

# Montelukast, Compared With Fluticasone, for Control of Asthma Among 6- to 14-Year-Old Patients With Mild Asthma: The MOSAIC Study

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**ABSTRACT.** *Background.* Guidelines recommend daily controller therapy for mild persistent asthma. Montelukast has demonstrated consistent benefit in controlling symptoms of asthma and may be an alternative, orally administered, nonsteroidal agent for treating mild asthma.

*Methods.* The Montelukast Study of Asthma in Children (MOSAIC study) was a 12-month, multicenter, randomized, double-blind, noninferiority trial to determine the effect of once-daily, orally administered montelukast (5 mg) ( $n = 495$ ), compared with twice-daily, inhaled fluticasone (100  $\mu$ g) ( $n = 499$ ), on the percentage of asthma rescue-free days (RFDs) (any day without asthma rescue medication and with no asthma-related resource use). Patients 6 to 14 years of age had mild persistent asthma (average percentage of predicted forced expiratory volume in 1 second: 87.2%; RFDs at baseline: 64%). Montelukast would be considered not inferior to fluticasone if the upper limit of the 95% confidence interval for the difference in mean percentages of RFDs (fluticasone minus montelukast) was above  $-7\%$  (a difference of  $\sim 2$  days/month).

*Results.* The mean percentage of RFDs was 84.0% in the montelukast group and 86.7% in the fluticasone group. The least-squares mean difference was  $-2.8\%$  (95% confidence interval:  $-4.7\%$  to  $-0.9\%$ ), within the noninferiority limit of  $-7\%$ . The proportion of patients requiring systemic corticosteroids and the number of patients with an asthma attack were greater in the montelukast group. Both montelukast and fluticasone were well tolerated.

*Conclusions.* Montelukast was demonstrated to be not inferior to fluticasone in increasing the percentage of RFDs among 6- to 14-year-old patients with mild asthma. Secondary end points, including percentage of predicted forced expiratory volume in 1 second value, days with  $\beta$ -receptor agonist use, and quality of life, improved in both groups but were significantly better in the fluticasone treatment group. *Pediatrics* 2005;116:360–369; *asthma, asthma control, inhaled corticosteroid, safety, randomized controlled trial.*

ABBREVIATIONS. FEV<sub>1</sub>, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; GINA, Global Initiative for Asthma; ANCOVA, analysis of covariance; CI, confidence interval; RFD, rescue-free day.

Asthma is the most prevalent chronic disease of childhood, affecting  $>4$  million children in the United States.<sup>1</sup> The number of patients diagnosed with asthma is increasing worldwide,<sup>2</sup> particularly among children and adolescents.<sup>1,3</sup> Chronic inflammation of the airways is a major component of the pathophysiologic mechanism of asthma. Cysteinyl leukotrienes play a key role in mediating this pathologic process.<sup>4</sup> Antileukotriene agents such as montelukast act by blocking the effects of the cysteinyl leukotrienes and have proved very effective in controlling symptoms of asthma among adults and in reducing markers of chronic inflammation among adults<sup>5</sup> and children.<sup>6,7</sup>

Current clinical practice guidelines from the National Heart, Lung, and Blood Institute<sup>8</sup> and the Global Initiative for Asthma (GINA)<sup>9</sup> recommend the use of antiinflammatory controller therapy for the long-term treatment of persistent asthma. Inhaled corticosteroids (ICS) are recommended and are used widely as first-line controller agents,<sup>8,9</sup> with leukotriene-modifying agents being recommended as alternative or add-on therapies. However, clinical trials among adults determined that montelukast is similar to beclomethasone in improving asthma control,<sup>10</sup> is similar to triamcinolone in reducing bronchial hyperresponsiveness,<sup>11</sup> and acts as an alternative to doubling the dose of inhaled budesonide, on the basis of multiple parameters of asthma control.<sup>12</sup> Although the goal of chronic therapy is to maintain control over symptoms and to minimize exacerbations, many clinical trials evaluate the efficacy of a therapeutic regimen based on objective measures of lung function. Studies have reported variable results when comparing montelukast with ICS in improving lung function end points such as peak flow and forced expiratory volume in 1 second (FEV<sub>1</sub>).<sup>13,14</sup> To obtain a more complete profile of therapeutic efficacy, measures of asthma control should also address the use of rescue medications and asthma-related health care utilization. Evaluating asthma control with these end points has shown sensitivity and responsiveness in studies among mild asthmatic patients, correlating with patient symptoms.<sup>15</sup>

Several large clinical trials among adults have

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Accepted for publication Dec 2, 2004.

doi:10.1542/peds.2004-1172

Conflict of interest: Ms Gilles and Drs Swern, Tozzi, and Polos are employees of Merck and Co.

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compared the efficacy of a leukotriene receptor antagonist with that of ICS with a variety of asthma end points.<sup>10,13,16</sup> However, no large study to date has evaluated pediatric patients. The purpose of this 12-month noninferiority trial was to compare the efficacy of orally administered montelukast with that of inhaled fluticasone in the percentage of asthma rescue-free days (RFDs) among 6- to 14-year-old patients with mild persistent asthma.

## METHODS

### Study Design

This was a 12-month, multicenter, double-blind, double-dummy, randomized, parallel-group study to determine the efficacy of once-daily, orally administered montelukast (5 mg), compared with twice-daily, inhaled fluticasone (100  $\mu$ g), in the percentage of asthma RFDs among 6- to 14-year-old patients with mild persistent asthma, as defined by the GINA guidelines.<sup>9</sup> The study was conducted at 104 sites in 24 countries in Asia, Africa, North America, and South America between July 2001 and June 2003. Written informed consent, approved by the respective institutional review boards or ethical review committees, was obtained from parents or legal guardians. Informed assent, approved by the respective institutional review boards and ethical review committees, was obtained from each patient.

The study consisted of a 4-week, single-blind, placebo run-in period, after which patients were randomized to receive montelukast (5-mg oral tablet [10 mg if the patient turned 15 years of age during the study], once at bedtime) or twice-daily fluticasone (100  $\mu$ g, through a metered dose inhaler; 2 puffs of 50  $\mu$ g morning and evening) and their respective dummy placebos and an open-label, short-acting,  $\beta$ -receptor agonist (salbutamol) inhaler to be used as needed for 12 months. The study was conducted with in-house blinding procedures. During the 4-week run-in period, patients discontinued any asthma controller medication and received image-matching, single-blind, montelukast and fluticasone and an open-label, short-acting,  $\beta$ -receptor agonist inhaler to be used as needed. Patients had 3 clinic visits, during which  $\beta$ -receptor agonist use and asthma symptoms were determined and baseline spirometry measurements, laboratory tests, and physical examinations were performed. Investigators instructed patients on the use of inhaler devices, with particular emphasis on the difference between the use of  $\beta$ -receptor agonist inhalers and the use of fluticasone inhalers. The use of spacer devices was optional but, if the devices were used, they were to be used consistently throughout the study. After the run-in period, patients who met inclusion criteria were allocated randomly, in a 1:1 manner, to a treatment group, according to an electronically generated schedule with a blocking factor of 4. Patients were allowed to take systemic corticosteroids for rescue or, if asthma symptoms were not controlled adequately, any other controller medication at the investigator's discretion. To mimic real-life practices, clinic visits were scheduled approximately every 4 months during the 12-month active treatment period. Before each visit, inhaled, short-acting,  $\beta$ -receptor agonists and short-acting antihistamines were withheld for  $\geq 6$  hours and long-acting antihistamines for  $\geq 48$  hours. A standard spirometer conforming to American Thoracic Society guidelines was used to measure FEV<sub>1</sub>. Because of circadian variations, pre-bronchodilator and postbronchodilator FEV<sub>1</sub> measurements were made at approximately the same time ( $\pm 2$  hours) at each visit. A validated, asthma-specific, diary card<sup>15</sup> was completed at home; patients recorded  $\beta$ -receptor agonist use, asthma medication use in addition to study medication, and any unscheduled, asthma-related visits to a physician, the emergency department, or the hospital each day when they occurred. Beyond reviewing the diary card at each visit, no efforts were made to maintain strict compliance with study procedures except for what would be performed during normal clinical practice, to approximate real-world use of the 2 treatments.

### Patients

Patients were male or female subjects between 6 and 14 years of age, with a clinical history of asthma of  $\geq 12$  months, who had mild persistent asthma at step 2 of the GINA guidelines. Patients

must have had a FEV<sub>1</sub> of  $\geq 80\%$  of the predicted value (prebronchodilator measurement), while  $\beta$ -receptor agonist was withheld for  $\geq 6$  hours, at least twice in the run-in period (visits 1, 2, or 3) and a FEV<sub>1</sub> or peak expiratory flow of  $\geq 70\%$  of the predicted value at visit 3. Diagnosis of mild asthma was defined on the basis of (1) an increase in FEV<sub>1</sub> or peak expiratory flow rate of  $\geq 12\%$  (absolute value), 20 to 30 minutes after inhaled  $\beta$ -receptor agonist administration, at visits 1, 2, or 3; (2) a positive methacholine or histamine provocative concentration causing a 20% decrease in FEV<sub>1</sub> of  $\leq 8$  mg/mL; or (3) a decrease in FEV<sub>1</sub> of  $\geq 15\%$  after an exercise challenge. Patients also had to demonstrate symptoms requiring  $\beta$ -receptor agonist use on  $\geq 2$  and  $\leq 6$  days of the week for the 2 weeks before visit 3. Patients had to be in good general health except for asthma, as indicated by medical history, physical examination, and routine laboratory data.

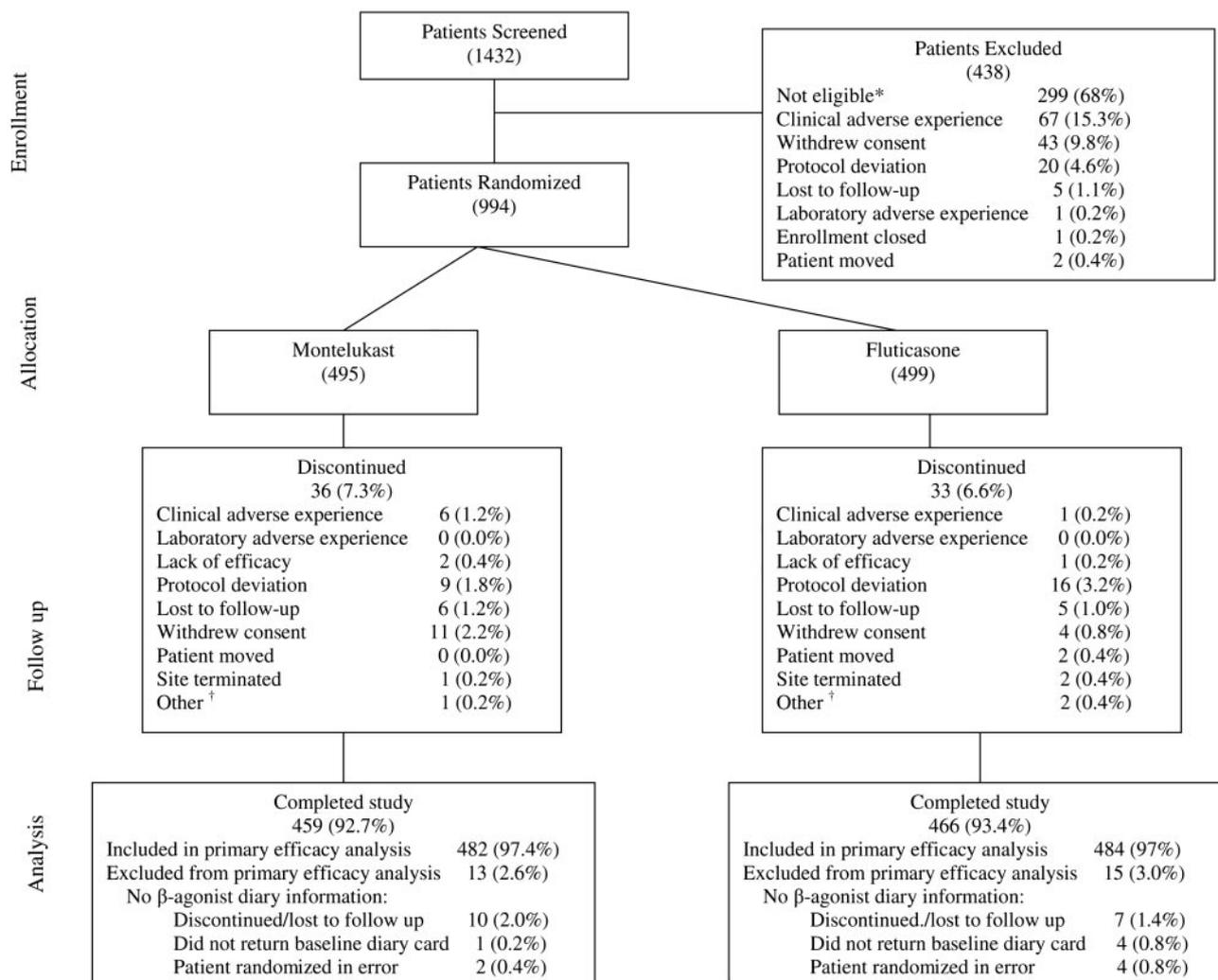
Current asthma medications could include a short-acting  $\beta$ -receptor agonist alone or a controller medication and a short-acting  $\beta$ -receptor agonist. Acceptable doses for controller medications included  $\leq 500$   $\mu$ g/day flunisolide,  $\leq 400$   $\mu$ g/day beclomethasone, budesonide, or triamcinolone, or  $\leq 200$   $\mu$ g/day fluticasone. Patients could continue immunotherapy at a stable dose if it had been initiated 3 months before the study. Patients could not take systemic corticosteroids (except as prespecified in the asthma rescue plan); intravenously administered  $\gamma$ -globulin or immunosuppressants within 1 month of visit 1; combination medication containing theophylline/aminophylline/caffeine or a  $\beta$ -receptor agonist preparation (except as prespecified in the asthma rescue plan);  $\beta$ -receptor-blocking agents; aspirin or nonsteroidal antiinflammatory medications (for sensitive individuals) for 2 weeks before visit 1; antiasthma medications for  $>7$  days after visit 1; or antibiotics for  $>7$  consecutive days in the 4 weeks before visit 1 or during the placebo run-in period (antibiotics were allowed during the double-blind period).

### Outcomes Measurements

The primary efficacy end point of the study was the percentage of asthma RFDs over 1 year of treatment, measured as a change from baseline. An asthma RFD was defined as any day during which a patient had no rescue medication use (ie,  $\beta$ -receptor agonists, systemic corticosteroids, or other asthma rescue medications) and no asthma-related health resource utilization (ie, an unscheduled visit to a physician, urgent/emergency care, or hospitalization). Secondary end points were the change from baseline in prebronchodilator percentage of predicted FEV<sub>1</sub>; the percentage of patients requiring antiasthma medications other than  $\beta$ -receptor agonist use; the percentage of patients with an asthma attack (defined as any period with worsening asthma that required an unscheduled visit to the doctor's office, emergency department, or hospital for treatment of asthma or treatment with systemic corticosteroids, as recorded on the diary cards); the average percentage of days with  $\beta$ -receptor agonist use; and the change in peripheral blood eosinophil levels from baseline. Patients 9 to 14 years of age, in selected countries with validated translations available, completed a self-administered quality of life questionnaire,<sup>17</sup> consisting of all domains and 3 individual domains of activity, symptoms, and emotions, at randomization and at the last visit. Questions were rated on a scale from 1 (worst response) to 7 (best response). Tertiary end points compared the effects of 1 year of treatment with montelukast versus fluticasone on patient reports of asthma control, asthma-related patient school loss, and parental work loss, assessed at 4-month intervals relative to the start of the trial. Assessment of asthma control and was based on a modification of questions from the control domain of the validated Pediatric Asthma Therapy Assessment Questionnaire.<sup>18</sup> Data on inhaler use were derived from the diary cards, rather than from the questionnaire.

### Safety

Safety was evaluated with adverse experience monitoring and with clinical evaluations, physical examinations, and vital signs. Height was measured during one of the prestudy visits and at each visit during the active treatment period, with a standard office stadiometer, and was recorded as the average of 2 separate measurements taken in centimeters.



**Fig 1.** Study design. \*Includes patients who took excluded medications, had unresolved upper respiratory tract infections, had clinically relevant active disease other than respiratory disease, had unexplained abnormal baseline laboratory values, were hospitalized, had been intubated for asthma or required acute asthma therapy within the run-in period, were unable to perform spirometry, or tended to move or vacation away from home for extended periods of time. †Includes a patient who was unwilling to participate, a patient who was unwilling to continue, and a patient for whom the investigator decided to discontinue participation.

### Statistical Analyses

The main efficacy analysis was based on an intention-to-treat principle; that is, all patients who had been treated for  $\geq 1$  day were included. The primary end point of the percentage of asthma RFDs was analyzed with an analysis of covariance (ANCOVA) model with factors for treatment and center and a covariate for percentage of days during the baseline period. The baseline covariate was included in the model because it was correlated highly with outcomes during the treatment period; it was used to reduce variability in the estimate of the treatment effect. To address the primary hypothesis of whether montelukast was not inferior to fluticasone with respect to the mean percentage of asthma RFDs during the double-blind treatment period, a 95% confidence interval (CI) was constructed for the difference in least-squares means between treatment groups (montelukast minus fluticasone). If the lower limit of the 95% CI was above  $-7\%$  (ie,  $\sim 2$  days/month), then montelukast would be considered not inferior to fluticasone.<sup>19</sup> The 95% CI was computed based on the least-squares means from an ANCOVA model including effects for treatment, center, and baseline percentage of asthma RFDs (calculated from period I).

A per-protocol analysis was performed for the primary end point, to corroborate the conclusions of the intention-to-treat approach. A corroborative analysis based on the rank-transformed data was also performed. Other continuous end points were analyzed with an ANCOVA model similar to that for the primary end point. Continuous end points that were not based on diary cards

were analyzed as changes from baseline. Comparisons between treatment groups were made with *F* tests. In addition, a 95% CI for the difference between means was constructed to estimate the treatment effect. Binary end points, such as the proportion of patients requiring additional asthma therapy, the proportion of patients with an asthma attack, and the proportion of patients whose asthma was well controlled, as judged by their caregivers, were summarized and analyzed with a logistic regression model with factors for treatment, region, and the value at baseline, if available. The number of days with school/work loss was analyzed with a cumulative logit model with factors for treatment and region and a covariate for the value at baseline. The number of asthma attacks and the percentage of days with additional rescue medication were summarized descriptively, and a 2-part model was used to analyze the data in an exploratory manner.

### Determination of Sample Size and Power to Address Study Hypotheses

Estimates for expected treatment differences and variability came from pilot studies with adult patients with mild asthma who received montelukast or an ICS (budesonide, beclomethasone, or fluticasone) and had their RFDs evaluated over 1 to 3 months.<sup>5,10,16,20</sup> On the basis of these results, the true difference in means between montelukast and fluticasone was taken to be  $\sim 2\%$ , favoring fluticasone, with a SD of 25%. A limit of 7 percentage points for the treatment difference, corresponding to  $\sim 2$  asthma

RFDs in 1 month, was used to assess whether montelukast was not inferior to fluticasone. With a true difference in means of 2% and a SD of 25%, 394 patients per group eligible for analysis provided 80% power to declare montelukast not inferior to fluticasone.

### Safety Analyses

Adverse experiences were recorded at each clinical visit. Clinical and laboratory adverse experiences were analyzed and summarized according to frequency of occurrence. Overall growth rates (centimeters per year) over the 12-month period were calculated and analyzed with an analysis of variance with factors for treatment and geographic region.

## RESULTS

### Patients

A total of 1432 patients were screened for eligibility, and 994 entered the double-blind active treatment period; 495 patients were randomized to montelukast and 499 to fluticasone. Of these, 459 in the montelukast group and 466 in the fluticasone group completed the 12-month trial, and 482 in the montelukast group and 484 in the fluticasone group were included in the intention-to-treat analysis (Fig 1). The majority of patients were boys (61.7%), and 65.0% were white. The age range at entry was 5 to 15 years, with a median age of 9 years. The median percentage of predicted FEV<sub>1</sub> was 87.2%. During the placebo run-in period, the median percentage of asthma RFDs was 64% and the median percentage of days with  $\beta$ -receptor agonist use was 35.7% (Table 1).

### Efficacy

#### Primary End Point

Montelukast was demonstrated to be not inferior to fluticasone in the percentage of asthma RFDs over the 12-month treatment period (Fig 2). The mean percentage of asthma RFDs was 84.0% in the montelukast group and 86.7% in the fluticasone group, favoring fluticasone. The difference in least-squares means was  $-2.8\%$  (95% CI:  $-4.7\%$  to  $-0.9\%$ ), a difference of  $<1$  day/month and above the noninferiority

limit of  $-7\%$  (Table 2). In a per-protocol analysis, the estimated difference between treatments in least-squares means was  $-3.2\%$  (95% CI:  $-5.2\%$  to  $-1.3\%$ ). An additional nonparametric analysis, using an ANCOVA on the ranks, corroborated these results.

#### Secondary End Points

The average percentage of predicted FEV<sub>1</sub> increased from 88.1% at baseline to 89.0% at 12 months in the montelukast group and from 88.9% to 91.7% in the fluticasone group; the difference in least-squares means was  $-2.2\%$  in favor of fluticasone ( $P = .004$ ) (Table 2). Because this was a 1-year study of growing children and height is a factor in the calculation of FEV<sub>1</sub> percentage of predicted value, FEV<sub>1</sub> was also calculated as a change from baseline. The least-squares mean changes from baseline in FEV<sub>1</sub> were 0.27 L and 0.30 L for montelukast and fluticasone, respectively ( $P = .232$ ) (Table 2; Fig 3).

Montelukast and fluticasone both significantly decreased the percentage of days with  $\beta$ -receptor agonist use from baseline ( $P \leq .001$ ) (Fig 4). The percentage of days with  $\beta$ -receptor agonist use was 15.4% in the montelukast group and 12.8% in the fluticasone group, favoring fluticasone ( $P = .003$ ) (Table 2). Averaged over the 12-month period, the percentage of days with  $\beta$ -receptor agonist use was decreased by 22.7% in the montelukast group and by 25.4% in the fluticasone group.

Over the 12-month period, the proportion of patients with additional asthma rescue medication, excluding short-acting  $\beta$ -receptor agonists, was 20.7% in the montelukast group and 13.5% in the fluticasone group; the relative risk was 1.56 (95% CI: 1.17 to 2.06) in favor of fluticasone. The majority of patients using rescue medications (17.5% of patients in the montelukast group and 10.5% of patients in the fluticasone group) used systemic corticosteroids. The

**TABLE 1.** Patient Demographic Features and Baseline Characteristics

	Montelukast (N = 495)	Fluticasone (N = 499)
Age, y, median (range)	9 (6–14)	9 (5–15)
Gender, n (%)		
Boys	321 (64.8)	292 (58.5)
Girls	174 (35.2)	207 (41.5)
Race, n (%)		
White	315 (63.6)	317 (63.5)
Hispanic	105 (21.2)	105 (21.0)
Asian	29 (5.9)	30 (6.0)
Black	2 (0.4)	4 (0.8)
Multiracial	36 (7.3)	36 (7.2)
Other*	8 (1.6)	7 (1.4)
History of allergic rhinitis, n (%)	304 (61.4)	309 (61.9)
Weight, kg, median (range)	N = 493; 33 (14.6–77)†	N = 499; 33 (14.6–103)†
Height, cm, median (range)	136 (106–181)	135 (108–174)
FEV <sub>1</sub> , L, median (range)	1.8 (0.5–4.6)	1.8 (0.8–4.1)
FEV <sub>1</sub> , % of predicted, median (range)‡	86.8 (34.2–129)	87.7 (51.8–125)
Asthma RFDs, %, median (range)§	N = 494; 63.7 (0.0–100)†	N = 495; 64 (0.0–100)†
Days with $\beta$ -receptor agonist use, %, median (range)§	N = 494; 35.6 (0.0–100)†	N = 495; 35.7 (0.0–100)†
$\beta$ -Receptor agonist use, puffs per wk, median (range)§	N = 495; 5 (0.0–77.9)†	N = 495; 4.8 (0.0–78.3)†

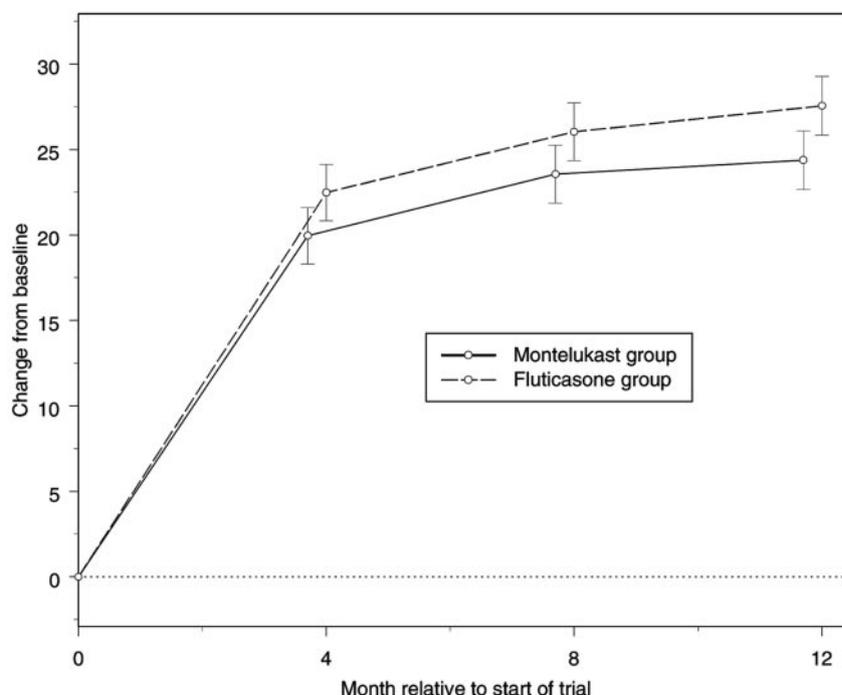
\* Other includes Indian and European.

† Patients with available information.

‡ FEV<sub>1</sub> is the value at randomization.

§ Data from diary cards collected during the 4-week run-in period.

**Fig 2.** Change in percentage of asthma RFDs (mean and 95% CI) over 12 months of treatment, summarized according to 4-month treatment periods.



**TABLE 2.** Efficacy End Points for Montelukast and Fluticasone Treatment Groups

	Montelukast		Fluticasone		Difference (Least-Squares Mean)	P
	N	Change From Baseline (95% CI)	N	Change From Baseline (95% CI)		
Asthma RFDs, %	482	22.4 (20.9 to 23.9)	484	25.2 (23.7 to 26.7)	-2.8 (-4.7 to -0.9)	
FEV <sub>1</sub> , % of predicted	439	0.6 (-0.6 to 1.7)	442	2.7 (1.6 to 3.8)	-2.2 (-3.6 to -0.7)	.004
FEV <sub>1</sub> , L	439	0.27 (0.24 to 0.30)	442	0.30 (0.27 to 0.33)	-0.02 (-0.06 to 0.02)	.232
Days with $\beta$ -receptor agonist use, %	439	-22.7 (-24.1 to -21.2)	442	-25.4 (-26.8 to -24.0)	2.7 (0.9 to 4.5)	.003
Quality of life, overall score	263	0.92 (0.83 to 1.10)	278	1.05 (0.96 to 1.14)	-0.13 (-0.25 to -0.01)	.036
Eosinophils, 10 <sup>3</sup> cells per $\mu$ L	401	-0.08 (-0.11 to -0.04)	392	-0.06 (-0.09 to -0.03)	-0.02 (-0.06 to 0.02)	.411

proportion of patients using rescue medications other than systemic corticosteroids was 4.6% in the montelukast group and 3.9% in the fluticasone group (Table 3). The percentages of days with additional rescue medications for patients with  $\geq 1$  day of additional rescue medication use were similar in the 2 treatment groups; the median percentage of days with additional rescue medication use was 2.2% (interquartile range: 1.0–3.9%) in the montelukast group and 2.2% (interquartile range: 1.1–4.6%) in the fluticasone group.

The proportion of patients with an asthma attack was 32.2% in the montelukast group and 25.6% in the fluticasone group; the relative risk of an asthma attack was 1.26 (95% CI: 1.04 to 1.52) in favor of fluticasone (Fig 5). For patients with  $\geq 1$  asthma attack, the numbers of attacks per year were similar in the 2 groups. In addition, montelukast and fluticasone were equivalent in the proportions of patients with asthma attacks for the 688 patients without any use of systemic corticosteroids during the previous year; the relative risk was 1.05 (95% CI: 0.80 to 1.38). For patients with  $\geq 1$  asthma attack, the median number of asthma attacks was 1.1 (interquartile range: 1.0–2.9) in the montelukast group and 1.8 (interquartile range: 1.0 to 2.8) in the fluticasone group.

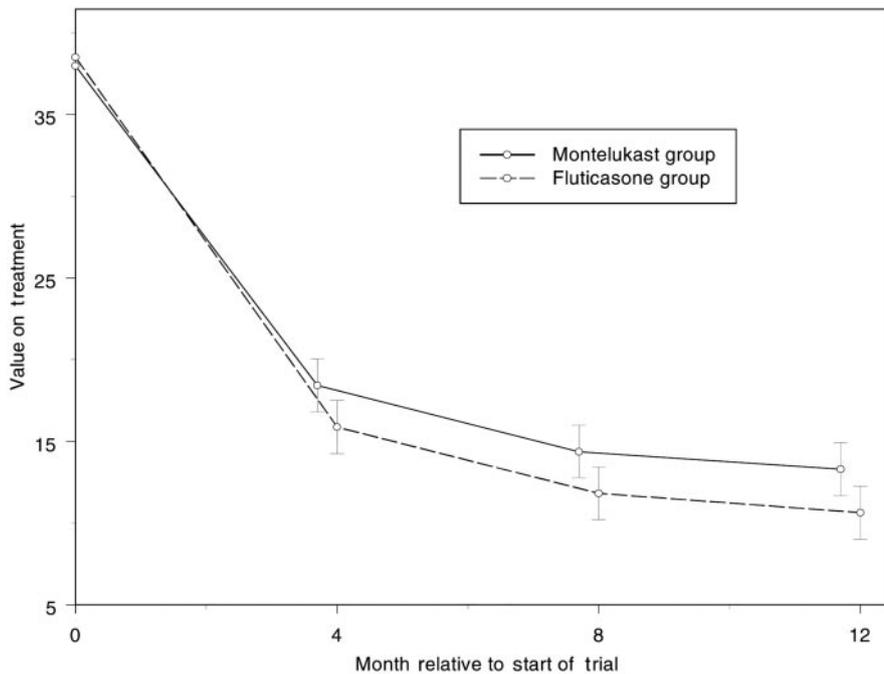
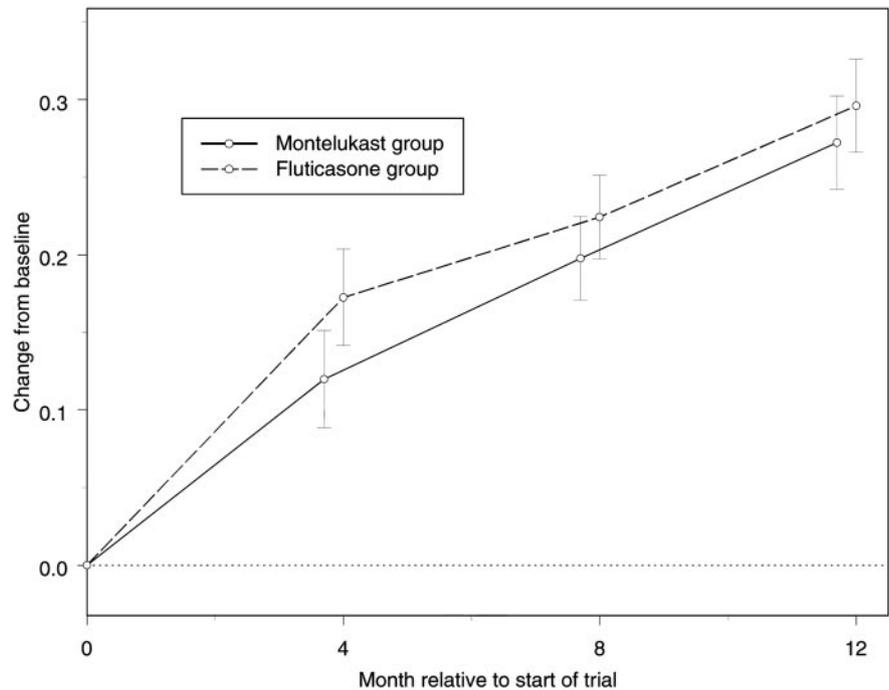
Both montelukast and fluticasone significantly improved the overall quality of life from baseline ( $P \leq .001$ ) at the end of the 12-month treatment period. The mean pediatric asthma-related quality of life score (averaged over the 4 domains) increased from 5.4 at baseline to 6.3 in the montelukast group and from 5.3 to 6.4 in the fluticasone group (Table 2).

Montelukast and fluticasone decreased the peripheral blood eosinophil count significantly from baseline over the 12-month period ( $P \leq .001$ ). The peripheral blood eosinophil count decreased from  $0.55 \times 10^3$  cells per  $\mu$ L to  $0.47 \times 10^3$  cells per  $\mu$ L in the montelukast group and from  $0.49 \times 10^3$  cells per  $\mu$ L to  $0.46 \times 10^3$  cells per  $\mu$ L in the fluticasone group (Table 2).

#### Tertiary End Points

Montelukast and fluticasone significantly improved patient asthma control over the 12-month treatment period ( $P \leq .001$ ). The average score for the control domain of the Pediatric Asthma Therapy Assessment Questionnaire decreased from 1.8 at baseline to 0.7 in the montelukast group and from 1.7 to 0.4 in the fluticasone group; the difference in least-squares means was 0.2 (95% CI: 0.1 to 0.4) in favor of fluticasone.

**Fig 3.** Change from baseline (mean and 95% CI) in prebronchodilator FEV<sub>1</sub> over the 12-month period, summarized according to 4-month periods.



**Fig 4.** Percentage of days (mean and 95% CI) with  $\beta$ -receptor agonist use over the 12-month treatment period, summarized according to 4-month periods.

The proportion of patients with  $\geq 1$  day lost from school during the 4 weeks preceding the month 12 visit was 8.8% in the montelukast group and 6.2% in the fluticasone group. The percentages of patients with  $>3$  lost school days were 1.9% and 2.1% in the montelukast and fluticasone groups, respectively. There were 13 patients (2.9%) in the montelukast group and 9 patients (2.0%) in the fluticasone group whose parents/legal guardians lost  $\geq 1$  day of work because of their child's asthma during the 4 weeks preceding the month 12 visit. The percentages of patients whose parents lost  $>3$  days were 0.4% and 0.2% in the montelukast and fluticasone groups, respectively. There were 435 patients (92.4%) in the

montelukast group and 453 patients (96.6%) in the fluticasone group whose asthma was well controlled, as judged by their caregivers.

Results were consistent among subgroups (gender, race, age categories [ $<12$  years or  $\geq 12$  years], baseline percentage of predicted FEV<sub>1</sub>, and baseline  $\beta$ -receptor agonist use) and across geographic regions. No significant treatment-subgroup interaction or treatment-region interaction was detected for any of the efficacy analyses.

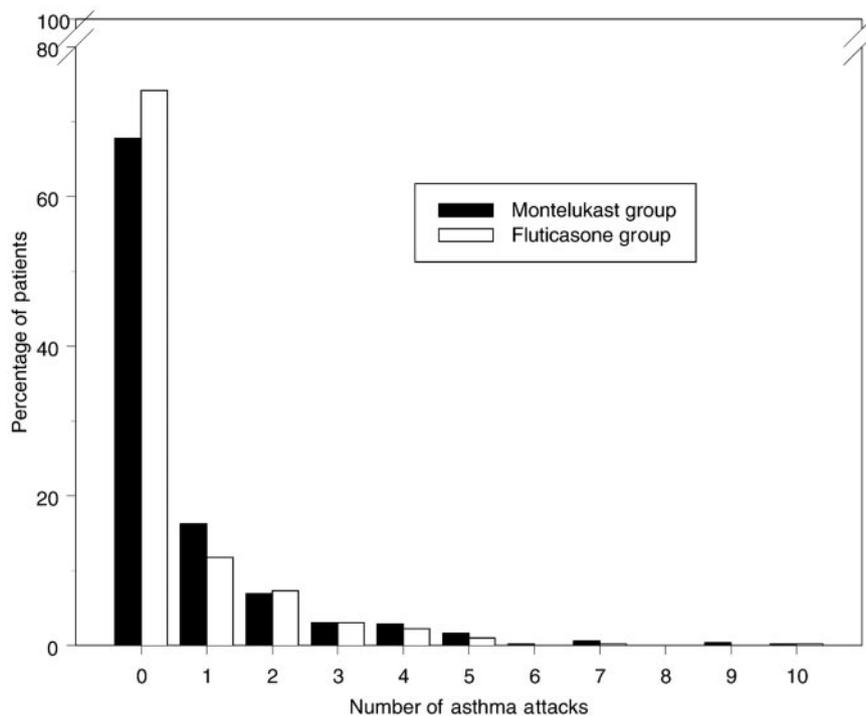
Compliance with the treatment regimen was similar in the 2 treatment groups. The average percentages of days fully compliant for montelukast were 97.8% and 98.1% for the placebo and active arms and

**TABLE 3.** Proportions of Patients in the Montelukast and Fluticasone Treatment Groups Using Rescue Medications During the 12-Month Treatment Period

Asthma Rescue Medication	Montelukast (N = 482)		Fluticasone (N = 484)		P
	n	%	n	%	
Systemic corticosteroid use*	86	17.8	51	10.5	≤.001
Any other additional medication	22	4.6	19	3.9	.617
Xanthines	3	0.6	3	0.6	
Beclomethasone dipropionate	10	2.1	9	1.9	
Fluticasone propionate plus salmeterol xinafoate	5	1.0	3	0.6	
Salmeterol xinafoate	6	1.2	4	0.8	
Montelukast sodium	0	0.0	2	0.4	

N indicates the number of patients in the modified intention-to-treat analysis; n, number of patients experiencing an event.

\* May include orally, rectally, intramuscularly, or intravenously administered corticosteroids.



**Fig 5.** Percentage of patients according to number of asthma attacks over the 12-month period.

for inhaled fluticasone were 97.5% and 98.0% for the placebo and active arms, respectively.

### Safety

There were no significant differences between treatment groups in the proportions of patients with clinical or laboratory adverse experiences over the 12-month period. Patients with a clinical drug-related adverse experience (determined by the investigator to be related to the study drug) represented 4.4% (22 of 495 patients) in the montelukast group and 3.2% (16 of 499 patients) in the fluticasone group; the most common experiences, occurring for >0.5% of patients, were headache (2.2% in the montelukast group and 1.0% in the fluticasone group) and asthma (0.6% in the montelukast group and 0.4% in the fluticasone group). There were no patients with serious clinical drug-related adverse experiences in either group. Six patients (1.2%) in the montelukast group and 1 patient (0.2%) in the fluticasone group discontinued treatment because of a clinical adverse experience. Patients with drug-related laboratory ad-

verse experiences represented 0.5% (2 of 434 patients) in the montelukast group and none in the fluticasone group. No laboratory adverse experience was considered to be serious. There was 1 death in the montelukast group, involving an 11-year-old boy who died as a result of gastroenteritis and dehydration, which was considered to be not related to the study drug.

The overall growth rate, averaged over the 12-month period, was less ( $P = .018$ ) in the fluticasone group (5.81 cm/year) than in the montelukast group (6.18 cm/year). The difference between treatments was 0.41 cm/year (95% CI: 0.07 to 0.75 cm/year) (Fig 6).

### DISCUSSION

This large clinical trial was the first to compare the efficacy of a leukotriene receptor antagonist, montelukast, with an ICS, fluticasone, in multiple parameters of asthma control among pediatric patients with mild asthma. This multicenter, double-blind, randomized, parallel-group study among 6- to 14-year-

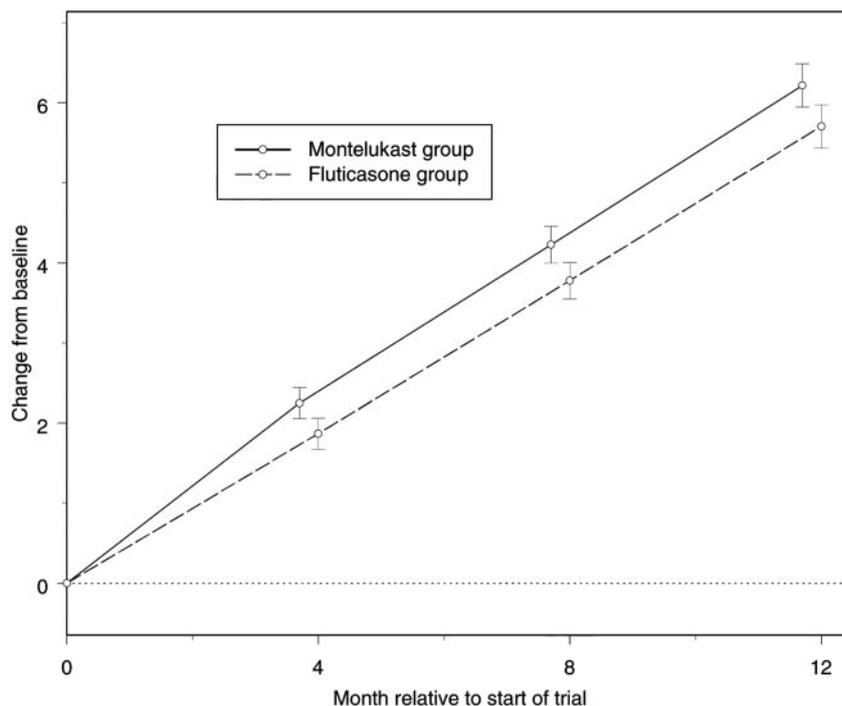


Fig 6. Change in body height (centimeters) over 12 months of treatment, summarized for each 4-month period and expressed as mean and 95% CI.

old patients demonstrated that orally administered montelukast was not inferior to inhaled fluticasone with respect to the level of asthma control (the percentage of asthma RFDs) over 12 months of treatment. Both treatment groups had >84% of days during the year with no need for any asthma rescue medications or resource utilization. The difference in RFDs between montelukast and fluticasone was <1 day/month. In addition, both groups showed significant changes from baseline in prebronchodilator FEV<sub>1</sub>, days with  $\beta$ -receptor agonist use, asthma-specific quality of life, and reduction of peripheral blood eosinophil levels. The difference between groups favored fluticasone for some secondary end points. The results were consistent among subgroups according to gender, race, age categories, baseline spirometry results,  $\beta$ -receptor agonist use, and geographic regions.

Several randomized, clinical trials among adults<sup>5,10,16</sup> and children<sup>6,7</sup> demonstrated the efficacy of montelukast in reducing asthma symptoms and  $\beta$ -receptor agonist use. In this study, multiple clinical control indices were combined into the primary end point of an asthma RFD. An asthma RFD evaluated measures of rescue medication use (including  $\beta$ -receptor agonists, systemic corticosteroids, and other asthma rescue medications) and asthma-related resource utilization. This composite end point incorporated elements representative of daily asthma control, in an effort to approximate actual clinical experience. These outcomes are relevant to patients and physicians because they are objective measures of asthma control.<sup>8,9</sup> The efficacy of montelukast, in comparison with fluticasone, in RFDs was similar to results from a 6-month, open-label trial comparing montelukast with beclomethasone among 6- to 11-year-old children.<sup>21</sup> In that study, montelukast and beclomethasone provided equivalent protection with

respect to asthma-related resource utilization, as well as other clinical end points.

Because this was not a placebo-controlled trial, it is important to establish that the efficacy demonstrated for fluticasone was within the range of what is expected for these patients and that the failure to reject our hypothesis of equivalence was attributable to the efficacy of montelukast and not a lack of treatment effect for fluticasone. There are few pediatric, placebo-controlled studies of this length that measured similar end points; however, one placebo-controlled trial among children 4 to 11 years of age compared fluticasone with placebo during a 12-week, double-blind period, followed by a 52-week, open-label, extension period. After 12 weeks, the improvement in FEV<sub>1</sub> for the 80 patients receiving 100  $\mu$ g of fluticasone twice per day was 0.23 L, compared with -0.04 L for placebo.<sup>22</sup> There was additional improvement during the 52-week, open-label phase; however, there was no placebo control during that period.<sup>22</sup> Another placebo-controlled trial, conducted among children with a mean age of 8 years, compared 2 doses of fluticasone with placebo over 12 weeks of treatment.<sup>23</sup> FEV<sub>1</sub> increased by 0.25 L at 12 weeks in the 100- $\mu$ g fluticasone (twice daily) group, with no change in the placebo group. A similar study conducted among 4- to 11-year-old children (reviewed by Purucker et al<sup>24</sup>) reported a 0.27-L change in FEV<sub>1</sub> over 12 weeks of treatment with a similar dose of fluticasone, with little placebo effect.<sup>24</sup> These studies showed changes comparable to the ~0.18-L change seen at 4 months and the 0.29-L change seen at 12 months for the fluticasone group in our trial. Another study, among 5- to 10-year-old children, measured rescue medication-free days, similar to our end point of RFDs.<sup>25</sup> Although that was a 4-month study, the placebo effect was consistent and the rescue medication-free days for the placebo group at the end of

4 months increased to 57% to 67%, compared with 83% to 86% for the fluticasone group. The difference (fluticasone minus placebo) was 16% to 29%, similar to our 25.9% change in RFDs from baseline for fluticasone. These studies suggest that the efficacy seen with fluticasone among patients with milder disease in our study is within the range of the expected effect for this therapy, confirming the efficacy of montelukast.

Data from this study indicated no major differences in the montelukast group, compared with the fluticasone group, in the percentage of days with  $\beta$ -receptor agonist use over the 1-year trial period. Both therapies reduced  $\beta$ -receptor agonist use by >50% from baseline within the first 4 months of therapy. The reduction in  $\beta$ -receptor agonist use continued throughout the remainder of the study and remained at >50% from baseline for both therapy groups. These results are consistent with results of a previous study in which montelukast reduced  $\beta$ -receptor agonist use significantly, compared with placebo, over 8 weeks among patients 6 to 14 years of age with mild/moderate asthma.<sup>6</sup> Although ~80% of patients required no additional rescue medications throughout the study, the proportion of patients with additional medication use excluding  $\beta$ -receptor agonists was greater in the montelukast group, compared with the fluticasone group. This was attributable to a difference in systemic corticosteroid use; the use of other rescue medications was similar between the groups. Similarly, asthma attacks that included the use of systemic corticosteroids were greater in the montelukast group. The majority of patients in the montelukast group (61.2%) and in the fluticasone group (55.8%) who used systemic corticosteroids required only 1 course during the 12-month study period. Similarly, of the patients who experienced an asthma attack, 51% of patients in the montelukast group and 52% of patients in the fluticasone group experienced only 1 attack during the 12-month treatment period.

Over the 12-month period, both treatments improved patients' control over their asthma, as reported with a pediatric asthma assessment questionnaire. Rescue  $\beta$ -receptor agonist use has been shown to predict quality of life among patients with mild asthma.<sup>26</sup> Therefore, it is not surprising that the significant reduction in  $\beta$ -receptor agonist use seen in this study might have been reflected in improved quality of life. In addition, >90% of caregivers in both treatment groups judged their children's asthma to be well controlled.

Both montelukast and fluticasone were generally well tolerated. There were no significant differences between treatment groups in the number of adverse experiences. Drug-related adverse experiences occurred for <5% of patients in both the montelukast and fluticasone groups; the most commonly reported experiences were asthma and headache. Patients in the fluticasone group had significantly lower overall growth, compared with those in the montelukast group, over the 12-month study period. The height difference of -0.41 cm seen in this trial with >400 patients receiving fluticasone was similar to the re-

sults of a study of 183 pediatric patients that documented a decrease in linear growth velocity of 0.43 cm/year with 200  $\mu$ g/day fluticasone, compared with placebo.<sup>27</sup> Studies with ICS have shown growth-suppressing effects, which vary according to ICS, dosage, and mode of delivery.<sup>28,29</sup> A study by Bisgaard et al<sup>30</sup> of patients  $\leq 3$  years of age found no effect on growth over 12 months of treatment with 200  $\mu$ g/day fluticasone, although there was suppression of serum and urinary cortisol levels. In another study, after twice-daily treatment with 100  $\mu$ g of budesonide for 9 to 12 months, patients 7 to 11 years of age had a significantly lower growth velocity, compared with placebo-treated patients. This finding was not seen among younger children receiving the same therapy,<sup>31</sup> similar to the study by Bisgaard et al.<sup>30</sup> The difference in height observed over 1 year of treatment with fluticasone in the current study is consistent with the results from studies of children of similar ages who were treated with ICS. These results are noteworthy and suggest that, even at low doses, fluticasone has systemic effects. The implications should be addressed in long-term studies.

A limitation of the study was the possible inclusion of patients who did not have mild asthma. More than 25% of patients had a percentage of predicted FEV<sub>1</sub> value that was <80% at baseline, which would classify them as having moderate asthma. However, these patients had FEV<sub>1</sub> values of  $\geq 80\%$  on other visits during the run-in period and puffs per week of  $\beta$ -receptor agonist, daily  $\beta$ -receptor agonist use, and asthma-free days (measured during the 1-month run-in period) that were comparable to values for the rest of the cohort, with a FEV<sub>1</sub> >80% of the predicted value. Another assessment of asthma severity would have involved recording daily asthma symptoms with a diary card. Because this study attempted to approximate a real-world clinical setting, only rescue medication use was reported in a diary. This study relied on an overall picture of asthma severity, in which FEV<sub>1</sub> was a single dimension used to categorize patients. However, it is possible that a percentage of patients had moderate asthma.

## CONCLUSIONS

Montelukast was proved to be not inferior to fluticasone in asthma RFDs, in a 1-year study involving 6- to 14-year-old patients with mild asthma. The difference between treatments was <1 day/month. Patients who received montelukast, compared with fluticasone, had more asthma attacks (32.2% for montelukast vs 25.6% for fluticasone) and required more systemic corticosteroids (17.8% for montelukast vs 10.5% for fluticasone). Both therapies were well tolerated; however, the fluticasone group had significantly lower final height, compared with the montelukast group.

## ACKNOWLEDGMENTS

The study was supported by a grant from Merck and Co.

The Montelukast Study of Asthma in Children (MOSAIC study) principal investigators were as follows: Australia: Drs Jodi Maree Hilton and Dominic Adam Fitzgerald; Austria: Dr Josef Riedler; Belgium: Drs Anne Malfroot, K. De Boeck, Marc Raes, and Kristine Desager; Chile: Drs Mario Calvo, Patricia Diaz, Claudio

Hoffmeister, and Ida Concha; Columbia: Drs Oscar Baron, Ricardo Aristizabal, and Alfredo Perez; Costa Rica: Drs Rafael Viquez and Rolando Vargas; Czech Republic: Drs Frantisek Kopriva, Jaroslav Matuska, Ondrej Rybnicek, Olga Skopkova, Sausen Sladkova, and Jarmila Turzikova; Egypt: Dr Ahmed Saad Elbeleidy; Estonia: Drs Maire Vasar and Urve Putnik; France: Drs Francois Payot, Eric Billard, Jacques Brouard, and Rabih Klink; Germany: Drs Werner Kuestermann, Reinhard Erdl, Peter Stutz, Sigrid Schloesser, Ulf Harnest, Wolfgang Kamin, Petra Mikloweit, Joachim Kuehr, Monika Gappa, Helen Koerbler, Juergen Funck, Juergen Giesler, Helge Hebestreit, Andrea Von Berg, and Antonio Pizzulli; Guatemala: Dr Luis Perez-Martini; Italy: Drs Luciana Dininnimeo, Gianluigi Marseglia, Antonio Carlucci, Lydia Pescolderung, Giovanni Pajno, Giuseppe Castellucci, Giacomo Vignola, Alfredo Boccaccino, and Paolo Mesirca; Lebanon: Drs Paul Henri Torbey, Salman Mroueh, Mariam Rajab, and Robert Sacy; Malaysia: Drs Jessie De Bruyne and Norzila Mohamed Zainudin; Netherlands: Drs E. Duiverman, N. Vanden Berg, B. Thio, A. Vaessen, C. Hugen, G. Gerrits, A. M. Landstra, and M. Affourtit; Peru: Drs Gladys Castilla and Jose Portugal; Romania: Drs Dimitrie Dragomir, Victor Mircea Nanulescu, Mihai Leonida Neamtu, and Stela Gotia; Slovakia: Drs Peter Ciznar, Klara Kossarova, Julia Michalickova, and Eva Dzurillova; Slovenia: Dr Vasilija Macek; Spain: Drs Montserrat Bosque-Garcia, Gloria Garcia-Hernandez, Concepcion Oliva-Hernandez, Javier Perez-Frias, Manuel Boquete-Paris, Amparo Escribano-Montener, and Joaquin Tejero-Garcia; Taiwan, Province of China: Drs Jing-Long Huang and Ko-Huang Lue; United Kingdom: Drs Somnath Mukhopadhyay, Douglas McKeith, Paul Fletcher, S. Langley, Christopher M. Booth, Jolly Zachariah, Alun Cooper, Simon Wright, Neil Warren Jackson, Ian Michael Orpen, Kevin Au, Albert Edward Burton, and Kevin Orion Thompson; Venezuela: Drs Fernan Migu Cabalero Fonseca and Mario Sanchez-Borges.

We thank Pam S. Dellea for coordination of the study, Dr Isabel Boaventura for assistance with protocol preparation, and Veerle Coenen for coordination of study data. We also acknowledge the excellent study monitors, investigators, and patients.

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