

Effect of montelukast for treatment of asthma in cigarette smokers

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Objective: Many asthmatic patients are unable to quit cigarettes; therefore information is needed on treatment options for smokers. This study evaluates 10 mg/d montelukast and 250 µg of fluticasone propionate twice daily, each compared with placebo, in patients with self-reported active smoking (unable to quit) and asthma.

Methods: Patients (ages 18-55 years, with asthma ≥ 1 year], FEV₁ of 60% to 90% of predicted value, airway reversibility $\geq 12\%$, and self-reported active smoking ≥ 0.5 to ≤ 2 packs per day) were randomized (after a 3-week, single-blind, placebo, run-in period) to 1 of 3 parallel, 6-month, double-blind treatment arms. The primary efficacy end point was the percentage of days with asthma control during treatment. Adverse experiences (AEs) were also evaluated.

Results: There were 347, 336, and 336 patients randomized to montelukast, fluticasone, and placebo, respectively. The mean percentage of days with asthma control over 6 months of treatment was 45% (montelukast, $P < .05$ vs placebo), 49% (fluticasone, $P < .001$ vs placebo), and 39% (placebo); the difference between montelukast and fluticasone was not significant ($P = .14$). Patients with a smoking history of ≤ 11 pack years (the median value) tended to show more benefit with fluticasone, whereas those with a smoking history of >11 pack

years tended to show more benefit with montelukast. AEs occurred in similar proportions among treatment groups. **Conclusions:** In a population of asthmatic patients actively smoking cigarettes, both 10 mg/d montelukast and 250 µg of fluticasone propionate twice daily significantly increased the mean percentage of days with asthma control compared with placebo. (J Allergy Clin Immunol 2013;■■■:■■■-■■■.)

Key words: Montelukast, smoking, fluticasone propionate, leukotriene receptor antagonist, asthma control, corticosteroids

In asthma treatment guidelines, inhaled corticosteroids are considered the standard of care based on their efficacy to improve symptoms, increase lung function, and reduce inflammation.¹⁻³ However, these guidelines are based on evidence from clinical trials that exclude patients who smoke cigarettes, and such patients account for a considerable proportion of the asthmatic population.^{4,5} Clinical trial data on treatment for this population are scant, despite evidence demonstrating that patients with asthma who smoke cigarettes have poorer asthma control (eg, worse asthma symptoms and more frequent exacerbations) compared with asthmatic nonsmokers.⁶⁻⁸ Data also show an inverse relationship between the number of cigarettes smoked each day and the level of asthma control.⁹ Effects of smoking in asthmatic patients include decreased nitric oxide levels and increased airway hyperresponsiveness. Finally, these patients not only have reduced FEV₁ but also have an acceleration in lung function decrease over time that is related to cigarettes smoked.¹⁰⁻¹²

Although clinical trial data are limited, some evidence suggests that corticosteroids have reduced efficacy in patients who smoke cigarettes.¹³⁻¹⁶ In these studies corticosteroid therapy did not improve lung function in asthmatic patients who were actively smoking, whereas nonsmoking asthmatic patients demonstrated significant improvements. A study by Chaudhuri et al¹⁶ found that smoking impaired the response to corticosteroids for asthma symptoms and lung function. Mechanisms for potential resistance to inhaled corticosteroid therapy caused by smoking are unclear; proposed mechanisms include increased clearance of inhaled corticosteroids (because of increased airway mucosal permeability), decreased histone deacetylase activity through oxidative stress, and reduced uptake of the inhaled drug in the inflamed tissues.¹⁷⁻²¹

Evidence has suggested that cigarette smoking induces production of cysteinyl leukotrienes,^{22,23} which could be expected to worsen asthma. Therefore patients with asthma who smoke might benefit from treatment with leukotriene antagonists, especially if their treatment response to corticosteroids is blunted. Lazarus et al¹⁵ found that patients who actively smoked had lung function improvements that, when compared with nonsmoking patients,

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Abbreviations used

AE: Adverse experience
 COPD: Chronic obstructive pulmonary disease
 FVC: Forced vital capacity
 PEF: Peak expiratory flow
 SABA: Short-acting β -agonist

were blunted after inhaled beclomethasone but were not blunted after the leukotriene receptor antagonist montelukast. To further explore the effect of smoking on response to asthma treatment, we conducted what we believe is the largest prospective, randomized clinical trial performed in this population. Our objective was to assess the effects of montelukast and fluticasone, each compared with placebo, in asthmatic patients who smoke cigarettes. The hypothesis of this study was that montelukast increases the percentage of days with asthma control over 6 months of treatment compared with placebo in this patient population.

METHODS

This double-blind, placebo- and active- controlled, randomized clinical trial (Merck protocol no. 332, Clinical Trials Registry no. NCT00284856) was conducted at 131 sites in 29 countries between May 2006 and April 2010 after approval by local independent ethics committees. Good Clinical Practice principles were followed. Before enrollment, all patients provided written informed consent.

Patients

Eligible patients were 18 or more to 55 or less years of age, self-reported active cigarette smokers (smoking frequency of ≥ 0.5 packs and ≤ 2 packs per day), had a smoking history of 30 pack years or less (pack years = cigarette packs per day multiplied by the number of years smoking), and had a clinical history of chronic asthma for 1 year or more with symptoms including dyspnea, wheezing, chest tightness, and/or cough. Eligible patients were previously unable to quit smoking; additionally, patients were encouraged to quit smoking during this study and did not discontinue study medication if they did quit. Patients were excluded if they were determined to have chronic obstructive pulmonary disease (COPD), emphysema, or both. Emphysema was diagnosed based on chest radiography within 1 year of randomization. COPD was identified by using the American Thoracic Society definition for chronic bronchitis: chronic cough and sputum for most days for 3 months for at least 2 consecutive years. Detailed patient inclusion/exclusion criteria are listed in the **Methods** section in this article's Online Repository at www.jacionline.org.

Study design

After a 3-week, single-blind, placebo run-in period, eligible patients were randomized into 3 parallel groups at visit 2 (in a double-blind, double-dummy manner with in-house blinding, according to a computer-generated allocation schedule) to receive montelukast (and fluticasone matching-image placebo), fluticasone propionate (and montelukast matching-image placebo), or placebo (matching-image placebos for both montelukast and fluticasone) for 6 months. Short-acting β -agonist (SABA; albuterol/salbutamol) use was allowed, but habitual use without symptoms was discouraged by the investigators. Visit 3 was scheduled to be 1 month after visit 2, visit 4 was to be 3 months after visit 2, and visit 5 was to be 6 months after visit 4.

Assessments

The primary efficacy end point was the percentage of days with asthma control; the 4 components of this end point (a day without >2 puffs of SABAs,

nighttime symptoms, an unscheduled health care visit, or oral corticosteroids) were collected daily in patient diaries. Secondary efficacy end points were change from baseline in daytime asthma symptom score (see the **Methods** section in this article's Online Repository)²⁴ and change from baseline in morning peak expiratory flow (PEF). Tertiary end points are detailed in the **Methods** section in this article's Online Repository and listed in **Table I**. Safety and tolerability were assessed based on review of spontaneously reported adverse experiences (AEs) and laboratory values.

Preplanned subgroup analyses were conducted examining consistency of treatment effects across subgroups defined by median smoking history (pack years), median smoking frequency (packs per day), and median baseline FEV₁ (in liters). Loess spline curves were generated *post hoc* to visualize the relationship between treatment response and the factor of interest.²⁵⁻²⁸

Statistical analysis

The mean percentage of days with asthma control was evaluated by using an ANOVA model (see the **Methods** section in this article's Online Repository). In a *post hoc* nonparametric analysis, the Mann-Whitney *U* version of the Wilcoxon rank test was used to estimate the probability that a randomly chosen patient in one treatment group will experience a greater treatment effect than a randomly chosen patient in another group; this method provides a patient-based rather than population-based analysis²⁹ to assess the overlap in patient distributions (expressed as a percentage; 100% equals complete overlap). The **Methods** section in this article's Online Repository describes statistical power, the methods for assessing the secondary and tertiary efficacy end points, and a stepwise regression analysis for the primary end point. Safety analyses included all randomized patients who took at least 1 dose of the double-blind study medication and all safety data that were collected within 14 days after the last intake of study medication.

RESULTS**Patients**

There were 1019 patients randomized to montelukast ($n = 347$), fluticasone ($n = 336$), and placebo ($n = 336$) (**Fig 1**). Among these patients, 53% were male, 65% were white, 48% were European, and the mean age was 38 years. Baseline demographics were generally similar among the treatment groups (**Table II**).

Smoking history across all patients was 13.1 pack years; by treatment group, mean pack years were 13.0, 12.4, and 13.9 for placebo, montelukast, and fluticasone, respectively. Approximately one third of the patients were smoking 0.5 packs per day (the minimal level allowed in the inclusion criteria); mean smoking frequency was 0.79 packs per day before study entry, and it decreased slightly during the study. Mean smoking frequency was similar among treatment groups: for montelukast, fluticasone, and placebo at screening, mean smoking frequency was 0.78, 0.82, and 0.77 packs per day, respectively; at month 3, it was 0.73, 0.77, and 0.70 packs per day, respectively; and at month 6, it was 0.72, 0.75, and 0.70 packs per day, respectively. Analysis of the post- β -agonist FEV₁/forced vital capacity (FVC) ratio at baseline showed that 21.8% had a ratio of 70% or less. The distribution of these patients was similar among the treatment groups: 23.1%, 23.3%, and 19.1% in the montelukast, fluticasone, and placebo groups, respectively.

Efficacy

Primary end point. Both active treatments provided statistically significant improvements in the mean percentage of days with asthma control: a *P* value of less than .05 for montelukast and a *P* value of less than .001 for fluticasone, each compared with placebo (**Table I**). A statistical difference between the 2 active

TABLE I. Summary of efficacy end points

End points	Montelukast	P value vs placebo	Fluticasone	P value vs placebo	Placebo
Primary end point					
Percentage of days with asthma control (95% CI)	45.0 (40.6 to 49.3)	.040	49.2 (44.9 to 53.5)	<.001	39.1 (34.7 to 43.5)
Primary end point adjusted for predictive factors from regression analysis					
Percentage of days with asthma control adjusted for smoking history and FEV ₁ percent predicted (95% CI)	50.3 (46.2 to 54.3)	.024	53.9 (49.9 to 58.0)	<.001	43.6 (39.5 to 47.7)
Secondary end points					
Change from baseline in daytime asthma symptom score (95% CI); 0- to 6-point scale	−0.45 (−0.53 to −0.37)	.004	−0.50 (−0.58 to −0.42)	<.001	−0.30 (−0.38 to −0.23)
Change from baseline in morning peak expiratory flow (L/min [95% CI])	15.3 (10.3 to 20.2)	.117	21.4 (16.5 to 26.3)	<.001	10.2 (5.2 to 15.1)
Tertiary end points					
Change from baseline in nighttime asthma symptom score (95% CI); 0- to 3-point scale	−0.32 (−0.37 to −0.28)	.003	−0.33 (−0.38 to −0.29)	.001	−0.23 (−0.28 to −0.18)
Percentage change from baseline in average puffs per day of SABA use (95% CI)	−34.7 (−40.2 to −29.2)	.010	−39.1 (−44.6 to −33.7)	<.001	−25.4 (−30.9 to −19.9)
Percentage of asthma-free days (95% CI)	26.3 (22.4 to 30.2)	.053	29.5 (25.6 to 33.4)	.002	21.3 (17.3 to 25.2)
Percentage of days with asthma exacerbation (95% CI)	14.3 (11.6 to 17.1)	.001	12.7 (9.9 to 15.4)	<.001	20.2 (17.4 to 23.0)
No. (%) of patients with asthma attack	36 (10.8)	.111	27 (8.2)	.008	48 (14.8)
No. (%) of patients using oral corticosteroid	32 (9.3)	.371	23 (6.9)	.035	38 (11.4)
Change from baseline in evening PEF (L/min [95% CI])	13.9 (9.2 to 18.6)	.294	17.5 (12.8 to 22.2)	.028	10.6 (5.8 to 15.4)
Percentage change from baseline in FEV ₁ (L)	7.7 (5.3 to 10.0)	.974	9.1 (6.8 to 11.5)	.360	7.7 (5.4 to 10.1)
No. (%) of patients with discontinuations because of asthma	3 (0.9)	NA	1 (0.3)	NA	2 (0.6)
Change from baseline in peripheral blood eosinophil count (10 ³ /μL [95% CI])	−0.04 (−0.07 to −0.02)	.039	−0.03 (−0.06 to −0.00)	.187	−0.01 (−0.03 to 0.02)

treatments was not observed ($P = .140$). Fig 2 shows the distribution of patients' responses on this end point; this histogram shows a bimodal distribution, with many patients showing either very good response or very poor response. Given this U-shaped (instead of normal) distribution, a nonparametric Mann-Whitney U statistic was used in a *post hoc* analysis to quantify the overlap in the distributions for each treatment group. The percentage of overlap for montelukast compared with placebo was 90.9% (95% CI, 82.0% to 99.7%), and that for fluticasone compared with placebo was 86.6% (95% CI, 77.7% to 95.4%). Because the upper bound of the 95% CI was less than 100% for each of these comparisons, montelukast and fluticasone were each significantly better than placebo in this distribution analysis. The percentage of overlap between montelukast and fluticasone was 95.0%, with a 95% CI of 86.2% to 100.0%, demonstrating that these distributions were not significantly different.

The 4 components of the primary end point that defined daily asthma control were SABA use of 2 puffs per day or less (eg, 2 puffs used as pre-exercise prophylaxis did not count as a lack of asthma control), no nighttime symptoms, no unscheduled asthma health care visit, and no systemic corticosteroid use for asthma. Asthma attacks (defined as a composite of unscheduled health care or systemic corticosteroid use, thus measuring the risk domain of asthma control³) were infrequent in all treatment

groups (Table I). Thus the components of the primary end point that drove the efficacy results were the percentage of days with SABA use of 2 puffs or less and the percentage of days with no nighttime symptoms, which are measures of the impairment domain of asthma control (Fig 3). Fig 4 shows the overall primary endpoint over time.

Secondary and tertiary end points. Results for the secondary end point of daytime asthma symptom score were similar to those observed with the primary end point (Fig 4). Significant differences were observed for montelukast and fluticasone versus placebo ($P < .010$ and $P < .001$, respectively). The secondary end point of morning PEF demonstrated a significant difference for fluticasone versus placebo only; on this end point, the separation between the montelukast and placebo groups was reduced at months 5 and 6 (Fig 4).

There were no statistical differences between either active treatment and placebo for the tertiary end point of percentage change from baseline in FEV₁ (Table I); it is relevant to note that in this study FEV₁ was obtained by using local/site spirometers and not by using standardized/centralized spirometric methods. Results for the remaining tertiary end points are shown in Table I.

Additional efficacy analyses. Lower frequency of smoking was associated with a higher percentage of days of asthma

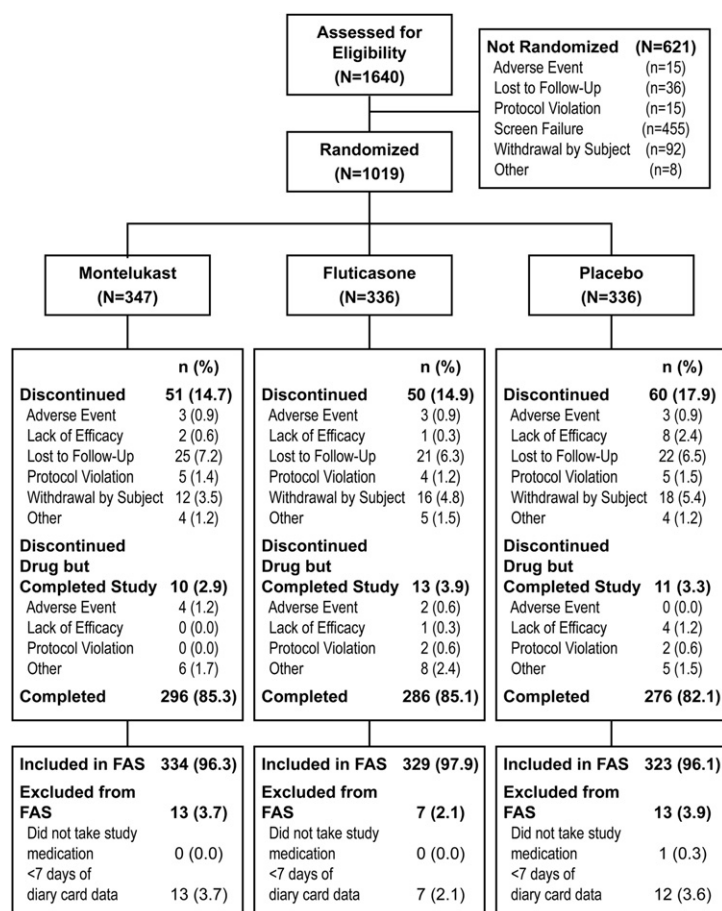


FIG 1. CONSORT diagram showing patient enrollment, randomization, discontinuation, completion, and inclusion of patients in analyses. FAS, Full analysis set.

control on treatment, as expected. In a subgroup analysis based on smoking frequency, both active treatments showed greater separation from placebo in the subgroup with higher smoking frequency, but this subgroup effect of smoking frequency was not significant. No differences in treatment effects were observed between the subgroup of patients with an FEV₁/FVC ratio of 70% or less and the subgroup with a ratio of greater than 70%.

To evaluate the effect of specific factors in an attempt to explain the pattern in secondary end points, particularly morning PEF, noted at months 5 and 6, *post hoc* analyses were performed for the 6-month treatment period, the 1- to 3-month treatment period, and the 4- to 6-month treatment period by using the following factors: differential dropouts by treatment group, degree of reversibility ($\leq 15\%$, $>15\%$, or less than or equal to or greater than the median of 19%), use of atopic medications, and frequency of smoking. These evaluations did not lead to a clear explanation for the lack of difference between montelukast and placebo at months 5 and 6.

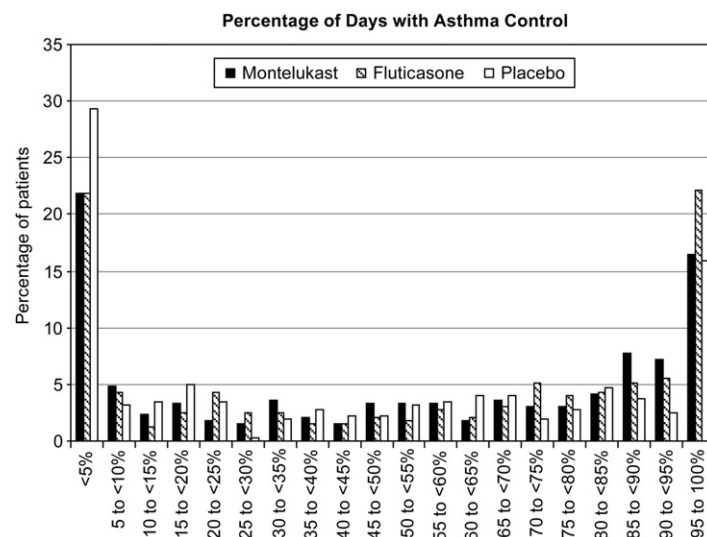
We also conducted a stepwise regression analysis to determine factors that were predictive of a therapeutic response in the study. Factors considered in this analysis were the following: history of allergic rhinitis, season of randomization (ie, during summer, fall, winter, or spring), age, airway reversibility at baseline, smoking history before the study (in pack years), smoking frequency (in packs per day) at baseline, smoking frequency on treatment, FEV₁ percent predicted, and peripheral blood eosinophil level at baseline. Of these, the following were found to be predictive factors:

smoking history ($P < .001$), FEV₁ percent predicted ($P < .001$), summer randomization ($P = .081$), and smoking frequency at baseline ($P = .150$); thus smoking history and FEV₁ percent predicted appeared to be the most important factors significantly influencing the percentage of days with asthma control. Fig 5 displays spline curves showing the effect of each treatment according to smoking history, as well as FEV₁ percent predicted. Patients with a smoking history of ≤ 11 pack years (the median value) tended to show more benefit with fluticasone, whereas those with a smoking history of >11 pack years tended to show more benefit with montelukast (Fig 5, A). For FEV₁ percent predicted, montelukast and fluticasone showed similar efficacy in patients with impaired lung function, whereas fluticasone had a larger response in patients with FEV₁ percent predicted values of greater than 75% (Fig 5, B). Finally, the primary analysis of the percentage of days with asthma control was repeated, adjusting for smoking history and FEV₁ percent predicted. Results are shown in Table I.

Safety and tolerability. AEs occurred in 37%, 39%, and 37% of montelukast-, fluticasone-, and placebo-treated patients, respectively. Serious AEs occurred in similar proportions of the treatment groups. Discontinuations because of AEs occurred in 2%, 1.5%, and 1.2% of montelukast-, fluticasone-, and placebo-treated patients, respectively (Table III). AEs that occurred in 3% or more of patients in 1 or more treatment groups are shown in Table III. The AEs generally occurred in similar proportions of

TABLE II. Patients' demographics

	Montelukast (n = 347)		Fluticasone (n = 336)		Placebo (n = 336)		Total (n = 1019)	
	No.	Percent	No.	Percent	No.	Percent	No.	Percent
Male subjects	184	53.0	189	56.3	170	50.6	543	53.3
Age (y)								
Mean (SD)	37.7 (10.4)		38.4 (10.7)		37.9 (9.9)		38.0 (10.3)	
Race								
Asian	76	21.9	70	20.8	73	21.7	219	21.5
Black or African American	4	1.2	4	1.2	4	1.2	12	1.2
Multiracial	43	12.4	41	12.2	41	12.2	125	12.3
White	224	64.6	221	65.8	218	64.9	663	65.1
Geographic region								
Middle East and South Africa	46	13.3	49	14.6	42	12.5	137	13.4
Asia/Pacific	76	21.9	70	20.8	72	21.4	218	21.4
Europe	170	49.0	160	47.6	163	48.5	493	48.4
North America	21	6.1	21	6.3	24	7.1	66	6.5
South America	34	9.8	36	10.7	35	10.4	105	10.3
History of allergic rhinitis								
No	199	57.3	167	49.7	183	54.8	549	54.0
Yes (all year long without seasonal flares)	62	17.9	71	21.1	66	19.8	199	19.6
Yes (only during certain seasons)	43	12.4	50	14.9	47	14.1	140	13.8
Yes (all year with seasonal flares)	43	12.4	48	14.3	38	11.4	129	12.7
Distribution of baseline FEV ₁ (percent predicted)								
≥80%	107	30.8	109	32.4	117	34.8	333	32.7
≥60 to <80%	228	65.7	210	62.5	210	62.5	648	63.6
<60%	12	3.5	17	5.1	9	2.7	38	3.7
Baseline FEV ₁								
Percent predicted, mean (SD)	74.06 (9.78)		74.06 (10.48)		74.35 (9.23)		74.16 (9.84)	
Percent reversibility, mean (SD)	22.55 (11.77)		21.57 (11.13)		22.43 (11.68)		22.19 (11.53)	
Baseline FEV ₁ /FVC ratio								
Patients with ratio ≤70%	23.1		23.3		19.1		21.8	

**FIG 2.** Distribution of percentage of days with asthma control by increments of 5%.

patients within each treatment group, although the difference between montelukast and placebo for headache had a 95% CI that excluded zero. There was 1 patient who died during the study because of a postoperative complication of thyroid surgery; this patient was in the fluticasone group, and the event was classified as not related to study medication.

DISCUSSION

The present study provides data on a population of asthmatic patients who are not commonly studied. We observed that montelukast demonstrated a statistically significant improvement over placebo on the primary end point of percentage of days with asthma control during a 6-month treatment period; a statistical

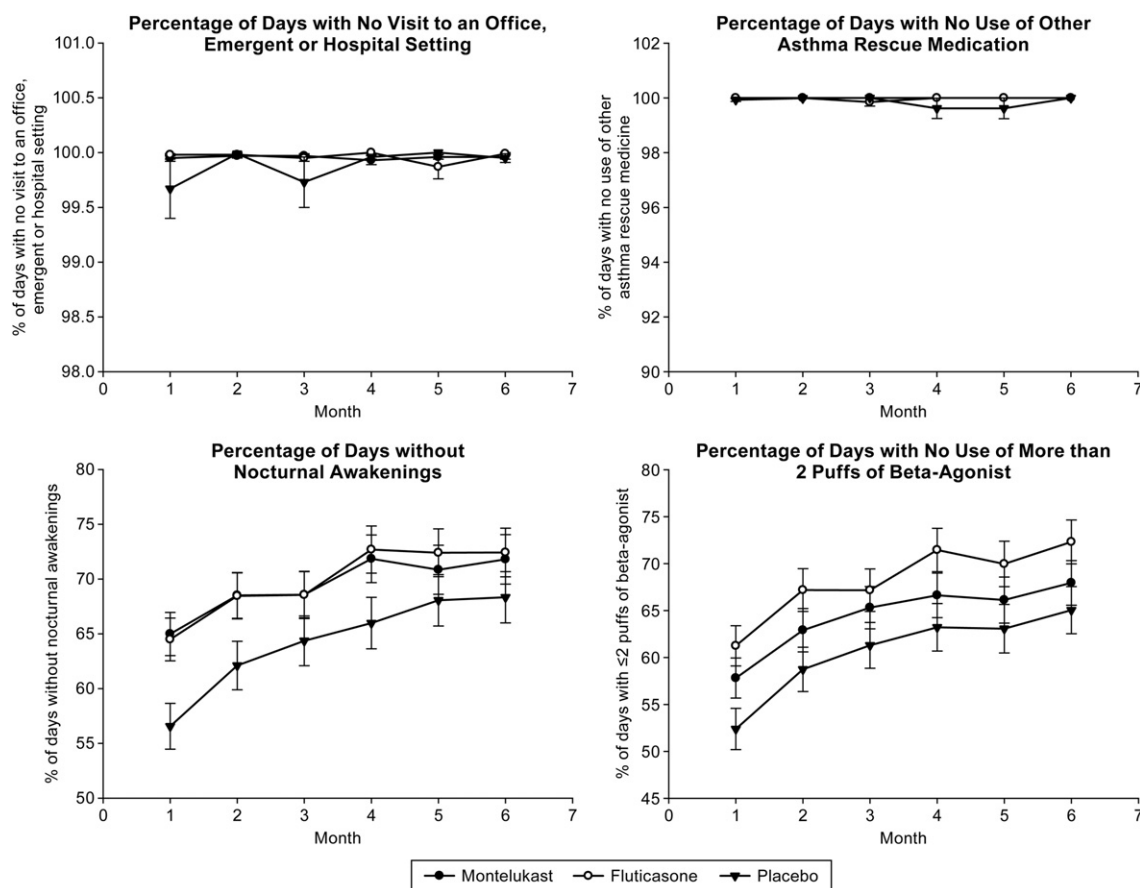


FIG 3. Components of primary end point: percentage of days with asthma control during treatment.

difference between 10 mg of oral montelukast daily and the active control, 250 μ g of inhaled fluticasone twice daily, was not observed. The components of the primary end point that drove these results were related mostly to daily symptom control (ie, rescue SABA use and nighttime symptoms). For daytime asthma symptom score (a secondary end point), both montelukast and fluticasone showed statistically significant improvement compared with placebo. For morning PEF (the other secondary end point), montelukast showed less efficacy during months 4 to 6 and thus did not achieve statistical significance compared with placebo, whereas fluticasone did achieve significance.

Previous clinical trials in nonsmokers have demonstrated clinically important benefits for montelukast that are superior to those for placebo,³⁰⁻³² whereas inhaled corticosteroids have shown benefits significantly greater than those of montelukast.³³⁻³⁵ In contrast to these studies, the results of the present trial demonstrate no significant difference between the inhaled corticosteroid fluticasone and montelukast, suggesting a differential effect of smoking on the efficacy of these treatments. Although it should be noted that this study was not designed to establish noninferiority, data from previous trials of smoking asthmatic patients, such as the Smoking Modulates Outcomes of Glucocorticoids study¹⁵ and the study by Price et al,³⁶ have similarly demonstrated an attenuation of efficacy from inhaled corticosteroids, whereas the efficacy and lung function improvements from montelukast were not reduced.

It can be hypothesized that these results are due to greater leukotriene synthesis in smokers, as supported by evidence for greater urinary excretion of cysteinyl leukotrienes in these

subjects.^{18,19} Some data from the present study further seem to support the importance of leukotriene synthesis in smokers; in particular, patients with a smoking history of less than the median value of 11 pack years tended to show more benefit of fluticasone, whereas those with a smoking history of greater than 11 pack years tended to show more benefit with montelukast. This could be due to greater leukotriene synthesis in patients with greater smoking exposure. Interestingly, in a 5-month study of children exposed to secondhand tobacco smoke while receiving daily inhaled corticosteroids for their asthma, an increased urinary leukotriene E₄ level was the only factor that identified the children at high risk for asthma exacerbations.³⁷ However, further research is needed to confirm a greater benefit of montelukast in patients with a greater (eg, >11 pack years) history of smoking.

The detrimental effect of smoking on the efficacy of inhaled corticosteroid therapy in this trial is also notable because it was observed in a population of relatively light smokers and against a relatively high dose of fluticasone. The allowed level of smoking in the trial was up to 2 packs per day, but the actual mean was only 0.79 packs per day. Resistance to treatment effects with fluticasone appeared to increase with greater smoking exposure. On the other hand, montelukast efficacy was relatively independent of smoking exposure, which is consistent with what was observed in the trial by Price et al.³⁶

In addition to efficacy, tolerability and costs are noteworthy considerations when choosing asthma treatments. In the present study AEs (as reported spontaneously by patients to investigators) were similar among the treatment groups, and no new or

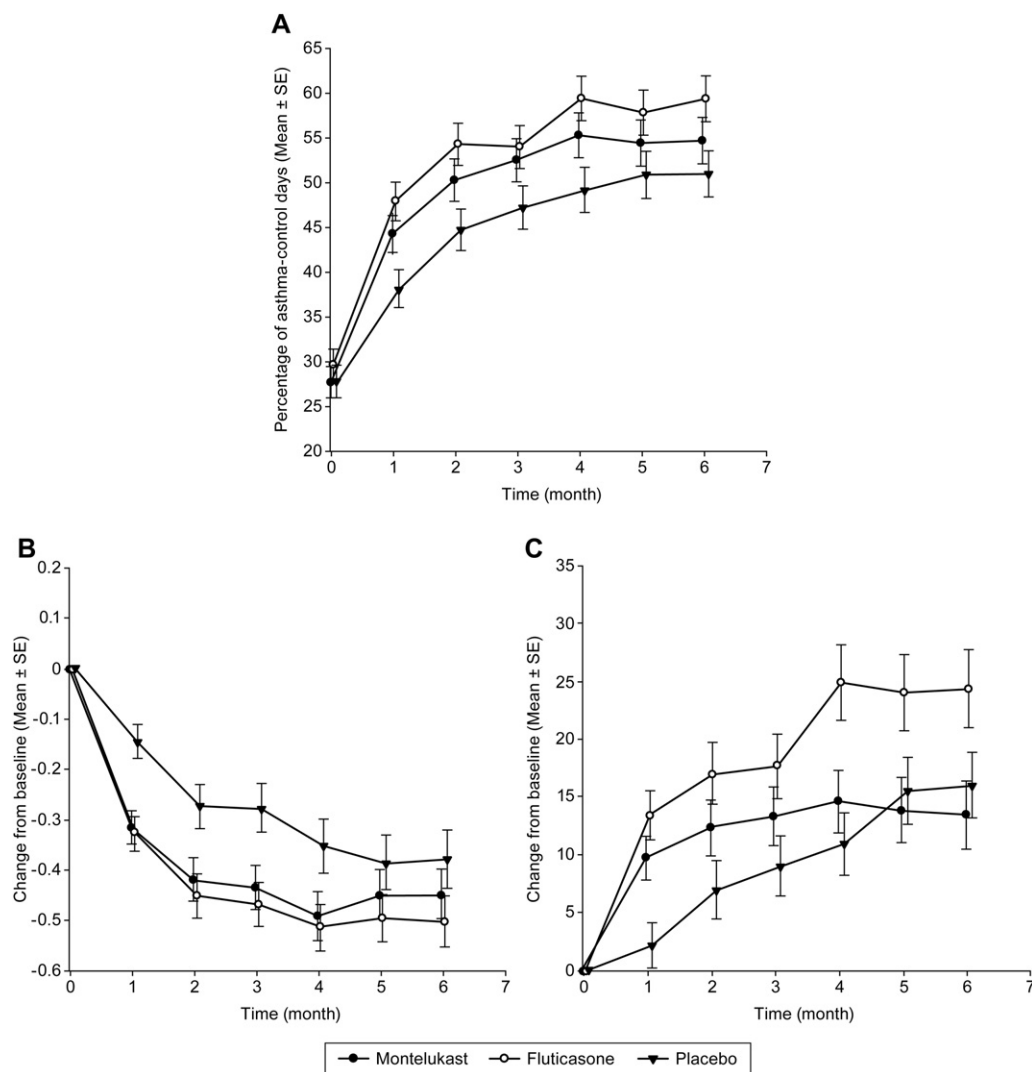


FIG 4. Primary and secondary endpoints over time. **A**, Percentage of asthma-control days (primary endpoint). **B**, Change from baseline in daytime asthma symptom score (0 to 6 scale). **C**, Change from baseline in morning peak expiratory flow (L/min).

unexpected findings related to safety were observed. However, systematic assessments for possible local and systemic side effects were not part of the study design. The relative cost of therapy varies among different countries, but considering the additional cost of a higher dose of fluticasone and the results observed in this study, in which fluticasone efficacy appeared diminished with greater smoking exposure, montelukast might be advantageous in asthmatic patients who have high smoking exposure, particularly those with a smoking history of greater than 11 pack years.

The present study provides important information on a population of patients who are rarely studied in trials of treatments for asthma. In addition to the primary results, we also performed regression analyses to identify the important role of 2 baseline factors, smoking history and FEV₁ percent predicted, which significantly influenced the percentage of days with asthma control. However, there were several limitations that should be considered when evaluating these results and when planning future research. The present study (in contrast to the Smoking Modulates Outcomes of Glucocorticoids study¹⁵) did not include nonsmoking patients to fully compare the efficacy of each treatment with

smoking patients. An additional limitation in this study was the absence of objective measures (eg, cotinine for smoking status); our data depended on patient-reported smoking status, and we did not measure urinary leukotriene levels. Other objective measures, such as fraction of exhaled nitric oxide and eosinophil and neutrophil counts in sputum, were not collected. Also, the aforementioned clustering of patients toward the lower bound of the allowed smoking frequency might be due to the presence of other comorbidities in heavy smokers that led to their exclusion from the study. Patient recruitment was a significant problem in this study, and in fact, the recruitment period was extended twice (requiring 3.5 years across 29 countries) to meet the targeted number of completed patients. It is unclear whether the distribution of patients with regard to smoking frequency and the exclusion of patients with greater disease burden linked to heavy smoking had an effect on the results observed in this study.

Finally, although the diagnostic criteria in this study support that this was a study of asthmatic smokers, it is possible that some patients also had mild COPD. Exclusion of such an overlapping phenotype is challenging, noting that approximately 17% of US

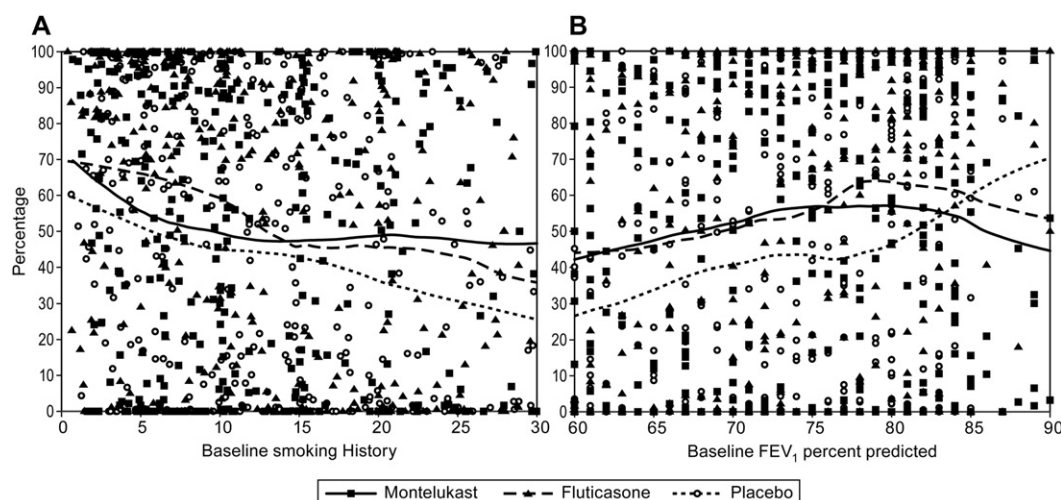


FIG 5. Smoothed *spline* plot of percentage of days with asthma control by treatment group versus smoking history (in pack years; **A**) and FEV₁ percent predicted at baseline (**B**).

TABLE III. AE summary

	Montelukast (n = 347)	Fluticasone (n = 336)	Placebo (n = 335)
No. (%) of patients with ≥ 1 AEs	129 (37.2)	131 (39.0)	123 (36.7)
No. (%) of patients with drug-related AEs*	15 (4.3)	10 (3.0)	7 (2.1)
No. (%) of patients with serious AEs	9 (2.6)	10 (3.0)	11 (3.3)
No. (%) of patients who discontinued because of an AE	7 (2.0)	5 (1.5)	4 (1.2)
Most common AEs (incidence $\geq 3\%$ in ≥ 1 treatment groups)			
Nasopharyngitis	23 (6.6)	27 (8.0)	22 (6.6)
Upper respiratory tract infection	8 (2.3)	13 (3.9)	7 (2.1)
Headache	17 (4.9)†	11 (3.3)	5 (1.5)
Asthma	46 (13.3)	36 (10.7)†	58 (17.3)

*Determined by the investigator to be at least possibly related to study medication.

†95% CI for the difference versus placebo did not include 0.

patients and 19% of United Kingdom patients with obstructive lung diseases (ie, asthma, chronic bronchitis, and emphysema) have more than one disorder concurrently.³⁸ Also, the criteria used to exclude COPD in this study were relatively imprecise. However, it should also be noted that the patients who entered this trial were relatively young, with a low pack year history, and that the guidelines definitions for asthma,¹⁻³ including airway reversibility by both percentage and volume, were met by this study population. Furthermore, although approximately 22% of patients in this study had a post β -agonist FEV₁/FVC ratio of 70% or less, no differences in treatment effects were observed between the subgroup of patients with FEV₁/FVC ratios of 70% or less and the subgroup with a ratio of greater than 70%. Therefore any effect on the study results of patients with possible comorbid COPD is likely minor, while understanding that diagnostic uncertainty remains.

In summary, in a population of patients with confirmed asthma who smoked, both montelukast and fluticasone were statistically superior to placebo in the primary end point of the percentage of days with asthma control. The difference between montelukast and fluticasone was not statistically significant, which contrasts previous studies in nonsmokers showing superiority of inhaled corticosteroids

to montelukast. These results support the notion that smoking attenuates the efficacy of corticosteroids in patients with asthma. Although these data also suggest that the efficacy of montelukast is not affected by smoking with regard to the primary end point, more research is needed to understand the relative effectiveness of montelukast versus middose fluticasone in this population.

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Key messages

- Evidence suggests that corticosteroids have reduced efficacy for treatment of asthma in smokers. Because smoking induces cysteinyl leukotriene production, treatment with a leukotriene receptor antagonist might be helpful in this population.
- Both montelukast and fluticasone were superior to placebo in this population; the difference between the 2 treatments was not statistically significant.
- Patients with a smoking history of less than 11 pack years tended to show more benefit with fluticasone, whereas those with a smoking history of greater than 11 pack years tended to show more benefit with montelukast.

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METHODS

Patients' entry criteria

Eligible patients were previously unable to quit smoking. Patients were encouraged to quit smoking during this study and did not discontinue study medication if they did quit.

Inclusion. Inclusion criteria verified the diagnosis of asthma (including that patients had symptomatic disease requiring preventer therapy in line with guidelines [ie, average SABA intake ≥ 2 puffs per day]), reduced lung function ($FEV_1 \geq 60\%$ and $\leq 85\%$ of predicted value), and airway reversibility (demonstrated by $\geq 12\%$ improvement from the pre- β -agonist absolute FEV_1 value [absolute value ≥ 200 mL from the baseline level] between 20 and 30 minutes after inhaled β -agonist administration at visit 1). Patients were required to be compliant with study procedures during a 3-week, single-blind, run-in period.

Exclusion. Exclusion criteria included a diagnosis of COPD or any medical condition that would compromise the safety of the patient or confound the results of the study; pregnant or breast-feeding patients were also excluded. Use of the following medications, based on timing before study start, was also a reason for study exclusion: oral, intravenous, intramuscular, or intra-articular corticosteroids within 1 month; antiasthma medications (inhaled corticosteroids, leukotriene receptor antagonists, inhaled cromolyn, or nedocromil, inhaled long-acting β -agonist, or inhaled anticholinergic agents) within 10 days; and intravenous gammaglobulin or immunosuppressants within 1 month. Allergen immunotherapy must have been started 6 months before the study and should have reached a steady maintenance level at the time of the study.

Efficacy measures

Daytime asthma symptom score. The daytime asthma symptom score is a 4-question symptom score (score of 0 [best] to 6 [worst] for each question) assessing the frequency and severity of asthma symptoms and the effect on daily activity.^{E1}

Tertiary efficacy end points. Tertiary efficacy end points included change from baseline in nighttime asthma symptom score (patients recorded whether they woke up with asthma symptoms; this daily score was averaged over the double-blind treatment period [period II] and compared with the average at baseline [during the single-blind placebo run-in period I]); change from baseline in evening PEF; percentage change from baseline in average daily SABA puffs; percentage of asthma-free days (ie, a day with no unscheduled visit for asthma care to an office, emergency, or hospital setting; no use of SABAs; no use of other asthma rescue medication; and no nocturnal awakening); percentage of patients with an asthma attack (defined as unscheduled asthma care in an office, emergency, or hospital setting and/or use of oral, intravenous, or intramuscular corticosteroid rescue medication to treat asthma); percentage change from baseline in FEV_1 ; discontinuation because of asthma; and change from baseline eosinophil count.

Statistical methods

Definition of full analysis set. The full analysis set population was used for the efficacy analyses, including the primary efficacy analysis of percentage of days of asthma control. This population included all observed on-treatment data from patients who had 1 or more weeks of diary data while receiving randomized treatment.

ANOVA model. The ANOVA model included factors for treatment, smoking frequency reported at baseline (packs per day less than or equal to or greater than the median), smoking history (pack years less than or equal to or greater than the median), and geographic region. The same analysis model was used for certain tertiary end points: percentage change from baseline in average daily number of SABA puffs, percentage of asthma-free days, and percentage change from baseline FEV_1 .

Additional analyses of the primary end point.

- Because bimodal distributions are not ideal for ANOVA, we conducted a *post hoc* nonparametric analysis of the primary end point by using the Mann-Whitney *U* test (with the formula $U^* = U/N_1 \times N_2$) to evaluate the overlap in patient distributions when comparing the treatment groups. Estimates and 95% CI limits were transformed to a percentage overlap scale ranging

from 0% to 100%,^{E2,E3} with 100% (ie, complete overlap of the population) corresponding to a *U* statistic of 0.5, to express the overlap in the distribution of percentage of days with asthma control.

The statistical null hypothesis of no treatment difference is equivalent to testing the null hypothesis of $U^* = 1/2$. The statistic U^* is symmetric in that a value of $1/2$ indicates that the 2 distributions are equal and that there is perfect overlap, and a value of 0 or 1 indicates that one distribution is greater than the other and there is no overlap. To describe the degree to which 2 distributions overlap one another in terms of a percentage overlap (O), one could define O as follows:

$$O = (1 - 2 \times |U^* - 0.5|) \times 100\%.$$

In this way a U^* value of 0.5 would correspond to an O value of 100% and U^* values of 0 or 1 would correspond to an O value of 0%.

- A *post hoc* stepwise regression analysis was conducted with an α value of .15 for entry in the model to determine factors that were predictive of a therapeutic response in the study.

Analyses of secondary and tertiary efficacy end points.

The secondary end points and other tertiary efficacy end points (ie, those tertiary end points not described above using the main ANOVA model) were evaluated by using an analysis of covariance model with the corresponding baseline as a covariate. The model included the following factors: treatment, smoking history, smoking frequency reported at baseline, and region.

Statistical power. Assuming an SD of 38 percentage points, a sample of 283 patients per treatment group provides 85% power at an α level of .050 (2-sided test) to detect a 9.6 percentage-point difference between montelukast and placebo in the percentage of days with asthma control.

Results from additional efficacy analyses. Preplanned subgroup analyses were conducted examining the consistency of treatment effects across subgroups defined by median smoking history (measured in pack years), median smoking frequency (measured in packs per day), and median baseline FEV_1 (measured in liters).

Smoking history

A preplanned subgroup analysis was performed, looking at the consistency of treatment effect on percentage of days with asthma control in patients with a smoking history of less than or equal to or greater than the median. The median value was equal to 11 pack years. Within- and between-treatment effects with associated 95% CIs are provided in Table E1. The treatment-by-subgroup interaction was also tested, and results are displayed in Table E2. There was some indication of an overall interaction between treatment and baseline smoking history ($P = .089$). This was mainly due to different treatment effects for montelukast and fluticasone across subgroups (interaction $P = .029$). As shown in Table E1, patients with a smoking history of less than 11.4 pack years tended to show more benefit with fluticasone, whereas a small numeric advantage for montelukast was observed in patients with a smoking history of greater than 11.4 pack years.

Baseline FEV_1

Results from the subgroup analysis by baseline FEV_1 percent predicted (in patients with FEV_1 percent predicted value of less than or equal to or greater than the median [75%]) are provided in Table E3.

Smoking frequency

Results from the preplanned subgroup analysis by smoking frequency (in patients with packs per day of less than or equal to or greater than the median [0.75 packs per day]) are provided in Table E4. The treatment-by-subgroup interaction was also tested, and results are displayed in Table E5. The overall interaction between treatment and baseline smoking frequency was not significant ($P = .360$), and none of the pairwise interactions were significant.

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TABLE E1. Subgroup analysis of percentage of asthma control days by smoking history (full analysis set)

Percentage of asthma control days during period II					
Treatment	No.	Mean (SD)	LS mean (95% CI)*	Difference in LS mean vs placebo (95% CI)*	Difference in LS mean vs fluticasone (95% CI)*
Smoking history ≤ median (11.4 pack years)					
Montelukast	186	53.37 (37.19)	47.29 (41.57 to 53.01)	3.90 (−3.97 to 11.77)	−10.35 (−18.18 to −2.52)
Fluticasone	155	63.04 (36.77)	57.64 (51.52 to 63.76)	14.25 (6.02 to 22.48)	
Placebo	152	49.13 (38.80)	43.39 (37.14 to 49.64)		
Smoking history > median (11.4 pack years)					
Montelukast	148	47.35 (39.28)	43.24 (37.03 to 49.45)	8.67 (0.59 to 16.74)	2.16 (−5.89 to 10.21)
Fluticasone	174	44.63 (39.10)	41.08 (35.31 to 46.84)	6.51 (−1.24 to 14.25)	
Placebo	171	39.13 (36.90)	34.57 (28.74 to 40.40)		

LS, Least squares.

*Based on ANOVA with terms for treatment, region, smoking history, smoking frequency at baseline, and treatment-by-smoking history interaction.

TABLE E2. Analysis of percentage of asthma control days: assessment of interaction between smoking history and treatment ANOVA (full analysis set)

Interaction between treatment and smoking history*	<i>P</i> value
Treatment	.089
Montelukast vs placebo	.407
Montelukast vs fluticasone	.029
Fluticasone vs placebo	.179

*Based on ANOVA with terms for treatment, region, smoking history, smoking frequency at baseline, and treatment-by-smoking history interaction.

TABLE E3. Subgroup analysis of percentage of asthma control days (full analysis set)

Percentage of asthma control days during period II					
Treatment	No.	Mean (SD)	LS mean (95% CI)*	Difference in LS mean vs placebo (95% CI)*	Difference in LS mean vs fluticasone (95% CI)*
Baseline FEV ₁ percent predicted ≤75% (median)					
Montelukast	183	48.70 (38.69)	42.79 (37.15 to 48.43)	10.40 (2.74 to 18.05)	−1.00 (−8.51 to 6.50)
Fluticasone	180	48.03 (39.88)	43.79 (38.17 to 49.41)	11.40 (3.71 to 19.09)	
Placebo	166	37.71 (35.70)	32.39 (26.53 to 38.25)		
Baseline FEV ₁ percent predicted >75% (median)					
Montelukast	151	53.13 (37.55)	47.31 (41.24 to 53.39)	1.59 (−6.58 to 9.76)	−8.03 (−16.29 to 0.22)
Fluticasone	149	59.67 (37.20)	55.35 (49.27 to 61.43)	9.63 (1.46 to 17.79)	
Placebo	157	50.32 (39.53)	45.72 (39.78 to 51.66)		

LS, Least squares.

*Based on ANOVA with terms for treatment, region, smoking history, smoking frequency at baseline, subgroup, and treatment-by-subgroup interaction.

TABLE E4. Subgroup analysis of percentage of asthma control days by smoking frequency (full analysis set)

Percentage of asthma control days during period II					
Treatment	No.	Mean (SD)	LS mean (95% CI)*	Difference in LS mean vs placebo (95% CI)*	Difference in LS mean vs fluticasone (95% CI)*
Smoking frequency ≤ median (0.75 packs per day)					
Montelukast	188	53.65 (37.95)	43.54 (36.69 to 50.38)	3.37 (−4.03 to 10.77)	−3.89 (−11.45 to 3.67)
Fluticasone	178	55.43 (38.01)	47.43 (40.66 to 54.20)	7.26 (−0.22 to 14.75)	
Placebo	193	48.57 (37.17)	40.17 (33.51 to 46.82)		
Smoking frequency > median (0.75 packs per day)					
Montelukast	146	46.91 (38.29)	46.57 (39.30 to 53.85)	9.48 (0.77 to 18.18)	−4.55 (−12.91 to 3.82)
Fluticasone	151	50.80 (40.26)	51.12 (43.88 to 58.36)	14.02 (5.40 to 22.65)	
Placebo	130	36.81 (38.46)	37.10 (29.33 to 44.87)		

LS, Least squares.

*Based on ANOVA with terms for treatment, region, smoking history, smoking frequency at baseline, and treatment-by-smoking frequency interaction.

TABLE E5. Analysis of percentage of asthma control days: assessment of interaction between smoking frequency and treatment ANOVA (full analysis set)

Interaction between treatment and smoking frequency at baseline*	<i>P</i> value
Treatment	.360
Montelukast vs placebo	.533
Montelukast vs fluticasone	.417
Fluticasone vs placebo	.155

*Based on ANOVA with terms for treatment, region, smoking history and smoking frequency at baseline, and treatment-by-smoking frequency at baseline interaction.