

The Back to School asthma study: the effect of montelukast on asthma burden when initiated prophylactically at the start of the school year

Kevin Weiss, MD*; James Gern, MD†; Neil Johnston, MSc‡; Malcolm Sears, MB, ChB§; Craig Jones, MD||; Gang Jia¶; Molly Watkins#; Steven Smugar**; Jonathan Edelman#; and Evalyn Grant#

Background: Pediatric asthma hospitalizations peak in early autumn.

Objective: To determine the effectiveness of montelukast therapy in reducing the asthma burden in children when initiated prophylactically on school return.

Methods: This was a randomized, multicenter, double-blind, placebo-controlled study of children with asthma aged 6 to 14 years. No minimum asthma symptoms were required, and patients could continue inhaled corticosteroid (ICS) use. Montelukast, 5 mg, chewable tablet (n = 580) or matching placebo (n = 582) was taken the night before the first day of school and nightly thereafter for 8 weeks. The primary end point was the percentage of days with worsening asthma, defined by one of the following: (1) increased β -agonist use, (2) increased daytime symptoms, (3) awake "all night," (4) oral corticosteroid rescue or increased ICS use for worsening asthma, or (5) unanticipated health care utilization.

Results: The reduction in the percentage of days with worsening asthma with montelukast use versus placebo use was not significant (24.3% vs 27.2%, $P = .07$). Prespecified subgroup analyses demonstrated nonsignificant trends favoring montelukast therapy in boys and older children but no effect by baseline ICS use or history of cold symptoms. Post hoc analysis showed a nonsignificant trend favoring montelukast therapy in reducing worsening asthma days for children commencing school after August 15 compared with earlier commencement.

Conclusions: Montelukast use was not significantly more effective than was placebo use in reducing the percentage of days with worsening asthma when initiated at the start of the school year. The effect of montelukast treatment on the fall peak in asthma burden may depend on sex, age, and the date of school return.

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INTRODUCTION

An annual peak in asthma exacerbations occurs each fall when children return to school. This seasonal morbidity,

which has been observed in all countries studied, leads to tens of thousands of hospitalizations and emergency department visits and disrupts the quality of life for families who have children with asthma.¹⁻⁶

The underlying mechanisms for this autumnal asthma morbidity epidemic are thought to include some combination of infectious, allergic, environmental, and climatic stimuli.^{7,8} Regardless of the underlying mechanism, the start of school is precisely synchronized with the peak of this epidemiologic

Affiliations: * Institute for Healthcare Studies and Department of Medicine, Northwestern Feinberg School of Medicine, Chicago, Illinois; † Departments of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; ‡ Department of Medicine, McMaster University, Hamilton, Canada; § Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Canada; || Division of Allergy & Immunology, Department of Pediatrics, Keck School of Medicine at University of Southern California, Los Angeles, California; ¶ Biostatistics and Research Decision Sciences, Merck Research Laboratories, Rahway, New Jersey; # Clinical Research, Merck Research Laboratories, Rahway, New Jersey; ** Medical Communications, Merck Research Laboratories, Rahway, New Jersey.

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by AstraZeneca and McMaster University. Dr Jones was on the scientific advisory committee for this study and has done consulting and advisory work for Merck and Genentech. Drs Jia, Smugar, Edelman, and Grant and Ms Watkins are employees of Merck & Co Inc and may own stock or have stock options in the company.

Contributions: All the authors contributed to the conception and design of the study. Dr Jia was responsible for data generation and analysis. All the authors were involved in the interpretation of the data and in the preparation or critical revision of the manuscript, and all approved the final version.

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phenomenon, and, thus, the related morbidity may potentially be controllable.^{5,9–12}

Although ultimately it will be important to fully understand the complex environmental and biological interactions that underlie the seasonal trend, there is a clear clinical need to address this major public health problem. Until the causes of these events are better understood, the only available strategy is a better approach to disease management.

The recently updated national asthma guidelines¹³ recognize this public health problem and suggest that management of this seasonal spike is by close individual monitoring and by tailoring therapy to severity. Owing to a lack of evidence, national guidelines have not as yet identified effective secondary prevention strategies for this autumn epidemic. Therefore, the purpose of this study was to conduct a large, multisite, randomized trial to examine the simple controller-based secondary prevention strategy of adding montelukast to usual therapy in children with asthma specifically aimed at reducing asthma morbidity associated with the start of school. This strategy had previously shown benefit in a smaller single-site study in Canada.¹⁴

METHODS

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted between June 28, 2006, and November 20, 2006. The protocol was approved by local institutional review boards or ethical review committees, and written informed consent was obtained from all the patients and parents or legal guardians before enrollment.

Study Participants

Patients were recruited from 165 allergy and clinical pediatric practices in 39 states in the United States and 3 provinces in Canada. Participants aged 6 to 14 years with a history of chronic asthma for at least 1 year requiring treatment with any asthma medication within 6 months before screening were eligible. Patients were required to have at least 1 asthma exacerbation associated with a cold in the previous year and a change in environment during August or September that was different than their typical school/educational environment (eg, summer camp).

The exclusion criteria included a prebronchodilator forced expiratory volume in 1 second less than 60% of predicted at screening; hospitalization for asthma within 4 weeks before randomization or more than 3 times in the previous year; moving to or vacationing in a different geographic area for more than 7 days after the first day of school; oral, intravenous, intramuscular, or intra-articular corticosteroid use within 4 weeks of randomization; and long-acting β -agonist use or leukotriene receptor antagonist use within 10 days of randomization. Inhaled corticosteroid (ICS) use was permitted. All dose changes were documented and recorded.

Study Design

During a screening period (2–12 weeks), baseline information, including vital signs, physical examination findings,

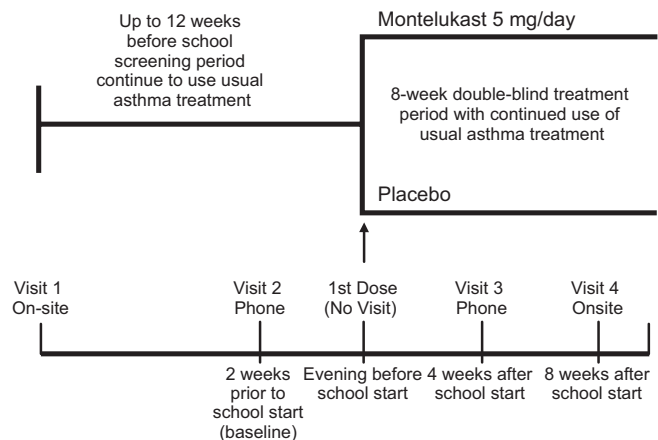


Figure 1. Study design.

laboratory test results, and spirometry (including reversibility) results, was obtained; skin testing was performed; and participant skill in using a validated electronic diary¹⁵ to monitor outcomes was reviewed (Fig 1). Eligible patients were allocated according to a computer-generated, randomized allocation schedule generated by the study statistician and were randomized to receive either montelukast, 5 mg, chewable tablets or matching placebo starting the night before the first day of school and nightly thereafter for 8 weeks. Numbered containers were used to implement allocation. Open-label albuterol was provided, and patients were given an action plan for worsening asthma. Participants were contacted via telephone at 4 weeks to review experiences and unused medications and to dispense additional inhaled β -agonists if needed. A final study visit was conducted at 8 weeks to review experiences, vital signs, and a global assessment of asthma by parent/guardian and investigator. Follow-up telephone contact was made 14 days after the 8-week visit (or discontinuation) to make a final assessment for adverse experiences (AEs).

All the study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel remained blinded to treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

Efficacy and Safety End Points

The primary efficacy end point was the percentage of days with worsening asthma,¹⁶ defined as any 1 of the following events: (1) increased β -agonist use greater than 70% from baseline and a minimum increase of 2 puffs, (2) an increased daytime symptoms score greater than 50% from baseline, (3) awake “all night,” (4) increased ICS use of at least 100% from baseline or oral corticosteroid rescue for worsening asthma, or (5) unanticipated visits to the physician, emergency department, or hospital for asthma. The hypothesis was that montelukast therapy would reduce the percentage of days

with worsening asthma during an 8-week period of treatment compared with placebo use.

Key secondary efficacy end points were the individual components of the primary composite end point, described previously herein, and included β -agonist use greater than 70% from baseline and a minimum increase of 2 puffs, an increased daytime asthma symptoms score greater than 50% from baseline, and unanticipated health care utilization for asthma. Other outcomes were also components of the composite measure and included ICS use of at least a 100% increase from baseline or oral corticosteroid use for worsening asthma and the percentage of days with all-night awakening. Safety variables included the occurrence of any AE, any serious AE, or any drug-related AE and discontinuation due to AEs.

Statistical Analysis

The primary efficacy analysis was based on the full analysis set population, which included all patients who received at least 1 dose of study medication and had a valid measurement of the percentage of days with worsening asthma during the study period, derived from at least 7 days of diary data. Missing data were not imputed. Rules for handling missing data are detailed in the Appendix.

The primary efficacy end point was analyzed using an analysis of variance (ANOVA) model that included factors for treatment, school start period (on or before August 15, August 16 to September 4, after September 4), investigator site type (generalist, specialist, research center), ICS use at entry, age group (6-9, 10-14 years), and sex. The same ANOVA model was used to analyze β -agonist use, daytime asthma symptom score, all-night awakening due to asthma, increased ICS use, hours lost from school per week, and hours lost from work per week for the parent or guardian. The end points of health care utilization and oral corticosteroid use were analyzed using logistic regression models with the same factors as included in the ANOVA model.

Prespecified subgroup analyses of the primary and secondary end points included analysis by age group (6-9, 10-14 years), sex, ICS use at entry, and the presence of cold symptoms. Additional post hoc subgroup analyses were performed on the primary end point for age plus sex, week of treatment, and school start date as defined in the ANOVA model.

Because there is only one primary comparison, no multiplicity adjustment was needed for the primary hypothesis. Treatment comparisons for key secondary variables were performed only if the comparison of the primary efficacy variable was significant. A Hochberg stepwise testing procedure was used to analyze the 3 key secondary variables.

Assuming a treatment difference of 5% and a standard deviation of 24%, 495 evaluable patients in each treatment group provide 90% power (2-sided $\alpha = .05$) to demonstrate the superiority of montelukast use compared with placebo use in reducing the percentage of days with worsening asthma.

All randomized patients who received at least 1 dose of study drug were included in the safety analysis and are

summarized by actual treatment received. The AEs that occurred after the first administration of the double-blind study drug and before 14 days after the last dose was administered were compared by treatment groups using the Wilson score method to obtain confidence intervals for differences in AE occurrence rates. The Fisher exact test was used to compare overall AEs, drug-related AEs, serious AEs, serious drug-related AEs, and discontinuations due to AEs.

RESULTS

Patients

There were 1,162 patients randomized, 580 to montelukast, 5 mg, and 582 to placebo (Fig. 2). Baseline patient demographics were similar for both treatment groups (Table 1). Baseline asthma-related measurements were similar between groups, and most patients' asthma was fairly well controlled.

Efficacy

For the primary end point of the percentage of days with worsening asthma, the effect of montelukast over placebo was not significant (24.3% vs 27.2%; least squares means difference [95% confidence interval], -3.0 [-6.21 to 0.29]; $P = .07$). Results of the per-protocol analysis were similar.

Prespecified subgroup analyses are shown in Figure 3. Compared with placebo, the percentage of days with worsening asthma with montelukast was lower in male patients (23.7% vs 28.9% placebo) than in female patients (25.3%

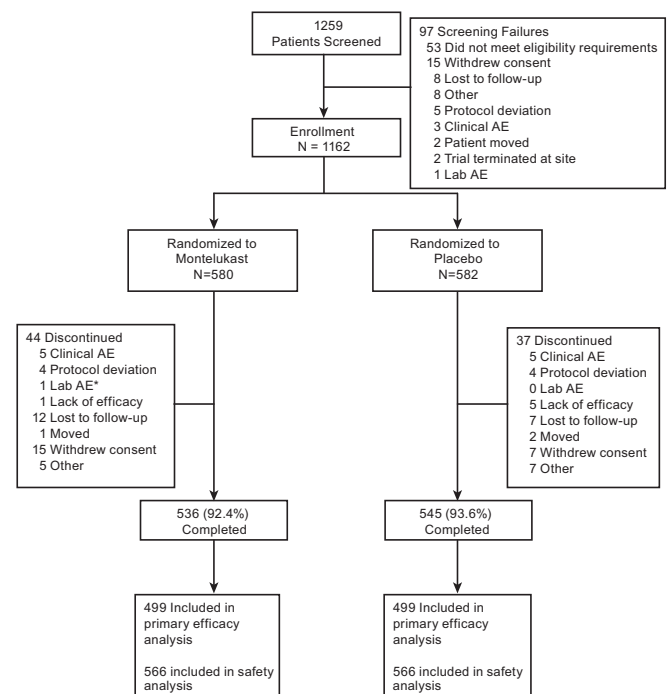


Figure 2. Patient flow through the study. *Occurred after randomization but before administration of the first study drug dose. AE indicates adverse experience.

Table 1. Baseline Patient Characteristics

	Montelukast, 5 mg, group (n = 580) ^a	Placebo group (n = 582)
Sex, No. (%)		
Female	225 (38.8)	236 (40.5)
Male	355 (61.2)	346 (59.5)
Age, mean (SD), y	9.9 (2.4)	9.9 (2.5)
Age group, No. (%)		
6-9 y	272 (46.9)	258 (44.3)
10-14 y	304 (52.4)	320 (55.0)
>14 y	4 (0.7)	4 (0.7)
Race, No. (%)		
Asian	13 (2.2)	14 (2.4)
Black	79 (13.6)	82 (14.1)
Hispanic	41 (7.1)	58 (10.0)
Native American	1 (0.2)	4 (0.7)
White	431 (74.3)	415 (71.3)
Other	15 (2.6)	9 (1.5)
FEV ₁ , mean (SD), L (% predicted)	89.8 (14.5)	90.1 (15.1)
Asthma symptoms during the past month, No. (%)		
None	147 (25.4)	156 (26.8)
≤2×/wk	298 (51.5)	284 (48.8)
>2×/wk	121 (20.9)	120 (20.6)
Every day	11 (1.9)	17 (2.9)
Continuously	2 (0.3)	5 (0.9)
Daytime asthma symptom score, mean (SD)	1.4 (1.9)	1.3 (1.8)
Nighttime asthma symptom score, mean (SD)	1.1 (0.3)	1.1 (0.3)
β-agonist use, mean (SD), puffs/d	0.5 (0.94)	0.6 (1.1)
Inhaled corticosteroid use in the past year, No. (%)	314 (54.1)	283 (48.7)
No. of days inhaled corticosteroid used in 2 wk, No. (%)		
0	136 (23.4)	115 (19.8)
1-4	21 (3.6)	16 (2.8)
5-7	4 (0.7)	8 (1.4)
8-14	153 (26.4)	144 (24.8)
Oral corticosteroid use in the past year, No. (%)	155 (26.7)	172 (29.6)
Unscheduled visits to health care provider due to asthma in the past year, No. (%)	243 (41.9)	237 (40.7)
Emergency department visit or hospitalization due to asthma in the past year, No. (%)	54 (9.3)	50 (8.6)
School start date, No. (%) ^b		
On or before August 15	110 (22.0)	104 (20.8)
August 16 to September 4	212 (42.5)	217 (43.5)
After September 4	177 (35.5)	178 (35.7)

Abbreviation: FEV₁, forced expiratory volume in 1 second.

^a Total is 579 rather than 580 because data are missing for one patient.

^b Percentages are based on the full analysis set population.

vs 25.0% placebo) and in patients 10 to 14 years old (21.4% vs 26.4% placebo) than in those 6 to 9 years old (27.4% vs 27.7% placebo). However, the treatment × subgroup interaction was not statistically significant.

Selected post hoc analyses were conducted based on trends in primary findings, which showed differential efficacy with montelukast for children starting school after August 15, younger boys, and older children (Fig. 4). However, there was no significant interaction between treatment and any of these subgroups. The percentage of days with worsening asthma increased during treatment weeks 3 and 4 in the placebo group but did not change during the 8-week study period in the montelukast group (Fig. 5). There were no significant differences in the secondary end points composing the primary end point (Fig. 6).

Safety

Both treatments were well tolerated, and no significant differences in safety variables were observed (Table 2). There were 4 serious AEs in the montelukast group and 1 in the placebo group, none of which was considered to be drug related. The most common AEs were infections and respiratory disorders related to the upper respiratory system.

DISCUSSION

The purpose of this study was to examine the use of montelukast in a simple clinical protocol designed to target the peak of asthma-related morbidity that is observed in North America each fall and that is closely associated with the start of school. There is currently no commonly accepted treatment strategy that specifically targets this predictable seasonal pattern. Without an evidence-based strategy for primary prevention, a simple secondary prevention strategy might significantly improve the health of many children with asthma as they return to school each year.

Several key attributes were considered in the design of this secondary prevention strategy¹⁷: the public health burden of seasonal exacerbations and the effectiveness, safety, ease of use (acceptability), and cost-effectiveness of the intervention strategy. As noted, there seems to be a significant and predictable public health burden. Regarding intervention strategies, montelukast was considered particularly well suited for seasonal use, having well-defined therapeutic efficacy for childhood asthma, rapid onset of action,¹⁸ a well-established safety profile,¹⁹⁻²¹ and high adherence to its once-daily oral administration.^{22,23} Thus, dispensing a single daily oral prescription with instructions to begin with the start of school was a treatment strategy that could readily be adopted by physicians, patients, and their parents/guardians.^{24,25}

The primary outcome analysis demonstrated that montelukast therapy was not significantly better than was placebo use in reducing the percentage of days with worsening asthma. Although none of the prespecified subgroup treatment interactions met the statistical threshold for interaction of $P < .05$, the results indicated a lower percentage of symptoms days for boys and older children.

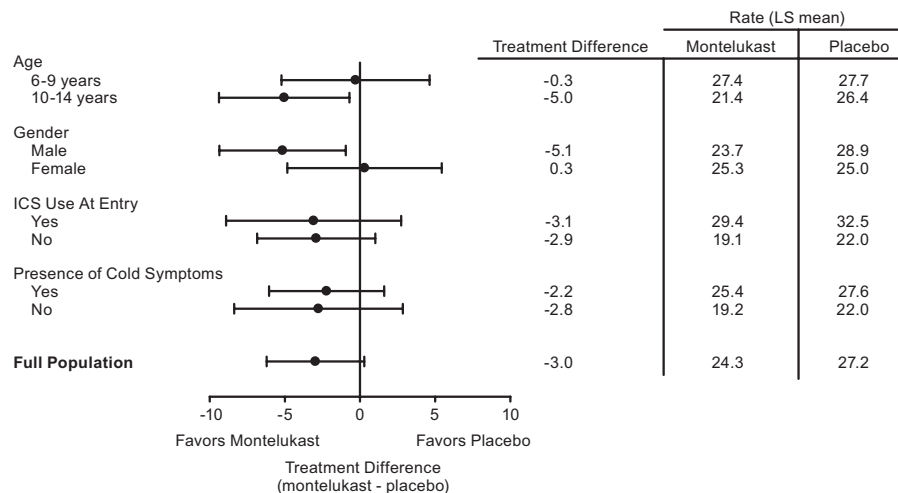


Figure 3. Prespecified subgroup analyses for the primary end point (percentage of days with worsening asthma). Tests for interaction between treatment and subgroup were not statistically significant. ICS indicates inhaled corticosteroid; LS, least squares.

An unanticipated observation was related to the difference in the timing of the start of school among the study sites. Although these did not strictly follow a north/south relationship, it was noted that many schools—primarily in the south—started school earlier than those in the north. To better characterize this phenomenon, a post hoc analysis was conducted that explored the treatment effect based on the start of school. The results showed a greater treatment effect with montelukast therapy compared with placebo use for children who started school after August 15 compared with those who started school earlier.

Another notable finding is that the percentage of days with worsening asthma was stable in the montelukast group but increased in the placebo group during weeks 3 and 4 and then decreased during weeks 5 to 8. This not only shows a period

of no worsening in the montelukast group during a period of worsening in the placebo group but also suggests that the period of risk on return to school may not extend beyond 4 weeks (ie, patients had begun to recover by weeks 5-6), after which treatment would not be expected to have an effect. Future intervention strategies should possibly be limited to 4 weeks.

Overall, the study showed a consistent trend toward improvement in the montelukast treatment group that was in general similar to findings in other studies, yet the main finding did not reach the prespecified level of statistical significance. In light of this negative main effect, much of the knowledge gained from this study can be hypothesis generating only. First, it is noteworthy that this study was designed for generalizability to more closely represent “real-world”

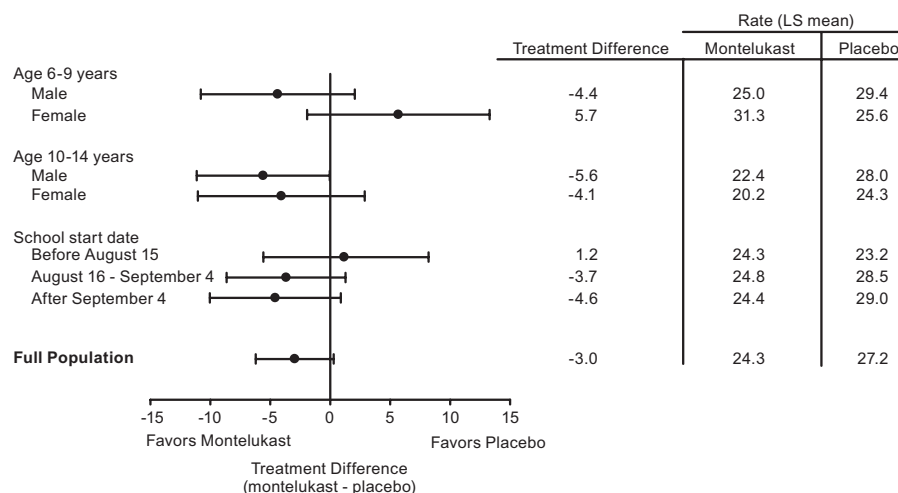


Figure 4. Post hoc analysis of the primary end point (percentage of days with worsening asthma) by age plus sex and school start date subgroups. Tests for interaction between treatment and subgroup were not statistically significant. LS indicates least squares.

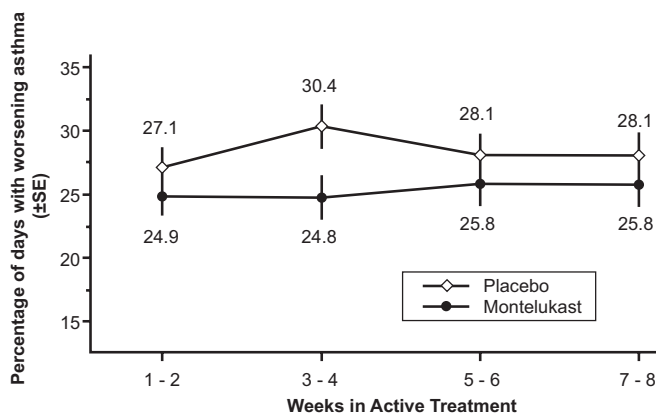


Figure 5. Post hoc analysis of the primary end point (percentage of days with worsening asthma) by time in treatment. Error bars represent SE.

conditions. For example, the population was generally healthier than in other pediatric studies with montelukast.^{18,26-30} In addition, patients were permitted to continue taking most of their baseline asthma medications, such as ICSs, to more accurately assess the protective efficacy of montelukast when given as monotherapy or as part of an add-on regimen. Collectively, these findings suggest that further studies are

Table 2. Clinical Adverse Experience Summary

	Patients, No. (%)	
	Montelukast, 5 mg, group (n = 566)	Placebo group (n = 566)
≥1 AEs	192 (33.9)	190 (33.6)
Serious AEs	4 (0.7)	1 (0.2)
Drug-related AEs ^a	11 (1.9)	13 (2.3)
Discontinuations due to AEs	4 (0.7)	4 (0.7)
Most common AEs		
Nasopharyngitis	31 (5.5)	24 (4.2)
Upper respiratory tract infection	31 (5.5)	45 (8.0)
Asthma	23 (4.1)	29 (5.1)
Sinusitis	15 (2.7)	11 (1.9)
Pharyngolaryngeal pain	13 (2.3)	9 (1.6)

Abbreviation: AE, adverse experience.

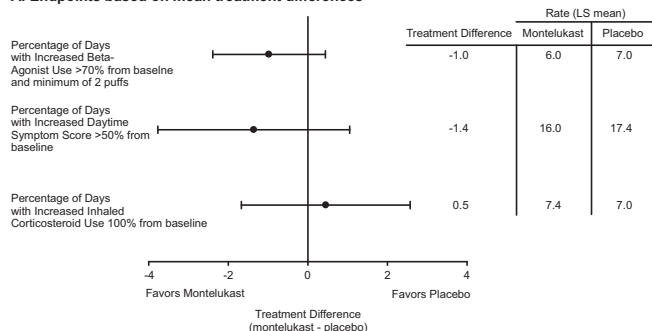
^a Determined by the site investigator to be possibly, probably, or definitely drug related.

warranted to determine whether specific populations might derive greater benefit and to explore whether this is a cost-effective public health strategy for attenuating the fall peak in asthma morbidity.

We are aware of only 1 other large randomized trial evaluating an intervention strategy for the September epidemic in children. Johnston and colleagues¹⁴ conducted a single-site, double-blind, placebo-controlled randomized trial of montelukast added to usual therapy in Hamilton, Ontario, Canada. That study included 194 children with asthma (aged 2-14 years) and reported a 53% reduction in days with worse asthma symptoms ($P < .02$) and a 78% reduction in unscheduled physician visits for asthma ($P = .01$) with montelukast therapy compared with placebo use. That study demonstrated the effect to be greater in younger boys (2-5 years) and older girls (10-14 years), which is generally consistent with the present findings of increased efficacy in boys (all ages) and older girls. As noted by Johnston et al,¹⁴ possible reasons for this age-related effect may be age- and sex-related perceptions in symptoms, pubertal/hormonal changes, and Cys-LT1 genetics.

There are several possible explanations for the disparate primary results between the Canadian study and the present study. First, the Canadian study population had more severe asthma, as represented by history of ICS use (approximately 94%), emergency department visits (approximately 25%), and hospitalizations (approximately 5%) in the preceding year. In contrast, only approximately 30% of patients in the present study were taking ICSs at randomization, and slightly more than 9% had an emergency department visit or hospitalization due to asthma in the previous year. It is possible that the present population with less severe asthma might have been less likely to experience an increase in symptoms on return to school. Second, the Canadian study was a single-site study, and all the patients began treatment on the same day (September 1). The present study was conducted

A. Endpoints based on mean treatment differences



B. Endpoints based on odds ratios

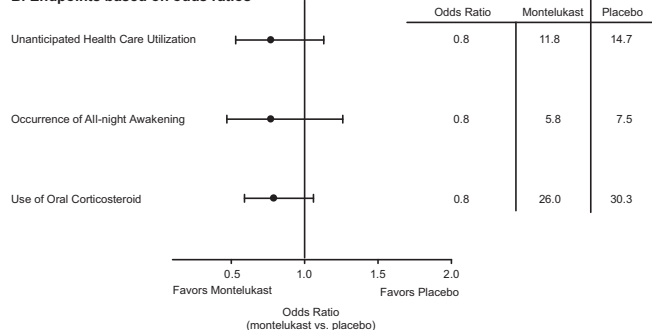


Figure 6. Secondary end points composing the primary end point (percentage of days with worsening asthma). LS indicates least squares. A. Endpoints based on mean treatment differences. B. Endpoints based on odds ratio.

throughout the United States and Canada in various geographic locations and with variable start dates, the combination of which may affect the impact of the September epidemic, particularly as it relates to the fall viral season. Third, the Canadian study was 6 weeks in duration compared with 8 weeks in the present study. As noted previously herein, given the worsening in the placebo group during weeks 3 and 4, a shorter intervention may have yielded different results. Fourth, the primary end point was measured considerably differently. In summary, although we were unable to replicate the results of the Canadian study, the overall positive direction of the results in the present study and the fundamental differences in study designs and populations make it impossible to exclude the potential of a properly targeted and timed intervention strategy.

The conflicting nature of the results of these two studies perhaps highlights the difficulty in managing presumed virus-induced wheezing and asthma in children. For example, previous studies in children have shown limited efficacy of ICSs,^{31,32} anticholinergic drugs,³³ and parent-initiated oral corticosteroids³⁴ in episodic childhood wheezing, which is thought to be primarily viral in nature, and of montelukast in post-respiratory syncytial virus bronchiolitis³⁵ despite the well-established efficacy of these medications in atopic asthma. Trials^{36–38} of montelukast for episodic wheezing in children have yielded primarily positive but inconsistent results. It is possible that the September epidemic, which is multifactorial but has a strong viral association, is similarly less amenable to intervention with traditionally efficacious asthma medications. A final consideration is that it is possible that asthma symptoms in the present study were related to increased physical activity (eg, physical education or the fall sports season) on return to school, which might have been the primary or secondary cause of asthma worsening in some children. However, such information was not collected.

In conclusion, there is a predictable and dramatic increase in asthma morbidity for children that occurs in the fall and is closely associated with the start of school. To date, there are no specific strategies to target this important public health concern. This study was designed to test the effectiveness of a simple secondary prevention approach to address this problem. Although the main effect of this study was negative, the findings are in the same direction as those of a smaller single-site study,¹⁴ which demonstrated a significant and large effect when this treatment strategy was implemented. Subgroup analyses from this study suggest that this approach may be more suited to a targeted population: either children starting school later in the year (after mid-August) or children with more moderate morbidity (such as those in inner-city populations). More studies are needed to identify cost-effective strategies to reduce the fall peak in asthma morbidity.

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APPENDIX

Rules for handling incomplete diary data based on the results of blinded diary data review and recommendations from the clinical study team and external scientific advisory committee.

If 1 or more of the following components of the primary efficacy end point were missing and no other events occurred that qualified as a day with worsening asthma, the primary variable was considered missing for that day and, therefore, was excluded from the numerator and denominator of the calculation: (1) an increase from baseline in β -agonist use of greater than 70% and a minimum increase of 2 puffs, (2) an increase of greater than 50% from baseline in daytime symptoms scores, or (3) an increase in ICS use of at least 100% from baseline. If 1 or more of the following components of the primary efficacy end point were missing and no other events occurred that qualified as a day with worsening asthma, that specific day was considered a day without worsening asthma and was included in the denominator of the calculation: (1) awake “all night,” (2) oral corticosteroid rescue for worsening asthma, or (3) unanticipated visits to the physician, emergency department, or hospital for asthma. When only incomplete diary data were available for the primary efficacy variable, the following rules were followed: (1) if any 1 of the components indicates a worsening asthma day it was considered a day with worsening asthma, regardless of the completeness of other components; (2) if no component indicated a day with worsening asthma and β -agonist use and daytime symptom scores were not missing, then it was not a day with worsening asthma; and (3) if no component indicated a day with worsening asthma and 1 or both of β -agonist use and daytime symptom scores are missing, then it was not evaluable for a day with worsening asthma.

Requests for reprints should be addressed to:

Steven S. Smugar, MD

Merck Research Laboratories

UG3D-32

351 N Sumneytown Pike

PO Box 1000

North Wales, PA 19454

E-mail: steven_smugar@merck.com