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# Inhaled Salmeterol/Fluticasone Propionate Combination

## A Review of its Use in Persistent Asthma

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**Data Selection**

**Sources:** Medical literature published in any language since 1966 on Salmeterol/Fluticasone-propionate, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

**Search strategy:** Medline search terms were 'Salmeterol Fluticasone'. EMBASE search terms were 'Salmeterol Fluticasone'. AdisBase search terms were 'Salmeterol/Fluticasone-propionate'. Searches were last updated 9 Oct 2000.

**Selection:** Studies in patients with persistent asthma who received combined salmeterol/fluticasone propionate. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

**Index terms:** asthma, fluticasone propionate, salmeterol, salmeterol/fluticasone propionate, pharmacodynamics, pharmacokinetics, therapeutic use.

## Contents

## Summary

**Abstract**

The long-acting $\beta_2$-agonist salmeterol and the corticosteroid fluticasone propionate are available as a combination inhalation device for the treatment of persistent asthma.

Well designed studies in adults, adolescents and children aged ≥4 years, demonstrate that combined salmeterol/fluticasone propionate 50/100, 50/250 and 50/500μg administered via a dry powder inhaler (DPI) is clinically equivalent to concurrent delivery of the same dosages of the 2 drugs via separate DPIs.

In adults and adolescents, combined salmeterol/fluticasone 50/100 and 50/250μg twice daily produced rapid improvements in lung function that were consistently greater than those in patients receiving monotherapy twice daily salmeterol 50μg, fluticasone propionate 100 or 250μg or placebo in 2 well designed studies. Recipients of the combination had a significantly greater probability of completing 12 weeks of treatment than patients receiving monotherapy or placebo. The combination also produced significant improvements between baseline and end-point in all secondary outcome variables (morning and evening peak expiratory flow, daytime symptom scores, days and nights without asthma symptoms and requirements for as-needed β-agonists) and health-related quality of life (QOL). Combination therapy was superior to monotherapy with salmeterol and placebo for all outcomes in both studies, and was superior to fluticasone propionate 100μg for all but 1 outcome (nights without awakenings) in 1 study. Similar results were obtained in patients who had previously been using short acting $\beta_2$-agonists alone.

Combined twice daily salmeterol/fluticasone propionate 50/100 and 50/250μg produced greater improvements in lung function than inhaled budesonide at higher dosages than fluticasone propionate in the combination.

Combined salmeterol/fluticasone propionate 50/250μg produced similar improvements in lung function to concurrent budesonide 800μg plus formoterol 12μg when given twice daily for 12 weeks. In another 12-week trial, combined salmeterol/fluticasone propionate 50/100μg was more effective than oral montelukast 10 mg/day plus fluticasone propionate 100μg twice daily in patients with suboptimally controlled asthma.

Salmeterol/fluticasone is more cost effective than monotherapy with fluticasone propionate or budesonide.

The most frequent adverse events associated with salmeterol/fluticasone propionate are headache, throat irritation, hoarseness and candidiasis.

*Conclusion*: Combined salmeterol/fluticasone propionate is as effective as the 2 drugs given concurrently via separate inhalers and significantly more effective than either drug given alone at the same nominal dosage. The combination is also significantly more effective than montelukast plus fluticasone propionate or monotherapy with inhaled budesonide. Furthermore, the combination is more cost effective than inhaled corticosteroid monotherapy.

## Pharmacodynamic Properties

Salmeterol, a long-acting inhaled $\beta_2$-agonist bronchodilator, protects against bronchoconstriction and may have some anti-inflammatory properties.

The inhaled corticosteroid fluticasone propionate inhibits eosinophil activation and the subsequent release of inflammatory mediators and may also reduce bronchial hyperresponsiveness in patients with asthma.

The systemic pharmacodynamic effects of salmeterol and fluticasone propionate administered together are similar to those observed when the drugs are given alone or concurrently. No evidence of interaction between the 2 drugs was observed in single and multiple dose studies of the effects of fluticasone propionate on 24-hour urinary cortisol excretion versus equivalent doses of fluticasone propionate alone. When salmeterol/fluticasone propionate 50/l00μg was compared with placebo, no significant effect on 24-hour urinary cortisol excretion was detected.

Similarly, in a cumulative dose study comparing the combination with equivalent doses of salmeterol alone, most pharmacodynamic responses to salmeterol were unaffected by the presence of fluticasone propionate.

In children aged 4 to 11 years who had previously been treated with inhaled corticosteroids, geometric mean morning serum cortisol levels increased during 12 weeks of twice daily treatment with salmeterol plus fluticasone propionate 50/100μg. However, no significant differences in the frequency of abnormal plasma cortisol values were detected in adults with persistent asthma during treatment with combined salmeterol/fluticasone propionate 50/250μg twice daily, either drug alone or placebo in a multicentre randomised double-blind study.

## Pharmacokinetic Properties

Salmeterol is not detectable in plasma after administration by inhalation and there is no evidence that concomitant administration of fluticasone propionate alters the systemic availability of salmeterol.

Studies comparing fluticasone propionate monotherapy with each strength of salmeterol/fluticasone propionate suggest that the systemic availability of fluticasone propionate is not increased when salmeterol is given concomitantly.

Both salmeterol and fluticasone propionate are metabolised by cytochrome P450 3A4. Renal clearance accounts for <0.02% of the total clearance of fluticasone propionate and for <5% of salmeterol.

## Therapeutic Efficacy

The therapeutic efficacy of combined salmeterol and fluticasone propionate in patients with persistent asthma has been established in large multicentre randomised double-blind parallel-group studies. With the exception of 1 study that enrolled patients with a history of recent salmeterol treatment alone, and 1 trial that recruited patients who had used short acting $\beta_2$-agonists only, eligible patients in all studies had symptomatic asthma despite ongoing treatment with inhaled corticosteroids. The dose of salmeterol (50 μg/actuation) was constant in all studies regardless of whether patients received the drug alone, or in combination or concurrently with fluticasone propionate. The dose of fluticasone

propionate varied (100, 250 or 500 μg/actuation). All inhaled products in these studies were administered as 1 actuation twice daily.

Studies in adults and adolescents aged ≥12 years and in children aged 4 to 11 years, have demonstrated the clinical efficacy of combined delivery of salmeterol/fluticasone propionate 50/100, 50/250 and 50/500μg twice daily via the Diskus dry powder inhaler (DPI) to be equivalent to that of concurrent delivery of the same dosages of the 2 drugs via separate Diskus DPIs as assessed by lung function and asthma symptom scores.

Combined salmeterol/fluticasone propionate has recently been formulated as a chlorofluorocarbon (CFC)-free pressurised metered dose inhaler (MDI). Two studies have demonstrated equivalency of this formulation with the Diskus DPI. Improvements in mean morning peak expiratory flow (PEF) were similar after 12 weeks of treatment with combined salmeterol/fluticasone propionate 50/100 or 50/500 delivered via the DPI or MDI.

The efficacy of combined salmeterol/fluticasone propionate was subsequently compared with that of the individual components in 3 well designed US studies which enrolled adults and adolescents aged ≥12 years. Combined salmeterol/fluticasone 50/100 or 50/250μg produced rapid and consistent improvements in lung function that were maintained throughout two 12-week studies in patients previously treated with inhaled corticosteroids or salmeterol. The combination had a significantly faster onset of effect on day 1 of the studies than placebo or fluticasone propionate. Improvements in forced expiratory volume in 1 second ($FEV_1$) between baseline and end-point were consistent between studies and were significantly greater in those treated twice daily with combined salmeterol/fluticasone propionate 50/100μg or 50/250μg than either salmeterol 50μg or fluticasone propionate 100 or 250μg. Improvements in $FEV_1$ were similar regardless of baseline corticosteroid therapy or whether patients were using inhaled corticosteroids or salmeterol alone prior to enrolment.

The probability of being withdrawn from either study because of asthma exacerbations was significantly lower in patients randomised to combination therapy (≤4%) than in each of the other groups. Placebo recipients had the highest rates of withdrawal for worsening asthma (≥49%) followed by salmeterol-treated patients (≥35%).

Treatment with combined salmeterol/fluticasone propionate produced significant improvements between baseline and end-point in all secondary outcome variables (morning and evening PEF, daytime symptom scores, days and nights without asthma symptoms and requirements for as-needed β-agonists) and health-related quality of life (QOL). Combination therapy was superior to monotherapy with salmeterol and placebo for all outcomes in both studies, and was superior to fluticasone propionate for all but 1 outcome (nights without awakenings) in the study that used the lower dosage (50/100μg). Clinically significant differences in total Asthma Quality of Life Questionnaire (AQLQ) scores (≥0.5 units), were obtained in patients treated with the combination compared with placebo (1.3 units) and salmeterol 50μg (≥1 units) but not fluticasone propionate 100 or 250μg.

Similar results were obtained in patients who had previously been using short acting $\beta_2$-agonists alone. Recipients of combined salmeterol/fluticasone propionate 50/100μg experienced significantly greater improvements in the area under the $FEV_1$ curve ($AUC_{0\text{-}12h}$ $FEV_1$), mean morning and evening PEF, and $FEV_1$ than did patients treated with salmeterol or fluticasone propionate alone after 12 weeks of treatment.

A further series of randomised double-blind parallel-group studies have compared

combined salmeterol/fluticasone propionate with inhaled budesonide or concurrent budesonide plus formoterol. Salmeterol/fluticasone propionate 50/250μg had a rapid onset of action, such that, throughout the first week of treatment with the combination, mean morning PEF was significantly greater and the proportion of patients with no symptoms or no need for as-needed $\beta_2$-agonists was significantly lower than in patients randomised to inhaled budesonide 800μg twice daily. These trends were maintained throughout the 24-week study. The combination also produced improvements in QOL scores that were clinically significant compared with baseline and statistically significant compared with scores in budesonide recipients after 24 weeks.

Improvements in mean morning and evening PEF were significantly greater among patients with persistent asthma randomised to combined salmeterol/fluticasone propionate 50/100μg twice daily than budesonide 400μg twice daily in a further 12-week study.

Similar improvements in lung function were obtained with combined salmeterol/fluticasone propionate 50/250μg and concurrent budesonide 800μg plus formoterol 12μg twice daily in a 12-week randomised double-blind multicentre study.

Combined salmeterol/fluticasone propionate 50/100μg was more effective than the addition of oral montelukast 10 mg/day to fluticasone propionate 100μg twice daily in patients aged ≥15 years with suboptimally controlled asthma according to the results of a 12-week study. Mean morning PEF, the primary efficacy variable in the study, was significantly greater among patients treated with the combination on each day during the first week of treatment and in each week of the study thereafter. Similar trends were evident for improvements in mean evening PEF, clinic $FEV_1$, and reductions in as-needed $\beta_2$-agonist usage, all of which were significantly greater in patients treated with combined salmeterol/fluticasone propionate than montelukast plus fluticasone propionate. Asthma exacerbations also occurred in significantly fewer patients treated with the combination than montelukast plus fluticasone propionate (2 *vs* 6%). The mean change in total Daytime Asthma Symptom Scores was similar in patients in both treatment groups.

## Pharmacoeconomic Considerations

Data from 3 studies comparing salmeterol/fluticasone propionate and fluticasone propionate have been subjected to cost-effectiveness analyses from the perspective of the Swedish healthcare system [valued in Swedish Kronor (SEK 1998)].

In all 3 studies, the total costs of asthma management were higher in the salmeterol/fluticasone propionate group than in the corresponding fluticasone propionate group. However, the cost per successfully-treated week was lower for salmeterol/fluticasone propionate across all 3 studies. The incremental cost effectiveness ratios varied from SEK12.6 ($US1.53) per additional successfully-treated week with salmeterol/fluticasone propionate 50/250μg to SEK192.1 ($US23.31) per additional successfully-treated week with salmeterol/fluticasone propionate 50/500μg.

A 24-week study comparing salmeterol/fluticasone propionate with budesonide has been subjected to cost-effectiveness analyses from Swedish, German and UK perspectives. Each analysis found salmeterol/fluticasone propionate to be more cost-effective than budesonide despite higher acquisition costs for the combination.

## Tolerability

As salmeterol/fluticasone propionate is a combination of 2 drugs, the type and severity of adverse events associated with each component drug may be expected

in patients receiving the combination product. There is no evidence, however, of additional adverse events following concurrent administration of the 2 drugs.

According to overall analysis of tolerability data from well designed studies the most frequent adverse events associated with salmeterol/fluticasone propionate are headache (incidence 2 to 5%), throat irritation (1 to 4%), hoarseness (≤4%) and oral candidiasis (1 to 4%).

The overall frequency of adverse events was similar between treatment groups in a comparative study in which patients received combined salmeterol/fluticasone propionate 50/250μg or budesonide 800μg twice daily for 24 weeks.

Withdrawal rates among patients treated with combined salmeterol/fluticasone propionate ranged from 0 to 10% and were similar to those in other treatment groups in the various studies.

**Dosage and Administration**

In the US, combined salmeterol/fluticasone propionate is indicated for long term maintenance treatment of asthma in patients aged ≥12 years. The recommended starting dosage is based on patients' current asthma therapy. Twice daily salmeterol/fluticasone propionate 100/50μg via DPI is the recommended initial dosage in patients not currently receiving inhaled corticosteroids.

In the UK, combined salmeterol/fluticasone propionate is indicated in the treatment of asthma where use of the combination of a long-acting inhaled $\beta_2$-agonist and inhaled corticosteroid is appropriate. This corresponds to 'Step 3' in the British Guidelines on Asthma Management.

The recommended dosages of salmeterol/fluticasone propionate in patients aged ≥12 years is 1 inhalation twice daily of the DPI (each inhalation contains 50μg salmeterol and either 100, 250 or 500μg fluticasone propionate) or 2 inhalations twice daily of the MDI (each inhalation contains salmeterol/fluticasone propionate 25/50μg, 25/125μg, or 25/250μg). The dosage of fluticasone propionate should be selected according to the severity of asthma in individual patients. In children aged <12 and ≥4 years, the recommended dosage is 1 inhalation twice daily of the lowest strength of the DPI (salmeterol/fluticasone propionate 50/100μg). No data are available regarding use of salmeterol/fluticasone propionate in children aged <4 years.

Salmeterol/fluticasone propionate should not be used to treat acute asthma symptoms for which a short acting $\beta_2$-agonist bronchodilator is required. Patients should be advised to have their relief medication available at all times.

No dosage adjustment is required in the elderly or in patients with renal impairment. Patients with hepatic disease should be closely monitored during treatment with the combination.

## 1. Introduction

The long-acting inhaled $\beta_2$-agonist salmeterol and the inhaled corticosteroid fluticasone propionate target different aspects of the disease process of asthma and available evidence suggests that the 2 drugs produce complementary effects in patients with this condition. The precise mechanism(s) by which salmeterol and fluticasone propionate interact to improve airway function remains unclear but potential mechanisms include:

- relief of residual bronchoconstriction during corticosteroid therapy;
- inhibition of endothelial cell contraction and resultant extravasation of plasma proteins by salmeterol;

- a protective effect of the corticosteroid against possible β-adrenoceptor downregulation.[1-4]

Based on evidence of a complementary effect, and the fact that compliance with inhaled asthma medication is generally poor, salmeterol and fluticasone propionate have been combined in a single inhalation device. The combination is commercially available in the Diskus™ (or Accuhaler™) dry powder inhaler (DPI). The clinical characteristics of this device have been extensively reviewed elsewhere.[5] A chlorofluorocarbon (CFC)-free pressurised metered dose inhaler (MDI), which uses HFA-134a as a propellent, has also been developed and is available in the UK.[6,7]

The use of such a combination falls within current recommendations for the management of asthma which suggest the addition of a long-acting $\beta_2$-agonist in patients in whom low to medium dosages of inhaled corticosteroids plus occasional as-needed use of short-acting $\beta_2$-agonist bronchodilators do not provide satisfactory control of symptoms.[8,9]

The salmeterol and fluticasone propionate combination product, hereafter referred to as salmeterol/fluticasone propionate, has been profiled in *Drugs* previously.[10] The present review updates and expands on this previous article.

## 2. Pharmacological Properties

### 2.1 Pharmacodynamic Properties

The pharmacodynamic properties of both salmeterol and fluticasone propionate have previously been reviewed in *Drugs*, both alone[11-14] and in combination.[10] As such, only an overview is presented here.

As mentioned above, salmeterol is a long-acting $\beta_2$-agonist. It has been shown to protect against histamine-, methacholine-, cold air- and sulphur dioxide-induced bronchoconstriction and exercise-induced asthma. The drug may also have some anti-inflammatory properties and can attenuate bronchial hyperresponsiveness in patients with asthma (reviewed by Adkins and Mctavish[14]).

Fluticasone propionate is an inhaled corticosteroid. The drug inhibits eosinophil activation and the subsequent release of inflammatory mediators. It also appears to reduce bronchial hyperresponsiveness in patients with asthma. However, as with all corticosteroids, the drug has the potential to suppress adrenal function and cause growth impairment in children (reviewed by Holliday et al.[11]).

Both salmeterol and fluticasone propionate are highly lipophilic and have long durations of effect at their sites of action in the lung.[1,15] The bronchodilatory effect of salmeterol persists for more than 12 hours as a result of high affinity binding to an exosite located within the $\beta_2$-adrenoceptor (reviewed by Spencer and Jarvis[10]). Fluticasone propionate has a similarly high affinity for the glucocorticoid receptor, and the half-life of the steroid-receptor complex is >10 hours.[15]

The systemic pharmacodynamic effects of salmeterol and fluticasone propionate administered together are similar to those observed when the drugs are given alone or concurrently.[10] No evidence of interaction between the 2 drugs was observed in single and multiple dose studies of the effects of fluticasone propionate on 24-hour urinary cortisol excretion versus equivalent doses of fluticasone propionate alone. Salmeterol/fluticasone propionate 50/l00μg had no significant effect on 24-hour urinary cortisol excretion compared with placebo.[10]

Similarly, in a cumulative dose study comparing a total of 8 doses of combined salmeterol/fluticasone propionate 50/500μg combination with equivalent doses of salmeterol alone, most pharmacodynamic responses to salmeterol (e.g. increased heart rate, electrocardiographic changes, decreased plasma potassium levels and increased blood glucose levels) were unaffected by the presence of fluticasone propionate.[16]

Geometric mean morning serum cortisol levels increased during 12 weeks of treatment with salmeterol plus fluticasone propionate 50/100μg twice daily in children aged 4 to 11 years who had previously been treated with inhaled corticosteroids for persistent asthma (section 3.1).[17] There

were no significant differences in serum cortisol levels, either at baseline or end-point, between patients randomised to combined administration of the 2 drugs via a single Diskus DPI or concurrent administration from 2 separate Diskus DPIs in this double-blind trial (fig. 1). Importantly, fewer patients had values outside the normal range after treatment than at baseline, although percentages were not provided in the paper.[17]

No significant differences in the number of patients with abnormal morning plasma cortisol values or responses to stimulation with synthetic corticotropin were detected in adults with persistent asthma during treatment with combined salmeterol/fluticasone propionate 50/250μg twice daily, either drug alone or placebo in a multicentre randomised double-blind study (section 3.3.1).[18]

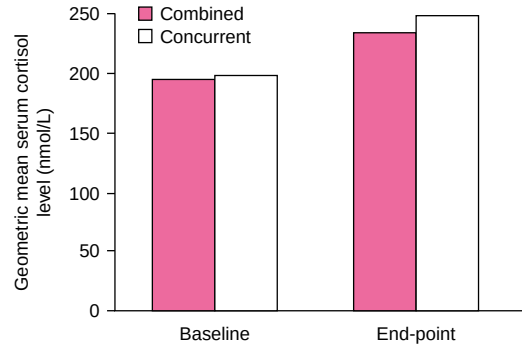


**Fig. 1.** Serum cortisol levels during treatment with salmeterol plus fluticasone propionate in children. Geometric mean serum cortisol levels at baseline and end-point in children aged 4 to ll years with persistent asthma during 12 weeks of twice daily treatment with salmeterol 50μg and fluticasone propionate 100μg either combined in a single Diskus dry powder inhaler (n = 125) or administered concurrently in 2 separate Diskus inhalers (n = 132). Children had been receiving treatment with inhaled corticosteroids (beclomethasone dipropionate, budesonide or flunisolide 400 to 500 μg/day or fluticasone propionate 200 to 250 μg/day) for ≥4 weeks prior to enrolment in this multicentre randomised double-blind trial.[17]

## 2.2 Pharmacokinetic Properties

Because the 2 drugs act locally in the lung, and because plasma concentrations of both salmeterol and fluticasone propionate are low or undetectable when administered by inhalation, few pharmacokinetic data are available. Pertinent pharmacokinetic data are reviewed below and readers are referred to previous reviews in *Drugs*[11-14] for more detailed information on the pharmacokinetics of these 2 entities. No pharmacokinetic data are available from studies in humans pertaining to administration of combined salmeterol/fluticasone propionate.

Salmeterol is not detectable in plasma after administration by inhalation. Both single and multiple dose studies have produced no evidence that concomitant administration of fluticasone propionate causes any alteration in the systemic availability of salmeterol (reviewed by Spencer and Jarvis[10]).

In healthy volunteers, 14.9% of a l000μg inhaled dose of fluticasone propionate, administered as a dry powder, was absorbed from the lungs.[19] Concentrations of the drug in peripheral lung tissue are ≈100-fold greater than those in plasma, and fluticasone propionate could be detected in lung tissue and serum for 16.3 and 13.3 hours, respectively, after inhalation of a single 1000μg dose in patients scheduled to undergo pneumonectomy or lobe resection.[20]

Studies comparing fluticasone propionate monotherapy with each strength of salmeterol/fluticasone propionate suggest that the systemic availability of fluticasone propionate is not increased when salmeterol is given concomitantly.[21]

Both salmeterol and fluticasone propionate are metabolised by cytochrome P450 (CYP) 3A4. Fluticasone propionate is rapidly cleared from the systemic circulation and the sole circulating metabolite, a 17β-carboxylic acid derivative, is not pharmacologically active. Renal clearance accounts for <0.02% of the total clearance of fluticasone propionate (reviewed by Jarvis and Faulds[12]). Salmeterol is transformed to α-hydroxy-salmeterol, which is eliminated predominantly in the faeces. After oral administration of 1mg [$^{14}$C]salmeterol to 2 volunteers, 57.4% of administered radioactivity was recovered in the faeces and 23% in the urine; most was recovered between 24 and 72 hours

after administration. Unchanged salmeterol accounted for <5% of the excreted dose in the urine.

## 3. Therapeutic Efficacy of Combined Salmeterol/Fluticasone Propionate in Patients with Persistent Asthma

The therapeutic efficacy of combined salmeterol/fluticasone propionate in patients with all severities of persistent asthma has been established in large multicentre randomised double-blind parallel-group studies. A series of studies conducted in adults and adolescents aged ≥12 years,[22-24] and 1 study in children aged 4 to 11 years,[17] have demonstrated combined delivery of salmeterol/fluticasone propionate via the Diskus DPI to be clinically equivalent to concurrent delivery of the same dosages of the 2 drugs delivered via separate Diskus DPIs (section 3.1).

Combined salmeterol/fluticasone propionate has recently been formulated as a CFC-free MDI. Two studies have been designed to demonstrate equivalency of this formulation with the Diskus DPI. Preliminary findings of these studies, which are available as abstracts,[25,26] are summarised in section 3.2.

The efficacy of combined salmeterol/fluticasone propionate was subsequently compared with that of the individual components in 3 well designed US studies which enrolled adults and adolescents aged ≥12 years (section 3.3).[18,27,28]

A further series of randomised double-blind parallel-group studies have compared combined salmeterol/fluticasone propionate with inhaled budesonide alone,[29-31] or administered concurrently with inhaled formoterol (section 3.4),[32] and with oral montelukast plus fluticasone propionate (section 3.5).[33] Two of these studies have not yet been published in full,[30,31] but some data are available in abstracts.

With the exception of 1 study that enrolled some patients with a history of recent salmeterol treatment alone (section 3.3.1),[27] and another trial, in which participants had previously used short acting $\beta_2$-agonists only (section 3.3.2),[28] eligible patients in all studies had symptomatic asthma despite ongoing treatment with inhaled corticosteroids.

The dose of inhaled salmeterol (50 μg/actuation) was constant in all studies regardless of whether patients received the drug alone, in combination or concurrently with fluticasone propionate. The dose of inhaled fluticasone propionate varied (100, 250 or 500 μg/actuation). All inhaled products were administered as 1 actuation twice daily. With the exception of studies described in section 3.2[25,26] and the study in section 3.3.2,[28,34] which used CFC-free MDIs, all inhaled drugs were administered via the Diskus DPI.

Compliance with inhaled therapies was generally good in all studies that reported this parameter. Overall mean compliance rates, as measured with the dose counter on the Diskus device, ranged from 91 to 100% in the various treatment groups.[17,18,22,23,27,33] No patients were withdrawn from 2 large US studies because of poor compliance with the study regimen.[18,27] In other trials ≤2% of patients were withdrawn because of noncompliance.[22-24]

### 3.1 Compared with Concurrent Salmeterol and Fluticasone Propionate

The results of a series of well-designed 12-week studies in patients with mild to severe persistent asthma demonstrate that combined administration of salmeterol/fluticasone propionate via a single Diskus DPI is clinically equivalent to concurrent administration of the 2 drugs by separate Diskus DPIs.[17,22-24] Patients eligible for these multicentre randomised double-blind parallel-group studies had symptomatic asthma and a peak expiratory flow (PEF) between 50 and 85% of the predicted value [measured 15 minutes after inhalation of salbutamol (albuterol) 400μg] despite ≥4 weeks treatment with inhaled corticosteroids (pretreatment dosage ranges are included in table I). A combined day- and night-time asthma symptom score of ≥2 on 3 or more of the last 7 days of the 2-week run-in period was required in adults and adolescents.[22-24] Children aged 4 to 11 years were eligible for inclusion if they had a combined day- and

**Table I.** Summary of multicentre randomised double-blind parallel-group studies in which patients with mild to severe persistent asthma (PEF = 50 to 85% predicted) received combined salmeterol/fluticasone propionate (S/FP) or concurrent salmeterol plus fluticasone propionate (S + FP) via separate inhalation devices for 12 weeks

| Reference | Regimen[a] (no. of pts) | Mean PEF (am, pm; L/min)[b] | | Mean $FEV_1$ (L) [% predicted] | | Median asthma symptom score of 0 (% of pts) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | daytime | | night-time | |
| | | BL | change at end-point | BL | change at end-point | BL | end-point | BL | end-point |
| **Adults and adolescents aged ≥12 years** | | | | | | | | | |
| Aubier et al.[22]c | S/FP 50/500 (167) | 359 | ↑35*, ↑29* | 2.44 [73] | ↑0.29 | NR | NR | NR | NR |
| | S50 + FP500 (171) | 345 | ↑33, ↑23 | 2.32 [73] | ↑0.16 | NR | NR | NR | NR |
| | FP500 (165) | 351 | ↑15, ↑9 | 2.33 [73] | ↑0.23 | NR | NR | NR | NR |
| Bateman et al.[23]c | S/FP 50/100 (121) | 368, 381 | ↑42, ↑36 | 2.42 [75] | ↑0.23[d] | 17 | 60 | 42 | 85 |
| | S50 + FP100 (123) | 365, 376 | ↑33, ↑30 | 2.33 [76] | ↑0.26[d] | 15 | 64 | 37 | 89 |
| Chapman et al.[24]c | S/FP 50/250 (180) | 398, 415 | ↑43, ↑35 | 2.51 [75] | ↑0.26[e] | 1 | 35 | 34 | 62 |
| | S50 + FP250 (191) | 391, 415 | ↑36, ↑25 | 2.55 [77] | ↑0.24[e] | 2 | 32 | 30 | 53 |
| **Children aged 4 to 11 years** | | | | | | | | | |
| Van den Berg et al.[17]c | S/FP 50/100 (125) | 226[d] | ↑33, ↑29 | 1.53 [86] | ↑0.21 | 24 | 61 | 49 | 78 |
| | S50 + FP100 (132) | 231[d] | ↑28, ↑25 | 1.57 [84] | ↑0.13 | 20 | 59 | 51 | 76 |

a Drug dose in μg. Inhaled twice daily from a Diskus dry powder inhaler.

b If only 1 value is provided, it is the morning value.

c All patients had been receiving inhaled corticosteroids for ≥4 weeks at baseline: 1500 to 2000 μg/day of BDP or BUD or 750 to 1000 μg/day of FP in the study by Aubier et al.;[22] 400 to 500 μg/day of BDP or BUD or 200 to 250 μg/day of FP in the study by Bateman et al.;[23] 800 to 1200 μg/day of BDP or BUD or 400 to 600 μg/day of FP in the study by Chapman et al.;[24] 400 to 500 μg/day of BDP, BUD or FLN or 200 to 250 μg/day of FP in the study by Van den Berg et al.[17]

d Values estimated from a graph.

e $FEV_1$ was determined after 28 weeks of treatment.

**am** = morning; **BDP** = beclomethasone dipropionate; **BL** = baseline; **BUD** = budesonide; **$FEV_1$** = forced expiratory volume in 1 second; **FLN** = flunisolide; **NR** = not reported; **PEF** = peak expiratory flow; **pm** = evening; **pts** = patients; ↑ indicates increase; * $p < 0.001$ *vs* FP.

night-time score of 1 or more on ≥4 of the last 7 days during the run-in phase.[17] Exclusion criteria included treatment with a long-acting $\beta_2$-agonist within the previous 4 weeks or treatment with systemic corticosteroids within the preceding 12 weeks.[17,23,24]

#### *3.1.1 Effects on Lung Function*

Compared with baseline values, lung function improved in patients treated with combined or concurrent salmeterol and fluticasone propionate for 12 weeks. No significant differences in mean morning PEF, the primary efficacy variable, mean evening PEF or forced expiratory volume in 1 second ($FEV_1$) were detected in adults or adolescents randomised to combined or concurrent therapy with salmeterol and fluticasone propionate 50/100,[23] 50/250[24] or 50/500μg[22] twice daily (table I).

Significantly greater improvements in mean morning PEF were obtained in patients receiving combined salmeterol/fluticasone propionate 50/500μg twice daily than monotherapy with fluticasone propionate 500μg twice daily (table I, $p < 0.001$).[22]

#### 3.1.2 Effects on Asthma Symptoms

Asthma symptoms generally improved during 12 weeks of treatment with combined or concurrent salmeterol plus fluticasone propionate.

Among adults or adolescents treated with salmeterol plus fluticasone propionate 50/100μg twice daily, the proportion of patients with a median daytime symptom score of 0 increased from ≤17% during the run-in period to ≥60% during 12 weeks of combined or concurrent treatment.[23] The results of the study which evaluated salmeterol/fluticasone propionate 50/250μg twice daily were consistent with these findings.[24] Baseline values were somewhat lower (≤2%) but, again, substantial increases in the proportion of patients with median daytime symptom scores of 0 (≥32%) occurred during combined and concurrent treatment (table I).

Similar trends were evident in the proportion of patients in whom ≥75% of days or nights were symptom free. During the run-in period, ≤3% of patients had ≥75% symptom-free days.[23,24] These proportions increased to ≥40% and ≥15% of patients during 12 weeks of treatment with salmeterol/fluticasone propionate 50/100[23] or 50/250μg.[24] Likewise the proportion of patients with ≥75% symptom-free nights increased from 10 to 20% during the run-in period to 42 to 57% during treatment. Importantly, there were no significant differences between patients randomised to combined or concurrent treatment in either study.[23,24]

During 12 weeks of treatment with salmeterol/fluticasone 50/500μg twice daily the mean percentage of days (39%) and nights (≥56%) with no symptoms, and days (≥46%) and nights (≥66%) with no need for as-needed bronchodilators was similar in patients randomised to combined or concurrent therapy.[22]

#### 3.1.3 In Children Aged 4 to 11 Years

Treatment with salmeterol plus fluticasone propionate improved lung function and reduced asthma symptoms in children aged 4 to 11 years who were previously being treated with inhaled corticosteroids (table I). Analogous to results obtained in adults and adolescents aged ≥12 years (sections 3.1.1, 3.1.2), the degree of improvement was similar in children randomised to combined or concurrent treatment.[17] After 12 weeks of combined or concurrent treatment with salmeterol/fluticasone propionate 50/100μg twice daily, mean morning PEF had increased by approximately 30 L/min and the proportion of patients who had median daytime symptom scores of 0 increased approximately 2.5- to 3-fold (table I). The median percentage of symptom-free days, symptom-free nights and rescue-medication-free days also increased to a similar extent during combined or concurrent treatment.[17]

### 3.2 Dry Powder Inhaler versus Metered Dose Inhaler

Most comparative studies involving combined salmeterol/fluticasone propionate used the Diskus DPI (sections 3.1, 3.3.1, 3.4, 3.5). However, the combination has been formulated as a CFC-free MDI and equivalency between the 2 delivery devices has been demonstrated in 2 multicentre randomised double-blind parallel-group studies (reported as abstracts).[25,26] Adults and adolescents enrolled in these studies had symptomatic mild to severe persistent asthma ($FEV_1$ = 50 to 100% predicted) despite ongoing treatment with inhaled corticosteroids. Improvements in mean morning PEF were similar after 12 weeks of treatment with combined salmeterol/fluticasone propionate 50/100[25] or 50/500[26] delivered via the DPI or MDI (table II).

Consistent with the findings of another study that used the CFC-free MDI (section 3.3.2)[28,34] and with several trials that used the Diskus DPI (section 3.1 and 3.3.1),[18,22,27] combined salmeterol/fluticasone propionate via MDI, but not DPI, produced significantly greater improvements in mean morning PEF than fluticasone propionate alone (table II).[25,26]

**Table II.** Summary of multicentre randomised double-blind parallel-group trials in which adults and adolescents aged ≥11 years with mild to severe persistent asthma ($FEV_1$ = 50 to 100% predicted) received combined salmeterol/fluticasone propionate S/FP administered by either a Diskus dry powder inhaler (DPI) or a chlorofluorocarbon-free metered dose inhaler (MDI) for 12 weeks

| Reference | Treatment[a] (no. of patients) | Morning PEF (L/min, change from baseline) |
|---|---|---|
| Bateman et al.[25] (abstract) | S/FP 50/100 DPI (167) | ↑46 |
| | S/FP 50/100 MDI (165) | ↑43* |
| | FP 100 MDI (165) | ↑24 |
| van Noord et al.[26] (abstract) | S/FP 50/500 DPI (161) | ↑48 |
| | S/FP 50/500 MDI (176) | ↑50* |
| | FP 500 MDI (172) | ↑27 |

a Inhaled twice daily.

**$FEV_1$** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; ↑ indicates increase; * $p < 0.001$ *vs* FP 100 MDI.

## 3.3 Compared with Salmeterol or Fluticasone Propionate Alone

### *3.3.1 In Patients Previously Treated with Inhaled Corticosteroids or Salmeterol*

The comparative efficacy of combined salmeterol/fluticasone propionate and the 2 drugs given as monotherapy has been evaluated in 2 multicentre randomised double-blind placebo-controlled parallel-group studies in the US. The design of these studies is presented in table III. In 1 study patients were stratified according to whether they had received inhaled corticosteroids for ≥12 weeks or monotherapy with inhaled salmeterol for ≥1 week prior to enrolment.[27] Of 356 patients enrolled in the trial, 250 (70%) had a history of recent inhaled corticosteroid use and 106 (30%) were using salmeterol before screening. All patients eligible for the second study had taken inhaled corticosteroids for ≥12 weeks prior to enrolment.[18]

Three primary efficacy variables were selected to evaluate both the bronchodilatory properties [area under the $FEV_1$ versus time curve ($AUC_{0\text{-}12h}$ $FEV_1$)] of the long-acting $\beta_2$-agonist and the increased disease stability resulting from the corticosteroid (probability of remaining in the study and morning predose $FEV_1$) in the combination product (table III).

#### Effects on Lung Function

Combined salmeterol/fluticasone produced rapid and consistent improvements in lung function that were maintained throughout the duration of the 2 studies. Significantly greater increases in $AUC_{0\text{-}12h}$ $FEV_1$ were apparent after 1 dose of combined salmeterol/fluticasone propionate compared with fluticasone propionate or placebo in both studies ($p \leq 0.028$; fig. 2). The magnitude of these improvements increased over the duration of the study such that $AUC_{0\text{-}12h}$ $FEV_1$ was significantly greater in

**Table III.** Design of 2 US studies in which patients with persistent asthma received combined salmeterol/fluticasone propionate administered by a Diskus dry powder inhaler[18,27]

| | |
|---|---|
| Design | Multicentre randomised double-blind parallel-group |
| Duration | Placebo run-in phase: 2 weeks |
| | Active treatment phase: 12 weeks |
| Treatments (inhaled twice daily) | Combined salmeterol/fluticasone propionate |
| | Salmeterol |
| | Fluticasone propionate |
| | Placebo |
| **Inclusion criteria** | |
| Aged ≥12 years | |
| ≥6 month history of asthma requiring pharmacotherapy | |
| $FEV_1$ 40 to 85% predicted | |
| ≥15% increase in $FEV_1$ 30 min after inhaling 2 puffs of salbutamol (albuterol) | |
| **Exclusion criteria** | |
| History of life threatening asthma | |
| Smoking within the previous year or >10 pack/year history | |
| Use of oral or injectable corticosteroids in the previous month | |
| Use of daily oral corticosteroids in the previous 6 months | |
| Awakenings because of asthma on >3 of 7 nights in the run-in phase | |
| Use of ≥12 puffs/day of salbutamol for >3 days during the run-in phase | |
| **Primary outcome measures** | |
| $AUC_{0\text{-}12hr}$ $FEV_1$ relative to baseline | |
| Morning predose $FEV_1$ | |
| Probability of remaining in the study. Withdrawal criteria included: | |
| • exacerbations requiring emergency treatment, hospitalisation or treatment with medication not allowed by the protocol | |
| • >20% decrease in $FEV_1$ from baseline | |
| • >20% decrease in mean morning PEF from baseline on 3 of 7 days | |
| • ≥12 puffs/day of salbutamol on >2 of 7 days | |
| • awakenings because of asthma on >2 of 7 days | |

**$AUC_{0\text{-}12hr}$** **$FEV_1$** = area under the $FEV_1$ *vs* time curve during the 12-hour dosage interval; **$FEV_1$** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow.

patients treated with the combination than in patients in each of the other study groups after 1 and 12 weeks of treatment (fig. 2).[18,27]

Improvements in $FEV_1$ were consistent between studies and were significantly greater in those treated with combined salmeterol/fluticasone propionate 50/100μg or 50/250μg than either salmeterol 50μg or fluticasone propionate 100 or 250μg twice daily alone (table IV). Between baseline and end-point, $FEV_1$ increased by 22[18] and 24%[27] in patients treated twice daily with the combination, 2[18] and 5%[27] in those treated twice daily with salmeterol 50μg and 12[18] and 13%[27] in those treated twice daily with fluticasone propionate 250 and 100μg, respectively. $FEV_1$ was little changed or deteriorated during the course of placebo administration. These findings demonstrate the complementary effects of combined therapy with salmeterol and fluticasone propionate.[18,27]

Retrospective analyses demonstrate that combined salmeterol/fluticasone propionate had a significantly ($p < 0.001$) faster onset of effect, defined as a ≥15% increase in $FEV_1$ within 4 hours of administration on day 1, than placebo or fluticasone propionate.[35,36] In the higher dose study,[18] this was achieved in 78% of patients treated with the combination, but in only 33 and 30% of patients treated with fluticasone propionate 250μg ($p \leq 0.001$) or placebo ($p \leq 0.019$).[35] A similar trend was observed with mean morning PEF within 24 hours (fig. 3).[35]

A series of subanalyses, which are available as abstracts, demonstrate that improvements in lung function ($FEV_1$) were similar in patients regardless of their baseline corticosteroid therapy in both studies,[37,38] or whether they were using inhaled corticosteroids or salmeterol prior to the study of Kavuru et al.[27,39]

As expected in patients who required pharmacotherapy for ≥6 months prior to enrolment in these studies, combination salmeterol/fluticasone propionate and fluticasone propionate monotherapy produced significantly greater improvements in lung function than placebo.[18,27] The marginal improvement obtained with salmeterol monotherapy

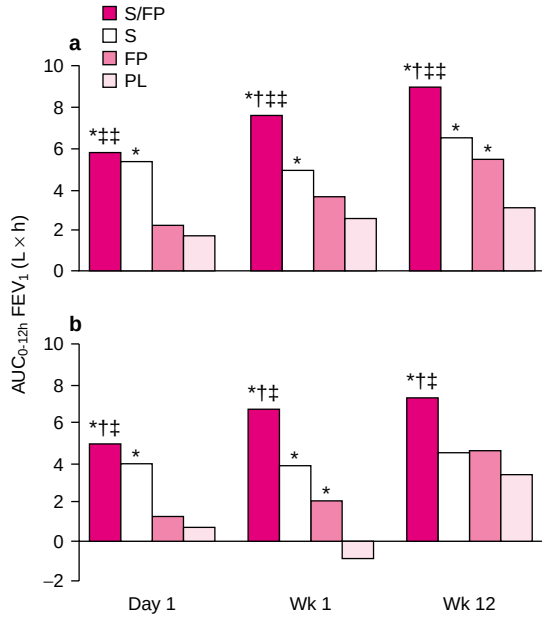


**Fig. 2.** Improvements in lung function during treatment with combined salmeterol/fluticasone propionate (S/FP) in adults and adolescents with persistent asthma. Area under the curve of forced expiratory volume in 1 second versus time ($AUC_{0\text{-}12h}$ $FEV_1$) after the first dose on day 1, and after 1 and 12 weeks of treatment in patients randomised to twice daily S/FP, S 50μg, FP or placebo (PL) in 2 multicentre randomised double-blind parallel-group trials. Patients received S/FP 50/100μg in the trial by Kavuru et al.[27] [n = 335 in total (**a**)] and S/FP 50/250μg in the trial by Shapiro et al.[18] [n = 336 (**b**)]. Dosages of FP corresponded to that in the combination in either trial. * $p \leq 0.028$ *vs* PL; † $p \leq 0.025$ *vs* S; ‡ $p = 0.003$, ‡‡ $p < 0.001$ *vs* FP.

substantiate recommendations in guidelines that this drug not be used as monotherapy in patients with persistent asthma.[8,9,40]

### Withdrawals Because of Worsening Asthma

At the end of 12 weeks of treatment, the probability of being withdrawn from either study was significantly lower in patients randomised to combination therapy than in each of the other groups (table IV). Placebo recipients had the highest rate of withdrawal for worsening asthma (≥49%) followed by salmeterol-treated patients (≥35%); findings which further demonstrate the need for

**Table IV.** Summary of multicentre randomised double-blind parallel-group trials in which adults and adolescents aged ≥12 years with mild to severe persistent asthma ($FEV_1$ = 40 to 85% predicted) received combined salmeterol/fluticasone propionate (S/FP), or monotherapy with the individual components for 12 weeks

| Treatment[a] (no. of patients randomised/included in efficacy analysis)[b] | Time | Results (mean change from baseline at the end of the study)[c] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $FEV_1$ (L) [% predicted] | PEF (am, pm; L/min) | daytime symptom score[d] | days with no asthma symptoms (%) | nights with no awakenings (%) | as-needed $\beta_2$-agonist usage (puffs/day) | no. of withdrawals for worsening asthma (%) |
| **In patients previously treated with inhaled corticosteroids or salmeterol** | | | | | | | | |
| ***Kavuru et al.*[27][e]** | | | | | | | | |
| S/FP 50/100 (92/87) | BL | 2.17 [64] | 393; 418 | 1.5 | 25.2 | 91.7 | 3.1 | 3 (3)*†‡ |
| | EP | ↑0.51*†‡‡‡ | ↑52.5*†‡; ↑35*†‡ | ↓0.7*†‡ | ↑22.6*†‡ | ↑4.6*† | ↓1.9*†‡ | |
| S50 (92/86) | BL | 2.13 [64] | 369; 396 | 1.8 | 12.6 | 91.6 | 3.3 | 30 (35)** |
| | EP | ↑0.11 | ↓1.7*; ↓7.4 | ↓0.1* | ↑8* | ↓5.3* | ↓0.3* | |
| FP100 (90/85) | BL | 2.11 [64] | 374; 390 | 1.6 | 19.4 | 91.3 | 3.1 | 9 (11)** |
| | EP | ↑0.28* | ↑17.3*; ↑18* | ↓0.2* | ↑7.2 | ↑2.4* | ↓0.4* | |
| PL (82/77) | BL | 2.15 [64] | 382; 398 | 1.8 | 15.8 | 89.9 | 3.2 | 38 (49) |
| | EP | ↑0.01 | ↓23.7; ↓13.3 | ↑0.4 | ↓3.8 | ↓16.5 | ↑1.7 | |
| ***Shapiro et al.*[18][f]** | | | | | | | | |
| S/FP 50/250 (84/81) | BL | 2.23 [69] | 367; 388 | 1.4 | 26.5 | 90.7 | 3.5 | 3 (4)**†††‡‡ |
| | EP | ↑0.48*†‡‡ | ↑53.5*†††; ↑45.4*††‡ | ↓0.8*††‡ | ↑33.8*††‡ | ↑7.2*††‡ | ↓2.3*††‡ | |
| S50 (88/84) | BL | 2.2 [67] | 372; 393 | 1.6 | 19.2 | 89.7 | 3.8 | 32 (38) |
| | EP | ↑0.05* | ↓11.6; ↓13.7 | ↑0.1* | ↑2.1 | ↓8.0 | 0* | |
| FP250 (84/81) | BL | 2.12 [66] | 374; 388 | 1.6 | 23.5 | 90.5 | 3.2 | 18 (22) |
| | EP | ↑0.25* | ↑15.2*; ↑7.9* | ↓0.4* | ↑15.4* | ↑2.8* | ↓0.9* | |
| PL (93/90) | BL | 2.19[68] | 373; 396 | 1.6 | 24.1 | 89.1 | 3.8 | 56 (62) |
| | EP | ↓0.11 | ↓14.1; ↓15.8 | ↑0.4 | ↓7.9 | ↓12.0 | ↑0.9 | |
| **In patients previously treated with as-needed short acting $\beta_2$-agonists alone** | | | | | | | | |
| ***Nelson et al.*[28,34] *(abstracts)*** | | | | | | | | |
| S/FP 50/100 (95) | BL | [40 to 85] | 356; 385 | NR | NR | NR | NR | (1) |
| | EP | ↑0.69†‡ | ↑66†††‡‡; ↑51†††‡‡ | NR | NR | NR | NR | |
| S50 (91) | BL | [40 to 85] | 364; 391 | NR | NR | NR | NR | (7) |
| | EP | ↑0.47 | ↑29; ↑22 | NR | NR | NR | NR | |
| FP100 (97) | BL | [40 to 85] | 361; 394 | NR | NR | NR | NR | (2) |
| | EP | ↑0.51 | ↑43; ↑30 | NR | NR | NR | NR | |

a Drug dose in μg. Inhaled twice daily from a Diskus dry powder inhaler,[18,27] or a chlorofluorocarbon-free pressurised metered dose inhaler.[28,34]

b Data from 1 site in the studies by Kavuru et al.[27] (n = 13) and Shapiro et al.[18] (n = 21) were excluded because of significant deviations from good clinical practice.

c Intention to treat analyses were used with the last measurement carried forward for patients with missing values.

d The daytime symptom score is the mean of the patient's responses to 4 questions (0 indicates best; 6 indicates worst).

e Patients had received inhaled corticosteroids continuously for ≥12 weeks [including either BDP (252 to 420 μg/day), TAA (600 to 1000 μg/day), FLN (1000 μg/day) or FP (176 μg/day) for ≥1 month] or inhaled salmeterol for ≥1 week prior to screening.

f Patients had received inhaled corticosteroids continuously for ≥12 weeks and had received either BDP (462 to 672 μg/day) TAA (1100 to 1600 μg/day) FLN (1250 to 2000 μg/day) or FP (440 μg/day) for ≥4 weeks prior to screening.

**am** = morning; **BDP** = beclomethasone dipropionate; **BL** = baseline; **EP** = end-point; **$FEV_1$** = forced expiratory volume in 1 second; **FLN** = flunisolide; **NR** = not reported; **PEF** = peak expiratory flow; **pm** = evening; **TAA** = triamcinolone acetonide; ↓ indicates decrease; ↑ indicates increase; * $p \leq 0.036$, ** $p \leq 0.007$ *vs* PL; † $p \leq 0.025$, †† $p \leq 0.003$ *vs* S; ‡ $p \leq 0.023$, ‡‡ $p \leq 0.003$, ‡‡‡ $p < 0.001$ *vs* FP.

anti-inflammatory therapy in patients similar to those enrolled in these studies.[18,27]

In the study by Kavuru et al.,[27] the probability of withdrawing from any randomised treatment because of worsening asthma was similar regardless of whether patients were receiving inhaled corticosteroids or salmeterol monotherapy immediately prior to the study.[38]

### Secondary Efficacy Variables

Consistent with the findings of the primary efficacy analyses (see above), treatment with combined salmeterol/fluticasone propionate produced substantial improvements between baseline and end-point in all secondary outcome variables (morning and evening PEF, daytime symptom scores, days and nights without asthma symptoms and requirements for as-needed β-agonists; table IV). Among patients treated with the combination, improvements in each variable consistently exceeded those obtained in recipients of salmeterol, fluticasone propionate or placebo. Combination therapy was superior to monotherapy with salmeterol and placebo for all outcomes in both studies, and was superior to fluticasone propionate for all but 1 outcome (nights without awakenings) in the study that used the lower dosage (50/100μg) [$p \leq 0.036$, table IV].[27] Monotherapy with fluticasone propionate 100 or 250 μg/day generally improved asthma control and produced significant improvements in secondary outcome parameters in both studies ($p \leq 0.036$ *vs* placebo; table IV).[18,27]

### Effects on Health-Related Quality of Life

Health-related quality of life (QOL) was measured with the Asthma Quality of Life Questionnaire (AQLQ) in the 2 US clinical trials.[41,42] A 3-item sleep scale (not defined) was also used in one study.[42] These studies are available as abstracts and thus only limited data are available.

In both studies, significantly greater improvements in total AQLQ scores were obtained in patients treated with combined salmeterol/fluticasone propionate than in those assigned to monotherapy with fluticasone propionate, salmeterol or placebo ($p \leq 0.05$).[41,42]

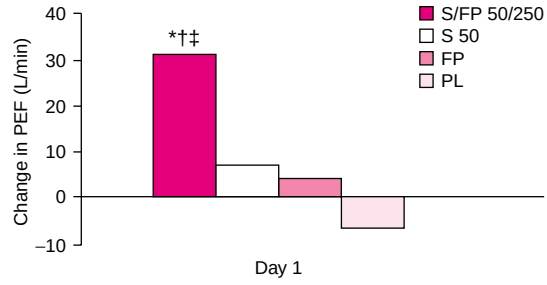


**Fig. 3.** Onset of effect of inhaled salmeterol/fluticasone propionate (S/FP) in patients with persistent asthma. Change in mean morning peak expiratory flow (PEF) within 24 hours of administration of twice daily S/FP 50/250μg, S 50μg, FP 250μg or placebo (PL) in 349 patients enrolled in a multicentre randomised double-blind parallel-group study.[18,35] * $p \leq 0.019$ *vs* PL; † $p \leq 0.025$ *vs* S; ‡ $p \leq 0.001$ *vs* FP.

Clinically significant differences in total AQLQ scores, defined as ≥0.5 units, were obtained in patients treated with the combined salmeterol/fluticasone propionate compared with placebo (1.3 units) and salmeterol 50μg (≥1 units) but not fluticasone propionate 100μg (0.43 units[42]) or 250μg (0.45 units[41]).[41,42]

Among patients receiving salmeterol/fluticasone propionate 50/100μg, sleep scores also improved significantly compared with those in the other 3 treatment groups.[42]

Patients treated with combined salmeterol/fluticasone propionate 50/250μg also had statistically and clinically significant improvements on each of the 4 subscales of the AQLQ (Activity Limitation, Asthma Symptoms, Emotional Function and Environmental Exposure) compared with recipients of salmeterol 50μg or placebo ($p \leq 0.05$).[41] When scores in patients treated with salmeterol/fluticasone propionate 50/250μg and fluticasone propionate 250μg were compared, significantly ($p \leq 0.05$) greater improvements in Asthma Symptoms, Emotional Function and Environmental Exposure were obtained in recipients of the combination, but only scores for Emotional Function exceeded the threshold for clinical significance (fig. 4).[41]

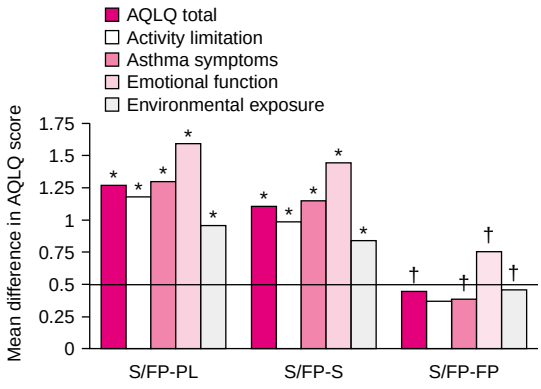


**Fig. 4.** Mean changes in Asthma Quality of Life Questionnaire (AQLQ) scores and subscores in patients with persistent asthma treated with combined salmeterol/fluticasone propionate (S/FP). Differences in AQLQ scores (including individual domains) after 12 weeks of treatment in recipients of twice daily S/FP 50/250μg and placebo (PL); S/FP 50/250μg and S 50μg; and S/FP 50/250μg and FP 250μg. Results of a multicentre randomised double-blind parallel-group study in 336 patients.[18,41] Differences ≥0.5 units (indicated by the horizontal line) are considered to be clinically significant. * $p \leq 0.001$ *vs* PL or S; † $p \leq 0.05$ *vs* FP.

#### *3.3.2 In Patients Previously Treated with As-Needed $\beta_2$-Agonists Alone*

Combined salmeterol/fluticasone propionate has been compared with salmeterol or fluticasone propionate monotherapy in patients who had previously been receiving as-needed short acting $\beta_2$-agonist bronchodilators alone. In contrast to the studies described in section 3.3.1, which used the Diskus DPI, drugs were delivered by CFC-free MDIs in this multicentre randomised double-blind study. Importantly, the Diskus DPI and CFC-free MDI formulations of combined salmeterol/fluticasone propionate have been shown to be clinically equivalent in well-designed studies (section 3.2). This study has not yet been fully published, but preliminary results are available in abstracts.[28,34]

Consistent with studies in patients previously treated with inhaled corticosteroids or salmeterol (section 3.3.1), combined salmeterol/fluticasone propionate 50/100μg produced greater improvements in lung function than either component alone. Compared with fluticasone propionate monotherapy, significantly greater increases in $AUC_{0\text{-}12h}$ $FEV_1$ were apparent on day 1 of treatment with combined salmeterol/fluticasone propionate ($p < 0.001$).[28] After 12 weeks of treatment with the combination, improvements in $AUC_{0\text{-}12h}$ $FEV_1$, mean morning and evening PEF, and $FEV_1$ were significantly greater than those in patients treated with salmeterol or fluticasone propionate alone ($p \leq 0.018$).[28,34] Recipients of the combination also required as-needed $\beta_2$-agonists on significantly fewer days than fluticasone propionate recipients ($p = 0.028$).[34] The frequency of withdrawals for asthma exacerbations was lowest in the group receiving the combination (table IV).[28]

### 3.4 Compared with Budesonide or Concurrent Budesonide plus Formoterol

Combined salmeterol/fluticasone propionate twice daily produced greater improvements in lung function and asthma symptoms than monotherapy with budesonide in patients with persistent asthma.[29,31]

Combined salmeterol/fluticasone propionate 50/250μg had a rapid onset of action, such that, throughout the first week of a randomised, double-blind study,[29,43] mean morning PEF was significantly greater, and the proportion of patients with no symptoms or no need for as-needed $\beta_2$-agonists was significantly lower than in patients treated with inhaled budesonide 800μg twice daily ($p < 0.05$). These trends were maintained throughout the 24-week study. In patients treated with the combination product for 24 weeks, mean morning (table V) and evening PEF (416 *vs* 398 L/min, $p < 0.001$), and mean $FEV_1$ (2.53 *vs* 2.44L, $p < 0.05$) were significantly greater than in patients treated with budesonide alone. Consistent with the improvements in lung function, the median number of days with no symptoms (60 *vs* 34%, $p \leq 0.001$) and days (68 *vs* 37%, $p \leq 0.001$) and nights (90 *vs* 82%, $p = 0.029$) in which no as-needed salbutamol was required were significantly lower in patients

**Table V.** Results of multicentre randomised double-blind parallel-group studies in which patients with mild to severe persistent asthma ($FEV_1$ 50 to 85%) were treated with combined salmeterol/fluticasone propionate (S/FP) or budesonide (BUD) alone or with concurrent formoterol (FM)

| Regimen (no. of patients)[a] | Duration (wk) | Morning PEF (L/min) | |
|---|---|---|---|
| | | baseline | end-point |
| **Jenkins et al.**[29][b] | | | |
| S/FP 50/250 (180) | 24 | 361 | 406** |
| BUD 800 (173) | 24 | 358 | 380 |
| **Johansson et al.**[31][b] **(abstract)** | | | |
| S/FP 50/100 (349)[c] | 12 | 383 | 427* |
| BUD 400 | 12 | 382 | 413 |
| **Ringdal et al.**[32][b] **(abstract)** | | | |
| S/FP 50/250 (428)[c] | 12 | 349 | 389 |
| BUD 800 + FM 12 | 12 | 348 | 393 |

a Dosages in μg. Inhaled twice daily from dry powder inhalers.

b Patients were receiving treatment with inhaled corticosteroids prior to enrolment: BUD 800-1200 or FP 400-600 μg/day for ≥4 weeks in the study by Jenkins et al.;[29] ≤500 μg/day in the study by Johansson et al.;[31] BUD 1000-1600 or FP 500-800 μg/day in the study by Ringdal et al.[32]

c Total no. of patients enrolled in the trial.

**$FEV_1$** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; * p = 0.006; ** p < 0.001 *vs* BUD.

treated with the combination than budesonide over 24 weeks.

The frequency and severity of asthma exacerbations was similar during treatment with either regimen. The majority of patients (70% in each group) experienced no asthma exacerbations over 24 weeks of treatment. Only 3 patients, including 1 who was receiving combined salmeterol/fluticasone propionate, experienced severe exacerbations during the study, which were defined as those requiring emergency hospital treatment.[29]

QOL was measured in a subset of patients enrolled in this trial. Consistent with studies described above (section 3.3.1), the combination produced clinically significant improvements (≥0.5 units) in total AQLQ score and scores on 3 of 4 individual domains (Asthma Symptoms, Emotion and Environment) compared with baseline. Although improvements in total AQLQ scores were significantly greater in patients treated with the combination than budesonide 800μg after 24 weeks (0.6 *vs* 0.33, $p < 0.05$); the difference did not exceed the threshold for clinical significance.[30]

Improvements in mean morning PEF were significantly ($p \leq 0.006$) greater among 349 patients with moderate persistent asthma (mean baseline $FEV_1$ 76% predicted) randomised to salmeterol/fluticasone propionate 50/100μg twice daily than budesonide 400μg twice daily in a further 12-week study (table V). Mean evening PEF also improved to a greater extent in recipients of the combination (difference 14L/min, $p = 0.002$) and $FEV_1$ and symptom scores improved with both treatments, although baseline and end-point values for these parameters were not presented in the abstract.[31]

Combined salmeterol/fluticasone propionate 50/250μg was equivalent to concurrent budesonide 800μg plus formoterol 12μg twice daily in a randomised double-blind multicentre study (table V). When averaged over 12 weeks of treatment, the mean morning PEF was identical (386 L/min) in the 2 treatment groups.[32]

### 3.5 Compared with Montelukast plus Fluticasone Propionate

Combined salmeterol/fluticasone propionate 50/100μg was more effective than the addition of oral montelukast 10 mg/day to fluticasone propionate 100μg twice daily in patients aged ≥15 years with suboptimally controlled asthma. Patients eligible for this 12-week multicentre randomised double-blind parallel-group trial had moderate to severe persistent asthma ($FEV_1$ 50 to 80% predicted), an increase of ≥12% in $FEV_1$ within 30 minutes of inhaling 2 puffs (200μg) of salbutamol and had been taking inhaled corticosteroids for ≥30 days.[33]

Patients with a recent history of hospitalisation for asthma (i.e. within ≤30 days) and those using medications that could interfere with the study (systemic corticosteroids within the previous 30 days, sodium cromoglycate or nedocromil, leukotriene antagonists, theophylline or other long-acting bronchodilators) were excluded.[33]

Patients received fluticasone propionate 100μg twice daily during a 3-week run-in phase. Those

**Table VI.** Summary of a multicentre randomised double-blind parallel-group trial in which patients aged ≥15 years with moderate to severe persistent asthma ($FEV_1$ 50 to 80% predicted) received combined salmeterol/fluticasone propionate 50/100μg twice daily (S/FP), or montelukast 10 mg/day (MK) plus fluticasone propionate 100μg twice daily (FP) for 12 weeks[33]

| Treatment[a] (no. of patients[b]) | Time | Results (mean change from baseline at the end of the study)[c] | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | $FEV_1$ (L) [% predicted] | PEF (am, pm; L/min) | daytime symptom score[d] | | | | patients with asthma exacerbations (%) |
| | | | | total | chest tightness | shortness of breath | wheeze | |
| S/FP (222) | BL | 2.38 [70.0] | 398; 419 | 1.36 | 1.39 | 1.52 | 1.18 | 4 (2)* |
| | EP | ↑0.34** | ↑24.9**; ↑18.9** | ↓0.49 | ↓0.49 | ↓0.56* | ↓0.41 | |
| MK + FP (225) | BL | 2.39 [70.8] | 392; 411 | 1.33 | 1.32 | 1.54 | 1.13 | 13 (6) |
| | EP | ↑0.20 | ↑13 ; ↑9.6 | ↓0.41 | ↓0.43 | ↓0.40 | ↓0.38 | |

a Inhaled medication was delivered via Diskus dry powder inhalers. Montelukast was given in the evening as per the manufacturer's recommendations.

b Patients had been treated with inhaled corticosteroids (beclomethasone dipropionate 252 to 420 μg/day, budesonide 400 μg/day, flunisolide 1000 μg/day, FP 176 to 220 μg/day or triamcinolone acetonide 600 to 800 μg/day) for ≥1 month prior to screening.

c Intention to treat analyses were used with the last measurement carried forward for patients with missing values.

d The daytime symptom score is the mean of the patient's responses to 4 questions (0 indicates best; 6 indicates worst).

**am** = morning; **BL** = baseline; **EP** = end-point; **$FEV_1$** = forced expiratory volume in 1 second; **PEF** = peak expiratory flow; **pm** = evening; ↓ indicates decrease; ↑ indicates increase; * $p \leq 0.032$, ** $p < 0.001$ *vs* MK + FP.

who had an $FEV_1$ between 50 and 80% predicted and who were symptomatic during the last 7 days of this period (use of ≥4 puffs/day of salbutamol and/or symptom score of ≥2 on ≥3 days and/or ≥3 night-time awakenings due to asthma) were randomised to 12 weeks of treatment with combined salmeterol/fluticasone propionate 50/100μg twice daily or montelukast 10 mg/day (taken at bedtime) plus fluticasone propionate 100μg twice daily.[33]

#### 3.5.1 Effects on Lung Function

Combined salmeterol/fluticasone propionate produced consistently greater improvements in lung function compared with montelukast plus fluticasone propionate. Mean morning PEF, the primary efficacy variable in the study, was significantly greater among patients treated with the combination on each day during the first week of treatment ($p \leq 0.021$ *vs* montelukast plus fluticasone propionate) and in each week of the study thereafter ($p \leq 0.011$ *vs* montelukast plus fluticasone propionate). Similar trends were evident with mean evening PEF during each week of the study ($p \leq 0.011$ *vs* montelukast plus fluticasone propionate), and clinic $FEV_1$, which was measured at weeks 1, 4, 8 and 12 ($p \leq 0.001$ *vs* montelukast plus fluticasone propionate). Mean changes from baseline in mean morning and evening PEF averaged over weeks 1 to 12 of the study and $FEV_1$ at the end of treatment are presented in table VI.[33]

#### 3.5.2 Effects on Asthma Symptoms

Consistent with improvements in lung function in recipients of combined salmeterol/fluticasone propionate, there were significant reductions in the frequency of as-needed $\beta_2$-agonist usage ($p = 0.014$ *vs* montelukast plus fluticasone propionate), and significant increases in the percentage of days on which as-needed bronchodilators were not required ($p = 0.032$ *vs* montelukast plus fluticasone propionate, fig. 5).[33]

The mean change in total Daytime Asthma Symptom Scores was similar in patients in both treatment groups (table VI) as were scores for Chest Tightness and Wheeze. However, improvements in Shortness of Breath scores decreased by a significantly greater amount in patients treated with the combination ($p = 0.017$ *vs* montelukast plus fluticasone propionate).[33]

Asthma exacerbations, which were defined as any requirement for additional asthma medication, were documented in significantly fewer patients who received the combination product than in those treated with montelukast plus fluticasone propionate during the 12-week study (2 *vs* 6%, p = 0.031, table VI).[33]

## 4. Pharmacoeconomic Considerations

### 4.1 Compared with Fluticasone Propionate

Data from 3 studies that compared the 3 available dosage strengths of combined salmeterol/fluticasone propionate (i.e. 50/100,[27] 50/250[18] and 50/500μg[22]) with equivalent dosages of fluticasone propionate monotherapy have been subjected to cost-effectiveness analyses from the perspective of the Swedish healthcare system.[44] Only direct costs, which were valued in Swedish Kronor (SEK 1998, SEK1 = $US0.12), were considered in these analyses. As described in sections 3.1 (table I) and 3.3.1 (table IV), combined salmeterol/fluticasone propionate was significantly more effective than fluticasone propionate monotherapy in each study.

#### *4.1.1 Total Direct Healthcare Costs*

In all 3 studies, the total costs of asthma management were slightly higher in the combination group than in the fluticasone propionate monotherapy group, largely because of higher acquisition costs. The additional costs varied from SEK0.7 ($US0.08) per day (salmeterol/fluticasone propionate 50/250μg *vs* fluticasone propionate 250μg) to SEK6.6 ($US0.80) per day (salmeterol/fluticasone propionate 50/500μg *vs* fluticasone propionate 500μg). Contacts with the healthcare system were infrequent in patients enrolled in the trials, although economically important. For example, in the studies involving salmeterol/fluticasone propionate 50/l00μg and 50/250μg, nearly 50% of the total costs of asthma management in the fluticasone propionate treatment groups were associated with primary and secondary care visits.[45]

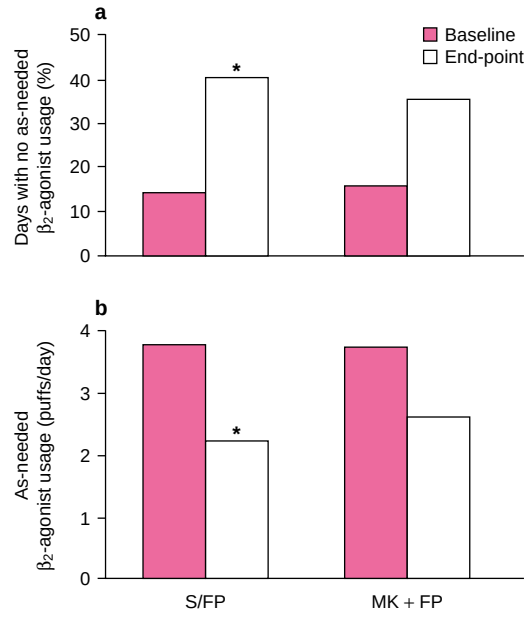


**Fig. 5.** Changes in as-needed $\beta_2$-agonist usage during treatment with combined fluticasone propionate in patients with moderate to severe persistent asthma ($FEV_1$ 50 to 80% predicted). Mean percentage of days in which no as-needed $\beta_2$-agonist bronchodilators were used (**a**) and mean quantity of $\beta_2$-agonist usage [puffs/day (**b**)] during 12 weeks of treatment with combined salmeterol/fluticasone propionate 50/100μg twice daily (S/FP, n = 222) or oral montelukast 10 mg/day plus fluticasone propionate 100μg twice daily (MK + FP, n = 225) in a multicentre randomised double-blind parallel-group study.[33] **$FEV_1$ =** forced expiratory volume in 1 second; * $p \leq 0.032$ *vs* MK + FP.

#### *4.1.2 Incremental Cost Effectiveness Ratios*

Incremental cost-effectiveness ratios (ICERs) comparing results across the 3 studies are presented in table VII. The cost per successfully-treated week was lower for the combination than monotherapy with fluticasone propionate in each study (table VII). For the end-point 'successfully-treated week' (defined as a week with a mean improvement in morning PEF ≥5% of the baseline value) the ICERs varied from SEK12.6 ($US1.53) per additional successfully-treated week with salmeterol/fluticasone propionate 50/250μg to SEK192.1 ($US23.31) per additional successfully-

**Table VII.** Cost effectiveness of twice daily combined salmeterol/fluticasone propionate (S/FP 50/100, 50/250 and 50/500μg) relative to the equivalent dose of fluticasone propionate (FP 100, 250 and 500μg) or budesonide 800μg (BUD) based on data from multicentre randomised double-blind parallel-group trials[44]

| Treatment | End-point (from the perspective of the Swedish healthcare system) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | successfully-treated weeks[a] | | | symptom-free days[b] | | | episode-free days[c] | | |
| | mean proportion (%) | cost/wk (SEK) [$US] | ICER (CI)[d] [SEK/wk] | mean proportion (%) | cost/day (SEK) [$US] | ICER (CI)[d] [SEK/day] | mean proportion (%) | cost/day (SEK) [$US] | ICER (CI)[d] [SEK/day] |
| **Johansson et al.[46] (based on Kavuru et al.[27])** | | | | | | | | | |
| S/FP 50/100μg | 65*** | 150.9 [18.31] | 133.4 (89.4, 215.6) | 44.1 | 31.2 [3.79] | 44.5[e] | 35.6 | 38.7 [4.7] | 46.9[e] |
| FP 100μg | 33 | 169.0 [20.50] | | 34.9 | 25.2 [3.06] | | 28 | 33.8 [4.10] | |
| **Palmqvist et al.[47] (based on Shapiro et al.[18])** | | | | | | | | | |
| S/FP 50/250μg | 74.5*** | 196.3 [23.82] | 12.6 (–82.2, 93.1) | 55.2** | 37.8 [4.59] | 3.9 (–27.8, 37.2) | 43.5** | 48.1 [5.84] | 3.9 (–25.4, 35.9) |
| FP 250μg | 35.1 | 404.5 [49.08] | | 37.1 | 54.5 [6.61] | | 25.2 | 80.1 [9.72] | |
| **Pieters et al.[48] (based on Aubier et al.[22])** | | | | | | | | | |
| S/FP 50/500μg | 57.5** | 365.1 [44.3] | 192.1 (58.3, 436.7) | 40* | 74.7 [9.06] | 66.8 (17.5, 318.2) | 30 | 98.8 [12.00] | 120.0[e] |
| FP 500μg | 33.6 | 487.8 [59.18] | | 30 | 77.2 [9.34] | | 24 | 94.2 [11.43] | |
| **Lundbäck et al.[49] (based on Jenkins et al.[29])** | | | | | | | | | |
| S/FP 50/250μg | 67† | 204 [24.75] | 31.6 (–37.6, 113.6) | 46† | 42.2 [5.12] | 9.2 (–11.8, 47.8) | 38† | 51.1 [6.20] | 7.7 (–7.8, 29.5) |
| BUD 800μg | 43 | 300 [36.40] | | 35 | 53 [6.43] | | 25 | 75.1 [9.11] | |

a During a successfully-treated week the mean morning PEF was ≥5% above the baseline value. Patients who withdrew for asthma- or medication-related reasons were assumed to have experienced no successfully-treated weeks for the remainder of the study.

b During a symptom-free day the patient had a symptom score of 0 for that 24-hour period (Aubier et al.[22]) or had a daytime symptom score of 0 and no asthma-related night-time awakenings (Kavuru et al.[27] and Shapiro et al.[18]).

c An episode-free day was a 24-hour period during which the patient did not experience an asthma episode, defined as an asthma attack, sleep disturbance caused by asthma or an adverse effect, and did not require rescue medication.

d The ICER was calculated by dividing the differences in the average direct healthcare costs between the S/FP and FP groups by the differences in the rate of success (i.e. successfully-treated week, symptom-free day, episode-free day).

e CIs were not calculated because of a lack of statistical difference in cost-effectiveness between treatments.

**CI** = 95% confidence interval; **PEF** = peak expiratory flow; **ICER** = incremental cost-effectiveness ratio; **SEK** = 1998 Swedish Kronor (SEK1 = $US0.12); * p = 0.012; ** p ≤ 0.0017; *** p < 0.00001 *vs* FP; † p < 0.001 *vs* BUD.

treated week with salmeterol/fluticasone propionate 50/500μg. This indicates that improved morning PEF with salmeterol/fluticasone propionate compared with fluticasone propionate costs an additional SEK12.6 ($US 1.53) to SEK192.1 ($US23.31) per week, depending on the asthma severity and the dose of salmeterol/fluticasone propionate or fluticasone propionate used.[45]

The cost per symptom-free day and episode-free day was lower with combined salmeterol/fluticasone propionate 50/250, but not the other dosages compared with monotherapy (table VII). For the end-point 'symptom-free days' (defined as no asthma symptoms during a 24-hour period), the ICER varied from SEK3.9 ($US0.47) per additional day with salmeterol/fluticasone propionate 50/250μg to SEK66.8 per additional day ($US8.l) in the higher dose study (table VII). A similar pattern was seen for the end-point 'episode-free days'. Sensitivity analyses did not change the pharmacoeconomic inferences, indicating that the results were robust to a range of assumptions used in the economic analyses.[45]

### 4.2 Compared with Budesonide

A 24-week study comparing combined salmeterol/fluticasone propionate 50/250μg with budesonide 800μg twice daily (Jenkins et al.[29] section 3.4, table V) has been subjected to cost effectiveness analyses from Swedish,[49] German[50] and UK[51] perspectives, only 1 of which has been published in full.[49]

Each analysis found combined salmeterol/fluticasone propionate to be more cost effective than budesonide based on the cost per successfully treated week (defined as a week with mean improvement in morning PEF of ≥5[49,51] or ≥10%[50] of the predicted value). The direct healthcare costs per week of treatment with salmeterol/fluticasone propionate and budesonide were generally similar in each country [SEK137 *vs* SEK130, 39.48 *vs* 38.01 Deutschmarks (DM) and UK£11.20 *vs* £12.39), but patients treated with salmeterol/fluticasone propionate had a significantly higher proportion of successfully-treated weeks than budesonide [67 *vs* 43% in the Swedish and UK analyses and 49 *vs* 26% in the German analysis (all $p < 0.001$)].[49-51]

In the Swedish analysis, the cost per successfully-treated week, symptom-free day and episode-free day were all lower among patients treated with combined salmeterol/fluticasone propionate than budesonide (table VII). The estimated cost of achieving an additional successfully-treated week, symptom-free day and episode-free day (equivalent to the ICER) with combination salmeterol/fluticasone was SEK31.6 ($US3.9), SEK9.2 ($US1.12) and SEK7.7 ($US0.93), respectively. A sensitivity analysis, which involved varying the definition of successfully-treated week between 1 and 10% from baseline, demonstrated that the results of the analysis were robust.[49]

## 5. Tolerability

### 5.1 Combined Salmeterol/Fluticasone Propionate

As salmeterol/fluticasone propionate is a combination of 2 drugs, the type and severity of adverse events associated with each component drug may be expected in patients receiving the combination product. There is no evidence, however, of additional adverse events following concurrent administration of the 2 drugs.[21]

In well designed comparative studies described in sections 3.1, 3.3.1, 3.4 and 3.5 the most frequent adverse events reported by adults and adolescents during ≥12 weeks' treatment with combined salmeterol/ fluticasone propionate (50/100, 50/250 or 50/500μg twice daily) were headache (incidence 2 to 5%), throat irritation (1 to 4%), hoarseness (≤4%) and oral candidiasis (1 to 4%).[18,22-24,27,29,33] The most frequent adverse event in children aged 4 to 11 years during treatment with salmeterol/fluticasone propionate 50/100μg twice daily for 12 weeks was oral candidiasis which was reported in 2% of patients (section 3.1.3).[17]

In a comparative study in which patients received combined salmeterol/fluticasone propionate 50/250μg or budesonide 800μg twice daily

the overall frequency of adverse events was similar (25 and 31 patients experienced treatment-related adverse events, respectively). Hoarseness (3%) and oral candidiasis (3%) were the most common events in recipients of the combination, while hoarseness (5%) and sore dry, irritated throat (4%) were most common among those treated with budesonide.[29]

Across all studies, the proportion of patients withdrawing from treatment with combined salmeterol/fluticasone propionate ranged from 0 to 10%.[17,18,22-24,27,29,33] Withdrawal rates were similar between treatment groups in the various studies and in the 2 studies which included placebo groups,[18,27] the frequency of withdrawals for adverse events was 0 and ≤1% in recipients of the combination and placebo, respectively.

### 5.2 Salmeterol

A prescription event monitoring survey involving >10 000 patients with asthma who received salmeterol over a 1-year period, revealed headache, nausea and vomiting, malaise/lassitude, tremor and palpitations to be significantly associated with the use of the drug. The event rates per 1000 patients for months 2 to 6 of treatment were 1.4 for headache and 0.9 for nausea and vomiting. For the other drug-related adverse events (malaise/lassitude, tremor and palpitations), this rate was in the range 0.4 to 0.6.[52]

### 5.3 Fluticasone Propionate

According to an overall analysis of tolerability data from several placebo-controlled studies, the incidence of adverse events ranged from 10 to 19% in patients treated with fluticasone propionate ≤250μg twice daily versus 4 to 11% in placebo recipients. In a single trial, adverse events were significantly more frequent in fluticasone propionate versus placebo recipients ($p = 0.05$ for fluticasone propionate 50 or l00μg twice daily vs placebo). Withdrawal because of an adverse events was infrequent, occurring in ≤4 and ≤2% of fluticasone propionate and placebo recipients, respectively. Oral candidiasis, dysphonia (hoarseness) or pharyngitis were reported by ≤6% and ≤3% of fluticasone propionate and placebo recipients, respectively (reviewed by Jarvis and Faulds[12]).

In trials comparing fluticasone propionate 50 to 250μg twice daily with either beclomethasone dipropionate 168 to 500μg twice daily or budesonide 100 to 600μg twice daily, the frequency of adverse events was similar (reviewed by Jarvis and Faulds[12]).

## 6. Dosage and Administration

In the US, combined salmeterol/fluticasone propionate is indicated for long term maintenance treatment of asthma in patients aged ≥12 years. The recommended starting dosage is based on patients' current asthma therapy. Twice daily salmeterol/fluticasone propionate 100/50μg is the recommended initial dosage in patients not currently receiving inhaled corticosteroids. Patients receiving inhaled corticosteroids should be switched to combined salmeterol/fluticasone propionate based on the recommendations in table VIII.[53] If the recommended dosage does not provide adequate disease control within 2 weeks, then a higher strength of combined salmeterol/fluticasone propionate may be appropriate.[53]

In the UK, combined salmeterol/fluticasone propionate is indicated in the treatment of asthma where use of the combination of a long-acting inhaled $\beta_2$-agonist and inhaled corticosteroid is appropriate. This corresponds to 'Step 3' in the British Guidelines on Asthma Management.[7,9] Salmeterol/fluticasone propionate is not intended for the initial management of asthma in the UK and should be reserved until the need for, and approximate dosage of, corticosteroid has been established.[21] The recommended dosage of salmeterol/fluticasone propionate in patients aged ≥12 years is 1 inhalation twice daily of the DPI (each inhalation contains 50μg salmeterol and either 100, 250 or 500μg fluticasone propionate) or 2 inhalations twice daily of the MDI (each inhalation contains salmeterol/fluticasone propionate 25/50μg, 25/125μg or 25/250μg).[7] The dosage of fluticasone propio-

**Table VIII.** Recommended initial dosage of combined salmeterol/fluticasone propionate (S/FP) in patients receiving inhaled corticosteroids[53]

| Current inhaled corticosteroid dosage (μg/day) | | Recommended twice daily dosage of S/FP (via DPI) |
|---|---|---|
| Beclomethasone dipropionate | ≤420 | 50/100μg |
| | 462-840 | 50/250μg |
| Budesonide | ≤400 | 50/100μg |
| | 800-1200 | 50/250μg |
| | 1600 | 50/500μg |
| Flunisolide | ≤1000 | 50/100μg |
| | 1250-2000 | 50/250μg |
| Fluticasone propionate MDI | ≤176 | 50/100μg |
| | 440 | 50/250μg |
| | 660-880 | 50/500μg |
| Fluticasone propionate DPI | ≤200 | 50/100μg |
| | 500 | 50/250μg |
| | 1000 | 50/500μg |
| Triamcinolone acetonide | ≤1000 | 50/100μg |
| | 1100-1600 | 50/250μg |

**DPI** = dry powder inhaler; **MDI** = pressurised metered dose inhaler.

nate should be selected according to the severity of asthma in individual patients.[21]

In children aged <12 and ≥4 years, the recommended dosage is 1 inhalation twice daily of the lowest strength of the DPI (salmeterol/fluticasone propionate 50/100μg). No data are available regarding use of combined salmeterol/fluticasone propionate in children aged <4 years.[21]

Salmeterol/fluticasone propionate should not be used to treat acute asthma symptoms for which a short acting bronchodilator is required. Patients should be advised to have their relief medication available at all times.[21,53]

Treatment with salmeterol/fluticasone propionate should not be stopped abruptly and caution is advised when transferring patients to salmeterol/fluticasone propionate therapy, particularly in cases where impaired adrenal function as a result of previous systemic steroid therapy is suspected.[21] Indeed, the manufacturer advises that combined salmeterol/fluticasone propionate should not be used for transferring patients from systemic corticosteroid therapy.[53]

Systemic effects may occur with any inhaled corticosteroid, particularly when high doses are taken for long periods. It is thus important that the dose of inhaled corticosteroid is titrated to the lowest dose at which effective control is maintained.[21,53]

Patients receiving combined salmeterol/fluticasone propionate should not use inhaled salmeterol for prevention of exercise-induced bronchospasm.[53]

No dosage adjustment is required in elderly patients or in those with renal impairment. There are no data available regarding the use of the combination in patients with hepatic dysfunction and no recommendations regarding dosage adjustments in this population are available.[21,53] However, patients with hepatic disease should be closely monitored during treatment with the combination.[53]

The manufacturer advises that the combination should be administered with caution in patients with cardiovascular disorders (especially coronary insufficiency, heart rhythm abnormalities and hypertension), diabetes mellitus, untreated hypokalaemia or thyrotoxicosis. In rare cases, eosinophilic conditions (e.g. Churg Strauss syndrome) may occur in patients on inhaled therapy. These cases have usually been associated with reduction or withdrawal of corticosteroid therapy.[21,53]

The use of salmeterol/fluticasone propionate has not been studied during human pregnancy. Thus, administration of salmeterol/fluticasone propionate to pregnant women should be contemplated only if the expected benefit to the mother is greater than any possible risk to the fetus. The lowest effective dose of fluticasone propionate needed to maintain adequate asthma control should be used in such cases. Similarly, salmeterol/fluticasone propionate should not be given to women who are breastfeeding unless the expected benefit is greater than any possible risk to the child.[21]

## 7. Place of Combined Salmeterol/Fluticasone Propionate in the Management of Asthma

An awareness that reliance on bronchodilatory therapy as the mainstay of pharmacological ther-

apy for asthma was a suboptimal strategy motivated the preparation and publication of formal asthma management guidelines.[8,9,40] Both UK and US guidelines for the management of asthma in adults and school children suggest a 5-step pharmacological treatment plan in response to asthma of increasing severity. The principal aim of treatment is suppression of airway inflammation, evident as a strong emphasis on the early use of inhaled corticosteroid therapy. Despite this advice, and clear evidence of the benefits of inhaled corticosteroid therapy in patients with mild asthma, several studies have shown this treatment strategy is underused (reviewed by Jarvis and Faulds[12]).

The places of the long-acting β-agonist salmeterol and the inhaled corticosteroid fluticasone propionate in the management of asthma have been reviewed previously.[11-14] These reviews and additional data show that each drug is effective in the context of its intended use according to current asthma management guidelines.[8,9] Indeed, it is noted in these guidelines that long-acting $\beta_2$-agonists added to standard doses of inhaled corticosteroid may provide more effective symptom control than an increase in inhaled corticosteroid dosage. In the case of salmeterol, a number of recent studies have confirmed this suggestion.[54-61] It has also been shown that addition of inhaled salmeterol to beclomethasone dipropionate at the minimal acceptable dosage (determined by downward dosage titration until asthma deteriorated) facilitated a 50% reduction in the daily dosage of the corticosteroid.[62] Salmeterol has also been shown to provide significantly greater improvement in overall asthma control than the leukotriene receptor antagonist zafirlukast in patients with symptomatic persistent asthma when added to ongoing inhaled corticosteroid therapy.[63]

Considerable data demonstrate that inhaled fluticasone propionate is an effective asthma treatment. At a dosage of ≤250μg twice daily the drug provides consistent asthma control in patients with mild to moderate asthma. In placebo-controlled trials, it produced significant improvements in objective and subjective measures of lung function, reduced the frequency of exacerbations and improved QOL (reviewed by Jarvis and Faulds[12]).

Well designed comparative clinical trials have clearly established that the combined salmeterol/fluticasone propionate is as effective as the same nominal doses of the 2 drugs administered via separate inhalers. Furthermore, the fixed combination was significantly more effective than inhaled fluticasone propionate, both alone and in combination with oral montelukast 10 mg/day, and inhaled budesonide. Combined salmeterol/fluticasone propionate 50/250 and concurrent budesonide 800μg plus formoterol 12μg produced similar improvements in lung function. Adverse events with the combination product were similar to those seen when the 2 component drugs were given concurrently and there is no evidence of additional adverse events when the 2 drugs are administered concomitantly.[21]

Combined salmeterol/fluticasone propionate simplifies the treatment regimen of patients already receiving this or a similar combination via separate inhalation devices. Simplification of asthma treatment regimens is one approach to the complex and vexed issue of patient compliance in this condition.

The many factors contributing to how, and when, antiasthma drugs are taken has been the subject of several recent reviews.[64-70] At a fundamental level, noncompliance can be described as unintentional or intentional.[70] Unintentional noncompliance can be overcome by improved communication between the healthcare provider and the patient. Intentional noncompliance may also be overcome by improved communication, although other interventions are likely to be necessary.

In theory, simplification of a pharmacological treatment regimen for asthma has the potential to improve several factors known to contribute to unintentional noncompliance; examples include forgetting to take medication and misunderstanding instructions.

Similarly, several factors that may contribute to intentional noncompliance are directly attributable to pharmacological treatment. These include cost,

perceived risks and benefits of treatment (particularly in the case of corticosteroids) and the inconvenience associated with taking medication on a regular basis. Selective noncompliance with an inhaled corticosteroid is not possible with products such as combined salmeterol/fluticasone propionate.

In addition to the benefits of a simplified treatment regimen, the findings that combined salmeterol/fluticasone propionate improves QOL and is more cost effective than monotherapy with fluticasone propionate or budesonide, may also lead to improved compliance. Combination products have the additional benefit of reduced cost in situations where dispensing fees are applied to each medication dispensed.

*Conclusion:* Combined salmeterol/fluticasone propionate is as effective as the 2 drugs given concurrently via separate inhalers and significantly more effective than either drug given alone at the same nominal dosage. The combination is also significantly more effective than montelukast plus fluticasone propionate or monotherapy with inhaled budesonide. Furthermore, the combination is more cost-effective than inhaled corticosteroid monotherapy.

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