

## ORIGINAL ARTICLE

# Rescue Use of Beclomethasone and Albuterol in a Single Inhaler for Mild Asthma

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## ABSTRACT

**BACKGROUND**

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Treatment guidelines recommend the regular use of inhaled corticosteroids for patients with mild persistent asthma. We investigated whether the symptom-driven use of a combination of beclomethasone dipropionate and albuterol (also known as salbutamol) in a single inhaler would be as effective as the regular use of inhaled beclomethasone and superior to the as-needed use of inhaled albuterol.

**METHODS**

We conducted a 6-month, double-blind, double-dummy, randomized, parallel-group trial. After a 4-week run-in, patients with mild asthma were randomly assigned to receive one of four inhaled treatments: placebo twice daily plus 250  $\mu\text{g}$  of beclomethasone and 100  $\mu\text{g}$  of albuterol in a single inhaler as needed (as-needed combination therapy); placebo twice daily plus 100  $\mu\text{g}$  of albuterol as needed (as-needed albuterol therapy); 250  $\mu\text{g}$  of beclomethasone twice daily and 100  $\mu\text{g}$  of albuterol as needed (regular beclomethasone therapy); or 250  $\mu\text{g}$  of beclomethasone and 100  $\mu\text{g}$  of albuterol in a single inhaler twice daily plus 100  $\mu\text{g}$  of albuterol as needed (regular combination therapy). The primary outcome was the morning peak expiratory flow rate.

**RESULTS**

In 455 patients with mild asthma who had a forced expiratory volume in 1 second of 2.96 liters (88.36% of the predicted value), the morning peak expiratory flow rate during the last 2 weeks of the 6-month treatment was higher ( $P=0.04$ ) and the number of exacerbations during the 6-month treatment was lower ( $P=0.002$ ) in the as-needed combination therapy group than in the as-needed albuterol therapy group, but the values in the as-needed combination therapy group were not significantly different from those in the groups receiving regular beclomethasone therapy or regular combination therapy. The cumulative dose of inhaled beclomethasone was lower in the as-needed combination therapy group than in the groups receiving regular beclomethasone therapy or regular combination therapy ( $P<0.001$  for both comparisons).

**CONCLUSIONS**

In patients with mild asthma, the symptom-driven use of inhaled beclomethasone (250  $\mu\text{g}$ ) and albuterol (100  $\mu\text{g}$ ) in a single inhaler is as effective as regular use of inhaled beclomethasone (250  $\mu\text{g}$  twice daily) and is associated with a lower 6-month cumulative dose of the inhaled corticosteroid. (ClinicalTrials.gov number, NCT00382889.)

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N Engl J Med 2007;356:2040-52.  
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**T**REATMENT GUIDELINES FOR ASTHMA<sup>1,2</sup> recommend regular treatment with inhaled corticosteroids for patients with mild persistent asthma, since this treatment regimen provides control of asthma,<sup>3-7</sup> suppresses airway inflammation,<sup>8,9</sup> and may prevent the progression of asthma.<sup>4-6,10</sup> Although the doubling of the dose of inhaled corticosteroids has been reported to be ineffective in preventing exacerbation of asthma,<sup>11,12</sup> high-dose inhaled corticosteroids administered at the onset of an exacerbation have been reported to enhance the control of asthma.<sup>13</sup> In addition, the control of mild persistent asthma achieved with the use of short courses of high-dose inhaled corticosteroids is similar to that achieved with the regular use of low-dose inhaled corticosteroids.<sup>14</sup> In patients with moderate-to-severe asthma, the use of a combination of an inhaled long-acting  $\beta_2$ -agonist and an inhaled corticosteroid for both maintenance and relief provides better asthma control than does use of the same combination for maintenance and use of a short-acting or long-acting  $\beta_2$ -agonist for relief.<sup>15,16</sup>

Short-acting  $\beta_2$ -agonists are recommended for the relief of asthma symptoms, even though the symptoms are associated not only with bronchoconstriction but also with enhanced airway inflammation.<sup>17</sup> Furthermore, inhaled corticosteroids may rapidly exert their antiinflammatory effects,<sup>18,19</sup> may enhance the effect of  $\beta_2$ -agonists,<sup>20,21</sup> and may be as effective as systemic corticosteroids in treating asthma exacerbations,<sup>22</sup> even if they are not consistently so in cases of severe exacerbation. On this basis, we hypothesized that the symptom-driven rescue use of a short-acting  $\beta_2$ -agonist in combination with a relatively high-dose inhaled corticosteroid is as effective in providing control of mild persistent asthma as is regular treatment with the same dose of the same inhaled corticosteroid twice daily plus a short-acting  $\beta_2$ -agonist as needed.

## METHODS

### STUDY DESIGN

Details of the methods and statistical analysis are provided in the Supplementary Appendix (available with the full text of this article at [www.nejm.org](http://www.nejm.org)). The study was designed by two academic authors, both of whom vouch for the accuracy and completeness of the data reported, and by an employee of the sponsor. All other authors had input into the study design and also helped to per-

form the trial. Statistical analyses were conducted at Contract Research Organization Statistics and Data Management and were reviewed by an academic author. All authors had full access to the data. The sponsor had no input in the writing of the manuscript.

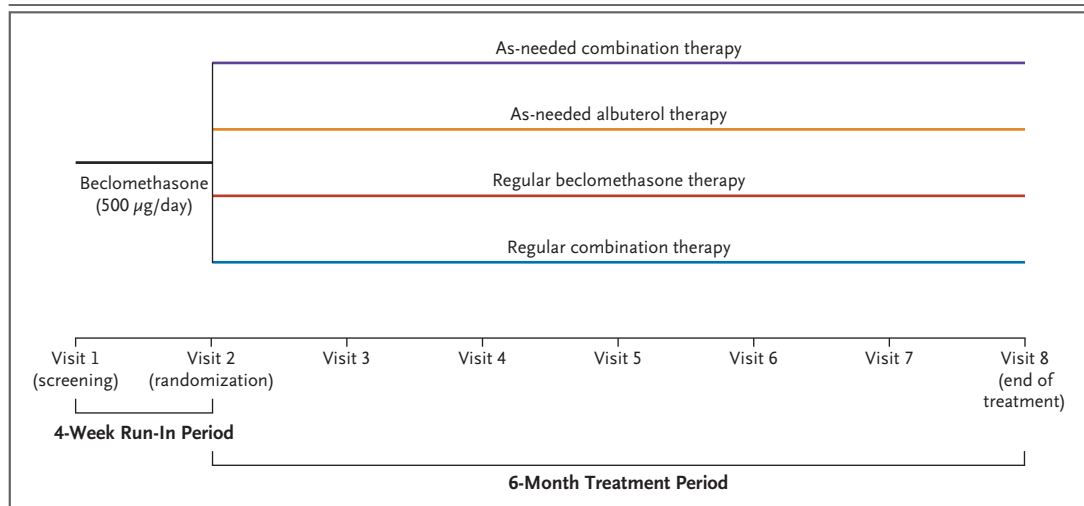
### PATIENTS

Patients were recruited between August 2002 and September 2004 in 25 centers. The inclusion criteria were a history of mild persistent asthma (according to published guidelines<sup>23</sup>) for at least 6 months, an age of 18 to 65 years, a prebronchodilator forced expiratory volume in 1 second (FEV<sub>1</sub>) of 75% or more of the predicted value, associated with either an increase in FEV<sub>1</sub> of 12% or more of the predicted value after inhalation of 200  $\mu$ g of albuterol (known as salbutamol outside the United States) or a positive methacholine challenge (in which a methacholine concentration of <8 mg per milliliter, or a methacholine dose of <1 mg, provokes a 20% decrease in the FEV<sub>1</sub>). Exclusion criteria are reported in the Supplementary Appendix. The protocol was approved by the institutional review board at each study site, and written informed consent was obtained from each participant.

### PROTOCOL

This was a multinational, multicenter, double-blind, double-dummy, randomized, four-group, parallel group, drug-controlled trial (Fig. 1 and 2). Patients were instructed in the use of a peak flow meter (Mini-Wright, Clement Clarke) and were told to record the following data in diary cards daily: rate of peak expiratory flow in the morning and evening, asthma symptoms, number of nocturnal awakenings, intake of study drugs, and number of puffs of rescue medication. Daytime symptoms were evaluated in the evening, and nighttime symptoms in the morning, with the use of a four-point scale.<sup>24</sup> Daytime symptom scores ranged from 0 (no symptoms) to 4 (symptoms occurring for most of the day and affecting normal daily activities); nighttime symptom scores ranged from 0 (no symptoms) to 4 (symptoms so severe that they did not allow any sleep).

Patients entered a 4-week run-in period during which they received 250  $\mu$ g of inhaled beclomethasone dipropionate twice daily and albuterol on an as-needed basis for the relief of symptoms. Patients then entered the study if their asthma was controlled, as defined as an absence of any of the following events during the last 2 weeks of the



**Figure 1. Study Design.**

At each visit, patients underwent a physical examination; measurement of blood pressure, heart rate, and pulmonary function; and evaluation of asthma symptoms, asthma exacerbations, and adverse events. As-needed combination therapy consisted of placebo twice daily plus 250 µg of beclomethasone and 100 µg of albuterol in a single inhaler as needed; as-needed albuterol therapy, placebo twice daily plus 100 µg of albuterol as needed; regular beclomethasone therapy, 250 µg of beclomethasone twice daily and 100 µg of albuterol as needed; and regular combination therapy, 250 µg of beclomethasone and 100 µg of albuterol in a single inhaler twice daily plus 100 µg of albuterol as needed.

run-in period<sup>25</sup>: diurnal variation in the peak expiratory flow rate of more than 20% on 2 consecutive days, use of four or more puffs of rescue albuterol per day on 2 consecutive days, use of oral corticosteroids, and at least 80% adherence to use of the diary and the medications.

On entry into the study, patients were randomly assigned to receive one of four inhaled treatments: placebo twice daily plus 250 µg of beclomethasone and 100 µg of albuterol in a single inhaler as needed (as-needed combination therapy); placebo twice daily plus 100 µg of albuterol as needed (as-needed albuterol therapy, as a control); 250 µg of beclomethasone twice daily and 100 µg of albuterol as needed (regular beclomethasone therapy); or 250 µg of beclomethasone and 100 µg of albuterol in a single inhaler twice daily plus 100 µg of albuterol as needed (regular combination therapy). Patients were not given a written plan of action to guide the as-needed use of study drugs but were simply instructed orally to use them any time they were needed for relief of symptoms.

Patients were randomly assigned to a treatment group according to a list prepared with the use of a random-number generator and a balanced-block design stratified according to center. Each inves-

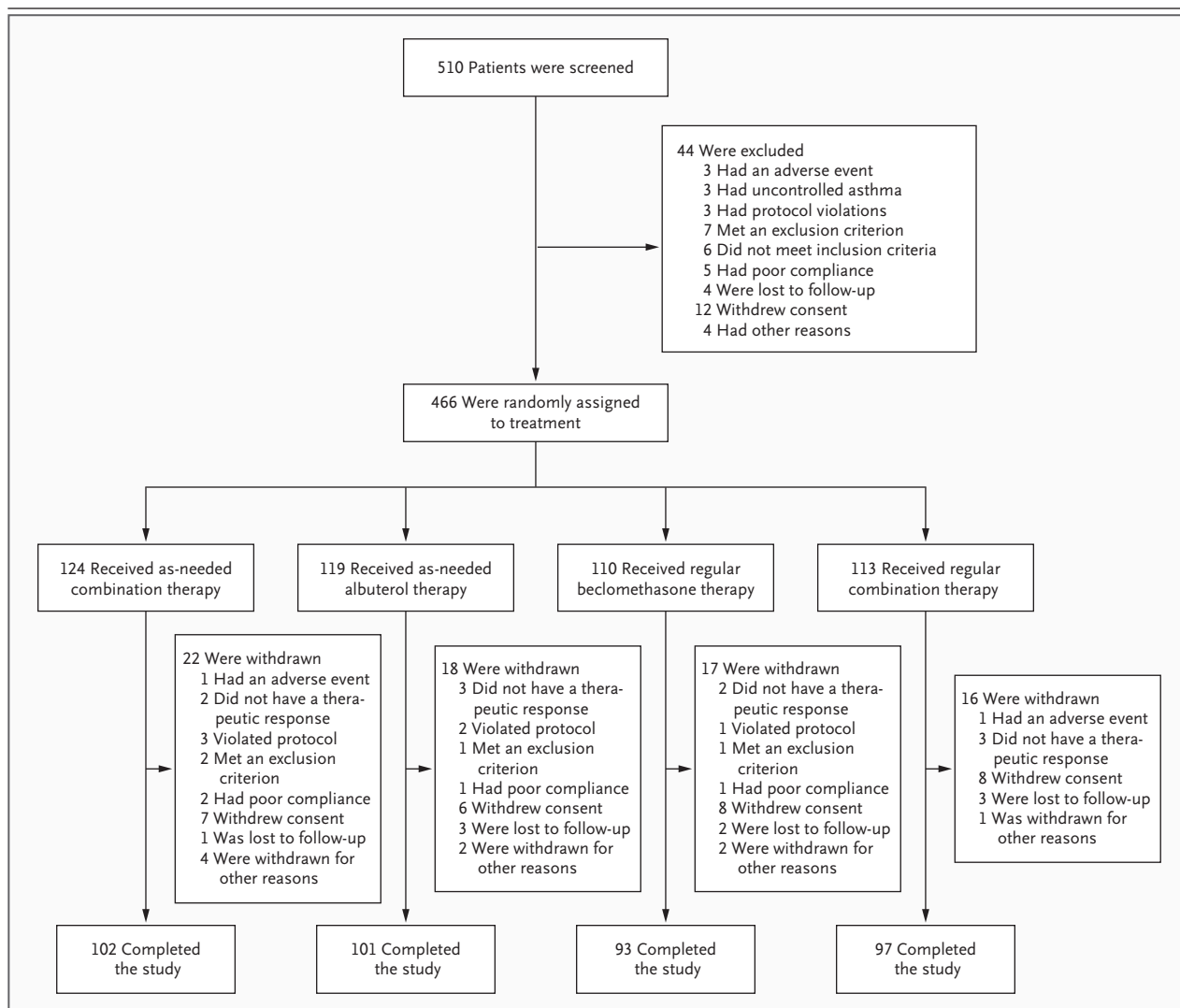
tigator assigned each patient the lowest number available at the site, according to chronologic order of entry into the study at the randomization visit.

Clinic visits took place at the beginning (visit 1) and end (visit 2) of the run-in period and thereafter on study weeks 4, 8, 12, 16, 20, and 24, for a total of 8 visits. During each visit, the investigator reviewed the diary cards and verified compliance with the assigned treatment. Compliant patients were considered to be those who had taken at least 80% of the study medication prescribed since the last visit and had filled in the diary cards consistently since the last visit.

#### OUTCOME VARIABLES

The primary outcome for comparison across treatment groups was the mean rate of morning peak expiratory flow during weeks 23 and 24. Secondary outcomes included other functional variables, symptom scores, and the number and severity of exacerbations (see the Supplementary Appendix).

During each visit, the clinician reviewed the diary cards to assess the number and severity of exacerbations, as previously defined.<sup>25</sup> A mild exacerbation was defined as awakening at night owing to asthma or as a decrease in the morning peak



**Figure 2. Screening, Randomization, and Study Completion.**

Some of the 44 patients who were excluded had more than one reason for exclusion. As-needed combination therapy consisted of placebo twice daily plus 250 µg of beclomethasone and 100 µg of albuterol in a single inhaler as needed; as-needed albuterol therapy, placebo twice daily plus 100 µg of albuterol as needed; regular beclomethasone therapy, 250 µg of beclomethasone twice daily and 100 µg of albuterol as needed; and regular combination therapy, 250 µg of beclomethasone and 100 µg of albuterol in a single inhaler twice daily plus 100 µg of albuterol as needed.

expiratory flow rate to more than 20% below the baseline value, the use of more than three additional puffs per day of rescue medication (either albuterol or beclomethasone and albuterol) as compared with during the baseline period (the last week of the run-in period) for 2 or more consecutive days, or both. Single, isolated days on which mild exacerbation occurred were not counted. A severe exacerbation was defined as a decrease in the morning peak expiratory flow rate to more than 30% below the baseline value on 2 consecu-

tive days or more than eight puffs per day of rescue medication for 3 consecutive days or the need for treatment with oral corticosteroids, as judged by the investigator. Days on which severe exacerbations occurred were excluded from the count of days with mild exacerbations.

**STATISTICAL ANALYSIS**

Our equivalence study was designed to investigate whether the effects of as-needed combination therapy with beclomethasone and albuterol (the inves-

tigational treatment) would be clinically similar to those of either the regular use of beclomethasone plus albuterol as needed (regular beclomethasone therapy, the recommended treatment according to standard guidelines) or the regular use of a beclomethasone and albuterol plus as-needed albuterol (regular combination therapy).

Equivalence was determined on the basis of the two-sided 95% confidence interval (CI) of the difference between treatment groups in the mean morning peak expiratory flow rate during the last 2 weeks of treatment. The maximum difference considered to indicate clinical equivalence between groups was 40 liters per minute (i.e., 10% of the expected mean morning peak expiratory flow rate of 400 liters per minute at the end of the study). This limit was selected a priori (and denoted in the protocol) on the basis of guidelines<sup>23</sup> suggesting that treatment should not be changed if the peak expiratory flow rate varies by less than 20% for a given patient. Thus, we speculated that there would be no clinical consequences of a difference of less than 10% between two groups at the end of the study.

We calculated that we would need to enroll 480 patients, on the basis of an expected mean morning peak expiratory flow rate of 400 liters per minute with an unadjusted SD of 95 liters per minute, a statistical power of the study of 80%, and a two-sided alpha of 0.05. To account for an estimated 15% dropout rate, we calculated that a sample of 552 patients would be required to have data that could be evaluated for 480 patients. After the final data were collected, we adjusted the standard deviation of the mean morning peak expiratory flow rate for the corresponding baseline values (see the Supplementary Appendix). The hypothesis of equivalence for the primary efficacy variable was tested with use of an analysis-of-covariance (ANCOVA) model. The 95% bilateral CI for the difference in least-squares means was evaluated to demonstrate equivalence. We then estimated that the actual statistical power of our study was more than 80% to detect a difference of 23 liters per minute (5.75%) in the mean morning peak expiratory flow rate between treatment groups.

As proof of sensitivity, our trial was also designed to demonstrate efficacy by showing the superiority of as-needed combination therapy over as-needed albuterol therapy, to verify whether asthma symptoms improved after additional treat-

ment with beclomethasone. We also tested the superiority of regular beclomethasone over as-needed albuterol. Using a total of 480 patients, a two-sided test, and an alpha of 0.05, we estimated the statistical power to be more than 80% to detect a significant difference between these treatments and an effect size of 0.42. The effect size is a dimensionless variable expressing the standardized difference (i.e., the mean difference divided by standard deviation) between, in our study, the mean morning peak expiratory flow rate after as-needed combination therapy and after as-needed albuterol therapy.

We first tested for the superiority of as-needed combination therapy over as-needed albuterol therapy with regard to morning peak expiratory flow. If superiority was shown, we tested for equivalence of rates of morning peak expiratory flow after as-needed combination therapy and after regular beclomethasone therapy. If this equivalence was shown, we then tested for equivalence of as-needed combination therapy and regular combination therapy.

Although in our original statistical plan we used the last-observation-carried-forward method to handle missing data, in the final analysis, the maximum-likelihood method of analysis was also used to test the hypothesis of superiority or equivalence with regard to primary and secondary efficacy variables (see the Supplementary Appendix). We used an ANCOVA model with terms for treatment group, geographic region, and baseline values as covariates. The 95% CI for the difference in least-squares means was evaluated to demonstrate equivalence. P values of less than 0.05 were considered to indicate statistical significance.

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## RESULTS

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Of the 510 patients screened during the 4-week run-in period, 466 were randomly assigned to a treatment group. Of these patients, 11 had no evidence of drug intake (2 receiving as-needed combination therapy, 1 receiving as-needed albuterol therapy, 4 receiving regular beclomethasone therapy, and 4 receiving regular combination therapy). Thus, data from only the remaining 455 patients were available for a modified intention-to-treat analysis. Since the results were essentially the same in the modified and full intention-to-treat populations, we report the results of the modified analy-

sis only. We report the results of prespecified analyses performed with the use of the last-observation-carried-forward method. In addition, we report the results of post hoc analyses performed with the use of the maximum-likelihood method.

A total of 73 patients were withdrawn after randomization. The number of patients withdrawn did not differ significantly between groups ( $P=0.76$ ) (Fig. 2), and 393 patients completed the study. The treatment groups were well matched

regarding demographic and clinical characteristics (Table 1).

#### LUNG FUNCTION

We examined 455 patients with mild asthma who had an FEV<sub>1</sub> of 2.96 liters (88.36% of the predicted value). In the analysis of the primary-outcome data, as compared with the control group receiving as-needed albuterol therapy, the morning peak expiratory flow rate at 6 months was

**Table 1. Characteristics of Patients at Baseline.\***

Characteristic	As-Needed Combination Therapy (N=122)	As-Needed Albuterol Therapy (N=118)	Regular Beclomethasone Therapy (N=106)	Regular Combination Therapy (N=109)
Male sex — no. (%)	50 (41.0)	49 (41.5)	45 (42.5)	43 (39.4)
Age — yr	36.8±13.1	40.6±13.8	37.9±13.5	39.9±14.4
Height — cm	168.6±10.5	168.4±9.1	168.6±8.3	167.3±8.8
Atopy — no. (%)	77 (63.1)	68 (57.6)	66 (62.3)	64 (58.7)
Weight — kg	69.0±13.3	71.9±14.7	67.1±12.2	69.5±13.3
Previous inhaled corticosteroids — no. (%)	36 (29.5)	36 (30.5)	33 (31.1)	39 (35.8)
Mean daily dose of inhaled corticosteroid (beclomethasone equivalent) at screening visit — μg†	458.8±163.7	468.6±155.8	472.7±122.7	439.7±168.3
Peak expiratory flow rate				
Morning — liters/min	441.5±103.1	436.4±112.5	428.5±106.0	431.9±103.0
Evening — liters/min	447.8±99.5	439.9±111.8	435.2±101.9	435.2±103.2
Variability — %	1.7±5.2	0.7±4.1	1.7±5.5	0.7±4.6
FEV <sub>1</sub>				
Mean ±SD — liters	3.0±0.8	3.0±0.9	3.0±0.7	2.9±0.7
Percentage of predicted value	88.5±11.3	88.9±10.5	88.8±11.1	87.2±10.7
Forced vital capacity				
Mean ±SD — liters	3.7±1.2	3.8±1.2	3.6±1.0	3.5±1.0
Percentage of predicted value	91.5±14.3	93.9±14.5	90.9±14.1	88.7±12.9
Asthma symptom score‡				
Daytime	0.7±1.0	0.9±1.4	1.2±2.1	0.8±1.2
Nighttime	0.7±1.0	1.0±1.4	1.1±1.7	0.9±1.2
Nocturnal awakenings — no.	0.1±0.2	0.1±0.3	0.1±0.3	0.1±0.2
Symptom-free days — %	55.7±37.5	51.6±40.3	49.1±40.4	47.0±38.4
Rescue medication — puffs/day	0.4±0.7	0.5±0.8	0.4±0.7	0.5±0.7

\* Plus-minus values are means ±SD. Baseline was defined as the last week of the run-in period. Values did not differ significantly among groups, according to analysis of variance for continuous variables and the chi-square test for categorical variables. FEV<sub>1</sub> denotes forced expiratory volume in 1 second.

† Mean daily dose was calculated only for patients who were regularly receiving an inhaled corticosteroid on entry into the study.

‡ Daytime and nighttime asthma symptom scores ranged from 0 (no symptoms) to 4 (symptoms occurring for most of the day and affecting normal daily activities and symptoms so severe that they did not allow any sleep at night).

**Table 2. Lung Function and Clinical Variables at the End of the Study in the Modified Intention-to-Treat Population.\***

Group	Missing Values Replaced by LOCF†		Missing Values Replaced by ML‡		P Value
	Value	Difference (95% CI)	Value	Difference (95% CI)	
<b>Morning PEF (liters/min)</b>					
As-needed combination	442.75±9.68	9.47 (0.83 to 18.11)	438.59±2.80	8.31 (0.58 to 16.04)	0.04
As-needed albuterol	428.52±10.49	-2.49 (-11.40 to 6.42)	430.29±2.84	-4.44 (-12.39 to 3.52)	
Regular beclomethasone	433.08±10.83	11.96 (2.96 to 20.97)	442.36±3.01	12.74 (4.74 to 20.74)	0.002
Regular combination	435.18±9.55	-1.36 (-10.13 to 7.42)	440.65±2.93	-2.05 (-9.89 to 5.78)	
<b>Evening PEF (liters/min)</b>					
As-needed combination	449.22±9.56	7.20	443.35±2.78	6.33	0.11
As-needed albuterol	434.55±10.45	-1.91 (-10.94 to 7.13)	437.02±2.84	-3.58 (-11.45 to 4.29)	
Regular beclomethasone	439.25±10.57	9.11	446.93±2.96	9.91	0.01
Regular combination	440.96±9.57	-3.59 (-12.56 to 5.38)	447.75±2.93	-4.40 (-12.21 to 3.41)	
<b>PEF variability (%)</b>					
As-needed combination	1.68±0.44	0.03	1.42±0.34	-0.16	0.74
As-needed albuterol	1.20±0.33	0.34 (-0.60 to 1.29)	1.58±0.35	0.12 (-0.85 to 1.09)	
Regular beclomethasone	1.33±0.41	-0.31	1.30±0.36	-0.28	0.57
Regular combination	1.29±0.38	-0.07 (-1.02 to 0.87)	1.71±0.36	-0.29 (-1.25 to 0.68)	
<b>FEV<sub>1</sub> (liters)</b>					
As-needed combination	3.11±0.08	0.12	3.08±0.03	0.10	0.01
As-needed albuterol	2.97±0.08	0.09 (-0.01 to 0.18)	2.98±0.03	0.07 (-0.01 to 0.15)	
Regular beclomethasone	3.04±0.08	0.04	3.02±0.03	0.03	0.44
Regular combination	2.93±0.08	0.05 (-0.04 to 0.14)	3.05±0.03	0.04 (-0.04 to 0.11)	
<b>FEV<sub>1</sub> (% of predicted value)</b>					
As-needed combination	92.23±1.05	3.89	91.92±0.79	3.29	0.003
As-needed albuterol	88.58±1.34	2.04 (-0.71 to 4.79)	88.63±0.80	1.39 (-0.85 to 3.63)	
Regular beclomethasone	90.32±1.25	1.86	90.53±0.84	1.90	0.10
Regular combination	89.49±1.21	1.79 (-0.95 to 4.54)	90.58±0.82	1.34 (-0.88 to 3.56)	
<b>FVC (liters)</b>					
As-needed combination	3.79±0.11	0.11	3.75±0.03	0.10	0.045
As-needed albuterol	3.76±0.11	0.07 (-0.03 to 0.18)	3.65±0.03	0.07 (-0.03 to 0.16)	
Regular beclomethasone	3.65±0.10	0.04	3.68±0.04	0.03	0.57
Regular combination	3.52±0.11	0.05 (-0.06 to 0.15)	3.70±0.04	0.05 (-0.04 to 0.14)	

FVC (% of predicted value)									
As-needed combination	94.22±1.29	3.63	0.008	93.77±0.83	3.28	0.005			
As-needed albuterol	92.41±1.47	1.72 (-1.04 to 4.48)		90.49±0.83	1.34 (-0.99 to 3.67)				
Regular beclomethasone	92.03±1.44	1.91	0.17	92.43±0.88	1.94	0.10			
Regular combination	90.81±1.42	1.31 (-1.45 to 4.07)		92.64±0.86	1.13 (-1.18 to 3.44)				
<b>Daytime asthma symptom score</b>									
As-needed combination	0.62±0.12	-0.28	0.11	0.65±0.10	-0.21	0.13			
As-needed albuterol	0.95±0.13	-0.03 (-0.38 to 0.32)		0.86±0.10	0.06 (-0.22 to 0.33)				
Regular beclomethasone	0.87±1.53	-0.25	0.17	0.60±0.10	-0.26	0.06			
Regular combination	0.83±0.16	-0.18 (-0.52 to 0.16)		0.81±0.10	-0.16 (-0.43 to 0.11)				
<b>Nighttime asthma symptom score</b>									
As-needed combination	0.80±0.15	-0.05	0.77	0.82±0.09	-0.10	0.43			
As-needed albuterol	1.04±0.14	0.01 (-0.35 to 0.37)		0.92±0.10	-0.01 (-0.28 to 0.26)				
Regular beclomethasone	1.04±0.17	-0.06	0.74	0.83±0.10	-0.09	0.49			
Regular combination	0.84±0.13	0.08 (-0.27 to 0.44)		0.79±0.10	0.03 (-0.23 to 0.30)				
<b>Nocturnal awakening (no.)</b>									
As-needed combination	0.10±0.03	-0.10	0.03	0.08±0.02	-0.09	0.005			
As-needed albuterol	0.21±0.04	-0.02 (-0.11 to 0.07)		0.17±0.02	-0.03 (-0.09 to 0.02)				
Regular beclomethasone	0.13±0.04	-0.07	0.11	0.12±0.02	-0.05	0.10			
Regular combination	0.14±0.03	-0.04 (-0.13 to 0.05)		0.12±0.02	-0.04 (-0.10 to 0.02)				
<b>Symptom-free days (%)</b>									
As-needed combination	61.89±3.21	5.69	0.13	61.12±2.61	4.93	0.18			
As-needed albuterol	53.83±3.59	-2.15 (-9.63 to 5.33)		55.20±2.65	-1.66 (-9.05 to 5.72)				
Regular beclomethasone	60.21±3.41	7.84	0.04	61.79±2.77	6.59	0.08			
Regular combination	56.83±3.54	-0.02 (-7.46 to 7.41)		60.19±2.72	-0.06 (-7.38 to 7.26)				
<b>Rescue medication (puffs/day)</b>									
As-needed combination	0.50±0.07	-0.16	0.11	0.50±0.06	-0.09	0.25			
As-needed albuterol	0.73±0.10	0.07 (-0.13 to 0.26)		0.59±0.06	0.09 (-0.08 to 0.25)				
Regular beclomethasone	0.44±0.07	-0.22	0.03	0.41±0.06	-0.18	0.03			
Regular combination	0.51±0.08	0.05 (-0.15 to 0.24)		0.48±0.06	0.02 (-0.14 to 0.18)				

\* Plus-minus values are means ±SE. Differences are between least-squares means. Confidence intervals (CIs) were reported for comparisons evaluating equivalence (as-needed combination therapy versus regular beclomethasone therapy or regular combination therapy) and P values were reported for comparisons evaluating superiority (as-needed combination therapy or regular beclomethasone therapy vs. as-needed albuterol therapy). For the primary outcome, morning peak expiratory flow rate (PEF), CIs were also reported for comparisons evaluating superiority (see the Discussion section). Daytime and nighttime asthma symptom scores ranged from 0 (no symptoms) to 4 (symptoms occurring for most of the day and affecting normal daily activities and symptoms so severe that they did not allow any sleep at night). FEV<sub>1</sub> denotes forced expiratory volume in 1 second, and FVC forced vital capacity.

† Between-group comparison data from the last-observation-carried-forward (LOCF) analysis are from an analysis-of-covariance model adjusted for baseline values (those during the last week of the run-in period or those measured at visit 2).

‡ Between-group comparison data from the maximum-likelihood (ML) analysis are from a mixed model adjusted for baseline values (those during the last week of the run-in period or those measured at visit 2).

significantly higher both among patients receiving as-needed combination therapy and among those receiving regular beclomethasone therapy (Table 2). In contrast, the morning peak expiratory flow rate did not differ significantly after as-needed combination therapy and after regular beclomethasone therapy or regular combination therapy (Table 2). As compared with the group receiving as-needed albuterol therapy, evening peak expiratory flow rate was significantly higher in the group receiving regular beclomethasone therapy but not in the group receiving as-needed combination therapy (Table 2). As compared with as-needed albuterol therapy, the prebronchodilator FEV<sub>1</sub> and forced vital capacity (FVC) were significantly higher after as-needed combination therapy but not after regular beclomethasone therapy (Table 2); these values did not differ significantly between patients receiving as-needed combination therapy and those receiving regular beclomethasone therapy or regular combination therapy.

In the group receiving as-needed albuterol therapy, the morning peak expiratory flow rate was lower during the first 2 weeks of treatment, as compared with baseline, and remained lower until the end of the study (Fig. 3, and Tables A and B of the Supplementary Appendix). According to maximum-likelihood analysis, the morning peak expiratory flow rate was significantly higher during weeks 17 and 18 and onward, as compared with baseline, in the group receiving regular beclomethasone therapy but not in the other three groups (Fig. 3B, and Table B of the Supplementary Appendix). As compared with baseline, the FEV<sub>1</sub> and FVC increased significantly, both in the as-needed combination group and in the regular combination group, and evening peak expiratory flow rate increased significantly in the regular combination group. According to the maximum-likelihood analysis only, the evening peak expiratory flow rate and FEV<sub>1</sub> (percentage of the predicted value) increased significantly in the regular beclomethasone group (Supplementary Appendix).

#### **SYMPTOMS AND USE OF RESCUE MEDICATION**

As compared with the group receiving as-needed albuterol therapy, the group receiving as-needed combination therapy had fewer nocturnal awakenings, and the group receiving regular beclomethasone had less daily use of rescue medication (Table 2). According to the last-observation-carried-for-

ward analysis only, the percentage of symptom-free days was significantly higher in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy (Table 2). As compared with baseline values, the percentage of symptom-free days increased significantly in all groups except the group receiving as-needed albuterol therapy, in which the number of nocturnal awakenings increased significantly (Tables A and B of the Supplementary Appendix). According to the maximum-likelihood analysis only, the regular beclomethasone group had fewer daytime asthma symptoms at 6 months than at baseline.

#### **EXACERBATIONS**

A total of 237 exacerbations (17 of which were severe) occurred during the study, 38 (none severe) in patients receiving as-needed combination therapy, 83 (including 10 severe) in those receiving as-needed albuterol therapy, 33 (including 4 severe) in those receiving regular beclomethasone therapy, and 83 (3 severe) in those receiving regular combination therapy. The mean number of exacerbations per patient per year was lower in the as-needed combination group (0.74) and in the regular beclomethasone group (0.71) than in the as-needed albuterol group (1.63,  $P < 0.001$ ) and in the regular combination group (1.76,  $P < 0.001$ ) (Table C in the Supplementary Appendix). The percentage of patients with at least one exacerbation was not significantly different in the group receiving as-needed combination therapy (4.92%) and the group receiving regular beclomethasone therapy (5.66%,  $P = 0.802$ ) or the group receiving regular combination therapy (10.09%,  $P = 0.133$ ). The percentage of patients with at least one exacerbation was significantly lower both in the group receiving as-needed combination therapy and in the group receiving regular beclomethasone therapy than in the group receiving as-needed albuterol therapy (17.80%) ( $P = 0.002$  and  $P = 0.005$ , respectively) (Table C and Fig. 1 in the Supplementary Appendix). Kaplan–Meier analysis showed that the time to first exacerbation differed significantly between groups, with the shortest time to first exacerbation in the as-needed albuterol group ( $P = 0.003$  by the log-rank test) (Fig. 4).

#### **INTAKE OF STUDY DRUG**

The cumulative dose (mean  $\pm$ SD) of as-needed short-acting  $\beta_2$ -agonists was lower among patients

receiving as-needed combination therapy ( $7.39 \pm 10.10$  mg) than among those receiving as-needed albuterol therapy ( $9.74 \pm 14.17$  mg) and was similar to that among patients receiving regular beclomethasone therapy ( $6.59 \pm 9.02$  mg) and those receiving regular combination therapy ( $7.25 \pm 10.50$  mg), but the differences were not significant (overall  $P=0.06$ ).

The cumulative dose of inhaled beclomethasone was significantly lower in the group receiving as-needed combination therapy ( $18.48 \pm 25.25$  mg) than in the group receiving regular beclomethasone therapy ( $76.97 \pm 17.35$  mg,  $P<0.001$ ) or the group receiving regular combination therapy ( $77.07 \pm 17.55$  mg,  $P<0.001$ ) (Fig. 2 of the Supplementary Appendix).

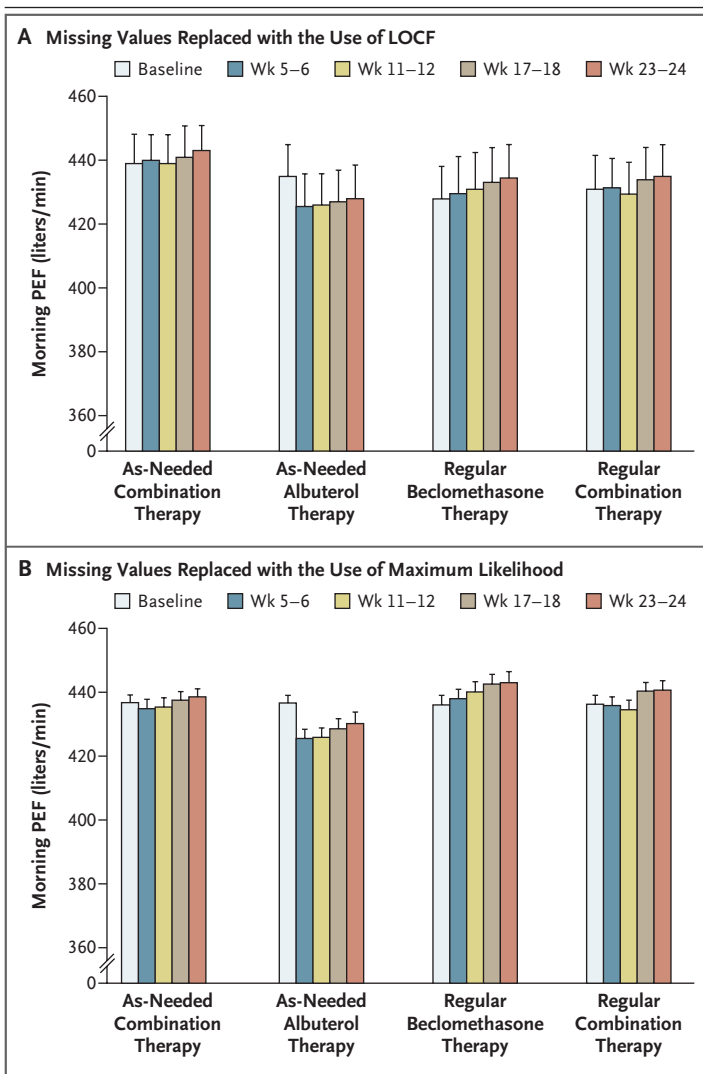
#### SAFETY

The number of adverse events did not differ significantly between the treatment groups (see the Supplementary Appendix). Serious adverse events were reported in only two patients: one patient receiving as-needed combination therapy had hemoptysis of undetermined cause, and one patient receiving regular beclomethasone therapy had myocardial ischemia.

#### DISCUSSION

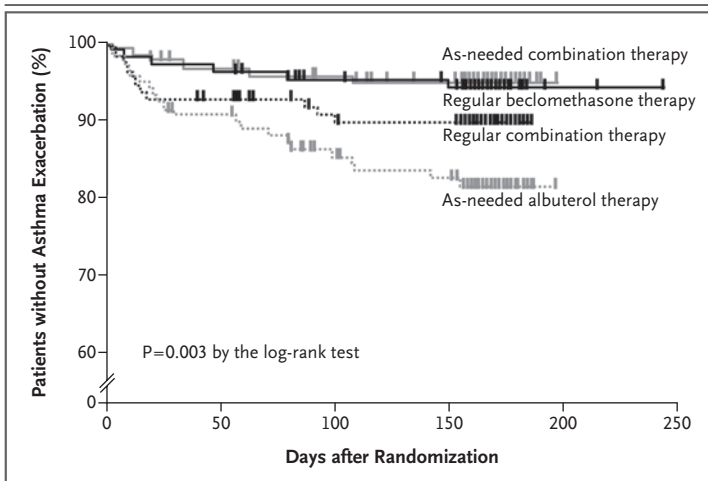
We found that symptom-driven rescue use of a combination of a short-acting  $\beta_2$ -agonist (albuterol,  $100 \mu\text{g}$  per puff) and a corticosteroid (beclomethasone,  $250 \mu\text{g}$  per puff) in a single inhaler is equivalent to regular treatment with inhaled beclomethasone ( $250 \mu\text{g}$  twice daily) in controlling mild persistent asthma. This finding suggests that mild persistent asthma may not require regular treatment with inhaled corticosteroids, but rather only as-needed use of an inhaled corticosteroid and an inhaled bronchodilator, although the dose of inhaled beclomethasone in our study was relatively high.

Regular beclomethasone therapy and as-needed combination therapy with beclomethasone and albuterol were superior to as-needed albuterol therapy with regard to morning peak expiratory flow and some clinical outcomes examined. This finding suggests that patients treated with albuterol as needed had symptoms of asthma after run-in treatment with regular beclomethasone was withdrawn. It seems likely that these patients re-



**Figure 3. Mean ( $\pm$ SE) Morning Peak Expiratory Flow (PEF) Rates in the Modified Intention-to-Treat Population.**

Missing values were replaced according to the last-observation-carried-forward (LOCF) technique (Panel A) or the maximum likelihood technique (Panel B). As-needed combination therapy consisted of placebo twice daily plus  $250 \mu\text{g}$  of beclomethasone and  $100 \mu\text{g}$  of albuterol in a single inhaler as needed; as-needed albuterol therapy, placebo twice daily plus  $100 \mu\text{g}$  of albuterol as needed; regular beclomethasone therapy,  $250 \mu\text{g}$  of beclomethasone twice daily and  $100 \mu\text{g}$  of albuterol as needed; and regular combination therapy,  $250 \mu\text{g}$  of beclomethasone and  $100 \mu\text{g}$  of albuterol in a single inhaler twice daily plus  $100 \mu\text{g}$  of albuterol as needed. P values for comparison with the mean for the last week of the run-in period (baseline) are as follows. In Panel A, among patients receiving as-needed albuterol therapy,  $P<0.001$  for weeks 5 and 6,  $P=0.001$  for weeks 11 and 12,  $P=0.01$  for weeks 17 and 18, and  $P=0.03$  for weeks 23 and 24. In Panel B, among patients receiving as-needed albuterol therapy,  $P<0.001$  for weeks 5 and 6,  $P<0.001$  for weeks 11 and 12,  $P=0.001$  for weeks 17 and 18, and  $P=0.009$  for weeks 23 and 24; among patients receiving regular beclomethasone therapy,  $P=0.01$  for weeks 17 and 18, and  $P=0.006$  for weeks 23 and 24.



**Figure 4. Kaplan–Meier Estimates of the Time to First Asthma Exacerbation in the Modified Intention-to-Treat Population.**

Tick marks represent a first asthma exacerbation. As-needed combination therapy consisted of placebo twice daily plus 250  $\mu\text{g}$  of beclomethasone and 100  $\mu\text{g}$  of albuterol in a single inhaler as needed; as-needed albuterol therapy, placebo twice daily plus 100  $\mu\text{g}$  of albuterol as needed; regular beclomethasone therapy, 250  $\mu\text{g}$  of beclomethasone twice daily and 100  $\mu\text{g}$  of albuterol as needed; and regular combination therapy, 250  $\mu\text{g}$  of beclomethasone and 100  $\mu\text{g}$  of albuterol in a single inhaler twice daily plus 100  $\mu\text{g}$  of albuterol as needed.

quired an additional controller treatment for more complete control of asthma. The differences between groups in the mean morning peak expiratory flow rates were small and fell within the CI of equivalence used to power the study. However, these differences were also associated with superiority with regard to some relevant clinical outcomes (e.g., number of exacerbations or nocturnal awakenings), a finding that suggests that they are clinically relevant. The same effects of regular beclomethasone were found with the as-needed use of a combination of beclomethasone and albuterol, which is a preferable option since it is simpler and is associated with a lower cumulative dose of inhaled corticosteroid.

Our results confirm and extend the conclusions of Boushey et al.,<sup>14</sup> who showed that mild persistent asthma is equally controlled by intermittent and regular treatment with inhaled corticosteroids. In contrast to that study, which included a 10-day course of high-dose inhaled corticosteroids for exacerbations and as-needed albuterol for relief, we tested the simpler alternative of as-needed use of a combination of an inhaled corticosteroid and an inhaled bronchodilator, albeit with a relatively high dose of beclomethasone. Thus, our

study went a step further than that of Boushey et al.: patients were not given a written action plan but rather were instructed orally to use the inhaled medications any time they needed relief from symptoms.

Previous studies have shown that the use of inhaled corticosteroids may reduce the rates of asthma-related hospitalization and death<sup>26,27</sup> and that regular therapy with inhaled corticosteroids for mild asthma reduces the frequency of exacerbations and may reduce the rate of decline in lung function.<sup>4-6,10</sup> However, these studies included patients with mild or moderate asthma, whereas our study included only those with mild persistent asthma. Our 6-month study was long enough to show that as-needed use of beclomethasone and albuterol is sufficient to control mild persistent asthma but was too short to determine whether the therapy affects the natural history of asthma. Since the role of inhaled corticosteroids in modifying the natural history of asthma is controversial, large, long-term studies will be needed to resolve this issue.

The simple, symptom-driven use of inhaled beclomethasone and albuterol may overcome one of the major problems in the treatment of chronic diseases such as asthma: poor compliance.<sup>28,29</sup> Poor compliance is especially likely to occur in patients with mild asthma who have infrequent symptoms.<sup>30</sup> In addition, even though regular low doses of inhaled corticosteroids are safe, prolonged intake is of some concern.<sup>31</sup> In our study, as compared with the regular use of beclomethasone, the symptom-driven use of beclomethasone plus albuterol was associated with a lower cumulative dose of beclomethasone (18.48 mg in 6 months), equivalent to a regular daily dose of 100  $\mu\text{g}$ . The exact reduction in the cumulative dose of inhaled corticosteroid could not be established in our study, since we did not titrate the dose of the inhaled beclomethasone and used a relatively high dose (250  $\mu\text{g}$  twice daily) in the regular beclomethasone group. A relatively high dose of beclomethasone may be required when the drug is taken on an as-needed basis, whereas a dose lower than 250  $\mu\text{g}$  twice daily might be sufficient to achieve the same degree of control; thus, the “corticosteroid-sparing” effect observed in this study may be an artifact of the study design.

Our data on exacerbations confirm that as-needed treatment with beclomethasone and albuterol, as well as regular treatment with beclo-

methasone, were superior to as-needed treatment with albuterol alone. However, these results should be interpreted with caution, since our study was not powered to detect the effect of treatment on asthma exacerbations.

The effects of regular treatment with a combination of beclomethasone and albuterol not only were similar to the effects of regular treatment with beclomethasone alone on most outcomes but also were associated with an increased incidence of exacerbations, which for unknown reasons contrasted with the improvement of almost all other end points. These findings suggest that regular treatment with a bronchodilator, particularly short-acting bronchodilators,<sup>7,32,33</sup> not only is ineffective<sup>32</sup> — even when given in combination with inhaled corticosteroids — but may be detrimental to patients with mild asthma.<sup>34-36</sup>

Supported by Chiesi Farmaceutici.

Presented in part at the VIth Annual Meeting of the Italian Union for Pneumology, Venice, Italy, October 27, 2005.

Dr. Papi reports receiving consulting fees from Chiesi Farmaceutici and GlaxoSmithKline; lecture fees from AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, GlaxoSmithKline, and Merck Sharp & Dohme; and grant support from AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, Merck Sharp & Dohme, and the Italian Ministry for University and Research. Dr. Canonica reports receiving consulting fees from Schering-Plough, Uriach, Almirall, Alk-Abello, GlaxoSmithKline, Novar-

ti, Menarini, and UCB; lecture fees from Boehringer Ingelheim, Novartis, Glaxo-SmithKline, Merck Sharp & Dohme, Dompé, Almirall, AstraZeneca, UCB, Schering-Plough, Altana, and Gentili; and grant support from Gaalem, Altana, Chiesi Farmaceutici, Merck Sharp & Dohme, UCB, GlaxoSmithKline, Novartis, Boehringer Ingelheim, Stallergenes, Alk-Abello, Schering-Plough, Uriach, and Almirall. Dr. Paggiaro reports receiving consulting fees from Altana Pharma; lecture fees from Novartis, Glaxo-SmithKline, Merck Sharp & Dohme, Dompé, and AstraZeneca; and grant support from Altana, Merck Sharp & Dohme, and AstraZeneca. Dr. Olivieri reports receiving consulting fees from Chiesi Farmaceutici, GlaxoSmithKline, Omni Medicamenta Pharma, and Pierre-Fabre; lecture fees from Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline and Pfizer; and grant support from GlaxoSmithKline and Zambon. Dr. Pozzi reports receiving lecture fees from Boehringer Ingelheim and GlaxoSmithKline. Dr. Morelli reports being the director of Contract Research Organization Statistics and Data Management, the contract research organization hired by Chiesi Farmaceutici for the statistical analysis. Dr. Nicolini reports being an employee of Chiesi Farmaceutici, the study sponsor. Dr. Fabbri reports receiving consulting fees and lecture fees from Altana Pharma, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche, and Pfizer and grant support from Altana Pharma, AstraZeneca, Boehringer Ingelheim, Menarini, Miat, Schering-Plough, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp & Dohme, UCB, and Pfizer. No other potential conflict of interest relevant to this article was reported.

We thank P.M. O'Byrne and M. FitzGerald for assistance with the design of the trial, G. Cremonesi and L. Cavalieri for their comments and contributions, O. Zerbini and M. Gonsalvi for assistance with the organization of the trial, M. McKenney for scientific assistance with the manuscript, and E. Veratelli for her scientific secretarial assistance.

#### APPENDIX

Members of the Beclomethasone plus Salbutamol Treatment (BEST) Study Group were as follows: Italy — A. Papi, G.W. Canonica, P. Maestrelli, P. Paggiaro, A.M. Vignola (deceased), L.M. Fabbri, D. Olivieri, N. Crimi, and E. Pozzi; Austria — J. Zarkovic and N. Wetter; Spain — P. Lloberes, J. Serra, and S. Bardagi; Poland — I. Grzelewska-Rzymowska, Z. Siemiejko, M. Pelc, P. Górski, J. Kruszewski, R. Chazan, M. Szmidi, G. Pinis, C. Palczynski, W. Droszcz, and B. Swierczynska.

#### REFERENCES

1. NAEP Expert Panel Report: guidelines for the diagnosis and management of asthma — update on selected topics 2002. Bethesda, MD: National Heart, Lung, and Blood Institute, 2002. (NIH publication no.02-5075.) (Accessed April 30, 2007, at [www.nhlbi.nih.gov/guidelines/asthma](http://www.nhlbi.nih.gov/guidelines/asthma).)
2. Global Initiative for Asthma. Global strategy for asthma management and prevention: NHLBI/WHO workshop report. Bethesda, MD: National Heart, Lung, and Blood Institute, 2006. (Accessed April 30, 2007, at [www.ginasthma.org](http://www.ginasthma.org).)
3. Juniper EF, Kline PA, Vanzieleghem MA, Ramsdale EH, O'Byrne PM, Hargreave FE. Long-term effects of budesonide on airway responsiveness and clinical asthma severity in inhaled steroid-dependent asthmatics. *Eur Respir J* 1990;3:1122-7.
4. Haahtela T, Jarvinen M, Kava T, et al. Comparison of a beta 2-agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
5. Haahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.
6. Pauwels RA, Pedersen S, Busse WW, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet* 2003;361:1071-6.
7. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001;164:1392-7.
8. Djukanovic R, Wilson JW, Britten KM, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. *Am Rev Respir Dis* 1992;145:669-74.
9. Jeffery PK, Godfrey RW, Adelroth E, Nelson F, Rogers A, Johansson SA. Effects of treatment on airway inflammation and thickening of basement membrane reticular collagen in asthma: a quantitative light and electron microscopic study. *Am Rev Respir Dis* 1992;145:890-9.
10. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med* 2000;343:1054-63.
11. FitzGerald JM, Becker A, Sears MR, et al. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 2004;59:550-6.
12. Harrison TW, Osborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet* 2004;363:271-5.
13. Foresi A, Morelli MC, Catena E. Low-dose budesonide with the addition of an increased dose during exacerbations is ef-

- fective in long-term asthma control. *Chest* 2000;117:440-6.
14. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.
15. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
16. Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.
17. Romagnoli M, Vachier I, Tarodo de la Fuente P, et al. Eosinophilic inflammation in sputum of poorly controlled asthmatics. *Eur Respir J* 2002;20:1370-7.
18. Gibson PG, Saltos N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: a randomized controlled trial. *Am J Respir Crit Care Med* 2001;163:32-6.
19. Ketchell RI, Jensen MW, Lumley P, Wright AM, Allenby MI, O'Connor BJ. Rapid effect of inhaled fluticasone propionate on airway responsiveness to adenosine 5'-monophosphate in mild asthma. *J Allergy Clin Immunol* 2002;110:603-6.
20. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. *Eur Respir J* 2002;19:182-91.
21. *Idem*. A single inhaler for asthma? *Am J Respir Crit Care Med* 2005;171:95-6.
22. Rodrigo GJ. Comparison of inhaled fluticasone with intravenous hydrocortisone in the treatment of adult acute asthma. *Am J Respir Crit Care Med* 2005;171:1231-6.
23. National Asthma Education and Prevention Program. Guidelines for the diagnosis and management of asthma: Expert Panel Report 2. Bethesda, MD: National Heart, Lung, and Blood Institute, 1997.
24. Ringdal N, Chuchalin A, Chovan L, et al. Evaluation of Different Inhaled Combination Therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus) vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. *Respir Med* 2002;96:851-61.
25. Pauwels RA, Lofdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11. [Erratum, *N Engl J Med* 1998;338:139.]
26. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA* 1997;277:887-91.
27. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
28. Breeckveldt-Postma NS, Gerrits CM, Lammers JW, Raaijmakers JA, Herings RM. Persistence with inhaled corticosteroid therapy in daily practice. *Respir Med* 2004;98:752-9.
29. Rabe KF, Vermeire PA, Soriano JB, Maier WC. Clinical management of asthma in 1999: the Asthma Insights and Reality in Europe (AIRE) study. *Eur Respir J* 2000;16:802-7.
30. Adams RJ, Fuhlbrigge A, Guilbert T, Lozano P, Martinez F. Inadequate use of asthma medication in the United States: results of the asthma in America national population survey. *J Allergy Clin Immunol* 2002;110:58-64.
31. Wong CA, Walsh LJ, Smith CJ, et al. Inhaled corticosteroid use and bone-mineral density in patients with asthma. *Lancet* 2000;355:1399-403.
32. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *N Engl J Med* 1996;335:841-7.
33. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting beta2-agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA* 2001;285:2583-93.
34. Sears MR. Adverse effects of beta-agonists. *J Allergy Clin Immunol* 2002;110:Suppl 6:S322-S328.
35. Sears MR, Lotvall J. Past, present and future — beta2-adrenoceptor agonists in asthma management. *Respir Med* 2005;99:152-70.
36. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med* 2006;144:904-12.

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