

## ORIGINAL ARTICLE

## As-Needed Budesonide–Formoterol versus Maintenance Budesonide in Mild Asthma

Eric D. Bateman, M.D., Helen K. Reddel, M.B., B.S., Ph.D.,  
 Paul M. O'Byrne, M.B., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D.,  
 Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D.,  
 Agnieszka Siwek-Posluszna, M.D., and J. Mark FitzGerald, M.D.

## ABSTRACT

**BACKGROUND**

Patients with mild asthma often rely on inhaled short-acting  $\beta_2$ -agonists for symptom relief and have poor adherence to maintenance therapy. Another approach might be for patients to receive a fast-acting reliever plus an inhaled glucocorticoid component on an as-needed basis to address symptoms and exacerbation risk.

**METHODS**

We conducted a 52-week, double-blind, multicenter trial involving patients 12 years of age or older who had mild asthma and were eligible for treatment with regular inhaled glucocorticoids. Patients were randomly assigned to receive twice-daily placebo plus budesonide–formoterol (200  $\mu$ g of budesonide and 6  $\mu$ g of formoterol) used as needed or budesonide maintenance therapy with twice-daily budesonide (200  $\mu$ g) plus terbutaline (0.5 mg) used as needed. The primary analysis compared budesonide–formoterol used as needed with budesonide maintenance therapy with regard to the annualized rate of severe exacerbations, with a prespecified noninferiority limit of 1.2. Symptoms were assessed according to scores on the Asthma Control Questionnaire–5 (ACQ-5) on a scale from 0 (no impairment) to 6 (maximum impairment).

**RESULTS**

A total of 4215 patients underwent randomization, and 4176 (2089 in the budesonide–formoterol group and 2087 in the budesonide maintenance group) were included in the full analysis set. Budesonide–formoterol used as needed was noninferior to budesonide maintenance therapy for severe exacerbations; the annualized rate of severe exacerbations was 0.11 (95% confidence interval [CI], 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16). The median daily metered dose of inhaled glucocorticoid was lower in the budesonide–formoterol group (66  $\mu$ g) than in the budesonide maintenance group (267  $\mu$ g). The time to the first exacerbation was similar in the two groups (hazard ratio, 0.96; 95% CI, 0.78 to 1.17). The change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy.

**CONCLUSIONS**

In patients with mild asthma, budesonide–formoterol used as needed was noninferior to twice-daily budesonide with respect to the rate of severe asthma exacerbations during 52 weeks of treatment but was inferior in controlling symptoms. Patients in the budesonide–formoterol group had approximately one quarter of the inhaled glucocorticoid exposure of those in the budesonide maintenance group. (Funded by AstraZeneca; SYGMA 2 ClinicalTrials.gov number, NCT02224157.)

From the Division of Pulmonology, Department of Medicine, University of Cape Town, Cape Town, South Africa (E.D.B.); Woolcock Institute of Medical Research, University of Sydney, Sydney (H.K.R.); Firestone Institute for Respiratory Health, St. Joseph's Healthcare and Department of Medicine, Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON (P.M.O.), and the Institute for Heart and Lung Health, University of British Columbia, Vancouver (J.M.F.) — both in Canada; Airway Disease Section, National Heart and Lung Institute, Imperial College, London (P.J.B.); State Key Laboratory of Respiratory Diseases, First Affiliated Hospital, Guangzhou Medical University, Guangzhou, China (N.Z.); AstraZeneca Research and Development, Gothenburg, Sweden (C.K., C.J.); AstraZeneca Research and Development, Barcelona (R.L.); and AstraZeneca Research and Development, Warsaw, Poland (A.S.-P.). Address reprint requests to Dr. Bateman at the University of Cape Town Lung Institute, George St., Cape Town 7700, South Africa, or at eric.bateman@uct.ac.za.

N Engl J Med 2018;378:1877-87.

DOI: 10.1056/NEJMoa1715275

Copyright © 2018 Massachusetts Medical Society.

MILD ASTHMA OFTEN REMAINS POORLY controlled despite the availability of effective treatments.<sup>1,2</sup> Current guidelines recommend that most patients with mild asthma be treated with regular, low-dose inhaled glucocorticoids as controller medication to reduce the risk of exacerbations, with short-acting  $\beta_2$ -agonists (SABAs) used as needed for symptom relief.<sup>2</sup> Despite the relatively low burden of symptoms in these patients, airway inflammation, although variable in intensity, is usually present.<sup>1</sup> The underuse of inhaled glucocorticoids, even in patients with mild asthma, is associated with severe asthma exacerbations<sup>3</sup> and death.<sup>1</sup> However, adherence to regular controller therapy, particularly inhaled glucocorticoids, is poor.<sup>4,5</sup> Instead, patients rely on SABAs to relieve symptoms, and overuse is common. This behavior is also associated with a risk of severe exacerbations<sup>6</sup> and death.<sup>7</sup>

The use of a combination of a fast-acting  $\beta_2$ -agonist and inhaled glucocorticoid on an as-needed basis — an antiinflammatory reliever approach — is a potential alternative strategy.<sup>8-10</sup> In the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 trial (the results of which are published in this issue of the *Journal*<sup>11</sup>), among closely monitored patients for whom Global Initiative for Asthma (GINA) step 2 treatment<sup>2</sup> was indicated, budesonide–formoterol used as needed was superior to the SABA terbutaline used as needed but was inferior to budesonide maintenance therapy in controlling asthma symptoms. The rate of severe exacerbations was lower among patients treated with budesonide–formoterol as needed than among those who used terbutaline as needed and was similar to the rate observed with regular low-dose budesonide maintenance therapy. The SYGMA 2 trial was designed in parallel with the SYGMA 1 trial to examine whether, in a more pragmatic study design without daily reminders to use maintenance medication, budesonide–formoterol used as needed would be noninferior to regular budesonide maintenance treatment in preventing severe exacerbations in patients with mild asthma.

## METHODS

### TRIAL DESIGN

In this double-blind, randomized, international, parallel-group, 52-week, phase 3 trial, we evalu-

ated the efficacy and safety of budesonide–formoterol (200  $\mu$ g of budesonide and 6  $\mu$ g of formoterol; Symbicort Turbuhaler, AstraZeneca) used as needed, as compared with twice-daily maintenance therapy with budesonide at a dose of 200  $\mu$ g (Pulmicort Turbuhaler, AstraZeneca) plus terbutaline at a dose of 0.5 mg (Turbuhaler, AstraZeneca) used as needed. The trial took place at 354 sites in 25 countries (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol, with the statistical analysis plan, is available at NEJM.org. The trial design has been published previously.<sup>12</sup>

### PATIENTS

Outpatients 12 years of age or older who had received a clinical diagnosis of asthma (according to GINA 2012 criteria<sup>13</sup>) at least 6 months previously were eligible if they were assessed by the investigator as needing GINA step 2 treatment (regular, low-dose inhaled glucocorticoid).<sup>13</sup> This was defined as asthma being uncontrolled while the patient was using inhaled short-acting bronchodilators as needed or as asthma that was well controlled while the patient was using low-dose inhaled glucocorticoid or leukotriene-receptor antagonist maintenance therapy plus a SABA as needed during the 30 days before visit 2.

Recruitment was stratified according to trial site. Key exclusion criteria were asthma worsening that involved a change in asthma treatment or the use of systemic glucocorticoids in the previous 30 days, current or former smoking with a history of 10 or more pack-years, and a history of life-threatening asthma. Details of the inclusion and exclusion criteria are provided in the Supplementary Appendix.

The trial was performed in accordance with the Declaration of Helsinki and with Good Clinical Practice guidelines. The protocol was approved by the relevant oversight authorities (see the Supplementary Appendix). Written informed consent was obtained from all patients and from parents or guardians of patients who were younger than 18 years of age.

### TRIAL TREATMENT

Before randomization, patients entered a run-in period lasting 2 to 4 weeks during which they used only terbutaline at a dose of 0.5 mg as needed for symptoms (Fig. S1 in the Supplementary Appendix). To progress to randomization, patients must

have had an indication for step 2 treatment by using terbutaline as needed on at least 3 days during the last week of the run-in period and by not having used at least six inhalations per day of terbutaline as needed for 2 or more days of 14 days in the run-in period (or for  $\geq 3$  days of 15 to 21 days or for  $\geq 4$  days of  $\geq 22$  days in the run-in period).

Eligible patients were randomly assigned to receive either twice-daily placebo plus budesonide-formoterol used as needed (budesonide-formoterol group) or twice-daily budesonide plus terbutaline used as needed (budesonide maintenance group). The use of all trial inhalers was electronically recorded with the use of Turbuhaler usage monitors (Adherium),<sup>14</sup> but these data were not available to sites during the trial.

#### END POINTS AND ASSESSMENTS

The primary objective was to evaluate whether budesonide-formoterol used as needed was noninferior to budesonide maintenance therapy in terms of the annualized rate of severe exacerbations. Initially, the trial had aimed to show superiority. However, a prespecified sample-size review of results of the blinded monitoring of exacerbations and rates of adherence to maintenance treatment, performed before the enrollment of the last patient, confirmed an overall exacerbation rate that was lower than anticipated (0.10 exacerbations per year vs. the value of 0.14 that was used in the power calculations) and a higher rate of adherence to maintenance treatment than had been seen in other studies that used electronically recorded adherence monitoring.<sup>15</sup> These data suggested that superiority would not be shown with the current sample size. Furthermore, it was recognized that noninferiority to an effective standard of care in mild asthma (budesonide maintenance therapy), with the use of an alternative treatment approach that would not depend on good adherence, could be clinically relevant. Consequently, the protocol was amended, and a noninferiority margin of 1.2 for the upper boundary of the 95% confidence limit of the rate ratio comparing the exacerbation rate in the budesonide-formoterol group with that in the budesonide maintenance group was prespecified on the basis of advice from an expert panel convened by the investigators.

Secondary end points included the between-group differences in efficacy in terms of the

time to the first severe exacerbation (worsening asthma leading to systemic glucocorticoid treatment for  $\geq 3$  days, hospitalization, or an emergency department visit leading to systemic glucocorticoid treatment), use of inhaled and systemic glucocorticoids, the forced expiratory volume in 1 second (FEV<sub>1</sub>) before bronchodilator use, trial-specific asthma-related discontinuation, use of maintenance therapy and as-needed reliever therapy, the percentage of reliever-free days, score on the Asthma Control Questionnaire-5 (ACQ-5), and score on the standardized Asthma Quality of Life Questionnaire (AQLQ). The ACQ-5 consists of 5 questions about asthma symptoms during the previous week, each of which is scored on a range from 0 (no impairment) to 6 (maximum impairment); the minimal clinically important difference is 0.5 units. The AQLQ contains 32 questions about asthma-related symptoms and limitations during the preceding 2 weeks. Each item is scored on a scale of 1 (severely impaired) to 7 (no impairment); the minimal clinically important difference is 0.5 units. Safety was evaluated in a standardized fashion.

#### TRIAL OVERSIGHT

Trial data were collected by the clinical investigators and analyzed by employees of the sponsor, AstraZeneca. The first and third authors vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol. All the authors helped draft each stage of the manuscript and read and approved the final version at the time of submission. Writing and editing assistance, including preparation of a draft manuscript under the direction and guidance of the authors, and manuscript submission was provided by inScience Communications, Springer Healthcare, with funding by the sponsor.

#### STATISTICAL ANALYSIS

Details of the sample-size calculation and statistical analyses have been published previously<sup>12</sup> and are provided in the protocol and statistical analysis plan. As noted above, the protocol was amended to include a noninferiority test as the primary analysis, with the use of a prespecified noninferiority limit of 1.2 (upper one-sided 95% confidence limit of the rate ratio). The primary variable of the rate of severe exacerbations was analyzed by a negative binomial regression model

with treatment, pretrial treatment, and geographic region as factors and with the logarithm of duration of treatment as an offset variable. The time to the first severe exacerbation and the time to discontinuation due to trial-specific asthma-related events were analyzed by a Cox proportional-hazards model that included the same adjustment factors. Changes from baseline in the FEV<sub>1</sub> before bronchodilator use, the ACQ-5 score, and the AQLQ score were analyzed with the use of a mixed model for repeated measures that included treatment, pretrial treatment, geographic region, visit, and the treatment-by-visit interaction as factors and with baseline values as covariates with an unstructured variance-covariance matrix. The change from baseline in “as-needed” use was analyzed with an analysis of covariance. No adjustments for multiple comparisons for secondary efficacy variables were made. Additional details of the sample-size calculation and analyses of primary and secondary end points are provided in the Supplementary Appendix.

## RESULTS

### PATIENTS

The trial was conducted from November 2014 through August 2017. Of 6634 patients screened, 4215 underwent randomization (Fig. S2 in the Supplementary Appendix). Overall, 4176 patients with data that could be evaluated were included in the full analysis set: 2089 patients were in the budesonide–formoterol group and 2087 in the budesonide maintenance group. On the basis of physician assessment before enrollment, 2242 patients (53.7%) had asthma that was well controlled while they were using an inhaled glucocorticoid (48.1%) or leukotriene-receptor antagonist (5.6%), and 1934 (46.3%) had uncontrolled asthma while they were using only a SABA (or a short-acting anticholinergic agent). A total of 3968 of 4215 patients (94.1%) completed the trial, and 3827 (90.8%) completed treatment.

The demographic and clinical characteristics of the patients at baseline are shown in Table 1, and in Table S1 in the Supplementary Appendix. The mean age of the patients was 41 years, 62.2% of the patients were female, and the median time since the diagnosis of asthma was 7.6 years (range, 0.4 to 71.2). Only 2.6% of the patients were current smokers. The baseline characteristics were consistent with mild asthma, with

mildly uncontrolled symptoms (mean [±SD] ACQ-5 score, 1.51±0.90) and well-preserved lung function (mean FEV<sub>1</sub> before bronchodilator use, 84.3±13.9% of the predicted value). The mean bronchodilator reversibility was 15.2±12.7%. A total of 22% of the patients in each group had had severe exacerbations previously. The treatment groups were well balanced with regard to asthma characteristics.

### PRIMARY EFFICACY END POINT

Budesonide–formoterol used as needed was non-inferior to budesonide maintenance therapy with regard to the annualized rate of severe asthma exacerbations; the rate was 0.11 (95% confidence interval [CI], 0.10 to 0.13) in the budesonide–formoterol group and 0.12 (95% CI, 0.10 to 0.14) in the budesonide maintenance group. The rate ratio between the budesonide–formoterol group and the budesonide maintenance group was 0.97 (one-sided 95% upper confidence limit, 1.16) (Fig. 1A).

### SECONDARY EFFICACY END POINTS

#### Exacerbations

A similar number of patients in each treatment group had severe exacerbations that led to an emergency department visit or hospitalization (Table 2). There was no significant difference between the two treatment groups in the time to the first severe asthma exacerbation (Fig. 1B), nor was there a significant difference in the rate of severe exacerbations according to pretrial treatment (Fig. S3 in the Supplementary Appendix).

#### Adherence and Treatment Exposure

The electronically recorded adherence to the blinded maintenance regimen did not differ substantially between the two groups; the mean percentage of daily doses was 64.0±30.0% of placebo doses in the budesonide–formoterol group and 62.8±29.4% of budesonide maintenance doses. The median daily dose of inhaled glucocorticoid was 75% lower in the budesonide–formoterol group than in the budesonide maintenance group (metered dose, 66 μg and 267 μg, respectively) (Table S2 in the Supplementary Appendix). The percentage of days with inhaled glucocorticoid use was lower in the budesonide–formoterol group than in the budesonide maintenance group (30.5% vs. 67.9%; difference, –37.5 percentage points; 95% CI, –39.2 to –35.8). The median number of

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline, According to Treatment Group.\***

Characteristic	Budesonide-Formoterol as Needed (N=2089)	Budesonide Maintenance Therapy (N=2087)	Total (N=4176)
Age — yr			
Mean	41.3±16.8	40.7±17.1	41.0±17.0
Range	12–82	12–83	12–83
Female sex — no. (%)	1308 (62.6)	1289 (61.8)	2597 (62.2)
Current smoking — no. (%)	53 (2.5)	54 (2.6)	107 (2.6)
Time since asthma diagnosis — yr			
Median	7.9	7.3	7.6
Range	0.5–62.4	0.4–71.2	0.4–71.2
ACQ-5 score†			
Mean	1.49±0.89	1.53±0.90	1.51±0.90
Score ≥1.5 — no./total no. (%)	943/2043 (46.2)	1000/2037 (49.1)	1943/4080 (47.6)
FEV <sub>1</sub> — % of predicted value			
Before bronchodilator use	84.4±13.9	84.1±13.9	84.3±13.9
After bronchodilator use	96.3±13.8	96.0±13.5	96.1±13.6
Bronchodilator reversibility — %‡	15.1±12.4	15.2±13.0	15.2±12.7
Asthma control according to pretrial treatment — no. (%)§			
Uncontrolled with short-acting bronchodilator	959 (45.9)	975 (46.7)	1934 (46.3)
Controlled with inhaled glucocorticoid or leukotriene-receptor antagonist	1130 (54.1)	1112 (53.3)	2242 (53.7)
No. of severe exacerbations in previous 12 mo — no. (%)			
0	1630 (78.0)	1627 (78.0)	3257 (78.0)
1	365 (17.5)	362 (17.3)	727 (17.4)
≥2	94 (4.5)	98 (4.7)	192 (4.6)

\* Plus-minus values are means ±SD. There were no significant between-group differences in the demographic or clinical characteristics at baseline. Baseline was defined as the assessment at visit 3 (i.e., the point at which randomization took place), after a run-in period of 2 to 4 weeks during which patients used a short-acting bronchodilator alone. Unless otherwise stated, values were obtained at the baseline visit. Complete demographic and clinical characteristics at baseline are shown in Table S1 in the Supplementary Appendix. Data on the forced expiratory volume in 1 second (FEV<sub>1</sub>) before bronchodilator use were missing for 10 patients in the budesonide-formoterol group and for 12 in the budesonide maintenance group, and data on bronchodilator reversibility were missing for 20 and 29, respectively.

† Shown are the scores on the Asthma Control Questionnaire-5 (ACQ-5) after a run-in period of 2 to 4 weeks during which patients used terbutaline alone on an as-needed basis, regardless of previous treatment. The ACQ-5 consists of five questions about asthma symptoms in the previous week, each of which is scored on a range from 0 (no impairment) to 6 (maximum impairment). Data were missing for 46 patients in the budesonide-formoterol group and for 50 in the budesonide maintenance group.

‡ The data for bronchodilator reversibility were measured at trial entry (visit 1 or 2). If the results were not confirmed, reversibility could also be measured at the baseline visit (visit 3). Alternatively, a documented positive reversibility test within the 12 months before randomization was acceptable to meet the inclusion criterion for reversibility.

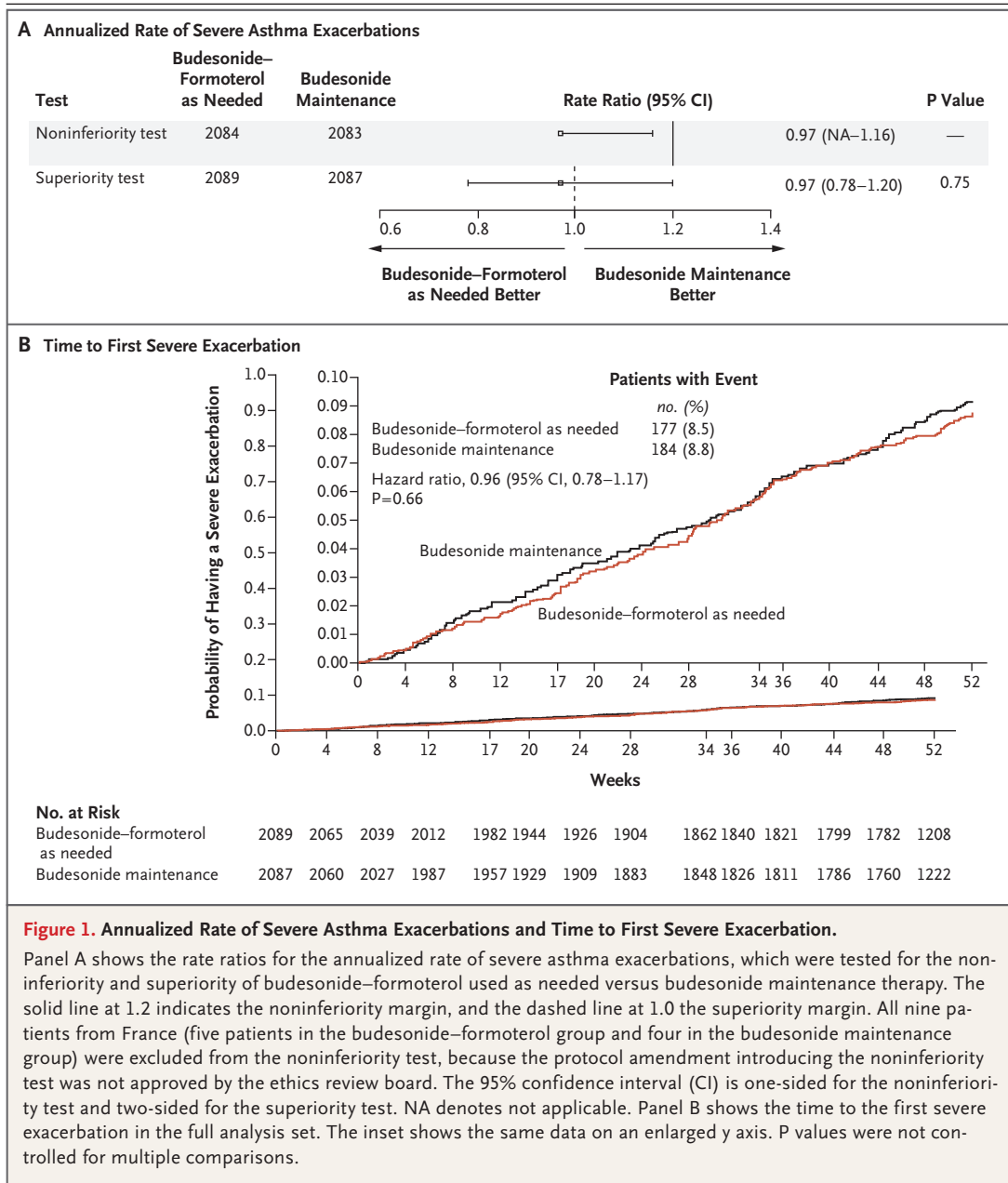
§ Control of asthma by the pretrial treatment was assessed by the physician.

days with systemic glucocorticoid treatment was the same in each group (6 days).

*As-Needed Medication*

A mean of 0.52±0.55 inhalations per day of budesonide-formoterol was used as needed, as compared with 0.49±0.70 inhalations per day of terbutaline used as needed in the budesonide

maintenance group. Patients who had been randomly assigned to the budesonide-formoterol group had fewer days with no use of an as-needed agent than those who had been randomly assigned to the budesonide maintenance group (69.0% vs. 75.9% of days) (Fig. S4 in the Supplementary Appendix). The mean change from baseline in the percentage of reliever-free days was lower in the



budesonide-formoterol group than in the budesonide maintenance group, but the mean change from baseline in the as-needed use of reliever treatment did not differ significantly between groups (Tables S3 and S4 in the Supplementary Appendix).

*Lung Function and Patient-Reported Outcomes*

The change from baseline in the FEV<sub>1</sub> both before and after bronchodilator use was less in the budesonide-formoterol group than in the

budesonide maintenance group (mean difference in FEV<sub>1</sub> before bronchodilator use, -32.6 ml [95% CI, -53.7 to -11.4]; mean difference in FEV<sub>1</sub> after bronchodilator use, -23.1 ml [95% CI, -41.9 to -4.2]) (Fig. 2A). The ACQ-5 score decreased (indicating less impairment) over time in each group. The decrease in the budesonide-formoterol group was less than in the budesonide maintenance group (mean difference, 0.11 units; 95% CI, 0.07 to 0.15) (Fig. 2B), and fewer patients in the budesonide-formoterol group than

**Table 2. Severe Asthma Exacerbations and Exacerbation Rate, According to Treatment Group.\***

Variable	Budesonide-Formoterol as Needed (N = 2089)	Budesonide Maintenance Therapy (N = 2087)
Total no. of patient-yr	1998	1981
All severe exacerbations		
Patients with ≥1 exacerbation — no. (%)	177 (8.5)	184 (8.8)
Total no. of exacerbations	217	221
Total no. of exacerbations per patient-yr	0.11	0.11
Severe exacerbation leading to systemic glucocorticoid use for ≥3 days		
Patients with ≥1 exacerbation — no. (%)	171 (8.2)	173 (8.3)
Total no. of exacerbations	209	207
Total no. of exacerbations per patient-yr	0.10	0.10
Severe exacerbation leading to emergency department visit and systemic glucocorticoid use		
Patients with ≥1 exacerbation — no. (%)	25 (1.2)	36 (1.7)
Total no. of exacerbations	26	40
Total no. of exacerbations per patient-yr	0.01	0.02
Severe exacerbation leading to hospitalization		
Patients with ≥1 exacerbation — no. (%)	17 (0.8)	17 (0.8)
Total no. of exacerbations	20	17
Total no. of exacerbations per patient-yr	0.01	0.01

\* Patient-years were assessed only during the trial period (i.e., during exposure to the trial medications and placebo).

in the budesonide maintenance group had a decrease from baseline in the ACQ-5 score of at least 0.5 units (40.3% vs. 44.3%; odds ratio, 0.86; 95% CI, 0.75 to 0.99). The change in the AQLQ overall score was less in the budesonide-formoterol group than in the budesonide maintenance group (mean difference, -0.10; 95% CI, -0.14 to -0.05). Details are provided in Figures S5 through S7 in the Supplementary Appendix.

*High Use of Reliever Therapy*

Fewer patients had high use of as-needed budesonide-formoterol than as-needed terbutaline. Fewer patients in the budesonide-formoterol group than in the budesonide maintenance group used more than 8 inhalations of the as-needed agent per day (10.4% vs. 15.0%) or more than 12 inhalations per day (4.1% vs. 7.4%) at least once (Table S5 in the Supplementary Appendix).

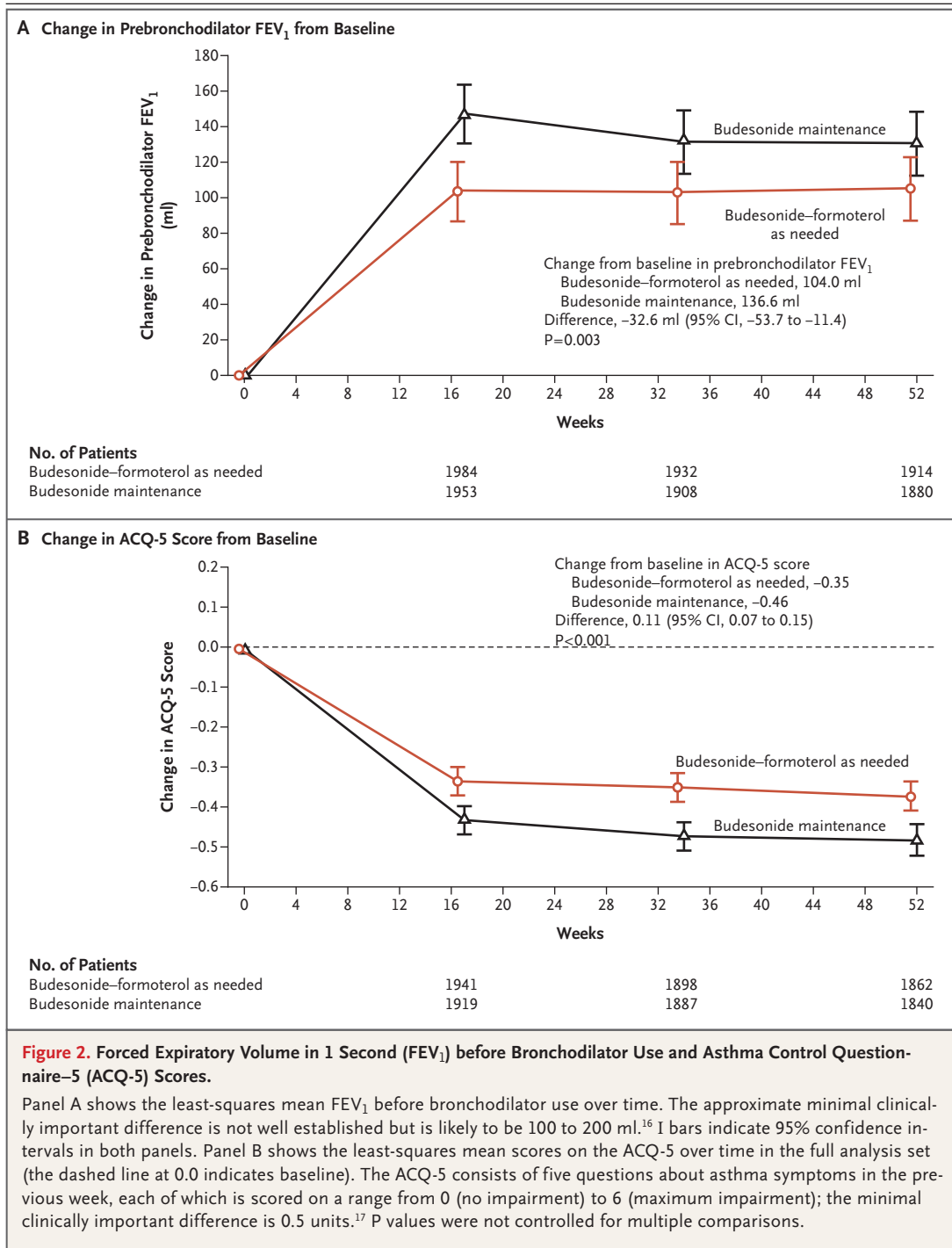
*Adverse Events and Asthma-Related Discontinuation*

Details of adverse events, which were similar in the two treatment groups, and trial-specific

asthma-related discontinuations are provided in Tables S6 and S7 in the Supplementary Appendix. There was one death in each group. Deaths were adjudicated by an external independent adjudication committee. The death in the budesonide maintenance group was deemed to be asthma-related, and the death in the budesonide-formoterol group was deemed to be a cardiorespiratory arrest and not asthma-related (Table S8 in the Supplementary Appendix).

DISCUSSION

This comparison of two approaches to antiinflammatory treatment in patients with mild asthma showed that budesonide-formoterol used as needed was noninferior to low-dose budesonide maintenance treatment in terms of the annualized rate of severe asthma exacerbations and the time to the first severe exacerbation. The rate of severe exacerbations in the budesonide-formoterol group was achieved with less than one quarter of the total exposure to inhaled glucocorticoid



received with budesonide maintenance therapy. Improvements in secondary end points reflecting control of asthma symptoms (according to the ACQ-5) and quality of life (according to the AQLQ) and the FEV<sub>1</sub> before bronchodilator use were larger with budesonide maintenance therapy than with

budesonide-formoterol used as needed. The differences in these treatment outcomes were smaller than the accepted minimal clinically important differences for these end points. Similar findings were observed in the companion SYGMA 1 trial.<sup>11</sup> The trial enrolled patients who had contrast-



ing previous treatment; almost half the patients had asthma that was uncontrolled while they were using short-acting bronchodilators on an as-needed basis, whereas the others had asthma that had been previously well controlled while they were using regular maintenance treatment. However, at baseline, all the patients were required to fulfill clinical criteria for mild asthma. Previous treatment did not appear to influence the results; the effect of the trial medications on exacerbations was similar. There were no safety concerns in terms of adverse events, a finding that is consistent with the well-established safety profile of the trial medications.

Although budesonide-formoterol used as needed met our prespecified noninferiority margin for the exacerbation rate, as compared with budesonide maintenance therapy, there are differences that might influence the choice of one treatment regimen over the other, and several uncertainties remain. A first consideration is the reason for treating mild asthma — whether for symptom control or for reduction in the risk of asthma exacerbations. Budesonide maintenance therapy, the current standard of care, is more effective in addressing symptoms, at least when adherence is at the level seen in this trial (63%); however, with regard to the prevention of risk, the treatments are similar.

Symptoms in mild asthma are highly variable, are often intermittent and tolerated by patients, and may be overlooked by clinicians.<sup>18</sup> In cases in which relief of symptoms is the concern and adherence is likely to be good, regular use of budesonide may be preferred. However, the potential role of an antiinflammatory reliever used as needed is to address the more common scenario of reliance on and overuse of SABAs, which is associated with worsening asthma, exacerbations,<sup>6,19,20</sup> and potentially death, which are often closely associated with poor adherence to the use of inhaled glucocorticoids.<sup>21</sup> Although exacerbations are less frequent in mild asthma than in more severe asthma (22% of the patients in this trial reported having had a severe exacerbation in the previous 12 months), they may have important consequences.<sup>1,7,9</sup> Severe exacerbations in patients who had been classified as having mild asthma represent 30 to 40% of the asthma exacerbations leading to emergency consultations.<sup>1</sup>

A second consideration involves patients' behavior and preference. Patients with asthma, par-

ticularly those with mild or infrequent symptoms, prefer as-needed treatment and favor a medication that provides immediate relief.<sup>6,7,10,19,22-25</sup> The risk of infrequent exacerbations may appear to be remote, so patients may not believe that taking daily treatment year-round is warranted. A further common reason for this behavior involves a concern about potential adverse effects of regular inhaled glucocorticoids, regardless of the veracity of the risk.<sup>15,26,27</sup> The addition of a controller with an antiinflammatory reliever leverages the patient's tendency to prefer a reliever agent, and only one inhalation device is required. In this way, the as-needed regimen may be considered to be tailored to the needs of individual patients and to the natural variation in their asthma symptoms.<sup>10,23</sup>

Strengths of the trial include the 1-year duration, large population, electronic monitoring of medication use, and relatively noninvasive pragmatic design, which involved only two midtrial visits, no daily diary, no monitoring of the peak expiratory flow, and no medication reminders. A limitation of this trial is the double-blind design, such that patients who had been randomly assigned to the budesonide-formoterol group still had to take placebo twice daily, which would not apply in clinical practice. A likely consequence of this limitation is that the overall rate of adherence to a maintenance regimen (budesonide or placebo) of approximately 60% was substantially higher than the rate observed in real-world studies of regular maintenance treatment measured electronically, in which values below 35% are more usual.<sup>28,29</sup> In the SYGMA trials, this situation would have favored the group that received budesonide maintenance therapy.

A further limitation is the absence of phenotyping with measurement of markers of inflammation, such as the fraction of exhaled nitric oxide (FENO), which might have revealed differences in responsiveness to the two treatment approaches. Such studies might also clarify whether there are differences in airway inflammation when budesonide is used on a regular or an as-needed basis.

In patients with mild asthma, the SYGMA 1 trial showed the superiority of budesonide-formoterol over terbutaline as a reliever agent used as needed,<sup>11</sup> both for symptom control and the prevention of exacerbations, with no evidence of overuse of budesonide-formoterol. The SYGMA

2 trial, which was conducted in a less intensively monitored context, confirmed the finding of the SYGMA 1 trial that, as compared with budesonide maintenance therapy, budesonide-formoterol used as needed was inferior with regard to symptom control but similar with regard to exacerbation reduction, without overuse of budesonide-formoterol.

This antiinflammatory reliever approach has been examined in previous studies. Budesonide-formoterol used as needed has been shown to be effective in patients with intermittent asthma and an elevated  $F_{ENO}$ ,<sup>30</sup> as well as when each drug is used with separate glucocorticoid and SABA inhalers in adults and children with mild asthma<sup>31,32</sup> and with combination glucocorticoid-SABA inhalers in adults with mild-to-moderate asthma.<sup>33</sup> Unanswered questions include how as-needed and regular treatments with antiinflammatory agents compare during open-label treatment and whether biomarkers of airway inflammation could be used to select treatment in patients with mild asthma. These and other questions, such as those regarding patients' experiences, attitudes, and preferences, are under investigation in ongoing pragmatic trials (Australian New Zealand Clinical Trials Registry numbers, ACTRN1261500099538 and ACTRN12616000377437).<sup>34,35</sup>

In conclusion, among patients with mild asthma, although budesonide-formoterol used as needed provided less symptom control than budesonide maintenance therapy, it resulted in a similar (noninferior) reduction in the risk of asthma exacerbations, at a substantially lower dose of daily inhaled glucocorticoid and without the need for twice-daily maintenance therapy.

Supported by AstraZeneca.

Dr. Bateman reports receiving grant support paid to his institution, fees for serving on a speakers bureau, and fees for serving on an advisory board from Novartis, fees for serving on an advisory board and lecture fees from Cipla, ALK, and AstraZeneca, consulting fees from Vectura Group, grant support

paid to his institution, fees for serving on an advisory board, and lecture fees from Boehringer Ingelheim, grant support paid to his institution from Merck, Takeda, GlaxoSmithKline, F. Hoffmann-La Roche, Actelion, Chiesi, Sanofi-Aventis, Cephalon, and Teva Pharmaceutical Industries, lecture fees from Menarini, fees for serving on a steering committee from ICON, and fees for serving on an advisory board from Sanofi-Regeneron and serving as a member of the Board and Science Committee of the Global Initiative for Asthma (GINA); Dr. Reddel, receiving grant support, fees for serving on a data and safety monitoring board, fees for serving on an advisory board, fees for providing independent medical education, and fees for serving on an advisory board and for serving on steering committees paid to her institution from AstraZeneca, grant support paid to her institution, fees for serving on a data and safety monitoring board, fees for serving on an advisory board, fees for providing independent medical education, fees for serving on an advisory board paid to her institution, and study medication from GlaxoSmithKline, fees for serving on a data and safety monitoring board from Merck, fees for serving on a data and safety monitoring board, fees for serving on an advisory board, and fees for serving as symposium chair paid to her institution from Novartis, honoraria and fees for serving on an advisory board from Boehringer Ingelheim, and honoraria from Mundipharma and Teva Pharmaceutical Industries and serving as chair of the GINA Scientific Committee; Dr. O'Byrne, receiving grant support and fees for serving on an advisory board from AstraZeneca, grant support from Novartis, MedImmune, and Genentech, and fees for serving on an advisory board from GlaxoSmithKline; Dr. Barnes, receiving grant support and fees for serving on an advisory board from AstraZeneca; Dr. Keen, being employed by and holding shares in AstraZeneca; Dr. Jorup, being employed by and holding shares in AstraZeneca; Dr. Lamarca, being employed by AstraZeneca, holding European patents (EP2100598A1 and EP2100599A1), licensed to Almirall, on an inhalation composition containing acclidinium for the treatment of asthma and chronic obstructive pulmonary disease, and holding a European patent (EP2666465), licensed to Almirall, on a pharmaceutical composition for inhalation comprising acclidinium in the form of a dry powder; Dr. Siwek-Posluszna, being employed by AstraZeneca; and Dr. FitzGerald, receiving grant support paid to his institution, fees for serving on an advisory board, and fees for serving on a speakers bureau from AstraZeneca, Boehringer Ingelheim, and Novartis and grant support paid to his institution and fees for serving on an advisory board from GlaxoSmithKline and Sanofi-Regeneron. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank the health care providers, research staff, patients, and caregivers who participated in this trial; and David Candlish, Vicky Hintridge, and Sophieanne Wastling of inScience Communications, Springer Healthcare, for medical writing support with an earlier version of the manuscript.

## REFERENCES

- Dusser D, Montani D, Chanez P, et al. Mild asthma: an expert review on epidemiology, clinical characteristics and treatment recommendations. *Allergy* 2007; 62:591-604.
- Global Initiative for Asthma (GINA). 2018 GINA report, global strategy for asthma management and prevention (<http://ginasthma.org/2018-gina-report-global-strategy-for-asthma-management-and-prevention/>).
- 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.
- Rand C, Bilderback A, Schiller K, Edelman JM, Hustad CM, Zeiger RS. Adherence with montelukast or fluticasone in a long-term clinical trial: results from the mild asthma montelukast versus inhaled corticosteroid trial. *J Allergy Clin Immunol* 2007;119:916-23.
- Jónasson G, Carlsen KH, Mowinckel P. Asthma drug adherence in a long term clinical trial. *Arch Dis Child* 2000;83:330-3.
- Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting  $\beta$ -agonist use and its ability to predict future asthma-related outcomes. *Ann Allergy Asthma Immunol* 2012;109:403-7.
- Suissa S, Ernst P, Boivin J-F, et al. A cohort analysis of excess mortality in

- asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994; 149:604-10.
8. Papi A, Caramori G, Adcock IM, Barnes PJ. Rescue treatment in asthma: more than as-needed bronchodilation. *Chest* 2009;135:1628-33.
  9. Beasley R, Weatherall M, Shirtcliffe P, Hancox R, Reddel HK. Combination corticosteroid/ $\beta$ -agonist inhaler as reliever therapy: a solution for intermittent and mild asthma? *J Allergy Clin Immunol* 2014;133:39-41.
  10. O'Byrne PM, Jenkins C, Bateman ED. The paradoxes of asthma management: time for a new approach? *Eur Respir J* 2017;50(3):1701103.
  11. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
  12. O'Byrne PM, FitzGerald JM, Zhong N, et al. The SYGMA programme of phase 3 trials to evaluate the efficacy and safety of budesonide/formoterol given 'as needed' in mild asthma: study protocols for two randomised controlled trials. *Trials* 2017; 18:12.
  13. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2012 (<http://ginasthma.org/>).
  14. Pilcher J, Shirtcliffe P, Patel M, et al. Three-month validation of a turbuhaler electronic monitoring device: implications for asthma clinical trial use. *BMJ Open Respir Res* 2015;2(1):e000097.
  15. Desager K, Vermeulen F, Bodart E. Adherence to asthma treatment in childhood and adolescence — a narrative literature review. *Acta Clin Belg* 2017;11: 1-8.
  16. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. *J Allergy Clin Immunol* 2012;129:Suppl: S65-S87.
  17. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the Asthma Control Questionnaire. *Respir Med* 2005;99:553-8.
  18. O'Byrne P, Cuddy L, Taylor DW, Birch S, Morris J, Syrotuik J. Efficacy and cost benefit of inhaled corticosteroids in patients considered to have mild asthma in primary care practice. *Can Respir J* 1996;3:169-75.
  19. Patel M, Pilcher J, Hancox RJ, et al. The use of  $\beta$ 2-agonist therapy before hospital attendance for severe asthma exacerbations: a post-hoc analysis. *NPJ Prim Care Respir Med* 2015;25:14099.
  20. Taylor DR, Sears MR, Herbison GP, et al. Regular inhaled beta agonist in asthma: effects on exacerbations and lung function. *Thorax* 1993;48:134-8.
  21. Williams LK, Peterson EL, Wells K, et al. Quantifying the proportion of severe asthma exacerbations attributable to inhaled corticosteroid nonadherence. *J Allergy Clin Immunol* 2011;128(6):1185-1191.e2.
  22. Bender BG, Long A, Parasuraman B, Tran ZV. Factors influencing patient decisions about the use of asthma controller medication. *Ann Allergy Asthma Immunol* 2007;98:322-8.
  23. Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med* 2006;6:13.
  24. Bärnes CB, Ulrik CS. Asthma and adherence to inhaled corticosteroids: current status and future perspectives. *Respir Care* 2015;60:455-68.
  25. 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.
  26. Boulet LP. Perception of the role and potential side effects of inhaled corticosteroids among asthmatic patients. *Chest* 1998;113:587-92.
  27. Horne R. Compliance, adherence, and concordance: implications for asthma treatment. *Chest* 2006;130:Suppl:65S-72S.
  28. Foster JM, Usherwood T, Smith L, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol* 2014;134(6):1260-1268.e3.
  29. Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006;118: 899-904.
  30. Haahntela T, Tamminen K, Malmberg LP, et al. Formoterol as needed with or without budesonide in patients with intermittent asthma and raised NO levels in exhaled air: a SOMA study. *Eur Respir J* 2006;28:748-55.
  31. Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012;308: 987-97.
  32. Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet* 2011;377:650-7.
  33. Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;356:2040-52.
  34. Beasley R, Pavord I, Papi A, et al. Description of a randomised controlled trial of inhaled corticosteroid/fast-onset LABA reliever therapy in mild asthma. *Eur Respir J* 2016;47:981-4.
  35. Fingleton J, Hardy J, Baggott C, et al. Description of the protocol for the PRACTICAL study: a randomised controlled trial of the efficacy and safety of ICS/LABA reliever therapy in asthma. *BMJ Open Respir Res* 2017;4(1):e000217.

Copyright © 2018 Massachusetts Medical Society.