# A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma

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**Background: Current treatments for acute asthma provide inadequate benefit for some patients. Intravenous montelukast may complement existent therapies.**
**Objective: To evaluate efficacy of intravenous montelukast as adjunctive therapy for acute asthma.**
**Methods: A total of 583 adults with acute asthma were treated with standard care during a ≤60-minute screening period. Patients with $FEV_1$ ≤50% predicted were randomly allocated to intravenous montelukast 7 mg (n = 291) or placebo (n = 292) in addition to standard care. This double-blind treatment period lasted until a decision for discharge, hospital admission, or discontinuation from the study. The primary efficacy endpoint was the time-weighted average change in $FEV_1$ during 60 minutes after drug administration. Secondary endpoints included the time-weighted average change in $FEV_1$ at various intervals (10-120 minutes) and percentage of patients with treatment failure (defined as hospitalization or lack of decision to discharge by 3 hours postadministration).**
**Results: Montelukast significantly increased $FEV_1$ at 60 minutes postdose; the difference between change from baseline for placebo (least-squares mean of 0.22 L; 95% CI, 0.17, 0.27) and montelukast (0.32 L; 95% CI, 0.27, 0.37) was 0.10 L (95% CI, 0.04, 0.16). Similar improvements in $FEV_1$-related variables were seen at all time points (all $P < .05$). Although treatment failure did not differ between groups (OR 0.92; 95% CI, 0.63, 1.34), a prespecified subgroup analysis suggests likely benefit for intravenous montelukast at US sites.**
**Conclusion: Intravenous montelukast added to standard care in adults with acute asthma produced significant relief of airway obstruction throughout the 2 hours after administration, with an onset of action as early as 10 minutes. (J Allergy Clin Immunol 2010;125:374-80.)**

***Key words:*** *Intravenous montelukast, acute asthma, asthma exacerbation, $FEV_1$, hospitalization, leukotriene receptor antagonist, randomized trial*

Asthma is characterized by exacerbations that may be life-threatening. These exacerbations are induced by triggers such as viruses, aspirin, allergens, and physical exertion that cause the release of inflammatory mediators, including leukotrienes.[1,2] Although current standard treatments for acute asthma—including supplemental oxygen, $\beta_2$-agonists, corticosteroids, and anticholinergics (for severe exacerbations)—are quite effective in most patients, they are inadequate for rapid and sustained improvement in a significant proportion.[3-5] Therefore, there is a need for new treatment options that provide benefits beyond the current standard treatments.

Kuitert and Watson[6] recently reviewed the efficacy of adjunctive oral and intravenous leukotriene inhibitors/receptor antagonists in acute asthma and noted the paucity of studies evaluating clinical outcomes with these agents. Montelukast is a potent leukotriene receptor antagonist that, when taken orally, provides benefit in asthma by decreasing airway inflammation and reversing bronchoconstriction.[7-9] Coadministration of montelukast with $\beta_2$-agonist bronchodilators or corticosteroids provides added benefit.[10-12] Dockhorn et al[13] showed that intravenous montelukast improved $FEV_1$ in patients with chronic asthma, and Camargo et al[14] found that the addition of intravenous montelukast to standard care produced a rapid improvement in $FEV_1$ in acute asthma. A role for montelukast in acute asthma was supported by the observation of increased urinary leukotriene $E_4$ levels in patients with acute asthma.[15] Studies of intravenous formulation of other antileukotriene agents, such as intravenous zileuton,[16] remain to be reported.

Asthma guidelines recognize the evaluation of lung function as critical to the management of acute asthma.[4,17] $FEV_1$ and peak expiratory flow measurements are objective assessments of the severity of asthma exacerbations and the response of patients to treatment. Indeed, lung function is the single strongest predictor of hospitalization.[18] Rapid and sustained bronchodilation, together with the attenuation of airway inflammation and the prevention of relapse, remain the immediate goals of emergency physicians treating patients with acute asthma.

Thus, the aim of this study was to investigate further the effect of intravenous montelukast in addition to standard therapy in the

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*Abbreviations used*
AE: Adverse experience
LS: Least squares
OR: Odds ratio

treatment of acute asthma. The primary endpoint of the study was change in lung function ($FEV_1$).

## METHODS

### Patients and study design

This study was conducted between July 2004 and February 2007 in the United States (34 sites) and 15 other countries (28 sites). Subjects were ≥15 years old, had ≥1 year history of physician-diagnosed asthma, and presented with an acute exacerbation of asthma. Patients >54 years were included if they also had documented $FEV_1$ reversibility ≥15% after $\beta_2$-agonist treatment during the current episode or within the past 5 years, or if their lifetime tobacco exposure was ≤10 pack-years. Exclusion criteria included clinically significant, active comorbid disease; a body mass index >35 kg/m$^2$; or a smoking history of >15 pack-years.

The study was designed to be consistent with the existing standard care for acute asthma. At the time patient recruitment began, the standard of care was most recently described in the 2002 Global Initiative for Asthma recommendations.[19] On arrival, patients received standard treatment during a ≤60-minute screening period (period I): oxygen, inhaled short-acting $\beta_2$-agonist (2.5-5 mg in 3 mL saline every 20 minutes) as needed, and inhaled ipratropium (not to exceed 36 μg per hour) or nebulized ipratropium (not to exceed 500 μg per hour) as needed. Patients with $FEV_1$ ≤50% predicted on all measurements were allocated (1:1) to double-blind therapy (according to a computer-generated randomization schedule with a blocking factor of 4 provided by the study sponsor) during the active treatment period (period II), which began with the intravenous administration (manual bolus over 2-5 minutes) of either placebo or montelukast 7 mg; allocation and administration of study drug had to occur within 60 minutes of initiation of the standard treatment. Study drug (light-protected lyophilized product reconstituted in 20 mL 3.3% dextrose/0.3% sodium chloride [supplied together with the study drug]) was prepared in a foil-wrapped syringe (to ensure adequate blinding) by a qualified person who was not directly associated with the care of the patients; the intravenous line was flushed with 5 mL diluent before and after administration of study drug. Investigators were instructed to administer systemic corticosteroids (60 mg prednisone or 50 mg prednisolone orally) mmediately after infusion of study drug. All patients continued to receive standard treatment in period II, consisting of oxygen therapy, $\beta_2$-agonist every 20 minutes as needed, and ipratropium every 60 minutes as needed. Period II lasted until a decision was made for discharge from the study site, admission to the hospital, or discontinuation from the study. A follow-up telephone interview was conducted approximately 14 days after the patient completed period II.

Parenteral corticosteroids or antileukotriene agents were not permitted within 12 hours of initial presentation or during period I; oral corticosteroids and antileukotriene agents were not allowed during period I. Additional medications were not permitted during periods I and II, including inhaled corticosteroids, long-acting $\beta_2$-agonists, long-acting anticholinergics (not permitted before presentation), methylxanthines, heliox, and magnesium salts.

The study (Protocol 288) was conducted in conformance with Good Clinical Practice standards and was approved by ethical review committees or institutional review boards for each study site. Written informed consent/assent was obtained from each patient before any study procedures were performed.

### Efficacy evaluations

The primary efficacy endpoint was the time-weighted average change in $FEV_1$ from prerandomization baseline during the first 60 minutes after drug administration ($\Delta FEV_1$ [0-60 minutes]). The percentage of patients with treatment failure, defined as patients who required hospitalization or for whom a decision to discharge was not made by 3 hours after administration of the drug, was a secondary endpoint. Other secondary endpoints included the total dose of as-needed $\beta_2$-agonist and the number of $\beta_2$-agonist administrations during 3 hours after drug administration; the time-weighted average $\Delta FEV_1$ (0-40 minutes) and $\Delta FEV_1$ (0-20 minutes); and the average change in $FEV_1$ after 10 minutes.

Spirometry readings were obtained using a standard spirometer (Spirotrac; Vitalograph Inc, Lenexa, Kan) supplied to each study site. The $FEV_1$ from at least 2, but preferably the 3 best, acceptable maneuvers were recorded. Spirometry was performed immediately before administering the study therapy (baseline) and at 10, 20, 40 minutes, and 1, 2, and 3 hours after the completion of study drug infusion and at the time the decision was made to discharge, admit, or discontinue the patient.

### Safety evaluations

Safety and tolerability were assessed by clinical evaluations (physical examinations) and adverse experience (AE) monitoring. Safety analyses were based on the All-Patients-as-Treated population, including all randomized patients who started the study drug.

### Statistical analysis

The primary hypothesis was that, in adult patients with acute asthma, the addition of intravenous montelukast 7 mg to standard therapy would cause a significant improvement in $FEV_1$ within the first 60 minutes after administration (ie, time-weighted average change in $FEV_1$ from preallocation baseline over the first 60 minutes after study drug administration), compared with placebo. The primary analysis was based on the Full Analysis Set population, which included all patients who started the study drug and who had at least 1 efficacy measurement at baseline and during the measurement period. $FEV_1$ endpoints were analyzed by using an analysis of covariance model with the baseline $FEV_1$ as a covariate, with factors for treatment, region (US/non-US site), and therapy before period I with systemic corticosteroids or leukotriene receptor antagonists (yes/no). Analyses of change from baseline at each time point were also performed by using the same analysis of covariance model. The percentages of treatment failures were compared by using a logistic model; analyses comparing the time to outcome were performed by using a Cox regression model. The dose of $\beta_2$-agonist administered per patient and the total number of administrations in period II were assessed by using nonparametric analysis of variance models.

A prespecified step-down procedure was used to adjust for the multiplicity of endpoints.[20] Time of onset of action of montelukast was determined by comparing the time-weighted average difference from baseline in $FEV_1$ during the first 60, 40, 20 and 10 minutes, and each comparison was performed only if the previous one was significant at $\alpha = 0.01$. Analyses of the percentage of treatment failures was performed only if the comparison between treatments for the primary endpoint was significant at $\alpha = 0.01$. Because all other comparisons were considered secondary, no adjustments were needed. Subgroup analyses of the $FEV_1$ and treatment failure variables were performed for age (by tertiles), sex, race, and the 4 variables assessing asthma severity: baseline $FEV_1$ (≤/> median), baseline dyspnea score, baseline respiratory rate (≤/> median), and pulse oximetry (≤/> median) to assess whether treatment effect was consistent across subgroups. Secondary and other endpoints were tested at the $\alpha = 0.05$ level.

A few *post hoc* analyses were performed. First, we computed the change in $FEV_1$ in period I before and after $\beta_2$-agonist to benchmark the bronchodilating effect of montelukast against short-acting $\beta_2$-agonist. Second, we examined the potential impact of baseline $FEV_1$ (<30% predicted) on the primary endpoint. Third, we examined the potential impact of practice variation on the clinical endpoints. For these final analyses, we used a 2-level hierarchical model (with site as a random effect) to control better for practice variation across the 62 sites. We also examined treatment efficacy in a model in which the difference between proportions was the metric of choice; the model included site as a fixed effect (Cochran-Mantel-Haenszel weights).