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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 care²) 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 asthma¹³ 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 μ g of budesonide and 6 μ g 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 μ g; 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 criteria¹⁶) at least 6 months previously were eligible if they had been assessed by the investigator as needing GINA step 2 treatment¹⁶ 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 pretreatment. 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 (FEV₁) 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

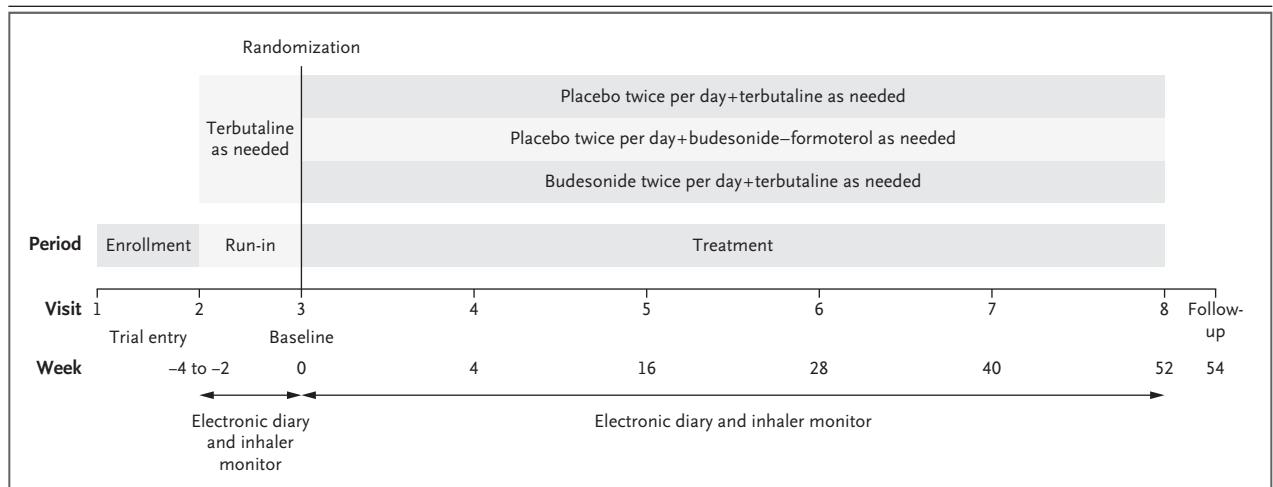


Figure 1. Trial Design.

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 submis-

sion. 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 FEV₁ 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 pre-trial 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§				
FEV ₁ — % of predicted value	5.25±0.99	5.20±1.01	5.27±1.01	5.24±1.00
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). FEV₁ 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).

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

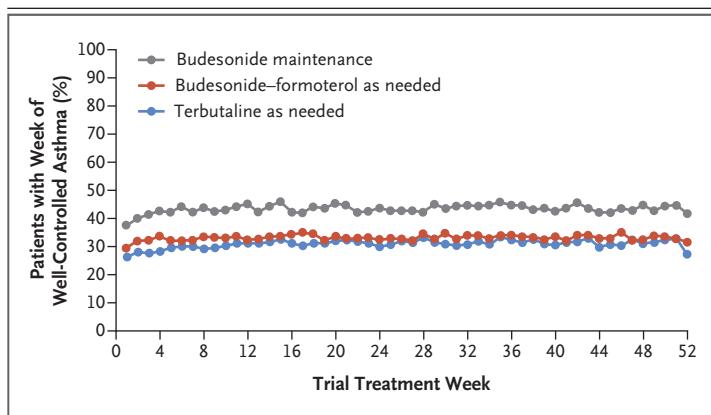


Figure 2. Overall Weeks of Well-Controlled Asthma, According to Data in the Electronic Diary.

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 FEV₁ 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.

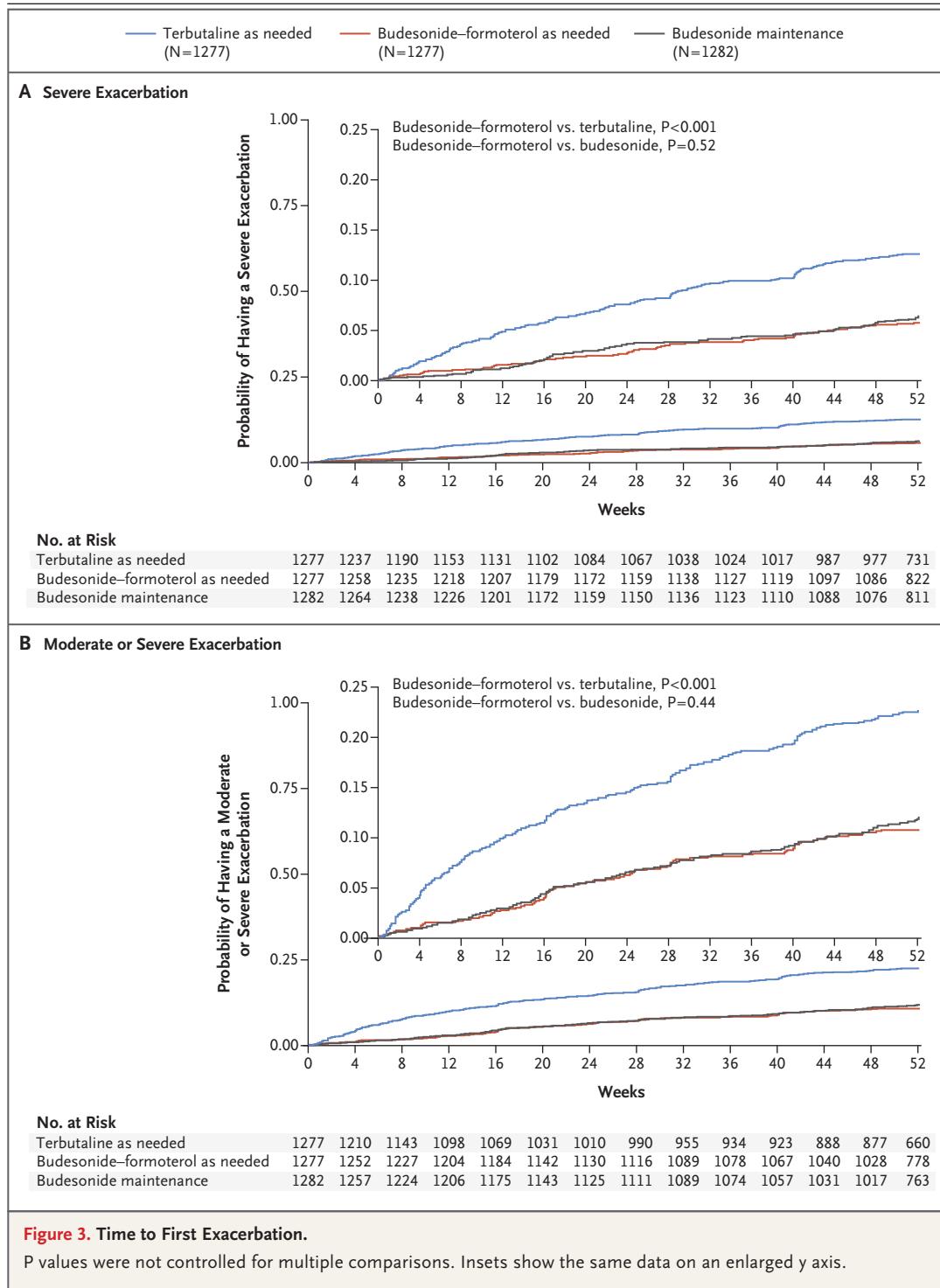


Figure 3. Time to First Exacerbation.

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 control¹ 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 antiinflamma-

tory reliever approach that leverages patients' inherent relief-seeking behavior to also deliver inhaled glucocorticoids as soon as symptoms appear, which provides a window of opportunity¹⁸⁻²⁰ 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 combination¹⁴ 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 lower³¹ 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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