not powered to detect a difference in this endpoint, and it is difficult to draw any conclusions regarding the clinical relevance of this finding. It is important to highlight that, even in the SFC group, nearly half of patients did not achieve well controlled asthma with once-daily administration during the 12-week treatment period. Control is defined by GINA as the absence of exacerbations; absence (or presence twice or less per week) of daytime symptoms (wheeze, dyspnoea and cough); absence of nocturnal waking or activity limitation; and absence (or use twice or less per week) of rescue medication.<sup>[1]</sup> GINA recommends that if three or more of these criteria are not fulfilled during an assessment period of 1 week (or if the patient experiences an exacerbation), the patient should be considered to have uncontrolled asthma and their treatment should be reviewed. The relatively small proportions of patients in this study whose asthma was brought under control was disappointing and suggests that many patients in both groups were undertreated.

The issues raised previously highlight a limitation of the study. Twice-daily FP should be the preferred option in mild asthma because the efficacy of this regimen is well established.<sup>[14,22]</sup> Once-daily FP is not currently indicated for asthma and although FP 500 µg once daily has been reported to be more efficacious than placebo in terms of lung function, symptom score, nocturnal awakenings and rescue use,<sup>[14]</sup> a US FDA review concluded that FP 100–200 µg once daily was no more efficacious than placebo in terms of lung function and is therefore not a recommended treatment for asthma.<sup>[23]</sup> Moreover, twice-daily FP has been shown to be more efficacious than the equivalent total daily dose given once daily.<sup>[14,23,24]</sup> Since publication of the FDA review, FP 250 µg once daily has been shown to provide greater improvements in lung function and symptom control than placebo.<sup>[12]</sup> In the current study, SFC 50 µg/100 µg once daily was chosen as the lowest appropriate dose for the study population, given the recommendation that medication should be started at low doses in mild asthma.<sup>[7]</sup> Therefore, to examine the contribution of the LABA component, FP 100 µg once daily was chosen as the most appropriate comparator regimen. Further research is required to determine whether twice-daily SFC would enable greater proportions of patients with mild asthma to achieve control. To this end, it might be beneficial for future studies comparing SFC in mild asthma to include treatment arms with higher doses of ICSs administered once and twice daily.

The results of this study highlight the need for stepping up treatment to achieve and maintain control, regardless of initial severity.<sup>[1]</sup> Guideline-defined control as an achievable aim is demonstrated by the results of the GOAL study, in which control was achieved in most patients through stepwise escalation of SFC or FP alone.<sup>[19]</sup>

Although the current GINA report recommends assessing and treating patients according to the level of disease control,<sup>[1]</sup> it states that classification of

patients according to severity could still be useful when making decisions about asthma management at the initial assessment. For this reason, the classification used in this study remains relevant to current clinical practice: clinicians could use disease severity at presentation to make decisions regarding the first choice of therapy. Furthermore, there is a need for additional studies assessing the safety and efficacy of ICS + LABA in patients with mild asthma.<sup>[25]</sup>

The long-term benefit of adding a LABA to an ICS in patients with mild asthma has previously been demonstrated by O'Byrne and colleagues in the OPTIMA (Oxis and Pulmicort Turbuhaler® In the Management of Asthma) trial.<sup>[6]</sup> In mild ICS-naïve patients, assessed over a 1-year treatment period, treatment with twice-daily formoterol 4.5 µg plus budesonide 100 µg resulted in greater improvements in lung function compared with budesonide alone; however, there was no difference in exacerbation rates.<sup>[6]</sup> Similar results have been found in a study of SFC 50 µg/100 µg once daily compared with budesonide 400 µg once daily in mild asthma.<sup>[26]</sup> In a recent study, symptom-driven use of beclometasone 250 µg and salbutamol 100 µg administered via a single inhaler had similar efficacy to inhaled beclometasone 250 µg twice daily and regular combination of beclometasone dipropionate and salbutamol from a single inhaler.<sup>[27]</sup> Although regular treatment with beclometasone and salbutamol, and as-needed treatment with beclometasone, were superior to treatment with salbutamol alone with regard to exacerbations in the study by Papi et al.,<sup>[27]</sup> that study was not powered to detect the effect of treatment on asthma exacerbations. Furthermore, as the study duration was 6 months, the long-term effect of treating asthma with as-needed beclo-metasone and salbutamol could not be assessed.<sup>[27]</sup> Additionally, in the Papi et al. study, patients across all four treatment regimens had between 53% and 62% symptom-free days on treat-

ments compared with 93% symptom-free days reported with SFC in the current study. Furthermore, combination therapy with a LABA and an ICS is recognized by physicians as an effective treatment for mild asthma. In an interactive poll, physicians voted a LABA plus an ICS once daily with as-needed rescue salbutamol as their preferred treatment for a patient with mild persistent asthma who wants to reduce his or her current dose of ICS treatment.<sup>[28]</sup>

Overall, as would be expected in a relatively short study of patients with mild asthma, the incidence of asthma exacerbations in the current study was low, with fewer patients in the SFC group than in the FP and placebo groups having exacerbations. Treatment was well tolerated and the incidence of adverse events was low and similar between groups.

## Conclusion

This study demonstrates that over a 12-week period, SFC 50 µg/100 µg once daily provides significantly greater improvements in lung function and in asthma symptoms than FP 100 µg once daily alone in patients with mild persistent asthma. Both treatments were associated with clinical benefits compared with placebo. However, even with once-daily SFC, only half of patients achieved sustained, well controlled asthma. Therefore, although once-daily SFC could be a viable treatment option for some patients with mild persistent asthma, twice-daily treatment, such as twice-daily SFC or ICSs plus SABAs, could be required to achieve guideline-defined asthma control in other patients.

## Acknowledgements

This study was sponsored by GlaxoSmithKline Research and Development Limited (protocol: SAS30023). Drs Jacques and Frith are employees of GlaxoSmithKline Research and Development Limited. Dr Boonsawat has received honoraria for speaking at scientific meetings and courses financed by GlaxoSmithKline and AstraZeneca. Dr Goryachkina has

no conflicts of interest directly related to the content of this study.

The authors would like to thank the following investigators for their assistance with this study:

*Australia:* Dr M. Chia, Dr D. Freiberg, Dr M. Phillips, Dr C. Cooper, Prof. P. Thompson, Dr F. DeLooze, Dr P. Bardin, Dr C. Steinfort, Dr M. Coffey.

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