

Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: A randomized, double-blind, placebo-controlled trial

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Background: Many patients with persistent asthma need both long-acting bronchodilators and inhaled corticosteroids for optimal asthma control.

Objective: Our purpose was to compare the efficacy and safety of salmeterol 50 µg combined with fluticasone 100 µg (in a combination dry powder product) with that of placebo, fluticasone, or salmeterol alone.

Methods: A 12-week randomized, double-blind, multicenter study was conducted in 356 patients aged 12 years or older with asthma. After a 14-day screening period, patients were randomized to treatment with salmeterol 50 µg combined with fluticasone 100 µg (combination product), salmeterol 50 µg, fluticasone 100 µg, or placebo administered in the Diskus dry powder inhaler (GlaxoWellcome, UK) twice daily.

Results: Mean change in FEV₁ at end point was significantly ($P \leq .003$) greater with the combination product (0.51 L) compared with placebo (0.01 L), salmeterol (0.11 L), and fluticasone (0.28 L). The combination product significantly increased ($P \leq .013$) area under the curve compared with placebo and fluticasone on day 1 and compared with placebo, salmeterol, and fluticasone at week 1 and week 12. Patients in the combination product group were less likely to withdraw from the study because of worsening asthma compared with those in the other groups ($P \leq .020$). The combination product significantly increased ($P \leq .012$) morning PEF (combination, 52.5 L/min; placebo, -23.7 L/min; salmeterol, -1.7 L/min; fluticasone, 17.3 L/min) and evening PEF at end point compared with the other groups. The combination product significantly ($P \leq .025$) reduced symptom scores and albuterol use compared with the other treatments and increased the percentage of nights with

no awakenings and the percentage of days with no symptoms compared with placebo and salmeterol. All treatments were equally well tolerated.

Conclusion: Salmeterol 50 µg and fluticasone 100 µg combined in the Diskus powder delivery device offers significant clinical advantages over salmeterol or fluticasone alone at the same doses. (*J Allergy Clin Immunol* 2000;105:1108-16.)

Key words: Asthma, fluticasone, salmeterol, inhaled corticosteroid, long-acting bronchodilator, Diskus dry powder inhaler

Several studies have shown the benefits of administering long-acting bronchodilators in conjunction with (rather than doubling the dose of) inhaled corticosteroids in patients with asthma who are symptomatic while receiving inhaled corticosteroids.¹⁻⁴ National guidelines for the treatment of asthma now recommend this treatment intervention as an appropriate option for asthma management with the recognition that many patients need both long-acting bronchodilators and inhaled corticosteroids for optimal asthma control.⁵ This concept of using a combination of drugs with different mechanisms of action in pharmacotherapy has been used effectively and is considered appropriate clinical practice in other disease states (eg, hypertension, tuberculosis, AIDS). However, multiple medication regimens for asthma or any chronic disease is potentially confusing to the patient and may result in an inability to adhere to a prescribed treatment plan.

The objective of this placebo-controlled study was to compare the efficacy and safety of salmeterol 50 µg and fluticasone propionate 100 µg in a combination dry powder product administered twice daily (through the Diskus device [GlaxoWellcome, UK]) with that of fluticasone propionate or salmeterol at the same doses in patients previously treated with low doses of inhaled corticosteroids or salmeterol.

METHODS

Patients

Male and female patients were eligible for the study if they were at least 12 years old and had a medical history of asthma (as defined by the American Thoracic Society⁶) of at least 6 months' duration that required pharmacotherapy over the 6 months preceding the

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Abbreviations used

AUC:	Area under the 12-hour serial FEV ₁ curve relative to baseline
ECG:	Electrocardiogram
PEF:	Peak expiratory flow

study. Patients were required to have an FEV₁ between 40% to 85% of the predicted value based on European Community for Coal and Steel standards for ages 18 years and older (and readjusted for African Americans)^{7,8} or Polgar standards for ages 12 to 17 years.⁹ Patients had greater than or equal to a 15% increase in FEV₁ 30 minutes after 2 puffs (180 µg) of inhaled albuterol. Patients were stratified into 2 groups according to type of asthma therapy used at enrollment. Group 1 patients must have been using inhaled corticosteroids for at least 3 months before the screening visit. Patients using salmeterol with inhaled corticosteroids were eligible to participate if they could replace salmeterol with as-needed β_2 -agonists at least 1 week before the screening visit. Patients taking inhaled corticosteroids must have been treated with a dose of 6 to 10 puffs per day of beclomethasone dipropionate (252-420 µg/d) or triamcinolone acetonide (600-1000 µg/d), 4 puffs per day of flunisolide (1000 µg/d), or 4 puffs per day of fluticasone propionate 44 µg per puff (176 µg/d) for at least 1 month before screening with no change in regimen. Group 2 patients must have been using salmeterol at least 1 week before screening. Patients treated with salmeterol must have demonstrated a screening FEV₁ $\leq$ 85% of predicted normal after 2 puffs of albuterol and should not have received concurrent inhaled corticosteroids for at least 1 month before screening.

Female patients had negative pregnancy tests and were either surgically sterile, postmenopausal for at least 1 year, or using acceptable birth control for at least 1 month before participation. Exclusion criteria included history of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history of >10 pack-years; use of oral, inhaled, or injectable corticosteroid therapy within the previous month; use of intranasal corticosteroids except for Flonase (GlaxoWellcome, Research Triangle Park, NC); use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that may affect the course of asthma or interact with sympathomimetic amines; abnormal chest x-ray films; clinically significant abnormal 12-lead electrocardiograms (ECG); or history of significant concurrent disease (eg, glaucoma, diabetes, hypertension). All patients (or guardians) gave informed consent before entry into the study.

Study design and interventions

This 12-week randomized, double-blind, parallel-group, placebo-controlled study (protocol No. SFCA3002) was approved by institutional review boards for each of the 42 investigative sites. Eligible patients entered a 2-week, single-blind placebo screening period to evaluate eligibility, assess compliance with therapy, obtain baseline data, and confirm asthma stability.

Patients were instructed on the use of the peak flow meter (Mini-Wright, Clement Clark, London, UK), metered-dose inhaler, and Diskus inhaler. Patients were instructed to complete daily diary cards, attend all scheduled study visits, and report medication compliance. Adherence to treatment was measured by the use of the dose counter on the Diskus device. Stable asthma was confirmed by diary cards at the end of the screening period and was a requirement for study continuation. During the screening period patients were not eligible if they had more than 3 nighttime awakenings caused by asthma that required treatment with albuterol during the 7 days

immediately preceding the randomization period. In addition, group 1 patients using 12 or more puffs of albuterol daily for more than 3 days and group 2 patients using 6 or more puffs daily for more than 3 days were ineligible. At the end of the screening period, FEV₁ had to be between 40% and 85% of the predicted value and had to be within $\pm$ 15% of the FEV₁ obtained at the beginning of the screening period.

Patients entering the double-blind phase were randomly allocated to receive one of the following treatments by the Diskus inhaler twice daily for 12 weeks: salmeterol 50 µg and fluticasone propionate 100 µg combination, salmeterol 50 µg, fluticasone propionate 100 µg, or placebo. Patients were permitted to take albuterol as needed for relief of symptoms. All active study medications were administered through Diskus inhalers with identical appearance to maintain double-dummy blinding.

Assessment of efficacy and safety

Primary efficacy end points included area under the 12-hour serial FEV₁ curve relative to baseline (AUC), morning predose FEV₁, and the probability of patients remaining in the study over time without being withdrawn for worsening asthma. Secondary efficacy measures included peak expiratory flow (PEF), daily patient-rated diary card symptom scores, albuterol use, and nighttime awakenings because of asthma requiring albuterol. At each clinic visit pulmonary function tests were performed in triplicate before the morning dose (only the best effort was recorded) with use of spirometric equipment that exceeded the minimal performance recommendations.⁸ Throughout the study patients measured PEF in triplicate (only the best effort was recorded) twice daily, rated daily symptoms (wheezing, shortness of breath, and cough) on a 6-point scale ranging from 0 = no symptoms to 5 = symptoms that severely interfered with daily activities, recorded the number of nighttime awakenings because of asthma symptoms requiring albuterol, and recorded the frequency of supplemental albuterol use.

Patients returned to the clinic (between 6 and 9 AM) on a weekly basis for the first 4 weeks and then every 2 weeks for 2 months, for a total of 12 weeks of double-blind treatment. At each clinic visit diary card information was assessed and pulmonary function tests were performed to determine whether patients met predetermined asthma stability criteria. Patients were withdrawn from the study because of worsening asthma if they met any of the following criteria: a clinical exacerbation requiring emergency treatment, hospitalization, or asthma medication not allowed by protocol; a 20% decrease from the randomization visit predose FEV₁; a 20% decrease from the mean morning baseline PEF on more than 3 of 7 days immediately preceding a visit; 12 or more albuterol puffs per day on more than 2 of 7 days immediately preceding a visit; or more than 2 nighttime awakenings because of asthma symptoms that required albuterol aerosol during the week immediately preceding a clinic visit.

Safety was assessed by examining adverse events, 24-hour Holter monitoring at selected sites, 12-lead ECGs, routine laboratory tests, and physical examinations. Adverse events were recorded at each clinic visit by the investigator who rated the relationship of the event to the study drug. Standard clinical laboratory tests and physical examinations were conducted at screening and at week 12.

Twelve-lead ECGs were obtained at screening and both before and after dosing on day 1, week 1, and week 12 during the 12-hour serial pulmonary function tests. A clinically significant abnormal ECG was defined as a 12-lead tracing consistent with ischemic changes, ventricular hypertrophy, intraventricular conduction abnormalities (eg, bundle branch block, Wolff-Parkinson-White syndrome), or clinically significant arrhythmias (eg, atrial fibrillation, ventricular tachycardia). Twenty-four-hour Holter monitors were connected and tapes started in the clinic within 2 days after screening and within 2 days before week 12.

Statistical analyses

The primary measures of efficacy were serial FEV₁ and the probability of remaining in the study over time. Previous studies indicated that a reasonable assumption for the SD of FEV₁ is 0.55 L. The sample size of 80 subjects per treatment was chosen to provide 80% power to detect a difference of 0.25 L for any pairwise treatment comparison, with use of a *t* test and a significance level of .05.

Regarding probability of remaining in the study over time, it was estimated that the proposed sample size of 80 subjects per treatment group would provide 85% power to detect a difference in dropout rates of 20%, assuming that 10% of subjects taking the combination product and 30% of subjects taking salmeterol would be withdrawn for lack of efficacy before the end of the study.

All statistical tests were 2 sided and based on a significance level of $P \leq .05$. Pairwise treatment comparisons were viewed solely as descriptive in cases where the overall treatment comparison was not statistically significant.

Descriptive statistics were calculated for demographic and other baseline variables. Overall treatment group differences were evaluated by use of ANOVA *F* tests and Cochran-Mantel-Haenszel tests for continuous and categorical variables, respectively, with each controlled for investigator cluster and stratum. (Because of the large number of investigators participating in this study, groups or clusters of investigators were used for statistical analysis instead of individual investigators. Clusters were defined before unblinding of the clinical trial and were defined to be of similar size. Investigators who screened fewer than 20 patients were grouped in clusters on the basis of geographic proximity of sites. Investigators who screened 20 or more patients were defined as stand-alone clusters.)

The population used for all efficacy analyses was the intent-to-treat population (all randomized patients who were exposed to study drug) minus 21 patients at one site who were excluded because of significant deviations from good clinical practice standards. Serial FEV₁ data and morning predose FEV₁ were analyzed by visit. All diary measures were analyzed by week and at study end point. To compensate for differential withdrawal rates among the treatment groups, end-point analyses were used. End-point analyses included data from the final visit during treatment for patients completing the study and the last available data for patients who were withdrawn early. The probability of remaining in the study at each week without being withdrawn because of worsening asthma was estimated with use of the Kaplan-Meier¹⁰ product-limit method on the basis of the number of efficacy failures in each treatment group. Log-rank tests of homogeneity were used to compare the resulting survival curves.

ANOVA *F* tests, controlled for investigator, were used to assess treatment differences in morning predose FEV₁, serial FEV₁ measures, and morning and evening PEF. Serial FEV₁ measures were also analyzed with use of a repeated-measures ANOVA. Patient-recorded diary data were analyzed with use of van Elteren tests¹¹ stratified by investigator cluster and stratum. The strata as defined by baseline asthma therapy (group 1, inhaled corticosteroids; group 2, salmeterol) were included as a covariate in the statistical hypothesis tests.

Safety analyses were based on the intent-to-treat population. Assessment of the incidence of adverse events was performed with use of Fisher's exact test; cardiac rates measured by Holter monitor were analyzed with ANOVA *F* tests controlled for investigator cluster and stratum. Abnormalities in cardiac rhythm were assessed with van Elteren tests, stratified by investigator cluster and stratum.

RESULTS

Of 527 patients screened, 356 patients were randomly assigned to treatment. The major reasons for screen failures were lack of reproducible lung function and FEV₁

<40% or >85% predicted. Randomization resulted in comparable treatment groups at baseline with respect to patient demographics and pulmonary lung function (Table I). Mean adherence to treatment ranged from 93% to 100% across treatment groups. No patient was withdrawn from the study because of poor adherence to study medication. The disposition of patients is shown in Table I. Overall, comparable results were obtained with or without data from 21 patients at one site who were excluded because of significant deviations from good clinical practice standards.

Efficacy

Spirometric data. The mean change from baseline at end point in morning predose FEV₁ is shown in Table II. Improvements in FEV₁ at end point were significantly ($P < .001$) greater in patients treated with the combination product compared with placebo (no improvement). Patients treated with the combination product had a 25% improvement from baseline in FEV₁ at end point compared with 5% and 15% improvements from baseline in patients treated with salmeterol or fluticasone propionate, respectively ($P \leq .008$).

The 12-hour serial FEV₁ improvements were significantly ($P < .001$) greater with the combination product compared with placebo at all time points at day 1, week 1, and week 12. In general, 12-hour serial FEV₁ results on treatment day 1, week 1, and week 12 revealed a greater sustained mean change from baseline improvements over 12 hours with the combination product than those achieved by treatment with salmeterol (at all time points at week 1 and week 12, $P \leq .047$) or fluticasone propionate (at all time points on day 1, week 1, and week 12; $P \leq .002$; Fig 1). A majority of patients treated with the combination product achieved a $\geq 15\%$ increase in FEV₁ within 30 minutes that was maintained during the 12-hour dosing interval. The improvement in FEV₁ during the 12-hour dosing interval progressively increased during the trial. At 12 weeks the improvement in FEV₁ with the combination product was 0.66 to 0.82 L over the 12 hours after dosing, which represents a 33% to 40% improvement from day 1 baseline. The mean AUCs at day 1, week 1, and week 12 are presented in Table II. The combination product significantly increased the mean AUC compared with placebo and fluticasone propionate on day 1 ($P < .001$) and compared with placebo, salmeterol, and fluticasone propionate at weeks 1 and 12 ($P \leq .013$).

Probability of remaining in the study without being withdrawn because of worsening asthma. Only 34% of patients in the placebo group remained in the study for the entire 12 weeks compared with 83%, 56%, and 74% of patients treated with the combination product, salmeterol, and fluticasone propionate, respectively. The percentage of patients withdrawn from the study because of worsening asthma was lowest with the combination product (3%) compared with placebo (49%), salmeterol (35%), and fluticasone propionate (11%) (Table II). Survival analysis revealed that patients in the combination product group had a significantly greater probability of

TABLE I. Background characteristics and patient disposition

	Placebo (n = 82)*	Combination product (n = 92)*	Salmeterol 50 µg (n = 92)*	Fluticasone propionate 100 µg (n = 90)*
Male/female ratio (%)*	51:49	59:41	51:49	52:48
Age (y)*				
Mean (range)	35 (12-66)	38 (12-70)	37 (12-67)	39 (12-67)
Ethnic origin (No. [%])*				
White	71 (87)	77 (84)	78 (85)	75 (83)
African American	7 (9)	6 (7)	6 (7)	11 (12)
Other	4 (4)	9 (9)	8 (8)	4 (5)
Mean baseline FEV ₁ *†				
Predicted (%)	64	64	64	64
Reversibility (%)	32	30	29	30
Baseline therapy (No.)				
Group 1 (inhaled corticosteroids)	55	66	66	63
Group 2 (salmeterol)	27	26	26	27
Completed (No. [%])†	26/77 (34%)	72/87 (83%)	48/86 (56%)	63/85 (74%)
Withdrawals (No. [%])†				
Worsening asthma	38/77 (49%)	3/87 (3%)	30/86 (35%)	9/85 (11%)
Albuterol use	2 (3%)	0	1 (1%)	0
Nighttime awakenings	20 (26%)	0	8 (9%)	3 (4%)
PEF stability limit	7 (9%)	0	7 (8%)	0
FEV ₁ stability limit	20 (26%)	3 (3%)	7 (8%)	4 (5%)
Clinical exacerbations	5 (6%)	0	14 (16%)	3 (4%)
Adverse event	1 (1%)	0	2 (2%)	1 (1%)
Other‡	12 (16%)	12 (14%)	6 (7%)	12 (14%)

All doses were administered twice daily.

*Based on intent-to-treat population.

†Based on efficacy population.

‡Includes inability to meet entry criteria, procedure or visit noncompliance, failure to return, or reason not recorded.

TABLE II. Predose FEV₁ (SE) and AUC (SE): intent-to-treat population

	Placebo (n = 77)	Combination product (n = 87)	Salmeterol 50 µg (n = 86)	Fluticasone propionate 100 µg (n = 85)
FEV ₁ (L)				
Baseline	2.15 (0.06)	2.17 (0.06)	2.13 (0.07)	2.11 (0.07)
Mean change, end point	0.01 (0.07)	0.51 (0.05)*†‡	0.11 (0.06)	0.28 (0.05)*
AUC (L-h)				
Treatment day 1	1.74 (0.55)	5.81 (0.52)*‡	5.24 (0.41)*	2.25 (0.36)
Treatment week 1	2.56 (0.78)	7.67 (0.62)*†‡	4.90 (0.55)*	3.58 (0.54)
Treatment week 12	3.01 (1.28)	8.94 (0.72)*†‡	6.43 (0.68)*	5.41 (0.74)*

All doses administered twice daily. End-point analyses included data from the final visit during treatment for patients completing the study and the last available data for patients who were withdrawn early.

* $P \leq .027$ versus placebo.

† $P \leq .013$ versus salmeterol 50 µg.

‡ $P < .001$ versus fluticasone propionate 100 µg.

remaining in the study over time without being withdrawn because of worsening asthma compared with those in the placebo, salmeterol, or fluticasone propionate treatment groups ($P \leq .020$, Fig 2). Similarly, patients treated with either salmeterol or fluticasone propionate alone had a significantly greater probability of remaining in the study over time without being withdrawn because of worsening asthma compared with placebo ($P \leq .007$). None of the patients treated with the combination product withdrew because of a clinical exacerbation compared with 6%, 16%, and 4% of patients treated with placebo, salmeterol, and fluticasone propionate, respectively (Table II).

Patient-recorded data. Baseline and mean change from baseline at end point for PEF, asthma symptom scores, percentage of days with no asthma symptoms, percentage of nights with no awakenings, and supplemental albuterol use are listed in Table III. Significant improvements from baseline at end point in morning and evening PEF, asthma symptom scores, percentage of days with no asthma symptoms, and rescue albuterol use were noted after treatment with the combination product compared with placebo, salmeterol, and fluticasone propionate ($P \leq .025$). Patients treated with the combination product had significant improvements in PEF within the first day of initiating treatment compared with placebo and fluticasone propionate (Fig 3).

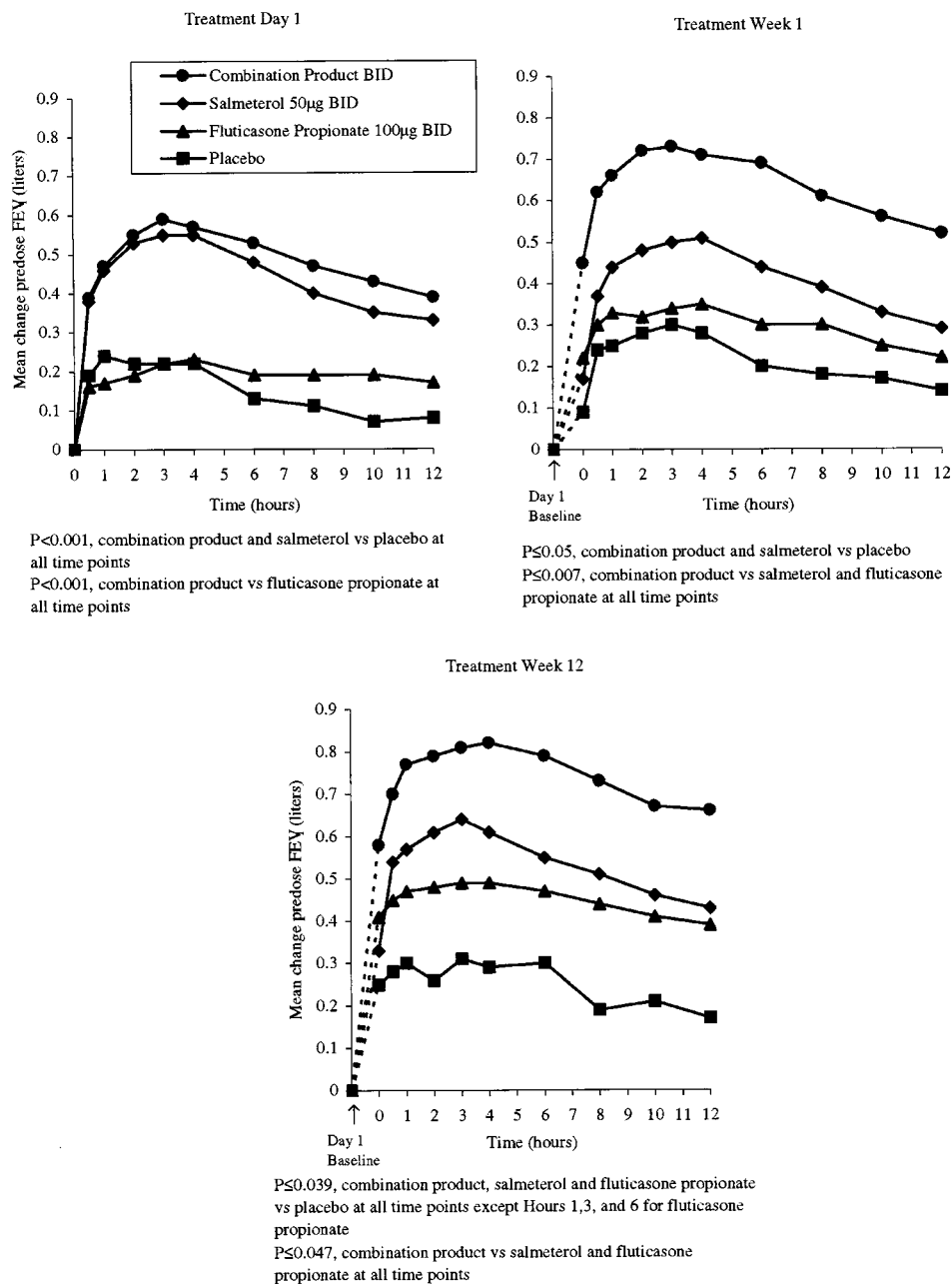


FIG 1. Mean change from baseline (before randomization of study drug) in serial FEV₁ over 12 hours at day 1, week 1, and week 12.

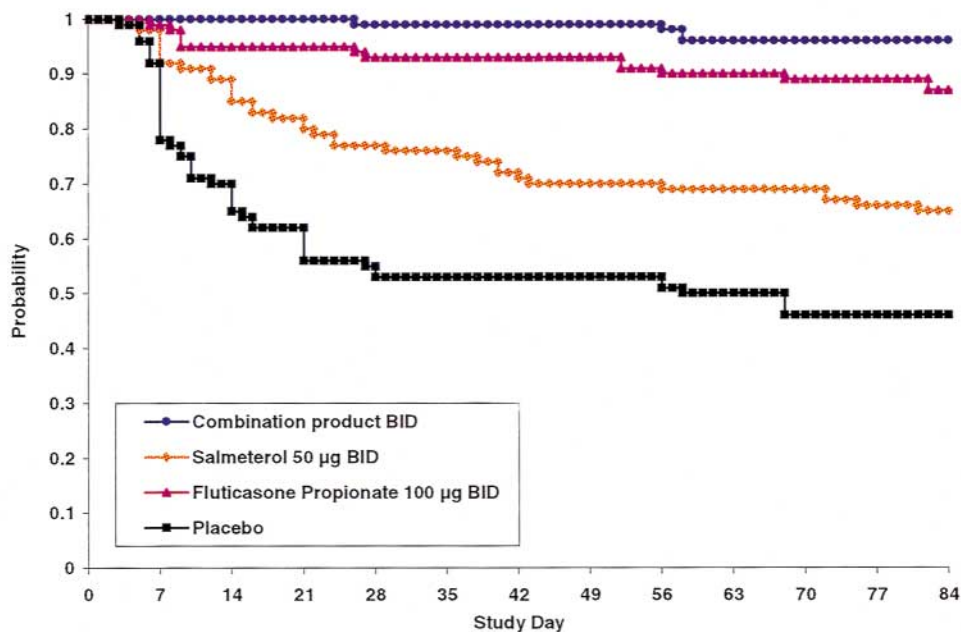
At baseline the mean percentage of nights with no awakenings because of asthma was approximately 90% across the various treatment groups. The mean change from baseline in the percentage of nights with no awakenings increased significantly ($P \leq .006$) with the combination product (4.6%) compared with a decline in the placebo and salmeterol treatment groups.

Analysis of results by the 2 groups defined by baseline asthma therapy (salmeterol or inhaled corticosteroids) yielded similar findings to the overall results (data not shown).

Safety

No clinically significant differences were noted among treatment groups with respect to abnormalities in physical examinations or clinical laboratory tests.

Adverse events. Each of the 3 treatment groups tolerated the regimen well over 12 weeks with no serious drug-related adverse events. Four patients withdrew from the study because of adverse events; however, these adverse events were considered by the investigator to be unrelated to study drug (placebo group: asthma



$p \leq 0.007$, all treatment groups vs placebo
 $p \leq 0.02$, Combination product vs salmeterol and fluticasone propionate

FIG 2. Probability of remaining in the study (Kaplan-Meier survival curve).

TABLE III. Baseline/mean change from baseline at end point (SE) in patient-rated variables: Intent-to-treat population

	Placebo (n = 77)	Combination product (n = 87)	Salmeterol 50 µg (n = 86)	Fluticasone propionate 100 µg (n = 85)
Morning PEF (L/min)				
Baseline	382 (11.7)	393 (10.6)	369 (9.5)	374 (11.3)
Mean change	-23.7 (4.8)	52.5 (5.3)*†‡	-1.7 (4.6)*	17.3 (4.4)*
Evening PEF (L/min)				
Baseline	398 (11.5)	418 (10.7)	396 (9.6)	390 (11.0)
Mean change	-13.3 (4.4)	35.0 (4.7)*†‡	-7.4 (4.9)	18.0 (4.6)*
Asthma symptom score				
Baseline	1.8 (0.11)	1.5 (0.11)	1.8 (0.10)	1.6 (0.11)
Mean change	0.4 (0.10)	-0.7 (0.11)*†‡	-0.1 (0.1)*	-0.2 (0.09)*
Percent of days with no asthma symptoms				
Baseline	15.8 (3.33)	25.2 (4.00)	12.6 (2.78)	19.4 (3.74)
Mean change	-3.8 (3.01)	22.6 (4.59)*†‡	8.0 (3.29)*	7.2 (4.09)
Percent of nights with no awakenings				
Baseline	89.9 (1.44)	91.7 (1.58)	91.6 (1.45)	91.3 (1.79)
Mean change	-16.5 (3.42)	4.6 (1.73)*†	-5.3 (2.57)*	2.4 (2.34)*
Albuterol use (puffs/d)				
Baseline	3.2 (0.24)	3.1 (0.28)	3.3 (0.28)	3.1 (0.27)
Mean change	1.7 (0.26)	-1.9 (0.26)*†‡	-0.3 (0.26)*	-0.4 (0.21)*

All doses were administered twice daily. End-point analyses included data from the final visit during treatment for patients completing the study and the last available data for patients who were withdrawn early.

* $P \leq .013$ versus placebo.

† $P \leq .023$ versus salmeterol 50 µg.

‡ $P \leq .025$ versus fluticasone propionate 100 µg.

exacerbation in one patient; salmeterol group: asthma exacerbation in one patient and fever in one patient; fluticasone propionate group: prolonged PR interval in one patient at screening). The asthma exacerbations and fever that occurred in placebo- and salmeterol-treated patients were designated as serious adverse events.

Adverse events considered by the investigators to be potentially related to treatment are listed in Table IV. The most commonly occurring adverse events (hoarseness, dysphonia, candidiasis, headache, tremor) were pharmacologically predictable events typical of these classes of medications.

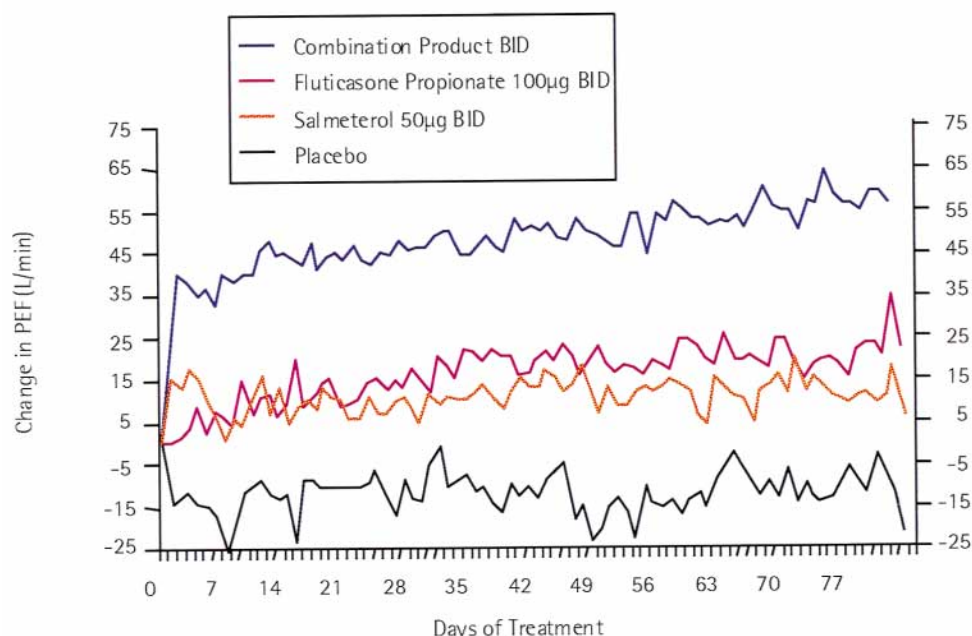


FIG 3. Mean change from baseline in daily mean morning PEF.

TABLE IV. Frequency ($\geq 2\%$) of drug-related adverse events*

Adverse event	Placebo (n = 82)	Combination product (n = 92)	Salmeterol 50 µg (n = 92)	Fluticasone propionate 100 µg (n = 90)
Headache	0	2 (2%)	0	0
Throat irritation	1 (1%)	4 (4%)	1 (1%)	2 (2%)
Hoarseness/dysphonia	0	3 (3%)	1 (1%)	1 (1%)
Candidiasis, unspecified site	0	3 (3%)	0	1 (1%)
Oropharyngeal candidiasis	0	1 (1%)	0	2 (2%)

All doses were administered twice daily.

*Events considered possibly, probably, or almost certainly related to drug treatment.

Holter monitor, 12-Lead ECG

Continuous 24-hour ambulatory electrocardiography revealed no significant differences among treatment groups in mean heart rate or in the occurrence of ventricular or supraventricular ectopy. Results from 12-lead ECG did not indicate any significant unfavorable changes from baseline at the end of 12 weeks of treatment.

DISCUSSION

The results of this study demonstrated that the combination product, salmeterol 50 µg/fluticasone propionate 100 µg, offered significant clinical advantages over the administration of salmeterol or fluticasone propionate alone.

Exacerbations of asthma are a major cause of morbidity and mortality and can be classified as mild, moderate, or severe depending on the level of treatment necessary to achieve remission. In the current trial, because patients treated with inhaled corticosteroids at baseline were switched to placebo or salmeterol alone, a significant percentage of patients were expected to worsen during the

course of the trial. To ensure that these patients did not have significant deterioration of their asthma, predefined criteria were used to withdraw patients with worsening asthma. The use of these criteria minimized the risk of patients having a severe asthma exacerbation because only one patient in the placebo group was withdrawn as the result of a serious adverse event described as an asthma exacerbation. Only 3% of patients treated with the combination product withdrew because of worsening asthma compared with 49%, 35%, and 11% in patients treated with placebo, salmeterol, and fluticasone propionate, respectively. These results corroborate the findings of a previous study that demonstrated a decrease in the incidence of asthma exacerbations after the addition of a long-acting bronchodilator to inhaled corticosteroid therapy.⁴

These data appear to be consistent with the findings of other investigators who reported increased improvements in pulmonary function and asthma symptom control, as well as reductions in rescue albuterol use and number of exacerbations after the addition of salmeterol or formoterol in patients previously treated with inhaled corti-

costeroids.^{1,2,4,12} The current study extends these findings to include patients treated with salmeterol alone at baseline because both groups, regardless of baseline asthma therapy, demonstrated greater improvements in asthma control compared with the individual agents. The consistent improvement in asthma control independent of baseline asthma therapy indicates that for many patients the combined use of these 2 classes of medications is necessary for optimal management of their asthma. The concept of using combinations of different classes of medications to achieve greater improvement than that possible by their use individually is consistent with common practice in many other disease states (eg, hypertension, tuberculosis, AIDS, cancer). The magnitude of improvements in pulmonary function and asthma symptom control with this combination product suggests that long-acting β_2 -agonist bronchodilators and inhaled corticosteroids may have complementary activity in the treatment of bronchoconstriction and inflammation associated with asthma.¹³⁻¹⁷

Studies with salmeterol have been conducted in patients already taking inhaled corticosteroids (which were continued when salmeterol was added) or in patients with milder asthma taking only as-needed β_2 -agonists. This is one of the first studies, however, in which salmeterol replaced treatment with inhaled corticosteroids. Patients in this study who received salmeterol in lieu of inhaled corticosteroids generally showed greater improvement than did patients treated with placebo in terms of bronchodilation and symptom control (serial FEV₁ AUC, symptom scores, percentage of days with no asthma symptoms, albuterol use) but did not fare as well in measures of asthma stability (percentage of patients withdrawn from the study because of worsening asthma, PEF, or morning predose FEV₁) compared with patients who continued to receive inhaled corticosteroid therapy. These results underscore the importance of anti-inflammatory therapy in overall asthma control and support current recommendations that salmeterol is not a complete substitute for inhaled corticosteroid therapy.^{5,18} These results are also reassuring because they demonstrate that clinical measures to assess asthma control are useful in identifying those patients treated with long-acting bronchodilators who have deteriorating asthma.

As expected, significant improvements in FEV₁ with combination therapy were evident within the first 30 minutes of initiating treatment and were maintained during the 12-hour dosing interval. By 12 weeks of treatment, the mean improvement in FEV₁ averaged 35% to 40% from the pretreatment baseline during the 12 hours after dosing with no evidence of a diminution in bronchodilation with chronic therapy. Additionally, treatment with the combination product was associated with significant improvements in PEF with the first dose, which progressively increased during the 12 weeks of treatment. Thus there was no evidence that clinical improvements observed with the combination product diminished over time.

Poor adherence to asthma treatment has been associated with inadequate control of asthma and associated morbidity.¹⁹ Although inhaled corticosteroids are the corner-

stone of asthma therapy, low adherence rates with inhaled corticosteroids in patients with asthma have been documented and range from 3% to 57%.²⁰⁻²⁴ Some of the postulated reasons for poor patient adherence to inhaled corticosteroid regimens include concerns regarding lack of perception of immediate benefits, concerns about their safety, and the need for multiple medications to control asthma. Although clinical results have demonstrated that the concurrent use of inhaled corticosteroids and long-acting β_2 -agonists substantially improves asthma control, this approach necessitates the use of multiple medications for maintenance treatment. Multiple medication regimens can be confusing and complicated and can lead to poor adherence to treatment.

The use of the combination product will help to simplify the treatment regimen for the many patients who need multiple controller medications for optimal control of their asthma. In addition, because of the presence of a long-acting β_2 -agonist, patients will perceive benefits with dosing that may address one of the current limitations with inhaled corticosteroid therapy.

The combination of salmeterol and fluticasone propionate was well tolerated over 12 weeks with no evidence of any additional safety risks compared with treatment with salmeterol or fluticasone propionate alone. Although assessments of hypothalamic-pituitary-adrenal axis function were not made in this trial, previous studies have not found discernible effects of fluticasone propionate on the hypothalamic-pituitary-adrenal axis at the dose used in this trial.²⁵⁻²⁷

In conclusion, the combination of salmeterol and fluticasone propionate powder in the Diskus inhalation device offered superior asthma control compared with administration of either salmeterol or fluticasone propionate alone. Furthermore, the convenience of having 2 effective long-term control medications in one single product simplifies a potentially complex asthma medication regimen and may thus enhance patient adherence. The availability of multiple strengths of fluticasone propionate in the combination product will allow flexibility in titrating the inhaled corticosteroid dose according to asthma severity.^{28,29}

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