

# Current trends in the treatment of asthma: focus on the simultaneous administration of salmeterol/fluticasone

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**Abstract:** Asthma is a chronic disease of the airways that affects over 20 million people in the United States. It is a complex disease that involves airway infiltration by different types of cells and cell mediators causing chronic inflammation of the airway as well as hyper-responsiveness and edema. Management of asthma symptoms often requires combination therapy with multiple medications. Long-acting beta-2 agonists and inhaled corticosteroids have become key medications in the prevention of asthma exacerbations. The bronchodilatory effects of the beta-2 agonists coupled with the anti-inflammatory action of the corticosteroids combat the multi-factorial causes of asthma. The combination inhaler containing salmeterol and fluticasone is one such product that has been proven safe and effective for asthma therapy.

**Keywords:** asthma, fluticasone, salmeterol, beta-2 agonist, inhaled corticosteroid

## Introduction

Asthma is a condition that develops due to chronic inflammation and infiltration of cellular components such as mast cells, eosinophils, neutrophils, lymphocytes, and macrophages. Inflammation cascades into remodeling and hyper-responsiveness of the airways which in turn produce the symptoms of asthma.<sup>1</sup> The clinical presentation of asthma includes wheezing, shortness of breath, chest tightness, and coughing which result from bronchoconstriction, hyper-responsiveness and airway edema. Several potential causes of asthma have been identified and include cytokine response, genetic component, and environmental stimuli such as airborne allergens, viral respiratory infections, tobacco smoke, and air pollution.<sup>2</sup>

Short-acting and long-acting bronchodilators have been a mainstay in asthma therapy. Acute asthma exacerbations are treated with short-acting bronchodilators and prevention of asthma attacks can be achieved through therapy management plans that include long-acting bronchodilators. To combat the inflammatory components of asthma, inhaled corticosteroids have been utilized to inhibit the recruitment, activation and function of pro-inflammatory cells.<sup>2</sup> Due to the multi-factorial aspects of asthma, combination therapies with medications that have complementary mechanisms have become an important tool in asthma therapy. This paper will review the combination product that includes the long-acting beta-2 agonist salmeterol, and the inhaled corticosteroid fluticasone, which is one such asthma therapy.

It should be noted that there is a second combination product consisting of formoterol, a long-acting beta-2 agonist, and the inhaled corticosteroid, budesonide. The combination formoterol/budesonide product is available in fixed-dose and adjustable-dose formulations. A comparison of fixed-dose and adjustable-dose

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formoterol/budesonide and fixed-dose salmeterol/fluticasone found all three to be equivalent in terms of asthma control and tolerability.<sup>3</sup> Clinically, formoterol and salmeterol are similar with the exception that formoterol has a quicker onset of action (within 5 minutes similar to short acting beta agonists) compared to salmeterol (within 15 minutes).<sup>2</sup> This paper, however, will focus on the combination product salmeterol/fluticasone.

A literature search of the PubMed, Medline, Cochrane, and GoogleScholar databases was conducted to identify relevant randomized controlled trials, systematic reviews, and meta-analyses. Search terms included salmeterol, fluticasone, long-acting beta agonists, LABA, inhaled corticosteroids, ICS, single inhaler, combination therapy, and asthma. The reference lists from the articles found were used to identify additional references.

## Pharmacodynamics

Fluticasone is a synthetic corticosteroid with potent anti-inflammatory properties. Inflammatory cell types including mast cells, eosinophils, basophils, lymphocytes, and macrophages along with inflammation mediators including histamine, leukotrienes and cytokines are inhibited by corticosteroids. The inhibition of these inflammatory components reduces plasma exudation, mucous secretion, airway membrane thickness, and hyper-responsiveness to stimuli.<sup>4,5</sup>

Salmeterol is a long-acting beta-2 adrenergic agonist which illicit its action partly through the stimulation of intracellular adenylyl cyclase. Stimulation of this enzyme catalyzes the conversion of adenosine triphosphate to cyclic-3',5'-adenosine monophosphate (cyclic AMP). This increase in cyclic AMP results in bronchodilation through relaxation of the bronchial smooth muscle and a reduction in the mediators responsible for hyper-responsiveness.<sup>4</sup>

In a study of 28 healthy volunteers, the potential for pharmacodynamic and pharmacokinetic interactions between inhaled salmeterol and fluticasone were examined by administering the drugs in combination and individually. After repeated administration of the treatments, no differences in pharmacodynamic action of the individual agents were seen when the drugs were co-administered. Parameters that were measured included 24-hour cortisol excretion, morning plasma cortisol levels, and lymphocyte beta-2 adrenoceptor polymorphism.<sup>6</sup> In addition, it has also been shown in vitro that the co-administration of inhaled corticosteroids and long-acting beta-2 agonists has a synergistic effect. Mechanisms that account for this additive activity include the potential for corticosteroids to increase the number of

beta-2 adrenoceptors and for increased binding affinity of the corticosteroids.<sup>7,8</sup>

## Pharmacokinetics

Key pharmacokinetic parameters of the individual agents are listed in Table 1.<sup>4</sup> The co-administration of these agents has not been shown to vary the pharmacokinetics with respect to peak serum concentration, time to peak serum concentration or elimination time.

In clinical studies of up to 12 weeks in duration, no difference in systemic effects to salmeterol or fluticasone was seen when comparing patients based on age. There are no gender differences in the pharmacokinetics of salmeterol or fluticasone. No formal kinetic studies have been done examining patients with renal or hepatic impairment. Due to the predominant hepatic metabolism of both agents, salmeterol and fluticasone may accumulate in patients with hepatic impairment and thus these patients should be monitored closely.<sup>4</sup>

Administration of beta-2 agonists, corticosteroids, antihistamines and theophylline had no significant effect on the pharmacokinetics of either fluticasone or salmeterol. Due to the metabolism of fluticasone via cytochrome P450 (CYP) 3A4 isoenzymes, co-administration of agents that inhibit this hepatic enzyme may cause an increase in fluticasone plasma concentrations. Concurrent administration of fluticasone and the strong CYP 3A4 inhibitor ritonavir should be avoided and administration with other potent inhibitors should be monitored closely.<sup>4</sup>

## Safety and tolerability

The safety and tolerability of the salmeterol/fluticasone combination (SFC) combination is comparable to the individual components across all dosage strengths. The most common adverse events include respiratory tract infection and inflam-

**Table 1** Pharmacokinetics of fluticasone and salmeterol

	Fluticasone	Salmeterol
Peak plasma concentrations (minutes)	60–120	5
Mean peak steady-state plasma concentrations (pg/mL)	110	167
Protein binding (%)	91	96
Metabolism	Hepatic via cytochrome P450 isoenzyme 3A4	Hepatic via hydroxylation
Half-life (hours)	7.8	5.5
Primary elimination	Feces	Feces

mation, pharyngitis, oral candidiasis, bronchitis, headache, nausea, and vomiting.<sup>4,9,10</sup> There were no clinically relevant changes in laboratory values with the use of inhaled SFC. The side effect profile was similar for children aged 4 to 11 years as was seen in adults and adolescents aged 12 years or greater.

The prescribing information for SFC does contain a black box warning due to an increased risk of asthma-related death seen with the use of long-acting beta agonist (LABA) monotherapy. In a large, randomized, double-blind, placebo-controlled trial enrolling over 26,000 patients, 13 deaths were seen in the salmeterol group as compared to only 3 deaths in the placebo group during 28 weeks of therapy.<sup>11</sup> As a result of this study, prescribers are urged to only prescribe salmeterol containing products to those patients that are not adequately controlled on other therapy options or whose disease severity is such that a two-medication regimen is warranted.<sup>4</sup>

## Goal study

Previous studies comparing inhaler treatments of salmeterol/fluticasone (SFC) to fluticasone or budesonide alone found that SFC was more effective than higher dose fluticasone or budesonide in preventing worsening asthma or improving peak expiratory flow rate (PEFR).<sup>3,12,13</sup> The GOAL Study was the first trial to compare the effectiveness of two asthma control treatments (SFC versus fluticasone monotherapy) in achieving Global Initiative for Asthma (GINA)/National Asthma Education and Prevention Program (NAEPP) guideline based asthma control rather than improvement in any one measure of asthma.<sup>2,9,14</sup> The 52-week study, involved 3416 subjects, aged 12 years and older, who had uncontrolled asthma on current therapy. The study compared the safety and efficacy of predefined stepwise dose increases of SFC or fluticasone alone in achieving one of two study defined (and guideline based) measures of asthma control.<sup>9</sup>

Subjects were randomized to either SFC or fluticasone monotherapy. Each treatment group was subdivided into three treatment strata based on inhaled corticosteroids (ICS) use in the 6 months prior to study screening: stratum 1, no inhaled corticosteroid use; stratum 2,  $\leq 500$   $\mu\text{g}$  of beclomethasone or equivalent; and stratum 3,  $> 500$  to  $1000$   $\mu\text{g}$  of beclomethasone or equivalent. Phase 1 was a 12-week period in which the treatment dose was increased every 12 weeks until the subject achieved totally controlled asthma or the maximum dose was reached (SFC  $50$   $\mu\text{g}/500$   $\mu\text{g}$  twice daily or fluticasone  $500$   $\mu\text{g}$  twice daily). During Phase 2, subjects continued the dose of study medication they reached during Phase 1. At the end of Phase 2, there was an additional 4 week phase for subjects who did not achieve totally controlled asthma in either of

the first two phases. In this phase, all subjects received oral prednisolone ( $0.5$   $\text{mg}/\text{kg}$  up to  $60$   $\text{mg}/\text{day}$ ) for 10 days in addition to SFC  $50$   $\mu\text{g}/500$   $\mu\text{g}$  twice daily for 4 weeks.<sup>9</sup>

The primary study endpoint was the proportion of patients who achieved control during Phase 1. The study used two definitions of control based on GINA/NAEPP guideline measures of asthma control: well-controlled asthma and totally controlled asthma. Both endpoints were defined by composite measures that included PEFR, symptoms, rescue inhaler use, night-time awakenings due to asthma symptoms, number of exacerbations, number of emergency room visits, and adverse events. A well-controlled week was defined as having a symptom score of greater than 1 on no more than 2 days in a week, using a rescue inhaler no more than 2 days in a week or on 4 or fewer occasions in a week, and having a PEFR  $\geq 80\%$  of predicted every day. A totally controlled week was defined as having no symptoms in a week, no use of rescue inhalers in a week, and a PEFR of  $\geq 80\%$  of predicted every day. Totally controlled asthma was defined as having 7 totally controlled weeks in an 8-week assessment period. Well-controlled asthma was defined as having 7 well-controlled weeks within the 8 weeks. Any exacerbations, emergency room visits, and adverse events in any one week of the assessment period caused the entire 8-week assessment period to be defined as uncontrolled.<sup>9</sup>

The study also examined secondary endpoints including the percentages of patients attaining well-controlled and totally controlled asthma during Phase II, the maximum doses of inhaled corticosteroid, and the treatment times needed to attain the first well-controlled week and the first totally controlled week, the rate of exacerbations (defined as requiring oral corticosteroids, an emergency room visit and/or hospitalization), and morning predose forced expiratory volume in the first second ( $\text{FEV}_1$ ) at clinic visits.

The study found that significantly greater proportions of subjects in all three strata of the SFC treatment group achieved well-controlled asthma and totally controlled asthma compared to subjects in the fluticasone treatment group.<sup>9,14</sup> During Phase I, significantly more patients in all strata of the SFC treatment group reached well-controlled or totally controlled asthma compared to patients in the fluticasone only group. In stratum 1, 71% of patients in the SFC group versus 65% of patients in the fluticasone group attained well-controlled asthma (odds ratio [OR], 1.32; 95% confidence interval [CI], 1.01 to 1.73;  $P = 0.039$ ). Well-controlled asthma was attained by 69% versus 52% of patients in stratum 2, in the SFC and fluticasone groups respectively (OR, 2.13; 95% CI, 1.65 to 2.74;  $P < 0.001$ ).<sup>9</sup>

These research results were reflected in the GINA and NAEPP guideline updates. The 2007 update of the NAEPP's guidelines recommend the combination treatment of a low to medium dose ICS with an inhaled LABA in preference to monotherapy with a high-dose ICS. In addition, the 2008 update of the GINA guidelines recommends combination therapy of an ICS with a LABA over monotherapy with medium- or high-dose of an ICS.

More recently, research has evaluated the effectiveness of SFC compared to concurrent therapy with salmeterol and fluticasone via separate inhalers. Combination inhalers represent an important treatment option because national and international asthma treatment guidelines recommend that LABAs should only be used as add-on therapy with an ICS due to an increased risk of asthma related death or life-threatening event. (GINA, NAEPP) The safety of LABAs has been a controversial issue for several years.<sup>15,16</sup> The current Food and Drug Administration (FDA) black box warning on all LABAs (salmeterol, formoterol) is based on evidence from three sources: the SMART trial, a meta-analysis by Mann et al of asthma exacerbations in trials submitted to the FDA for approval of formoterol, and a meta-analysis of LABAs by Salpeter et al.<sup>2</sup>

As discussed earlier, the SMART trial evaluated the safety of salmeterol compared to placebo when added to current asthma therapy.<sup>11</sup> The primary endpoint was a composite of respiratory-related death and respiratory-related, life-threatening experiences which were defined as treatment requiring intubation and mechanical ventilation. Secondary endpoints included all-cause mortality, combined asthma-related deaths and all cause hospitalizations. The study originally planned to randomize 60,000 subjects.<sup>11</sup> A planned interim analysis was conducted after 26,355 subjects were randomized to treatment. Although the results of the analysis did not meet the pre-defined criteria for early termination, the sponsors terminated the trial. The interim analysis found that while there were no statistically significant differences between the placebo and salmeterol groups in terms of the primary endpoint, there were statistically significant differences in the secondary endpoints. The salmeterol group experienced 37 asthma-related deaths versus 3 in the placebo group ( $P < 0.05$ ) and 37 combined asthma-related deaths or life-threatening experiences versus 22 in the placebo group ( $P < 0.05$ ).<sup>11</sup>

Additional analyses were done based on race and use of ICS. The analyses found that for Caucasian subjects (71% of the study population), there were no statistically significant differences between the salmeterol and placebo groups in

either the primary endpoint (29 [ $<1\%$ ] versus 28 [ $<1\%$ ], respectively) or the secondary endpoints. Among African American subjects (18% of the study population), however, there were statistically significant differences between the salmeterol and placebo groups in the primary endpoint and in two of the secondary endpoints. In terms of the primary endpoint, 20 ( $<1\%$ ) African Americans in the salmeterol group experienced a respiratory-related death or life-threatening experience versus 5 ( $<1\%$ ) in the placebo group ( $P < 0.05$ ). Also, 19 ( $<1\%$ ) African Americans in the salmeterol group experienced the secondary endpoint of combined asthma-related death or life-threatening experience compared to 4 ( $<1\%$ ) in the placebo group ( $P < 0.05$ ). The reason for the higher incidence of events is unclear. The sub-analysis suggested that African Americans patients may have had worse disease than Caucasian patients at screening as evidenced by lower PEFR, fewer patients using ICS therapy, and a higher percentage of emergency department visits. However, the study authors could not draw any conclusions as the study was not designed to evaluate the effect of other factors such as genetics, patient behaviors, concurrent medical conditions, and socioeconomic status on study outcomes.<sup>11</sup>

Post hoc analyses were done on the intent- to-treat population to evaluate the effect of ICS therapy on the primary and secondary endpoints of the trial.<sup>11</sup> Baseline ICS therapy was reported by 47% of patients in both the salmeterol and placebo groups. The analyses found that among subjects reporting baseline ICS therapy, there were no differences in the number of primary or secondary events between the salmeterol and placebo groups. Among subjects who reported no baseline ICS therapy, the salmeterol group experienced a greater number of primary and secondary events compared to the placebo group but the differences were only statistically significant for the secondary endpoints of asthma-related death (9 versus 0, for salmeterol and placebo, respectively;  $P < 0.05$ ) and combined asthma-related death or life-threatening experience (21 versus 9, for salmeterol and placebo, respectively;  $P < 0.05$ ). Nelson et al noted that since the effect of ICS on study outcomes was not part of the study design, they could not form a conclusion based on the post hoc analyses.<sup>11</sup>

Additionally, two meta-analyses found that treatment with LABAs increased the risk of asthma-related exacerbations. Mann et al reviewed three randomized controlled trials that were submitted to the FDA for approval of formoterol. The analysis found that patients treated with formoterol 24  $\mu\text{g}$  twice daily had more serious asthma exacerbations than patients treated with formoterol 12  $\mu\text{g}$  twice daily, placebo or albuterol. Because it was a post hoc exploratory study it



did not include a statistical analysis. However, the analysis concluded that treatment with formoterol 24 µg twice daily may be associated with an increase in serious asthma-related exacerbations.<sup>17</sup>

Salpeter et al performed a meta-analysis of 19 randomized controlled trials of LABAs (salmeterol, formoterol, eformoterol), including the SMART trial, with a total of 33,826 asthma patients. They examined the Peto OR and risk differences between LABA treatment and placebo in asthma-related death, exacerbations requiring hospitalization, and exacerbations requiring intubation and mechanical ventilation. The analysis found that compared to placebo, treatment with a LABA increased the risk of asthma-related deaths (OR, 3.5), exacerbations requiring hospitalization (OR, 2.6), and life threatening exacerbations (OR, 1.8). The study concluded that LABA therapy increases asthma-related deaths and severe asthma exacerbations.<sup>15</sup> Ernst et al cautioned that the Salpeter meta-analysis did not include studies that evaluated the benefit of adding LABAs to ICS therapy. The article noted that the Salpeter analysis failed to include two meta-analyses that evaluated the risk of severe exacerbations in patients on ICS therapy with LABA add-on therapy. The trials in these two meta-analyses required patients to remain on ICS therapy.<sup>18</sup>

The exact cause of this increased risk is unknown. LABAs do not provide any clinically significant anti-inflammatory effect. It has been suggested that LABA monotherapy may worsen disease control by masking worsening or persistent airway inflammation through decreasing signs and symptoms of an exacerbation.<sup>2,19</sup> Lazarus et al evaluated the use of salmeterol as replacement therapy in patients with persistent asthma who were controlled on an ICS. The study of 165 patients aged 12 to 64, found that although patients in the salmeterol group experienced improved airway function, symptoms, and a decreased use of rescue inhalers, their rate of exacerbations and treatment was similar to patients in the placebo group.<sup>20</sup>

McIvor et al evaluated the hypothesis that LABAs may mask airway inflammation in a randomized, controlled, crossover study of 17 patients who were controlled on high dose ICS therapy. The study compared the effect of salmeterol 50 µg twice daily to matching placebo, with a progressive reduction in ICS therapy, on the extent of inflammation (measured by sputum eosinophilia) that developed prior to an exacerbation. Eosinophilia, a biomarker for airway inflammation, was used because it is unaffected by the bronchodilator effect of salmeterol. Patients in the salmeterol group were able to significantly reduce their ICS dose compared to the placebo group prior to an exacerbation ( $P = 0.01$ ). As the ICS dose

decreased, eosinophilia counts trended higher. Compared to the placebo arm, the salmeterol arm had higher eosinophilia counts in the 3 weeks prior to an exacerbation but they were statistically significantly higher only in the week prior to an exacerbation (mean eosinophilia count  $9.3 \pm 17.6\%$  versus  $19.9 \pm 29.8\%$ , placebo and salmeterol, respectively;  $P = 0.006$ ). Patients' FEV<sub>1</sub> and symptoms remained stable even with the higher eosinophilia counts. The study concluded that the bronchodilating and symptom relief effects of salmeterol treatment may mask increasing inflammation and worsening asthma control.<sup>19</sup>

## Single inhaler versus separate inhalers

As previously discussed, research indicates that LABAs when used as add-on therapy to ICS therapy can provide better asthma control than higher dose ICS monotherapy.<sup>2,9,14</sup> Evidence suggests that adherence to asthma treatment decreases with complexity.<sup>12,21</sup> In particular, multiple inhalers are confusing to patients.<sup>12,21</sup> Additionally, patients have a tendency to stop ICS therapy when symptoms improve.<sup>12</sup> Combination inhalers may provide a means for improving asthma control while increasing patient compliance with therapy and ensuring that LABAs are given in addition to ICS therapy.<sup>12,21</sup>

Several studies (Table 2) demonstrated that a combined ICS/LABA inhaler is as effective and safe as concurrent therapy with separate inhalers.<sup>9,22</sup> In a 12-week study, Bateman et al evaluated the efficacy and tolerability of SFC versus concurrent treatment with salmeterol and fluticasone in separate inhalers in subjects who were symptomatic on current therapy.<sup>23</sup> 244 subjects, aged 12 years and older, were randomized to SFC 50 µg/100 µg twice daily versus concurrent therapy with salmeterol 50 µg twice daily plus fluticasone 100 µg twice daily. The primary end-point was the mean morning PEFR with secondary end-points of FEV<sub>1</sub>,

**Table 2** Combined inhaler vs concurrent inhalers

Study	Adjusted mean change from baseline morning PEFR (L/min)		CI	P value
	SFC	S + F		
Aubier <sup>24</sup>	35	33	90% (-10, 4)	0.535
Bateman <sup>23</sup>	42	33	90% (-17, 0)	0.098
Chapman <sup>26</sup>	43	36	90% (-13, 0)	0.114
Van den Berg <sup>22</sup>	33	28	90% (-10, 0)	0.103

**Abbreviations:** CI, confidence interval; PEFR, peak expiratory flow rate; SFC, salmeterol/fluticasone; S + F, salmeterol and fluticasone monotherapies.

rescue inhaler use, and symptom score. The study found no statistical difference between treatments for the primary endpoint of PEFR or for any of the secondary end-points. The mean PEFR improved by 42 and 33 L/min for SFC and separate inhalers respectively ( $P = 0.098$ ).<sup>23</sup> At the end of the trial, 60% of the subjects in the SFC group compared to 64% in the separate inhaler group were asymptomatic. Additionally, the study found that the SFC inhaler was as well tolerated as the separate inhalers. 15% of subjects in the single inhaler group had an adverse event compared to 14% in the separate inhaler group.<sup>23</sup>

Van den Berg et al studied the safety and efficacy of the SFC inhaler compared to concurrent therapy with separate inhalers in children aged 4 to 11 years who were symptomatic on ICS therapy. The primary endpoint was mean morning PEF. Secondary endpoints included mean evening PEFR,  $FEV_1$ , and symptom scores for day and night-time. Two hundred fifty-seven subjects were randomized to SFC 50 µg/100 µg twice daily versus concurrent therapy with salmeterol 50 µg twice daily plus fluticasone 100 µg twice daily. The study found that the single inhaler was clinically equivalent to concurrent therapy with separate inhalers in improvement of mean morning PEFR ( $P = 0.103$ ). Additionally, the results for the secondary endpoints also demonstrated clinical equivalence between the two treatments: improvement in mean evening PEFR ( $P = 0.164$ ), improvement in  $FEV_1$  ( $P = 0.052$ ), and improvement in daytime and night-time symptom scores ( $P = 0.904$  and  $P = 0.779$  respectively).<sup>22</sup>

Two additional studies indicated that the SFC inhaler was clinically equivalent to concurrent therapy with separate inhalers. Aubier et al evaluated SFC compared to concurrent therapy with separate inhalers in subjects requiring high dose inhaled corticosteroids within the 4 weeks prior to randomization. Five hundred and three subjects were randomized to one of three treatment groups: SFC 50 µg/500 µg twice daily, salmeterol 50 µg and fluticasone 500 µg given by separate inhalers twice daily, and fluticasone 500 µg twice daily. The primary efficacy end-point of mean morning PEFR was evaluated over a 12-week treatment period. Safety was evaluated over a 28-week period. The combination inhaler group had slightly better improvement in mean morning PEFR from baseline compared to concurrent therapy (12% improvement versus 10%, respectively) but the difference was not statistically significant. However, as in previous studies, Aubier et al found that SFC therapy was superior to fluticasone alone ( $P = 0.001$ ).<sup>24,25</sup>

In another 28-week trial, Chapman et al compared combined with concurrent therapy in 371 subjects, aged 13 and older, who were symptomatic on therapy that included ICS. Subjects were randomized to SFC 50 µg/250 µg twice daily or salmeterol 50 µg and fluticasone 250 µg given by separate inhalers twice daily. Mean morning PEFR, the primary efficacy end-point, was measured over the first 12 weeks. Safety data were collected over the 28-week treatment period. The results of the first 12 weeks, showed equivalency in adjusted mean morning PEF improvement between the two treatments (90% CI, -13 to 0 L/min;  $P = 0.114$ ).<sup>25,26</sup>

Additional research suggests that treatment with a combination inhaler may be superior to concurrent therapy.<sup>25,27</sup> The four trials discussed above demonstrated the clinical equivalency of SFC compared to concurrent therapy with separate inhalers. The data from these studies trended towards the use of the single inhaler. Using these data, Nelson et al performed a meta-analysis to further evaluate the benefit of a single inhaler compared to separate inhalers.<sup>25</sup> The primary endpoint was the change in mean morning PEF from baseline over 12 weeks. The analysis included mean change in evening PEF, and clinic  $FEV_1$ . In addition, the mean percentage of symptom-free days and nights, individually and together, was evaluated. The analysis found that in the primary endpoint, SFC demonstrated a superior effect of 5.4 L/min over the 12-week treatment period compared to concurrent therapy with separate inhalers ( $P = 0.006$ ; 95% CI, 1.52 to 9.17). In terms of the secondary endpoints, the study found that SFC also had a statistically significant improvement in mean evening PEF of 6.11 L/min compared to the concurrent inhalers ( $P < 0.001$ ; 95% CI, 2.48 to 9.75). SFC showed a trend towards improvement in  $FEV_1$  compared to concurrent therapy with separate inhalers but it was not statistically significant ( $P = 0.54$ ; 95% CI, 0.00 to 0.08). No difference was found between the two treatments in terms of symptom free days, nights, or both.<sup>25</sup>

Angus et al performed a retrospective longitudinal analysis of a national primary care database and evaluated the use of rescue inhalers (short-acting beta agonists, SABA) and oral corticosteroids (OC) in SFC compared to therapy with beclomethasone and a LABA in separate inhalers. Patients with a diagnosis of asthma who were 12 to 55 years old were included in the analysis if they had a prescription for SFC or beclomethasone and LABA in separate inhalers (date of the first prescription for SFC or beclomethasone and LABA was defined as the index event). Additionally the patients had to have 6 months of data prior to and after the index event and no prescription for a LABA prior to the index event.

Patients were excluded if they had a diagnosis of COPD. The study identified 211 patients using SFC and 377 patients using beclomethasone and LABA. The primary end-points were the number of doses of SABA prescribed and the percentage of patients who were prescribed at least one course of OCs. The treatment groups were statistically different at baseline in terms of age, gender, and rescue inhaler use. The SFC group was younger compared to the beclomethasone and LABA treatment group (33 versus 37 years, respectively;  $P = 0.0007$ ) and also had fewer female patients (48.8% versus 61.3%, SFC and beclomethasone and LABA respectively;  $P = 0.0034$ ). In the preindex period, the median number of SABA dosages was 400 for the SFC group and 500 for the beclomethasone and LABA group ( $P = 0.038$ ).<sup>28</sup>

The analysis found that the difference in the postindex median number of doses of SABA prescribed was statistically significant. In the SFC group, the median number of doses decreased by 100, while in the beclomethasone and LABA group the median number remained the same (median difference -100; 95% CI, -200 to -60;  $P < 0.0001$ ). In addition, the difference in the percentage of patients in SFC group (13.7%) requiring at least one course of OCs postindex compared to the percentage in the beclomethasone and LABA group (20.7%) was statistically significant (difference 6.9%; 95% CI, -13.1 to -0.8;  $P = 0.036$ ).<sup>27</sup>

## Conclusion

Asthma is a chronic disease of the airways that affect approximately 23.4 million people in the US.<sup>2</sup> It is a complex disease that involves airway infiltration by different types of cells and cell mediators causing chronic inflammation of the airway as well as hyper-responsiveness and edema.<sup>29</sup> Management of asthma symptoms often requires combination therapy with multiple medications.

Previous research demonstrated that combination therapy with an ICS and LABA was superior in efficacy to higher dose ICS monotherapy.<sup>3,12,13</sup> More recent research has demonstrated that SFC therapy is clinically equivalent to concurrent salmeterol and fluticasone therapy with separate inhalers.<sup>22–26</sup> Two analyses also suggest that SFC therapy may provide more benefit compared to concurrent therapy with separate inhalers.<sup>25,28</sup> This has important treatment implications. Studies indicate that as the number of asthma inhalers increases, treatment adherence declines.<sup>12,21</sup> In addition, many patients will stop ICS therapy once they are less symptomatic.<sup>12</sup> Combination therapy with SFC may simplify asthma treatment and help improve treatment adherence.

## Disclosures

The authors declare no conflicts of interest.

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