Maintaining asthma control in persistent asthma: Comparison of three strategies in a 6-month double-blind randomised study

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Summary
In patients controlled with SFC250 Diskus bd, this double-blind, randomised 6-month study compared continuing SFC250 to stepping down to either SFC100 bd or FP250 bd. Six hundred and three patients previously using 1000 \( \mu \)g BDP (or equivalent) daily \(+LABA\) and controlled according to investigator’s judgement were recruited. Patients received SFC250 bd during an 8-week open run-in period. Four hundred and seventy six patients (mean age \( \approx 43 \) years, mean \( \text{FEV}_1 \) \( \approx 2.9 \pm 1.0 \)) who fulfilled the randomisation criterion (‘Well-controlled’ asthma according to the GOAL weekly definition for the last 2 weeks of the run-in period) entered a 24-week treatment period. The statistical hypothesis was based on a non-inferiority of SFC100 or FP250 compared to SFC250. The main criterion was the change from baseline in morning PEF over weeks 1–12 in the per-protocol population. The non-inferiority limit was \(-15 \) L/min. At inclusion, the three treatment groups were well balanced. Mean morning PEF was 476, 470 and 465 L/min in the SFC250, SFC100 and FP250 groups, respectively. The adjusted mean change in morning PEF over weeks 1–12 was \( +1.76 \pm 2.43 \) L/min for SFC250, \( -3.07 \pm 2.32 \) L/min for SFC100 and \( -16.51 \pm 2.46 \) L/min for FP250. SFC100 was at least as effective as SFC250...
Introduction

Asthma is a chronic inflammatory disorder of hyper-responsive airways. Symptoms and airflow limitation can occur when the airways are exposed to a variety of stimuli.1

Control of asthma, as outlined by asthma management guidelines,2–4 is the goal of the treatment.1,2 The international Global Initiative for Asthma (GINA) guidelines5 recommend that the aims of asthma management are to achieve and maintain control of symptoms, to maintain normal activity levels, to maintain pulmonary function as close to normal as possible, to prevent asthma exacerbations, to avoid adverse effects from asthma medications and to prevent asthma mortality. GINA has defined three levels of asthma control (controlled, partly controlled or uncontrolled). The Gaining Asthma Control (GOAL) study4 has shown that control can be achieved in a majority of patients.

Due to the underlying airway inflammation, inhaled corticosteroids (ICS) remain the cornerstone of maintenance treatment medication, but if asthma control is inadequate, adding a long-acting β2-agonist (LABA) has been shown to provide a better clinical benefit than increasing the ICS dose.5,6 In the GOAL study6 salmeterol/fluticasone propionate combination was significantly superior to fluticasone propionate alone in achieving both ‘Well- and Totally controlled’ asthma. In addition, ICSs and LABAs have been shown to have complementary effects when administered together.7

Once asthma control has been achieved, ongoing monitoring is essential in order to assess that control is maintained for a prolonged period (at least 3 months) before considering stepping down to establish the lowest effective dose of treatment.2,3

Few studies were available on the step-down approach at the time the study was initiated. Should the LABA be stopped with the ICS dose maintained, or should the ICS dose be reduced whilst maintaining the LABA? Several studies have shown that salmeterol allows a greater reduction in the dose of ICS when stepping down compared to ICS alone.5,10 A long-term study also demonstrated that a low-dose of ICS (200 µg/day) administered for one year with a LABA did not show any significant difference with a higher dose of ICS alone (800 µg/day) on asthma control and sputum markers of inflammation.11,12

The objective of this prospective double-blind randomised 24-week study in asthmatics whose asthma was “well-controlled” with an ICS/LABA combination, was to compare two step-down strategies (to reduce ICS dosing or to withdraw the LABA) to the ICS/LABA combination strategy maintenance at the same dosing regimen. The methodology was based on a non-inferiority sequential hierarchized design in order to answer the following two questions: (a) is stepping down a viable option when control is achieved and maintained for 3 months and (b) if so, which option is superior: withdrawing the LABA or maintaining the LABA and reducing the ICS dose?

Methods

Study design

This was a prospective multicentre randomised, three-arm, 24-week study. Patients were enrolled into an 8-week run-in period and received an open-label treatment of salmeterol/fluticasone propionate combination (SFC) 50/250 µg twice daily. All previous asthma medications were discontinued at entry into the run-in period, except the short-acting bronchodilators previously used by the patient as rescue medication and antihistamines which could be continued if they were previously used for at least 4 weeks.

Patients whose asthma was assessed as “Well-controlled” over the last 2 weeks of the run-in period, were eligible to enter the treatment period and were randomised to receive twice daily either SFC 50/250 µg (SFC 250), SFC 50/100 µg (SFC 100) or fluticasone propionate 250 µg (FP 250) for a period of 24 weeks. Every morning and evening, patients were required to complete a diary card to record their morning and evening peak expiratory flow (best of three measurements), rescue use and occurrence of symptoms.

The primary endpoint was mean morning peak expiratory flow (PEF) over the first 12 weeks of treatment. Secondary endpoints were morning PEF over the last 12 weeks of the treatment period, evening PEF, daily symptoms, short-acting bronchodilator use as rescue medication, exacerbations, forced expiratory volume in 1 s (FEV1) and asthma control using the GOAL definitions of total and well-control.4 Exacerbations were defined as follows: Moderate exacerbation = worsening of asthma leading to a prescription for a short use of oral corticosteroids.

(treatment difference –4.83 [–12.39; 2.72], p = 0.151) whereas FP250 was not (treatment difference –18.27 [–26.05; –10.49], p < 0.001). Similar results were observed over weeks 13–24 in morning PEF (SFC100–SFC250 = –4.54 ± 3.84, p = 0.238; FP250–SFC250 = –20.11 ± 3.92, p < 0.0001). Secondary endpoints showed a similar pattern. Over weeks 1–12, SFC250 was significantly more effective than FP250 on evening PEF, daily symptoms and bronchodilator use. There was no difference between SFC100 and SFC250. The mean annual rate of moderate exacerbations was 0.16 in both SFC 250 and SFC 100 groups, and 0.21 in FP 250 group (ns, Poisson analysis). All treatments were well tolerated.

Conclusion: In patients achieving asthma control with SFC250, stepping treatment down with SFC100 was at least as effective on lung function and symptoms as continuing SFC250, whereas FP250 was not.

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Severe exacerbation = worsening of asthma leading to hospitalisation.

Patients

The study was approved by the relevant local ethics committee, and all patients gave written informed consent. Male and female subjects, at least 18 years old, with a documented history of asthma (for at least 6 months), whose asthma was controlled with the current treatment (inhaled corticosteroids at a dose of 1000 μg of CFC beclomethasone dipropionate or equivalent and a long-acting β2-agonist at recommended dose) at a stable dose for at least 4 weeks, were enrolled into the run-in period. Patients were excluded from entry into the run-in period if they had a smoking history of 10 pack-years or more, a respiratory tract infection during the last 4 weeks prior to V1 (12 weeks for depot corticosteroids), or any change in their asthma maintenance treatment regarding the suitability of a reduction in maintenance corticosteroids, respiratory tract infection and/or insufficient asthma control according to daily record card or Asthma Control Questionnaire (ACQ) and/or investigator’s judgement; this population was named PPDRC.

At the end of the run-in period, asthma control was assessed and subjects were randomised if they fulfilled the weekly criteria for ‘Well-controlled’ asthma (as defined in GOAL4) during the last 2 weeks of the run-in period.

Key exclusion criteria for entry into the treatment period were changes in asthma medication (excluding study rescue medication), use of oral/parenteral or depot corticosteroids, respiratory tract infection and/or insufficient asthma control according to daily record card or Asthma Control Questionnaire (ACQ) and/or investigator’s judgement regarding the suitability of a reduction in maintenance treatment.

Statistical methods

The methodology was based on a non-inferiority, sequential hierarchized design.

The primary efficacy endpoint was the variation in mean morning PEF over the first 12 weeks of the treatment period compared to the last 2 weeks of the run-in period (baseline). In order to demonstrate non-inferiority and to minimise the type-1 error rate, hierarchized tests were performed: first, each of the step-down strategies (SFC 100 or FP 250) were tested versus SFC 250, based on the two-sided 97.5% confidence interval (97.5% CI), in order to show that SFC 100 and FP 250 were at least as effective as SFC 250. Then a comparison of SFC 100 versus FP 250 was made, based on the 95% CI, if the previous non-inferiorities were established. The non-inferiority margin which was used to compare the lower bound of CI was set to −15 L/min.

The method of Jones et al.13 was used to estimate the sample size needed, based on the variation of morning PEF. The standard deviation (SD) was estimated at 35 L/min in controlled asthmatic adults. With a power of 90% and a two-sided 97.5 % CI, a total of 408 randomised and evaluable subjects (136 per arm) were required.

The safety population consisted of all subjects who had received at least one dose of study medication. The Full Analysis Set (FAS) population consisted of all subjects who had received at least one dose of study medication and for whom the assessment data for at least one assessment criterion was available whilst the Per-Protocol population (PP) consisted of all subjects in the FAS who did not have any major protocol deviations. In addition, a subset of patients was defined within PP population where the assessment of control at inclusion was based only on the DRC only and not on the investigator’s assessment; this population was named PP DRC. This population was defined to provide additional exploratory data on patients with asthma that was, at least, ‘Well-controlled’ at randomisation according to the DRC.

Baseline was defined as the last 2 weeks of the run-in period. Change from baseline in mean morning PEF over weeks 1–12 was analysed using an analysis of covariance (ANCOVA) with treatment group as factor and age, sex and baseline value as covariates.

Since the primary efficacy analysis was a non-inferiority analysis, it was conducted on the PP population. Morning PEF over weeks 13–24, evening PEF, percentages of symptom-free days, percentages of days and nights with no use of rescue bronchodilator and clinic visit FEV₁ were to be analysed in the same way on the FAS if normality assumptions were met, otherwise the Wilcoxon test on ranks was to be used. The total number of exacerbations and the percentage of subjects with at least one exacerbation were analysed using a generalised linear model, assuming a Poisson distribution, adjusted on the on-treatment duration (offset variable) and with age and sex as covariates. Asthma control was assessed for each week and also over the last 8 weeks of each of the two 12-week treatment periods (i.e. weeks 5–12 and weeks 17–24).

Statistical analyses were performed by using SAS version 8.2 (SAS Institute Inc, Cary, NC, USA).

Results

Population

One hundred and twenty-four centres assessed a total of 603 patients for eligibility. At the end of the run-in period, 475 were randomised and included in the treatment phase (Fig. 1). Demographic characteristics were comparable in the three groups; however, in the SFC 250 group, there were more smokers and ex-smokers. Baseline characteristics were similar for all groups for PEF, symptoms and rescue use. Asthma was overall controlled as shown by the high percentage of symptom-free days, nights without awakenings and rescue-free days, however, in the SFC 250 group there was a higher percentage of symptom-free days, nights without awakenings and rescue-free days, however, in the SFC 250 group there was a higher percentage of non-controlled patients at baseline (35.1%) compared to the SFC 100 group (28.6%) (Table 1).

There was a higher proportion of withdrawals during the treatment period in the FP 250 group (20.1%) than in either the SFC 250 (11.3%) or SFC 100 treated group (9.5%). The most frequent reason given for patients in the FP 250 group discontinuing was “lack of efficacy” (33% of withdrawals versus 25% and 11% in SFC 100 and SFC 250, respectively). Withdrawals occurred mainly during the second 12-week treatment period.
Effect of step-down treatment

Primary outcome: Morning PEF (PP population)
SFC 100 was at least as effective as SFC 250 in maintaining morning PEF over 12 weeks, whereas FP 250 was not. Patients treated with the reference treatment SFC 250 had an adjusted mean change in morning PEF over 12 weeks of 1.76 ± 2.43 L/min. The adjusted mean change was −3.07 ± 2.32 L/min in the SFC 100 group and −16.51 ± 2.46 L/min in the FP 250 group. Compared to SFC 250, patients treated
with SFC 250 and FP 250 had a mean difference of $-4.83$ L/min (97.5% CI $[-12.39; 2.72]$, $p = 0.151$) and $-18.27$ (97.5% CI $[-26.05; -10.49]$, $p < 0.0001$), respectively (Fig. 2). This demonstrated the non-inferiority of SFC 100 versus SFC 250 whilst, FP 250 failed to demonstrate non-inferiority versus SFC 250.

**Secondary outcomes (FAS population)**

**Others results on PEF**

The mean morning PEF change from baseline over weeks 13–24 was 5.54 ± 2.76 L/min in the SFC 250 group and 1 L/min ± 2.68 in the SFC 100 group (SFC 100–SFC 250 = $-4.54$ L/min ± 3.84, $p = 0.238$). Conversely in the FP 250 group, morning PEF decreased by $-14.6 ± 2.79$ L/min (FP 250–SFC 250 = $-20.11$ L/min ± 3.92, $p < 0.0001$) (Fig. 3).

A similar pattern was observed on evening PEF over weeks 1–12 and 13–24 with no significant difference between SFC 100 and SFC 250 and a significant difference between FP 250 and SFC 250 in favour of SFC 250 (SFC 100–SFC 250 = $-5.31$ L/min ± 3.42, $p = 0.121$ over weeks 1–12 and $-2.65$ L/min ± 3.92, $p = 0.498$ over weeks 13–24; FP 250–SFC 250 = $-17.43$ L/min ± 3.43, $p < 0.0001$ over weeks 1–12 and $-18.71$ L/min ± 3.43, $p < 0.0001$ over weeks 13–24).

**Symptoms and rescue medication use**

Over the first 12 weeks of the treatment period, the mean percentage of symptom-free days remained stable in both SFC 250 (from 90.2% to 89.4%) and SFC 100 groups (from 94.8% to 93.2%). In the FP 250 group, the percentage of symptom-free days decreased slightly from 91.2% to 85.8%. The difference between FP 250 and SFC 250 was statistically significant ($p = 0.012$) whereas there was no difference between SFC groups. A similar pattern was observed over weeks 5–12 for the percentage of rescue-free days (SFC 250 from 89.6% to 89.0%, SFC50/100 from 95.7% to 93.5% and FP 250 from 93.6% to 88.2%). The difference between FP 250 and SFC 250 was significant ($p = 0.014$). There was no difference between SFC groups.

No difference was found between groups on daily symptoms and rescue use over weeks 13–24. The percentage of nights without awakening remained stable in the three groups with no differences observed over the whole 24-week treatment period.

**Pre-bronchodilator FEV₁ and reversibility**

FEV₁ remained stable in the SFC50/100 group (from 91.2% predicted at baseline to 92.2% at week 24) and slightly increased in the SFC 250 group (from 87.8% predicted at baseline to 90.3%). The difference between the two SFC groups was not significant. The FEV₁ slightly decreased in the FP 250 group with a significant difference versus SFC 250 (FP 250-SFC 250 = $-3.72$% expressed as percentage of predicted values $p = 0.002$ at week 12 and $-4.55$, $p < 0.001$ at week 24).

Reversibility in FEV₁ from baseline decreased in both SFC groups (from 4.9% to 2.8% and from 4.3% to 2.8 % for SFC250

**Table 1** Patient characteristics at baseline (FAS population)

<table>
<thead>
<tr>
<th></th>
<th>FSC 250/50 (n = 154)</th>
<th>FSC 100/50 (n = 156)</th>
<th>FP 250 (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (min–max)</td>
<td>46.5 (18.0–81.0)</td>
<td>43.0 (18.0–75.0)</td>
<td>42.0 (18.0–77.0)</td>
</tr>
<tr>
<td>% Females</td>
<td>48.1</td>
<td>46.2</td>
<td>51.3</td>
</tr>
<tr>
<td>Smokers or ex-smokers</td>
<td>24.7%</td>
<td>21.3%</td>
<td>16.2%</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁ L mean (SD)</td>
<td>2.8 (0.9)</td>
<td>3.0 (1.0)</td>
<td>2.9 (1.0)</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁ (% predicted), mean (SD)</td>
<td>87.8 (18.2)</td>
<td>91.2 (17.8)</td>
<td>90.8 (17.2)</td>
</tr>
<tr>
<td>Reversibility of FEV₁ (%)</td>
<td>4.9</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Morning PEF L/min mean (SD)</td>
<td>465.6 (113.2)</td>
<td>467.9 (111.2)</td>
<td>463.7 (105.1)</td>
</tr>
<tr>
<td>% Symptom-free days, mean (SD)</td>
<td>90.2 (22.1)</td>
<td>94.8 (14.1)</td>
<td>91.2 (21.7)</td>
</tr>
<tr>
<td>% Days without rescue use, mean (SD)</td>
<td>89.6 (25.1)</td>
<td>95.7 (13.2)</td>
<td>93.3 (19.1)</td>
</tr>
<tr>
<td>% Nights without awakening, mean (SD)</td>
<td>97.6 (9.6)</td>
<td>97.7 (8.0)</td>
<td>98.0 (9.5)</td>
</tr>
<tr>
<td>Total control, n (%)</td>
<td>49 (31.8%)</td>
<td>61 (39.1%)</td>
<td>91 (39.6%)</td>
</tr>
<tr>
<td>Well-control, n (%)</td>
<td>51 (33.1%)</td>
<td>57 (36.5%)</td>
<td>49 (31.8%)</td>
</tr>
<tr>
<td>Uncontrolled, n (%)</td>
<td>54 (35.1%)</td>
<td>38 (24.4%)</td>
<td>44 (28.6%)</td>
</tr>
</tbody>
</table>
and SFC100, respectively) and increased from 3.0% to 4.7% in the FP 250 group.

Exacerbations
No subjects experienced a severe exacerbation during the study. The mean annual rate of moderate exacerbations was 0.16 in both SFC 250 and SFC 100 groups, and 0.21 in FP 250 group. A total of 5.8% of the subjects in the SFC 250 group and 4.4% in the SFC 100 group were ‘Totally controlled’ at week 12 and 4% over weeks 17 and 24, 91% had at least two criteria involved in the loss of control based on one criterion of asthma control as supported by the observation that 91% of the subjects in the SFC 100 group and 10.4% of the subjects in the FP 250 group.

Fewer exacerbations were reported in patients of both SFC groups in the PPDRC population than in the same treatment group in the FAS population, whereas the percentage was similar for the FP 250 group in both the FAS and PPDRC populations. The difference between groups was not statistically significant with 3.6% of the subjects reporting at least one exacerbation over 6 months in the SFC 250 group compared with 5.9% and 9.1% for SFC 100 and FP 250 groups, respectively.

Asthma control
At baseline, the three arms were somewhat different with respect to the percentage of controlled/non-controlled patients. There were less controlled (‘Total and Well-controlled’) patients in the SFC 250 group than in either the SFC 100 and FP 250 groups (Table 1). The percentage of ‘Totally controlled’ patients increased from 31.8% to 39.6% in the SFC 250 group whilst the percentage of well-controlled patients remained stable.

Assessment of sustained asthma control using the last 8-weeks’ data from the two periods of 12-week treatment (i.e. weeks 5–12 and weeks 17–24), showed a higher percentage of patients with asthma that was ‘Totally controlled’ in both SFC groups than in the FP 250 group (21.4%, 26.5% and 9.7% over weeks 5–12 and 24.7%, 27.6% and 13% over weeks 17–24 for SFC 250, SFC 100 and FP 250, respectively). Similar results were observed for ‘Well-controlled’ asthma (45.4%, 58.3%, 37.6% over weeks 5–12 and 44.2%, 58.3%, 37.6% over weeks 17–24 for SFC 250, SFC 100 and FP 250, respectively).

Based on the PPDRC population (i.e. excluding patients not ‘Well-controlled’ at baseline based on an analysis of the diary card data alone) the % of patients whose asthma was at least ‘Well-controlled’ at week 24 was 85%, 92% and 77%, respectively, for SFC 250, SFC 100 and FP 250. For patients who were ‘Totally controlled’ at randomisation, the percentage of patients who maintained ‘Total control’ at week 24 was 73.5% for the SFC 250 group 62.3% for the SFC 100 group and 47.5% for the FP 250 group.

In patients exhibiting a loss of asthma control at week 24, 91% had at least two criteria involved in the loss of control as observed in the GOAL study. The median time to the loss of control based on one criterion of asthma control was 1 week for PEF, 1–2 weeks for rescue use, 2–4 weeks for daytime symptoms and night-time awakenings and 3.5–9 weeks for exacerbations.

Adverse events
All treatments were well tolerated. Adverse events were reported by 31% subjects in the SFC 250 group, 29% subjects in the SFC 100 group and 27% subjects in the FP 250 group. The most common adverse events among all patients were bronchitis, rhinitis and sinusitis. Four serious adverse events were reported by three subjects in the SFC 250 group (one loss of consciousness, one car crash, one breast cancer, one chest pain), no subjects in the SFC 100 group and one subject in the FP 250 group (pulmonary embolism). None was drug-related. There was no fatal serious adverse event.

Discussion
This study was based on a sequential hierarchized design investigating step-down therapy strategies compared to maintaining the treatment in asthmatics previously controlled with a combination therapy for at least 3 months. The study demonstrated that the better option for reducing treatment in controlled asthma patients on an ICS/LABA combination was to reduce the ICS dose and to maintain the LABA.

These findings are similar to those of a previously published study which directly compared the same step-down strategies given for 12 weeks in patients uncontrolled at inclusion but who achieved asthma control with SFC 250 twice daily. This last study concluded that SFC 100 twice daily regimen was more effective than switching to FP 250, i.e. to an inhaled corticosteroid alone. The study did not define the optimal control level nor the time when a dose reduction should be attempted once control is achieved, however the study suggested that when stepping down, control was better maintained in patients who had been controlled for longer.

Both studies were designed and powered for non-inferiority comparison. In the published step-down study, the authors were able to demonstrate superiority of SFC 100 over FP 250. At the time our study was designed, the results of the previous step-down study were not known and could not be considered in the analysis plan of our study. A non-inferiority trial was justified considering the main objective was to compare two step-down strategies to the maintenance of the previous treatment (SFC 250) which allowed achieving asthma control, whereas in the study by Bateman et al. the main objective was to compare two step-down therapies. Moreover, another study conducted in controlled patients on high dose ICS demonstrated that, when adopting a step-down approach, a reduction in the ICS dose could be achieved without compromising asthma control. Considering these results, we expected minimal changes at 12 weeks in the two step-down arms, and we hypothesised that approximately the same number of patients would have a deterioration of asthma, regardless of the step-down strategy, as compared to the reference treatment SFC 250.

Morning PEF was chosen as primary endpoint because it is easily performed and is a well established outcome measure for monitoring asthma. Asthma control may have been a more suitable endpoint, but, at the time our study was designed, the GOAL study investigating guideline derived control definition was not yet published. Moreover, PEF in this study appears to be a good predictor of loss of asthma control as supported by the observation that 91%
of patients who lost control of their asthma failed not only on PEF but at least on two criteria. PEF was also the first criterion to fail, followed by rescue use, daytime symptoms, night-time awakenings and exacerbations, and can be considered as the most sensitive in this population of moderate asthmatics.

The selected non-inferiority limit for morning PEF of −15 L/min has been used in previous studies,16,17 and is in accordance with European Guidelines.18,19 Previous studies also considered standard deviation of 35 L/min as a reasonable estimate in controlled patients.

Our study showed that SFC 100 was at least as effective as SFC 250 whereas FP 250 was not, based on mean morning PEF over the first 12-week period. The mean difference between FP 250 and SFC 250 in morning PEF was below the non-inferiority limit of the confidence interval allowing the conclusion to be made regarding the superiority of SFC 250, in line with recent guidelines concerning switching from non-inferiority to superiority.18 The mean change from baseline over 12 weeks in both step-down groups was similar to that observed in the earlier step-down study.14 The mean morning PEF remained stable in the SFC 100 group and decreased in the FP 250 over 12 weeks. However, the comparison between these two groups was not performed as planned a priori as the non-inferiority of the main comparison versus SFC 250 was not achieved.

Results on symptoms and rescue use also favoured the step-down strategy with SFC 100 during the first 12-week treatment period. Both the percentages of symptom-free and rescue-free days remained stable in both SFC groups, whereas they decreased with the ICS alone. No difference was observed between both SFC groups and SFC 250 was significantly superior to FP 250, despite a higher proportion of non-controlled patients in the SFC 250 group at baseline which could have minimized the potential difference between groups over the 12-week period. These results confirm those previously published over 12 weeks.14

An area of strength of this study was to provide data over 24 weeks. In the Bateman study, the authors expressed concern that slow but steady deterioration might occur over a longer period of follow-up. That was not observed in our study. Over weeks 17–24, similar results to those over weeks 5–12 were observed on PEF: there was no difference between SFC groups and SFC 250 was significantly superior to FP 250. On symptoms and rescue use, no difference was noticed between the three treatment groups. This was due to an improvement in the FP 250 group and may be explained by the differences at baseline between groups (i.e. a higher number of controlled subjects in the FP 250 group) and the higher proportion of withdrawals for ‘lack of efficacy’ during the second 12-week treatment period in the FP 250 group than in the SFC groups. The observed differences in efficacy between SFC groups and FP 250 could be an underestimation of the actual differences as the FP 250 group had more symptomatic patients discontinued from the study. Moreover, the higher percentage of withdrawals due to ‘lack of efficacy’ in the FP 250 group was observed despite a higher percentage of controlled patients and a lower reversibility of FEV1 at baseline in this group than in the others which may also have minimized the difference between groups. A lower percentage of withdrawals for ‘lack of efficacy’ was observed in the SFC 250 group indicating a better efficacy.

Due to the higher percentage of uncontrolled patients in the SFC 250 group at baseline in the FAS population, asthma control was also analysed in the PPDRC population (excluding uncontrolled patients at baseline). In the FAS population, asthma control evaluated each week, was superior in the SFC 100 group than in the FP 250 group over 24 weeks. The percentage of ‘Well and Totally controlled’ patients evaluated over 8 weeks (weeks 5–12 and 17–24) was superior in both SFC groups compared to the FP 250 group. The percentage was slightly superior in the SFC 100 group than in the SFC 250 group. This small difference may be explained by the differences observed at baseline (i.e. the higher percentage of uncontrolled patients and smokers in the SFC 250 group). However, in patients ‘Totally controlled’ at randomisation, SFC 250 allowed more patients to maintain ‘Total control’ at week 24 than SFC 100 and FP 250. Even though the study was not powered to detect a difference in asthma control, these results confirm that when a step-down strategy is chosen, a lower strength of combination therapy is a better option than withdrawing the LABA to maintain control. However, it seems that the maintenance of the initial level of treatment with SFC 250 gives slightly better results on the maintenance of ‘Total control’. This finding should be confirmed.

The percentage of patients with at least one exacerbation was numerically higher in the FP 250 group; however, due to the low frequency of exacerbations during the trial there were no statistically significant differences between groups. In the PPDRC population, the overall incidence was lower than in the FAS population, but the relative decreases were less in the FP 250 group than in the SFC groups. This suggests that SFC may be more effective than FP alone in the prevention of exacerbations which was also demonstrated in the GOAL study.4

In this moderate asthmatic population, the loss of control in the FP arm confirms that two controllers including a LABA were needed to maintain asthma control and were a better option than a high dose of ICS. Similar findings were shown in the study published by Papi even if in a mild population.20

Conclusion

This study showed that, in asthmatic patients whose asthma is controlled with salmeterol/fluticasone propionate 50/250, a step-down strategy with salmeterol/fluticasone propionate 50/100 is at least as effective as maintaining a constant dose. This was not shown with fluticasone propionate 250 alone. Also, stepping down should be considered in patients with a sufficient level of control. The differences were maintained over 24 weeks and confirmed the previously published results supporting a step-down strategy which reduces the ICS dosage and maintains the long-acting β2 agonist in patients who have achieved and maintained control for at least 3 months.
Conflict of interest statement

Pr Philippe Godard has attended Advisory Boards and given lectures sponsored by AstraZeneca and GlaxoSmithKline, and has received sponsorship for investigator-generated research from AstraZeneca and GlaxoSmithKline.

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References