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Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

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ABSTRACT

BACKGROUND

In patients with mild asthma, as-needed use of an inhaled glucocorticoid plus a fast-acting β_2-agonist may be an alternative to conventional treatment strategies.

METHODS

We conducted a 52-week, double-blind trial involving patients 12 years of age or older with mild asthma. Patients were randomly assigned to one of three regimens: twice-daily placebo plus terbutaline (0.5 mg) used as needed (terbutaline group), twice-daily placebo plus budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol) used as needed (budesonide–formoterol group), or twice-daily budesonide (200 μg) plus terbutaline used as needed (budesonide maintenance group). The primary objective was to investigate the superiority of as-needed budesonide–formoterol to as-needed terbutaline with regard to electronically recorded weeks with well-controlled asthma.

RESULTS

A total of 3849 patients underwent randomization, and 3836 (1277 in the terbutaline group, 1277 in the budesonide–formoterol group, and 1282 in the budesonide maintenance group) were included in the full analysis and safety data sets. With respect to the mean percentage of weeks with well-controlled asthma per patient, budesonide–formoterol was superior to terbutaline (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% confidence interval [CI], 1.00 to 1.30; P=0.046) but inferior to budesonide maintenance therapy (34.4% and 44.4%, respectively; odds ratio, 0.64; 95% CI, 0.57 to 0.73). The annual rate of severe exacerbations was 0.20 with terbutaline, 0.07 with budesonide–formoterol, and 0.09 with budesonide maintenance therapy; the rate ratio was 0.36 (95% CI, 0.27 to 0.49) for budesonide–formoterol versus terbutaline and 0.83 (95% CI, 0.59 to 1.16) for budesonide–formoterol versus budesonide maintenance therapy. The rate of adherence in the budesonide maintenance group was 78.9%. The median metered daily dose of inhaled glucocorticoid in the budesonide–formoterol group (57 μg) was 17% of the dose in the budesonide maintenance group (340 μg).

CONCLUSIONS

In patients with mild asthma, as-needed budesonide–formoterol provided superior asthma-symptom control to as-needed terbutaline, assessed according to electronically recorded weeks with well-controlled asthma, but was inferior to budesonide maintenance therapy. Exacerbation rates with the two budesonide-containing regimens were similar and were lower than the rate with terbutaline. Budesonide–formoterol used as needed resulted in substantially lower glucocorticoid exposure than budesonide maintenance therapy. (Funded by AstraZeneca; SYGMA 1 ClinicalTrials.gov number, NCT02149199.)

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Mild asthma, which can be well controlled either with reliever medication (short-acting β_2-agonists [SABAs]) used alone as needed or with low-dose inhaled glucocorticoid or leukotriene-receptor antagonist used as maintenance controller medication,[1] occurs in approximately 50 to 75% of patients with asthma.[2] Symptoms may not necessarily be burdensome, but airway inflammation is usually present,[3] and patients with mild asthma remain at risk for severe exacerbations (which account for 30 to 40% of asthma exacerbations leading to emergency care[2]) and asthma-related death.[2]

Guidelines recommend that most adults and adolescents with asthma use regular daily low-dose inhaled glucocorticoids as maintenance treatment to reduce airway inflammation, symptoms, and the risk of exacerbations.[1,4] However, in clinical practice, poor adherence to asthma medications, particularly inhaled glucocorticoids as maintenance therapy, is a major problem across all severities of asthma,[4-7] leading to undertreatment of underlying inflammation and to an increased risk of exacerbations.[8-10] In parallel, patients rely on SABAs for symptom relief. However, SABAs do not address the underlying inflammatory process or protect against exacerbations; indeed, increased use of SABAs is associated with a higher exacerbation risk.[11,12]

One potential strategy to address these issues is the use of a combination of a fast-acting β_2-agonist and an inhaled glucocorticoid taken only on an as-needed basis. This approach has proved effective with beclomethasone and SABAs in patients with mild asthma[13] and those with mild-to-moderate asthma.[14] The objectives of the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 trial were to assess, among patients with mild asthma, the long-term efficacy and safety of budesonide–formoterol used as needed, measured according to electronically recorded weeks with well-controlled asthma and the rate of severe exacerbations, as compared with terbutaline used as needed or budesonide maintenance therapy.

Methods

Trial Design

We conducted a double-blind, randomized, parallel-group, 52-week, phase 3 trial that evaluated the efficacy and safety of budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol; Symbicort Turbuhaler, AstraZeneca) used as needed, as compared with terbutaline (0.5 mg; terbutaline Turbuhaler, AstraZeneca) used as needed and with twice-daily budesonide (200 μg; Pulmicort Turbuhaler, AstraZeneca) plus terbutaline (0.5 mg) used as needed (Fig. 1). The trial sites are listed in 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.[15]

Patients

Patients, 12 years of age or older, who had received a clinical diagnosis of asthma (Global Initiative for Asthma [GINA] 2012 criteria[16]) at least 6 months previously were eligible if they had been assessed by the investigator as needing GINA step 2 treatment[16] for the 30 days before visit 2. Step 2 treatment is considered to be appropriate in patients with asthma that is uncontrolled while the patient is taking inhaled short-acting bronchodilators on an as-needed basis (subgroup 1 in our trial) or asthma that is well controlled while the patient is taking maintenance therapy with a low-dose inhaled glucocorticoid or leukotriene-receptor antagonist plus short-acting bronchodilators used as needed (subgroup 2). Recruited patients were stratified according to pretrial treatment. Confirmation of the asthma diagnosis was required, either by a documented history of reversible airway obstruction or by means of a bronchodilator reversibility test conducted at visit 2 or 3 with an increase in the forced expiratory volume in 1 second (FEV_1) of at least 12% and 200 ml from the value obtained before bronchodilator use. Details of the inclusion and exclusion criteria and stratification technique are provided in the Supplementary Appendix.

The trial was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, and the protocol was approved by relevant authorities (Table S1 in the Supplementary Appendix). All the patients provided written informed consent (for patients younger than 18 years of age, written informed consent was also obtained from a parent or guardian).

Trial Treatment

Before randomization, to confirm the appropriateness of GINA step 2 treatment,[16] eligible patients entered a run-in period lasting 2 to 4 weeks

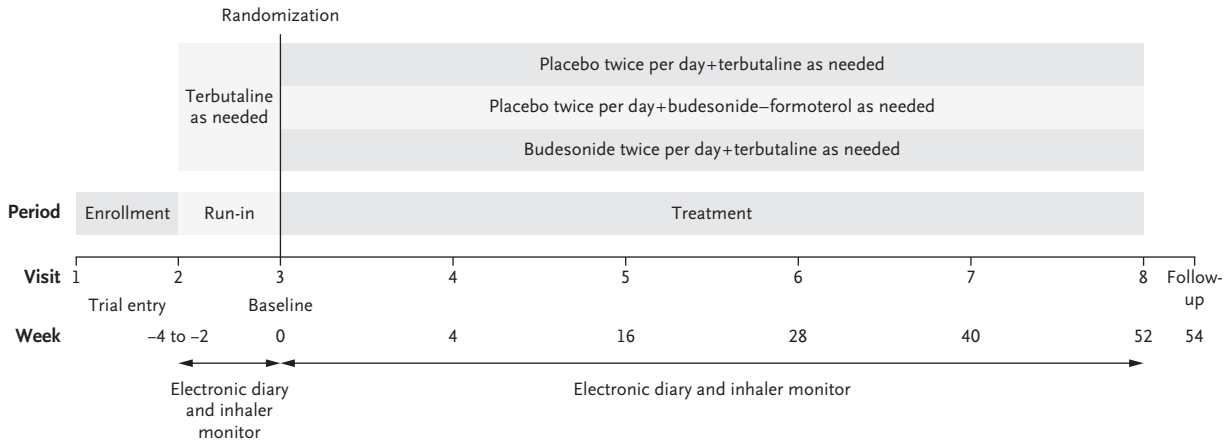


Figure 1. Trial Design.

The terbutaline dose used during the run-in period (0.5 mg) corresponded to a delivered dose of 0.4 mg of terbutaline, delivered by a Turbuhaler during the double-blind phase for blinding purposes. Pretrial asthma treatments were discontinued at visit 2. In order for patients to be eligible to undergo randomization, morning and evening data must have been recorded for at least 8 days (any 8) of the previous 10 days of the run-in period. The dose of budesonide–formoterol during the treatment period corresponded to a delivered dose of 160 μg of budesonide and 4.5 μg of formoterol. An inhaler monitor recorded terbutaline use during the run-in period as well as the use of each blinded trial inhaler. An electronic diary recorded the morning and evening peak expiratory flow, asthma symptoms, and nighttime awakenings due to asthma and prompted the use of the blinded maintenance inhaler. Follow-up was conducted by means of a telephone call.

during which they received only terbutaline on an as-needed basis (Fig. 1). To progress to randomization (visit 3), patients must have used terbutaline on an as-needed basis on at least 3 days during the last week of the run-in period but could not have used six or more inhalations of terbutaline per day for 2 or more days of 14 days in the run-in period (or for ≥3 days of 15 to 21 days or for ≥4 days of ≥22 days in the run-in period). Patients were also required to use the trial-medication inhaler device and the electronic diary correctly.

Patients were randomly assigned to one of three regimens: twice-daily placebo plus terbutaline (0.5 mg, used on an as-needed basis; terbutaline group); twice-daily placebo plus budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol, used on an as-needed basis; budesonide–formoterol group); or twice-daily budesonide (200 μg) plus terbutaline (0.5 mg, used on an as-needed basis; budesonide maintenance group). During the trial, patients who had asthma exacerbations or long-term poor asthma control were permitted to receive additional treatment with open-label budesonide at a dose of 200 μg twice daily for 2 to 4 weeks or longer, at the investigator's discretion. The prescription of additional inhaled glucocorticoids was recorded.

Use of all trial medications or placebo during the double-blind period and of terbutaline during the run-in period was recorded electronically with the use of an inhaler monitor (Turbuhaler usage monitor, Adherium).[17] An electronic diary was used to record the morning and evening peak expiratory flow, asthma symptoms, and nighttime awakenings due to asthma, and prompted use of the blinded maintenance inhaler.

END POINTS AND ASSESSMENTS

The primary objective was to show that budesonide–formoterol used as needed was superior to terbutaline used as needed in terms of asthma symptom control, measured according to the electronically recorded weeks with well-controlled asthma (see the Supplementary Appendix). This measurement was based on as-needed use (according to the inhaler-monitor data), electronic-diary data for asthma symptom scores (scores were assessed on a 4-point scale ranging from 0 to 3, with higher values indicating more severe asthma symptoms), nighttime awakenings, and morning peak expiratory flow, and data from an electronic case-report form for the ad-

ditional use of inhaled or systemic glucocorticoids. A week could not be classified with well-controlled asthma unless the electronic diary was completed for at least 5 days, but a week could be classified with asthma being not well controlled with as little as 1 day of data.

Secondary objectives included showing the noninferiority of budesonide–formoterol used as needed to budesonide maintenance therapy with regard to electronically recorded weeks with well-controlled asthma and comparing the rates and time to the first severe exacerbation (defined as worsening asthma leading to the use of systemic glucocorticoids for ≥3 days, inpatient hospitalization, or an emergency department visit leading to the use of systemic glucocorticoids) and the rates and time to the first moderate-to-severe exacerbation (including worsening asthma requiring the addition of inhaled budesonide at a dose of 200 μg twice daily to avoid progression to a severe exacerbation) in the budesonide–formoterol group versus the terbutaline group and versus the budesonide maintenance group. The descriptions of other secondary efficacy end points, including Asthma Control Questionnaire–5 (ACQ-5) scores, lung-function variables, and quality of life (according to the Asthma Quality of Life Questionnaire [AQLQ] score), have been published previously.[15] The ACQ-5 consists of 5 questions about asthma symptoms during the previous week, each 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 according to the type, incidence, and severity of adverse events and by monitoring of vital signs.

TRIAL OVERSIGHT

Trial data were collected by the clinical investigators and were 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, the incorporation of author feedback, and manuscript submission, was provided by inScience Communications, Springer Healthcare (funded by the sponsor), and by the sponsor.

STATISTICAL ANALYSIS

The sample size was estimated at 3750 patients (see the Supplementary Appendix). We estimated that 625 patients per treatment group and per subgroup according to pretrial treatment would provide the trial with at least 95% power to compare budesonide–formoterol used as needed with terbutaline used as needed, assuming an odds ratio of 1.39 between twice-daily budesonide plus as-needed terbutaline and terbutaline used as needed with regard to the electronically recorded weeks with well-controlled asthma and assuming that budesonide–formoterol used as needed would have the same level of efficacy as twice-daily budesonide. Testing was carried out at a two-sided alpha level of 0.05. In addition, the sample size allowed for 90% power to establish noninferiority with regard to the electronically recorded weeks of well-controlled asthma with budesonide–formoterol used as needed as compared with twice-daily budesonide plus as-needed terbutaline, with a prespecified noninferiority limit of 0.8 (i.e., noninferiority was concluded if the lower limit of the two-sided 95% confidence interval of the odds ratio for budesonide–formoterol used as needed, as compared with twice daily budesonide plus terbutaline, was ≥0.8).

The primary variable, electronically recorded weeks with well-controlled asthma, was analyzed by a repeated measures logistic-regression model with treatment, pretrial treatment, and geographic region as fixed effects, and with trial week as a categorical time variable. The model used an exchangeable correlation structure. Odds ratios averaged over the 52-week period and their corresponding 95% confidence intervals were derived from the model. The primary treatment comparison was budesonide–formoterol used as needed versus terbutaline used as needed (superiority test; the primary objective), and the secondary comparison was budesonide–formoterol used as needed versus budesonide maintenance therapy (noninferiority test; the secondary ob-

jective). A hierarchical testing procedure was performed, testing first the comparison of budesonide–formoterol used as needed versus terbutaline used as needed and then moving to test budesonide–formoterol used as needed versus twice-daily budesonide plus as-needed terbutaline if the result of the preceding test was significant. Details of the analyses of the primary outcome, secondary outcomes, and superiority and noninferiority testing are provided in the Supplementary Appendix. There was no adjustment for multiplicity testing of secondary variables.

RESULTS

PATIENTS

The trial was conducted from July 2014 through August 2017. Of the 5721 patients who were enrolled, 3849 underwent randomization: 1280 patients were assigned to the terbutaline group, 1279 to the budesonide–formoterol group, and 1290 to the budesonide maintenance group (Fig. S1 in the Supplementary Appendix). Overall, 3836 patients had data that could be evaluated for the full analysis and safety data sets, and 3363 patients (87.4%) completed the trial.

The demographic and clinical characteristics of the patients at baseline are shown in Table 1, and in Table S2 in the Supplementary Appendix. At trial entry, participants had uncontrolled asthma symptoms (mean ACQ-5 score, 1.54) and a mean bronchodilator reversibility of 15.4%. Airflow limitation was mild (mean baseline FEV_1 before bronchodilator use, 84% of the predicted value). In the year preceding enrollment, 19.7% of the patients had had a severe exacerbation. The treatment groups were well balanced, with no clinically relevant differences in the baseline characteristics. The subgroups according to pretrial treatment had similar characteristics at baseline, except that patients in subgroup 2 had slightly higher lung function than those in subgroup 1.

PRIMARY EFFICACY OUTCOME

Budesonide–formoterol used as needed was superior to terbutaline used as needed with regard to the primary outcome of the mean percentage of electronically recorded weeks with well-controlled asthma per patient (34.4% vs. 31.1% of weeks; odds ratio, 1.14; 95% confidence interval [CI], 1.00 to 1.30; P=0.046). Thus, the odds of having a week with well-controlled asthma during the 52-week trial period were 14% higher in the budesonide–formoterol group than in the terbutaline group.

SECONDARY EFFICACY OUTCOMES

Electronically Recorded Weeks with Well-Controlled Asthma

Budesonide–formoterol used as needed was inferior to budesonide maintenance therapy with regard to the percentage of electronically recorded weeks with well-controlled asthma per patient (34.4% vs. 44.4%; odds ratio, 0.64; 95% CI, 0.57 to 0.73). The treatment effect was similar in subgroup 1 and subgroup 2 (Fig. S2 in the Supplementary Appendix). Time-course results for the electronically recorded weeks with well-controlled asthma overall are shown in Figure 2, and the individual components are shown in Figure S3 and Table S3 in the Supplementary Appendix. A prespecified analysis of the electronically recorded weeks with well-controlled asthma, with removal of the "as-needed" component, showed a decreased difference in the treatment effect of budesonide maintenance therapy versus budesonide–formoterol used as needed, from 36% to 22% (Table S4 in the Supplementary Appendix). Post hoc analysis of a modified end point of the electronically recorded weeks with well-controlled asthma, in which the first two inhalations used as needed per day were not counted (i.e., were included as if they had been taken as maintenance doses), showed no difference between the budesonide–formoterol group and the budesonide maintenance group (Table S5 in the Supplementary Appendix).

Exacerbations and Asthma-Related Discontinuations

Budesonide–formoterol used as needed resulted in a 64% lower rate of severe exacerbations than terbutaline used as needed (annualized exacerbation rate, 0.07 vs. 0.20; rate ratio, 0.36; 95% CI, 0.27 to 0.49) (Table 2, and Fig. S4 in the Supplementary Appendix). The rates of severe exacerbations in the budesonide–formoterol group and the budesonide maintenance group did not differ significantly (annualized exacerbation rate, 0.07 and 0.09, respectively; rate ratio, 0.83; 95% CI, 0.59 to 1.16). Budesonide–formoterol used as needed also resulted in a 60% lower rate of moderate-to-severe exacerbations than terbuta-

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

Characteristic	Terbutaline as Needed (N = 1277)	Budesonide–Formoterol as Needed (N = 1277)	Budesonide Maintenance Therapy (N = 1282)	Total (N = 3836)
Age — yr	40.0±16.3	39.8±16.9	39.0±16.7	39.6±16.6
Female sex — no. (%)	771 (60.4)	777 (60.8)	797 (62.2)	2345 (61.1)
Time since asthma diagnosis — yr				
Median	6.3	6.5	6.3	6.4
Range	0.5–62.4	0.4–65.7	0.5–57.1	0.4–65.7
ACQ-5 score†				
Mean score				
At trial entry	1.52±0.96	1.57±0.97	1.53±0.97	1.54±0.97
At baseline	1.54±0.95	1.61±0.97	1.55±0.96	1.57±0.96
Score ≥1.5 — no./total no. (%)				
At trial entry‡	549/1160 (47.3)	601/1174 (51.2)	568/1177 (48.3)	1718/3511 (48.9)
At baseline	602/1256 (47.9)	649/1257 (51.6)	596/1257 (47.4)	1847/3770 (49.0)
AQLQ score§	5.25±0.99	5.20±1.01	5.27±1.01	5.24±1.00
FEV_1 — % of predicted value				
Before bronchodilator use	84.13±14.08	84.18±14.24	84.23±13.91	84.18±14.07
After bronchodilator use	95.27±13.53	95.86±14.02	95.67±13.43	95.60±13.66
Peak expiratory flow ≥80% of the predicted value every morning — no./total no. (%)¶	362/1276 (28.4)	340/1277 (26.6)	376/1282 (29.3)	1078/3835 (28.1)
Bronchodilator reversibility — %	14.4±11.5	14.9±11.3	14.6±11.6	14.6±11.5
Asthma control according to pretrial treatment — no. (%)‖				
Uncontrolled with short-acting bronchodilator alone	565 (44.2)	565 (44.2)	576 (44.9)	1706 (44.5)
Controlled with inhaled glucocorticoid or leukotriene-receptor antagonist	712 (55.8)	712 (55.8)	706 (55.1)	2130 (55.5)
Severe exacerbation in previous 12 mo — no. (%)	256 (20.0)	257 (20.1)	241 (18.8)	754 (19.7)

* 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). FEV_1 denotes forced expiratory volume in 1 second.

† The Asthma Control Questionnaire (ACQ-5) consists of five 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. Trial entry was defined as the assessment at the visit before the run-in period (i.e., visit 1 or 2). Data at trial entry were missing for 117 patients in the terbutaline group, for 103 in the budesonide–formoterol group, and for 105 in the budesonide maintenance group; and data at baseline were missing for 21, 20, and 25 patients, respectively.

‡ These calculations for data at trial entry were performed post hoc.

§ The standardized version of the Asthma Quality of Life Questionnaire (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 at all); the minimal clinically important difference is 0.5 units.

¶ Peak expiratory flow at this level was defined as a morning peak expiratory flow of at least 80% of the predicted value on every day of the previous 10 days in the run-in period.

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

line used as needed (0.14 vs. 0.36), but the rate in the budesonide–formoterol group did not differ significantly from that in the budesonide maintenance group (rate ratio, 0.95; 95% CI, 0.74 to 1.21) (Table 2, and Fig. S4 in the Supplementary Appendix).

Budesonide–formoterol used as needed prolonged the time to the first severe exacerbation, as compared with terbutaline used as needed (hazard ratio, 0.44; 95% CI, 0.33 to 0.58). The results in the budesonide–formoterol group did not differ significantly from those in the budesonide maintenance group (hazard ratio, 0.90; 95% CI, 0.65 to 1.24) (Fig. 3). More patients in the terbutaline group had asthma-related discontinuations than did those in the budesonide–formoterol group or the budesonide maintenance group (1.6% vs. 0.3% and 0.5%, respectively). The hazard ratio for the risk of asthma-related discontinuation in the trial was 0.18 (95% CI, 0.06 to 0.52) in the budesonide–formoterol group versus the terbutaline group and 0.66 (95% CI, 0.19 to 2.35) in the budesonide–formoterol group versus the budesonide maintenance group (Fig. S5 in the Supplementary Appendix).

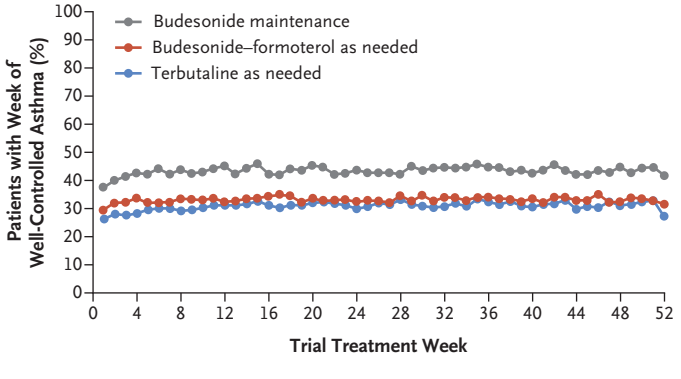


Figure 2. Overall Weeks of Well-Controlled Asthma, According to Data in the Electronic Diary.

Adherence and Glucocorticoid Dose

Adherence to the twice-daily, blinded maintenance regimen did not differ significantly across the trial groups: the mean (±SD) percentage of doses taken was 79.0±23.3% in the terbutaline group, 79.1±23.0% in the budesonide–formoterol group, and 78.9±22.4% in the budesonide maintenance group. Similar rates of adherence were seen with the electronic diary.

Additional inhaled or systemic glucocorticoids for asthma were prescribed in fewer patients receiving budesonide–formoterol as needed (12.8%) than in those receiving terbutaline as needed (27.0%) or budesonide maintenance therapy (14.6%). The time to the use of additional glucocorticoids for asthma was shorter in the terbutaline group than in the budesonide–formoterol group (hazard ratio in the terbutaline group, 0.41; 95% CI, 0.34 to 0.50); the time did not differ significantly between the budesonide maintenance group and the budesonide–formoterol group (hazard ratio in the budesonide maintenance group, 0.87; 95% CI, 0.70 to 1.07) (Fig. S6 in the Supplementary Appendix).

The median daily dose of inhaled glucocorticoid in the budesonide–formoterol group was 17% of that in the budesonide maintenance group (metered dose, 57 μg and 340 μg, respectively) (Table S6 in the Supplementary Appendix). The total number of days with systemic glucocorticoid treatment for asthma was 465 days in the budesonide–formoterol group, 500 days in the budesonide maintenance group, and 1237 days in the terbutaline group.

Asthma-Control Questionnaire and Lung Function

There were differences in the change from baseline in the ACQ-5 score in favor of the budesonide–formoterol group versus the terbutaline group (mean difference, −0.15; 95% CI, −0.20 to −0.11) and in favor of the budesonide maintenance group versus the budesonide–formoterol group (mean difference, 0.15; 95% CI, 0.10 to 0.20) (Table S7 in the Supplementary Appendix). Similarly, there were differences between the budesonide–formoterol group and the other two groups with regard to the average change from baseline in the FEV_1 before bronchodilator use (mean change from baseline, 65.0 ml [95% CI, 47.6 to 82.4] in the budesonide–formoterol group vs. 11.2 ml [95% CI, −6.4 to 28.9] in the terbutaline group and 119.3 ml [95% CI, 101.9 to 136.7] in the budesonide maintenance group) (Table S8 in the Supplementary Appendix).

ADVERSE EVENTS

Adverse events were more frequent in the terbutaline group (in 545 of 1277 patients [42.7%]) than in the budesonide–formoterol group (485 of 1277 [38.0%]) or the budesonide maintenance group (512 of 1282 [39.9%]) (Table S9 in the

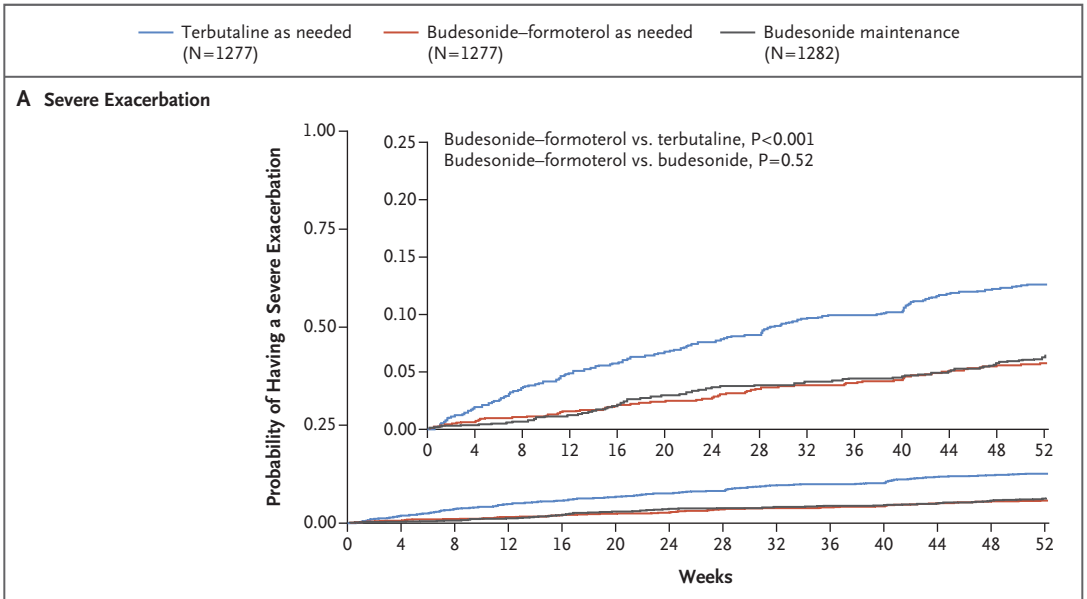
Table 2. Summary of Asthma Exacerbations, According to Treatment Group.

Variable	Terbutaline as Needed (N=1277)	Budesonide–Formoterol as Needed (N=1277)	Budesonide Maintenance Therapy (N=1282)
All severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	152 (11.9)	71 (5.6)	78 (6.1)
Total no. of exacerbations	188	77	89
Annualized exacerbation rate	0.20	0.07	0.09
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.36	—	0.83
95% CI	0.27–0.49	—	0.59–1.16
P value	<0.001	—	0.28
Severe exacerbation leading to hospitalization			
Patients with ≥1 exacerbation — no. (%)	15 (1.2)	6 (0.5)	8 (0.6)
Total no. of exacerbations	21	6	8
Severe exacerbation leading to emergency department visit and systemic glucocorticoid use			
Patients with ≥1 exacerbation — no. (%)	29 (2.3)	7 (0.5)	10 (0.8)
Total no. of exacerbations	29	8	10
Severe exacerbation leading to systemic glucocorticoid use for ≥3 days			
Patients with ≥1 exacerbation — no. (%)	141 (11.0)	70 (5.5)	74 (5.8)
Total no. of exacerbations	173	76	84
All moderate or severe exacerbations			
Patients with ≥1 exacerbation — no. (%)	274 (21.5)	131 (10.3)	143 (11.2)
Total no. of exacerbations	372	164	170
Annualized exacerbation rate	0.36	0.14	0.15
Comparison between as-needed budesonide–formoterol and other regimen			
Rate ratio	0.40	—	0.95
95% CI	0.32–0.49	—	0.74–1.21
P value	<0.001	—	0.66

Supplementary Appendix). There were no notable differences in the adverse-event profile between treatments, except that more adverse events led to discontinuation in the terbutaline group (37 patients [2.9%]) than in the budesonide–formoterol group (10 patients [0.8%]) or the budesonide maintenance group (15 patients [1.2%]). The number of patients with at least one severe exacerbation leading to hospitalization was greater in the terbutaline group (15 patients [1.2%]) than in the budesonide–formoterol group (6 patients [0.5%]) or the budesonide maintenance group (8 patients [0.6%]) (Table 2). There were two deaths in the budesonide maintenance group (upper gastrointestinal hemorrhage and brain neoplasm, in 1 patient each) (Table S10 in the Supplementary Appendix).

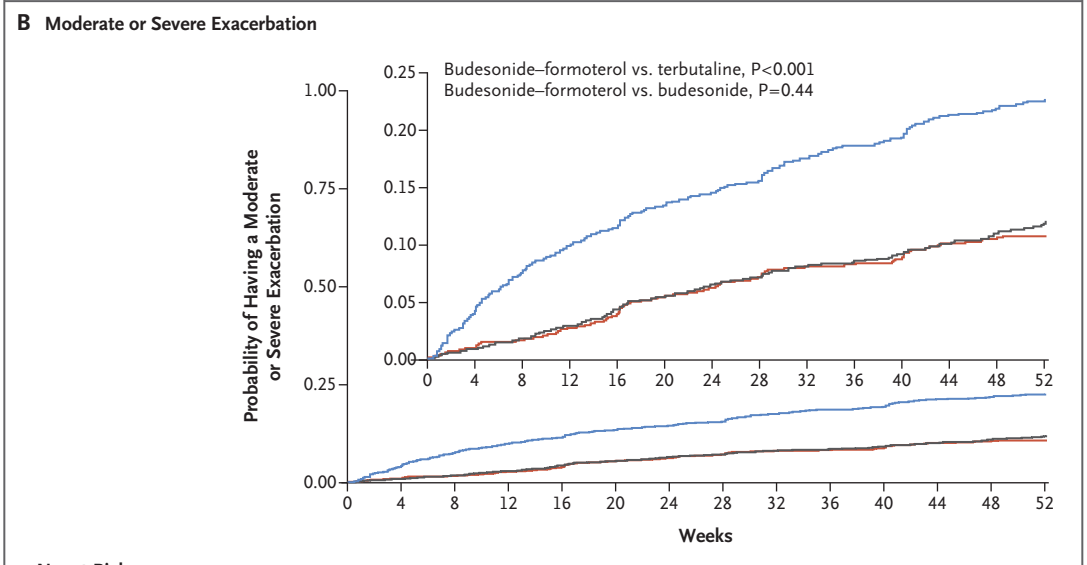
OTHER SECONDARY END POINTS

The results for the other secondary end points, including peak expiratory flow values, symptom and control scores, nighttime awakenings due to asthma, and medication use, are reported in Tables S11 through S19 and Figures S7 and S8 in the Supplementary Appendix. The numbers of patients with high use (>8 and >12 inhalations in 1 day) of as-needed medication are reported in Table S20 in the Supplementary Appendix.



No. at Risk

Terbutaline as needed	1277	1237	1190	1153	1131	1102	1084	1067	1038	1024	1017	987	977	731
Budesonide–formoterol as needed	1277	1258	1235	1218	1207	1179	1172	1159	1138	1127	1119	1097	1086	822
Budesonide maintenance	1282	1264	1238	1226	1201	1172	1159	1150	1136	1123	1110	1088	1076	811



No. at Risk

Terbutaline as needed	1277	1210	1143	1098	1069	1031	1010	990	955	934	923	888	877	660
Budesonide–formoterol as needed	1277	1252	1227	1204	1184	1142	1130	1116	1089	1078	1067	1040	1028	778
Budesonide maintenance	1282	1257	1224	1206	1175	1143	1125	1111	1089	1074	1057	1031	1017	763

Figure 3. Time to First Exacerbation.

P values were not controlled for multiple comparisons. Insets show the same data on an enlarged y axis.

DISCUSSION

This trial showed that budesonide–formoterol used as needed was a more effective treatment than a SABA alone in patients with mild asthma; budesonide–formoterol used as needed was superior to terbutaline used as needed for both symptom control, measured according to the percentage of electronically recorded weeks with well-controlled asthma per patient, and the pre-

vention of moderate-to-severe and severe exacerbations. Although budesonide–formoterol used as needed was equally effective as budesonide maintenance therapy in preventing moderate-to-severe exacerbations, budesonide–formoterol used as needed was inferior to budesonide maintenance therapy in achieving electronically recorded weeks with well-controlled asthma but exposed the patients to less than one fifth of the amount of inhaled glucocorticoid.

In interpretation of the comparisons of budesonide–formoterol used as needed with budesonide maintenance therapy, an important consideration is the extent to which the primary end point of the percentage of electronically recorded weeks with well-controlled asthma per patient was driven by the as-needed medication component. Conventionally, symptoms and reliever use are both included in guideline-assessed symptom control[1] because, independent of symptoms, a higher use of SABAs is associated with an increased exacerbation risk, which indicates a greater need for preventive therapy. When the reliever is a combined inhaled glucocorticoid plus β_2-agonist, the amount used also represents the amount of preventive therapy that has been delivered. Prespecified removal of the "as-needed" component from the definition of electronically recorded weeks with well-controlled asthma improved the treatment effect of budesonide–formoterol used as needed versus both terbutaline used as needed and budesonide maintenance therapy; however, the results still favored budesonide maintenance therapy.

In addition to day-to-day symptom control, overall asthma control also includes the minimization of the risk of adverse outcomes, including exacerbations and adverse effects of medications.[1] The exacerbation rates in the terbutaline group in this trial showed that patients with mild asthma were at risk for exacerbations. The facts that severe exacerbations and even death occur in patients with mild asthma,[2] who represent approximately 50 to 75% of patients with asthma,[2] and that 19.7% of the patients who underwent randomization in our trial reported having had a severe exacerbation in the previous year, provide clinical relevance to the substantial reduction in exacerbations achieved with budesonide–formoterol used as needed as compared with terbutaline used as needed. We think that this finding is explained by the antiinflammatory reliever approach that leverages patients' inherent relief-seeking behavior to also deliver inhaled glucocorticoids as soon as symptoms appear, which provides a window of opportunity[18-20] that reduces the likelihood of progression to an exacerbation. Previous trials involving patients with moderate-to-severe asthma using maintenance and reliever therapy,[21-27] involving patients with mild asthma using separate regimens,[13] and involving patients with moderate asthma using combination[14] as-needed inhaled glucocorticoid plus a SABA have also shown the advantages of this approach in reducing exacerbations and maintaining symptom control at a lower total dose of glucocorticoid.[21-28]

The results of this trial also suggest that the as-needed use of budesonide–formoterol in mild asthma could address patients' concerns about the risks of treatment, another issue that causes overreliance on SABAs and poor adherence to maintenance treatment with an inhaled glucocorticoid.[11] Patients are often more concerned about adverse effects of inhaled glucocorticoids,[7,29] even when low inhaled doses are used, than their health care providers, and conversely they are less concerned about their level of symptom control.[18,30] Since budesonide–formoterol used as needed was as effective as budesonide maintenance therapy in reducing exacerbation risk, without the need for regular, twice-daily treatment, and resulted in only 17% of the inhaled glucocorticoid load, it would probably be acceptable to patients who have this concern and fits with patients' behavior.

The strengths of this trial include the 1-year duration; the electronic monitoring of medication use, symptoms, and lung function; and the freedom to add open-label inhaled glucocorticoid to avoid imbalance of withdrawals. The trial was designed to satisfy regulatory requirements for efficacy studies, and the high observed rate of adherence, approaching 80% with twice-daily reminders, means that budesonide maintenance therapy was being evaluated under appropriate conditions. Whether the results will be more favorable with budesonide–formoterol used as needed in real-world populations in which adherence rates are considerably lower[31] is currently being explored in ongoing studies (Australian New Zealand Clinical Trials Registry numbers, ACTRN12615000999538 and ACTRN12616000377437).[32,33]

One feature of this trial is the derivation of

the weeks with well-controlled asthma from the twice-daily electronically recorded diary, reliever use, and peak expiratory flow; this approach avoided retrospective data entry by patients and may have resulted in a higher rate of reporting of symptoms, awakenings, and reliever use than has occurred in earlier studies in which patients used paper-based diaries,[34-36] thereby reducing the overall percentage of electronically recorded weeks with well-controlled asthma. The double-blind, double-dummy design, although essential for showing the efficacy of a new regimen, meant that patients who had been randomly assigned to the budesonide–formoterol group still had to use a twice-daily (placebo) inhaler, which would not apply in clinical practice. These factors, together with the high rate of adherence to the maintenance regimen, may explain why budesonide–formoterol used as needed was inferior to twice-daily budesonide maintenance therapy with regard to the electronically recorded weeks with well-controlled asthma. Nevertheless, the findings indicate that, in patients with mild asthma who were able to maintain high adherence to twice-daily medication, regular low-dose inhaled glucocorticoid remained more effective in achieving daily asthma control and equally effective with respect to severe exacerbations, albeit with greater glucocorticoid exposure, than budesonide–formoterol used as needed. This relationship has been explored in the SYGMA 2 trial (the results of which are reported in this issue of the *Journal*[37]), which used a more pragmatic design to compare budesonide–formoterol used as needed with budesonide maintenance therapy.

In conclusion, this trial showed that budesonide–formoterol used as needed was superior to the SABA terbutaline used as needed both for asthma symptom control and for reducing the risk of asthma exacerbations among patients with physician-assessed mild asthma. Furthermore, budesonide–formoterol used as needed was inferior to budesonide maintenance therapy with regard to electronically recorded weeks with well-controlled asthma but was similar to budesonide maintenance therapy in reducing the risk of asthma exacerbations, at a substantially lower total glucocorticoid load and without the need for adherence to a twice-daily maintenance-therapy schedule.

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

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ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Patients with mild asthma often rely on inhaled short-acting β_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 μg of budesonide and 6 μg of formoterol) used as needed or budesonide maintenance therapy with twice-daily budesonide (200 μg) 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 μg) than in the budesonide maintenance group (267 μg). 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.)

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Mild asthma often remains poorly controlled despite the availability of effective treatments.[1,2] 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 β_2-agonists (SABAs) used as needed for symptom relief.[2] Despite the relatively low burden of symptoms in these patients, airway inflammation, although variable in intensity, is usually present.[1] The underuse of inhaled glucocorticoids, even in patients with mild asthma, is associated with severe asthma exacerbations[3] and death.[1] However, adherence to regular controller therapy, particularly inhaled glucocorticoids, is poor.[4,5] Instead, patients rely on SABAs to relieve symptoms, and overuse is common. This behavior is also associated with a risk of severe exacerbations[6] and death.[7]

The use of a combination of a fast-acting β_2-agonist and inhaled glucocorticoid on an as-needed basis — an antiinflammatory reliever approach — is a potential alternative strategy.[8-10] In the Symbicort Given as Needed in Mild Asthma (SYGMA) 1 trial (the results of which are published in this issue of the *Journal*[11]), among closely monitored patients for whom Global Initiative for Asthma (GINA) step 2 treatment[2] 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 evaluated the efficacy and safety of budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol; Symbicort Turbuhaler, AstraZeneca) used as needed, as compared with twice-daily maintenance therapy with budesonide at a dose of 200 μg (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.[12]

Patients

Outpatients 12 years of age or older who had received a clinical diagnosis of asthma (according to GINA 2012 criteria[13]) 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).[13] 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 ≥3 days of 15 to 21 days or for ≥4 days of ≥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),[14] 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.[15] 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 ≥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_1) 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[12] 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_1 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_1 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 noninferior 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_1 — % 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_1) 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

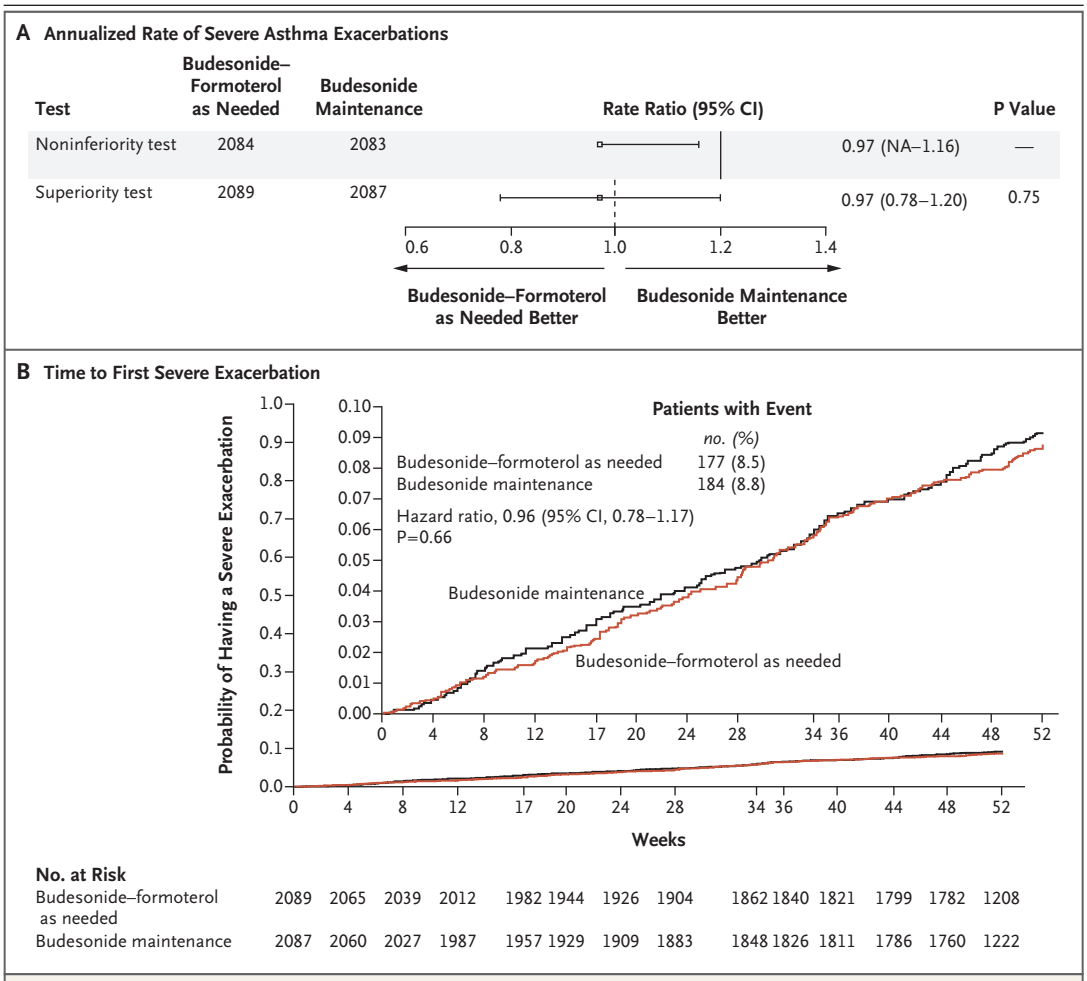

Figure 1. Annualized Rate of Severe Asthma Exacerbations and Time to First Severe Exacerbation.

Panel A shows the rate ratios for the annualized rate of severe asthma exacerbations, which were tested for the noninferiority and superiority of budesonide–formoterol used as needed versus budesonide maintenance therapy. The solid line at 1.2 indicates the noninferiority margin, and the dashed line at 1.0 the superiority margin. All nine patients from France (five patients in the budesonide–formoterol group and four in the budesonide maintenance group) were excluded from the noninferiority test, because the protocol amendment introducing the noninferiority test was not approved by the ethics review board. The 95% confidence interval (CI) is one-sided for the noninferiority test and two-sided for the superiority test. NA denotes not applicable. Panel B shows the time to the first severe exacerbation in the full analysis set. The inset shows the same data on an enlarged y axis. P values were not controlled for multiple comparisons.

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_1 both before and after bronchodilator use was less in the budesonide–formoterol group than in the budesonide maintenance group (mean difference in FEV_1 before bronchodilator use, –32.6 ml [95% CI, –53.7 to –11.4]; mean difference in FEV_1 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

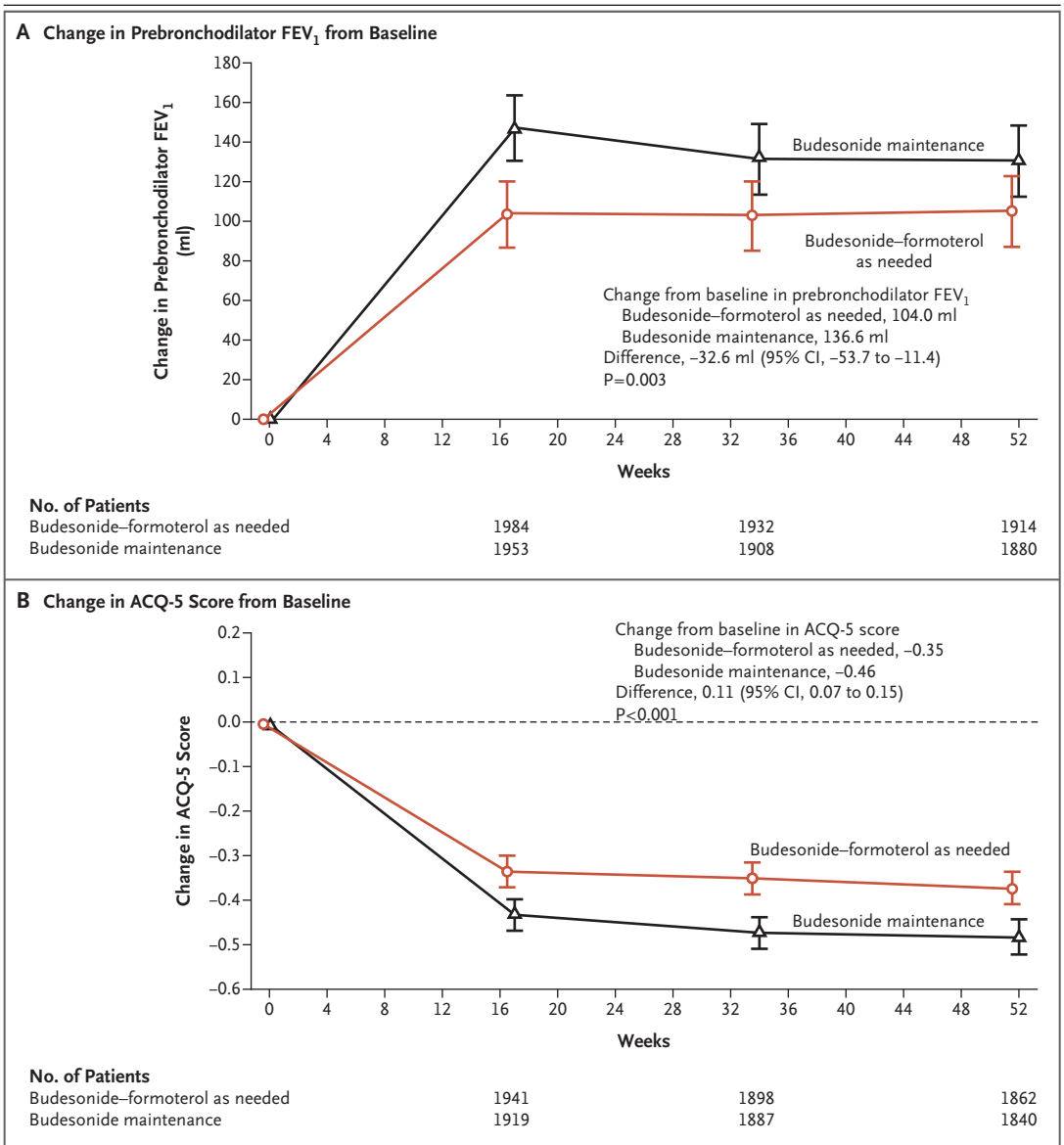

Figure 2. Forced Expiratory Volume in 1 Second (FEV_1) before Bronchodilator Use and Asthma Control Questionnaire–5 (ACQ-5) Scores.

Panel A shows the least-squares mean FEV_1 before bronchodilator use over time. The approximate minimal clinically important difference is not well established but is likely to be 100 to 200 ml.[16] I bars indicate 95% confidence intervals in both panels. Panel B shows the least-squares mean scores on the ACQ-5 over time in the full analysis set (the dashed line at 0.0 indicates baseline). 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); the minimal clinically important difference is 0.5 units.[17] P values were not controlled for multiple comparisons.

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_1 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.[11]

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.[18] 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,[6,19,20] and potentially death, which are often closely associated with poor adherence to the use of inhaled glucocorticoids.[21] 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.[1,7,9] Severe exacerbations in patients who had been classified as having mild asthma represent 30 to 40% of the asthma exacerbations leading to emergency consultations.[1]

A second consideration involves patients' behavior and preference. Patients with asthma, particularly those with mild or infrequent symptoms, prefer as-needed treatment and favor a medication that provides immediate relief.[6,7,10,19,22-25] 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.[15,26,27] 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.[10,23]

Strengths of the trial include the 1-year duration, large population, electronic monitoring of medication use, and relatively nonintrusive 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.[28,29] 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,[11] 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 FENO,[30] as well as when each drug is used with separate glucocorticoid and SABA inhalers in adults and children with mild asthma[31,32] and with combination glucocorticoid–SABA inhalers in adults with mild-to-moderate asthma.[33] 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, ACTRN12615000999538 and ACTRN12616000377437).[34,35]

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.

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