

Onset and duration of attenuation of exercise-induced bronchoconstriction in children by single-dose of montelukast

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ABSTRACT

Single-dose montelukast attenuates exercise-induced bronchoconstriction (EIB) in adults within 2 hours postdose and lasting through 24 hours. This study evaluated the onset and duration of EIB attenuation in children after a single dose of montelukast. A randomized, double-blind, placebo-controlled, two-period crossover study was performed. Patients ($n = 66$) aged 4–14 years, with preexercise forced expiratory volume in 1 second of (FEV_1) $\geq 70\%$ predicted and maximum percentage fall in FEV_1 of $\geq 20\%$ at two screening exercise challenges were eligible. Patients were to receive single-dose montelukast (4 or 5 mg) or placebo before performing standardized exercise challenges at 2 and 24 hours postdose. A 3- to 7-day washout separated the two crossover periods. The primary end point was maximum percentage fall in FEV_1 after exercise challenge 2 hours postdose. Secondary end points included maximum percentage fall in FEV_1 after the 24-hour postdose challenge; each of the following at 2 and 24 hours postdose—maximum percentage fall in FEV_1 categorized as $<10\%$, $10\text{--}20\%$, or $>20\%$; area under the curve (AUC) during 60 minutes postchallenge; time to recovery of FEV_1 to within 5% of preexercise baseline; and need for rescue medication. The mean maximum percentage fall in FEV_1 after the 2-hour postdose exercise challenge was significantly attenuated after single-dose montelukast compared with placebo (15.35% versus 20.00%; $p = 0.020$). Montelukast was also significantly more effective than placebo for maximum percentage fall after the 24-hour challenge (12.92% versus 17.25%; $p = 0.005$), the categorized maximum percent fall in FEV_1 at 2 hours ($p = 0.034$), and AUC at 2 hours ($p = 0.022$) and 24 hours ($p = 0.013$). Single-dose montelukast provided rapid and sustained EIB attenuation in children. Clinicaltrials.gov identifier: NCT00534976

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Physical activity in children is important not only to general health and fitness, but also to normal child psychosocial development.^{1,2} Proper management of exercise-induced bronchoconstriction (EIB) in children, therefore, has importance and implications beyond symptom control. Pharmacologic options for prophylaxis of EIB before exercise generally include short-acting β -agonists (SABAs), cromones, and anti-leukotrienes.³ However, both SABAs and cromones are somewhat limited by a relatively short duration of action,⁴ which may be a particularly important consideration in children, who often engage in unplanned physical

activity.² Therefore, a treatment that is both fast acting and long acting would be of significant benefit.

Three studies of montelukast in adult EIB showed that a single dose of montelukast provided significant attenuation of EIB within 2 hours of administration, with duration lasting through 24 hours.^{5–7} In pediatric patients, montelukast has been shown to attenuate EIB when administered on a chronic basis over 4 weeks⁸ and at the end of the dosing period (20–24 hours) after 2 days of treatment.⁹

Two single-dose studies of montelukast in pediatric EIB by Peroni *et al.*^{10,11} showed that montelukast was effective in attenuating EIB 12 hours after dosing but not at 2 or 24 hours postdose. However, unlike the aforementioned studies,^{5–9} which explicitly required a fall in forced expiratory volume in 1 second (FEV_1) of ≥ 15 or $\geq 20\%$ at two screening exercise challenges, in the studies by Peroni *et al.*, the authors state that baseline preexercise fall in FEV_1 of $\geq 15\%$ was considered diagnostic of FEV_1 , but did not explicitly state that patients with $<15\%$ fall were excluded. Thus, it is unclear whether the children in these pediatric single-dose studies, who had a history of EIB, required a minimum fall in FEV_1 after baseline exercise challenge to be eligible. In addition, preexercise challenges were performed at baseline before study medication administration, but not at screening. Therefore, the results of

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these two studies are difficult to interpret because of the potential methodological ambiguities compared with other studies of montelukast in EIB requiring clear objective and reproducible evidence of EIB. Therefore, the purpose of the present study was to evaluate the onset and duration of single-dose montelukast in children with EIB as documented by screening exercise challenges.

METHODS

Patients

Boys and girls aged 4–14 years with a history of EIB or wheeze/shortness of breath with exercise (with or without persistent asthma) and preexercise FEV₁ of $\geq 70\%$ predicted were eligible for enrollment. Pertinent exclusion criteria included an asthma exacerbation requiring a change in type, dose, or frequency of medications and/or an unscheduled health care provider visit within 4 weeks or previous intubation for asthma. Excluded medications included oral, i.v., rectal, intramuscular, or intraarticular corticosteroids; cromolyn or nedocromil; leukotriene receptor antagonists or 5-lipoxygenase inhibitors; theophylline; oral or long-acting β -agonists or inhaled anticholinergics; astemizole; SABAs other than albuterol or salbutamol, which could, however, be used as rescue therapy no less than 8 hours before an exercise challenge; antihistamines or decongestants; or ketotifen.

Use of inhaled corticosteroids (ICSs) at chronic (≥ 4 weeks), stable, low doses (≤ 200 $\mu\text{g/day}$ of beclomethasone dipropionate or equivalent) was permitted in up to 50% of patients. ICSs were withheld for at least 12 hours before each visit to avoid any acute ICS effects. Nasal steroids, nasal cromolyn, topical corticosteroids ($\leq 2.5\%$ hydrocortisone, if started ≥ 2 weeks before screening), and immunotherapy (started ≥ 6 months before screening) were permitted. Parents/legal guardians provided written informed consent for all patients before enrollment; patients aged ≥ 7 years also provided a written consent to participate.

Study Design

The study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. This study (Protocol 377; clinical trial identifier # NCT00534976) was a randomized, double-blind, placebo-controlled, multicenter, crossover study conducted from February 2008 to March 2010 at 22 sites in the United States, Colombia, Costa Rica, and Estonia. During a run-in period (period I), patients performed two screening treadmill exercise challenges, the second of which occurred 2 hours after a witnessed dose of single-blind matching-image placebo for montelukast. The two screening exercise challenges were separated

by 3–7 days. After both exercise challenges, patients were required to show a maximum percent fall in postexercise FEV₁ of $\geq 20\%$ within 60 minutes, in accordance with regulatory guidance.¹² Patients with a fall of $\geq 40\%$ or who required rescue SABA treatment and did not return to within 20% of their preexercise FEV₁ within 30 minutes were excluded. Eligible patients were to be randomized to double-blinded oral montelukast chewable tablet (4 mg for patients aged 4–5 years and 5 mg for patients aged 6–14 years) or matching placebo (period II). Treatment was administered as a single witnessed dose and was followed by exercise challenges at 2 and 24 hours postdose. After a washout period of 3–7 days, patients crossed over to the other treatment (period III). As in period II, exercise challenges were performed at 2 and 24 hours postdose during period III.

Treatment allocation was determined according to a computer-generated schedule. Numbered vials were used to implement allocation. All 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.

Exercise Challenges and Spirometry

A standard spirometer (nidd EasyOne; nidd Medical Technologies, Inc., Andover, MA) was provided. Exercise challenges were performed keeping a constant condition of dry air at room temperature delivered *via* tubing and face mask from a compressed air tank. Patients exercised for 6 minutes on a treadmill at a speed and incline to a workload that increased heart rate to 80–90% of their age-predicted maximum ($220 - \text{age}$). Spirometry measurements were obtained 5 minutes preexercise; immediately after exercise; and at 5, 10, 15, 30, 45, and 60 minutes after exercise. Patients who had not returned to within 5% of their preexercise FEV₁ by 60 minutes postexercise had additional measurements at 75 and 90 minutes.

Efficacy End Points

The primary end point was the maximum percent fall from preexercise baseline in FEV₁ after the exercise challenge performed at 2 hours postdose (Fig. 1). Secondary end points included the maximum percent fall from preexercise FEV₁ after exercise challenge at 24 hours postdose, the measurements after exercise challenges at 2- and 24-hour postdose of the categorized maximum percent fall in FEV₁ ($<10\%$, $10\text{--}20\%$, and $>20\%$), the area under the curve over the first 60 minutes ($\text{AUC}_{0-60 \text{ min}}$) for the percent fall from preexercise FEV₁, the time to recovery of FEV₁ to within 5% of

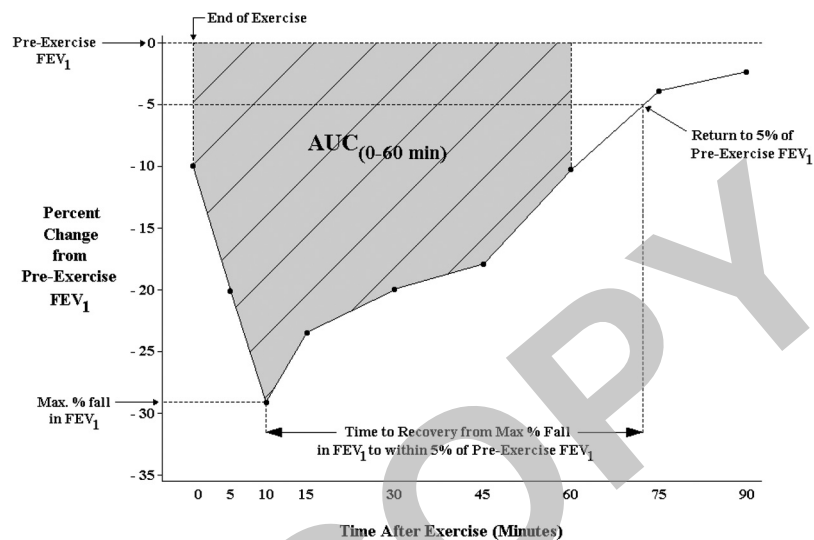


Figure 1. Illustration of efficacy end points. $AUC_{0-60 \text{ min}}$ the area under the FEV_1 time curve during the first 60 minutes after exercise; FEV_1 , forced expiratory volume in 1 second.

baseline, and the need for rescue medication. In addition, the proportion of patients achieving maximum percentage fall in FEV_1 of $\leq 20\%$ (i.e., protection against EIB) after exercise challenges was also analyzed at 2 and 24 hours postdose.

Tolerability End Points

Tolerability was assessed through clinical evaluation, vital signs, and clinical adverse experiences (AEs).

Statistical Methods

The primary hypothesis was that in pediatric patients (aged 4–14 years) with EIB (with or without persistent asthma), a single dose of oral montelukast, compared with placebo, would reduce the exercise-induced maximum percent fall in FEV_1 after the exercise challenge performed 2 hours postdose. The primary efficacy analysis was based on the completers population, which included all randomized patients who received the witnessed dose of study drug in both treatment periods and had at least one postexercise FEV_1 measurement in both treatment periods at a specific time point. Patients also had to have a preexercise FEV_1 to be included in the analyses of the efficacy end points derived from fall in FEV_1 . The primary end point was analyzed using a crossover analysis of variance model with factors for patient, treatment, and period effects. Treatment comparison was performed using adequate contrast within the analysis of variance model. Nominal two-sided p values were presented. In addition, least squares means and corresponding 95% confidence intervals (CIs) were computed for each treatment as well as the treatment differences. Given the pharmacokinetic and pharmacodynamic characteristics of montelukast and the 3- to 7-day washout period, the analyses were performed under the assumption of no differential carryover effect. Prespecified

subgroup analyses of the primary end point included gender (male/female), race (white/nonwhite), age group ($<$ median/ $\geq$ median), concomitant ICS use (yes/no), and maximum percent fall in FEV_1 at the first prerandomization exercise challenge ($<$ median/ $\geq$ median). Only summary statistics (least squares means and 95% CIs without formal testing) were provided for these subgroup analyses because the study was not powered to show superiority within each of the subgroups.

Maximum percent fall in FEV_1 after exercise challenge at 24 hours postdose, $AUC_{0-60 \text{ min}}$, and time to recovery were analyzed using a similar model as for the primary efficacy end point. The distribution of the categorized fall in FEV_1 was compared between treatments using Cochran-Mantel-Haenszel. The proportions of patients requiring SABA rescue within 90 minutes after exercise were compared between treatments using an exact McNemar test. An exact McNemar's test was also used to compare the proportions of patients achieving maximum percentage fall in FEV_1 of $\leq 20\%$.

Tolerability and safety outcomes were assessed based on the all patients as treated population, which included all randomized patients who received at least 1 dose of study medication, and patients were assessed based on the treatment actually received. AEs that occurred during the washout period were assigned to the previous treatment received. AEs were summarized and 95% CIs for the between-treatment differences were presented for AE categories (any AE, serious AE, drug-related AE, serious and drug-related AE, and discontinuations due to AE) as calculated using Tango's method.

Because there was one primary hypothesis assessed with one variable and one between-treatment comparison at one primary time point (2 hours postdose), no multiplicity adjustment was required for the primary end point. The analyses at the secondary time point (24

hours postdose) were used to assess the duration of treatment effect only if the primary comparison at 2 hours was significant. If the test was significant at 2 hours postdose at level $\alpha = 0.05$, the test at 24 hours postdose was considered valid at $\alpha = 0.05$. To adjust for multiplicity between secondary efficacy end points, a step-down procedure was applied. Specifically, $AUC_{0-60 \text{ min}}$ at 2 hours and the categorized maximum percent fall in FEV_1 at 2 hours were assessed only if the primary end point was significant at the $\alpha = 0.05$ level. Time to recovery and need for rescue medication were assessed at 2 hours if $AUC_{0-60 \text{ min}}$ at 2 hours was significant at level $\alpha = 0.05$. The analyses at 24 hours postdose for the secondary end points were assessed only if the comparison for the particular secondary end point was significant at 2 hours (at $\alpha = 0.05$) and if the maximum percent fall in FEV_1 at 24 hours was also significant ($p < 0.05$). A sample size of 60 completed patients would provide 90% power ($\alpha = 0.05$, two-sided test, assumed SD of difference of 14%) to detect a treatment difference of 6% between montelukast and placebo for the primary end point, maximum percent fall in FEV_1 at 2 hours postdose.

RESULTS

Patients

Patient disposition is shown in Fig. 2. One patient in each treatment sequence was missing exercise challenge data at 2 hours postdose; thus, both were excluded from the primary analysis. Baseline patient characteristics are shown in Table 1. Although patients as young as 4 years were eligible, no patients <6 years old met the inclusion criteria for randomization. No patients were >14 years old at visit 1; however, one patient turned 15 years after the first study visit but before randomization.

Efficacy

For the primary efficacy end point, the mean maximum percentage fall in FEV_1 after the 2-hour postdose exercise challenge was significantly attenuated after a single dose of montelukast compared with placebo (15.35% versus 20.00%; $p = 0.020$; Fig. 3; Table 2). Results for the primary end point were generally consistent among the prespecified subgroups, including concomitant ICS use.

As summarized in Table 2, montelukast was also significantly more effective than placebo for the maximum percentage fall in FEV_1 after exercise challenge performed at 24 hours postdose ($p = 0.005$), the categorized maximum percentage fall in FEV_1 at the 2-hour postdose challenge ($p = 0.034$), and $AUC_{0-60 \text{ min}}$ at both the 2- ($p = 0.022$) and 24-hour ($p = 0.013$) postdose challenges. For the categorized maximum percentage fall in FEV_1 after the 24-hour exercise challenge and

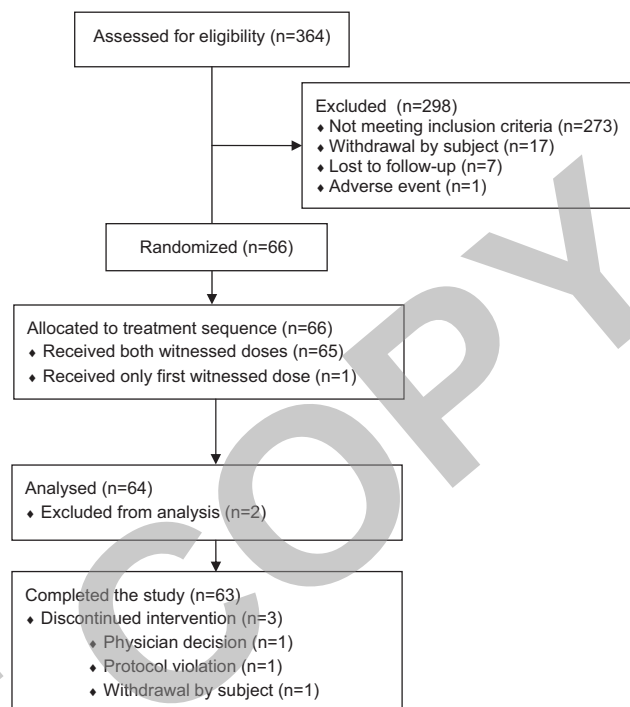


Figure 2. Patient disposition.

time to recovery at both time points, montelukast was numerically better than placebo, but treatment differences did not reach statistical significance (value range of $p = 0.054$ – 0.064). A total of only three patients required rescue medication at 2 hours postdose (one on montelukast and two on placebo). Only two patients required rescue medication at 24 hours postdose (both were on placebo). The proportion of patients with maximum percentage fall in FEV_1 of $\leq 20\%$ (i.e., protection against EIB) was significantly higher with montelukast compared with placebo after exercise challenges at 2 hours postdose ($p = 0.015$); montelukast was numerically better than placebo at 24 hours postdose, but the difference was not statistically significant ($p = 0.077$).

Tolerability

There were few clinical AEs: 4 (6.2%) with montelukast and 5 (7.6% with placebo). There were no serious AEs or drug-related AEs, and no patients discontinued due to an AE with either montelukast or placebo.

DISCUSSION

In this study, we found that montelukast provided significant attenuation of EIB, compared with placebo, as measured by the primary end point, the maximum percentage fall in FEV_1 after exercise challenge 2 hours after drug administration. Montelukast was also significantly more effective than placebo in attenuating EIB for most secondary end points, including the maximum percentage fall in FEV_1 after 24-hour exercise challenge, the AUC after both exercise challenges, and

Table 1 Baseline patient characteristics

	<i>n</i> = 66
Age (yr)	
Mean (SD)	11.2 (2.1)
Range	6–15*
Gender, <i>n</i> (%)	
Male	37 (56.1)
Female	29 (43.9)
Race, <i>n</i> (%)	
Black	11 (16.7)
White	49 (74.2)
Other	6 (9.1)
Concomitant inhaled corticosteroids, <i>n</i> (%)	17 (25.8)
Preexercise FEV ₁ (% predicted), mean (SD)	
Prestudy challenge 1	91.65 (10.80)
Prestudy challenge 2	88.78 (11.74)
Maximum percentage fall in FEV ₁ (%), mean (SD)	
Prestudy challenge 1	27.22 (7.30)
Prestudy challenge 2	28.54 (6.84)
AUC _{0–60 min} (% · min), mean (SD)	
Prestudy challenge 1	687.34 (308.20)
Prestudy challenge 2	674.43 (309.76)
Time to recovery (min), mean (SD)	
Prestudy challenge 1	34.00 (24.80)
Prestudy challenge 2	32.02 (23.62)
Need for rescue medication following challenge, <i>n</i> (%)	
Prestudy challenge 1	4 (6.1)
Prestudy challenge 2	2 (3.0)

*One patient became 15 years old after the prestudy visit 1 but before randomization; no patients were >14 years old at visit 1. AUC_{0–60 min} = area under the curve over the first 60 min; FEV₁ = forced expiratory volume in 1 second.

the categorized maximum percentage fall in FEV₁ after the 2-hour exercise challenge. The differences between treatments for the categorized maximum percentage fall at 24 hours and the time to recovery after both exercise challenges were numerically better with montelukast compared with placebo without reaching statistical significance.

Importantly, not only was montelukast significantly more effective than placebo for most end points after both the 2- and 24-hour challenges, but also, the magnitude of the differences between montelukast and placebo was similar after both challenges, suggesting attenuation that is both continuous and stable through the dosing period. The result of the categorized maximum percentage fall in FEV₁ appeared to be an exception to this pattern, in which montelukast showed a substantial shift toward even greater attenuation of EIB with montelukast at 24 hours compared with 2 hours (e.g., the percentage of

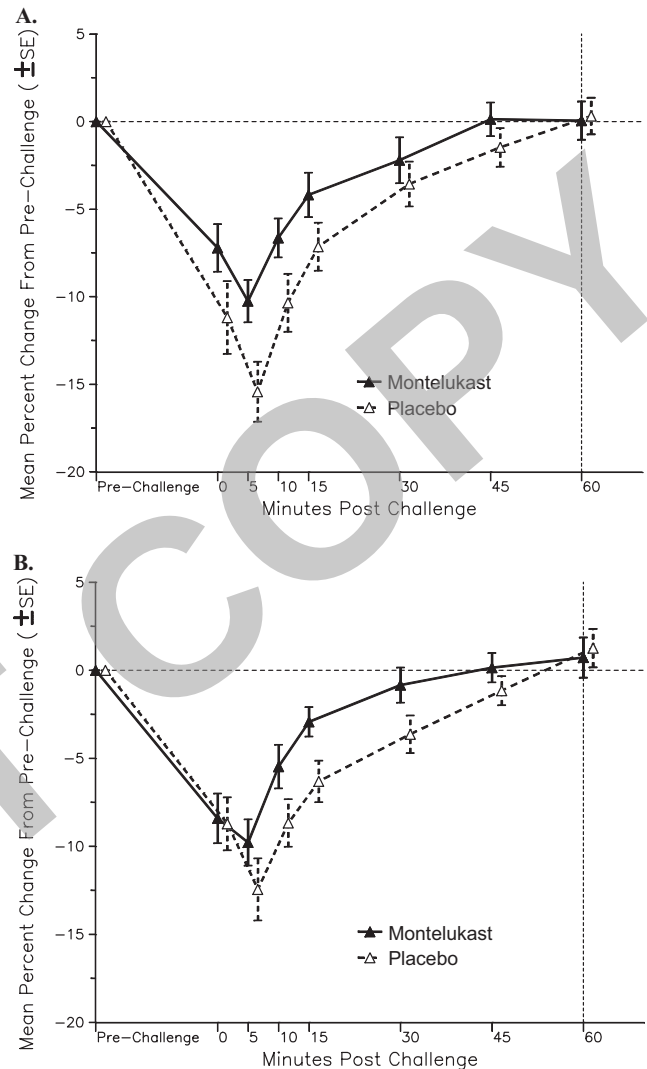


Figure 3. Mean percentage change in FEV₁ during 60 minutes after exercise. (A) At 2 hours postdose (primary end point). (B) At 24 hours postdose. FEV₁, forced expiratory volume in 1 second; SE, standard error.

patients with <10% fall at 24 hours was 45.2% versus 26.6% at 2 hours). However, there was also a sizeable shift with placebo.

Our results at 24 hours generally confirm those reported in a study by Kemp and colleagues,⁹ in which patients 6–14 years of age with EIB underwent exercise challenge 20–24 hours after receiving montelukast or placebo nightly for two nights. For the primary end point of the change in area above the postexercise FEV₁ time curve through 60 minutes from preexercise baseline, montelukast was significantly more effective than placebo (–265% · min versus –590% · min; *p* = 0.013). Montelukast was also significantly more effective than placebo in attenuating the maximum percentage fall in FEV₁ (–18% versus –26%; *p* = 0.009). The time to recovery to within 5% of the preexercise FEV₁ was numerically better with montelukast than placebo (18 minutes versus 28 minutes; *p* = 0.079).

Table 2 Efficacy results*

Time after Exercise	Montelukast	Placebo	Treatment Difference Montelukast Minus Placebo Estimate (95% CI)	<i>p</i> Value
Maximum percentage fall in FEV ₁ after exercise challenge				
2 hr postdose	15.35 (12.60, 18.11)	20.00 (17.25, 22.76)	−4.65 (−8.55, −0.75)	0.020
24 hr postdose	12.92 (10.81, 15.04)	17.25 (15.14, 19.36)	−4.33 (−7.31, −1.34)	0.005
Categorized maximum percentage fall in FEV ₁ #				
2 hr postdose				0.034
<10%	26.6%	25.0%	—	
≥10% to ≤20%	50.0%	31.3%	—	
>20%	23.4%	43.8%	—	
24 hr postdose				0.061
<10%	45.2%	30.6%	—	
≥10% to ≤20%	35.5%	37.1%	—	
>20%	19.4%	32.3%	—	
AUC _{0–60 min} (% · min)				
2 hr postdose	294.50 (221.73, 367.27)	415.37 (342.60, 488.13)	−120.86 (−223.77, −17.95)	0.022
24 hr postdose	227.98 (160.44, 295.51)	350.80 (283.26, 418.34)	−122.82 (−218.36, −27.29)	0.013
Time to recovery (min)				
2 hr postdose	16.21 (10.01, 22.42)	24.48 (18.27, 30.68)	−8.27 (−17.04, 0.51)	0.064
24 hr postdose	11.49 (6.42, 16.56)	18.55 (13.48, 23.62)	−7.06 (−14.23, 0.11)	0.054
Need for rescue medication				
2 hr postdose	1.6%	3.1%	−1.6% (−9.27, 5.63)	1.000
24 hr postdose	0.0%	3.2%	−3.2% (−11.02, 3.06)	—
Maximum percentage fall in FEV ₁ of ≤20%				
2 hr postdose	76.6%	56.3%	20.3% (5.17, 34.20)	0.015
24 hr postdose	80.6%	67.7%	12.9% (0.13, 25.30)	0.077

*All values are least squares means (95% CI) unless otherwise noted.

#The *p* value for the montelukast vs placebo comparison based on Cochran-Mantel-Haenszel analysis of the three categories. AUC_{0–60 min} = area under the curve over the first 60 min; CI = confidence interval; FEV₁ = forced expiratory volume in 1 second.

It is notable that the differences between montelukast and placebo were considerably smaller in the present study compared with those in the Kemp study. This appears to be caused by a substantially larger placebo response in the present study (e.g., maximum percentage fall in FEV₁ at 24 hours for placebo: 26% previously versus 17% presently), whereas the response to montelukast was fairly consistent, if not better, in the present study (18% previously versus 13% presently). It is further notable that 25.0 and 30.6% of patients receiving placebo had no or minimal EIB, defined as a <10% fall in FEV₁, at 2 and 24 hours postdose, respectively. A sizeable placebo response was also seen in the three single-dose studies in adults^{5–7} as well as in the study by Kemp *et al.*⁹ Indeed, the placebo response in EIB^{13,14} and asthma in general¹⁵ is not uncommon and has been well described.

The requirement of a ≥20% maximum fall in FEV₁ at screening is, in part, an attempt to limit the placebo response in EIB by ensuring that patients show objective evidence of EIB. The requirement to demonstrate this

minimum requirement at two screening visits helps to decrease disease variability; patients with more variable disease may be more apt to have spontaneous improvement. The aforementioned ambiguity regarding objective evidence of EIB as determined by entry criteria requiring a minimum fall in FEV₁ may help explain the findings by Peroni *et al.*,^{10,11} in which single-dose montelukast attenuated EIB in children at 12 hours but not at 2 or 24 hours. Given the mean baseline fall of ~22% reported in the studies by Peroni *et al.*,^{10,11} it would appear that at least some proportion of those patients had baseline falls in FEV₁ of <20% and possibly <15% and thus did not have EIB as defined in regulatory guidance documents,¹² or had only mild or variable EIB. Therefore, it is, perhaps, not surprising that the mean baseline maximum fall in FEV₁ of ~22% in the Peroni studies was considerably lower than the 28% fall at screening in the present study, the 36% fall at screening reported in the 2-dose montelukast study by Kemp *et al.*,⁹ and the ~28% fall at screening in the three single-dose montelukast adult studies.^{5–7}

We acknowledge, however, that opinions differ regarding the minimum degree of fall in FEV₁ that is considered diagnostic of EIB. As noted, Food and Drug Administration regulatory guidance suggests a 20% cutoff. On the other hand, others have suggested cutoffs as low as 6–10% as diagnostic of EIB.^{16–19} Thus, although our study design was within regulatory compliance, the selection of a patient population with more severe EIB could have affected our results. Thus, because of apparent less severe EIB in the Peroni studies, there may have been less room for improvement with montelukast, which may also account for the differences in results compared with our study.

Concomitantly, we excluded patients with maximum fall in FEV₁ of >40, consistent with the safety concerns expressed in regulatory EIB guidance documents.¹² It is unclear whether similar exclusion criteria were in place in the Peroni studies. Therefore, because there could be more room for improvement on placebo in the Peroni studies, it is not surprising that the improvement on montelukast did not significantly exceed that on placebo at 2 and 24 hours in those studies. Interestingly, a recent pooled analysis of three studies of single-dose montelukast in EIB²⁰ found that a greater response to placebo was generally associated with less severe baseline asthma/EIB, which may further help explain the discrepancy between our results and those by Peroni *et al.*; *i.e.*, a greater placebo response would be expected in the Peroni studies, given the smaller baseline falls in FEV₁ when compared with our study. Moreover, those results may also explain the larger placebo response in our study compared with the Kemp study, given lower average screening maximum percentage fall in FEV₁ in our study (28%) compared with the Kemp study (36%).⁹

A limitation of this study was that there was no interim time point exercise challenge between 2 and 24 hours. However, given the consistent significant (or near significant) differences between montelukast and placebo at both time points for all measured end points, and given that the maximum percentage fall in FEV₁ was statistically superior to placebo at the interim time point in two^{5,7} of the three⁶ single-dose studies of montelukast in adult EIB, it is reasonable to infer generally continuous efficacy between the two time points.

In conclusion, we found that, compared with placebo, single-dose montelukast significantly attenuated EIB in children, both within 2 hours of administration and through 24 hours, based on the primary end point of maximum percentage fall in FEV₁ and on various secondary end points. The data from this study support a treatment effect of montelukast for attenuation of acute EIB in pediatric patients.

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