ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

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ABSTRACT

BACKGROUND

In double-blind, placebo-controlled trials, budesonide–formoterol used on an as-needed basis resulted in a lower risk of severe exacerbation of asthma than as-needed use of a short-acting β_2-agonist (SABA); the risk was similar to that of budesonide maintenance therapy plus as-needed SABA. The availability of data from clinical trials designed to better reflect clinical practice would be beneficial.

METHODS

We conducted a 52-week, randomized, open-label, parallel-group, controlled trial involving adults with mild asthma. Patients were randomly assigned to one of three treatment groups: albuterol (100 μg, two inhalations from a pressurized metered-dose inhaler as needed for asthma symptoms) (albuterol group); budesonide (200 μg, one inhalation through a Turbuhaler twice daily) plus as-needed albuterol (budesonide maintenance group); or budesonide–formoterol (200 μg of budesonide and 6 μg of formoterol, one inhalation through a Turbuhaler as needed) (budesonide–formoterol group). Electronic monitoring of inhalers was used to measure medication use. The primary outcome was the annualized rate of asthma exacerbations.

RESULTS

The analysis included 668 of 675 patients who underwent randomization. The annualized exacerbation rate in the budesonide–formoterol group was lower than that in the albuterol group (absolute rate, 0.195 vs. 0.400; relative rate, 0.49; 95% confidence interval [CI], 0.33 to 0.72; P<0.001) and did not differ significantly from the rate in the budesonide maintenance group (absolute rate, 0.195 in the budesonide–formoterol group vs. 0.175 in the budesonide maintenance group; relative rate, 1.12; 95% CI, 0.70 to 1.79; P=0.65). The number of severe exacerbations was lower in the budesonide–formoterol group than in both the albuterol group (9 vs. 23; relative risk, 0.40; 95% CI, 0.18 to 0.86) and the budesonide maintenance group (9 vs. 21; relative risk, 0.44; 95% CI, 0.20 to 0.96). The mean (±SD) dose of inhaled budesonide was 107±109 μg per day in the budesonide–formoterol group and 222±113 μg per day in the budesonide maintenance group. The incidence and type of adverse events reported were consistent with those in previous trials and with reports in clinical use.

CONCLUSIONS

In an open-label trial involving adults with mild asthma, budesonide–formoterol used as needed was superior to albuterol used as needed for the prevention of asthma exacerbations. (Funded by AstraZeneca and the Health Research Council of New Zealand; Novel START Australian New Zealand Clinical Trials Registry number, ACTRN12615000999538.)

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Mild asthma imposes a substantial burden with respect to risk of exacerbations.[1] The risk is reduced by the use of inhaled glucocorticoid therapy,[2] but this treatment is often not used as recommended because of both the reluctance of health care professionals to prescribe inhaled glucocorticoid maintenance treatment and the reluctance of patients to take it when their symptoms are mild and infrequent.[3] An alternative strategy is the use of an inhaler containing a combination of an inhaled glucocorticoid and a fast-onset β_2-agonist on an as-needed basis as reliever therapy; this strategy takes advantage of patients' natural behavior to take reliever therapy when symptomatic[4-6] and allows them to manage their own use of inhaled glucocorticoid therapy according to variations in asthma symptoms.

Recently, two randomized, double-blind, placebo-controlled trials showed the efficacy and safety of budesonide–formoterol as reliever therapy in the absence of regular maintenance treatment in patients with mild asthma.[7,8] However, although these trials have high internal validity, they have limited external validity; whether the findings translate to clinical practice outside the setting of a rigidly controlled trial is unclear. Both trials required participants to use an inhaler twice a day for 12 months so that double-blinding could be maintained, but this requirement removed the advantage of a single inhaler for symptom relief. In addition, both trials required that low-dose inhaled glucocorticoid therapy or leukotriene-receptor antagonist therapy (taken by slightly more than half the participants) be withdrawn during a run-in phase to allow for asthma control to worsen, a requirement that is not consistent with clinical practice. Furthermore, as a result of a baseline eligibility requirement that a short-acting β_2-agonist (SABA) be taken more than twice in a week, both trials excluded patients with intermittent symptoms for whom regular inhaled glucocorticoid therapy is currently recommended.[9,10]

To overcome these limitations, we conducted an open-label clinical trial (Novel Symbicort Turbuhaler Asthma Reliever Therapy [Novel START]) to investigate budesonide–formoterol reliever therapy used on an as-needed basis among adults with mild asthma who had been treated with only as-needed SABA. We hypothesized that as-needed budesonide–formoterol would be superior to as-needed SABA (i.e., continuation of the patients' current class of treatment) and to inhaled glucocorticoid maintenance therapy plus as-needed SABA (as recommended in current guidelines) in preventing asthma exacerbations.[9,10]

Methods

Trial Design and Oversight

This 52-week, randomized, open-label, parallel-group, controlled trial was conducted at 16 trial centers that were based in primary and secondary care in New Zealand, the United Kingdom, Italy, and Australia; a list of the participating centers is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was designed by the trial investigators before consultation with AstraZeneca, who funded the trial. A summary of the trial design has been published previously,[11] and the full trial protocol and statistical analysis plan are available at NEJM.org. The protocol was approved by all the relevant state and national ethics committees. Written informed consent was obtained from all the patients before the performance of any trial procedures. The global sponsor of the trial, the Medical Research Institute of New Zealand (Wellington, New Zealand), had overall responsibility for the conduct of the trial and for data management. An independent data and safety monitoring committee performed regular safety surveillance. The authors had full access to the trial data and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript, and all the authors reviewed and edited subsequent drafts and agreed with the decision to submit the manuscript for publication. AstraZeneca was provided with a draft copy of the manuscript but had no involvement in the collection or analysis of the data, in the preparation of the manuscript, or in the decision to submit the manuscript for publication.

Patients

Patients were eligible for enrollment in the trial if they were 18 to 75 years of age and if they reported that they had received a diagnosis of asthma from a doctor. The main inclusion criteria were the use of a SABA as the sole asthma therapy in the previous 3 months and patient report of the use of the SABA on at least two occasions, but on an average of two or fewer occasions per day,

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in the previous 4 weeks. There was no minimum requirement for SABA use among patients who had had a severe exacerbation in the previous 12 months. Key exclusion criteria were hospitalization for asthma in the previous 12 months and either a patient-reported smoking history of more than 20 pack-years or the onset of respiratory symptoms after the age of 40 years in current or previous smokers with a smoking history of at least 10 pack-years (further details are provided in the Supplementary Appendix).

RANDOMIZATION AND TREATMENT

After enrollment, patients were randomly assigned, in a 1:1:1 ratio, to one of three treatment groups: albuterol used as needed for asthma symptoms (albuterol group), budesonide plus as-needed albuterol (budesonide maintenance group), or budesonide–formoterol used as needed (budesonide–formoterol group). Randomization was stratified according to country and was performed with the use of a computer-generated sequence with a block size of nine. An electronic clinical record system concealed the patients' treatment assignments until the time of randomization. Patients, investigators, and the statistician were all aware of the treatment-group assignments.

Patients in the albuterol group received albuterol (Ventolin, GlaxoSmithKline), 100 μg, with two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 μg, one inhalation twice daily, plus albuterol (Ventolin), 100 μg, two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200 μg of budesonide and 6 μg of formoterol, one inhalation as needed for symptom relief. Patients were provided with asthma action plans that included instructions that specified the circumstances under which they should seek medical evaluation for worsening asthma as well as a log for recording urgent medical visits and use of systemic glucocorticoids (Figs. S18 through S29 in the Supplementary Appendix). Electronic inhaler usage monitors (Adherium), which record the date and time of inhaler actuations,[12,13] were incorporated in all inhalers dispensed in the trial.

PROCEDURES

Seven trial visits occurred over the course of 52 weeks: at weeks 0 (randomization), 6, 12, 22, 32, 42, and 52. Patients were withdrawn because of treatment failure if they had one severe exacerbation, three exacerbations separated by at least 7 days, unstable asthma that resulted in a change in the treatment assigned to them, or any combination of these. If none of these events occurred, patients remained under the care of their primary care physician for management of their asthma throughout the period of the trial.

PRIMARY OUTCOME MEASURE

The primary outcome was the annualized rate of asthma exacerbations per patient. An exacerbation was defined as worsening asthma that resulted in one or more of the following: an urgent medical care consultation (e.g., a primary care visit, an emergency department [ED] visit, or hospital admission); a prescription of systemic glucocorticoids for any duration; or an episode of high β_2-agonist use, which was defined as more than 16 actuations of albuterol or more than 8 actuations of budesonide–formoterol over the course of 24 hours.[14]

SECONDARY OUTCOME MEASURES

Key secondary outcome measures included the number of exacerbations, defined according to each of the three criteria described above, and the time to the first exacerbation; the number of severe exacerbations, according to American Thoracic Society and European Respiratory Society criteria,[15] with a severe exacerbation defined as worsening asthma leading to the prescription of systemic glucocorticoid treatment for at least 3 days or hospitalization or an ED visit leading to systemic glucocorticoid treatment (the number of severe exacerbations represents the number of patients who had a severe exacerbation, since patients were withdrawn from the trial after they had one severe exacerbation); the number of patients who were withdrawn as a result of treatment failure; the score on the Asthma Control Questionnaire–5 (ACQ-5; the mean score of five questions that assess asthma symptoms during the previous week, each of which is scored on a 7-point scale that ranges from 0 [no impairment] to 6 [maximum impairment], in which a 0.5-unit change represents the minimal clinically important difference)[16]; the on-treatment forced expi-

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ratory volume in 1 second (FEV_1, in liters)[15]; the fraction of exhaled nitric oxide (FENO, in parts per billion); the electronically recorded daily dose of budesonide; oral prednisone use (in milligrams); the electronically recorded number of β_2-agonist actuations per day; and adverse events.

STATISTICAL ANALYSIS

The statistical analysis was an intention-to-treat superiority analysis. The prespecified treatment comparisons were between as-needed budesonide–formoterol and as-needed albuterol and between as-needed budesonide–formoterol and maintenance budesonide plus as-needed albuterol.

The primary analysis was a comparison of the rate of exacerbations per patient per year with the use of a Poisson regression model, with days of observation as an offset variable. Two sensitivity analyses were performed to account for potential predictors of response. The first analysis modeled a fixed effect for baseline SABA use and the number of severe exacerbations in the previous 12 months. The second analysis included the same two covariates plus age, sex, smoking status, baseline score on the ACQ-5, FENO, blood eosinophil count, and serum periostin level. A time-to-event analysis with Kaplan–Meier plots and a Cox proportional-hazards model were used to estimate the hazard ratio for a first exacerbation. Interaction models were used to test for subgroup effects.

Continuous variables were compared with the use of Student's t-test and linear mixed-effects models to account for repeated measurements and to examine change over time. For the analysis of FENO, the data were log-transformed, and differences in the logarithms were analyzed as the ratio of geometric means.

We estimated that with a sample of 225 patients in each treatment group, the trial would have 80% power to detect a difference of 0.3 exacerbations per patient per year (1.2 vs. 0.9) between the budesonide–formoterol group and the albuterol group and between the budesonide–formoterol group and the budesonide maintenance group, which represents a relative risk of exacerbation of 0.75, at a two-sided alpha level of 0.05. This estimated sample size accounted for an anticipated dropout rate of 20%.[11] All analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From March 2016 through August 2017, a total of 675 participants underwent randomization; the last participant visit occurred in August 2018. The baseline characteristics of the 668 patients who were included in the analyses are shown in Table 1. No follow-up data were available for 13 patients. No participants were withdrawn by the sponsor. Patients had mild asthma, with a mean score on the ACQ-5 of 1.1; 7.3% of the patients reported a severe exacerbation in the previous 12 months, and 54% reported using SABA on two or fewer occasions per week in the previous 4 weeks. Additional details about the patients are provided in Figure S1 and Tables S2 and S3 in the Supplementary Appendix.

PRIMARY OUTCOME

The asthma exacerbation rate in the budesonide–formoterol group was lower than that in the albuterol group (absolute rate per patient per year, 0.195 vs. 0.400; relative rate, 0.49; 95% confidence interval [CI], 0.33 to 0.72; P<0.001) and did not differ significantly from that in the budesonide maintenance group (absolute rate per patient per year, 0.195 in the budesonide–formoterol group vs. 0.175 in the budesonide maintenance group; relative rate, 1.12; 95% CI, 0.70 to 1.79; P=0.65) (Fig. 1A and 1B, and Tables S5a and S6 in the Supplementary Appendix). These relative rates were similar in sensitivity analyses that included covariates, that included censored exacerbations identified after patients were withdrawn owing to discontinuation of treatment, and that used single-value imputation models that addressed the potential effects of informative censoring of data from patients who were withdrawn because of unstable asthma that resulted in a change in the randomly assigned treatment before the end of the trial (Tables S7 and S50 through S55 in the Supplementary Appendix).

SECONDARY EXACERBATION OUTCOMES

The risk of exacerbation in the budesonide–formoterol group was lower than that in the albuterol group, as assessed in a time-to-first-event analysis (hazard ratio, 0.46; 95% CI, 0.29 to 0.73) and did not differ significantly from that in the budesonide maintenance group (hazard ratio, 0.93; 95% CI, 0.55 to 1.57) (Fig. 2A, and Table S8 in the Supple-

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
Age — yr	35.8±14.0	34.9±14.3	36±14.1
Female sex — no. (%)	113 (50.7)	129 (57.3)	122 (55.5)
Current smoker — no. (%)	24 (10.8)	22 (9.8)	18 (8.2)
Patient-reported SABA use in the 4 weeks before enrollment			
No. of occasions per wk			
Mean	3.4±3.3	3.2±3.0	3.8±3.5
Median (IQR)	2 (1–4)	2 (1–4)	3 (1–5)
Range	0–14	0.5–14	0.5–14
Patients who had ≤2 occasions per wk — no. (%)	127 (57.0)	132 (58.7)	105 (47.7)
Puffs per wk			
Mean	6.52±7.83	5.82±5.25	6.98±6.91
Median (IQR)	4 (2–8)	4 (2–7)	4 (2–8)
Range	0–84	0.5–28	0.5–42
No. of hospital admissions for asthma at any time before enrollment — mean per patient	0.3±0.9	0.3±0.9	0.3±1.3
No. of severe exacerbations in the previous 12 mo. — no. (%)			
0	203 (91.0)	208 (92.4)	208 (94.5)
1	20 (9.0)	15 (6.7)	12 (5.5)
2	0	2 (0.9)	0
Any	20 (9.0)	17 (7.6)	12 (5.5)
ACQ-5 score†	1.1±0.7	1.1±0.7	1.1±0.7
On-treatment FEV_1 — % of predicted value‡	89.2±13.7	90.3±13.6	89.8±14.1
Median FENO (range) — ppb	40 (5–235)	38 (5–200)	37 (3–300)
Periostin — ng/ml	69.3±28.9	70.6±27.8	70.8±27.0
Blood eosinophil count — $\times 10^{-9}$ per liter	0.3±0.2	0.3±0.2	0.3±0.2

* Plus–minus values are means ±SD. Patients in the albuterol group received albuterol (Ventolin, GlaxoSmithKline), 100 μg, with two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 μg, one inhalation twice daily, plus albuterol (Ventolin), 100 μg, two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200 μg of budesonide and 6 μg of formoterol, one inhalation as needed for symptom relief. FENO denotes fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, IQR interquartile range, ppb parts per billion, and SABA short-acting β_2-agonist.

† The Asthma Control Questionnaire–5 (ACQ-5) consists of five questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no impairment) to 6 (maximum impairment), in which a 0.5-unit change represents the minimal clinically important difference.

‡ Patients receive no specific instruction to withhold use of their bronchodilator before measurement of FEV_1.[15]

mentary Appendix). For example, at 300 days of follow-up, the Kaplan–Meier estimates of the percentage of patients who had had an exacerbation were 23.0% in the albuterol group, 12.5% in the budesonide maintenance group, and 11.9% in the budesonide–formoterol group.

The number of severe exacerbations in the budesonide–formoterol group was lower than the number in both the albuterol group (9 vs. 23; relative risk, 0.40; 95% CI, 0.18 to 0.86) and the budesonide maintenance group (9 vs. 21; relative risk, 0.44; 95% CI, 0.20 to 0.96) (Figs. 1C and 2B, and Table S13 in the Supplementary Appendix).

A set of prespecified subgroup analyses, which

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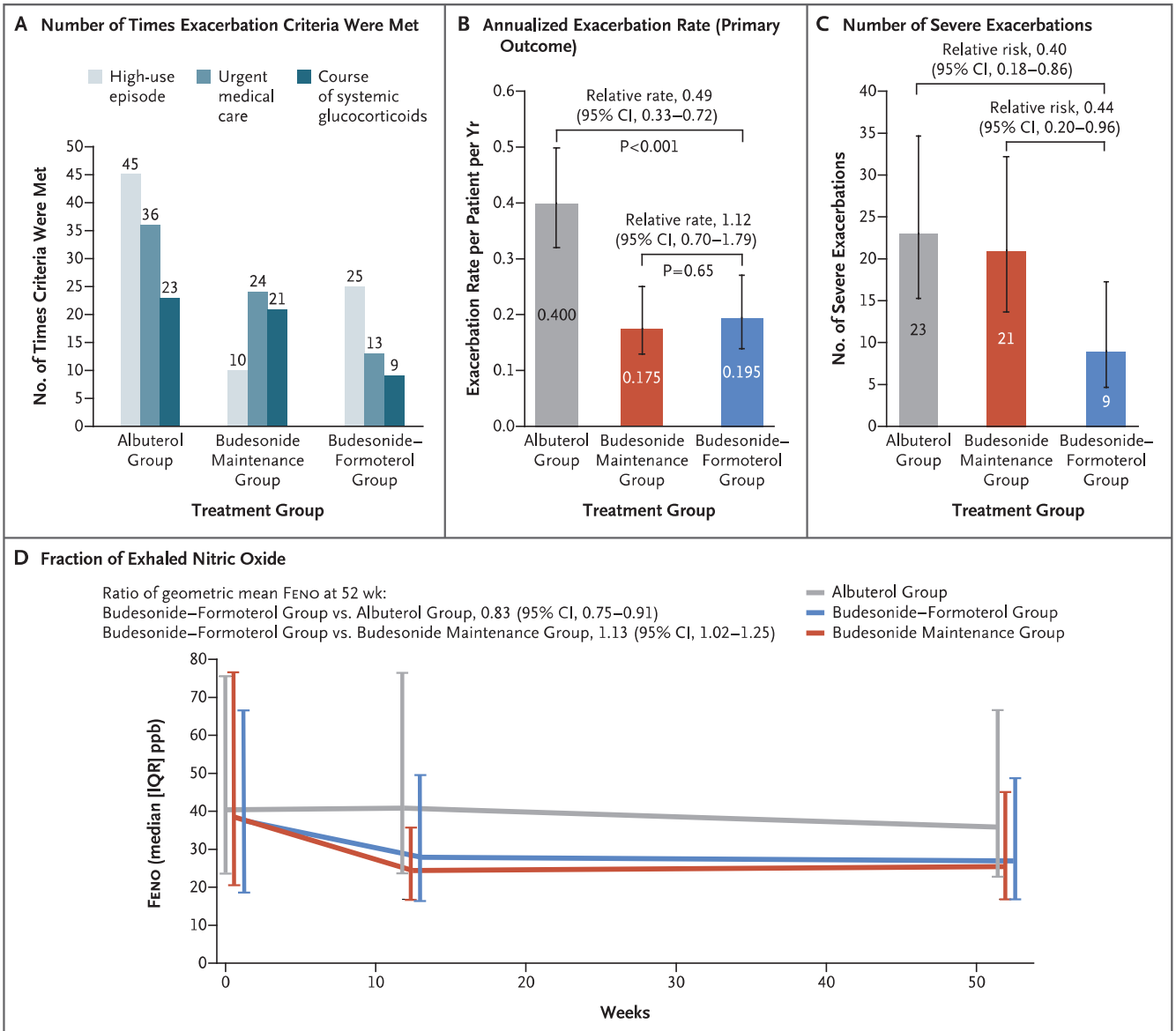

Figure 1. Exacerbation Results and Median FENO over Time.

Patients in the albuterol group received albuterol (Ventolin, GlaxoSmithKline), 100 μg, with two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide maintenance group received budesonide (Pulmicort Turbuhaler, AstraZeneca), 200 μg, one inhalation twice daily, plus albuterol (Ventolin), 100 μg, two inhalations from a pressurized metered-dose inhaler as needed for symptom relief. Patients in the budesonide–formoterol group received budesonide–formoterol (Symbicort Turbuhaler, AstraZeneca), 200 μg of budesonide and 6 μg of formoterol, one inhalation as needed for symptom relief. Panel A shows the number of times exacerbation criteria were met (with exacerbation defined as worsening asthma that resulted in an episode of high β_2-agonist inhaler use, in an urgent medical care consultation, or in a course of systemic glucocorticoids). A single exacerbation could have been characterized by more than one criterion. For example, a patient could have had an episode of high β_2-agonist use, after which the patient sought urgent medical care and then received a course of systemic glucocorticoids; this scenario would represent a single exacerbation, in which the patient met all three criteria. Panel B shows the rate of exacerbations per patient per year, and Panel C the number of severe exacerbations. In both panels, I bars indicate 95% confidence intervals. Panel D shows the median fraction of exhaled nitric oxide (FENO, in parts per billion [ppb]) at baseline (visit 1), at 12 weeks (visit 3), and at 52 weeks (visit 7); I bars indicate the interquartile range (IQR).

tested the interaction of randomly assigned treatment with various subgroups, identified no consistent evidence of effect modification with respect to exacerbations, severe exacerbations, or score on the ACQ-5 in subgroups defined according to age, sex, baseline smoking status, history of ex-

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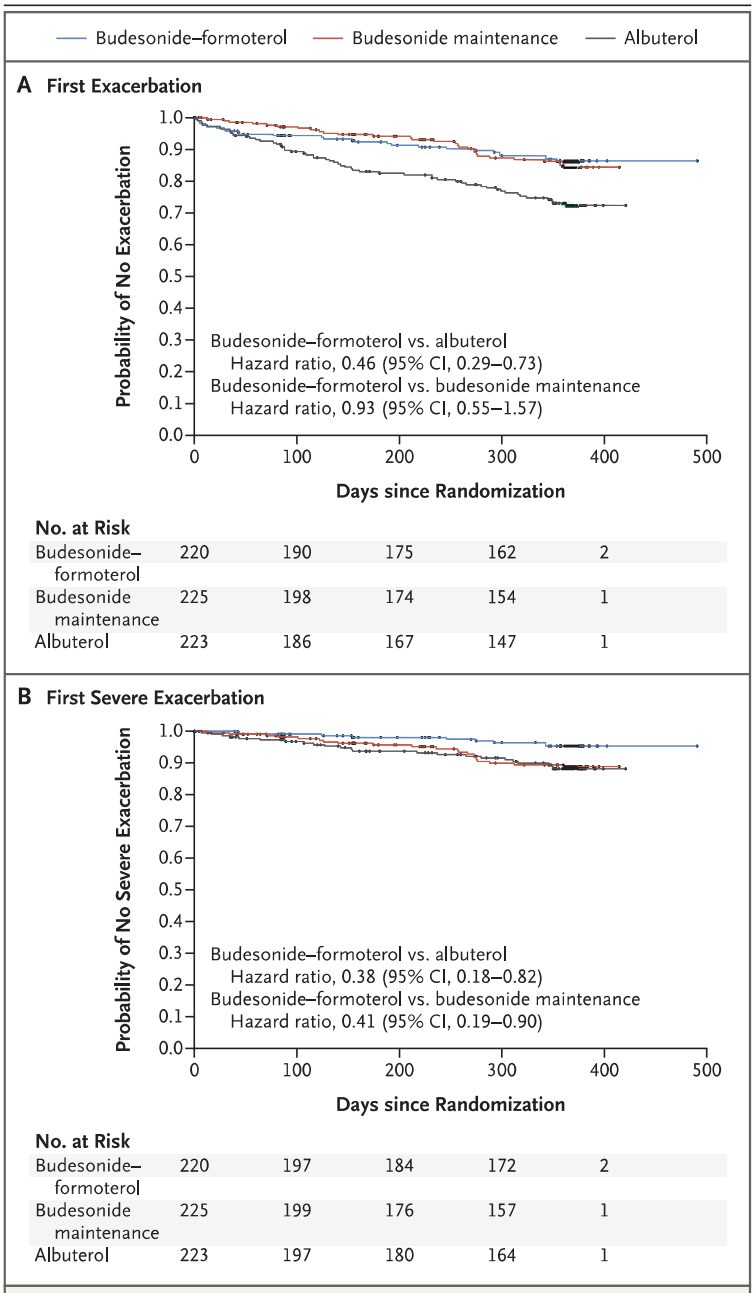

Figure 2. Kaplan–Meier Estimates of the First Occurrence of Exacerbation in a Time-to-Event Analysis.

acerbations, baseline SABA use, baseline score on the ACQ-5, predicted FEV_1, baseline blood eosinophil count, baseline FENO, baseline serum periostin level, and baseline score for type 2 airway inflammation (which was based on thirds of each baseline measurement of eosinophil count, FENO, and periostin level). (Details are provided in Tables S56 through S58 and Figures S12 through S17 in the Supplementary Appendix.)

The number of patients who were withdrawn because of treatment failure in the budesonide–formoterol group was lower than the number in the albuterol group (12 vs. 37; relative risk, 0.33; 95% CI, 0.17 to 0.63) but did not differ significantly from the number in the budesonide maintenance group (12 in the budesonide–formoterol group vs. 22 in the budesonide maintenance group; relative risk, 0.56; 95% CI, 0.28 to 1.13) (Table S18 in the Supplementary Appendix).

OTHER SECONDARY OUTCOMES

Across all time points, the score on the ACQ-5 was lower in the budesonide–formoterol group than in the albuterol group (mean difference, −0.15; 95% CI, −0.24 to −0.06) but was higher in the budesonide–formoterol group than in the budesonide maintenance group (mean difference, 0.14; 95% CI, 0.05 to 0.23) (Table S35 and Fig. S8 in the Supplementary Appendix).

Across all time points, the FEV_1 in the budesonide–formoterol group did not differ significantly from the FEV_1 in either the albuterol group (mean difference, 0.03 liters; 95% CI, −0.006 to 0.07) or the budesonide maintenance group (mean difference, 0.004 liters; 95% CI, −0.03 to 0.04) (Table S38 and Fig. S9 in the Supplementary Appendix).

The distribution of FENO was widely skewed at baseline; the median FENO was 40 parts per billion (ppb) (range, 5 to 235; interquartile range, 23 to 75) in the albuterol group, 38 ppb (range, 5 to 200; interquartile range, 20 to 76) in the budesonide maintenance group, and 37 ppb (range, 3 to 300; interquartile range, 18 to 66) in the budesonide–formoterol group. At 12 months (visit 7), the median FENO values were 36 ppb (range, 5 to 201; interquartile range, 22 to 66) in the albuterol group, 25 ppb (range, 4 to 186; interquartile range, 16 to 45) in the budesonide maintenance group, and 26 ppb (range, 5 to 238; interquartile range, 16 to 48) in the budesonide–formoterol group (Fig. 1D, and Fig. S6 and Table S25 in the Supplementary Appendix). The geometric mean FENO in the budesonide–formoterol group was lower than that in the albuterol group (ratio of geometric means, 0.83; 95% CI, 0.75 to 0.91) but higher than that in the budesonide maintenance group (ratio of geometric means, 1.13; 95% CI, 1.02 to 1.25) at 12 months (Table S32 in the Supplementary Appendix).

The mean (±SD) dose of budesonide was 107±109 μg per day in the budesonide–formoterol

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Table 2. Medication Outcomes.*

Outcome	Albuterol Group (N=223)	Budesonide Maintenance Group (N=225)	Budesonide–Formoterol Group (N=220)
Glucocorticoid use			
No. of inhaled glucocorticoid-containing actuations per day			
Mean	NA	1.11±0.56	0.53±0.54
Median (IQR)	NA	1.23 (0.66–1.57)	0.37 (0.15–0.73)
Range	NA	0–2.01	0–3.95
Daily budesonide dose — μg			
Mean	NA	222±113	107±109
Median (IQR)	NA	247 (132–314)	73 (31–146)
Range†	NA	0–402	0–790
Oral glucocorticoid use, prednisone — mg	17.4±59.8	14.5±51.0	7.5±40.2
No. of β_2-agonist–containing actuations per day			
Mean	1.01±1.60	0.52±1.03	0.53±0.54
Median (IQR)	0.50 (0.18–1.18)	0.18 (0.06–0.46)	0.37 (0.15–0.73)
Range	0.0–16.3	0.0–8.7	0–3.95

* Plus–minus values are means ±SD. Inhaled glucocorticoid and β_2-agonist use was determined with the use of electronic monitoring of the trial inhalers. NA denotes not applicable.
† The range refers to the minimum mean daily dose and the maximum mean daily dose.

group and 222±113 μg per day in the budesonide maintenance group (Table 2). Overall mean adherence to twice-daily doses of budesonide maintenance therapy was 56%.

Adverse events and serious adverse events are summarized in Table 3, and in Tables S59 through S62 in the Supplementary Appendix. There was one death (motor vehicle accident) in the budesonide–formoterol group and one death (suicide) in the budesonide maintenance group (Table S62 in the Supplementary Appendix).

DISCUSSION

The results of this randomized, open-label, controlled trial showed that, among patients with mild asthma who had previously been taking only a SABA on an as-needed basis, the risk of asthma exacerbations was lower with budesonide–formoterol used as needed than with albuterol used as needed. Treatment with as-needed budesonide–formoterol was superior to both as-needed albuterol and budesonide maintenance therapy plus as-needed albuterol in reducing the risk of severe exacerbations. This finding suggests that the use of an inhaled glucocorticoid in the situation of worsening asthma as perceived by the patient, through the vehicle of a coadministered bronchodilator (such as formoterol) used on an as-needed basis, may reduce the risk of the exacerbation becoming severe enough for the patient to seek urgent care. However, maintenance treatment with budesonide was superior for control of asthma symptoms, which suggests that for the patient for whom asthma symptoms rather than exacerbations are the most bothersome, maintenance treatment has value.

This trial extends the findings of the double-blind, double-dummy Symbicort Given as Needed in Mild Asthma (SYGMA) trials[7,8] to an open-label treatment regimen that reflects real-world practice. Our population had less severe asthma than the patients in the SYGMA trials, given that the patients in our trial were taking only a SABA at enrollment and approximately half reported using a SABA on an average of two or fewer occasions per week at enrollment, which was a key exclusion criterion in the final week of run-in in the SYGMA trials. As a result, our trial extends the evidence for the efficacy of as-needed use of

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Table 3. Adverse Events.

Event	Albuterol Group (N=226)	Budesonide Maintenance Group (N=227)	Budesonide–Formoterol Group (N=222)
		number of patients (percent)	
Any adverse event	185 (81.9)	190 (83.7)	174 (78.4)
Adverse events that occurred in ≥2% of patients in any group			
Upper respiratory tract infection	75 (33.2)	75 (33.0)	71 (32.0)
Nasopharyngitis	46 (20.4)	35 (15.4)	47 (21.2)
Asthma	46 (20.4)	26 (11.5)	17 (7.7)
Influenza	17 (7.5)	25 (11.0)	20 (9.0)
Lower respiratory tract infection	20 (8.8)	18 (7.9)	14 (6.3)
Headache	15 (6.6)	14 (6.2)	9 (4.1)
Cough	12 (5.3)	14 (6.2)	10 (4.5)
Respiratory tract infection	7 (3.1)	11 (4.8)	10 (4.5)
Seasonal allergy	12 (5.3)	8 (3.5)	7 (3.2)
Sinusitis	7 (3.1)	10 (4.4)	9 (4.1)
Back pain	9 (4.0)	7 (3.1)	7 (3.2)
Oropharyngeal pain	10 (4.4)	7 (3.1)	5 (2.3)
Ligament sprain	7 (3.1)	6 (2.6)	8 (3.6)
Gastroenteritis	8 (3.5)	8 (3.5)	4 (1.8)
Anxiety	7 (3.1)	6 (2.6)	6 (2.7)
Viral upper respiratory tract infection	5 (2.2)	8 (3.5)	6 (2.7)
Toothache	4 (1.8)	9 (4.0)	1 (0.5)
Migraine	7 (3.1)	2 (0.9)	5 (2.3)

budesonide–formoterol to a level at which initiation of inhaled glucocorticoid therapy is recommended by the Global Initiative for Asthma for risk reduction[9] — although the therapy is often not prescribed or taken. The SYGMA 1 trial showed that the risk of severe exacerbation was 64% lower with as-needed budesonide–formoterol than with as-needed SABA,[7] which was similar to the estimate of 60% in the current trial. However, whereas the SYGMA 1 and 2 trials showed no significant difference in the risk of severe exacerbations between as-needed budesonide–formoterol and budesonide maintenance therapy plus as-needed terbutaline (risk ratios of 0.83 and 0.97, respectively),[7,8] we observed fewer severe exacerbations with as-needed budesonide–formoterol than with budesonide maintenance therapy plus as-needed albuterol (relative risk, 0.44). This difference may relate to our open-label design, which, through avoidance of a double-dummy design, allowed the use of a single inhaler for both an inhaled glucocorticoid and a beta agonist and no requirement for regular inhaler use twice daily (i.e., the placebo inhalers in the two SYGMA trials), which are real-world advantages of the regimen of as-needed budesonide–formoterol.

An unexpected observation was that budesonide maintenance therapy plus as-needed albuterol did not appear to result in a lower number of severe exacerbations than as-needed albuterol. The most likely explanation for this finding is bias due to protocol-driven withdrawals. Patients were withdrawn because of treatment failure if they had one severe exacerbation, three exacerbations separated by at least 7 days, unstable asthma that resulted in a change in the assigned treatment,

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or any combination of these. The criterion for a change in the assigned treatment by the treating physician because of unstable asthma was met by 11 patients in the albuterol group; for all these patients, an inhaled glucocorticoid or an inhaled glucocorticoid–long-acting beta agonist (LABA) was subsequently prescribed, whereas these medications were not prescribed for unstable asthma for any patients in the other two groups, because no patients in those groups met the criteria for unstable asthma that resulted in a change in the assigned treatment. In the albuterol group, withdrawal because of a change in the assigned treatment owing to unstable asthma may have led to a healthy survivor effect because of a reduced pool of patients in unstable condition who could otherwise have gone on to have a severe exacerbation. When withdrawal because of treatment failure according to all three criteria was taken into account, the number of withdrawals was higher in the albuterol group than in the budesonide maintenance group (37 vs. 22).

The findings of our trial are consistent with evidence regarding the treatment of moderate and severe asthma — that maintenance and reliever therapy with inhaled glucocorticoid–formoterol results in a lower risk of severe exacerbations than maintenance therapy with an inhaled glucocorticoid–LABA and as-needed SABA[14,17]; that frequent repeated administration of high-dose inhaled glucocorticoid in patients with acute severe asthma has similar efficacy to an oral glucocorticoid[18,19]; that in adults, quadrupling the dose of inhaled glucocorticoid during worsening asthma results in fewer severe exacerbations[20]; and that combination beclomethasone dipropionate–albuterol used as needed has greater efficacy than as-needed albuterol alone.[21]

A reduction in the median FENO from baseline to month 12 was observed with budesonide maintenance therapy (from 38 to 25 ppb) and with as-needed budesonide–formoterol (from 37 to 26 ppb), which indicates that in patients with mild asthma who have not been treated previously with a glucocorticoid, airway inflammation as measured by FENO is highly responsive to inhaled glucocorticoid therapy. These findings show that budesonide–formoterol therapy has antiinflammatory activity in the airway when administered according to an as-needed reliever regimen for the treatment of mild asthma.

Limitations of the current trial include the occurrence of more frequent scheduled clinic visits than would be expected in routine clinical practice and patient awareness of the electronic monitoring of inhaler use. The open-label design introduced potential for bias but avoided the requirement for double-dummy medication use. The exacerbation rate was lower than anticipated; however, the magnitude of the difference between the budesonide–formoterol group and the albuterol group in the relative rate was greater than predicted, and there was sufficient power to identify a significant difference in these exacerbation rates, although confidence intervals were wide. Secondary outcomes were not adjusted for multiplicity of analyses and should not be used to infer definitive treatment effects. Strengths of the trial include the use of validated electronic inhaler monitors to calculate inhaled glucocorticoid exposure and to identify otherwise unreported exacerbations that were not severe.[14] The analysis of the primary outcome of the asthma exacerbation rate was based on a composite indication of worsening asthma that included both urgent medical review or prescription of systemic glucocorticoids and episodes of high β_2-agonist use — thereby including exacerbations that did not lead the patient to seek urgent care. The thresholds for high β_2-agonist use were based on recommended levels at which a patient should seek medical review[22] and reflect that repeat administration of formoterol at a dose of 6 μg results in a short-term bronchodilator response that is similar to that observed with repeat administration of albuterol at a dose of 200 μg in the treatment of acute asthma.[23,24]

In conclusion, this clinical trial, in which an open-label design was used to reflect clinical practice, showed that budesonide–formoterol used as needed was superior to albuterol used as needed for the prevention of exacerbations in adults with mild asthma.

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