

# Montelukast, a Leukotriene Receptor Antagonist, for the Treatment of Persistent Asthma in Children Aged 2 to 5 Years

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**ABSTRACT.** *Background.* The greatest prevalence of asthma is in preschool children; however, the clinical utility of asthma therapy for this age group is limited by a narrow therapeutic index, long-term tolerability, and frequency and/or difficulty of administration. Inhaled corticosteroids and inhaled cromolyn are the most commonly prescribed controller therapies for young children with persistent asthma, although very young patients may have difficulty using inhalers, and dose delivery can be variable. Moreover, reduced compliance with inhaled therapy relative to orally administered therapy has been reported. One potential advantage of montelukast is the ease of administering a once-daily chewable tablet; additionally, no tachyphylaxis or change in the safety profile has been evidenced after up to 140 and 80 weeks of montelukast therapy in adults and pediatric patients aged 6 to 14 years, respectively.

To our knowledge, this represents the first large, multicenter study to address the effects of a leukotriene receptor antagonist in children younger than 5 years of age with persistent asthma, as well as one of the few asthma studies that incorporated end points validated for use in preschool children.

*Objective.* Our primary objective was to determine the safety profile of montelukast, an oral leukotriene receptor antagonist, in preschool children with persistent asthma. Secondly, the effect of montelukast on exploratory measures of asthma control was also studied.

*Design and Statistical Analysis.* We conducted a double-blind, multicenter, multinational study at 93 centers worldwide: including 56 in the United States, and 21 in countries in Africa, Australia, Europe, North America, and South America. In this study, we randomly assigned 689 patients (aged 2–5 years) to 12 weeks of treatment with placebo (228 patients) or 4 mg of montelukast as a chewable tablet (461 patients) after a 2-week placebo

baseline period. Patients had a history of physician-diagnosed asthma requiring use of  $\beta$ -agonist and a predefined level of daytime asthma symptoms. Caregivers answered questions twice daily on a validated, asthma-specific diary card and, at specified times during the study, completed a validated asthma-specific quality-of-life questionnaire. Physicians and caregivers completed a global evaluation of asthma control at the end of the study.

Efficacy end points included: daytime and overnight asthma symptoms, daily use of  $\beta$ -agonist, days without asthma, frequency of asthma attacks, number of patients discontinued because of asthma, need for rescue medication, physician and caregiver global evaluations of change, asthma-specific caregiver quality of life, and peripheral blood eosinophil counts. Although exploratory, the efficacy end points were predefined and their analyses were written in a data analysis plan before study unblinding. At screening and at study completion, a complete physical examination was performed. Routine laboratory tests were drawn at screening and weeks 6 and 12, and submitted to a central laboratory for analysis. Adverse effects were collected from caregivers at each clinic visit.

An intention-to-treat approach, including all patients with a baseline measurement and at least 1 postrandomization measurement, was performed for all efficacy end points. An analysis-of-variance model with terms for treatment, study center and stratum (inhaled/nebulized corticosteroid use, cromolyn use, or none) was used to estimate treatment group means and between-group differences and to construct 95% confidence intervals. Treatment-by-age, -sex, -race, -radioallergosorbent test, -stratum, and -study center interactions were evaluated by including each term separately. Fisher's exact test was used for between-group comparisons of the frequency of asthma attacks, discontinuations from the study because of worsening asthma, need for rescue medication, and the frequencies of adverse effects. Because of an imbalance in baseline values for eosinophil counts for the 2 treatment groups, an analysis of covariance was performed on the eosinophil change from baseline with the patient's baseline as covariate.

*Study Participants.* Of the 689 patients enrolled, approximately 60% were boys and 60% were white. Patients were relatively evenly divided by age: 21%, 24%, 30%, and 23% were aged 2, 3, 4, and 5 years, respectively. For 77% of the patients, asthma symptoms first developed during the first 3 years of life. During the placebo baseline period, patients had asthma symptoms on 6.1 days/week and used  $\beta$ -agonist on 6.0 days/week.

*Results.* In over 12 weeks of treatment of patients aged 2 to 5 years, montelukast administered as a 4-mg chewable tablet produced significant improvements

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compared with placebo in multiple parameters of asthma control including: daytime asthma symptoms (cough, wheeze, trouble breathing, and activity limitation); overnight asthma symptoms (cough); the percentage of days with asthma symptoms; the percentage of days without asthma; the need for  $\beta$ -agonist or oral corticosteroids; physician global evaluations; and peripheral blood eosinophils. The clinical benefit of montelukast was evident within 1 day of starting therapy. Improvements in asthma control were consistent across age, sex, race, and study center, and whether or not patients had a positive radioallergosorbent test. Montelukast demonstrated a consistent effect regardless of concomitant use of inhaled/nebulized corticosteroid or cromolyn therapy.

Caregiver global evaluations, the percentage of patients experiencing asthma attacks, and improvements in quality-of-life scores favored montelukast, but were not significantly different from placebo.

There were no clinically meaningful differences between treatment groups in overall frequency of adverse effects or of individual adverse effects, with the exception of asthma, which occurred significantly more frequently in the placebo group. There were no significant differences between treatment groups in the frequency of laboratory adverse effects or in the frequency of elevated serum transaminase levels. Approximately 90% of the patients completed the study.

**Conclusions.** Oral montelukast (4-mg chewable tablet) administered once daily is effective therapy for asthma in children aged 2 to 5 years and is generally well tolerated without clinically important adverse effects. Similarly, in adults and children aged 6 to 14 years, montelukast improves multiple parameters of asthma control. Thus, this study confirms and extends the benefit of montelukast to younger children with persistent asthma. *Pediatrics* 2001;108(3). URL: <http://www.pediatrics.org/cgi/content/full/108/3/e48>; *asthma, cysteinyl leukotrienes, leukotriene receptor antagonist, montelukast, preschool children.*

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ABBREVIATIONS. RAST, radioallergosorbent test; ANCOVA, analysis of covariance; CAMP, Childhood Asthma Management Program.

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Most childhood asthma begins during the first 3 years of life,<sup>1</sup> and the greatest prevalence of asthma is in preschool children.<sup>2,3</sup> The clinical utility of asthma therapy available for this age group is limited by a narrow therapeutic index (theophylline, oral  $\beta$ -agonists, inhaled corticosteroids), a requirement for blood level monitoring (theophylline), the need for frequent administration (cromolyn), and/or difficulty in administration (inhaled agents, in general).

Despite the need for new asthma therapies for preschool children, there is minimal information available on use in children, particularly those younger than age 6, for some asthma therapies.<sup>4</sup> This may, in part, be because of the difficulties in assessing new asthma therapies in preschool children. For example, pharmacokinetic studies (namely, for dose selection) are difficult to perform because they require repeated blood sampling. There are no reliable or validated measures of either airways function<sup>5</sup> or asthma symptoms in this age group for use in multicenter trials. Preschool children cannot reliably per-

form pulmonary function tests such as forced expiratory volume in 1 second and peak flow maneuvers. Therefore, in addition to the need for new asthma therapies for preschool children, there is a need for methods validated for use in assessing the treatment effects of asthma therapies in multicenter studies in these children.

Leukotriene blockers (receptor antagonists and 5-lipoxygenase inhibitors) are the first new class of asthma therapy in nearly 2 decades. These agents, which include montelukast, pranlukast, zafirlukast, and zileuton, block the action or inhibit the synthesis of the cysteinyl leukotrienes, bioactive mediators with proinflammatory effects that play an important role in the pathophysiology of asthma. Cysteinyl leukotrienes cause bronchoconstriction, mucus secretion, increased vascular permeability, and eosinophil migration to the airways, as well as promote smooth muscle proliferation.<sup>6-10</sup> Their synthesis and release appear not to be blocked by corticosteroid therapy.<sup>11</sup>

Montelukast is a potent, specific leukotriene receptor antagonist. Administered once daily in tablet form, montelukast reduces the signs and symptoms of chronic asthma in adults and children as young as 6 years of age, with a tolerability profile similar to that of placebo.<sup>12-13</sup> Additionally, montelukast had been shown to attenuate exercise-induced bronchoconstriction in these patients.<sup>14-15</sup>

Although single center studies have been performed,<sup>16</sup> to our knowledge, no large, multicenter studies have addressed the effects of leukotriene blockers in children with persistent asthma younger than 5 years of age. The primary purpose of this 12-week phase III study was to determine the safety profile of montelukast (4-mg chewable tablet administered once daily at bedtime) in 2- to 5-year-old children with asthma. Also studied was the effect of montelukast, compared with placebo, on exploratory measures of asthma control that were specifically validated for use in this study, including caregiver-assessed asthma symptoms, asthma outcomes, and supplemental rescue medication use.<sup>17</sup>

## METHODS

### Patients

After screening 1148 patients, we randomized 689 patients aged 2 to 5 years with a history of physician-diagnosed asthma (at least 3 episodes of asthma symptoms during the previous year, including, but not limited to cough, wheezing, and shortness of breath). Patients were also required to have a total asthma symptom score of 1 or more (of a possible total of 24) on at least 8 days during the 2-week placebo baseline period. Additionally, patients were required to have used  $\beta$ -agonists on at least 8 days during the 2-week placebo baseline period. All patients were in good health, other than asthma, on the basis of results of medical history, physical examination, and routine laboratory tests. The radioallergosorbent test (RAST) was performed at screening and included testing for dog and cat dander, cockroach, *Alternaria alternata*, dust mites, and serum immunoglobulin E levels.

Patients were not eligible for the study if they had ever required intubation for asthma, had been treated for asthma in an emergency department or had been hospitalized for asthma within 1 month before the study, or had unresolved sinus disease or an unresolved upper or lower respiratory tract infection within 3 weeks before the study. The use of astemizole within 3 months; oral, intramuscular, or intravenous corticosteroids within 1 month; nedocromil, cromolyn, long-acting  $\beta$ -agonists, ketotifen, or

an antimuscarinic within 2 weeks; and theophylline within 1 week before the study were also reasons for exclusion. Up to 50% of enrolled patients were permitted the concomitant use of inhaled (or nebulized) corticosteroids or inhaled (or nebulized) cromolyn at a constant dosage beginning at least 1 month before and throughout the study. Immunotherapy at a constant dosage was allowed. As-needed treatment with  $\beta$ -agonists (oral, inhaled, or nebulized) was permitted according to each investigator's usual clinical practice. Oral corticosteroid rescue for worsening asthma was permitted according to a predefined plan.

Patients were withdrawn from the study if treatment was interrupted for >5 consecutive days, an excluded medication was initiated, >1 rescue with oral corticosteroids for worsening asthma was required, or worsening asthma required additional treatment.

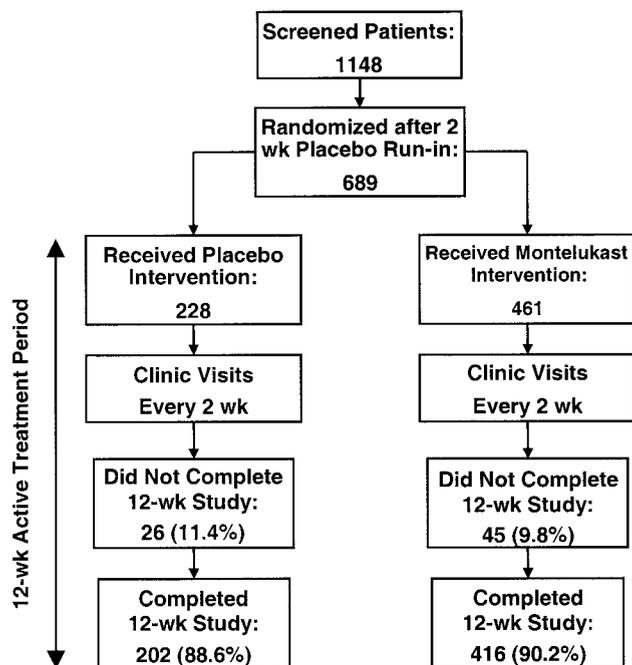
The protocol was approved by the institutional review boards (in the United States) or ethical review committees (in other countries) of all participating centers. Written informed consent was obtained from the parents or guardians of all patients.

## Study Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter study comparing the clinical effect of montelukast 4-mg chewable tablet with matching placebo once daily in the evening at bedtime, with or without food, in 2- to 5-year-old children with asthma. The ratio of montelukast to placebo recipients was 2 to 1. The study consisted of a 2-week, single-blind placebo baseline period and a 12-week double-blind, active treatment period (Fig 1). Study visits were scheduled every 2 weeks.

The study was conducted worldwide at 93 centers between December 29, 1997, and March 28, 1999. Fifty-six centers were in the United States and 21 in countries in Africa, Australia, Europe, North America, and South America.

An interim analysis of 6-week safety data from the first 314 patients enrolled in the study was performed by the study coordinating center (Merck Research Laboratories). The double-blind coding (ie, masking of patient allocation to treatment to investigators, patients, and parents participating in the study) was maintained throughout the entire study. The results of the full study (all 689 patients) are reported here.



**Fig 1.** Study profile. Patients received montelukast (4 mg as a chewable tablet) or matching placebo. Approximately 90% of patients completed the study. Of the 1148 screened patients, 459 did not qualify for randomization (approximately 304 for inclusion/exclusion criteria, 60 who withdrew, 21 unavailable for follow-up, and 74 for other reasons).

## Pediatric Asthma Caregiver Diary

Caregivers of these preschool children answered questions twice daily on a validated asthma-specific caregiver diary card.<sup>17</sup> Diary questions assessed daytime asthma symptoms, overnight asthma symptoms, use of  $\beta$ -agonist, and use of resources for worsening asthma. The daily daytime asthma symptoms score was the average of scores of 4 questions concerning severity of asthma symptoms (cough, wheeze, trouble breathing, and activity limitation), each scored on a 6-point scale from 0 (no symptoms or interference with activities) to 5 (very severe symptoms or interference with activities). Overnight symptoms (cough) were scored on a 5-point scale from 0 (no overnight cough and caregiver not disturbed) to 4 (coughed all night and caregiver disturbed all night).

A day without asthma was defined as a day during which the patient experienced no asthma symptoms (daytime and overnight), no use of  $\beta$ -agonist, and no asthma attacks (defined as worsening asthma requiring oral corticosteroid rescue or an unscheduled visit to a doctor's office, emergency department, or hospital).

## Global Assessment of Asthma Control

Caregivers and investigators independently evaluated the overall control of asthma after the 12-week treatment using a 7-point scale to answer the following question: "Compared with when my/the child entered this study, his/her asthma is now very much better (score, 3), somewhat better (2), a little better (1), the same (0), a little worse (-1), somewhat worse (-2), and very much worse (-3)."

## Asthma-Specific Caregiver Quality of Life

Caregivers completed an asthma-specific, caregiver quality-of-life questionnaire<sup>18</sup> that had been previously validated in children aged 7 to 17 years. Caregivers rated their response to questions using a 7-point scale ranging from 1 (worst) to 7 (best) on 3 occasions: immediately before randomization to the 12-week, double-blind treatment period, after 6 weeks, and at the completion of treatment. The questionnaire, which was designed to evaluate how a child's asthma interfered with the caregiver's normal daily activities and emotions, contained 13 questions, 4 and 9 pertaining to the activity and emotions domains, respectively.

## Safety Assessment

A complete physical examination including a gross neurologic evaluation, height, and weight was performed at screening and at completion of the 12-week, double-blind treatment period. At each clinic visit, vital signs (sitting blood pressure, heart rate, respiratory rate, and temperature) were recorded, and adverse effects reported by caregivers were summarized. Routine laboratory tests (complete blood count, platelet count, and serum biochemical analyses) were drawn at screening and after 6 and 12 weeks of double-blind treatment and were submitted to a central laboratory (SmithKline Beecham Clinical Laboratories, Van Nuys, CA).

## Statistical Analysis

Efficacy end points included daytime asthma symptoms, overnight asthma symptoms, daily use of  $\beta$ -agonist, days without asthma, frequency of asthma attacks, number of patients discontinued because of asthma, need for rescue medication according to the action plan, physician and caregiver global evaluations of change, asthma-specific caregiver quality of life, and peripheral blood eosinophil counts. The end points were considered exploratory because their performance characteristics had not previously been evaluated in a placebo-controlled study in this age group. Although exploratory, however, the efficacy end points were predefined and their analyses were in a written data analysis plan before unblinding of the study.

An intention-to-treat approach, including all patients with a baseline measurement and at least 1 postrandomization measurement, was performed for all efficacy end points. For end points that were analyzed as averages over the treatment period, data points were not carried forward in the place of missing values. The average change or percent change from baseline over the 12-week treatment period was calculated for the following efficacy end

**TABLE 1.** Baseline Characteristics of the Patients

Characteristic	Placebo ( <i>n</i> = 228)	Montelukast (4 mg) ( <i>n</i> = 461)
Age (y)	3.6 ± 1.1	3.6 ± 1.1
Range*	2–6	2–6
Male sex (%)	58	59
Race (%)		
White	57	56
Hispanic	20	21
Black	9	8
Other†	14	15
Weight (kg)	17.5 ± 4.1	17.6 ± 4.3
Height (cm)	103 ± 9	102 ± 10
Duration of asthma (y)	2.4 ± 1.3	2.4 ± 1.3
Range	0.5–6	0.5–6
History of activity-induced asthma (%)	81	77
Concomitant inhaled corticosteroid (%)	29	27
Concomitant cromolyn (%)	11	14
Abnormal RAST‡ (%)	51	47
Asthma symptoms (days/wk)	6.1	6.2
β-agonist use (days/wk)	5.6	5.6

\* Nine patients were 6 years old at randomization: 8 patients turned 6 between prestudy and randomization visits; and one 6-year-old's age was erroneously reported as 5 years at the prestudy visit.

† Other includes American and Canadian Indian, Arabic, Asian, mestizo, and other races.

‡ Normal values, ≤11 IU/mL at 1 to 2 years of age, ≤23 IU/mL at 3 years, and ≤49 IU/mL at 4 to 5 years.

Plus-minus values are means ± standard deviation.

points: daytime asthma symptom scores (including the individual components of daytime asthma symptoms: cough, wheeze, trouble breathing, and activity limitations), overnight asthma symptoms scores, asthma-specific caregiver quality-of-life scores, and peripheral blood eosinophil counts. Baseline was defined as the average value during the placebo run-in period (daytime asthma symptoms) or the value obtained before randomization (asthma-specific caregiver quality of life, peripheral blood eosinophil count). The change in overnight symptoms was determined for the group of patients with 2 or more nights with symptoms per week during the baseline period. Different formulations of β-agonist were permitted; therefore, the percentage of days with any β-agonist use, rather than the dose, was analyzed. Also analyzed were the percentages of days with daytime asthma symptoms, of days without asthma, of patients with corticosteroid rescues, and of patients with asthma attacks.

An analysis-of-variance model with terms for treatment, study center, and stratum (inhaled/nebulized corticosteroid use, cromolyn use, or none) was used to estimate treatment group means and between-group differences and to construct 95% confidence intervals. Treatment-by-age, -sex, -race, -RAST, -stratum, and -study center interactions were evaluated by including each term separately. Both between-group differences and within-group changes from baseline were estimated and tested by least-squares mean. Normality and homogeneity of variances assumptions were

verified. We used Fisher's exact test for between-group comparisons of the frequency of asthma attacks, discontinuations from the study because of worsening asthma, need for rescue medication, and the frequencies of adverse effects. We also determined the 95% confidence intervals for differences between treatment groups in the adverse effect rates. All randomized patients were included in the safety evaluations.

In addition, because of an imbalance in baseline values for eosinophil counts for the 2 treatment groups, an analysis of covariance (ANCOVA) was performed on the eosinophil change from baseline with the patient's baseline as covariate.

The onset of the clinical benefit of montelukast was examined by evaluating the daily scores for daytime asthma symptoms over the first 21 days of treatment. A slope analysis via a mixed-model approach was used to evaluate the treatment response over time and compare the time course between the treatment groups. An overall test of equal intercepts and slopes between the treatment groups was used.

All significance testing was 2-tailed and was only performed between treatment groups; a *P* value of .05 or less was considered to indicate statistical significance.

The study sample size was selected to examine safety and tolerability of montelukast in preschool children; it was not based on power calculations for any of the exploratory efficacy end points. A total of 510 patients (170 in the placebo group and 340 in the montelukast group) was required to detect, at a power of 90%, a 7.8% incidence in the montelukast group of an adverse effect occurring with 1% incidence in the placebo group ( $\alpha = 0.05$ , 2-tailed).

## RESULTS

### Patient Accounting

Of the 689 patients enrolled in the study, 228 were randomly assigned to the placebo group and 461 to the montelukast group (Fig 1). Overall, approximately 60% of patients were boys and approximately 60% were white. Patients were relatively evenly divided by age: 21%, 24%, 30%, and 23% were aged 2, 3, 4, and 5 years, respectively. For 77% of patients, asthma symptoms had first developed, according to caregivers, during the first 3 years of life. During the placebo baseline period, patients had asthma symptoms on 6.1 days/week and used β-agonist on 6.0 days/week. There were no clinically important demographic differences between the 2 treatment groups (Table 1).

Seventy-one patients (10% of the total) did not complete the study: 26 patients (11%) in the placebo group and 45 (10%) in the montelukast group. In the placebo group, 12 patients were withdrawn because of protocol deviations, 7 stopped treatment because of adverse effects, 4 withdrew consent, 2 were lost to follow-up, and 1 stopped treatment because of an elevated alkaline phosphatase value. In the monte-

**TABLE 2.** Analysis of End Points Without Baseline Measurements

End Point	Mean Value During the 12 Weeks of Treatment*		Least-Square Mean (95% CI) Difference Between Groups	<i>P</i> Value
	Placebo	Montelukast		
Days with daytime asthma symptoms (%)	64	59	−5.57 (−9.91 to −1.23)	.012
Days with β-agonist use (%)	55	49	−6.25 (−10.06 to −2.43)	.001
Patients requiring oral corticosteroid rescue (%)	28	19	—	.008
Patients experiencing ≥1 asthma attack (%)	32	26	—	.107
Days without asthma (%)	28	34	6.87 (2.60 to 11.13)	.002
Physician global evaluation score	1.38	1.11	−0.27 (−0.47 to −0.07)	.007
Caregiver global evaluation score	1.12	0.97	−0.16 (−0.35 to 0.03)	.107
Average global evaluation score	1.27	1.05	−0.23 (−0.41 to −0.04)	.015

CI indicates confidence interval.

\* Global evaluations were performed at the end of the treatment period. All other end points are mean values during treatment.

lukast group, 12 were withdrawn because of protocol deviations, 16 patients stopped treatment because of adverse effects, 8 withdrew consent, 7 were lost to follow-up, and 1 each discontinued because of lack of efficacy and an error by the study center.

A total of 12 and 17 patients in placebo and montelukast groups, respectively, were excluded from 1 or more efficacy analyses because they lacked baseline or treatment period data.

### Results of Treatment as Recorded in the Pediatric Asthma Caregiver Diary

Over 12 weeks of treatment, the percentage of days with daytime asthma symptoms was significantly lower ( $P = .012$ ) and the percentage of days without asthma was significantly higher ( $P = .002$ ) in the montelukast group compared with the placebo group (Table 2). Moreover, the improvements for the montelukast group in overall daytime asthma symptom scores and in individual symptoms scores for cough, wheeze, trouble breathing, and activity limitations (Fig 2) were significantly greater than those for the placebo group (daytime asthma symptoms [ $P = .003$ ], cough [ $P = .003$ ], wheeze [ $P = .042$ ], trouble breathing [ $P = .007$ ], and activity limitation

[ $P < .001$ ]). Furthermore, the percentage of days on which  $\beta$ -agonist was used and percentage of patients requiring oral corticosteroid rescue (Fig 3) were significantly lower ( $P = .001$  and  $P = .008$  for  $\beta$ -agonist use and corticosteroid rescues, respectively) in the montelukast group (Tables 2 and 3). Additionally, the percentage of patients experiencing at least 1 asthma attack was also lower, although not significantly lower ( $P = .107$ ), in the montelukast group (Table 2).

There were 556 patients (189 and 367 in placebo and montelukast groups, respectively) who reported overnight asthma symptoms on 2 or more nights per week during the baseline period. Among these patients, montelukast produced a significant reduction ( $P = .026$ ), compared with placebo, in overnight asthma symptom score during the 12-week treatment period (Table 3).

### Global Assessment of Asthma Control and Asthma-Specific Caregiver Quality of Life

Physician global evaluation scores for change in asthma control after 12 weeks of treatment were significantly better ( $P = .007$ ) for montelukast-treated patients than for placebo-treated patients

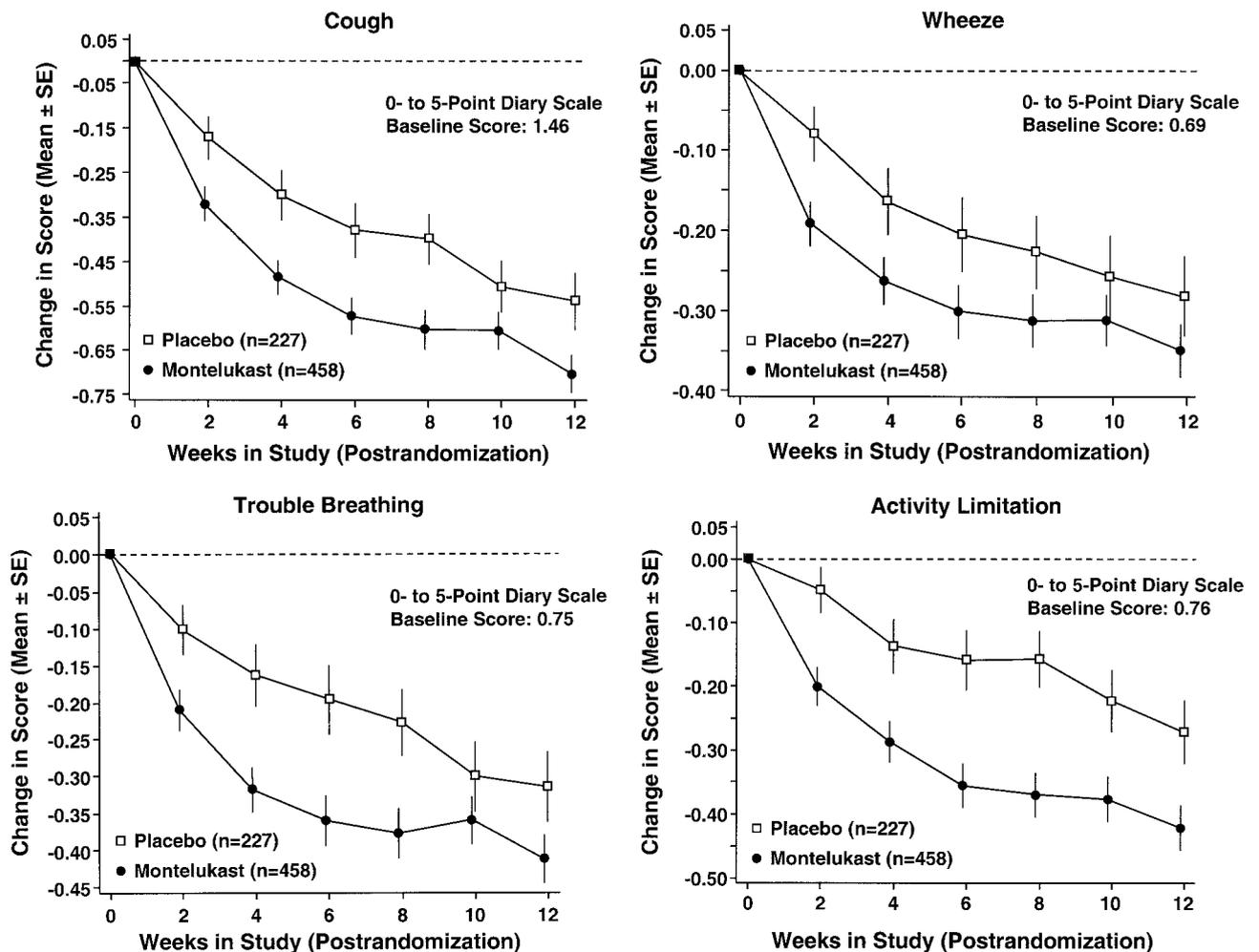
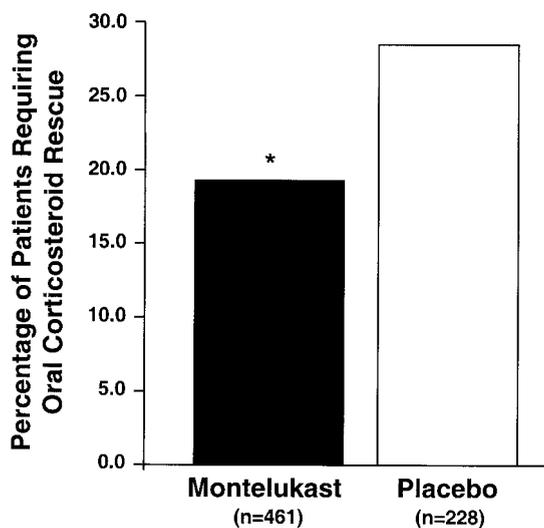


Fig 2. Mean ( $\pm$  standard error) change from baseline in individual daytime asthma symptoms scores during 12 weeks of treatment with montelukast or placebo. Treatment with montelukast (closed circles) was associated with a significant improvement in the severity of cough ( $P = .003$ ), wheeze ( $P = .042$ ), trouble breathing ( $P = .007$ ), and activity limitation ( $P < .001$ ) for the comparison with placebo (open squares).



\*  $P = .008$  compared with placebo

Fig 3. Percentage of patients requiring oral corticosteroid rescue during 12 weeks of treatment with montelukast or placebo. Treatment with montelukast was associated with a significant reduction in the percentage of patients requiring oral corticosteroid rescue ( $P = .008$  for the comparison with placebo).

(Table 2). Caregiver global evaluations favored montelukast but were not significantly different ( $P = .107$ ) for the 2 treatment groups. Similarly, improvements in quality-of-life scores were numerically greater in the montelukast than the placebo group, but there were no significant differences between groups (Table 3).

#### Onset of Action

The onset of action of montelukast was analyzed by evaluating the time-response profile over the first 21 days of therapy for the end point of daytime asthma symptoms (Fig 4). In terms of clinical effectiveness, montelukast had a rapid onset of action (within 1 day of dosing). The difference in average values after the first dose between the montelukast and placebo groups was significant ( $P = .017$ ). The between-group difference remained consistent throughout the 12-week treatment period.

#### Other End Points

The percentages of patients who discontinued therapy because of worsening asthma were 3.1% and 2.4% in the placebo and montelukast groups, respectively; this difference was not significant.

The mean peripheral eosinophil count was higher at baseline in the placebo group ( $580/\mu\text{L}$  vs.  $500/\mu\text{L}$  in the montelukast group). Using an ANCOVA with the baseline score as covariate to account for differences in baseline values, the decrease in eosinophil counts was significantly greater in the montelukast group than in the placebo group ( $P = .034$ ).

Of note, there were no significant treatment interactions by age, sex, race, RAST, stratum, and study center, indicating that the effects of montelukast were consistent across the 2- to 5-year-old age range, across sexes, across races, in those patients with positive and negative RAST results, regardless of con-

comitant use of inhaled/nebulized corticosteroids or cromolyn, and across study centers.

#### Adverse Effects

There were no clinically meaningful differences between groups in the overall frequency of clinical adverse effects. The 3 most commonly reported adverse effects were asthma, fever, and upper respiratory infection (Table 4). There were no notable differences between montelukast and placebo treatment groups in the frequency of any individual adverse effect, with the exception of asthma, which occurred significantly more frequently in the placebo group than the montelukast group (8.0% difference [95% confidence interval, 0.18%–16.36%]).

Twenty-three patients were discontinued from the study because of an adverse effect, 7 (3.1%) in the placebo group and 16 (3.5%) in the montelukast group. In the placebo group, 3 patients were discontinued because of asthma, 2 because of rash, and 1 each because of bipolar disorder and hepatitis A. In the montelukast group, 9 patients were discontinued because of asthma, 3 because of drug “overdose,” and 1 each because of rash, paresthesia, gastroesophageal reflux, and varicella. Four children in each treatment group had drug overdoses after having been inadvertently allowed access to study medication by their caregivers. Three of the 4 children in the montelukast group who had an overdose (of 52–72 mg) experienced clinical adverse effects and were discontinued from the study—1 experienced thirst, 1 thirst and mydriasis, and 1 somnolence. No abnormal laboratory findings were associated with the overdoses, and all children recovered fully from effects of the overdose within 24 hours.

There were no significant differences between treatment groups in the frequency of laboratory adverse effects, with 12 (5.4%) of 224 patients in the placebo group and 16 (3.5%) of 451 patients in the montelukast group experiencing 1 or more laboratory adverse effects. Importantly, there were no significant differences between treatment groups in the frequency of elevated serum transaminase levels. The only patient to discontinue from the study because of a laboratory adverse effect was the aforementioned patient in the placebo group who had an increased alkaline phosphatase value.

#### DISCUSSION

We found that once-daily treatment with 4 mg of montelukast (chewable tablet), as compared with placebo, improved multiple efficacy end points over a 12-week period in children with persistent asthma aged 2 to 5 years. In these young children with asthma, montelukast produced significant improvements, compared with placebo, in daytime and overnight symptom scores, the percentage of days with asthma symptoms, the need for  $\beta$ -agonist therapy or oral corticosteroid rescue, and physician global evaluations. Similarly, in adults and children aged 6 to 14 years, montelukast improves multiple parameters of asthma control.<sup>12,13</sup> Thus, this study confirms and extends the benefit of montelukast in persistent asthma to younger children with asthma.

**TABLE 3.** Changes From Baseline in End Points Averaged Over the 12 Weeks of Treatment

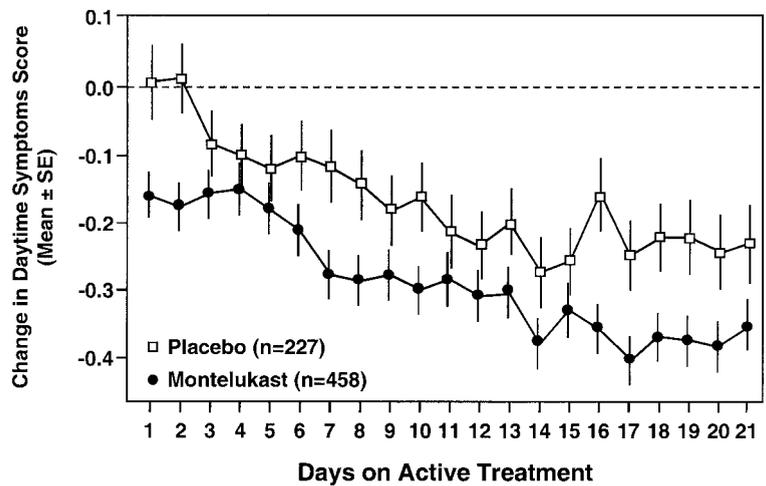
End Point	Mean Baseline Value	Mean Change From Baseline	Least-Square Mean (95% CI) Difference Between Groups	P Value
Daytime asthma symptom score				
Placebo	0.95	-0.26		
Montelukast	0.98	-0.37	-0.12 (-0.20 to -0.04)	.003
Cough symptom score				
Placebo	1.43	-0.37		
Montelukast	1.48	-0.52	-0.16 (-0.27 to -0.06)	.003
Wheeze symptom score				
Placebo	0.69	-0.19		
Montelukast	0.69	-0.27	-0.09 (-0.17 to -0.00)	.042
Trouble breathing symptom score				
Placebo	0.74	-0.21		
Montelukast	0.76	-0.32	-0.12 (-0.20 to -0.03)	.007
Activity limitation symptom score				
Placebo	0.73	-0.17		
Montelukast	0.77	-0.32	-0.16 (-0.25 to -0.08)	<.001
Overnight asthma symptom score*				
Placebo	1.20	-0.37		
Montelukast	1.18	-0.46	-0.11 (-0.21 to -0.01)	.026
Quality-of-life score—activity domain				
Placebo	5.0	0.5		
Montelukast	5.1	0.6	0.07 (-0.16 to 0.31)	.545
Quality-of-life score—emotions domain				
Placebo	5.0	0.4		
Montelukast	5.1	0.5	0.12 (-0.06 to 0.31)	.176
Quality-of-life score—combined domain				
Placebo	5.0	0.5		
Montelukast	5.1	0.6	0.10 (-0.10 to 0.29)	.325
Peripheral blood eosinophil counts ( $10^3/\mu\text{L}$ )†				
Placebo	0.58	-0.07		
Montelukast	0.50	-0.07	-0.04 (-0.09 to -0.00)	.034

CI indicates confidence interval.

\* In the placebo and montelukast groups, 189 and 367 patients, respectively, were included in the analysis of overnight asthma symptom scores.

† Based on an ANCOVA, with baseline value as covariate, because of the imbalance in baseline values between the placebo and montelukast groups.

**Fig 4.** Onset of action of montelukast. The effect of montelukast (closed circles) and placebo (open squares) on daytime asthma symptoms (mean change from baseline) during the first 21 days of treatment with montelukast or placebo. Vertical lines represent standard errors.



In the present study, improvements in asthma control were consistent across age, sex, race, and study center, and whether or not patients had a positive RAST. Notably, montelukast demonstrated a consistent effect regardless of concomitant use of inhaled/nebulized corticosteroid or cromolyn therapy. This has also been the case in adult and other pediatric studies.<sup>12,13</sup> In fact, in a recent study of adults with chronic asthma, montelukast provided additional asthma control to patients benefiting from, but incompletely controlled on, inhaled beclomethasone.<sup>19</sup>

Of note, there are few randomized controlled studies of asthma therapies for preschool children. This may be partly because clinical end points are difficult to measure in this patient population and symptom burden and  $\beta$ -agonist use in children is less than that seen in adults.<sup>17,20-30</sup> Most studies have shown symptom scores of <1.0, leaving little room to observe an improvement (floor effect of measures). Additionally, some of the asthma studies in preschool children that have been published are small and include efficacy end points that have not been vali-

**TABLE 4.** Frequency of Most Common Clinical Adverse Effects\*

Adverse Effect	Placebo (n = 228)	Montelukast (n = 461)
Asthma†	86 (38%)	137 (30%)
Upper respiratory infection	63 (28%)	123 (27%)
Fever	61 (27%)	125 (27%)
Vomiting	45 (20%)	75 (16%)
Pharyngitis	35 (15%)	54 (12%)
Cough	26 (11%)	58 (13%)
Abdominal pain	21 (9%)	51 (11%)
Diarrhea	17 (8%)	45 (10%)

\* Most common adverse effects were those occurring in 8% or more of patients in either treatment group.

† Notable difference between treatment groups (30% vs 38% for montelukast and placebo, respectively, representing an 8% difference with a 95% confidence interval [0.18% to 16.36%]).

dated for use in multicenter trials in this age group. To our knowledge, this large study of montelukast in preschool children is the first multicenter study evaluating the effects of a leukotriene receptor antagonist in children <5 years of age, as well as one of the few clinical studies enrolling preschool children with asthma that used end points validated for this age group.

Although cross-study comparisons are difficult because of differences in study designs, the treatment effect of montelukast in this study seemed to be consistent with those observed in several well-designed studies in children comparing inhaled corticosteroids with placebo.<sup>20–27,29–30</sup> For example, in Childhood Asthma Management Program (CAMP) Study,<sup>26,27</sup> the investigators found mean symptom score changes which were similar (0.44 change for budesonide compared with 0.37 change for placebo, a difference of about 0.07) to those reported in our study. Likewise, “episode-free days,” an end point similar in definition to “days without asthma” used in our study, were comparable (11.3 days per month for budesonide compared with 9.3 days per month for placebo in the CAMP Study and 10.2 days per month for montelukast compared with 8.4 days per month for placebo in our study). Data from 2 clinical trials comparing inhaled corticosteroid treatment with placebo in young children show similar results to those reported in this study.<sup>20,22</sup> In the Bisgaard et al<sup>20</sup> study, the 12th week median change from baseline in percentage of symptom-free days was approximately 29% for fluticasone 100 µg per day and approximately 21% for placebo. A similar analysis of our data shows generally comparable results, 30.6% symptom-free days for montelukast and 18.3% symptom-free days for placebo for weeks 11 and 12 combined.

Similar to the symptom scores, the change in the use of β-agonist in this study is consistent with what has been reported in the literature for studies in young children. The use of β-agonist decreased (from a baseline of 5.6 days per week in both treatment groups) to approximately 3.4 days per week in the montelukast group and to approximately 3.8 days per week in the placebo group. This approximate decline of 2.2 days in montelukast compares with 1.7 days in placebo for a difference of 0.4 days

per week on average, similar to that observed in the Kemp et al<sup>22</sup> study for budesonide 0.25 mg per day compared with placebo (a difference of approximately 0.6 days per week). The Bisgaard et al<sup>20</sup> study reported small (and not significant) changes in days with β-agonist use for fluticasone 100 µg per day (estimated median difference <5.0% from placebo). Similarly, in the CAMP Study,<sup>26,27</sup> the investigators reported a difference between budesonide and placebo of approximately 2 puffs per week of β-agonist use (a decrease of 7.4 budesonide puffs per week decrease and 5.3 placebo puffs per week). When we examine our data by the number of β-agonist treatment episodes per week (puffs, teaspoons/tablets, and/or nebulizations), we find a difference for montelukast from placebo of 2.1 treatment episodes per week ( $P = .003$ ) which is very consistent with the CAMP Study<sup>26,27</sup> results.

Additionally, in 2 pediatric open-label, crossover montelukast/cromolyn preference studies, an overwhelming percentage of parents (87% to 88%) and patients (80% to 82%) were significantly more satisfied with montelukast compared with cromolyn ( $P < .001$ ). Importantly, in these studies, montelukast demonstrated greater effectiveness (fewer discontinuations because of asthma and decreased β-agonist use) compared with inhaled cromolyn.<sup>31,32</sup>

Commonly used objective measures of respiratory function, such as forced expiratory volume in 1 second or peak expiratory flow, are not reliable or reproducible for use in large, multicenter studies in very young children.<sup>33</sup> Additionally, very young children cannot adequately describe their asthma symptoms and, therefore, caregivers may not appreciate the severity of their children’s asthma symptoms. Nonetheless, assessing asthma and its treatment in this age group relies primarily on caregiver reporting of asthma symptoms and impact. The pediatric asthma caregiver diary used in this study was developed from a previously validated pediatric asthma symptom diary for children aged 6 to 14 years, as well as from published unvalidated diaries for parents of preschool children, and was then validated for use by caregivers of children aged 2 to 5 years with asthma.<sup>17</sup> Notably, during the placebo baseline period in this study, caregivers reported that patients had symptoms on 6.1 days per week and used β-agonist on 5.6 days per week, but the actual symptom scores reported at baseline were low (an approximate mean score of 1 on a 0– [no symptoms] to 5– [very severe symptoms] point scale). Hence, it is important to use validated instruments to reliably assess asthma therapies in young children.

The effect of montelukast as measured by caregiver global evaluations and the caregiver quality-of-life questionnaire, however, was not significantly different from that of placebo. Although the caregiver quality-of-life questionnaire had been examined previously in an observational study of parents of children aged 7 to 17 years,<sup>18</sup> the questionnaire’s responsiveness to asthma therapy and the minimum duration of therapy needed to see a response are not known. It is possible that substantial changes in caregiver emotions and activities in caring for preschool

children with asthma may not become evident in a short-term study such as this one. This lack of a statistically significant impact on the caregivers' quality of life is consistent with that reported in another 12-week study of fluticasone.<sup>20</sup>

A 4-mg chewable-tablet dose of montelukast was selected for use in this age group based on results of an open-label pharmacokinetic study enrolling 15 children with asthma aged 2 to 5 years.<sup>34</sup> Because of the limited amount of blood that could be collected from these young patients, a 1-compartment pharmacokinetic model with first-order absorption and elimination was used to estimate the population area under the curve for montelukast.<sup>35</sup> The 4-mg dose yielded a single-dose population pharmacokinetic profile similar to that of the 10-mg film-coated tablet in adults, the optimal dose selected by dose-ranging studies.

Important issues to consider in the treatment of preschool children with asthma are the ease of drug administration and the long-term tolerability of therapy because treatment is typically chronic. Inhaled corticosteroids and inhaled cromolyn are the most commonly prescribed controller therapies; however, very young patients may have difficulty using inhalers, and dose delivery can be variable.<sup>36–38</sup> Moreover, reduced compliance with inhaled therapy for asthma relative to orally administered therapy has been reported.<sup>39</sup> Additionally, inhibition of linear growth (height) in children has been observed with the administration of inhaled corticosteroids.<sup>26,27,40,41</sup> One potential advantage of montelukast is the ease of administering a once-daily chewable tablet. Moreover, no tachyphylaxis or change in the safety profile is evident after up to 140 weeks of montelukast therapy in adults and 80 weeks of montelukast therapy in pediatric patients aged 6 to 14 years.<sup>42,43</sup> However, the long-term profile of montelukast in preschool children with asthma will need to be established in future studies.

In this 12-week study, montelukast was generally well tolerated without clinically important adverse effects. There were few discontinuations secondary to adverse effects, and the frequency of discontinuations was similar in the 2 treatment groups. Moreover, accidental ingestion of montelukast at doses as high as 72 mg was generally well tolerated.

## CONCLUSION

Oral montelukast (4-mg chewable tablet) administered once daily is generally well tolerated without clinically important adverse effects in preschool children. Additionally, montelukast improved multiple exploratory efficacy end points, which is consistent with clinically important improvements in the treatment of asthma. Moreover, the results of this study are consistent with and confirm results seen in studies in adults and older pediatric patients (aged 6–14 years). Overall, the results of this study suggest that montelukast would be a well tolerated and effective therapeutic option in patients aged 2 to 5 years with asthma.

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