
Intermittent or daily montelukast versus placebo for episodic asthma in children

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Background: No standard, optimal treatment exists for severe intermittent (ie, episodic) asthma in children. However, evidence suggests that both daily and episode-driven montelukast are effective for this phenotype.

Objective: To assess the regimen-related efficacy of montelukast in treating pediatric episodic asthma.

Methods: A multicenter, randomized, double-blind, double-dummy, parallel-group, 52-week study was performed in children 6 months to 5 years of age comparing placebo with two regimens of montelukast 4 mg: (1) daily; or (2) episode-driven for 12 days beginning with signs/symptoms consistent with imminent cold or breathing problem. The main outcome measure was the number of asthma episodes (symptoms requiring treatment) culminating in an asthma attack (symptoms requiring physician visit, emergency room visit, corticosteroids, or hospitalization).

Results: Five hundred eighty-nine patients were randomized to daily montelukast, 591 to intermittent montelukast, and 591 to placebo. Compared with placebo, no significant difference was seen between daily montelukast ($P = .510$) or intermittent montelukast ($P = .884$) in the number of asthma episodes culminating in an asthma attack over 1 year. Daily montelukast reduced symptoms over the 12-day treatment period of asthma episodes compared with placebo ($P = .045$). Beta-agonist use was reduced with both daily ($P = .048$) and intermittent montelukast ($P = .028$) compared with placebo. However, because of prespecified rules for multiplicity adjustments (requiring a positive primary endpoint), statistical significance for secondary endpoints cannot be concluded. All treatments were well tolerated.

Conclusions: Montelukast did not reduce the number of asthma episodes culminating in an asthma attack over 1 year in children 6 months to 5 years of age, although numerical improvements occurred in some endpoints.

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INTRODUCTION

Asthma is one of the most common diseases of childhood: one third of children experience a wheezing episode by 3 years of age, and nearly 50% experience a wheezing episode by the age of 6.^{1,2} Despite the high prevalence, asthma

in infants and preschool-age children presents unique difficulties in both diagnosis and management. Foremost, acute breathing difficulties in this age group often represent an entity separate from true asthma. Affected children tend not to display signs of atopy, bronchial responsiveness,³ or other features common to persistent or atopic asthma such as airway remodeling or eosinophilic inflammation.^{4,5} They also tend to have discrete episodes typically triggered by viral upper respiratory infections (ie, not immunoglobulin E-mediated), separated by long asymptomatic periods.³ A variety of terms have been used to describe this intermittent condition, such as “infrequent episodic asthma,” “transient wheeze,” and “viral wheeze.” For the purposes of this study, the phenotype is referred to as “episodic asthma.”

Despite its intermittent course, episodic asthma is associated with significant morbidity: Rates for wheezing-related emergency department visits and hospitalizations are highest in children younger than 5 years⁶ and may be related to the difficulty in managing such patients. Indeed, meta-analyses in pediatric episodic asthma have not shown consistent benefits of medications traditionally effective in persistent asthma, including inhaled corticosteroids.^{7–9} Accordingly, guidelines for episodic asthma recommend as-needed short-acting β -agonists and, if needed, oral corticosteroids for moderate to severe exacerbations.^{2,10,11}

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Three studies have suggested that montelukast is efficacious in managing episodic asthma in children when given either on a daily preventative basis¹² or on an episode-driven basis.^{13,14} However, whether daily or episode-driven intervention is a preferred management option is unknown.

Therefore, the purpose of this study was to evaluate daily montelukast and episode-driven montelukast versus placebo in children with episodic asthma.

METHODS

Patients

Boys and girls age 6 months to 5 years were eligible. Patients were required to have had episodes of asthma symptoms in the past year (2–4 episodes for patients < 2 years old; 3 to 6 episodes for patients $\geq$ 2 years old, including 1 in the past 6 months) lasting approximately 3 days that, at a minimum, required short-acting β -agonist treatment, with asymptomatic periods between episodes. In addition, patients had at least 1 corticosteroid treatment (oral, rectal, inhaled, or parenteral) or hospitalization for asthma in the year before screening. Pertinent exclusion criteria included history of persistent asthma symptoms and asthma controller medication or immunotherapy in the previous 2 weeks.

Conduct of this study was consistent with the standards of the Declaration of Helsinki. The protocol was approved by local institutional review boards or ethics committees, and the parent/guardian of each patient provided written informed consent before participation.

Study Design

This study (Merck Protocol 302) was a 52-week, multicenter, randomized, double-blind, double-dummy, parallel group trial conducted at 111 multinational sites from November 2006 to August 2009, comparing two regimens of montelukast (daily dosing and intermittent, episode-driven dosing) with placebo in patients age 6 months to 5 years with episodic asthma. After a 2-week placebo run-in period, eligible patients were randomized to 1 of 3 treatment arms for 52 weeks: daily montelukast plus intermittent, episode-driven matching placebo; episode-driven montelukast plus daily matching placebo, or daily placebo plus episode-driven placebo, all administered once nightly. Montelukast was administered as 4-mg oral granules to patients 6 to 23 months of age, and as a 4-mg chewable tablet to patients 2 to 5 years of age. Patients who turned 6 years of age during the study were switched to the 5-mg chewable tablet, consistent with approved labeling. Short-acting β -agonists were available to all patients for use every 4 to 6 hours as needed. An action plan for treatment of worsening asthma was provided to parents/guardians. Parents/guardians were contacted by telephone every 2 to 3 weeks during the active treatment period to assess compliance and to inquire about possible adverse experiences (AEs). Medication compliance was assessed by pill count.

Allocation was determined according to a computer-generated schedule. Numbered packaging was used to implement allocation. All study personnel, including investigators, study

coordinators, patients, parents/guardians, monitors, and central laboratory staff, remained blinded to treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

Parents/guardians completed a symptom calendar every evening consisting of 2 questions documenting whether their child had: (1) experienced any respiratory symptoms or (2) taken any episode-driven medication in the previous 24 hours. If the patient had any symptoms, this marked the start (or continuation) of an episode, and episode-driven medication (montelukast or placebo) was started that evening (given in addition to the daily medication) and continued nightly for 12 days. Short-acting β -agonists were administered every 4 to 6 hours as needed for at least 24 hours. Parents/guardians also completed an episode diary documenting the following parameters for the preceding 24 hours: (1) overnight symptoms, measured as the presence of cough (0 = “did not cough at all” to 4 = “coughed almost all night”); (2) daytime symptoms, measured as cough, wheezing, and trouble breathing (each on a scale of 0 = “none” to 5 = “very severe”); (3) activity limitations (0 = “did not interfere” to 5 = “unable to do activities”); (4) medication use and frequency (short-acting β -agonists; inhaled, oral, or rectal corticosteroids); and (5) healthcare resource utilization (HRU), defined as an unscheduled visit to a doctor, urgent care clinic, or emergency department or hospital for breathing problems, or treatment with corticosteroids (oral, rectal, inhaled, or parenteral). The episode diary was completed for at least the 12-day duration of episode-driven medication or until breathing problems resolved.

Efficacy and Safety Endpoints

The primary efficacy measure was the number of asthma episodes culminating in an asthma attack (ie, attacks that occurred within episodes). The beginning of an episode was defined by the start day of episode-driven treatment. The start of an asthma attack was the first day the patient’s symptoms required HRU. Key secondary endpoints included symptoms during the 3 days before an asthma attack (mean of the daily average of the individual symptom scores for wheeze and difficulty breathing), and during the 12-day treatment episode (mean of the daily average of the individual symptom scores for wheeze, difficulty breathing, interference with activity; days after an attack were not included if an attack occurred). Other endpoints included the number of asthma attacks, the number of asthma episodes, the percentage of asthma-free days (defined as a day with no symptoms, no β -agonist use, and no HRU), and the daily average β -agonist use over the 12-day treatment period of asthma episodes. The difference in efficacy between the 2 montelukast regimens was an exploratory endpoint.

Safety was assessed by the incidence of clinical AEs, serious AEs, drug-related AEs, and AEs resulting in discontinuation.

Statistical Methods

The primary hypothesis was that montelukast (daily or intermittent regimens) compared with placebo would decrease the number of asthma episodes culminating in an asthma attack—in other words, attacks that occurred within episodes, irrespective of when in the course of an episode a given attack occurred. Only one asthma attack was counted per episode. The primary efficacy analysis was based on all patients who received at least one dose of study drug. A supportive per-protocol approach excluding patients with important protocol violations was performed for the primary and key secondary endpoints.

The primary analysis was performed using a Poisson regression model with factors for treatment group, age group (<2 years, ≥2 years), geographical region, and an offset for number of days in the study. Prespecified subgroup analyses included sex, race (white, black, Hispanic, other), age group (<2, ≥2 to <3, ≥3 years), number of asthma attacks during the previous year, asthma predictive index (API) status, and geographical region.

To adjust for multiple statistical comparisons, a step-down approach was used in comparing the 2 montelukast regimens with placebo: the daily regimen was tested first, and no significant effect on an endpoint would be claimed for the intermittent regimen if the effect on the endpoint with the daily regimen was not significant. Within a given regimen, the two key secondary endpoints assessing symptom severity would be tested only if a significant difference in the primary endpoint was detected, and was performed using Hochberg's method: significance would be demonstrated if the *P*-values associated with these 2 endpoints were .05 or less or if 1 *P*-value was greater than .05 and the other was .025 or less. All other endpoints were considered to be supportive or exploratory, and multiplicity adjustment was, therefore, not required.

Based on findings after results unblinding, additional post-hoc analyses were carried out in the subset of children 2 years of age or older with at least 1 asthma episode.

The primary variable for safety was the overall incidence of AEs, and included all randomized patients who received at least one dose of study drug. The 95% confidence intervals were determined using the Miettinen and Nurminen method.

Based on the previous studies of montelukast in episodic asthma,^{12,13} a dropout rate of approximately 20% was anticipated. A sample size of 450 evaluable patients per treatment arm provides 90% power ($\alpha = 0.05$) to detect a difference of 23% in episodes leading to asthma attacks, assuming a rate of 2 attacks/year in the placebo group and 1.54 attacks/year in the montelukast groups.

RESULTS

Patients

Patient disposition is shown in Figure 1. Compliance was greater than 98% for all treatment groups. Baseline patient

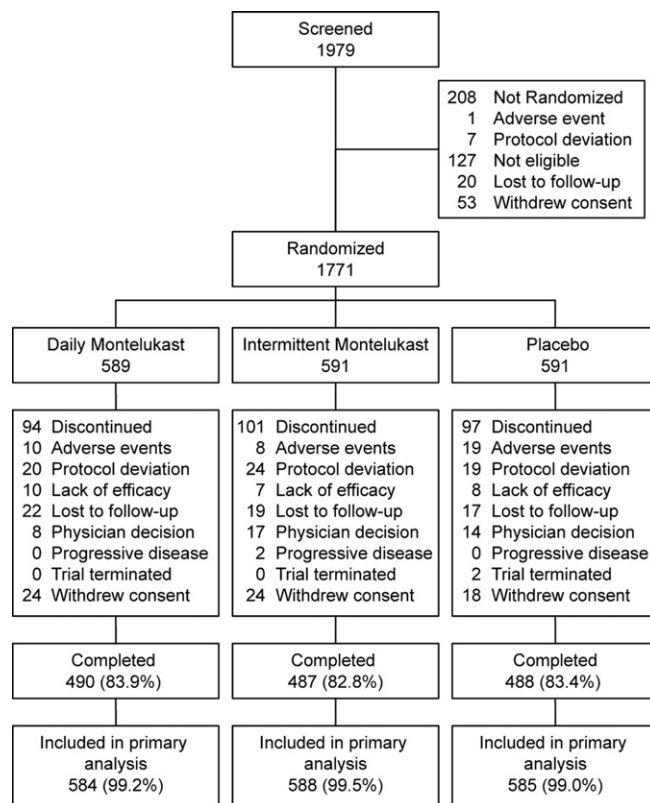


Figure 1. Patient accounting.

characteristics were generally similar across treatment groups (Tables 1 and 2).

Efficacy

Primary Endpoint. No significant difference was seen between either montelukast regimen and placebo for the primary endpoint of the number of asthma episodes culminating in an asthma attack (Table 3). Approximately 75% of patients had at least 1 asthma episode and, as shown in Figure 2, only approximately 50% had at least 1 episode culminating in an attack. The average time between the start of an episode and the start of an attack was 1.5 days, 1.3 days, and 1.6 days, for daily montelukast, intermittent montelukast, and placebo, respectively. The most common component of an attack was treatment with corticosteroids (~71%), followed by unscheduled physician visit (~38%), emergency department visit (~13%), urgent care clinic visit (9%), unscheduled visit to another medical facility (~6%), and hospitalization (3%).

No significant differences were seen in the prespecified subgroup analyses, including API status. However, some subgroups showed numerical trends in which daily montelukast appeared to be either more effective than placebo (patients aged 18–35 months: adjusted annual rate 0.86 vs 1.22) or less effective than placebo (patients aged 6–17 months: 1.38 vs 0.75; patients 2 years of age or younger with more than 4 episodes: 1.31 vs 0.74).

Following these trends seen based on patient age, post-hoc analyses of the primary endpoint were carried out in a subgroup of children age 2 years of age or older who had at least one asthma episode (Table 4). No significant differences were seen between montelukast (either daily or intermittent) and placebo in this subgroup, although the daily montelukast group had a slightly greater reduction in primary events

Table 1. Patient Characteristics

	Daily montelukast (N = 584)	Intermittent montelukast (N = 588)	Placebo (N = 585)
Gender, n (%)			
Male	346 (59.2)	363 (61.7)	349 (59.7)
Female	238 (40.8)	225 (38.3)	236 (40.3)
Age			
Months, mean (SD)	38.9 (16.3)	39.5 (16.5)	39.2 (16.4)
<2 years, n (%)	91 (15.6)	96 (16.3)	101 (17.3)
Race, n (%)			
American Indian or Alaska Native	31 (5.3)	27 (4.6)	35 (6.0)
Asian	15 (2.6)	13 (2.2)	22 (3.8)
Black or African American	15 (2.6)	17 (2.9)	13 (2.2)
Multiracial	84 (14.4)	83 (14.1)	90 (15.4)
Native Hawaiian or other Pacific Islander	1 (0.2)	0 (0.0)	0 (0.0)
White	438 (75.0)	448 (76.2)	425 (72.6)
Ethnicity, n (%)			
Hispanic or Latino	378 (64.7)	369 (62.8)	373 (63.8)
Not Hispanic or Latino	206 (35.3)	219 (37.2)	212 (36.2)
Geographical region, n (%)			
Europe and Middle East	95 (16.3)	99 (16.8)	88 (15.0)
North and Central America	224 (38.4)	223 (37.9)	271 (46.3)
South America	214 (36.6)	210 (35.7)	163 (27.9)
Other ^a	51 (8.7)	56 (9.5)	63 (10.8)
Allergic rhinitis, n (%)	308 (52.7)	284 (48.3)	262 (44.8)
Atopic dermatitis, n (%)	175 (30.0)	158 (26.9)	160 (27.4)
API positive, n (%)^b	312 (53.4)	316 (53.7)	331 (56.6)
Previous inhaled corticosteroid use, n (%)	291 (49.9)	305 (51.9)	259 (44.3)
Previous systemic corticosteroid use, n (%)	434 (74.3)	430 (73.3)	443 (75.9)

Abbreviations: API, asthma predictive index; SD, standard deviation.

^a Other geographical regions include Australia, Singapore, and South Africa;

^b API status was defined as positive if any of the following criteria were met: history of atopic dermatitis, at least one positive skin testing, or parent history of asthma.

Table 2. Baseline Measures of Episodic Asthma Reported in the Previous Year

	Daily montelukast (N = 584)	Intermittent montelukast (N = 588)	Placebo (N = 585)
Episodes of breathing problems	4.0 (1.0)	4.0 (1.1)	3.9 (1.0)
Missed days at school, daycare, and scheduled activities	14.7 (17.2)	14.9 (19.8)	16.2 (26.3)
Healthcare resource utilization			
Courses of inhaled corticosteroids	1.0 (1.4)	1.1 (1.5)	1.0 (1.5)
Courses of oral/rectal corticosteroids	1.4 (1.3)	1.4 (1.3)	1.4 (1.3)
Unscheduled visits to health care provider for breathing problems	3.6 (2.5)	3.6 (2.7)	3.5 (2.5)
Emergency room visits for breathing problems without admission	1.1 (1.6)	1.1 (1.4)	1.1 (1.6)
Hospital admissions for breathing problems	0.3 (0.7)	0.4 (0.8)	0.3 (0.6)

All values are mean (standard deviation).

compared with placebo than in the main analysis (8.4% vs 5.3% reduction). A categorical analysis of this post-hoc subgroup showed that numerically fewer patients in the daily montelukast group had an episode culminating in attack than those in the placebo group (59.3% vs 66.6%; $P = .041$) (Fig 3).

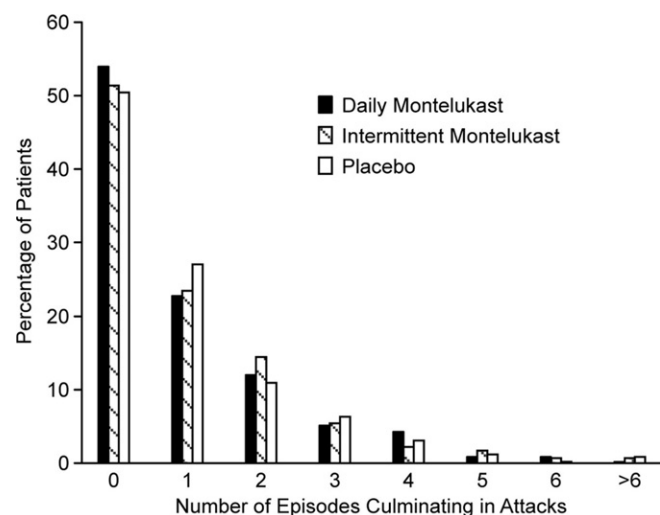


Figure 2. Number of asthma episodes culminating in asthma attacks.

Table 3. Primary and Key Secondary Results

Treatment	N	Adjusted Mean	Comparison with placebo	P-value
Number of asthma episodes culminating in asthma attack (primary endpoint)				
		Adjusted annual rate (95% CI)	Rate reduction (95% CI)	P-value
Daily Montelukast	584	0.99 (0.86, 1.14)	5.3% (−11.4, 19.6)	.510
Intermittent montelukast	588	1.06 (0.92, 1.22)	−1.2% (−19.2, 14.0)	.884
Placebo	585	1.05 (0.92, 1.20)		
Symptoms during the 3 days prior to start of an asthma attack (daily average of wheeze and difficulty breathing score)				
		LS mean (95% CI)	LS mean difference (95% CI)	P-value
Daily montelukast	138	1.69 (1.49, 1.88)	−0.19 (−0.46, 0.09)	.176
Intermittent montelukast	162	1.70 (1.52, 1.89)	−0.17 (−0.44, 0.09)	.202
Placebo	152	1.88 (1.69, 2.07)		
Symptoms during the 12-day treatment episode (daily average of wheeze, difficulty breathing, daytime cough, and interference with daily activity score)				
		LS mean (95% CI)	LS mean difference (95% CI)	P-value
Daily montelukast	365	1.08 (1.00, 1.16)	−0.12 (−0.24, 0.00)	.045
Intermittent montelukast	387	1.09 (1.01, 1.17)	−0.11 (−0.23, 0.00)	.061
Placebo	368	1.20 (1.12, 1.28)		
Number of asthma attacks				
		Adjusted rate (95% CI)	Rate reduction (95% CI)	P-value
Daily montelukast	584	1.17 (1.02, 1.34)	3.3% (−13.1, 17.3)	.676
Intermittent montelukast	588	1.23 (1.08, 1.40)	−2.0% (−19.2, 12.7)	.802
Placebo	585	1.21 (1.07, 1.37)		
Number of asthma episodes				
		Adjusted rate (95% CI)	Rate reduction (95% CI)	P-value
Daily montelukast	584	2.26 (2.06, 2.47)	5.6% (−5.2, 15.3)	.295
Intermittent montelukast	588	2.48 (2.26, 2.72)	−3.6% (−15.4, 7.0)	.521
Placebo	585	2.39 (2.19, 2.61)		
Percentage of asthma-free days				
		LS mean (95% CI)	LS mean difference (95% CI)	P-value
Daily montelukast	584	92.8 (91.9, 93.6)	1.06 (−0.10, 2.23)	.074
Intermittent montelukast	588	91.4 (90.6, 92.3)	−0.27 (−1.43, 0.90)	.654
Placebo	585	91.7 (90.9, 92.5)		
β-agonist use (times per day in patients with an asthma episode)				
		LS mean (95% CI)	LS mean difference (95% CI)	P-value
Daily montelukast	365	2.14 (1.94, 2.34)	−0.29 (−0.57, 0.00)	.048
Intermittent montelukast	387	2.11 (1.92, 2.31)	−0.31 (−0.59, −0.03)	.028
Placebo	368	2.42 (2.22, 2.62)		

Abbreviations: CI, confidence interval; LS, least squares; N, Number of patients in the analysis; SE, standard error.

Table 4. *Post-Hoc* Analysis of Primary and Key Secondary Endpoints (Patients Age ≥ 2 Years with ≥ 1 Asthma Episode)

Treatment	N	Adjusted mean	Comparison with placebo	P-value
Number of asthma episodes culminating in attacks				
		Adjusted rate (95% CI)	Rate reduction (95% CI)	P-value
Daily montelukast	376	1.28 (1.13, 1.45)	8.4% (−8.1, 22.4)	.297
Intermittent montelukast	385	1.37 (1.21, 1.56)	1.7% (−16.1, 16.7)	.844
Placebo	365	1.40 (1.24, 1.58)		
Symptoms during the 3 days prior to start of an asthma attack (daily average of wheeze and difficulty breathing score)				
		LS mean (95% CI)	LS mean difference (95% CI)	P-value
Daily montelukast	110	1.64 (1.42, 1.86)	−0.18 (−0.48, 0.12)	.233
Intermittent montelukast	136	1.67 (1.47, 1.87)	−0.15 (−0.44, 0.14)	.318
Placebo	130	1.82 (1.62, 2.03)		
Symptoms during the 12-day treatment episode (daily average of wheeze, difficulty breathing, daytime cough, and interference with daily activity score)				
		LS mean (95% CI)	LS mean difference (95% CI)	P-value
Daily montelukast	309	1.01 (0.93, 1.10)	−0.15 (−0.27, −0.03)	.017
Intermittent montelukast	334	1.04 (0.96, 1.13)	−0.12 (−0.25, 0.00)	.046
Placebo	313	1.16 (1.08, 1.25)		

Abbreviations: CI, confidence interval; LS, least squares; N, number of patients in the analysis; SE, standard error.

Secondary and Exploratory Endpoints. Secondary efficacy endpoints are summarized in Table 3. Over the 12-day treatment episode, daily montelukast reduced symptoms compared with placebo ($P = .045$), and β -agonist use was reduced with both daily ($P = .048$) and intermittent montelukast ($P = .028$) compared with placebo. However, because statistical adjustments for multiple comparisons re-

quired a positive primary endpoint, statistical significance cannot be concluded for these secondary endpoints. No significant difference was seen between the two montelukast regimens in the primary efficacy variable.

Notable differences were seen based on age group, with generally better outcomes for patients 2 years of age or older in symptoms during the 3 days before the start of attack ($P = .015$) and symptoms during the 12-day episode treatment period ($P < .001$). However, analyses to support a treatment-by-age interaction did not reach significance.

Post-hoc analyses in children 2 years of age or older with at least one episode showed improvements with both daily ($P = .017$) and intermittent ($P = .046$) montelukast over placebo for symptoms over the 12-day treatment episode.

Safety

No clinically meaningful differences were seen in AEs between montelukast and placebo, and few patients discontinued because of AEs (Table 5). Three serious AEs were considered by the investigator to be drug related: pneumonia and asthma in a patient receiving placebo, and somnolence associated with overdose in a patient receiving daily montelukast. The most common AEs (regardless of treatment group) were asthma, upper respiratory infections, nasopharyngitis, cough, and fever. No meaningful differences were seen between daily montelukast, intermittent montelukast, or placebo in these AEs, or in the rates of nervous system

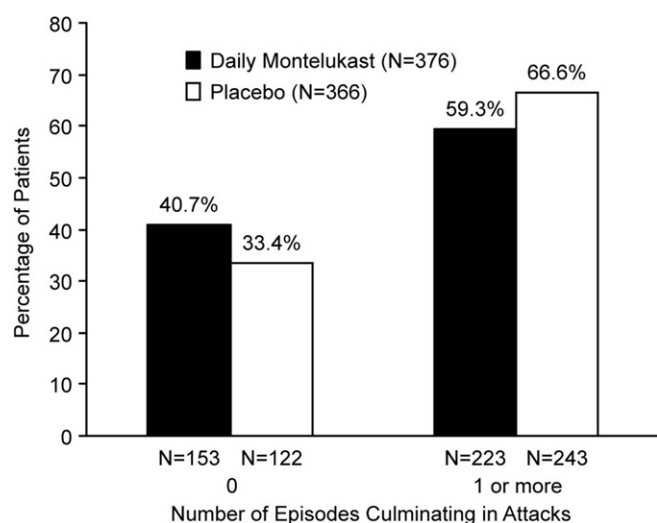


Figure 3. Number of asthma episodes culminating in asthma attacks; post-hoc analysis of patients ≥ 2 years. $P = .041$ for daily montelukast vs placebo (χ^2 test).

Table 5. Adverse Experiences

	Daily montelukast N = 584	Intermittent montelukast N = 588	Placebo N = 585
Clinical AE (%)	510 (87.3)	533 (90.6)	516 (88.2)
Drug-related AE ^a (%)	3 (0.5)	6 (1.0)	5 (0.9)
Serious AE (%)	28 (4.8)	41 (7.0)	33 (5.6)
Discontinuation because of AE (%)	10 (1.7)	8 (1.4)	18 (3.1)
Asthma	336 (57.5)	342 (58.2)	326 (55.7)
Nasopharyngitis	110 (18.8)	110 (18.7)	81 (13.8)
Cough	91 (15.6)	101 (17.2)	93 (15.9)
Fever	94 (16.1)	87 (14.8)	80 (13.7)
Upper respiratory infection	83 (14.2)	78 (13.3)	82 (14.0)
Pharyngitis	59 (10.1)	64 (10.9)	67 (11.5)

^a Determined by the investigator to be possibly, probably, or definitely drug-related.

disorders (3.8%, 2.7%, 2.2%, respectively) or psychiatric disorders (1.5%, 1.4%, 1.5%).

DISCUSSION

The efficacy of an episode-driven treatment strategy can be assessed only in terms of effects seen once an episode starts. Although the primary endpoint of the current study was chosen because it could be applied fairly to both treatment regimens, the study design requires (or presumes) that intermittent treatment will be initiated promptly on the observation of relevant signs/symptoms, that reporting of symptom patterns will be thorough and accurate, and that HRU (including corticosteroid use) is consistent across participating regions. Ultimately, in the current study, neither daily montelukast nor episode-driven montelukast was significantly better than placebo for the primary endpoint of the number of asthma episodes culminating in attacks. Both montelukast regimens, however, reduced β -agonist use compared with placebo, and daily montelukast also reduced symptoms over the 12-day treatment episode. Although these latter results cannot be considered statistically significant because of the prespecified adjustments for multiple comparisons, they are nonetheless consistent with findings of previous studies of montelukast in episodic wheezing.

Three previous year-long studies support the efficacy of montelukast in children 2 or more years with episodic wheezing. In the Preventing Virus-Induced Asthma (PREVIA) study, which enrolled 549 children age 2 to 5 years with a history of intermittent asthma symptoms resulting from an upper respiratory infection,¹² daily montelukast was significantly better than placebo for the primary endpoint of asthma exacerbations. Montelukast was also associated with significantly longer time to first exacerbation and reduced overall rate of inhaled corticosteroid use.

In the PRE-EMPT study, which enrolled 220 children age 2 to 14 years with intermittent asthma, episode-driven mon-

telukast was significantly more effective than placebo for the primary endpoint of unscheduled HRU for asthma in children 2 to 14 years of age.¹³ Montelukast was also associated with significantly better symptom scores and missed school or work.

In the Acute Intervention Management Strategies (AIMS) trial,¹⁴ neither episode-driven montelukast nor budesonide inhalation suspension was significantly better than placebo when added to albuterol for the primary endpoint of episode-free days in 238 children 12 to 59 months with wheezing associated with an upper respiratory tract infection. However, both budesonide and montelukast significantly improved symptom and activity scores. Interestingly, the investigators found that children with positive API scores showed greater benefit from study medication than did those with negative API scores.

We found several trends suggesting better outcomes in children aged 2 or more years compared with those younger than 2 years. Episodic wheezing in infants and preschool-age children tends to be associated with a respiratory infection rather than an immunoglobulin E-mediated process. Early intervention in episodic wheezing does not affect progression to persistent wheezing,^{15,16} suggesting that pediatric episodic asthma and wheezing/asthma later in life may be distinct disease entities. These observations may account for the limited efficacy of ICS,⁷ anticholinergic drugs,⁸ and oral corticosteroids (initiated by parents)⁹ in episodic wheezing, and of montelukast in post-respiratory syncytial virus bronchiolitis,¹⁶ despite the established efficacy of these medications in persistent (and likely atopic) asthma. Thus, established asthma therapies may not be consistently effective in heterogeneous populations comprising patients that will go on to have persistent or atopic asthma as well as those who will not. An additional consideration for the variable effect of asthma medications in episodic wheezing is that efficacy may be difficult to demonstrate in an intermittent disease compared with a more chronic, predictable disease.

Several observations from the current study give our results perspective in the context of the results from PREVIA, PRE-EMPT, and AIMS. Perhaps most notable is the mild degree of disease in our study population. Symptom scores were quite low (1.08–1.88 on a 0–5 scale). Thus, it may not be surprising that only 50% of episodes culminated in (ie, included) attacks. Furthermore, the observed rate of asthma episodes culminating in attacks was substantially lower than expected for the placebo group (1.0/year was only half the rate expected), and 32% lower than expected for daily montelukast; the expected rates were derived from the PRE-EMPT results and served as the basis for our sample size calculations. With such mild disease and low event rates, demonstrating a treatment effect would inevitably be considerably difficult with the current sample size.

The mild disease burden and results in our study may be related to several factors. First, the inclusion of children younger than 2 years may have played a role in the outcomes because of the aforementioned heterogeneous population and

cause of wheezing, and limited efficacy of traditional asthma medications in this age group. Both PREVIA and PRE-EMPT had statistically significant primary outcomes, and both excluded children younger than 2 years. Conversely, AIMS, which had results somewhat similar to ours (ie, impact on symptoms but not episodes), enrolled children as young as 12 months.

Second, differences were also seen in other patient characteristics among the four studies. For instance, approximately 15% of patients in PREVIA¹² had symptoms consistent with persistent asthma rather than intermittent asthma, and might be more likely to respond to intervention. In PRE-EMPT, 64% of patients in the montelukast group and 49% in the placebo group had atopic dermatitis,¹³ compared with only approximately 28% of patients in our study. Possibly, patients in PRE-EMPT were more likely to have atopic asthma and thus were more likely to show a response to treatment. Conversely, only approximately 35% of patients in AIMS had eczema, and 60% were API positive, which is more similar to our population (~55% API positive), and consistent with the more similar study outcomes.

Third, although the entry criteria for the 3 previous studies and our study were generally similar with respect to previous symptoms, children in our study could have diagnoses based on parent/guardian verbal report, whereas children in PREVIA, PRE-EMPT, and AIMS had at least 1 healthcare provider–diagnosed episode of intermittent asthma. Diagnosis in this age group can be difficult, even by physicians,² because of the need to rely on patient or caregiver history, lack of agreement of terms used to describe symptoms, and variability of presentation. Therefore, using a caregiver-confirmed history of episodes may have been an inherent limitation in our study.

Finally, the short period (average ~1.4 days) between the start of an episode and the start of an attack in this study—reflecting, by definition, how caregivers chose to interpret signs and symptoms—may limit the ability of an episode-driven medication to reduce symptoms quickly enough to prevent an attack.

Montelukast was generally well tolerated and similar to placebo with respect to AEs. Most AEs were related to asthma or respiratory tract infections, which is to be expected given the patient population, and our findings are similar to those in the PRE-EMPT study.¹³

In conclusion, neither daily nor intermittent montelukast reduced the number of asthma episodes culminating in attacks in children with episodic wheezing, although both regimens had some positive effects on symptoms. These results, in the context of the variable results of similar studies with other controller medications that have well-established efficacy in persistent asthma, underscore the difficulty in managing episodic wheeze in preschool-aged children and the need to further study possible interventions to decrease the significant morbidity associated with this condition.

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