

ASTHMA TREATMENT

# A Phase I Randomized, Placebo-Controlled, Dose-Exploration Study of Single-Dose Inhaled Montelukast in Patients with Chronic Asthma

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**Background.** The efficacy of oral montelukast has been well established in asthma and allergic rhinitis in adults and children. The purpose of this study was to evaluate dose-related bronchodilation and tolerability of inhaled montelukast. **Methods.** Randomized, double-blind, crossover, adaptive-design study comparing single-dose administration of inhaled montelukast versus placebo in patients age 15–65 years with chronic asthma ( $n = 68$ ). Montelukast was delivered as a witnessed dose through dry powder inhaler at doses of 25, 250, or 1000  $\mu\text{g}$ , and doses of 50, 100, and 500  $\mu\text{g}$  could be used if needed based on a prespecified dose-response algorithm. Each administration was followed by a 4- to 7-day washout period before crossing over to the next treatment. The primary endpoint was the change from baseline in a forced expiratory volume in 1 second ( $\text{FEV}_1$ ) over the first 4 hours after administration, calculated as a time-weighted average ( $\Delta\text{FEV}_1$  [0–4 hours]). Other endpoints included the onset and duration of bronchodilation and the effect of albuterol when added to inhaled montelukast. **Results.** Over 4 hours postdose, and compared with placebo (least-squares [LS] mean 0.03 L), inhaled montelukast 100  $\mu\text{g}$  (0.13 L;  $p \leq .001$ ), 250  $\mu\text{g}$  (0.10 L;  $p < .01$ ), and 1000  $\mu\text{g}$  (0.12 L;  $p \leq .001$ ) had significantly greater  $\Delta\text{FEV}_1$  (0–4 hours). At 24 hours postdose, inhaled montelukast 100  $\mu\text{g}$  (0.10 L) and 1000  $\mu\text{g}$  (0.09 L) had significantly greater bronchodilation compared with placebo (0.02 L;  $p < .05$  vs. montelukast). Montelukast 1000  $\mu\text{g}$  provided significant bronchodilation versus placebo within 20 minutes of administration (0.03 L vs.  $-0.05$  L), whereas montelukast 100  $\mu\text{g}$  provided significant bronchodilation relative to placebo within 2 hours of dosing (0.09 L vs. 0.01 L). Montelukast (pooled doses) plus albuterol was significantly more effective than montelukast plus placebo for  $\Delta\text{FEV}_1$  (0–90 minutes) (0.34 L vs. 0.15 L;  $p = .015$ ). The tolerability of inhaled montelukast was similar to that of placebo. No serious adverse experiences were reported. **Conclusions.** Inhaled montelukast provided significant bronchodilation compared with placebo as early as 20 minutes after the administration that persisted for 24 hours and provided additive bronchodilation to albuterol.

**Keywords** asthma, clinical trial,  $\text{FEV}_1$ , montelukast, Phase I, placebo

## INTRODUCTION

Montelukast has well-established efficacy and safety in asthma (1), exercise-induced asthma (1, 2), and allergic rhinitis (1–3). This efficacy, which includes a significant increase in a forced expiratory volume in 1 second ( $\text{FEV}_1$ ) when used alone or added to inhaled corticosteroids (ICS) (4) in patients with airflow limitation, illustrates the importance of blocking cysteinyl leukotrienes in asthma.

Improvement in  $\text{FEV}_1$  following the oral administration of montelukast occurs as early as 2 hours with single doses of montelukast 100–250 mg (5, 6) in patients with persistent asthma. Although the montelukast doses in these early clinical trials were considerably higher than the current approved dose in adults of 10 mg, it was

subsequently shown that the efficacy of oral montelukast dosing at 10, 100, and 200 mg daily resulted in similar efficacy on endpoints of asthma control (7).

Montelukast has also been evaluated as an intravenous administration in chronic asthma. Dockhorn et al. (8) compared intravenous montelukast, oral montelukast, and placebo in adult subjects with persistent asthma and  $\text{FEV}_1$  between 40% and  $\leq 80\%$  predicted. The authors found that intravenous montelukast produced a significantly better response ( $\%\Delta\text{FEV}_1$ ) than oral montelukast at early time points (15 minutes to 1 hour) with changes similar to oral montelukast from 2 to 24 hours. Both intravenous and oral montelukast were significantly better than placebo over 24 hours.

To further explore alternative routes of administration, the purpose of this study was to evaluate single-dose inhaled montelukast in patients with chronic asthma. Specifically, we sought to explore the doses of inhaled montelukast that could provide acute bronchodilation using an adaptive-dose crossover design, as well as to assess the safety profile across the range of doses.

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## METHODS

### Patients

Eligible patients were 15–65 years of age and had chronic asthma for at least 1 year, an FEV<sub>1</sub> 50–85% predicted while withholding short-acting  $\beta$ -agonists (SABA) and reversible airway obstruction  $\geq 12\%$  after SABA administration. Pertinent exclusion criteria included emergency room visit for asthma within 4 weeks, hospitalization for asthma within 2 months, respiratory tract infection within 4 weeks (or within 2 months if antibiotics were required), evidence of another clinically significant, active pulmonary disorder (e.g., chronic obstructive pulmonary disease), and body mass index (BMI)  $<18.5$  or  $>40$  kg/m<sup>2</sup>. Excluded medications included oral, intravenous, intramuscular, or rectal corticosteroids, antileukotriene medications, inhaled long- or short-acting anticholinergics, inhaled long-acting  $\beta$ -agonists (LABA), or fixed-dose LABA combinations with ICS. Patients were permitted to use ICS at stable doses, and albuterol on an as-needed basis, but were required to withhold albuterol 6 hours before study visits and ICS 1 hour before study visits.

### Study Design

This trial (Merck Protocol 388, clinicaltrials.gov identifier: NCT00739297) was a 4-week multicenter, randomized, double-blind, placebo-controlled, crossover, adaptive-design study conducted from August 2008 to December 2008 at six sites in the United States. All patients and/or legal guardians provided written informed consent before participation. This study was conducted in accordance with the standards of Good Clinical Practice and consistent with the standards established by the Declaration of Helsinki, and the protocol was approved by the appropriate institutional review boards. Eligible patients were to receive, during four treatment periods, a randomized sequence (using a computer-generated allocation scheme) of three active doses of inhaled montelukast and matching placebo. All single-dose administrations of study medication were given as witnessed doses delivered by dry powder inhaler (DPI).

For the adaptive-dose design, FEV<sub>1</sub> responses obtained during the course of the study were analyzed as frequently as new data became available to allow ongoing and iterative assessment, using a prespecified algorithm, to analyze and generate a montelukast dose–response curve. Dose adaptation meant that changes could be made during the

course of the study to the doses chosen for administration in the three active treatment periods (vs. placebo in the fourth period) among the available doses of 25, 50, 100, 250, 500, and 1000  $\mu$ g, to target a dose that would yield 75% of maximal placebo-adjusted montelukast efficacy. For each individual patient, the three active doses to be administered were selected just before his/her randomization and could not be modified thereafter for that patient. The dose–response curve data were assessed by an unblinded statistician who communicated adaptive-dose assignments to an independent designee who, in turn, communicated the dose assignments to an unblinded study coordinator/pharmacist at the study site, who had no contact with any site personnel dealing with patients or patient data. The results of the unblinded evaluations were not shared with investigators or other sponsor personnel.

During each treatment period, spirometry (Figure 1) was performed 5 minutes before witnessed blinded study drug administration, and 10, 20, 30, 45, and 60 minutes and 2, 3, 8, and 24 hours after administration. In addition, blinded albuterol or matching placebo was administered 4 hours after study medication, which was followed by serial spirometry at 15, 30, 60, and 90 minutes. Visits were scheduled to begin between 6 am and 10 am. Patients crossed over to other doses after a 4- to 7-day washout period.

Numbered DPI devices, blister packaging, and albuterol/placebo inhalers were used to implement blinded treatment allocation. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel—other than those involved in the adaptive-dose design, as noted above—remained blinded to the treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

### Spirometry and Efficacy Measurements

The FEV<sub>1</sub> and forced vital capacity from the three best acceptable maneuvers were recorded and the largest value was used as the true value. Spirometry conformed to American Thoracic Society standards for acceptability (9). The primary endpoint was the change from baseline in FEV<sub>1</sub> over the first 4 hours after administration, calculated as a time-weighted average ( $\Delta$ FEV<sub>1</sub> [0–4 hours]). Other endpoints included acute onset of bronchodilation as measured as the time-weighted average  $\Delta$ FEV<sub>1</sub> over 10, 20, 30, 45, and 60 minutes and 2 and 3 hours.

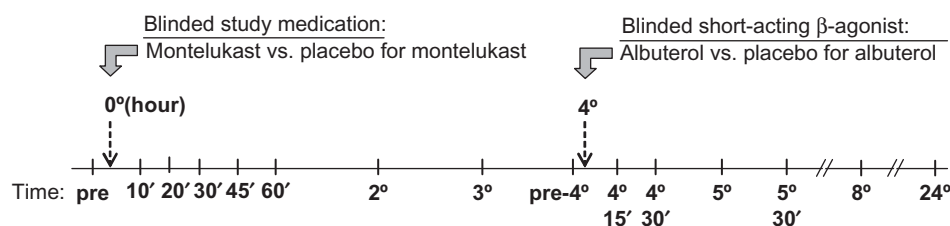


FIGURE 1.—Schedule of spirometry for each dose of study medication.

Duration of bronchodilation was assessed as the change from baseline in FEV<sub>1</sub> at 8 and 24 hours.

The post-albuterol time-weighted average change in FEV<sub>1</sub> from baseline was calculated to evaluate the effect of treatment with inhaled montelukast plus albuterol versus inhaled montelukast plus placebo over 90 minutes after administering the blinded albuterol ( $\Delta_{\text{albuterol}} \text{FEV}_1$  [0–90 minutes]). The effect over 60, 30, and 15 minutes was also calculated.

### Safety Measurements

Safety and tolerability were assessed by clinical review of vital signs, clinical examination, and adverse experiences (AEs).

### Statistical Methods

There were no *a priori* hypotheses defined for this study. The primary pharmacodynamic analysis compared all active montelukast doses versus placebo with respect to the time-weighted average change from baseline in FEV<sub>1</sub> over the first 4 hours after single-dose administration of inhaled montelukast ( $\Delta \text{FEV}_1$  [0–4 hours]). The primary and other efficacy endpoints were based on the full analysis set population, which included all patients receiving at least one dose of study medication who had a baseline endpoint value and at least one on-treatment endpoint data value. Patients were analyzed according to the treatment dose assigned, regardless of the actual treatment received. A supportive analysis based on a completers population (patients treated during the four treatment periods with baseline and on-treatment endpoint values available) was also performed. Prespecified subgroup analyses for the primary endpoint included age ( $\leq$  vs.  $>$  median), sex (male/female), race (White/non-White), and baseline FEV<sub>1</sub> % predicted ( $\leq$  vs.  $>$  median).

A mixed-effects model was used to analyze the efficacy variables and included terms for treatment (including dose of montelukast), period, and baseline covariate. Pairwise treatment comparisons and their 95% confidence intervals (CI) were performed using a linear contrast from the mixed model. Given the pharmacodynamic characteristics of montelukast and the washout period of 4–7 days, no carryover effect was expected and all analyses were performed under the assumption of no carryover effect.

To determine the onset of action of inhaled montelukast versus placebo, a step-down procedure was used. If a significant difference was found in the primary endpoint, then the following endpoints were examined in order:  $\Delta \text{FEV}_1$  over 3 hours, 2 hours, 60, 45, 30, 20, and 10 minutes. Duration of action at 8 and 24 hours was evaluated using a mixed effect model with terms for treatment, period, and baseline covariate. As noted, albuterol or placebo was administered at 4 hours. Given the 3-hour median and 6-hour maximum duration of action for albuterol (10), it was expected that albuterol administered at 4 hours would not appreciably confound the measurements of montelukast effects at 8 and 24 hours.

The  $\Delta_{\text{albuterol}} \text{FEV}_1$  was based on data from the three montelukast treatment periods only (i.e., data adding albuterol to the placebo for montelukast were not analyzed), and was evaluated using a longitudinal data analysis model with terms for treatment (albuterol vs. placebo for albuterol), dose (six available active dose-strengths of montelukast), treatment-by-dose interaction, and baseline covariate. This endpoint was evaluated in a stepwise fashion for the change in FEV<sub>1</sub> over 90, 60, 30, and 15 minutes in that order.

Approximately 64 patients were planned to be randomized to one of the four possible sequences (sequence of three active dose strengths and placebo). A number of efficacy scenarios were evaluated for power through simulations. Simulations assumed a maximum difference of 8%, a within-subject standard deviation (SD) of 13%, and a between-subject total SD of 18%. Assuming an average baseline value of 2.3 L, a detectable difference of 8% corresponds to approximately 0.18 L in change from baseline with a within-subject SD of 0.30 L. Based on the underlying dose-response scenario used in the simulations, the average number of observations on the most frequently studied (mode) dose ranged from 43 to 60. Based on the scenario, the power of the adaptive design to declare the mode dose significantly different from placebo ranged from 75% to 91% with most scenarios yielding power 80% or greater. If no dose adaptation occurred, the study would reduce to a standard four-period crossover study with the initially selected four doses (25, 250, and 1000  $\mu\text{g}$  and placebo). In this case, with a sample size of 64 patients, there would be 92% power ( $\alpha = 0.05$ ) to detect a difference of 0.18 L between a montelukast dose and a placebo, assuming a within-subject SD (root mean-squared error from the crossover) of 0.30 L corresponding to a SD of the differences of 0.42 L. Because there is no formal hypothesis testing in this study, no multiplicity adjustments were necessary beyond the step-down procedures described above.

Safety assessments were based on the “All Patients as Treated” population, which included all patients who received at least one dose of study medication. Patients were analyzed according to the treatment actually received. No formal hypothesis testing or statistical analyses were performed for safety variables.

## RESULTS

### Patients and Doses Studied

Patient flow through the study is shown in Figure 2. Of 68 patients enrolled, 65 (95.6%) completed the study. The mean age was 39.1 years and most patients were male (52.9%) and White (91.2%) (Table 1). Approximately 47.1% of all patients were using ICS. Starting from the three active dose strengths initially selected for use in the study (25, 250, 1000  $\mu\text{g}$ ), dose adaptation (using the adaptive-trial design) then enabled a total of five active dose strengths to be studied: montelukast 25, 100, 250, 500, and 1000  $\mu\text{g}$ ; 250  $\mu\text{g}$  was the mode dose ( $n = 66$ ).

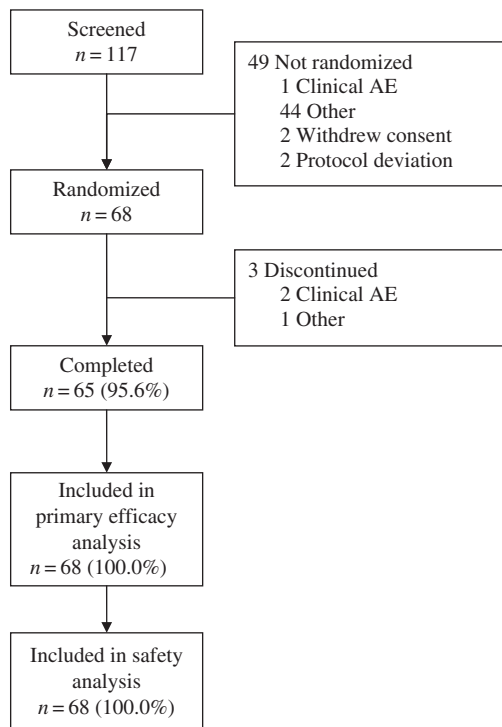


FIGURE 2.—Study flow diagram.

TABLE 1.—Patient characteristics.

|                                                  | Total (n = 68) |
|--------------------------------------------------|----------------|
| Age (years)                                      |                |
| Mean (SD)                                        | 39.1 (12.6)    |
| Range                                            | 16.0–63.0      |
| Gender, n (%)                                    |                |
| Male                                             | 36 (52.9)      |
| Female                                           | 32 (47.1)      |
| Race, n (%)                                      |                |
| Asian                                            | 2 (2.9)        |
| Black                                            | 4 (5.9)        |
| White                                            | 62 (91.2)      |
| BMI (kg/m <sup>2</sup> ), mean (SD) <sup>a</sup> | 28.2 (4.7)     |
| Duration of asthma (years), mean (SD)            | 26.0 (11.5)    |
| FEV <sub>1</sub> , mean (SD)                     |                |
| L                                                | 2.44 (0.63)    |
| % predicted                                      | 67.93 (11.11)  |
| Reversibility (%)                                | 21.19 (8.18)   |
| Concomitant inhaled corticosteroid use, n (%)    | 32 (47.1)      |

Note: <sup>a</sup>Based on 67 patients.

### Efficacy

**Primary Endpoint.** For the primary efficacy endpoint, compared with placebo (least-squares [LS] mean = 0.03 L), inhaled montelukast 100 µg (LS mean = 0.13 L;  $p \leq .001$ ), 250 µg (LS mean = 0.10 L;  $p < .01$ ), and 1000 µg (LS mean = 0.12 L;  $p \leq .001$ ) significantly improved the time-weighted average change from baseline in FEV<sub>1</sub> over 4 hours (Table 2, Figure 3). The efficacy of montelukast approached a plateau at the 100 µg dose, which also showed the largest treatment effect compared with placebo. The results based on the completers

TABLE 2.—Change from baseline in FEV<sub>1</sub> (L) over 4 hours (primary endpoint) and at 24 hours.

| Treatment (µg)                     | n  | Baseline Mean (SD) | Change from baseline LS Mean (95% CI) |
|------------------------------------|----|--------------------|---------------------------------------|
| Time-weighted average over 4 hours |    |                    |                                       |
| Placebo                            | 67 | 2.45 (0.64)        | 0.03 (–0.03, 0.10)                    |
| 25                                 | 42 | 2.39 (0.64)        | 0.07 (0.00, 0.14)                     |
| 100                                | 30 | 2.55 (0.68)        | 0.13 (0.06, 0.20)*                    |
| 250                                | 66 | 2.46 (0.64)        | 0.10 (0.04, 0.16)**                   |
| 500                                | 25 | 2.56 (0.61)        | 0.09 (0.01, 0.16)                     |
| 1000                               | 36 | 2.38 (0.59)        | 0.12 (0.05, 0.19)*                    |
| Average at 24 hours                |    |                    |                                       |
| Placebo                            | 67 | 2.45 (0.64)        | 0.02 (–0.06, 0.09)                    |
| 25                                 | 42 | 2.39 (0.64)        | 0.05 (–0.03, 0.13)                    |
| 100                                | 29 | 2.55 (0.69)        | 0.10 (0.01, 0.19)***                  |
| 250                                | 66 | 2.46 (0.64)        | 0.06 (–0.01, 0.13)                    |
| 500                                | 25 | 2.56 (0.61)        | 0.08 (–0.01, 0.18)                    |
| 1000                               | 36 | 2.38 (0.59)        | 0.09 (0.01, 0.18)***                  |

Note: \* $p \leq .001$ ,  
\*\* $p < .01$ , and  
\*\*\* $p < .05$  vs. placebo.

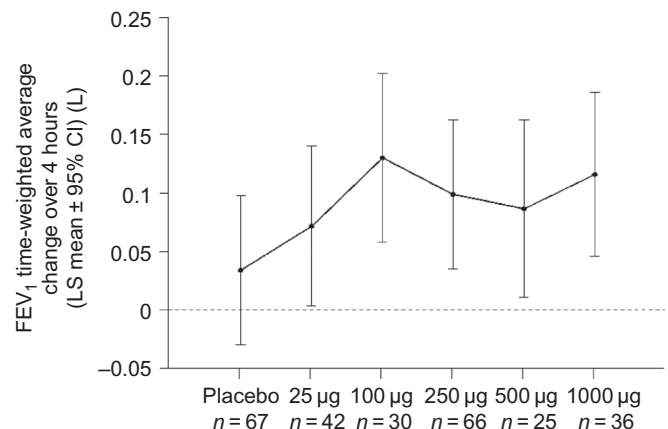


FIGURE 3.—Dose-response curve after single-dose administration of inhaled montelukast: Change from baseline in FEV<sub>1</sub> (L) as the time-weighted average over the initial 4 hours postdose. Values are least-squares (LS) mean with 95% confidence intervals (CI).

population were consistent with that of the full analysis set population, and prespecified subgroup analyses indicated general consistency of treatment effect across the different subgroups studied (data not shown).

**Duration and Onset.** For the change in FEV<sub>1</sub> from baseline at 24 hours, montelukast 100 µg (LS mean = 0.10 L;  $p < .05$ ) and 1000 µg (LS mean = 0.09 L;  $p < .05$ ) were significantly more effective than placebo (LS mean = 0.02 L) (Table 2, Figure 4). Onset of action occurred as quickly as 20 minutes with both montelukast 1000 µg (LS mean = 0.03 L;  $p < .05$ ) and 250 µg (LS mean = 0.02 L;  $p < .05$ ), compared with placebo (LS mean = –0.05 L). Onset with inhaled montelukast 100 µg occurred after 2 hours, compared with placebo (0.09 L vs. 0.01 L;  $p < .05$ ).

**Additive Bronchodilation with Albuterol.** Inhaled montelukast (all doses pooled) plus albuterol (LS mean = 0.34 L) was significantly more effective than montelukast

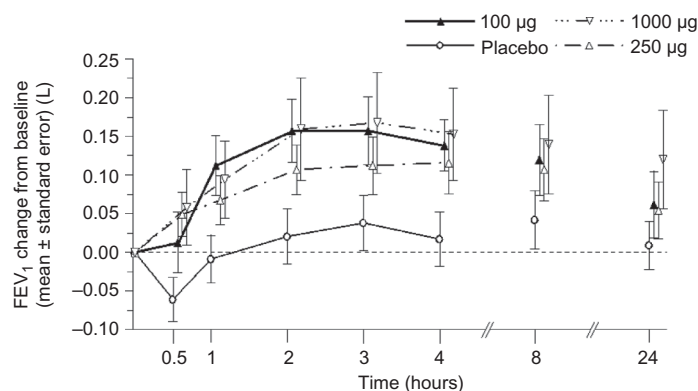


FIGURE 4.—Time course of bronchodilation after single doses of inhaled montelukast: Change from baseline in FEV<sub>1</sub> (L) by time point (selected doses and selected time points). To improve legibility of the graph, some intermediate doses and intermediate time points are not shown. Values represent mean  $\pm$  standard error.

plus placebo (LS mean = 0.15 L;  $p < .05$ ) as measured by the time-weighted average change from baseline in FEV<sub>1</sub> over 90 minutes post-albuterol administration (Figure 5). A significant difference was observed as early as 15 minutes after albuterol administration, compared with the placebo for albuterol (0.34 L vs. 0.16 L;  $p < .05$ ).

### Tolerability

The incidence of AEs was low and similar among treatments. There were 4 (6.0%) patients with clinical AEs on placebo; 1 (2.4%) on inhaled montelukast 25  $\mu$ g; 3 (4.5%) on 250  $\mu$ g; 3 (12.0%) on 500  $\mu$ g; and 0 (0%) on inhaled montelukast 100 and 1000  $\mu$ g. No serious AEs or drug-related AEs were reported. One patient discontinued because of an AE, which occurred 8 days after receiving placebo. No reports of cough or symptoms of bronchoconstriction were reported in association with (i.e., on the same day as) any administration of active montelukast; there was one report each of cough and asthma after administration of placebo. Reported AEs included nasopharyngitis and eczema in patients receiving inhaled montelukast 500  $\mu$ g and sinus congestion in patients receiving inhaled montelukast 25  $\mu$ g, but no AEs occurred in more than one patient on any particular treatment.

### DISCUSSION

This early Phase I study of inhaled montelukast showed that for the primary endpoint of the time-weighted average change in FEV<sub>1</sub> over 4 hours after administration, single doses of 100, 250, and 1000  $\mu$ g were each significantly more active than placebo, whereas the individual doses of 25 and 500  $\mu$ g did not reach statistical significance. For the change from baseline in FEV<sub>1</sub> at 24 hours, inhaled montelukast at doses of 100 and 1000  $\mu$ g were each significantly better than placebo. It is important to note that the primary intent of this study was not to demonstrate the efficacy of the various individual dose strengths versus placebo. Instead, the intent of the adaptive-dose study design was to construct a dose-response curve of inhaled montelukast for acute bronchodilation that could identify the “steep part of the curve,” that is, targeting a curve that delineates 75% of the maximal (“plateau”) placebo-adjusted effect of montelukast. Because the dose adaptations meant that the number of patients receiving a particular dose varied considerably ( $n = 25$  for 500  $\mu$ g to  $n = 66$  for 250  $\mu$ g), the errors of estimation of response at doses varied accordingly. The true dose-response curve is likely to lie within the band constituted by the CI at each dose strength, but the true response at any particular dose may differ from the corresponding point estimate obtained in the study. Nevertheless, the adaptive design

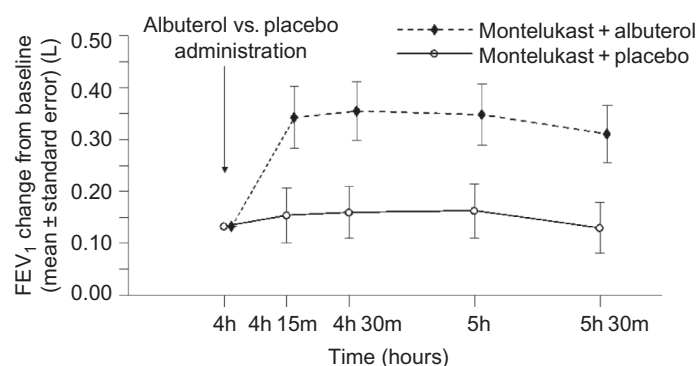


FIGURE 5.—Additive bronchodilation with albuterol: Change from baseline in FEV<sub>1</sub> (L) by time point after albuterol administration, pooling all active montelukast doses. Values represent mean  $\pm$  standard error.  $P < 0.05$  for montelukast + albuterol vs. montelukast + placebo.

of this Phase I study enabled some early exploration of doses that could potentially be associated with efficacy, in preparation for larger (and more definitive) dose-ranging studies that will still need to be performed in clinical asthma.

Our results suggest a steep dose-response curve at doses less than 100  $\mu$ g and a plateau from 100 to 1000  $\mu$ g, with 100  $\mu$ g representing the lowest effective dose studied here. These results are consistent with the dose-ranging studies of oral montelukast, in which changes in FEV<sub>1</sub> (after 3–6 weeks of treatment) were similar for montelukast 2–50 mg (11) and for montelukast 10–200 mg (7), showing that the steep part of the dose-response curve for lung function was below 2 mg of montelukast and the plateau above 10 mg, when delivered orally. In addition, Reiss et al. (5) found that, compared with placebo, single doses of oral montelukast 100 and 250 mg provided similar and significant bronchodilation as defined by the mean maximum increase in FEV<sub>1</sub>.

Despite studying doses that appear to be at the plateau of the dose-response curve, the observed effects on FEV<sub>1</sub>, though significant versus placebo for 100 and 1000  $\mu$ g, were fairly modest in magnitude, as a weighted average over the time points from 10 minutes to 4 hours (0.13 and 0.12 L, respectively) and also at 24 hours (0.10 and 0.09 L). Given a baseline FEV<sub>1</sub> of 2.55 L, this equates to a time-weighted average change from baseline over the initial 4 hours postdose of approximately 5.1% for inhaled montelukast 100  $\mu$ g and a corresponding change of approximately 1.2% for placebo (baseline = 2.45 L, change from baseline = 0.03 L). By comparison, in two studies of oral montelukast by Reiss et al., the authors found that the mean change from baseline in FEV<sub>1</sub> measured at the time of peak plasma levels—that is, 4 hours after oral administration—was approximately 14% with oral montelukast 250 mg and approximately 3% with placebo in one study (6) and approximately 22% with oral montelukast 100 or 250 mg and approximately 13% with placebo in another study (5). In the trial of intravenous montelukast in chronic asthma, the changes at 4 hours were approximately 23%, 17%, and 10% for intravenous montelukast, oral montelukast, and placebo, respectively (8). In the longer term dose-ranging studies of oral montelukast, the changes in FEV<sub>1</sub> from baseline ranged from 6.3% to 13.5% for montelukast 10 mg and 1.5–6.2% for placebo (7, 11).

It is important to note that although the magnitude of bronchodilation in this study appears to be approximately one-fifth to half that observed in the oral montelukast dose-ranging studies and intravenous study, the reduction in bronchodilation appears to be similar for both the montelukast and placebo treatments, suggesting perhaps a broader phenomenon of attenuated bronchodilatory responses rather than merely a modest response to inhaled montelukast. This possibility appears to be supported by the relative contributions of inhaled montelukast and albuterol to total bronchodilation. In this study, we found that albuterol added to inhaled montelukast resulted in an approximately 14% improvement in FEV<sub>1</sub> from baseline

(0.34 L from 2.44 L baseline). Thus, the relative contributions to overall percentage change from baseline in FEV<sub>1</sub> of montelukast and montelukast plus albuterol in our study were 5% : 14%, or about 1 : 3. By comparison, in the study by Reiss et al. comparing single-dose montelukast 100 or 250 mg with placebo, the authors found that salbutamol administered 9 hours after the initial study drug administration (a second dose was administered after 6 hours), increased the change from baseline in FEV<sub>1</sub> from 20% to 55% in the montelukast groups (5), which is similar to the 1 : 3 ratio observed in our study.

Thus, importantly, although the absolute level of bronchodilation in our study was lower than that observed in earlier studies with oral and intravenous montelukast, not only were the levels of bronchodilation by montelukast and placebo affected to a similar extent but the relative contributions of montelukast and albuterol to total bronchodilation in the oral studies were also similar. Cross-study comparisons are inherently limited and should be interpreted with caution, particularly given the time span between studies. However, these results suggest that factors other than efficacy may account for the magnitude of our results, such as differences in patient populations, advances in asthma treatment, more or earlier aggressive management, environmental factors, or combinations thereof. Further detailed speculation is beyond the scope of this early Phase I study of inhaled montelukast.

The main limitation of this study is the lack of a positive control such as oral montelukast, which would have greatly aided in the interpretation and context of the findings with inhaled montelukast. However, as this was a dose-adaptive study, such a design was not easily incorporated. In addition, we evaluated the effect of montelukast plus albuterol, as prespecified in the protocol, but we did not evaluate the effect of placebo plus albuterol, which was not prespecified. It is possible that such data might yield additional useful information regarding the relative contributions of montelukast and albuterol to overall bronchodilation.

The tolerability of inhaled montelukast was similar to that of placebo, without any local AEs following inhalation of montelukast. No dose-related changes in tolerability were observed.

In conclusion, these early Phase I results have shown that a single administration of inhaled montelukast provided rapid and sustained bronchodilation compared with placebo. Further studies are ongoing to better determine its role in the treatment of clinical asthma.

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#### DECLARATION OF INTEREST

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