

Low-dose fluticasone propionate compared with montelukast for first-line treatment of persistent asthma: A randomized clinical trial

William Busse, MD,^a Gordon D. Raphael, MD,^b Stanley Galant, MD,^c Chris Kalberg, PhD,^d Stacey Goode-Sellers, BS,^d Sharon Srebro, MD,^d Lisa Edwards, PhD,^d and Kathy Rickard, MD,^d for the Fluticasone Propionate Clinical Research Study Group* *Madison, Wis, Bethesda, Md, Orange, Calif, and Research Triangle Park, NC*

Background: Both inhaled corticosteroids and leukotriene modifiers are used in the maintenance treatment of persistent asthma.

Objective: The goal was to compare the efficacy and safety of low-dose fluticasone propionate (FP) and montelukast as first-line maintenance therapy in symptomatic patients by using short-acting β_2 -agonists alone to treat persistent asthma.

Methods: In this multicenter, randomized, double-blind, double-dummy, parallel-group study, 533 patients (>15 years old) with persistent asthma who remained symptomatic while taking short-acting β_2 -agonists alone were treated with FP (88 μ g [2 puffs of 44 μ g] twice daily) or montelukast (10 mg once daily) for 24 weeks.

Results: Compared with treatment with montelukast, treatment with FP resulted in significantly greater improvements at endpoint in morning predose FEV₁ (22.9% vs 14.5%, $P < .001$), forced midexpiratory flow (0.66 vs 0.41 L/sec, $P < .001$), forced vital capacity (0.42 vs 0.29 L, $P = .002$), morning peak expiratory flow (PEF) (68.5 vs 34.1 L/min, $P < .001$), and evening PEF (53.9 vs 28.7 L/min, $P < .001$). Similar improvements in PEF were observed in patients with milder asthma (>70%-80% predicted FEV₁). At endpoint, FP was more effective than montelukast at decreasing rescue albuterol use (3.1 puffs/day vs 2.3 puffs/day, $P < .001$), asthma symptom scores (-0.85 [48.6% decrease] vs -0.60 [30.5%], $P < .001$), and nighttime awakenings due to asthma (-0.64 awakenings/night [62% decrease] vs -0.48 awakenings/night [47.5%], $P = .023$), and FP increased the percentage of symptom-free days (32.0% vs 18.4% of days, $P < .001$) compared with montelukast. The adverse event and asthma exacerbation profiles for FP and montelukast were similar.

Conclusions: Low-dose FP is more effective than montelukast as first-line maintenance therapy for patients with persistent asthma who are undertreated and remain symptomatic while taking short-acting β_2 -agonists alone. (*J Allergy Clin Immunol* 2001;107:461-8.)

Key words: Asthma, fluticasone propionate, inhaled corticosteroid, montelukast, leukotriene modifier

Current asthma management guidelines recognize inhaled corticosteroids as the most effective anti-inflammatory asthma medications available and recommend their use as first-line maintenance therapy for mild-to-severe persistent asthma.¹ The beneficial clinical effects of inhaled corticosteroids may, in part, be the result of reduced airway inflammation and hyperreactivity, reduced inflammatory cell recruitment into the airways, reduced epithelial cell damage, and decreased subepithelial fibrosis.² Data obtained from medical claims databases have shown that the use of inhaled corticosteroids reduces the frequency of hospitalization for asthma and reduces the risk of life-threatening asthma attacks, and potentially death, due to asthma.³⁻⁵

Leukotriene-modifying agents are another class of asthma medications indicated for the maintenance treatment of persistent asthma. These medications, either through inhibition of the leukotriene-synthesizing enzyme 5-lipoxygenase or specific inhibition of the cysteinyl leukotriene receptor (Cys-LT₁), inhibit the physiologic effects of the cysteinyl leukotrienes (ie, LTC₄ and LTD₄). Cysteinyl leukotrienes are one of many mediators of acute airway obstruction.^{6,7} In clinical studies, leukotriene-modifying agents have been shown to improve pulmonary function and asthma symptom control compared with placebo.⁸⁻¹⁰

To date, few clinical trials have compared the clinical efficacy and safety of inhaled corticosteroids and leukotriene modifiers for the treatment of persistent asthma. Available data have consistently shown low-dose inhaled corticosteroids to be clinically more effective, but similar with regard to adverse event profiles, compared with leukotriene modifiers in patients with asthma who are symptomatic while taking short-acting β_2 -agonists alone.^{11,12} None of these studies, however, has lasted longer than 12 weeks, and no double-blind, randomized studies have compared a low dose of the inhaled

^aUniversity of Wisconsin-Madison Medical School; ^bPrivate practice, Bethesda; ^cClinical Trials of Orange County; ^dGlaxo Wellcome Inc, Research Triangle Park.

*Member names are listed in the Appendix.

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Reprint requests: William Busse, MD, University of Wisconsin-Madison Medical School, H6/367 Clinical Research Unit, 600 Highland Ave, Madison, WI 53792-3244.

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Abbreviations used

AQLQ:	Asthma quality-of-life questionnaire
BID:	Twice daily
FEF _{25%-75%} :	Forced midexpiratory flow
FP:	Fluticasone propionate
FVC:	Forced vital capacity
MDI:	Metered-dose inhaler
PEF:	Peak expiratory flow
QD:	Once daily

corticosteroid fluticasone propionate (FP) with the orally available leukotriene receptor antagonist montelukast.

This study compared the efficacy and safety of low-dose FP 88 µg (2 puffs of 44 µg) twice daily (BID) with that of montelukast 10 mg once daily (QD) during a 24-week period in adolescent and adult patients with persistent asthma who were symptomatic while taking short-acting β_2 -agonists alone.

METHODS

Patients

Patients aged 15 years or older with a diagnosis of asthma as defined by the American Thoracic Society¹³ for at least 6 months before screening were eligible for the study if they demonstrated a predose FEV₁ of 50% to 80% of the predicted normal value^{14,15} and an increase in FEV₁ of 15% or more after inhalation of 2 puffs (180 µg) of albuterol at screening. Eligible patients must have used an inhaled or oral short-acting β_2 -agonist on a regular or as-needed basis during the 3 months before screening. Exclusion criteria included use of inhaled corticosteroids within 2 months of screening, pregnancy, use of tobacco products within the previous year, a smoking history of 10 pack-years or more, hospitalization for asthma within 3 months of screening, respiratory tract infections within 4 weeks of screening, and hypersensitivity to any β_2 -agonist, sympathomimetic drug, leukotriene antagonist, or corticosteroid.

Study design

This was a multicenter, randomized, double-blind, double-dummy, parallel-group study. All patients (or parent/guardian) gave written informed consent, and each site's institutional review board approved the protocol (FLTA4038). After screening, patients entered an 8- to 14-day run-in period to confirm each patient's eligibility for the study and to obtain baseline data. During run-in, all patients used albuterol (Ventolin Inhalation Aerosol; Glaxo Wellcome Inc, Research Triangle Park, NC) as needed to relieve asthma symptoms. At randomization, patients were required to demonstrate that additional asthma therapy was warranted using the following criteria: an unmedicated FEV₁ value of 50% to 80% of predicted normal that was within 15% of the FEV₁ value obtained at screening, use of albuterol on 6 or more of the 7 days before randomization, and an asthma symptom score of 2 or more (on a scale of 0-5) on 4 or more of the 7 days before randomization.

Eligible patients were randomly assigned to receive 1 of the following double-blind, double-dummy treatments for 24 weeks: FP 88 µg BID (Flovent Inhalation Aerosol, Glaxo Wellcome Inc; 2 puffs of 44 µg strength administered through a metered-dose inhaler [MDI] BID) and a placebo capsule in the evening, or oral montelukast 10 mg (Singulair; Merck & Co, Whitehouse Station, NJ) in the evening and 2 puffs of placebo twice daily through an MDI. Treatment assignments were computer generated in blocks of 4 so that each treatment was represented twice in random order. Patients used inhaled albuterol as needed to relieve breakthrough asthma

symptoms. Concurrent use of additional asthma medications was not allowed during the study. Use of medications for the treatment of rhinitis was allowed.

Procedures

Clinic visits were scheduled between 6 AM and 10 AM after weeks 2, 4, 8, 12, 16, 20, and 24 during the double-blind treatment period. At each visit (including any early withdrawal visits) spirometric determination of FEV₁ was performed, and adverse events and concurrent medications were assessed. At randomization and after weeks 12 and 24, physicians rated the overall effectiveness of the blinded study medication in controlling the patient's asthma using a 4-point scale ranging from 0 (ineffective) to 3 (very effective). Patients were asked to complete questionnaires, including the asthma quality-of-life questionnaire (AQLQ; weeks 0, 8, 16, and 24), and assessment of satisfaction with study medication (weeks 2 and 24). Patients that were withdrawn or terminated from the study for any reason completed each questionnaire at the early withdrawal visit.

Each morning and evening during the study, patients rated their asthma symptoms, measured peak expiratory flow (PEF), and recorded the information on diary cards along with the number of puffs of albuterol used, the number of nighttime awakenings due to asthma, and the amount of study medication taken. PEF measurements were obtained before the study medication was taken, by use of a hand-held Astech Peak Flow Meter (Center Laboratories, Port Washington, NY). Symptoms of chest tightness, wheeze, shortness of breath, and cough were rated on a 6-point scale.

The primary measure of efficacy was the mean percent change from baseline in morning premedication FEV₁ obtained at endpoint. Secondary efficacy endpoints included mean change from baseline at endpoint for forced vital capacity (FVC), forced midexpiratory flow (FEF_{25%-75%}), morning and evening PEF, the percentage of symptom-free days, asthma symptom scores, nighttime awakenings due to asthma, daily rescue albuterol use, and percentage of rescue-free days. Additional endpoints included physicians' global assessment of medication effectiveness, duration of patient participation, AQLQ, and patient-rated satisfaction with treatment.

Safety was evaluated with clinical adverse event monitoring and asthma exacerbation assessments. An asthma exacerbation was defined as any event that required an emergency department visit and/or hospitalization, an unscheduled doctor visit, or treatment with oral or parenteral corticosteroids. Patients who had an asthma exacerbation that required treatment with oral or parenteral corticosteroids were withdrawn from the study.

Statistical methods

The intent-to-treat population, defined as all patients randomly assigned to receive the study drug, was used for all safety and efficacy analyses. Clinical efficacy data for 13 patients at 1 site (7 FP-treated patients and 6 montelukast-treated patients) were removed from the efficacy analyses due to deviations from good clinical practice standards. The sample size in this study (≥ 250 completed patients per treatment group) provided at least 80% power to detect a difference in percent change in FEV₁ of 6 percentage points between the two treatment groups based on a 2-sample *t* test with a significance level of .05. All statistical tests were 2-sided, with a significance level of .05. All analyses were adjusted for investigative site.

ANOVAs and Cochran-Mantel-Haenszel tests¹⁶ were conducted to determine the comparability of the treatment groups at baseline. Change and percent change from baseline at each clinic visit and at endpoint were examined for each spirometric measure. Endpoint was defined as the last value obtained during the treatment period. Changes from baseline at each week and at endpoint were analyzed for each of the patient-recorded diary measures. Data for nighttime awakenings were limited to a subset of patients who reported hav-

TABLE I. Patient demographics, characteristics, and disposition based on intent-to-treat population

	FP 88 µg BID (n = 271)	Montelukast 10 mg QD (n = 262)
Mean age, y (range)	35.4 (15-83)	34.4 (15-67)
Sex, n (%)		
Male	128 (47)	111 (42)
Female	143 (53)	151 (58)
Ethnic origin, n (%)		
White	228 (84)	215 (82)
African American	27 (10)	28 (11)
Other	16 (6)	19 (7)
% Predicted FEV ₁ , mean (SD)	65.6 (9.2)	65.4 (8.2)
No. (%) completed	194 (72)	187 (71)
No. (%) withdrawn	77 (28)	75 (29)
Adverse event	10 (4)	4 (2)
Consent withdrawn	12 (4)	11 (4)
Lost to follow-up	16 (6)	14 (5)
Protocol violation	7 (3)	9 (3)
Lack of efficacy	5 (2)	10 (4)
Asthma exacerbation*	10 (4)	16 (6)
Other†	17 (6)	11 (4)

*Patients were withdrawn from the study if they had an asthma exacerbation that required treatment with oral or parenteral corticosteroids.

†Includes study closure, noncompliance, pregnancy, and patient relocation.

ing nocturnal asthma (≥ 2 awakenings/week due to asthma at baseline).¹² For each diary measure, endpoint was the mean of the last available week of data from the treatment period. Analyses of covariance were conducted to test for treatment differences. Estimates of the probability of remaining in the study at each week were calculated by the Kaplan-Meier product-limit method based on the number of treatment failures in each treatment group. The resulting survival curves were compared with a log-rank test of homogeneity.

Comparisons of the distribution of physicians' global assessment and patient satisfaction scores between treatment groups were performed with Cochran-Mantel-Haenszel tests at baseline and at endpoint. The AQLQ was a 32-item questionnaire that investigated the effects of asthma on four domains (activity limitation, asthma symptoms, emotional function, and environmental exposure). Analyses of covariance were conducted to test for differences between treatment groups in AQLQ global and domain scores. An improvement in global or individual domain scores of 0.5 is the smallest difference regarded to be clinically meaningful by the developer of the questionnaire.¹⁷

The frequencies of patients in each treatment group experiencing an asthma exacerbation were compared using a Cochran-Mantel-Haenszel test. The incidence of patients experiencing at least one adverse event was compared between treatments with the Fisher Exact test.

RESULTS

A total of 1428 patients were screened for participation at 52 study sites. Of these, 533 patients were randomly assigned to receive treatment with low-dose FP or montelukast. Treatment groups were comparable with respect to baseline demographic characteristics and pulmonary function (Table I). Mean percentage predicted FEV₁ values were 65.6% and 65.4% in the FP and montelukast treatment groups, respectively.

A total of 381 patients (71%) completed the study, and the number of patients who discontinued study participation was similar in both treatment groups (Table I). The most common reasons for discontinuation were loss to

follow-up (6% of all patients), asthma exacerbations (5%), and other (5%; includes study closure, noncompliance, pregnancy, and patient relocation). The duration of patient participation was similar between treatment groups. Mean values for patient-reported compliance with the MDI and capsules were 91.4% or more.

Efficacy

Mean changes from baseline at endpoint for primary and secondary efficacy measures are presented in Table II.

Pulmonary function

Treatment with low-dose FP resulted in significantly greater improvement in all spirometric measures of airway obstruction (FEV₁, FVC, FEF_{25%-75%}) compared with montelukast ($P \leq .002$ at endpoint, Table II). Mean FEV₁ values were significantly greater in the FP treatment group than in the montelukast group at the first treatment assessment (week 2), and significantly greater improvements in FEV₁ were maintained in the FP treatment group throughout the study ($P < .001$, all assessments; Fig 1).

Improvements in morning PEF were significantly greater in the FP treatment group as early as day 2 of treatment, were consistently greater by week 2 ($P = .008$), and remained significantly greater for the duration of the double-blind treatment period ($P \leq .001$, Fig 2). When stratified by baseline severity of airway obstruction (percentage predicted FEV₁), improvements in morning PEF values were significantly greater after treatment with FP than after treatment with montelukast, regardless of the severity of airway obstruction at baseline ($P \leq .007$, Fig 3). In patients with milder asthma ($>70\%$ predicted FEV₁), treatment with FP resulted in significantly greater improvements in morning PEF compared with treatment with montelukast. Significantly

TABLE II. Mean (SE) change from baseline at endpoint for primary and secondary efficacy variables

Variable	FP 88 µg BID (n = 271)		MON 10 mg QD (n = 262)		P value (vs MON)
	Baseline	Change at endpoint*	Baseline	Change at endpoint	
Morning FEV ₁ , L	2.33 (0.03)	0.51 (0.03)	2.35 (0.04)	0.33 (0.03)	<.001
Percent change in FEV ₁	—	22.87 (1.41)	—	14.47 (1.29)	<.001
FEF _{25%-75%} , L/sec	1.65 (0.03)	0.66 (0.04)	1.70 (0.04)	0.41 (0.04)	<.001
FVC, L	3.50 (0.06)	0.42 (0.03)	3.45 (0.05)	0.29 (0.03)	.002
Morning PEF, L/min	349.6 (6.3)	68.5 (5.2)	357.8 (6.1)	34.1 (4.2)	<.001
Evening PEF, L/min	386.5 (6.6)	53.9 (4.7)	396.6 (6.4)	28.7 (4.2)	<.001
Mean symptom score	1.65 (0.05)	-0.85 (0.06)	1.69 (0.05)	-0.60 (0.06)	<.001
% Symptom-free days	1.9 (0.5)	32.0 (2.5)	2.3 (0.4)	18.4 (2.1)	<.001
Albuterol use, puffs/day	5.07 (0.17)	-3.10 (0.17)	5.29 (0.16)	-2.31 (0.17)	<.001
% Rescue-free days	2.5 (0.4)	45.9 (2.5)	2.5 (0.4)	31.2 (2.3)	<.001
Nighttime awakenings/night, n†	0.99 (0.06)	-0.64 (0.06)	0.96 (0.06)	-0.48 (0.06)	.023

Data expressed as mean (SEM).

MON, Montelukast.

*Endpoint was defined as the last postbaseline observation for FEV₁ and as the last postbaseline week of diary measurements.

†Analysis of this variable was performed in a subset of patients with nocturnal asthma (≥2 awakenings/week due to asthma at baseline; 167 FP-treated patients, 161 montelukast-treated patients).

greater improvements in evening PEF were seen in patients treated with FP compared with those treated with montelukast ($P < .001$ at endpoint).

Asthma symptoms, rescue albuterol use, and nighttime awakenings

At endpoint, mean values for improvements in asthma symptom scores, percentage of symptom-free days, rescue albuterol use, percentage of rescue-free days, and nighttime awakenings were all significantly greater in the FP treatment group than in the montelukast group ($P \leq .023$; Table II). During the double-blind treatment period, the percentage of rescue-free days was consistently greater in the FP treatment group beginning at week 2 ($P \leq .031$), whereas the percentage of symptom-free days was consistently greater in the FP treatment group beginning at week 3 ($P \leq .003$). Patients treated with FP had 62% more days with no asthma symptoms (39.3 vs 24.3 days, respectively) and 49% more days on which they required no rescue albuterol (62.1 vs 41.6 days, respectively) compared with montelukast-treated patients. A significantly greater reduction in the number of nighttime awakenings due to asthma was noted in the FP treatment group compared with the montelukast group at most time points during the double-blind treatment period, beginning at week 3 ($P \leq .035$).

Physicians' global assessment, patient satisfaction, and AQLQ

The physicians' global assessment of study medication significantly favored low-dose FP over montelukast ($P < .001$ at endpoint). More physicians rated FP therapy as either effective or very effective (71%) compared with montelukast (53%). Overall patient satisfaction with study medication significantly favored FP compared with montelukast ($P < .001$ at endpoint, Fig 4); more patients were satisfied with FP (85%) than with montelukast (65%). Patient ratings of how well, how

fast, and how long the medication worked, as well as how good the medication made them feel, all significantly favored FP over montelukast ($P \leq .001$ at endpoint). At endpoint, improvements in global and individual domain AQLQ scores were significantly greater in FP-treated patients than in montelukast-treated patients ($P \leq .001$); however, a difference of 0.5 or more between treatment scores, which is regarded as clinically meaningful by the developer of the questionnaire, was seen only in the asthma symptoms and emotional function domains.

Safety

The overall incidence of adverse events was similar between groups (71% of FP-treated patients vs 68% of montelukast-treated patients); very few were considered by investigators to be drug related. Adverse events most commonly considered by investigators to be possibly drug related ($\geq 1\%$ in any group) were headache (3% with FP, 1% with montelukast), sore throat (2% with both FP and montelukast), hoarseness (2% with FP), and oral pharyngeal candidiasis (1% with FP).

Ten FP-treated patients and 4 montelukast-treated patients withdrew from the study due to adverse events. Of these, 2 withdrawals in the FP group (due to rash and dizziness) and 1 in the montelukast group (due to rash) were considered by investigators to be possibly drug related. Six FP-treated patients and 2 montelukast-treated patients had serious adverse events that resulted in withdrawal from the study; however, none of the serious adverse events was considered to be drug related. One death, attributed to myocardial infarction, occurred in this study. The death, which occurred in a 20-year-old woman in the montelukast treatment group, was considered to be unrelated to use of the study drug.

Asthma exacerbations were experienced by 12 (4%) and 21 (8%) patients in the FP and montelukast treatment groups, respectively. The difference between treatment groups was not statistically significant.

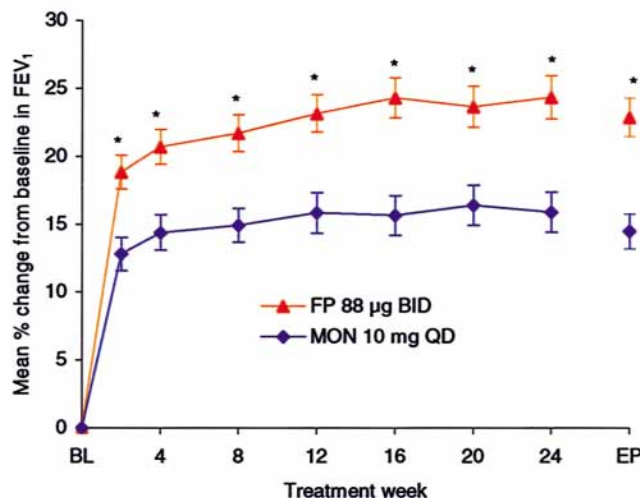


FIG 1. Mean percent change from baseline in FEV₁ in patients receiving FP or montelukast (MON) during the 24-week double-blind treatment period. **P* < .001, FP versus montelukast. BL, Baseline; EP, endpoint.

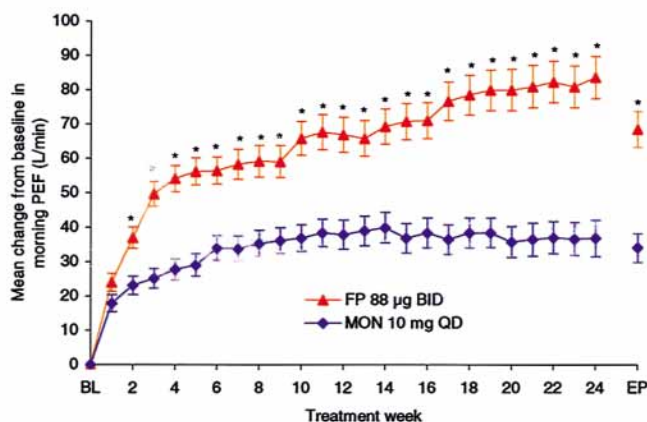


FIG 2. Mean change from baseline in morning PEF in patients receiving FP or montelukast (MON) during the 24-week double-blind treatment period. **P* < .001, FP versus montelukast. BL, Baseline; EP, endpoint.

DISCUSSION

The results from this study demonstrate that first-line maintenance therapy with low-dose FP (88 µg BID) was more effective than with montelukast (10 mg QD) at improving overall asthma control during a 24-week treatment period. This was characterized by significantly greater improvements in the primary (FEV₁) and secondary (FVC, FEF_{25%-75%}, morning and evening PEF, percentage of symptom-free days, asthma symptom scores, nighttime awakenings due to asthma, rescue albuterol use, and percentage of rescue-free days) efficacy parameters. Additional efficacy endpoints (eg, physician global assessment of efficacy, patient satisfaction with treatment, and AQLQ scores) significantly favored FP over montelukast, whereas results for the duration of patient participation were similar. Significantly greater

improvements in clinical measures of asthma control were noted as early as 2 days after initiation of treatment with FP, and significant between-group differences were maintained for the duration of the study.

It should be noted that because FP was administered twice daily (morning and evening) and montelukast was administered once daily (evening), morning measurements of pulmonary function (FEV₁, FEF_{25%-75%}, FVC, PEF) were obtained at the end of the dosing period for FP versus the midpoint of the dosing period for montelukast. Despite this inequity, which theoretically would favor montelukast, treatment with FP resulted in significantly greater improvements in all measures of pulmonary function compared with montelukast. Improvements in FEV₁ with FP (22.9%) and montelukast (14.5%) from this study are comparable to results of other studies that used

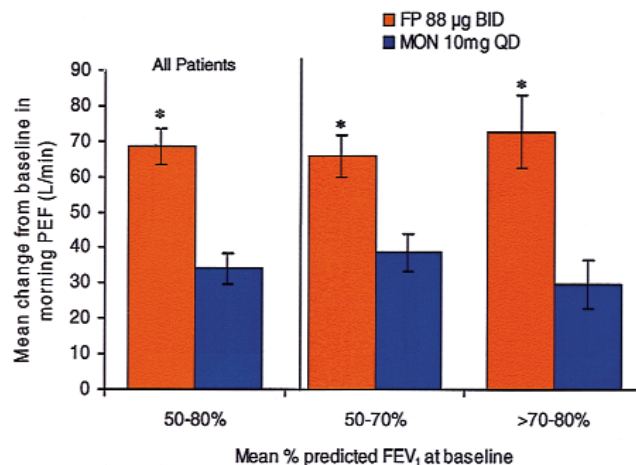


FIG 3. Mean change from baseline in morning PEF stratified by baseline percent predicted FEV₁. * $P \leq .007$, FP versus montelukast (MON) at endpoint.

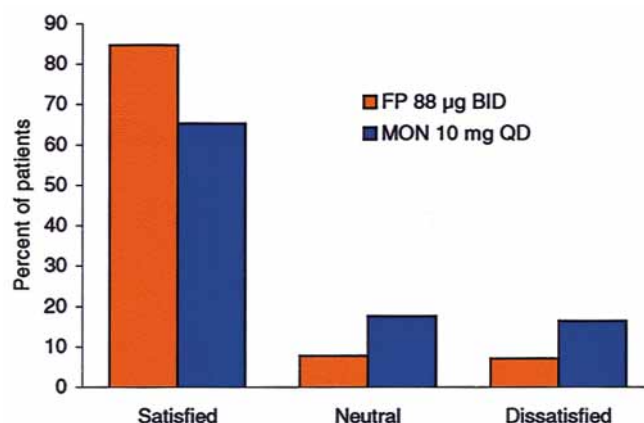


FIG 4. Percentages of patients who rated their overall satisfaction with FP or montelukast (MON) as satisfied, neutral, or dissatisfied. *Satisfied* includes patients who were slightly satisfied, satisfied, or very satisfied with treatment; *Dissatisfied* includes patients who were slightly dissatisfied, dissatisfied, or very dissatisfied with treatment. $P < .001$, FP versus montelukast.

similar dosing schedules and patient populations. For example, improvements of approximately 17% to 24% were reported for FP at the same dosage used in this study,^{11,18,19} whereas increases in FEV₁ of 13.1% and 7.4% were reported after treatment with montelukast.^{8,12} Exclusion of a placebo group in this study, primarily due to ethical considerations, did not allow for assessment of a placebo or study effect. Incorporation of a placebo effect similar to that reported previously for asthma studies would likely have resulted in a more favorable magnitude of effect for FP over montelukast.^{8,20}

With the same dosage of FP used in this study, Bleeker et al¹¹ reported significantly greater improvements in measures of pulmonary function, symptom control, and rescue albuterol use with FP compared with zafirlukast during a 12-week treatment period in a similar patient

population. Malmstrom et al¹² reported significantly greater improvements in FEV₁, daytime asthma symptom scores, rescue albuterol use, and nighttime awakenings with a low dose of beclomethasone dipropionate (200 µg BID) compared with montelukast (10 mg QD) during a 12-week period in patients with chronic asthma who were previously using inhaled β_2 -agonists alone. Additional studies suggest that asthma control is reduced when leukotriene-modifying drugs are substituted for inhaled corticosteroids. For example, Kim et al²¹ reported increased use of rescue albuterol when patients were switched from low doses of beclomethasone dipropionate or triamcinolone acetonide to zafirlukast, and Laviolette et al²² reported a decline in pulmonary function and asthma symptom control when patients were switched from beclomethasone dipropionate to montelukast therapy.

Meeting patients' and physicians' expectations with asthma care is a key goal of asthma therapy.¹ In this study patient and physician satisfaction measures were evaluated with a double-blind, double-dummy design; consequently, the satisfaction ratings reported in this study are likely to reflect satisfaction with clinical efficacy rather than the method of drug delivery. Previous data indicate that patients with asthma do not have a strong preference regarding inhaled or oral as the route of administration for asthma controller medications.²³ Patients treated with FP were significantly more satisfied with treatment with regard to overall satisfaction; how well, how fast, and how long the medication worked; and how good the medication made them feel. These results were consistent with the physicians' rating of global effectiveness and with clinical efficacy measures, all of which favored FP over montelukast.

Asthma is characterized by marked airway inflammation that is present early in the pathologic process and in all severities of asthma including mild asthma.^{24,25} The greater improvement in asthma control seen with FP compared with montelukast may have been due to the broad anti-inflammatory effects of FP. Inhaled corticosteroids exert multiple anti-inflammatory effects in the airways, including leukotriene inhibition and the inhibition of inflammatory cells such as eosinophils and proinflammatory cytokines such as IL-5 and GM-CSF, which are integrally involved in eosinophil recruitment, activation, and survival.²⁶⁻³⁰ Current NIH guidelines and data from several studies suggest that early treatment with inhaled corticosteroids is associated with greater clinical effects and possible protection against reduced lung function, increased asthma symptoms, and airway remodeling.^{1,31-34} Numerous biopsy studies have demonstrated that inhaled corticosteroids reduce the number of eosinophils, mast cells, and lymphocytes in the airways of patients with persistent asthma.^{27,35,36}

The incidence of adverse events seen in this study was consistent with that reported in the prescribing information for FP and montelukast.^{37,38} Systemic adverse effects associated with inhaled corticosteroids, such as hypothalamic-pituitary-adrenal axis function, were not monitored due to the low dose of FP used in this study. FP at a dosage of 220 µg BID, which is several-fold higher than the dosage of FP used in this study, was shown to have no clinically relevant adverse effects on hypothalamic-pituitary-adrenal axis function.³⁷

In conclusion, low-dose FP was more effective than montelukast at improving long-term asthma control and measures of patient and physician satisfaction in patients with persistent asthma who were symptomatic while taking short-acting β_2 -agonists alone. The incidence of adverse events was similar with both treatments. This study demonstrates that low-dose FP is more effective than montelukast as first-line maintenance therapy for persistent asthma. These data support the national treatment guidelines, which recommend the use of inhaled corticosteroids as the preferred first-line maintenance therapy for persistent asthma.¹

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38. Singulair® (montelukast sodium) tablets and chewable tablets. Package insert. Whitehouse Station (NJ): Merck & Co.

APPENDIX

Fluticasone Propionate Clinical Research Study Group

We thank the following for their participation in this study (FLTA4038): Wilfred N. Beaucher, MD, Chelmsford, Mass; William Berger, MD, Mission Viejo, Calif; Robert B. Berkowitz, MD, Atlanta, Ga; David I. Bernstein, MD, Cincinnati, Ohio; S. Allan Bock, MD, Boulder, Colo; Howard Boltansky, MD, Washington, DC; David P. Bowman, DO, Idaho Falls, Idaho; Emil Burger, Jr, MD, Downey, Calif; Bradley E. Chipps, MD, Sacramento, Calif; Gary A. Cohen, MD, San Diego, Calif; Carolyn B. Daul, MD, PhD, Metairie, La; David Denmead, MD, Danville, Calif; Lawrence M. DuBuske, MD, Gardner, Mass; Constantine Falliers, MD, Denver, Colo; Albert F. Finn, MD, Charleston, SC; Charles Fogarty, MD, Spartanburg, SC; Ronald M. Gilman, East Providence, RI; Marc F. Goldstein, MD, Mt Laurel, NJ; George R. Gottlieb, MD, Snellville, Ga; Howard A. Hassman, DO, Berlin, NJ; Alan M. Heller, MD, San Jose, Calif; Robert L. Jacobs, MD, San Antonio, Tex; William Jannetti, MD, Buena Park, Calif; Edward F. Kent, Jr, MD, South Burlington, Vt; Edward M. Kerwin, MD, Medford, Ore; Kirk A. Kinberg, MD, Lincoln, Neb; Stephen Kreitzer, MD, Tampa, Fla; Bob Lanier, MD, Ft Worth, Tex; Michael Lawrence, MD, Taunton, Mass; Edward Lisberg, MD, River Forest, Ill; Jonathan Matz, MD, Baltimore, Md; Don Q. Mitchell, MD, Jackson, Miss; Amit Patel, MD, Corona, Calif; David Pearlman, MD, Aurora, Colo; Patrick Perin, MD, Teaneck, NJ; Frank J. Picone, MD, Tinton Falls, NJ; Jacob L. Pinnas, MD, Tucson, Ariz; Brace M. Prenner, MD, San Diego, Calif; Ernie Riffer, MD, Phoenix, Ariz; Ronald H. Saff, MD, Tallahassee, Fla; Paul Scheinberg, MD, Atlanta, Ga; Eric J. Schenkel, MD, Easton, Pa; Pankaj K. Shah, MD, Houston, Tex; Gary C. Steven, MD, PhD, Milwaukee, Wis; James R. Taylor, MD, Tacoma, Wash; Ita Tripathy, MD, Rolla, Mo; Julius van Bavel, MD, Austin, Tex; John A. Winder, MD, Sylvania, Ohio; James D. Wolfe, MD, San Jose, Calif; and Kelvin Wynn, MD, Henderson, NC.