Pediatr Allergy Immunol 2009: 20: 763–771
DOI: 10.1111/j.1399-3038.2009.00861.x



PEDIATRIC ALLERGY AND IMMUNOLOGY

# Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children

de Blic J, Ogorodova L, Klink R, Sidorenko I, Valiulis A, Hofman J, Bennedbaek O, Anderton S, Attali V, Desfougeres J-L, Poterre M. Salmeterol/fluticasone propionate vs. double dose fluticasone propionate on lung function and asthma control in children.
Pediatr Allergy Immunol 2009: 20: 763–771.


There is a large body of data to support the use of an inhaled corticosteroid (ICS) plus a long-acting $\beta_2$-agonist vs. increasing the dose of ICS in adults, but less data in children. This double-blind, parallel group, non-inferiority study compared lung function and asthma control, based on Global Initiative for Asthma guidelines, in children receiving either salmeterol/fluticasone propionate (SFC) 50/100 μg bd (n = 160) or fluticasone propionate (FP) 200 μg bd (n = 161) for 12 wks. Change from baseline in mean morning peak expiratory flow increased following both treatments, but was significantly greater in the SFC group compared with FP [Adjusted mean change (s.e.) (l/min): SFC: 26.9 (2.13), FP: 19.3 (2.12); treatment difference: 7.6 (3.01); 95% CI: 1.7, 13.5; p = 0.012)]. Asthma control improved over time in both groups. Mean pre-bronchodilator maximal-expiratory flow at 50% vital capacity and percentage rescue-free days showed significantly greater improvements in the SFC group compared with FP. All other efficacy indices showed comparable improvements in each group. Treatment with SFC 50/100 μg bd compared with twice the steroid dose of FP (200 μg bd), was at least as effective in improving individual clinical outcomes and overall asthma control, in asthmatic children previously uncontrolled on low doses of ICS.

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Key words: salmeterol/fluticasone propionate; fluticasone propionate; half steroid dose; asthma control; children

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Accepted 12 January 2009

The prevalence of childhood asthma has increased worldwide and is associated with considerable morbidity, and a large social and economic burden in terms of days lost from school/work and healthcare resource use (1–4). The aim of asthma management should be to achieve and maintain overall symptom control, and to prevent exacerbations and long-term complications (5). However, both parents and physicians generally overestimate asthma control in children and, together with an under use of inhaled corticosteroids (ICS). In persistent asthma, many children are failing to reach the goals of good asthma control (6, 7). In children, asthma control is usually assessed using both lung function and symptoms but GINA (Global Initiative for Asthma) guideline-derived control has not been pro-actively studied in children as it has been for adults and adolescents where the composite measures of 'Controlled' asthma were validated in the Gaining Optimal Asthma Control (GOAL) study (8).

There is also no clear evidence in children, unlike in adults, that adding a long-acting $\beta_2$-agonist (LABA) is superior to doubling the dose of ICS in patients not controlled by ICS

alone (9), even though this is a recommended step in the GINA guidelines (5). There is a need for additional data in children regarding asthma control and a comparison of treatment strategies in patients whose asthma is not well controlled with low-dose ICS. The objective of this study was to compare the efficacy and safety of salmeterol/fluticasone propionate (SFC) 50/100 μg bd with fluticasone propionate (FP) 200 μg bd and to test the hypothesis that SFC could provide at least as good control as FP at half the steroid dose, in children uncontrolled on low dose ICS.

## Material and methods

### Subjects

Children, aged 4–11 yrs, with a clinical history of asthma for at least 6 months, a documented reversibility in forced expiratory volume in 1 s ($FEV_1$) or peak expiratory flow (PEF) of ≥15%, and who were currently receiving inhaled ICS [beclomethasone dipropionate (BDP), non-fine particle, 400 μg/day or equivalent] were eligible for entry into the study. In addition, all patients were required to be able to measure PEF using a Mini-Wright peak flow meter (Clement Clarke International Ltd, Harlow, UK), to use a Diskus™ inhaler, and to be able to perform a $FEV_1$ manoeuvre correctly. At the end of the 4-wks run-in period, during which all subjects received FP 100 μg twice daily via the Diskus™ inhaler (GlaxoSmithKline, Evreux, France), subjects were eligible for randomization if their asthma had been assessed as 'Not controlled' for at least 2 of the 4 wks of the run-in period. Subjects who had experienced a respiratory tract infection or an acute asthma exacerbation requiring emergency room treatment within the previous 4 wks, or hospitalization due to asthma or use of systemic corticosteroids in the previous 12 wks, were excluded from the study.

Atopic status was determined by standard skin prick tests and by measuring levels of IgE specific for house dust mites, cat, grass pollen, and cockroaches. Skin prick tests were considered positive if the weal was 3 mm larger than the negative control to one or more allergens, or if specific IgE levels were at least 3.5 kU/l. The presence of eczema and allergic rhinitis were determined through a combination of these results together with the investigator's assessment of clinical signs/symptoms and medical history.

This international study was approved by a national, regional, or investigational center ethics committee or institutional review board according to local laws and regulations. Written informed consent was obtained from each subject and at least one parent/guardian prior to any study-specific procedures.

### Study design

This was a randomized, double-blind, double-dummy, parallel group, non-inferiority study conducted at 46 sites in 12 European countries (Study Number SAM104926). Following the 4-wks run-in period, during which daily symptoms were recorded in an electronic daily record card (eDRC), eligible subjects were randomized to receive either SFC 50/100 μg bd or FP 200 μg bd via the Diskus inhaler for 12 wks. Subjects were assessed after 4, 8, and 12 wks of treatment. All study treatments were supplied by GlaxoSmithKline (GSK, Evreux, France) and subjects were randomized to treatment by GSK's internal system: RANDALL. All study inhalers were identical in appearance and the use of dummy inhalers ensured that both subjects and site personnel remained blinded to an individual's treatment allocation. Compliance was checked by counting the number of remaining doses in the Diskus inhalers.

### Outcome measures

The primary end-point was change in mean morning PEF over 12 wks. The highest of three measurements were recorded by the parent/guardian on the eDRC each morning and evening, prior to taking any study medication. The child's ability to measure PEF correctly was checked at each visit. Symptoms, number of night-time awakenings and amount of rescue use were also recorded. The asthma symptom rating was recorded each evening, relating to the previous 24 h and based on a six-point scale from 0 (no symptoms) to 5 (symptoms so severe that the subject could not attend school or perform normal activities).

Asthma control was assessed each wk over the last 8 wks of the 12-wks treatment period. A 'Well-controlled' asthma wk was defined as no night-time awakenings, no exacerbations, no emergency visits, no treatment-related adverse events, and having two out of three of: symptoms on $<3$ days, rescue $\beta_2$-agonist use on $<3$ days and daily morning PEF ≥80% predicted (6). A 'Totally-controlled' asthma wk was the same except that subjects were to have no symptoms nor rescue medication use. Each individual wk was classified as 'Totally controlled', 'Well controlled', 'Not controlled' or 'unevaluable'. A subject must have had a minimum of 4 wks of evaluable DRC data during the assessment

period (wks 5–12) in order to be assessed for control of their asthma, or they were documented as unevaluable. Subjects needed to achieve 7 out of 8 wks 'Well-controlled' or 'Totally-controlled' to achieve the status of 'Well-control' or 'Total-control' over the study.

At each visit, the highest of three technically acceptable measurements of $FEV_1$, Maximal-expiratory flow at 50% vital capacity ($MEF_{50}$) and PEF were taken before and 20 mins after inhalation of 200 μg salbutamol. Reversibility in $PEF/FEV_1$ was calculated at each visit using the highest pre-bronchodilator and post-bronchodilator values. Subjects were asked to refrain from using short-acting bronchodilators for at least 6 h prior to each clinic visit and study medication in the 12 h prior to each visit.

Exacerbations were assessed throughout the study and were defined as: a deterioration of asthma requiring administration of oral corticosteroids (OCS) and/or a deterioration in asthma requiring emergency room visit and/or admission to hospital. Individual courses of OCS administered within 1 wk of a previous course finishing were considered as treatment for the same exacerbation. Safety was also evaluated by monitoring of adverse events (AEs). An AE was defined as any untoward medical occurrence temporally associated with the use of the study medication, whether or not it was considered related to the medication. The investigator was responsible for detecting AEs thorugh diary card inspection and discussions with the subject or their parent/guardian.

### Statistical analysis

The estimated sample size, powered at 90%, was 132 subjects per group derived from a s.d. in morning PEF of 30 l/min and using 12 l/min non-inferiority criteria bound (lower CL limit of −12). In the event that the lower confidence limit (2.5% 1-sided significance) exceeded 0, and using a separate closed testing procedure, superiority could be established. The populations used for the primary analysis were the intent-to-treat (ITT) and the per protocol population (PP), consisting of all subjects in the ITT Population who did not have any protocol violations which could impact treatment effect. The ITT population was used for all secondary analyses.

The PEF meters used varied between countries in terms of the measurement scale used and therefore, for the purposes of analyses, all PEF measurements made using the European Union (EU) or American Thoracic Society (ATS) scale were converted to the Wright/McKerrow peak flow meter scale. Changes from baseline in mean morning PEF were compared between treatment groups using an analysis of covariance (ANCOVA) model, allowing for the effects due to treatment, baseline morning PEF, age, sex, and country.

The proportions of subjects in each treatment group who achieved either 'Totally controlled' or 'Well controlled' asthma status during the last 8 wks of treatment were analyzed using logistic regression, allowing for effects due to sex, country, age, treatment group, and baseline pre-bronchodilator $FEV_1$. The time to achieving the first wk of 'Totally controlled' or 'Well controlled' asthma was compared using the Logrank test stratified by country amalgamation and the overall probabilities were calculated by the Kaplan–Meier method.

Pre-bronchodilator $FEV_1$, daytime symptoms and night-time awakenings were analyzed using the ANCOVA model, as described above. The percentage of symptom-free days was subject to proportional odds modeling using mean baseline, age, sex, and country amalgamation as covariates. The median rescue use per day and percentage of rescue-free days were analyzed using the Van Elteren extension to the Wilcoxon rank sum test for pair wise comparisons, stratified by country.

## Results

### Subjects

A total of 584 subjects were screened for entry to this study and of these 160 were randomized to SFC and 161 to FP (Fig. 1). Two hundred and sixty three (45%) subjects were withdrawn prior to randomization, the most common reason for withdrawal being 'did not fulfill eligibility criteria' [231 (40%) subjects]. The majority of these were 'Well-controlled' on FP 100 μg bd during the run-in period [219 (38%) subjects]. Data from subjects at one site were excluded from the ITT population due to an audit finding that implied that the integrity of the eDRC data may have been compromised.

The two treatment groups were well matched demographically and for baseline lung function and symptoms (Table 1).

The level of treatment compliance was high in both treatment groups with the majority of subjects taking ≥75% of their prescribed medication [SFC: 138/150 (92%); FP: 144/153 (94%)].

### Efficacy

*Mean morning peak expiratory flow*. An increase in mean morning PEF was shown following both

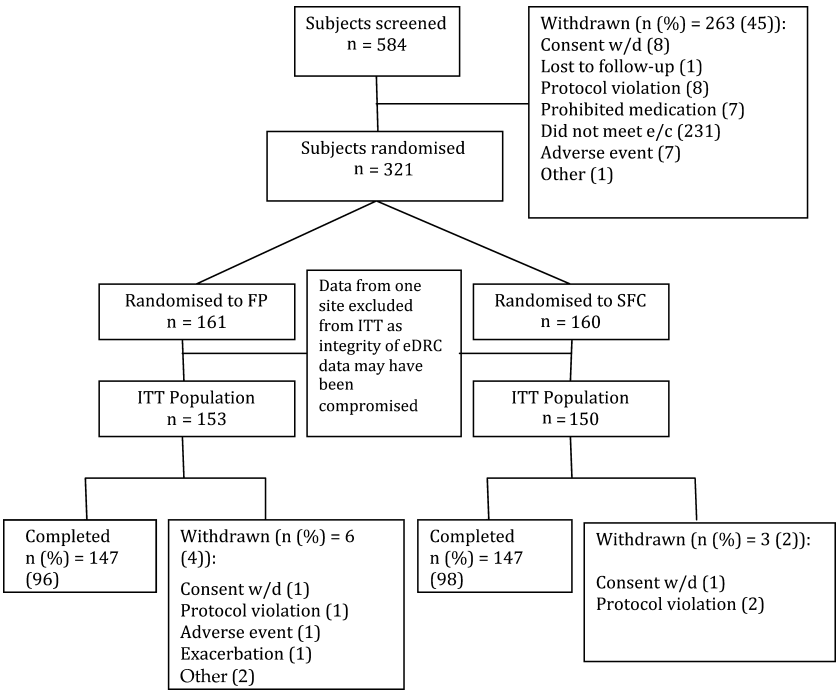


*Fig. 1.* Subject flow through the study. SFC, salmeterol/fluticasone propionate 50/100 μg bd; FP, fluticasone propionate 200 μg bd; w/d, withdrawn; e/c, entry criteria; ITT, intent-to-treat; eDRC, electronic daily record card.

treatments but to a greater degree in the SFC group (Table 2, Fig. 2). The statistical comparison between the two groups showed a lower limit of the confidence interval (CI) of greater than −12 l/min in both the ITT and PP populations, demonstrating that SFC was non-inferior to FP. Since the lower bound of the CI was also greater than zero, there was evidence of superiority and subsequent testing showed that SFC was statistically significantly superior to FP for both the ITT and PP populations (Table 2).

Table 1. Baseline characteristics

| Parameter | SFC (n = 150) | FP (n = 153) |
|---|---|---|
| Age (yrs), mean (range) | 8.1 (4–11) | 8.0 (4–11) |
| Sex, n (%) male | 97 (65) | 98 (64) |
| Atopic Status, n (%) | | |
| Positive skin prick test/specific IgE | 126 (84) | 139 (91) |
| Positive eczema history* | 62 (41) | 58 (38) |
| Positive allergic rhinitis history* | 107 (71) | 117 (76) |
| Duration of asthma, n (%) | | |
| ≥6 months–<1 yr | 5 (3) | 75 (50) |
| ≥1 yr–<5 yrs | 10 (7) | 82 (54) |
| ≥5 yrs–<10 yrs | 68 (45) | 59 (39) |
| ≥10 yrs | 2 (1) | 2 (1) |
| Baseline lung function and symptoms | | |
| Am PEF during run-in (l/min), mean (s.d.) | 268.1 (68.44) | 264.5 (69.49) |
| $FEV_1$ (l), mean (s.d.) | 1.7 (0.47) | 1.7 (0.48) |
| Reversibility in $FEV_1$, mean % (s.d.) | 9.9 (10.32) | 10.2 (12.79) |
| Symptom score†, mean (s.d.) | 1.2 (0.77) | 1.1 (0.73) |
| Number of night-time awakenings†, mean (s.d.) | 0.6 (0.99) | 0.4 (0.40) |
| Rescue medication use*, mean (s.d.) | 0.4 (0.66) | 0.5 (0.73) |

SFC, salmeterol/fluticasone propionate 50/100 μg bd; FP, fluticasone propionate 200 μg bd; PEF, peak expiratory flow; $FEV_1$, forced expiratory volume in 1 s, s.d., standard deviation.
*Presence determined using clinical signs/symptoms and positive result for skin prick test/serum specific IgE.
†Mean over 4 wks run-in period.

*Asthma control*. The proportion of subjects achieving either a 'Totally controlled' asthma status (meaning no clinical feature of asthma) or a 'Well controlled' asthma status, were similar in both groups (Table 3). The time by which subjects reached their first 'Totally controlled' wk was also similar in each treatment group with approximately 50% of subjects in each group having achieved a 'Totally controlled' wk by wk 6. The median time to first wk of 'Totally controlled' asthma was 6 wks in the SFC group and 7 wks in the FP group. The median time to first wk of 'Well controlled' asthma was 2 wks in both treatment groups and the time by which 75% of subjects in each group had achieved at least one 'Well controlled' wk was 4 wks in the SFC group and 6 wks in the FP group with no statistically significant differences between groups.

*Symptoms and clinic lung function*. Symptom scores, rescue medication use and clinic lung function assessments showed improvements in both groups during treatment (Table 4). Mean pre-bronchodilator $MEF_{50}$ and percentage rescue-free days showed significantly greater improvements in the SFC group compared with FP. The difference between groups in percentage

Table 2. Mean change in morning PEF over wks 1–12

| | ITT population | | PP population | |
|---|---|---|---|---|
| PEF (l/min) | SFC (n = 150) | FP (n = 153) | SFC (n = 129) | FP (n = 136) |
| B/L raw mean (s.d.) | 270.4 (71.16) | 266.0 (70.26) | 270.8 (71.23) | 265.3 (70.96) |
| Adjusted mean change from B/L (s.e.) | 26.9 (2.13) | 19.3 (2.12) | 27.7 (2.21) | 18.4 (2.14) |
| SFC-FP | | | | |
| Difference (s.e.) | 7.6 (3.01) | | 9.3 (3.08) | |
| 95% CI | 1.7, 13.5 | | 3.2, 15.3 | |
| p-value | 0.012 | | 0.003 | |

ITT, intent-to-treat population; PP, per protocol population; SFC, salmeterol/fluticasone propionate 50/100 μg bd; FP, fluticasone propionate 200 μg bd; PEF, peak expiratory flow; B/L, baseline; s.e., standard error; s.d., standard deviation; CI, confidence interval.

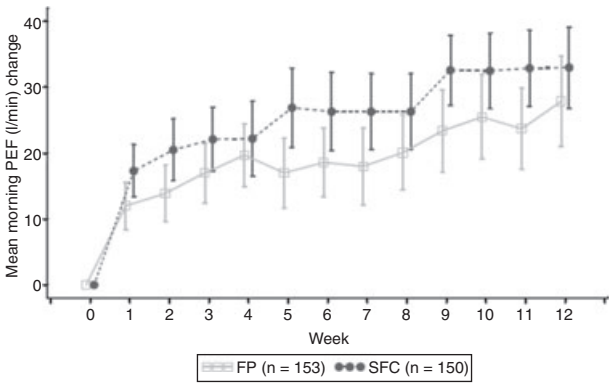


*Fig. 2.* Change from baseline in morning PEF. SFC, salmeterol/fluticasone propionate 50/100 μg bd; FP, fluticasone propionate 200 μg bd; PEF, peak expiratory flow.

Table 3. Asthma control

| | SFC (n = 150) | FP (n = 153) |
|---|---|---|
| Well controlled (WC) asthma | | |
| Achieved WC asthma | 65 (43) | 61 (40) |
| Not achieved WC Asthma | 75 (50) | 81 (63) |
| Unevaluable | 10 (7) | 10 (7) |
| Odds to FP | 1.16 | 1.16 |
| 95%CI | 0.7, 1.9 | 0.7, 1.9 |
| p-value | 0.535 | 0.535 |
| Totally controlled (TC) asthma | | |
| Achieved TC asthma | 28 (19) | 23 (15) |
| Not achieved TC asthma | 112 (75) | 119 (78) |
| Unevaluable | 10 (7) | 10 (7) |
| Odds to FP | 1.31 | |
| 95%CI | 0.7, 2.4 | |
| p-value | 0.389 | |

SFC, salmeterol/fluticasone propionate; FP, fluticasone propionate; CI, confidence interval.

rescue-free days was largely accounted for by the number of subjects achieving 100% rescue-free days [SFC: 43 (29%) subjects, FP: 29 (19%) subjects] (Table 4). There was a reduction in PEF reversibility in both groups, and this was greater in the SFC group. At baseline reversibility was 13% in both treatment groups; at wk 12 reversibility was 7% in the SFC group and 9% in the FP group (SFC-FP difference: −1.7, 95% CI: −3.3, −0.2; p = 0.028). There was also a small reduction in $FEV_1$ reversibility over treatment in both groups (not statistically different). All other indices showed comparable improvements in each group.

*Exacerbations.* Two (1%) subjects in each treatment group had an exacerbation of asthma during the treatment period. In the SFC group both exacerbations were treated with OCS and one also resulted in the hospitalization of the subject (serious event) but neither resulted in the withdrawal of the subjects from the study. In the FP group, one of the exacerbations required treatment with OCS and the other required hospitalization but the subject refused to be hospitalized; this was considered as a serious adverse event, resulting in the withdrawal of the subject from the study.

## Safety

The proportion of subjects reporting at least one adverse event during treatment was similar in both treatment groups [SFC: 87 (58%) subjects, FP: 86(56%) subjects], the most common events reported being headache and nasopharyngitis in both groups. Three subjects (2%) in each group reported a serious adverse event during treatment. In the SFC group, there was one report each of laryngotracheitis, asthma exacerbation and concussion. None of these events were assessed as related to study treatment or resulted in the subjects' withdrawal from the study. In the FP group, there was one report each of wound infection, asthma exacerbation and gastritis, none of which were assessed as related to study

Table 4. Symptoms, rescue medication use and clinic lung function

| Parameter | SFC (n = 150) | | FP (n = 153) | |
|---|---|---|---|---|
| % Symptom-free days | B/L | Wks 1–12 | B/L | Wks 1–12 |
| 0–<25% | 80 (53) | 31 (21) | 77 (50) | 30 (20) |
| 25–<50% | 15 (10) | 17 (11) | 20 (13) | 25 (16) |
| 50–<75% | 18 (12) | 27 (18) | 18 (12) | 26 (17) |
| 75–<100% | 13 (9) | 62 (41) | 13 (8) | 59 (39) |
| 100% | 24 (16) | 13 (9) | 24 (16) | 12 (8) |
| Odds to FP (95% CI) | 0.84 (0.5, 1.3) | | | |
| p-value | 0.436 | | | |
| Night-time awakenings | | | | |
| Baseline mean (s.d.) | 0.6 (1.18) | | 0.4 (0.58) | |
| Wk 12 adjusted mean (s.e.) | 0.3 (0.08) | | 0.3 (0.08) | |
| SFC-FP difference (95% CL) | 0 (−0.2, 0.3) | | | |
| p-value | 0.721 | | | |
| Rescue medication use | B/L | Wk 12 | B/L | Wk 12 |
| Percentage rescue-free days | | | | |
| 0–<25% | 27 (18) | 4 (3) | 37 (24) | 7 (5) |
| 25–<50% | 17 (11) | 4 (3) | 19 (12) | 7 (5) |
| 50–<75% | 30 (20) | 11 (7) | 22 (14) | 20 (13) |
| 75–<100% | 16 (11) | 88 (59) | 22 (14) | 89 (58) |
| 100% | 60 (40) | 43 (29) | 52 (34) | 29 (19) |
| Median % rescue-free days, wks 1–12 | 95.1 | | 94.0 | |
| SFC-FP difference (95% CI) | 1.4 (0.0, 3.4) | | | |
| p-value | 0.025 | | | |
| $FEV_1$ (L) | | | | |
| Baseline mean (s.d.) | 1.7 (0.47) | | 1.7 (0.48) | |
| Wk 4 adjusted mean change (s.e.) | 0.05 (0.015) | | 0.06 (0.015) | |
| Wk 8 adjusted mean change (s.e.) | 0.08 (0.017) | | 0.09 (0.017) | |
| Wk 12 adjusted mean change (s.e.) | 0.10 (0.017) | | 0.10 (0.016) | |
| Wk 12 SFC-FP difference (95% CI) | 0.0 (−0.04, 0.05) | | | |
| p-value | 0.940 | | | |
| $MEF_{50}$ (l/s) | | | | |
| Baseline mean (s.d.) | 2.2 (0.68) | | 2.2 (0.69) | |
| Wk 4 adjusted mean change (s.e.) | 0.23 (0.041) | | 0.08 (0.041) | |
| Wk 8 adjusted mean change (s.e.) | 0.28 (0.043) | | 0.11 (0.043) | |
| Wk 12 adjusted mean change (s.e.) | 0.33 (0.046) | | 0.16 (0.046) | |
| SFC-FP difference (95% CI) | 0.17 (0.04, 0.29) | | | |
| p-value | 0.011 | | | |

SFC, salmeterol/fluticasone propionate 50/100 μg bd; FP, fluticasone propionate 200 μg bd; PEF, peak expiratory flow; $FEV_1$, forced expiratory volume in 1 s, $MEF_{50}$, maximal-expiratory flow at 50% vital capacity; s.d., standard deviation; s.e., standard error; CI, confidence interval.

treatment. The asthma exacerbation resulted in the subject's withdrawal from the study. Very few AEs were assessed as related to treatment [SFC: 1 (< 1%) subject, FP: 3 (2%) subjects] and only two subjects, both from the FP group, were withdrawn from the study due to an AE. One of these was withdrawn due to events of asthenia, hallucination and headache all of which were non-serious but were assessed as drug-related. The other was withdrawn due to an exacerbation of asthma which was serious but not assessed as related to study treatment.

## Discussion

The main aim of this study was to test the hypothesis that SFC at half the steroid dose could provide asthma control at least as effective as double the dose of FP in children uncontrolled on low doses of ICS. For the primary efficacy end-point, change from baseline in morning peak flow, non-inferiority of SFC to FP was demonstrated. There were also no significant differences between SFC and FP for the majority of other key secondary end-points including symptoms, $FEV_1$ and the composite, GINA-derived, measure of asthma control. SFC was shown to be statistically significantly superior in improving PEF, percentage rescue-free days and $MEF_{50}$. The beneficial results in lung function are anticipated effects of adding a LABA to an ICS: this is consistent with other similar findings (10–13), although it could be argued that in our study, the entry requirement for all patients to demonstrate reversibility may have favoured the SFC group with respect to lung function outcomes. The

result for rescue-free days does indicate a better effect of SFC treatment over FP at half the steroid dose with at least the same level of control. This study adds useful evidence to the role of SFC in treating childhood asthma. Previous studies in children have shown that treatment with SFC is an effective and safe treatment (14–16) but this is the first study to show that adding a LABA to existing steroid therapy is at least as effective as increasing the dose of ICS alone; concurring with previous data found in adults (9).

Current treatment guidelines recommend a management approach based on asthma control with the emphasis placed on establishing the lowest step and dose of treatment necessary to maintain control, thus minimizing cost and maximizing the safety of treatment (5). The evidence for adding a LABA to low dose ICS instead of increasing the dose of ICS has previously been more compelling for adults (5) but the results of this study show that a treatment strategy of using SFC at half the steroid dose of FP provides at least as good control and even better efficacy on some parameters in children. GINA guideline-derived control was achieved by a similar proportion of subjects in both treatment groups with approximately 40% of subjects achieving 'Well controlled' asthma sustained for at least seven out of the last 8 wks of treatment. Furthermore, 19% in the SFC group and 15% of subjects in the FP group achieved 'Total control' meaning that, despite their entry to the study with significant symptoms, they remained completely asthma free for at least the last 2 months of treatment (i.e. normal lung function, no day or night-time symptoms, no rescue use and no exacerbations). Even if ICS have shown a good safety profile, obtaining at least a similar level of control at half the steroid dose is in line with the guideline recommendations. This is also likely to be well received by parents and physicians and to increase compliance to treatment which remains an issue in asthma treatment.

Two previous pediatric studies, comparing salmeterol and BDP with twice the dose of BDP, found no additional benefits of the combination treatment (17, 18). These differences may be due to different inclusion criteria being used, patients for our own study being required to be symptomatic during the run-in. Another explanation could be the synergy between the two components of the SFC fixed combination, due to the co-deposition in the lung (19–21). Our own results provide important data for the role of combination therapy in children, reinforcing previous data showing that combination therapy results in better lung function than treatment with an equivalent dose of ICS alone (14–16). Most recently, Sorkness et al. compared FP 100 μg bd vs. SFC 50/100 μg once daily in the morning and salmeterol 50 μg in the evening (Pediatric Asthma Controller Trial, combination) vs. montelukast 5 mg in the evening in children with mild to moderate asthma based on $FEV_1$ and symptoms (22). Both FP and PACT resulted in a similar level of asthma control. The results on inflammation parameters in this study (exhaled nitric oxide and bronchial responsiveness to methacholine) showed that the control of inflammation was less effective in the PACT combination group, suggesting that the patients may have received a sub-optimal dose of ICS compared to the FP monotherapy arm, indicating that a higher dosage of SFC (i.e. 100 μg twice daily) would probably have been more appropriate.

The choice of PEF as the primary end-point in this study, which included children as young as 4 yrs old, may be criticized. The use of PEF as a measure to accurately predict airflow obstruction in children has been questioned (23, 24). However, PEF is an objective and simple measure, often used in children as a primary end-point (14–17). Children of 4 and 5 yrs can be taught how to use a PEF meter, most accurate results obtained with parental supervision (5), as was the case in this study. Moreover, the inclusion criteria and training provided ensured that all children who entered the study were capable of performing the PEF manoeuvre. The non-inferiority results for PEF in our own study were supported by all the secondary end-points including the composite measure for asthma control.

Both treatments were well tolerated with the incidence of AES being similar in both groups. The incidence of serious adverse events, drug-related events and withdrawals due to events was low in both groups, and no safety issues or significant differences between treatments were identified. The regular use of LABAs in children has been questioned, particularly with respect to the development of tolerance and the associated increased risk of exacerbations over time (25). Although there was a decrease in PEF reversibility during both treatments, significantly more so in the SFC group, the post-bronchodilator PEF was greater at wk 12 than at baseline indicating that the decrease in reversibility was not due to tolerance but rather influenced by the increased pre-bronchodilator lung function. In addition, very few exacerbations were recorded in this study, although a study duration of

12 wks could be considered too short to gather any meaningful data. The results of this study support the use of a LABA as recommended in treatment guidelines i.e. in combination with an ICS (4).

Another possible limitation of the 12-wk duration is that it was probably too short to demonstrate maximal potential treatment effect, in particular with regard to asthma control. Adult patients in the GOAL study showed improvements in asthma control over time until wk 52, although the treatment difference between SFC and FP was already evident by wk 12 (8). The design of the GOAL study allowed for several dose escalations but this approach was not possible in children as only one strength of SFC is indicated in this population. In addition the 4 wks run-in period did not allow a full evaluation of control based on GOAL criteria (8 wks) at entry. However, it would have been difficult to justify a longer run-in period in these patients, previously uncontrolled despite receiving ICS therapy.

In conclusion, this is the first study to clearly demonstrate that, in children symptomatic on low dose ICS, switching to SFC 50/100 μg bd is at least as effective in improving individual clinical outcomes and overall guideline-derived asthma control as doubling the dose of ICS (FP 200 μg bd).

## Acknowledgments

This study was funded by GlaxoSmithKline. The authors thank Martyn Gilson from GlaxoSmithKline for his support of the study, the clinical investigators who recruited and cared for the patients in the study and Kate Hollingworth for technical support in the preparation of the manuscript.

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