ORIGINAL ARTICLE

Serious Asthma Events with Budesonide plus Formoterol vs. Budesonide Alone

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ABSTRACT

BACKGROUND

Concerns remain about the safety of adding long-acting β_2-agonists to inhaled glucocorticoids for the treatment of asthma. In a postmarketing safety study mandated by the Food and Drug Administration, we evaluated whether the addition of formoterol to budesonide maintenance therapy increased the risk of serious asthma-related events in patients with asthma.

METHODS

In this multicenter, double-blind, 26-week study, we randomly assigned patients, 12 years of age or older, who had persistent asthma, were receiving daily asthma medication, and had had one to four asthma exacerbations in the previous year to receive budesonide–formoterol or budesonide alone. Patients with a history of life-threatening asthma were excluded. The primary end point was the first serious asthma-related event (a composite of adjudicated death, intubation, and hospitalization), as assessed in a time-to-event analysis. The noninferiority of budesonide–formoterol to budesonide was defined as an upper limit of the 95% confidence interval for the risk of the primary safety end point of less than 2.0. The primary efficacy end point was the first asthma exacerbation, as assessed in a time-to-event analysis.

RESULTS

A total of 11,693 patients underwent randomization, of whom 5846 were assigned to receive budesonide–formoterol and 5847 to receive budesonide. A serious asthma-related event occurred in 43 patients who were receiving budesonide–formoterol and in 40 patients who were receiving budesonide (hazard ratio, 1.07; 95% confidence interval [CI], 0.70 to 1.65]); budesonide–formoterol was shown to be noninferior to budesonide alone. There were two asthma-related deaths, both in the budesonide–formoterol group; one of these patients had undergone an asthma-related intubation. The risk of an asthma exacerbation was 16.5% lower with budesonide–formoterol than with budesonide (hazard ratio, 0.84; 95% CI, 0.74 to 0.94; P=0.002).

CONCLUSIONS

Among adolescents and adults with predominantly moderate-to-severe asthma, treatment with budesonide–formoterol was associated with a lower risk of asthma exacerbations than budesonide and a similar risk of serious asthma-related events. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01444430.)

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N Engl J Med 2016;375:850-60.
DOI: 10.1056/NEJMoa1511190

Current guidelines for the management of asthma suggest that inhaled glucocorticoids should be used as initial controller therapy, with a long-acting beta-agonist (LABA) then added if symptoms remain uncontrolled or increase in severity.[1] Although LABAs have been an available treatment option for asthma since 1990,[2] questions remain regarding the safety of this drug class.[3] These concerns originate mainly from the results of two large studies in which the effects of adding the LABA salmeterol to existing asthma treatment were reviewed.[4,5] These studies showed higher rates of asthma-related death and other serious outcomes related to asthma among patients receiving salmeterol than among patients receiving the short-acting beta-agonist salbutamol[4] or placebo.[5]

In response to these concerns, the safety of LABAs, including formoterol, has been examined in numerous meta-analyses.[6-8] A pooled analysis of safety data from more than 68,000 patients in 64 randomized trials of formoterol for the treatment of asthma showed a significantly lower risk of asthma-related serious adverse events among those receiving formoterol than among those receiving non-LABA therapy and no significantly higher risk of asthma-related death with formoterol.[6] However, given the rarity of asthma-related death, there was insufficient power to reject any association between this event and formoterol use.[6] An updated version of this analysis including 32 additional studies of formoterol that involved more than 26,000 patients and were completed between 2007 and 2011 corroborated the earlier findings, with no new asthma-related deaths reported.[7]

The possibility that LABAs may increase the risk of serious asthma-related events has been discussed at several advisory committee meetings conducted by the Food and Drug Administration (FDA). In 2008, the FDA requested that all manufacturers of LABA-containing products intended for the treatment of asthma provide additional data on the risk of serious asthma-related events from all completed double-blind, randomized, controlled studies in which therapies containing LABAs were compared with those that did not contain LABAs. In response, AstraZeneca conducted a meta-analysis of all eligible AstraZeneca-sponsored studies in which the effects of formoterol-containing therapy were compared with the effects of non-LABA treatment in patients with asthma.[8] The results of the analysis, which include data from 23,510 patients in 42 double-blind trials, revealed no asthma-related deaths and no data supporting evidence of a higher risk of asthma-related hospitalization or intubation among participants receiving formoterol-containing therapy than among those receiving non-LABA treatment.[8] However, since no asthma-related deaths were observed, and asthma-related hospitalizations and intubations were rare, even this large and stringent data set was not considered to be sufficient to definitively refute the possibility of potential risk that had been generated in previous studies.[8]

In 2009, the FDA issued a mandate to each of the four manufacturers of LABA-containing products in the United States (including AstraZeneca) to conduct similarly designed postmarketing safety studies comparing the effect of inhaled glucocorticoid–LABA combination therapy on the incidence of serious asthma-related events (including hospitalization, intubation, or death) with the effect of inhaled glucocorticoids alone.[9] In this 26-week, randomized, double-blind, multicenter study, we evaluated whether the addition of formoterol to budesonide in a fixed-dose combination was associated with a higher risk of serious asthma-related events than that with budesonide alone. The secondary objective was to evaluate efficacy.

Methods

Study Oversight

The study protocol, which was developed in discussion with the FDA, was aligned across all four safety studies mandated for the manufacturers of LABAs that are marketed for adults and adolescents with asthma in the United States.[10] Oversight of each of the four studies was the purview of four types of committee. Three of these committees were responsible for all four studies: the oversight steering committee; a data monitoring committee, which was responsible for monitoring pooled data, with a focus on asthma-related mortality across all studies; and an independent adjudication committee, which was responsible for assessing whether potentially serious asthma-related events were, in fact, asthma-related (the members of this third com-

mittee were unaware of the study sponsor and the study treatment). The fourth committee was a study-specific data monitoring committee that monitored all aspects of safety.

Scientific oversight was provided by the first author and employees of AstraZeneca, who were responsible for the design, analysis plan, and conduct of the trial. None of the study investigators were employees of AstraZeneca. An initial outline of the manuscript was prepared with professional writing assistance from inScience Communications (funded by AstraZeneca) with input from the first author. All the authors worked collaboratively to prepare subsequent drafts and the final content. Statistical analyses were performed by employees of AstraZeneca and Pharmaceutical Product Development. All the authors had full access to the study data, confirmed the accuracy and completeness of the data, and agreed to submit the manuscript for publication. The protocol, available with the full text of this article at NEJM.org, was approved by national regulatory authorities before the study began, and the study was approved by local ethics committees and institutional review boards and was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki. The authors vouch for the fidelity of the study to the protocol.

CRITERIA FOR STUDY ENTRY

Eligible patients were 12 years of age or older and had had a clinical diagnosis of asthma[11-13] for at least 1 year, were receiving daily asthma medication, and had a history of at least one asthma exacerbation in the previous year but none in the previous 4 weeks. Eligible patients included those who were being currently treated with an inhaled glucocorticoid or inhaled glucocorticoid–LABA combination as well as those whose disease severity (or level of asthma control) warranted initiation of such therapy. Patients were excluded from the study if they had a history of life-threatening asthma or had had more than four separate exacerbations or more than two hospitalizations for asthma in the previous year, had unstable asthma within 7 days before randomization (rescreening was permitted after 4 weeks), or had a smoking history of more than 10 pack-years. Full criteria are provided in the protocol. All adult patients provided written informed consent, and all adolescent patients provided assent.

STUDY DESIGN AND TREATMENT

Patients were stratified to a dose level of inhaled glucocorticoid on the basis of asthma control and prior asthma therapy. Asthma control was assessed by means of the six-item Asthma Control Questionnaire (ACQ-6), on which asthma symptoms are rated on a scale of 0 to 6, with higher values indicating worse symptoms. An interactive voice-response–Web-response system was used to manage patient enrollment and randomization. Patients were randomly assigned in a 1:1 ratio within their stratum to receive budesonide–formoterol (Symbicort, AstraZeneca) through an open-label inhaler (two actuations of 80 μg of budesonide plus 4.5 μg of formoterol or 160 μg of budesonide plus 4.5 μg of formoterol) or budesonide alone through a pressurized metered-dose inhaler (two actuations of 80 μg or 160 μg) twice daily for 26 weeks. Adherence to the required dosing regimen was assessed by means of the dose-actuation counter on each inhaler. A pressurized metered-dose inhaler was provided as a rescue medication for all patients, with patients in the United States receiving albuterol and patients outside the United States receiving salbutamol. During the treatment period, patients had three scheduled clinic visits (on days 28 and 84 and at treatment end; Fig. S1 in the Supplementary Appendix, available at NEJM.org) and received a monthly telephone call between visits.

END POINTS AND ASSESSMENTS

The primary objective was to evaluate the risk of serious asthma-related events (defined as a composite of asthma-related deaths, intubations, and hospitalizations), with the first serious asthma-related event as the primary end point, assessed in a time-to-event analysis. Additional safety assessments were limited to serious adverse events (including death from any cause), discontinuations resulting from adverse events, and discontinuations resulting from exacerbations.

The secondary objective was to evaluate efficacy, with the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for at least 3 days, an inpatient

hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) as the primary efficacy end point, assessed in a time-to-event analysis. Secondary efficacy end points included assessment of current asthma control (by means of the ACQ-6), the use of rescue medication, symptoms of asthma, symptoms of asthma that limited activity, and night-time awakenings (as recorded daily by patients in a diary).

STATISTICAL ANALYSIS

To meet the prespecified noninferiority margin, the upper limit of the two-sided 95% confidence interval of the hazard ratio for the first serious asthma-related event with budesonide–formoterol versus budesonide had to be less than 2.0. The incidence rate of serious asthma-related events in the budesonide-only treatment group was predicted to be 0.0075 over a 26-week period; the prediction was based on meta-analyses of products containing LABAs (as conducted for an FDA advisory committee meeting in 2008) and FDA guidance.[10] It was calculated that 87 events would have to occur for the study to have 90% power to rule out an event rate with budesonide–formoterol that was twice as high as the rate with budesonide alone. We calculated that for 87 events to occur, 11,664 patients would have to undergo randomization, assuming that the study would have a 6-month duration and an approximately constant event rate over time. The framework for the design and the related assumptions were agreed on with the FDA.[10]

In accordance with the intention-to-treat principle, analyses included all patients who were randomly assigned to receive a study drug; patients were analyzed according to initial group assignment. All patients were followed for the full study period for the purpose of assessing the primary end point, irrespective of early discontinuation of the study treatment, which allowed for a full intention-to-treat analysis of serious asthma-related events, including all events occurring up to 26 weeks after randomization or up to 7 days after the last date of study treatment, whichever was later.

Efficacy data were collected during the period in which the patients received treatment with a study drug. The analyses of asthma exacerbations and a supplementary analysis of serious asthma-related events included events that occurred up to 7 days after the last date of treatment with the study drug.

For the primary analysis of serious asthma-related events and asthma exacerbations, a Cox proportional-hazards model was used to compare budesonide–formoterol with budesonide, with a term for randomized treatment and a term for dose strata according to asthma treatment and asthma control at the time of randomization. Estimated hazard ratios, two-sided 95% confidence intervals, and P values are presented. The number of asthma exacerbations was also evaluated by means of a Poisson regression model, with terms for dose strata (based on asthma treatment and asthma control at the time of randomization) and randomized treatment and with a logarithm of the time in study as offset. Prespecified clinical subgroup analyses of the primary and secondary end points were performed in subgroups defined according to age, race, sex, region (U.S. region vs. non-U.S. region), and dose. Information on health care utilization was collected during the study; formal analyses of these data were not specified in the primary analysis plan and are not presented here.

RESULTS

PATIENTS

Patients were enrolled from December 2011 through April 2015 at 534 centers in 25 countries. In total, 11,693 patients underwent randomization and were included in the intention-to-treat population. Among these patients, 12 did not receive treatment (2 patients withdrew their consent and 10 patients did not receive treatment for unknown reasons). A total of 11,551 patients completed the study (Fig. 1). Overall, 80% of all patients (80.4% of those receiving budesonide–formoterol and 79.5% of those receiving budesonide alone) had 80% or more adherence to the study regimen.

The treatment groups had similar demographic profiles and baseline characteristics and were broadly representative of the asthma population at large that is eligible for inhaled glucocorticoid–LABA therapy, including patients with controlled disease and those with uncontrolled disease and patients who had been receiving a wide range of glucocorticoid doses (9.9% were

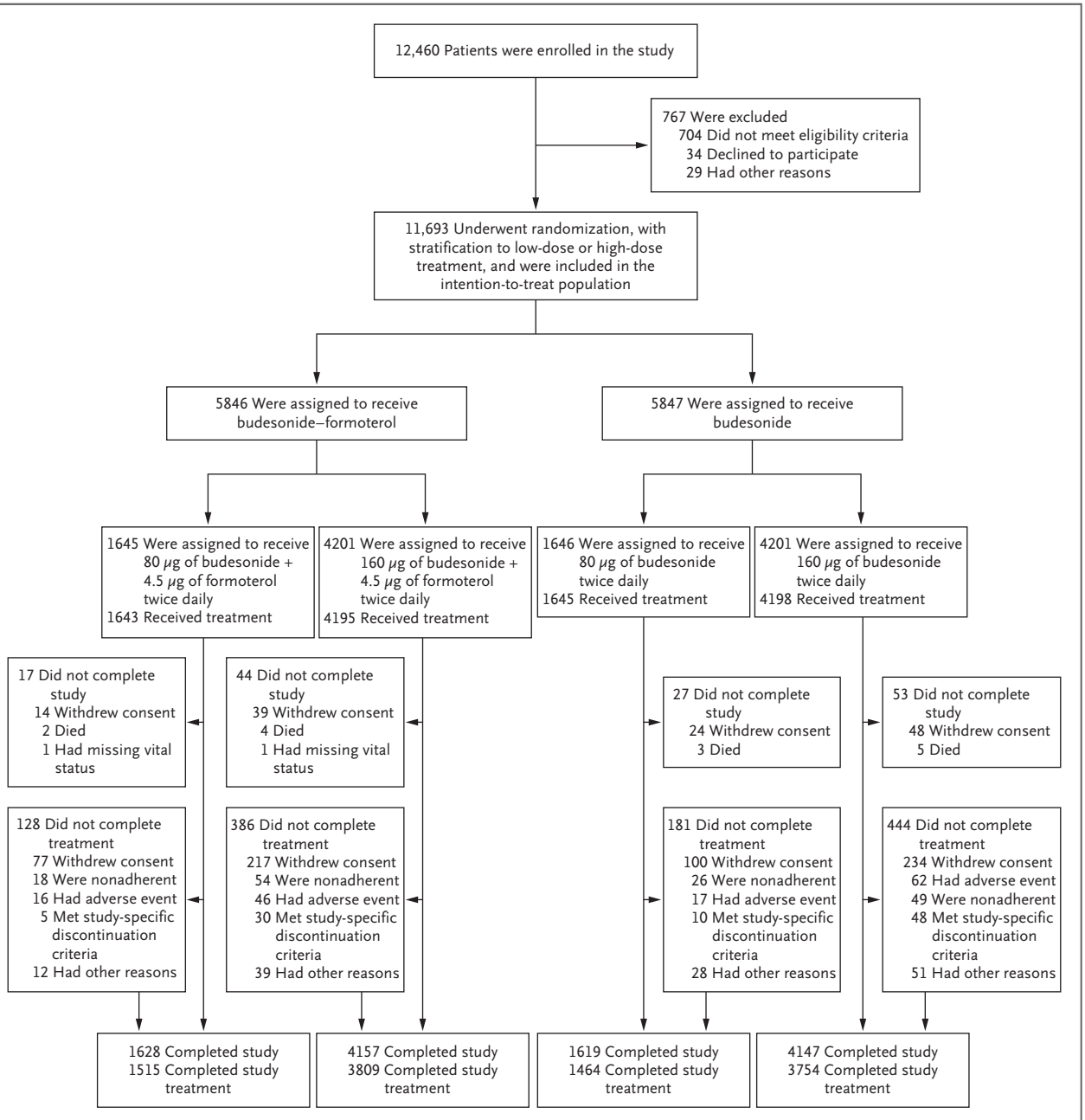

Figure 1. Screening, Randomization, and Follow-up.

All patients who underwent randomization to treatment were included in the intention-to-treat population, regardless of whether they received treatment. Each dose of medication was provided through two actuations of a pressurized metered-dose inhaler. Owing to missing information in the electronic case-report form, one patient in the group receiving 160 μg of budesonide was not included in the number of patients who completed the study, but the patient underwent follow-up for the complete duration of the study. The study-specific discontinuation criteria are related to asthma exacerbation.

not using inhaled glucocorticoids at baseline) (Table 1). At study entry, most patients were receiving either low-dose or medium-dose inhaled glucocorticoids, and 40.1% of the patients had uncontrolled asthma (i.e., an ACQ-6 score ≥1.5).

PRIMARY END POINT

Among the patients who received budesonide–formoterol, 43 had serious asthma-related events, for a total of 49 such events, and among the patients receiving budesonide, 40 had serious asthma-

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Low Dose		High Dose		Total	
	Budesonide–Formoterol 80 μg+4.5 μg (N=1645)	Budesonide 80 μg (N=1646)	Budesonide–Formoterol 160 μg+4.5 μg (N=4201)	Budesonide 160 μg (N=4201)	Budesonide–Formoterol (N=5846)	Budesonide (N=5847)
Age — yr	39.3±18.4	40.4±18.2	45.1±16.7	44.7±16.8	43.4±17.4	43.5±17.3
Age group — no. (%)						
12–17 yr	304 (18.5)	277 (16.8)	328 (7.8)	359 (8.5)	632 (10.8)	636 (10.9)
18–64 yr	1188 (72.2)	1208 (73.4)	3384 (80.6)	3360 (80.0)	4572 (78.2)	4568 (78.1)
≥65 yr	153 (9.3)	161 (9.8)	489 (11.6)	482 (11.5)	642 (11.0)	643 (11.0)
Female sex — no. (%)	1043 (63.4)	1032 (62.7)	2806 (66.8)	2788 (66.4)	3849 (65.8)	3820 (65.3)
Race — no. (%)†						
White	1150 (69.9)	1137 (69.1)	2900 (69.0)	2866 (68.2)	4050 (69.3)	4003 (68.5)
Black	111 (6.7)	103 (6.3)	285 (6.8)	298 (7.1)	396 (6.8)	401 (6.9)
Asian	267 (16.2)	291 (17.7)	581 (13.8)	616 (14.7)	848 (14.5)	907 (15.5)
Other	117 (7.1)	115 (7.0)	435 (10.4)	421 (10.0)	552 (9.4)	536 (9.2)
Smoking status — no. (%)						
Never	1439 (87.5)	1383 (84.0)	3502 (83.4)	3538 (84.2)	4941 (84.5)	4921 (84.2)
Current	47 (2.9)	53 (3.2)	139 (3.3)	127 (3.0)	186 (3.2)	180 (3.1)
Former	159 (9.7)	210 (12.8)	560 (13.3)	536 (12.8)	719 (12.3)	746 (12.8)
Mean time since asthma diagnosis — yr	14.7	15.3	15.5	15.5	15.3	15.4
Mean ACQ-6 score at randomization‡	1.2±0.9	1.2±0.9	1.4±0.9	1.4±0.9	1.4±0.9	1.4±0.9
Asthma-control status at randomization — no. (%)						
Controlled: ACQ-6 <1.5	1154 (70.2)	1186 (72.1)	2321 (55.2)	2342 (55.7)	3475 (59.4)	3528 (60.3)
Uncontrolled: ACQ-6 ≥1.5	491 (29.8)	460 (27.9)	1880 (44.8)	1859 (44.3)	2371 (40.6)	2319 (39.7)
Exacerbations in past 12 mo — no. (%)						
0	1 (0.1)	2 (0.1)	6 (0.1)	6 (0.1)	7 (0.1)	8 (0.1)
1	1444 (87.8)	1403 (85.2)	3433 (81.7)	3421 (81.4)	4877 (83.4)	4824 (82.5)
2	161 (9.8)	197 (12.0)	611 (14.5)	599 (14.3)	772 (13.2)	796 (13.6)
3	35 (2.1)	39 (2.4)	120 (2.9)	141 (3.4)	155 (2.7)	180 (3.1)
≥4	4 (0.2)	4 (0.2)	31 (0.7)	32 (0.8)	35 (0.6)	36 (0.6)
Daily dose of inhaled glucocorticoid — no. (%)§						
None	474 (28.8)	464 (28.2)	103 (2.5)	120 (2.9)	577 (9.9)	584 (10.0)
Low	1068 (64.9)	1062 (64.5)	707 (16.8)	689 (16.4)	1775 (30.4)	1751 (29.9)
Medium	76 (4.6)	84 (5.1)	2823 (67.2)	2815 (67.0)	2899 (49.6)	2899 (49.6)
High	27 (1.6)	36 (2.2)	568 (13.5)	577 (13.7)	595 (10.2)	613 (10.5)

* Plus–minus values are means ±SD. At the time of randomization, patients were stratified to a low dose or a high dose of inhaled glucocorticoids on the basis of asthma control and prior asthma therapy. According to a post hoc analysis, there were no significant between-group differences in baseline characteristics.

† Race was self-reported.

‡ The six-item Asthma Control Questionnaire (ACQ-6) assesses asthma symptoms on a scale of 0 to 6, with higher values indicating worse symptoms.

§ On the basis of the latest dose taken within 4 weeks before randomization, a low dose was defined as 250 μg or less of beclomethasone dipropionate with a hydrofluoroalkane propellant (BDP-HFA) or fluticasone propionate or 400 μg or less of budesonide, a medium dose as 251 to 500 μg of BDP-HFA or fluticasone propionate or 401 to 800 μg of budesonide, and a high dose as more than 500 μg of BDP-HFA or fluticasone propionate or more than 800 μg of budesonide.[14]

Table 2. Patients with Serious Asthma-Related Events.*

End Point or Event	Low Dose		High Dose		Total	
	Budesonide–Formoterol 80 μg+4.5 μg (N=1645)	Budesonide 80 μg (N=1646)	Budesonide–Formoterol 160 μg+4.5 μg (N=4201)	Budesonide 160 μg (N=4201)	Budesonide–Formoterol (N=5846)	Budesonide (N=5847)
	number (percent)					
Composite end point	6 (0.4)	8 (0.5)	37 (0.9)	32 (0.8)	43 (0.7)	40 (0.7)
Asthma-related hospitalization	6 (0.4)	8 (0.5)	36 (0.9)	32 (0.8)	42 (0.7)	40 (0.7)
Asthma-related intubation	0	0	1 (<0.1)	0	1 (<0.1)	0
Asthma-related death	0	0	2 (<0.1)	0	2 (<0.1)	0

* Serious asthma-related events were defined as asthma-related deaths, asthma-related intubations, or asthma-related hospitalizations; the composite end point included all three types of events. All data in this table are derived from the intention-to-treat population, which comprised all patients who were randomly assigned to receive treatment. All events were adjudicated by an independent joint adjudication committee whose members were unaware of the study-group assignments and who adjudicated all potential primary end-point events.

related events, for a total of 45 such events. There were two asthma-related deaths, both of which occurred in the budesonide–formoterol group; one of these patients had undergone an asthma-related intubation. One of these patients was a 68-year-old woman who stopped taking the study medication after 104 days, after having respiratory and cardiac arrest for which she required treatment in the emergency department and intubation; she died 8 weeks later from cardiopulmonary failure. The other patient was a 22-year-old woman who, after taking the study medication for 109 days, had dyspnea, took three doses of salbutamol, and suddenly became cyanotic, lost consciousness, and died. The cause of death was listed as pneumonia, and the antecedent cause was listed as bronchial asthma. (For further information, see the section on adjudication in the Supplementary Appendix.) The remaining events were asthma-related hospitalizations (Table 2). Statistical noninferiority was demonstrated for the time to first serious asthma-related event on the basis of an upper limit of the 95% confidence interval for the hazard ration being less than 2 (hazard ratio, 1.07; 95% confidence interval [CI], 0.70 to 1.65) (Fig. 2A). Results for low-dose and high-dose groups (Fig. S3 in the Supplementary Appendix) were consistent with the overall results. The results of the analyses in prespecified subgroups defined according to age, sex, race, and region were also consistent with the profile of the overall population (Fig. S4 in the Supplementary Appendix), although it should be noted that the study was not powered to detect noninferiority in subgroups and that the confidence intervals were broad within the smaller subgroups.

OTHER SAFETY ASSESSMENTS

Death (from any cause) was reported in 6 patients receiving budesonide–formoterol and 8 patients receiving budesonide. A total of 2.1% of the patients in each group had a serious adverse event (Table 3). Overall, 1.6% of the patients taking budesonide–formoterol versus 2.3% of patients taking budesonide discontinued treatment because of adverse events; 0.9% of patients taking budesonide–formoterol versus 1.2% of patients taking budesonide discontinued treatment due to exacerbations.

PRIMARY EFFICACY END POINT

In total, 539 patients (9.2%) in the budesonide–formoterol group reported 637 exacerbations and 633 patients (10.8%) in the budesonide group reported 762 exacerbations. The risk of an asthma exacerbation (the primary efficacy end point) was 16.5% lower with budesonide–formoterol than with budesonide (hazard ratio, 0.84; 95% CI, 0.74 to 0.94; P=0.002) (Fig. 2B), and these efficacy findings were consistent for both doses of budesonide (Fig. S5). The results across subgroups were generally consistent with the overall results, although the confidence intervals were

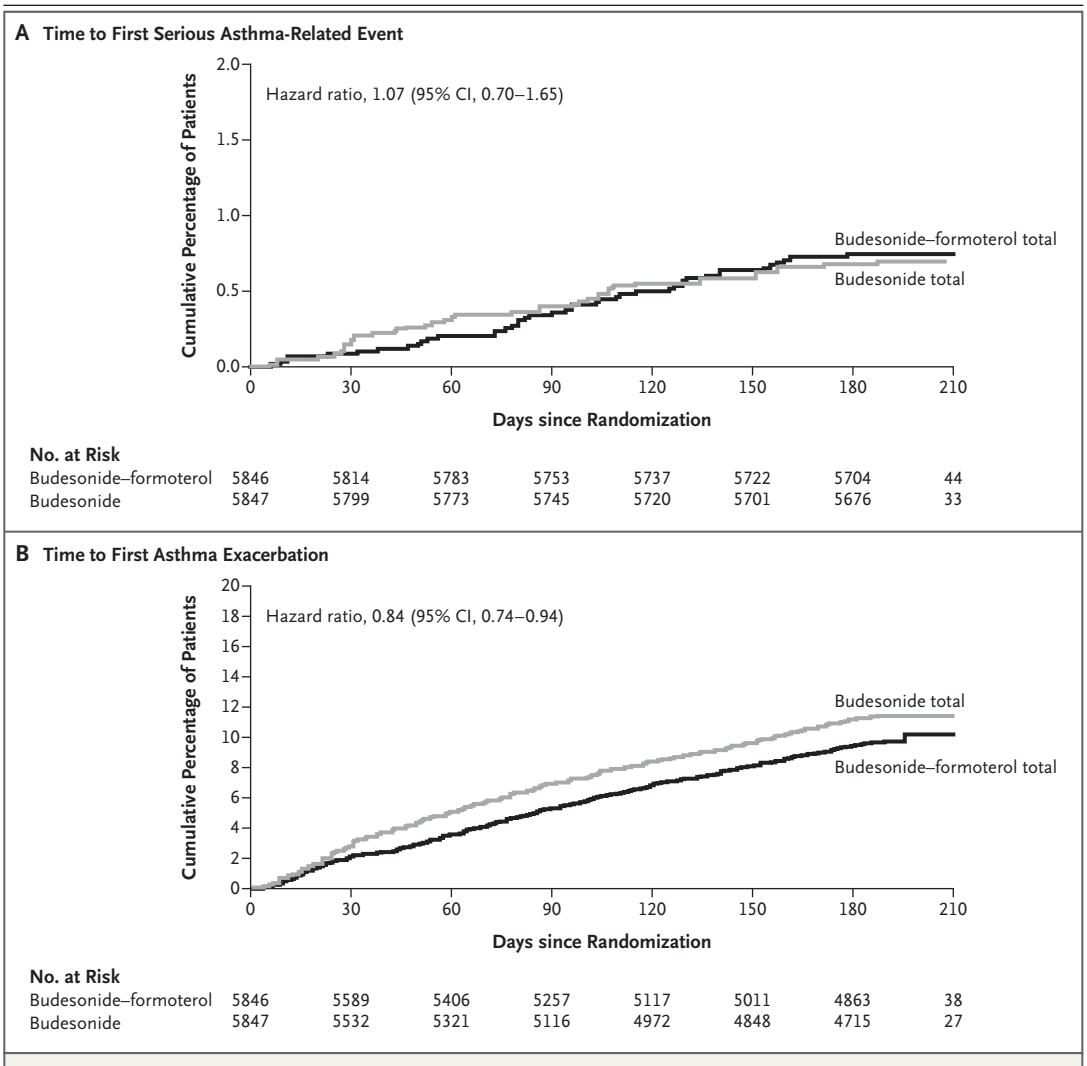

Figure 2. Time-to-Event Analysis of the Risk of a First Serious Asthma-Related Event and the Risk of a First Asthma Exacerbation.

Statistical noninferiority was shown on the basis of an upper limit of the 95% confidence interval of the hazard ratio ofless than 2.0. Kaplan–Meier plots are shown in Panel A for the risk of a first serious asthma-related event (the primary end point of the study) and in Panel B for the risk of a first asthma exacerbation (the primary efficacy end point), as assessed in a time-to-event analysis. The numbers beneath the plot indicate the number of patients in each treatment group who were at risk for a serious asthma-related event or an exacerbation at the given time point. Patients who had an asthma exacerbation that did not respond to treatment within 14 days and patients who had one or more asthma exacerbations within 13 weeks or two or more exacerbations within 26 weeks (within the treatment period) were withdrawn from study treatment.

broad within the smaller subgroups (Tables S1, S2, and S3 in the Supplementary Appendix).

SECONDARY EFFICACY END POINTS

There was a clinically relevant improvement in asthma control (mean average decrease from baseline ACQ-6 ≥0.5) in both treatment groups (budesonide–formoterol, −0.67; budesonide, −0.58). The greater improvement observed with budesonide–formoterol than with budesonide was statistically significant (least-squares mean [±SE], −0.08±0.01; 95% CI, −0.10 to −0.06; P<0.001) (Table S4 in the Supplementary Appendix). The proportion of patients with a clinically relevant

Table 3. Rates of Adverse Events.*

Event	Low Dose		High Dose		Total	
	Budesonide–Formoterol 80 μg+4.5 μg (N=1645)	Budesonide 80 μg (N=1646)	Budesonide–Formoterol 160 μg+4.5 μg (N=4201)	Budesonide 160 μg (N=4201)	Budesonide–Formoterol (N=5846)	Budesonide (N=5847)
	number (percent)					
Any serious adverse event	21 (1.3)	31 (1.9)	104 (2.5)	92 (2.2)	125 (2.1)	123 (2.1)
Any adverse event leading to study discontinuation	20 (1.2)	27 (1.6)	73 (1.7)	105 (2.5)	93 (1.6)	132 (2.3)
Any adverse event with outcome of death	2 (0.1)	3 (0.2)	4 (0.1)	5 (0.1)	6 (0.1)	8 (0.1)

* All data in this table were derived from the intention-to-treat population, which comprised all patients who were randomly assigned to treatment.

improvement at the end of treatment also favored budesonide–formoterol over budesonide alone (58.7% vs. 54.4% [data not shown]).

Budesonide–formoterol was superior to budesonide in all but one of the variables related to symptom control (with the exception being limitation of activity because of asthma), including a greater mean number of symptom-free days, fewer night-time awakenings, and the use of fewer doses of rescue medication (Table S5 in the Supplementary Appendix). For secondary efficacy end points, comparisons of treatment within the dose strata were generally consistent with the overall comparison between treatment groups (Tables S4 and S5 in the Supplementary Appendix).

DISCUSSION

The results of this prospective, randomized, clinical trial showed that the addition of formoterol to budesonide monotherapy did not appear to increase the risk of serious asthma-related events in adolescent and adult patients with predominantly moderate-to-severe asthma. This finding is consistent with findings of meta-analyses of data from clinical trials of formoterol-containing therapy, in which serious asthma-related events were measured as secondary end points.[7,8] The results of the current study are also in line with findings from an analysis of six randomized trials, including those in which budesonide–formoterol was used in an alternative maintenance-and-reliever dosing regimen.[15] One of the other three FDA-mandated studies, the AUSTRI trial, has now been published and showed similar results, with no data revealing evidence of an increased risk of serious asthma-related events with the addition of a LABA (salmeterol) to fluticasone monotherapy.[16]

The majority of serious asthma-related events were hospitalizations, but one intubation and two deaths (three events in two patients) were also reported in the budesonide–formoterol group. Given the rarity of asthma-related deaths, none of the individual FDA-requested studies were powered for a separate analysis of these events, and any between-group differences in asthma-related death will need to be evaluated in the context of pooled data from the four studies, once they are all completed. Two asthma-related deaths have been observed in a combined population of more than 23,000 patients from this trial and the AUSTRI trial, in contrast with the 28 deaths projected for all four studies requested by the FDA.

Although the current study was designed primarily to assess safety, the evaluation of prespecified efficacy measures was included to further assess the benefit:risk profile of the treatment groups. The risk of asthma exacerbation, the primary efficacy variable, was 16.5% lower with budesonide–formoterol than with budesonide alone; this significantly lower risk was observed despite the high percentage of patients reporting asthma control at baseline.

These findings are commensurate with those of previous studies.[17-22] Furthermore, budesonide–formoterol was significantly superior to budesonide in all but one of the secondary efficacy variables, although the magnitude of the differences was modest.

Previous data suggested a higher risk of asthma-related deaths and serious asthma-related events in black patients than in white patients.[5] In this study, black patients were found to be at higher risk of serious asthma-related events than the overall population, but there was no evidence of an increased risk of serious asthma-related events associated with the use of LABA in this or any other prespecified clinical subgroups. This finding is in line with previous reports that have supported the safety of budesonide–formoterol in black patients.[23] Among adolescent patients (12 to 17 years of age), the risk of serious asthma-related events was very low in the current study, with no evidence of a higher risk with budesonide–formoterol than with budesonide alone (although the small number of events [three in each treatment group] precluded the calculation of hazard ratios).

The current study included a broad population of patients with moderate-to-severe asthma, controlled or uncontrolled, who were at risk for serious asthma-related events and who had had one or more exacerbations during the previous year. The total number of patients with serious asthma-related events (83) was close to that assumed in the determination of sample size (87), which indicates that the patient population recruited was as planned in the study protocol and that the study was adequately powered for this end point. However, the study has some limitations, and its results may therefore not be applicable to all patients with asthma, most notably those with a history of life-threatening asthma, who were not eligible for inclusion. The exclusion of patients with life-threatening asthma was a joint decision of the FDA, the study sponsors, and the independent joint oversight committee. The decision was made on the basis of patient safety, given our inability to provide effective therapy beyond LABA plus inhaled glucocorticoids and the possibility of a patient with life-threatening asthma receiving only monotherapy for 6 months. This group of patients constitutes a small proportion of the asthma population, who tend to require more specialized or individualized treatment regimens. Patients with a history of life-threatening asthma may also represent a phenotypically or genotypically distinct subgroup of all patients with asthma; for example, an increased number of serious asthma-related events has been observed in patients with rare variants in the β_2-adrenergic receptor gene.[24] As part of this study, DNA samples were collected for future exploratory research. A further possible limitation of this study is that the high rate of adherence to the prescribed regimen observed in both treatment groups, which may be related to the frequent patient contact and built-in alerts communicated through the interactive voice-response system, may not be akin to what is observed in real-life settings, where the lack of adherence could increase the risk of serious asthma-related events.

In conclusion, the results reported here established the noninferiority of budesonide–formoterol to budesonide with regard to the risk of serious asthma-related events in adults and adolescents with predominantly moderate-to-severe asthma; in addition, budesonide–formoterol therapy resulted in a 16.5% lower risk of asthma exacerbations than budesonide alone. These results are an important addition to the large body of evidence on the profile of benefits and risks associated with LABAs when they are administered in a fixed-dose combination with an inhaled glucocorticoid.

Supported by AstraZeneca.

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

We thank Eva-Lena Alenhag, Fredrik Frick, Patrik Bondarov, Åsa Westin, Gun Almqvist, Magnus B. Lindberg, Kristine Pemberton, Lisa Barrett, Tomas L.G. Andersson, Lars-Göran Carlsson, Peter Held, and Göran Eckerwall; the members of the joint adjudication committee (Anne Fuhlbrigge, Christine Jenkins, and Emilio Pizzichini); the members of the joint oversight steering committee (William Busse, Eric Bateman, William Kelly, Paul O'Byrne, Klaus Rabe, Arthur Caplan, and Vernon Chincilli); the members of the joint data monitoring committee (Helen Reddel, Lee-Jen Wei, Robert Wise, James Kemp, Monica Kraft, Sally Wenzel, and Victor Larcher); the members of the trial-specific data monitoring committee (Monica Kraft, James Neaton, Kelly Michelson, Gerard Criner, and Ian Pavord); all the study investigators, whose names are listed in the Supplementary Appendix; and Clair Clowes and Hanna Mourad-Agha of inScience Communications for medical-writing assistance, funded by AstraZeneca.

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