

Steroid-sparing effects of fluticasone propionate 100 μ g and salmeterol 50 μ g administered twice daily in a single product in patients previously controlled with fluticasone propionate 250 μ g administered twice daily

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Background: Concurrent use of an inhaled corticosteroid (ICS) and an inhaled long-acting β_2 -agonist provides better overall asthma control than the use of higher doses of ICS alone.

Objective: The purpose of this investigation was to determine whether fluticasone propionate (FP) combined with salmeterol in the Diskus device can be used to reduce the dose of ICS in patients currently stable on medium-dose ICS while maintaining asthma control.

Methods: This was a randomized, double-blind, parallel-group, 12- to 24-week trial consisting of a 3-part run-in period. The run-in period was designed to first establish FP 250 μ g administered twice a day (bid) via Diskus as the minimum effective dose. During run-in period 1, patients received FP 220 μ g bid or the equivalent for 10 to 14 days. Controlled patients moved to run-in period 2 (5-28 days), which assessed asthma stability on FP 100 μ g bid administered via Diskus. Only patients who became unstable on FP 100 μ g bid were eligible to enter run-in period 3 (26-30 days), during which they were placed on FP 250 μ g bid and those regaining asthma control were eligible for randomization. The primary efficacy endpoint was the proportion of patients who remained in the study with no evidence of worsening asthma. Secondary efficacy measures included FEV₁, morning peak expiratory flow, percent of symptom-free days, and daily albuterol use.

Results: Only 5% of patients treated with FP100/salmeterol withdrew because of worsening asthma in the first 12 weeks; this compared with 7% in the FP250 group. All patients from a subset of sites continued in the study for an additional 12 weeks; only an additional 1% of patients treated with either FP100/salmeterol or FP250 withdrew because of worsening

asthma. Secondary efficacy measures confirmed primary efficacy results.

Conclusion: In patients requiring FP250 bid for asthma stability, FP100/salmeterol bid was steroid-sparing, allowing a 60% reduction in the FP dose while maintaining overall asthma control. (*J Allergy Clin Immunol* 2003;111:57-65.)

Key words: Fluticasone propionate, salmeterol, asthma, corticosteroid-sparing, inhaled corticosteroid, long-acting β_2 -agonist

Inhaled corticosteroids (ICSs) are the most effective long-term control medications available for asthma.¹ Of the available asthma maintenance medications, only ICSs have been shown to reduce major asthma morbidity, including hospitalizations^{2,3} and asthma-associated deaths.⁴ In addition, undertreatment with ICSs has been associated with poor clinical outcomes⁵ and might be associated with an irreversible loss of lung function if treatment with effective anti-inflammatory therapy is delayed relative to the onset of persistent asthma symptoms.⁶

The precise mechanisms for the beneficial anti-inflammatory effects of ICS in asthma are not fully understood, but they are thought to be mediated through glucocorticoid receptors that function to regulate inflammatory mediator gene expression.⁷ In this regard, effects of glucocorticoids on histopathologic features of asthma include restoration of airway epithelial cell integrity, reduction of inflammatory cell infiltration and mediator release, reduction of subepithelial collagen deposition, decreases in bronchial hyperresponsiveness, decreases in airway vascular permeability, decreases in mucosal edema, and upregulation of β_2 -adrenoreceptors.⁷⁻¹⁰ ICSs are generally well tolerated when taken at recommended doses. Despite these beneficial effects of ICSs, long-term use of moderate or high doses of an ICS might lead to undesired systemic side effects in some individuals; among these side effects are bone mineral density changes and suppression of the hypothalamic-pituitary-adrenal axis.¹

To reduce the risk of potential adverse effects from long-term ICS use, patients should use the lowest ICS dose necessary for asthma control.¹ A number of studies have shown that the use of lower doses of an ICS with an inhaled long-acting β_2 -agonist (LABA) results in greater

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Abbreviations used

bid: Twice daily
 FP: Fluticasone propionate
 ICS: Inhaled corticosteroid
 LABA: Long-acting β_2 -agonist
 PEF: Peak expiratory flow

improvements in overall asthma control and lower rates of asthma exacerbations than the use of higher doses of an ICS alone.¹¹⁻¹³ In accord with these clinical observations, bronchial lavage and biopsy studies have shown that use of a lower dose of an ICS with an LABA is at least as effective in controlling the underlying airway inflammation as higher doses of ICS alone.^{14,15}

These data suggest that the combination of a lower dose of ICS and an LABA might be steroid-sparing. However, few clinical studies have directly examined this postulate. This investigation was therefore designed to evaluate whether FP 100 μ g and salmeterol 50 μ g administered twice daily (bid) via a single Diskus inhaler (Glaxo-SmithKline) was ICS-sparing in patients with persistent asthma requiring FP 250 μ g bid for asthma stability.

METHODS

Patient selection

Male and female patients aged 12 years and older were eligible if they had had asthma for at least 6 months and been treated with a medium dose of ICS on a scheduled basis for at least 30 days before screening, such a dose being defined as any one of the following: beclomethasone dipropionate, 504-840 μ g/day; budesonide, 400-800 μ g/day; FP, 440-660 μ g/day; flunisolide, 1000-1500 μ g/day; triamcinolone acetonide, 1200-1600 μ g/day. At the screening visit, each patient was required to have an FEV₁ between 65% and 95% of predicted normal (Crapo¹⁶ or Polgar¹⁷ standards, race-adjusted for African American patients) and an increase in FEV₁ of at least 12% within 30 minutes of inhaling 2 to 4 puffs of albuterol.

Exclusion criteria included the following: pregnancy and/or lactation; life-threatening asthma; asthma hospitalization within 3 months of screening; a change in asthma regimen 30 days before screening; significant concurrent diseases, including a recent upper or lower respiratory tract infection. Medications prohibited throughout the study included oral or parenteral corticosteroids, theophylline or other bronchodilators, anticholinergics, leukotriene modifiers, cromolyn, nedocromil, salmeterol, and formoterol. Patients had not used oral or parenteral corticosteroids for at least 30 days before screening.

Study design and intervention

This randomized, double-blind, parallel-group, multicenter study (SAS40027) was conducted at 90 sites in the United States. An Institutional Review Board approved the study protocol, and each patient signed a written informed consent document before enrollment.

Eligible patients entered a 10- to 14-day run-in period (run-in period 1) to collect baseline data on FEV₁, peak expiratory flow (PEF), albuterol use, and asthma symptoms while dosing with open-label FP 220 μ g metered-dose inhaler bid (Flovent Inhalation aerosol, GlaxoSmithKline) or equivalent ICS. Before this period, all oral and inhaled short-acting β_2 -agonists were replaced with albuterol (Ventolin Inhalation aerosol, GlaxoSmithKline). Patients recorded asthma symptom scores daily. Symptoms were self-

assessed through use of a 0- to 5-point Likert scale, 0 representing no symptoms and 5 representing severe symptoms. Any patient whose condition exacerbated at any time during screening was discontinued from the study. At run-in visit 1A (10-14 days after the screening visit), each patient was required to demonstrate the following asthma stability criteria in order to continue: a best FEV₁ within $\pm 15\%$ of the best predose FEV₁ obtained at screening, no more than 1 nighttime awakening requiring albuterol, and use of fewer than 18 puffs of albuterol during the previous week.

Patients meeting these criteria were dispensed open-label FP (Flovent Diskus) 100 μ g for 5 to 28 days; this was run-in period 2. Meeting any one (or more) of the following asthma instability criteria was used to indicate the need for additional ICS: a $\geq 20\%$ decrease from the screening visit predose FEV₁; a $\geq 20\%$ decrease from the mean morning baseline PEF on any one of the 7 days immediately preceding a visit; a total symptom score of ≥ 8 during any 1 week before run-in visit 1B; 18 or more puffs of albuterol during any 1-week period before run-in visit 1B; 2 or more nighttime awakenings due to asthma requiring treatment with albuterol during any 1-week period before run-in visit 1B. Patients who did not meet at least one of these criteria were considered to have stable asthma on FP 100 μ g bid and were discontinued from the study.

Patients who met at least one of the criteria received step-up therapy to open-label FP (Diskus) 250 μ g bid for 4 weeks to regain asthma control; this was run-in period 3. Patients who regained asthma control proceeded to the randomization visit. All patients (n = 308) from a subset of preselected sites continued randomized treatment for an additional 12 weeks to determine whether asthma control was maintained for up to 24 weeks.

Patients who met the qualification criteria at the randomization visit (a best FEV₁ of $\geq 65\%$ of predicted and $\geq 15\%$ of the best predose FEV₁ obtained at visit 1A) were randomly assigned to one of the following treatments for 12 or 24 weeks: FP100/salmeterol Diskus combination product (Advair Diskus, 100/50, Glaxo-SmithKline); FP Diskus (Flovent Diskus, GlaxoSmithKline) 250 μ g bid. After randomization, patients were discontinued from the study for lack of efficacy if they satisfied any of the following criteria preceding or during each clinic visit: a $\geq 20\%$ decrease from the mean morning baseline PEF on 3 consecutive days; a $\geq 20\%$ decrease from baseline FEV₁ at any visit; an exacerbation (defined as any worsening of asthma that required asthma medication beyond blinded study drugs or albuterol).

Patients self-administered 1 inhalation from the Diskus in the morning and in the evening and returned to the clinic after 1, 4, 8, and 12 weeks of treatment. Each day, patients recorded the following on a diary card: morning and evening PEF, albuterol use, number of nighttime awakenings due to asthma, and symptom scores. Compliance with study medication was calculated through use of diary counts and from the number of doses contained in the Diskus before dispensing and at the clinic visits. Morning PEF was measured before the morning dose of inhaled medication; evening PEF was measured before the evening dose of inhaled medication.

Statistical methods

The sample size for this study (at least 250 patients per treatment arm who could be evaluated at week 12) provided at least 80% power to ensure that a 90% CI of the difference between survival proportions at week 12 was contained within the margin of equivalence ($\Delta = 0.15$, assuming survival rates of $\pi_{FSC} = 0.85$ and $\pi_{FP} = 0.80$ for FP100/salmeterol and FP250, respectively). The sample size at week 24 provided at least 80% power to ensure that a 90% CI of the difference between survival proportions at week 24 was contained within the margin of equivalence ($\Delta = 0.20$, assuming survival rates of $\pi_{FSC} = 0.80$ and $\pi_{FP} = 0.75$ for FP100/salmeterol and FP250, respectively).

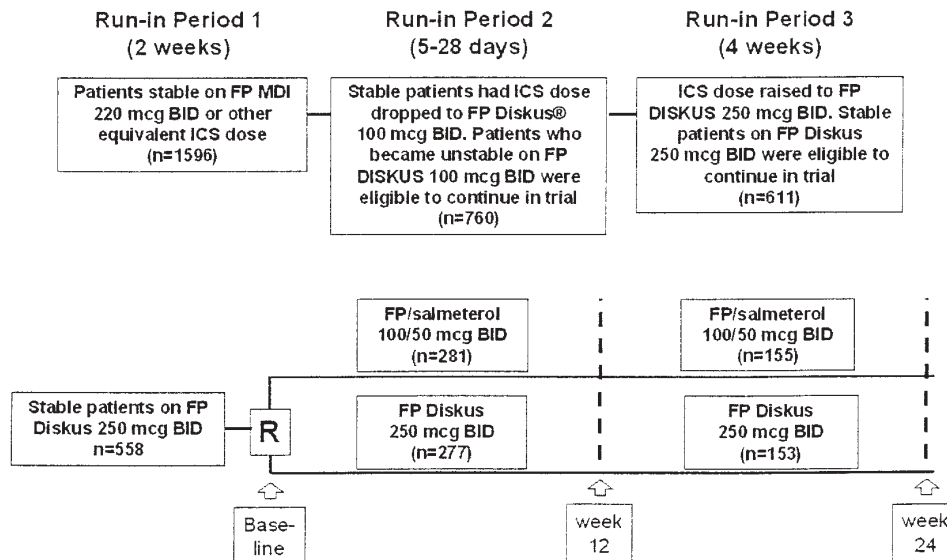


FIG 1. Flow diagram shows study progression.

All analyses for efficacy and safety were conducted through use of the intent-to-treat population (all randomized patients). All data from patients who were withdrawn from the study early were included in the analyses, data available up to the time of study discontinuation being used. No interpolation was used for missing data.

The primary efficacy measure was the proportion of patients who remained in the study after 12 weeks of double-blind treatment and did not withdraw because of lack of efficacy; a related efficacy measure was the proportion of patients who remained in the study after 24 weeks of double-blind treatment and did not withdraw because of lack of efficacy. The estimates of the proportion of patients who remained in the study after 12 weeks of double-blind treatment were calculated from a Kaplan-Meier survival curve on the basis of product limit estimates; 90% CIs were constructed for the difference in the survival estimates. Secondary efficacy measures were clinic FEV₁, morning PEF, symptom-free days, and rescue albuterol use.

Baseline values were collected at the randomization visit for diary card parameters and were the means of all measurements from 7 days preceding randomization. Treatment groups were compared for all efficacy measures by analyzing the mean change from baseline at endpoint. For FEV₁, baseline was defined as the predose measurement from the randomization visit. Mean changes in FEV₁ from baseline at each clinic visit and at the endpoint were compared between treatment groups. Endpoint assessments compared the last available data values for all patients, regardless of their duration of participation; these were calculated as the means of the measurements from the last week before the week 12 visit or the week 24 visit.

Comparisons between treatment groups for FEV₁, PEF, albuterol use, and nights per week with awakenings were made through use of analysis of covariance (including terms for treatment, investigator, and baseline); comparisons for symptoms and percent of symptom-free days, rescue-free days, and awakening-free nights were made through use of a van Elteren test, controlling for investigator.

Safety was assessed by clinical adverse events and exacerbations. Adverse events were reported spontaneously by the patient, or such information was elicited during clinic visits. All medical problems that occurred during the study were considered adverse events, regardless of their suspected relationship with the study treatment.

The incidence of asthma exacerbations was compared between treatments through use of a Cochran-Mantel-Haenszel test, controlling for investigator.

RESULTS

Patients

Of the 760 patients who entered the first run-in period, 281 and 277 were randomized to FP100/salmeterol and FP250, respectively (Fig 1). As noted previously, the 3 run-in periods were designed to ensure that randomized patients required FP 250 µg bid for asthma stability. A total of 149 patients were discontinued during the FP100 run-in period, primarily because their asthma remained stable after dropping from higher-dose ICS to FP 100 µg bid. An additional 53 patients were discontinued during the FP250 run-in period, primarily because their asthma failed to stabilize when the FP dose was increased from FP 100 µg bid to FP 250 µg bid.

Baseline demographic characteristics were similar between groups (Table I). Fifty-three percent of patients reported having asthma symptoms for more than 15 years. The mean percent reversibility was 19.0% ± 7.8%, and the mean percent predicted FEV₁ before randomization (ie, while the patient's asthma was stable on FP250) was 80.5% ± 9.7% for FP100/salmeterol and 80.9% ± 9.4% for FP250. Mean treatment compliance rates ranged from 96% to 97%. A summary pertaining to the patients who discontinued the study prematurely is shown in Table II.

Efficacy

Probability of remaining in the study without being withdrawn due to worsening asthma. Fig 2 shows that 5% of the 281 patients assigned to FP100/salmeterol for 12 weeks were withdrawn because of worsening asthma;

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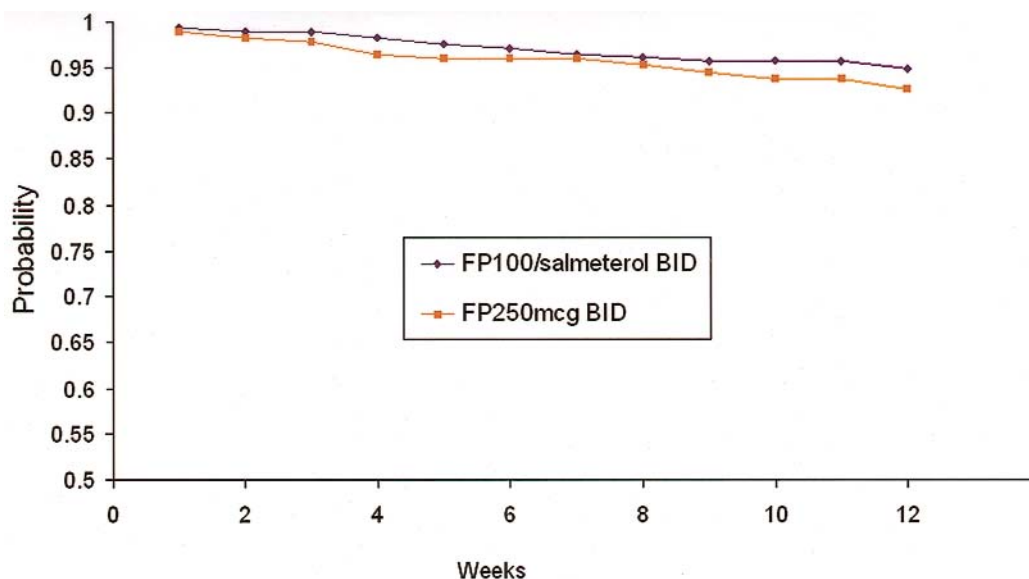


FIG 2. Kaplan-Meier survival curve reflects asthma stability based on predefined criteria for worsening asthma at 12-week endpoint.

TABLE I. Demographics and baseline characteristics

	FP 100 µg/ salmeterol bid	FP 250 µg bid
Age (y): mean (range)	38 (12-77)	39 (12-72)
Male/female (%/%)	41/59	43/57
Ethnic origin		
White	253 (90%)	243 (88%)
Black	14 (5%)	13 (5%)
Asian	2 (<1%)	5 (2%)
American Hispanic	11 (4%)	16 (6%)
Other	1 (<1%)	0
FEV ₁ (L): mean (SD)	2.74 (0.67)	2.80 (0.70)
FEV ₁ percent predicted (SD)	80.5 (9.7)	80.9 (9.4)
Percent reproducibility (SD)	6.9 (6.7)	7.6 (7.4)

this compared with 7% of the 277 patients assigned to FP ($P = .264$; 90% CI, $-0.11, 0.058$). Of the 155 FP100/salmeterol-treated patients and the 153 FP250-treated patients who were initially randomized to receive study medication for a total of 24 weeks, 135 and 131, respectively, remained in the study after 12 weeks of treatment. Within this cohort, only an additional 1% in each group were withdrawn over weeks 13 to 24 because of worsening asthma ($P = .156$; 90% CI, $-0.008, 0.103$).

Spirometric data. Table III shows that patients treated with FP100/salmeterol had improvements from baseline in FEV₁ of 0.07 ± 0.01 L and 0.10 ± 0.02 L at the 12- and 24-week endpoints, respectively; this compared with -0.03 ± 0.01 L and 0 ± 0.02 L in patients treated with FP250 at the 12- and 24-week endpoints, respectively ($P < .001$). However, the differences between treatments were within the 90% CIs for equivalence.

Patient-recorded data. Baseline and mean change from baseline values at endpoint for morning and

evening PEF, percent of symptom-free days, percent of rescue-free days (24-hour period), and daily albuterol use are shown in Table III. Patients treated with FP100/salmeterol had greater improvements than patients treated with FP250 ($P < .001$) in morning PEF (Fig 3); these improvements began within the first week of initiating treatment. Similarly, patients treated with FP100/salmeterol had greater improvements from baseline in evening PEF at the 12- and 24-week endpoints than patients treated with FP250 (Table III; $P \leq .039$). For both morning and evening PEF, the differences between treatments were within the 90% CIs for equivalence.

Both treatments resulted in improvements in symptom scores and symptom-free days (Table III). Likewise, both treatments resulted in decreased need for supplemental albuterol (Fig 4). The differences between treatments for each of these parameters were within the 90% CIs for equivalence.

Safety

Adverse events. In general, both treatments were well tolerated, and the incidence of common and pharmacologically predictable adverse events over both the 12-week and the 24-week study periods were similar for the 2 treatments. Of the 558 patients who were randomized to the 12-week portion of the study, 50% and 56% of patients in the FP100/salmeterol and FP250 treatment groups, respectively, reported 1 or more adverse events. Of the 266 patients who continued for an additional 12 weeks, 44% of the FP100/salmeterol-treated patients and 47% of the FP250-treated patients reported 1 or more adverse events. Upper respiratory tract infection was the most frequently reported adverse event. Drug-related adverse events occurred in 4% and 5% of patients treated with FP100/salmeterol and FP250, respectively, during weeks 1 through 12 of double-blind treatment and in

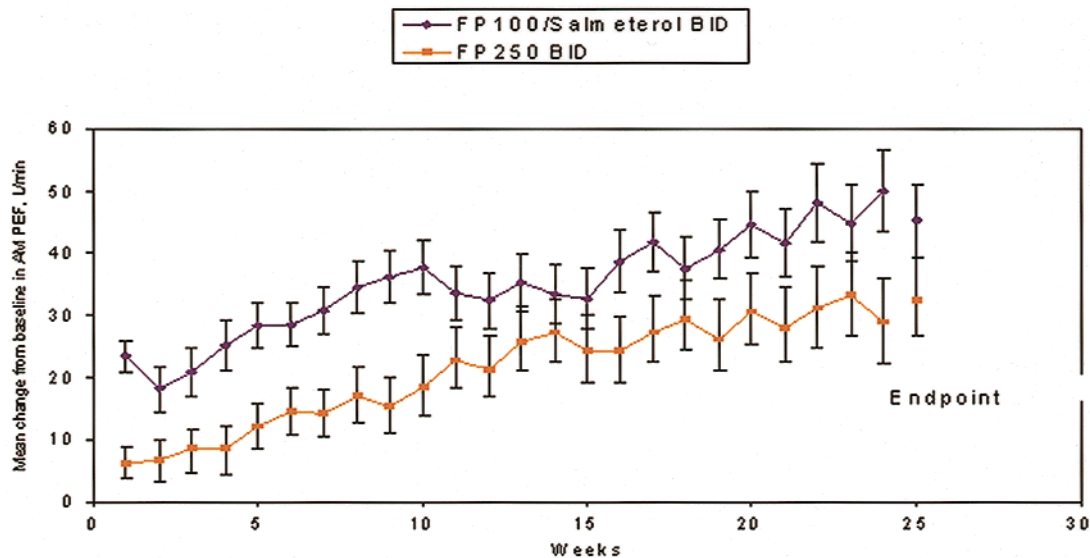


FIG 3. Mean change from baseline in AM PEF. Patients treated with FP100/salmeterol had 36.7 ± 3.7 L/min and 45.2 ± 5.9 L/min improvements from baseline in morning PEF at the 12- and 24-week endpoints, respectively, compared with 18.5 ± 3.6 L/min and 32.5 ± 6.8 L/min, respectively, in patients treated with FP250 ($P < .0001$, week 12 endpoint). Baseline AM PEF values were 458.0 L/min for FP100/salmeterol and 457.4 L/min for FP250. Patients treated with FP100/salmeterol had 36.8 ± 3.7 L/min and 49.4 ± 5.9 L/min improvements from baseline in evening PEF at the 12- and 24-week endpoints, respectively compared with 20.9 ± 3.7 L/min and 31.3 ± 6.2 L/min in patients treated with FP250 ($P = .001$, weeks 1-12; $P = .039$, weeks 1-24).

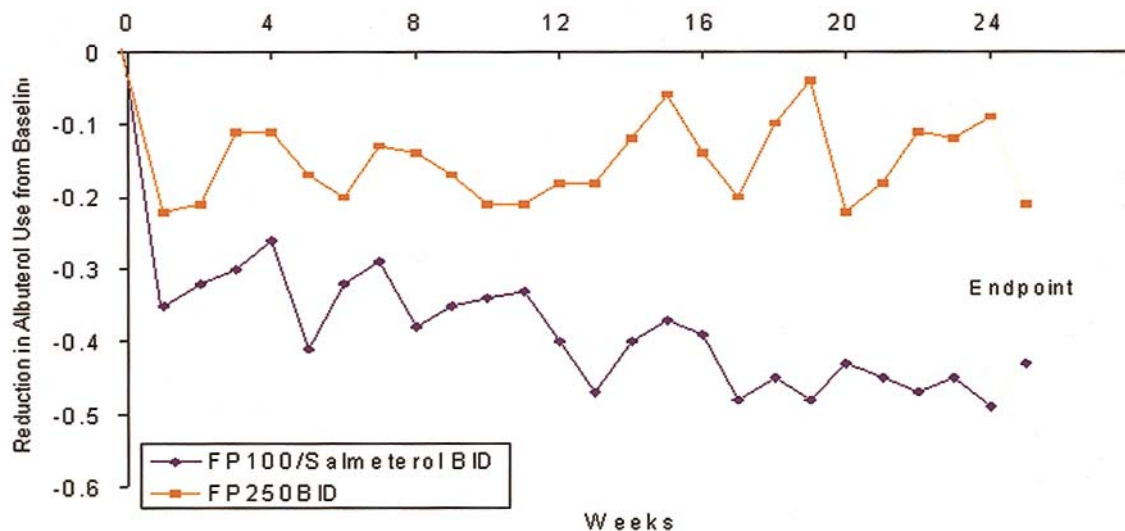


FIG 4. Reduction in albuterol use from baseline. At the 12-week endpoint, treatment with FP100/salmeterol resulted in a 0.30 ± 0.07 puffs/24 hours reduction in supplemental albuterol compared with a 0.18 ± 0.06 puffs/24 hours reduction after treatment with FP250 ($P = .045$). At the 24-week endpoint, treatment with FP100/salmeterol resulted in a 0.43 ± 0.11 puffs/24 hours reduction in supplemental albuterol use compared with 0.21 ± 0.07 puffs/24 hours reduction after treatment with FP250 ($P = .022$).

<1% and 3% of patients treated with FP100/salmeterol and FP250, respectively, during weeks 13 through 24.

Five patients withdrew from double-blind treatment during the study because of adverse events. Two events were considered by the investigator to be related to the study drug (FP250 group: candidiasis; intermittent shortness of breath).

Exacerbations. The numbers of patients who experienced asthma exacerbations were similar for the 2 treatment groups. During weeks 1 through 12, 3% and 2% of patients treated with FP100/salmeterol and FP250, respectively, experienced exacerbations ($P = .820$). During weeks 13 through 24, 2% of patients

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TABLE II. Summary of patient disposition

	FP 100 µg/salmeterol bid	FP 250 µg bid	Total
No. of patients screened	—	—	760
FP100 Run-in screen failures	—	—	149
FP250 Run-in screen failures	—	—	53
Total randomized	281	277	558
Total completed	235 (84%)	223 (81%)	458 (82%)
Total discontinued	46 (16%)	54 (19%)	100 (18%)
Discontinued (weeks 1-12)	35 (12%)	42 (15%)	77 (14%)
Adverse event	1 (<1%)	2 (<1%)	3 (<1%)
Consent withdrawn	0	4 (1%)	4 (<1%)
Lost to follow-up	1 (<1%)	6 (2%)	7 (1%)
Protocol violation	9 (3%)	7 (3%)	16 (3%)
Lack of efficacy	14 (5%)	20 (7%)	34 (6%)
Other	10 (4%)	3 (1%)	13 (2%)
Randomized (weeks 1-24)	155	153	308
Remaining at week 13	135 (87%)	131 (86%)	266 (86%)
Discontinued (weeks 13-24)	11 (4%)	12 (4%)	23 (4%)
Adverse event	1 (<1%)	2 (<1%)	3 (<1%)
Consent withdrawn	0	0	0
Lost to follow-up	0	0	0
Protocol violation	4 (1%)	2 (<1%)	6 (1%)
Lack of efficacy	3 (1%)	4 (1%)	7 (1%)
Other	3 (1%)	4 (1%)	7 (1%)

treated with FP100/salmeterol experienced exacerbations ($P = .104$).

DISCUSSION

Corticosteroids are the only antiasthma medications that have been shown to reduce hospitalizations and mortality and consistently improve morphologic alterations associated with asthma, including changes in basement membrane thickness and airway inflammatory cell infiltration.^{1,2,4,8,9,18,19} Expert panel guidelines for the treatment of asthma consider ICSs the cornerstone of asthma therapy but suggest that an ICS should be titrated to the lowest effective dose.¹ However, the clinical decision-maker has limited evidence regarding strategies for reducing the ICS dose while maintaining good overall asthma control.

This study demonstrated that in patients requiring moderate doses of an ICS (ie, FP 250 µg bid) to maintain asthma control, the use of the inhaled long-acting β_2 -agonist salmeterol enabled a 60% reduction in the dose of ICS while effectively maintaining asthma control. This result is consistent with recent studies demonstrating that the use of salmeterol permitted asthma control to be maintained while the ICS dose was reduced by approximately 50%,^{20,21} but asthma control cannot be maintained if ICSs are completely withdrawn.²²

The interpretation of results from steroid-sparing trials might be confounded by study designs that do not establish a minimum requirement for ICS during screening. For example, Lofdahl et al²³ examined the steroid-sparing effect of montelukast and fixed the ICS taper during screening to 2 steps rather than to the point of lost asthma control. Similarly, the study by Wilding et al¹² evaluating

the steroid-sparing effects of salmeterol did not include an ICS taper during screening to establish the point of lost asthma control. The current study overcame these limitations by enrolling only patients who were shown during screening to have unstable asthma when receiving FP 100 µg bid and stable asthma when receiving FP 250 µg bid. As such, the results provide clinically relevant information regarding the steroid-sparing properties of FP100/salmeterol administered via the Diskus.

The relationship between clinical parameters and pathophysiologic changes (eg, inflammatory cell influx and mediator release), on the one hand, and the dose of ICS needed to effectively control both, on the other, is poorly described but might be dose-dependent. Whereas patients can easily report changes in clinical parameters, pathophysiologic changes such as those associated with airway inflammation are best assessed through use of biopsies. However, biopsies are not practical in clinical practice and remain primarily a research tool. Nevertheless, there is general agreement that the best clinical measure of overall asthma control, including control of the underlying inflammation, is the rate of asthma exacerbations/worsening asthma. This was the basis for selecting worsening asthma/asthma exacerbations as the primary endpoint for the present study. The fact that FP100/salmeterol was equivalent to FP250 at the week-12 and week-24 endpoints in preventing worsening asthma suggests that the use of salmeterol with a lower dose of ICS effectively treated the underlying pathophysiology and is consistent with recommendations in current treatment guidelines.

There is increasing evidence that LABAs and ICSs have complementary mechanisms of action in the treatment of asthma.²⁴⁻²⁶ Regular use of ICS has been shown

TABLE III. Mean change from baseline (\pm SEM) at endpoint in patient-recorded data

	FP 100 μ g/salmeterol bid	FP 250 μ g bid	P value*
FEV ₁ (L)			
12 weeks			$\leq .001$
Baseline	2.74 (0.04)	2.80 (0.04)	
Endpoint	0.07 (0.01)	−0.03 (0.01)	
24 weeks			$\leq .007$
Baseline	2.72 (0.06)	2.82 (0.06)	
Endpoint	0.10 (0.02)	0.00 (0.02)	
AM PEF (L/min)			
12 weeks			$< .001$
Baseline	458.0 (8.7)	457.4 (8.9)	
Endpoint	36.7 (3.7)	18.5 (3.6)	
24 weeks			.180
Baseline	438.4 (11.2)	451.9 (11.7)	
Endpoint	45.2 (5.9)	32.5 (6.8)	
PM PEF (L/min)			
12 weeks			.001
Baseline	460.0 (8.4)	462.0 (8.8)	
Endpoint	36.8 (3.7)	20.9 (3.7)	
24 weeks			.039
Baseline	443.2 (10.9)	458.4 (11.6)	
Endpoint	49.4 (5.9)	31.3 (6.2)	
Percent of symptom-free days			
12 weeks			.028
Baseline	42.7 (2.5)	42.1 (2.5)	
Endpoint	11.8 (2.0)	5.8 (1.8)	
24 weeks			.078
Baseline	44.5 (3.5)	43.0 (3.5)	
Endpoint	11.6 (3.0)	6.2 (2.9)	
Daily asthma symptom score			
12 weeks			.232
Baseline	1.03 (0.06)	1.04 (0.06)	
Endpoint	−0.20 (0.04)	−0.12 (0.04)	
24 weeks			.137
Baseline	1.0 (0.08)	1.06 (0.09)	
Endpoint	−0.22 (0.06)	−0.14 (0.06)	
Albuterol use (puffs/24 h)			
12 weeks			.045
Baseline	0.82 (0.07)	0.82 (0.07)	
Endpoint	−0.30 (0.07)	−0.18 (0.06)	
24 weeks			.022
Baseline	0.83 (0.10)	0.92 (0.10)	
Endpoint	−0.43 (0.11)	−0.21 (0.07)	
Percent rescue-free days			
12 weeks			.008
Baseline	64.3 (2.3)	63.3 (2.3)	
Endpoint	14.7 (2.0)	9.3 (2.0)	
24 weeks			.032
Baseline	64.9 (3.1)	62.1 (3.3)	
Endpoint	14.9 (3.2)	8.3 (2.7)	
Nighttime awakenings			
12 weeks			.566
Baseline	0.43 (0.06)	0.50 (0.07)	
Endpoint	−0.29 (0.09)	−0.34 (0.10)	
24 weeks			1.000
Baseline	0.49 (0.12)	0.49 (0.08)	
Endpoint	−0.37 (0.05)	−0.43 (0.09)	

*Differences between treatments for all endpoints were within the 90% CIs for equivalence.

Asthma, rhinitis,
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to modulate β_2 -agonist receptor function.²⁴ In addition, β_2 -agonists are potent activators of the glucocorticoid receptor in vitro.²⁶ Although the exact mechanism of interaction of ICSs and LABAs in the treatment of asthma remains unknown, the magnitude and consistency of clinical benefit has been demonstrated in numerous clinical studies.^{11,13,20,22,27,28}

The results of the present study are consistent with prior studies showing that asthma exacerbation rates are lower with LABA plus low-dose ICS than with higher-dose ICS alone.^{11,13,22,27,28} As such, these clinical findings suggest that inflammation was not undertreated, inasmuch as undertreatment would be expected to result in higher, not lower, rates of exacerbations. In accord with these clinical observations, lung biopsy and lavage studies have shown that airway inflammation is controlled at least as effectively with an LABA and a lower dose of an ICS as with a higher dose of an ICS alone.^{14,15,29}

Long-term safety is a concern with any chronic disease therapy, including asthma. Although systemic effects appear to be minimal with low doses of ICS, they can occur during the use of ICS and have been raised as potential safety concerns with these agents. The present study indicates that a lower dose of ICS used with an LABA was steroid-sparing and enabled patients who required FP 250 μ g bid for asthma stability to undergo a 60% reduction in total daily ICS dose while maintaining asthma stability. As such, the systemic effects of ICSs in patients requiring higher-dose ICS (eg, FP 250 μ g bid) for asthma stability could be reduced with this approach.^{1,30}

In summary, this equivalence study demonstrated that in patients requiring FP 250 μ g bid to maintain asthma stability, FP 100 μ g/salmeterol bid resulted in similar or improved asthma control compared with FP250 and hence was ICS-sparing, allowing the dose of FP to be reduced by 60%.

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